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Associate Editor of *World Journal of Transplantation*, Maria Irene Bellini, MD, PhD, FEBS (Transplant), Assistant Professor, Department of Surgical Sciences, Quarta Clinica Chirurgica, Sapienza University, Roma 00161, Italy. mariairene.bellini@uniroma1.it

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OPINION REVIEW

Human pegivirus infection after transplant: Is there an impact?

Anna Mrzljak, Bojana Simunov, Ivan Balen, Zeljka Jurekovic, Tatjana Vilibic-Cavlek

ORCID number: Anna Mrzljak 0000-0001-6270-2305; Bojana Simunov 0000-0002-1768-2277; Ivan Balen 0000-0002-7071-539X; Zeljka Jurekovic 0000-0003-0690-2577; Tatjana Vilibic-Cavlek 0000-0002-1877-5547.

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Anna Mrzljak, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Bojana Simunov, Zeljka Jurekovic, Department of Medicine, Merkur University Hospital, Zagreb 10000, Croatia

Ivan Balen, Department of Gastroenterology and Endocrinology, General Hospital "Dr. Josip Bencevic", Slavonski Brod 35000, Croatia

Tatjana Vilibic-Cavlek, Department of Virology, Croatian Institute of Public Health, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Corresponding author: Anna Mrzljak, FEBG, PhD, Associate Professor, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, School of Medicine, University of Zagreb, Kispaticeva ulica 12, Zagreb 10000, Croatia. anna.mrzljak@gmail.com

Abstract

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. In the transplantation setting, pegivirus infection does not seem to have a negative impact on the outcomes of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The possible immunomodulatory effect of pegivirus infections remains to be elucidated in further trials.

Key Words: Virome; Human pegivirus; Epidemiology; Solid-organ transplant; Hematopoietic stem cell transplantation

Core Tip: Pegiviruses are single-stranded positive-sense RNA viruses, historically associated with liver disease, but their pathogenicity is controversial. Pegivirus infection does not seem to have a negative impact on the outcome of solid-organ and hematopoietic stem cell transplant recipients. However, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals.

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INTRODUCTION

The microbiome's role in transplantation has received growing interest, but the role of virome remains understudied. Several studies have shown that the virome changes upon immunosuppression initiation[1,2]. Most notable is the increase in the anellovirus but also in pegiviruses.

Pegiviruses are single-stranded positive-sense RNA viruses, most closely related to hepatitis C virus (HCV) in terms of genome organization with structural genes located at the 5' genomic region and non-structural genes at the 3' end[3]. The genome encodes a polyprotein that is co- and post-translationally cleaved into individual viral proteins. Structural proteins common to all pegiviruses are the envelope glycoproteins (E1 and E2), and non-structural proteins are NS2-NS5B[4]. Pegiviruses are classified into eleven species (pegivirus A-K) within the genus *Pegivirus* in the *Flaviviridae* family. Two pegiviruses are known to infect humans, the human pegivirus (HPgV) and the HPgV-2, but their pathogenicity is limited and no clear association with any human disease has been established[5].

HPgV was discovered in 1995 from the sera of patients with hepatitis by two independent investigator groups, who named it GB virus C and hepatitis G virus (HGV), respectively. The HPgV's E2 glycoprotein, involved in the adhesion and fusion with the host cells, targets the production of anti-HPgV antibodies, which appear after the viral clearance and provide partial protection against reinfection[6]. The virus is efficiently transmitted through sexual contact and intravenous substance use, vertically from mother to child, and through exposure to infected blood and blood components[7].

Available data suggest a high prevalence of HpgV viremia (> 40%) in populations with parenteral exposure risk[8]. Although early studies indicated that the HPgV is hepatotropic, numerous subsequent studies have shown that HPgV is rarely detectable in infected individuals' liver tissue. In addition, no evidence of a liver disease potentially linked to HPgV was observed during the follow-up of different patient categories[7].

HPgV-2 was isolated in 2015 from the plasma of HCV-infected patients with multiple blood-borne exposures in the United States[8]. A low prevalence of HPgV-2 viremia has been noted in the general population, but there is an increase in patients with HCV infection and injecting drug users co-infected with HCV[9]. Further studies indicated that HPgV-2 is a lymphotropic but not a hepatotropic virus, which may explain the lack of association with liver disease[10].

HPgVs are distributed globally, and viral RNA is present in roughly 750 million people[6], making it ubiquitous in human populations. The prevalence of HPgV viremia from cross-sectional studies of healthy blood donors in developed countries ranges between 1% and 5%. Nearly 200000 units of HPgVs-contaminated blood products are transfused each year in the United States[11]. In comparison, in developing countries, up to 20% of blood donors have an active infection[12]. Data suggest that approximately 1.5-2.5 billion people are currently infected or have evidence of prior HPgV infection[6].

Numerous studies examined the presence of HPgV in several countries. Generally, a high HPgV prevalence is observed among subjects with parenteral exposure, including those exposed to blood and blood products, those on hemodialysis, those with a history of intravenous substance use, and patients with chronic hepatitis C or human immunodeficiency virus (HIV) infection[13].

HPGV AFTER TRANSPLANTATION OF SOLID ORGANS AND NON-SOLID ORGANS

HPgVs have received much attention due to the possible beneficial immunomodulatory effects by reducing immune activation in patients with other viral diseases such as HIV infection, hepatitis B, and Ebola virus disease[14-17]. On the other hand, HPgV

viremia has also been associated with the development of non-Hodgkin lymphoma (NHL). HPgV is a lymphotropic virus that may cause persistent infection in T and B lymphocytes, reduced Fas-mediated apoptosis, and impaired T cell and interleukin-2 receptor signaling[18]. HPgV infection anticipates the development of NHL by several years and resolved infection was not associated with NHL risk[19]. Pegiviruses have been studied both in hematopoietic stem cell transplantation (HSCT) and solid-organ transplant (SOT) recipients (Table 1).

Studies in HSCT recipients are limited. The prevalence of HPgV in HSCT patients ranges from 18.6%, as described in the study from Switzerland[20], to almost 30% in an earlier French study[21]. As in the general population, the risk of viremia rises with the number of received blood products[20,22]. No significant influence of pegiviruses on HSCT patient outcomes was found. On the other hand, no beneficial effect of pegivirus infections is currently proven; therefore, some studies warrant HPgV donor screening for blood products used in HSCT recipients until more conclusive studies are performed[22].

Early studies in SOT recipients were done mostly in liver transplant (LT) recipients, due to the presumed hepatotropic nature of the virus, all showing a high prevalence but no significant influence on patient outcomes[23-26]. The largest of the studies included in this review is the recent Japanese study on 313 LT recipients. This monocentric study showed an increased prevalence of HPgV in LT recipients compared to hepatectomy controls[27]. As in the earlier studies, there was no significant association between HPgV infection and LT outcomes. The study showed that HPgV infection induced the up-regulation of interferon-stimulated gene (ISG) expression in peripheral blood mononuclear cells[27].

HPgV is transmitted through parenteral, sexual, and perinatal routes[28]. Parenterally exposed individuals such as hemodialysis patients, therefore, have a higher risk of infection. An Indian study using univariate analysis showed that the prevalence of GB virus C/HGV RNA was significantly associated with ≥ 20 hemodialysis sessions[29]. After the transition from dialysis, the prevalence remains high in kidney transplant (KT) recipients, ranging from 12% to 47% in different countries[30-33]. A large Italian study in KT recipients (n = 155) showed an HGV RNA and anti-HGV prevalence of 24% and 17%, respectively[34]. None of the studies above, found any influence on patient outcomes, including kidney or liver function. On the other hand, the largest study in KT recipients (Germany, n = 221)[33] showed that a much higher proportion of KT recipients were exposed to HGV, than that suggested by HGV RNA detection alone. The prevalence of HGV RNA and anti-HGV in the study was 14% and 40%, respectively. Most infected individuals eliminate the virus over time. Unfortunately, the majority of other studies did not include serological analyses. Most of the studies on HPgV were done immediately after the discovery of the virus, focusing mostly on hepatic function or the function of the transplanted organ. Only the most recent study[1] tried to include other post-transplant complications in the analysis, *e.g.*, new-onset diabetes after transplantation or nephrotoxicity in LT recipients. The study highlighted a potential use of anellovirus infection as a proxy for determining the immunological status. At the moment there is no standard way to measure total immunosuppression, besides the widely available through levels of immunosuppressant drugs. In the same study, all of the HPgV positive participants were still alive 5 years after LT, indicating a protective role of HPgV in post-transplantation survival[1].

The paucity of other SOT recipient studies probably reflects the proportionately lower number of those transplants performed. We found no studies evaluating HPgV in simultaneous pancreas-kidney transplantations or lung transplant recipients. The studies in heart transplant recipients are concordant to those in other SOT, showing no adverse outcome but a high HPgV prevalence, up to 36%[35-42].

CONCLUSION

To conclude, pegivirus infection does not seem to have a negative impact on the outcome of transplant recipients. Nevertheless, studies are limited and lacking prospective data. What remains to be elucidated is the possible immunomodulatory effect of pegivirus infections. Also, the role of pegiviruses as proxies in immunosuppression monitoring brings novelty to the field of virome research in immunocompromised individuals. The subject deserves further research and evaluation.

Table 1 Seroprevalence and RNA prevalence studies in different transplant populations

Type of transplant and period	Country/region	Patients (*n*)	RNA prevalence	Seroprevalence	Comment	Ref.
Liver transplant; 1997-2017	Japan	313	14.1%	/	No significant association between HPgV infection and liver transplant outcomes; HPgV infection induced the up-regulation of ISG expression in peripheral blood mononuclear cells	Izumi *et al*[27], 2019
Renal transplant; 1989-1996	Italy	155	24%	17%	Not associated with disease pathogenicity; Lower serum levels of HCV-RNA in HGV/HCV co-infected carriers compared to those infected with HCV only	De Filippi *et al*[34], 2001
Renal transplant; 2015-2016	Brazil	61	36.1%	/	Most common genotype 2 (80.9%), followed by G3 (9.5%), G1 (4.85), and G5 (4.8%); no significant impact on patient outcomes	Savassi-Ribas *et al*[31], 2020
Renal transplant	France	103 HCV positive RT recipients	28%	/	HGV infection has no detrimental effect on liver enzymes or liver histology in HCV-positive patients	Rostaing *et al*[37], 1999
Heart transplant; 1993-1998	Germany	51 transplant candidates	2.0%; 0	0; 6.0%	RNA persisted after transplant; anti-E2 antibodies persisted after transplant	Kallinowski *et al*[38], 2002
		Post-transplant	36.0% *de novo*	/	RNA persisted in 94% infected patients; No significant correlation between the number of blood transfusions and the infection; No impact on liver disease or patient outcome	
Liver transplant; 1993-1998	Germany	72 transplant candidates	11.%	/	RNA persisted in 88% of infected patients	Kallinowski *et al*[38], 2002
		Post-transplant	36% *de novo*	/	RNA persisted in 87% of infected patients; no significant correlation between the number of blood transfusions and the infection; no impact on liver disease or patient outcome	
Kidney transplant; 1997	Thailand	94	43%	/	Co-circulation of HGV and HCV RNA was detected in 12 patients (13%)	Raengsakulrach *et al*[30], 1997
Heart transplant; 1993-1996	Germany	243	24%	/	HGV infections are transfusion related; not related to the use of mechanical circulatory assist devices or immunosuppression	Wolff *et al*[36], 1996
Liver transplant; 1989-1996	Germany	98	Pre-tx 8.2%; post-tx 44%	/	None of the hepatitis B, hepatitis C, or fulminant hepatitis, were HGV-RNA positive preoperatively; HGV was frequently acquired after LT but had no impact on the short- and medium-term clinical course post-LT	Fischer *et al*[23], 1999
Liver transplant; 2007-2010	Iran	106	9.4%	/	Moderate prevalence of HGV infection in liver transplant recipients	Ebadi *et al*[39], 2011
Kidney transplant; 1986-1990	United States	93	12%	/	HGV infection does not adversely affect clinical outcome during early follow-up	Isaacson *et al*[32], 1999
Liver transplant; 1989-1996	Italy	136	Pre-tx 18.4%; post-tx 47.8%	Pre-tx 26.5%	Liver transplant patients are heavily exposed to HGV before and after transplantation; HGV does not induce liver disease; most infections are self-limited and induce a protective immunity (anti-E2 antibodies presence)	Silini *et al*[40], 1998
HSCT; 1985-1996	France	95	29.5%	/	Acute GVHD, chronic GVHD, or veno-occlusive disease are similar in HGV+ and HGV- recipients in early period after allogenic BMT	Corbi *et al*[21], 1997
Kidney transplant; 1997	Germany	221	14%	40%	The majority of infected individuals eliminate the virus over time	Stark *et al*[33], 1997
Kidney transplant; NA	Turkey	69	42%	/	Genotype 2 is the dominant type; subgroup 2a most common of the isolates	Erensoy *et al*[41], 2002

Liver transplant; 1993-1995	United Kingdom	47	47%	/	HGV does not cause significant liver disease after LT	Karayiannis *et al* [42], 1998
Liver transplant; 1979-1990	Netherlands	39	Pre-tx 15.4%; post-tx 43.6%	/	HGV infection is highly prevalent in liver transplant patients; in the absence of HBV or HCV co-infection with, no long-term negative influence on the graft	Haagsma *et al* [24], 1997
Kidney transplant; 1997-2000	India	70	52.9%	58.6%	GBV-C/HGV RNA significantly associated with ≥ 20 hemodialysis sessions	Abraham *et al* [29], 2003
Liver transplant; 1990-1994	United States	179	Pre-tx 15%; post-tx 50%	/	HGV infection not associated with poor outcome	Hoofnagle *et al* [26], 1997
HSCT; 2011-2017	China	188	18.6%	/	HPgV is highly prevalent in HSCT patients; blood transfusions significantly increase the risk of HPgV infection	Li *et al*[22], 2019
HSCT; 2014-2015	Switzerland	40	35%	/	HPgV is highly prevalent and persists for several months	Vu *et al*[20], 2019

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HGV: Hepatitis G virus; HSCT: Hematopoietic stem cell transplantation; HpgV: Human pegivirus; GBV-C: GB virus C; GVHD: Graft *versus* host disease; BMT: Bone marrow transplantation; ISG: Interferon-stimulated gene.

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CASE REPORT

Diagnosis of acute intermittent porphyria in a renal transplant patient: A case report

Cristina Sirch, Niloufar Khanna, Lynda Frassetto, Francesco Bianco, Mary Louise Artero

ORCID number: Cristina Sirch 0000-0002-8433-3034; Niloufar Khanna 0000-0001-6651-6147; Lynda Frassetto 0000-0002-4199-019X; Francesco Bianco 0000-0003-7688-0201; Mary Louise Artero 000-0001-8322-3338.

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Cristina Sirch, Francesco Bianco, Mary Louise Artero, Nefrologia e Dialisi, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste 34100, Italy

Niloufar Khanna, Medicine, California Northstate University, Elk Grove, CA 95757, United States

Lynda Frassetto, Internal Medicine, Division of Nephrology, University of California San Francisco, San Francisco, CA 94193, United States

Corresponding author: Cristina Sirch, MD, Doctor, Nefrologia e Dialisi, Azienda Sanitaria Universitaria Giuliano Isontina, Piazza dell'Ospitale 2, Trieste 34100, Italy.
cristina.sirch@asugi.sanita.fvg.it

Abstract

BACKGROUND

Acute intermittent porphyria (AIP) is an inherited disorder of porphyrin metabolism with a worldwide distribution and a prevalence ranging from 1 to 9 per million population. AIP is caused by an autosomal dominant-inherited mutation of low penetrance resulting in a deficiency of porphobilinogen deaminase (PBGD) activity. Acute attacks are provoked by stressors such as certain medications, alcohol, and infection. We herein present the first case report of AIP detected in a post-renal transplant patient.

CASE SUMMARY

The patient was a 65-year-old man who underwent transplantation 2 years previously for suspected nephroangiosclerosis and chronic interstitial nephropathy. He subsequently developed diabetes mellitus which required insulin therapy. He had been treated in the recent past with local mesalamine for proctitis. He presented with classic but common symptoms of AIP including intense abdominal pain, hypertension, and anxiety. He had multiple visits to the emergency room over a 6-mo period for these same symptoms before the diagnosis of AIP was entertained. His urinary postprandial blood glucose level was 60 mg/24 h (normal, < 2 mg/24 h). He was placed on a high carbohydrate diet, and his symptoms slowly improved.

CONCLUSION

This case report describes a common presentation of an uncommon disease, in which post-transplant complications and medications may have contributed to precipitating the previously undiagnosed AIP. We hypothesize that the low-

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carbohydrate diet and insulin with which our patient was treated may have led to the attacks of AIP. Alternatively, our patient's mesalamine treatment for proctitis may have led to an acute AIP crisis. A high index of suspicion is needed to consider the diagnosis of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety.

Key Words: Acute intermittent porphyria; Post-transplantation diabetes; Mesalamine; Tacrolimus; Renal transplantation; Case report

Core Tip: This case report describes a common presentation of an uncommon disease, in which post-transplant complications and medications may have contributed to precipitating his previously undiagnosed acute intermittent porphyria. A high index of suspicion is needed to consider the diagnosis of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety in a post-renal transplantation patient.

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INTRODUCTION

Acute intermittent porphyria (AIP) is an inherited disorder of porphyrin metabolism with a worldwide distribution and a prevalence ranging from 1 to 9 per million population with the highest prevalence found in northern Europe[1]. AIP is caused by an autosomal dominant inherited mutation of low penetrance resulting in a deficiency of porphobilinogen deaminase (PBGD) activity[1]. Acute attacks are provoked by stressors such as certain medications, alcohol, and infection. Symptoms include abdominal pain mimicking acute surgical abdomen, sometimes leading to unnecessary laparotomy, as well as neuromuscular and psychiatric disturbances. Late-stage associated conditions include renal insufficiency and hepatocellular cancer[2,3].

We present a patient who underwent deceased donor renal transplantation and subsequently developed AIP. Experience of renal transplantation in patients with AIP is limited. We found three previous reports describing renal transplantation[4,5] or combined liver-renal transplantation[6] in patients with a history of known AIP, but none reporting the diagnosis of AIP in a previously transplanted patient.

CASE PRESENTATION

Chief complaints

Recurrence of abdominal pain, nausea, and vomiting in a kidney transplant patient.

History of present illness

A 65-year-old man reported the appearance of rectal blood in March 2017 and visited a proctologist. He started local mesalamine therapy for proctitis, but the drug was discontinued a few days later due to abdominal pain and constipation. During the subsequent 6 mo, he presented several times to the emergency department complaining of severe abdominal pain, nausea, and vomiting. He related an anxious mood and low energy level in addition to tachycardia and an increase in blood pressure which was no longer well-controlled with his usual therapy. He presented to the emergency room eight times for various complaints (Figure 1): Epigastric pain without mention of mesalamine, agitation and anxiety, thoracic pain, abdominal pain, and precordial pain.

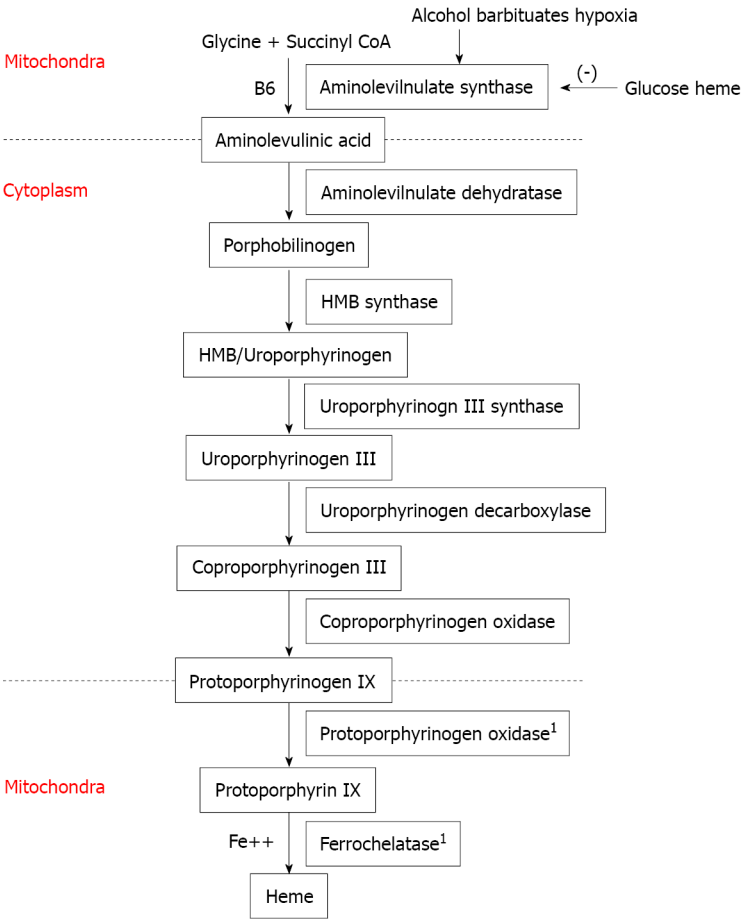

Figure 1 Heme synthesis pathway. [1]Mitochondrial enzyme.

History of past illness

The patient had been treated for hypertension since 1994 and developed ischemic heart disease. His renal function gradually deteriorated over the years due to suspected nephroangiosclerosis and chronic interstitial nephropathy, as ultrasound examination demonstrated small echogenic kidneys. He started hemodialysis in 2008 and was evaluated for renal transplantation; a left nephrectomy was performed for a small incidental renal carcinoma. The histopathologic examination of the nephrectomy specimen revealed angiosclerosis and tubulointerstitial fibrosis. He underwent a deceased-donor kidney transplant in 2015, for which he was treated with tacrolimus, mycophenolate mofetil, and methylprednisolone. He developed diabetes mellitus post-transplant and insulin therapy was initiated (see Table 1).

Personal and family history

The patient had no known family history of porphyria.

Physical examination

The patient was hemodynamically stable with a heart rate of 90 bpm and blood pressure of 160/90 mmHg, but appeared in mild distress. The physical examination revealed an intermittently tender, non-distended abdomen with normal bowel sounds and absent rigidity, rebound, and guarding. The remainder of the physical examination was unremarkable.

Laboratory examinations

Serum levels of hemoglobin, electrolytes, hepatic transaminases, amylase, thyroid function, protein electrophoresis, and C-reactive protein were normal, as was the urine analysis. Renal function was stable with a serum creatinine of 1.2 mg/dL; the urine culture was negative.

Table 1 Medications used

Medication list	Dose	Time
Tacrolimus	0.5 mg; 0.5 mg	08:00; 20:00
Mycophenolate mofetil	1000 mg; 500 mg	08:00; 20:00
Methylprednisolone	2 mg	08:00
Aspirin	100 mg	13:00
Ranitidine	300 mg	08:00
Cinacalcet	30 mg	08:00
Bisoprolol	5 mg	08:00
Amlodipine	10 mg	20:00
Nitroglycerin TTS	10 mcg	1 d
Atorvastatin	40 mg	20:00
Calcitriol	0.25 mcg	08:00
Na bicarbonate	1000 mg qd	
Insulin		
Bromazepam	2.5 mg/mL 5 drops bid	

TTS: Transdermal therapeutic system.

Imaging examinations

Plain X-rays of the abdomen showed distended colon and fecal impaction, and ultrasound revealed that the liver, spleen, pancreas, and transplanted kidney were of normal size and consistency and that the site of the left nephrectomy was occupied by intestinal loops.

FINAL DIAGNOSIS

Based on the clinical symptoms and the radiologic and laboratory findings, a diagnosis of porphyria was attained. The level of postprandial blood glucose (PBG) in a 24-h urine sample was determined utilizing spectrophotometric technique (ClinRep for the porphyrins and ClinEasy for PBG; RECIPE Chemicals and Instruments, Munich, Germany). The level of PBG was significantly elevated to - 60 mg/24 h in the first sample (normal value, < 2 mg/24 h), whereas the values for porphyrins and coproporphyrins were negative, supporting the hypothesis of AIP (Figure 2).

TREATMENT

After AIP was confirmed, treatment was initiated with a carbohydrate-rich diet, and the patient's symptoms slowly improved. The timeline of events is listed in Figure 1.

The patient was referred to the genetics division for analysis of the PBGD (also known as the hydroxymethylbilane synthase) gene and also splicing variants using sequencing and polymerase chain reaction amplification, but tested negative for the most common available single nucleotide polymorphisms (SNPs). It is notable that the patient's insulin requirements did not change after the high-carb diet was started; his insulin doses, glycated hemoglobin, and glucose levels did not change.

OUTCOME AND FOLLOW-UP

The patient's symptoms slowly improved with a carbohydrate-rich diet.

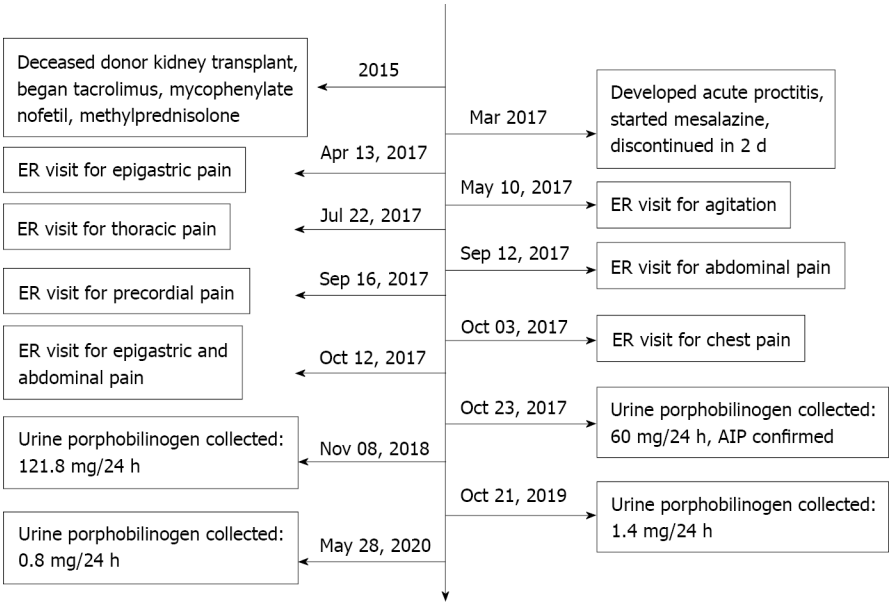

Figure 2 Timeline of patient symptoms and response to treatment. ER: Emergency room; AIP: Acute intermittent porphyria.

DISCUSSION

To our knowledge, this is the first report of new onset AIP symptomatology in a renal transplant patient. We hypothesize that our patient had pre-existing but undetected AIP, and that he may have a genetic predisposition due to his European ancestry. Although Lazareth *et al*[7] have reported improved AIP outcomes following renal transplantation, the hepatic origin of the disease may present a risk of acute attack in case of post-transplant complications, medications, infection, or reduced carbohydrate intake.

As mentioned in the History of Past Illness section, the nephrectomy specimen, in addition to the small renal carcinoma, revealed chronic tubulointerstitial lesions and nephroangiosclerosis. According to Pallet *et al*[8], in a large cohort of patients with porphyria-associated kidney disease, kidney biopsies revealed "diffuse glomerulosclerosis and chronic interstitial changes", and thus it is conceivable that the AIP was responsible for the renal insufficiency in the native kidneys. On the other hand, these findings are very common and nonspecific in nephropathy patients, and may not accurately reflect the etiology of the renal disease.

Over 500 PBGD mutations have been described in AIP. Penetrance is incomplete, and less than 10 per cent of individuals with each genetic defect may have phenotypic expression of the disease[9]. The enzyme deficiency alone is not sufficient to trigger crises; environmental factors are required. Thus, 80%-90% of those with the enzyme deficiency never manifest symptoms[10]. Acute attacks are often precipitated by drugs such as barbiturates and other anticonvulsants, calcium channel blockers, sedatives, antibiotics, hormones, alcohol, tobacco, calorie-restricted or low carbohydrate diets, infection, surgery, psychological disorders, or other comorbid conditions. In some patients, no precipitating stressor is found[11].

The diagnosis of acute porphyria is challenging - symptoms are not specific and may mimic various digestive and neuropsychiatric diseases. Very intense, diffuse abdominal pain is often the earliest characteristic symptom. Nausea, vomiting, constipation, urinary retention, arrhythmias, labile blood pressure, and hyponatremia may coincide with the pain[11]. The AIP crisis may also have associated neurological complications such as respiratory arrest due to bulbar involvement, quadriplegia, neuropathic limb pain, depression, and suicide[12]. In the present case, the patient presented with the principal signs and symptoms of AIP: Very intense abdominal pain, hypertension, and anxiety/depression disorder.

The clinical criteria for AIP diagnosis include the paroxysmal nature of the symptoms, while the biochemical criteria include a more than fivefold increase in urinary porphobilinogen excretion, which is also elevated in 88% of AIP patients in remission. DNA analysis of the *PBGD* gene is the most reliable diagnostic method.

Current treatment options include heme preparations during an acute attack; intravenous glucose 10% alone (see discussion below) - at least 300 g daily - may

resolve mild attacks or may be given while waiting for heme arginate to be available. During acute attacks, correction of dehydration and electrolyte imbalances as well as monitoring of vital capacity and expiratory flow rate is important. This patient responded to a high complex carbohydrate diet. No variation of the immunosuppressive protocol has been required.

A high prevalence of AIP among the Spanish population has been reported, and variations on the CYP2D6 enzyme, important for hepatic drug metabolism, in this population may impact the penetrance of this disorder in those with a PBGD enzyme mutation[13]. Additionally, G6PD deficiency is common among Mediterranean populations[14], and the levels of G6PD can affect AIP exacerbations[15]. Although our patient tested negative for the most common SNPs, with over 500 mutations identified affecting the *PBGD* gene[16]which can cause AIP, it is possible that our patient had a rarer or undescribed mutation.

Aminolaevulinic acid synthase is the first enzyme in the heme synthesis pathway (see Figure 2 for details of the heme synthesis pathway) and is regulated by glucose and heme, such that high levels of glucose inhibit heme synthesis and prevent attacks of AIP. Although AIP is caused by a defect in the third enzyme of the heme synthesis pathway (PBGD), stimulation of aminolevulinate synthase by decreased glucose leads to activation of the heme synthesis pathway and causes an acute attack of AIP. Increased glucose, including glucose infusions and avoidance of fasting between attacks, has been shown to be beneficial in the management of AIP[17]. The American Porphyria Foundation suggests a 55%-60% carb-based diet for patients with AIP and cautions against fasting or crash-dieting[18]. This patient recovered upon being placed on a high-carb diet, supporting the hypothesis that a low-glucose state triggered his attack.

It is possible that the patient's diabetes combined with his low carbohydrate intake resulted in low uptake of glucose into the cells, mimicking the fasting state known to trigger AIP attacks[11]. Post-transplant diabetes is commonly induced by tacrolimus treatment through decreased insulin secretion, increased insulin resistance, and beta-islet cell toxicity[19]. A case report of a patient with hereditary coproporphyria showed that high levels of tacrolimus triggered an acute attack and that the patient's symptoms resolved once tacrolimus levels were lowered into the therapeutic range, thereby suggesting a role for tacrolimus in precipitation of AIP attacks[20].On the other hand, hyperinsulinism may be associated with clinically stable AIP[21].

Mouse models of AIP show key differences in glucose metabolism between AIP and non-AIP mice. There are also differences in the level of enzymes in the pentose-phosphate pathway and glutathione metabolism, which can lead to decreased hepatic glucose and exacerbate AIP. AIP mice have been shown to rely more on gluconeogenesis and fatty acid metabolism for maintaining blood glucose levels as compared to control mice, which rely more on glycogen metabolism[22].

Although medications are a common trigger for AIP, the patient was not taking any medications commonly known to cause AIP. He was transiently treated with mesalamine, although the Norwegian Porphyria Center website[23],which serves as a clearinghouse for information on drug "porphyrinogenicity", indicates that mesalamine has low porphyrinogenic potential. In addition, the patient's symptoms continued several months after stopping the drug. The patient had not been exposed to other new drugs, had not undergone surgery, and had no recent infections during this time, rendering this etiology less likely.

CONCLUSION

We present an older subject with a common presentation of an uncommon disease, whose post-transplant complications and medications may have contributed to precipitating his previously undiagnosed AIP. A high index of suspicion is needed to consider the possibility of a heme synthesis disorder, which presents with the common symptoms of abdominal pain, high blood pressure, and anxiety, in renal transplant patients.

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CASE REPORT

Is *de novo* membranous nephropathy suggestive of alloimmunity in renal transplantation? A case report

Prakash I Darji, Himanshu A Patel, Bhavya P Darji, Ajay Sharma, Ahmed Halawa

ORCID number: Prakash I Darji 0000-0002-1072-5430; Himanshu A Patel 0000-0001-6641-8088; Bhavya P Darji 0000-0001-7458-4676; Ajay Sharma 0000-0003-4050-6586; Ahmed Halawa 0000-0002-7305-446X.

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Prakash I Darji, Himanshu A Patel, Department of Nephrology and Renal Transplantation, Zydus Hospitals, Ahmedabad 380059, Gujarat, India

Bhavya P Darji, Internship, Department of Medicine, GCS Medical College, Hospital and Research Centre, Ahmedabad 380025, Gujarat, India

Ajay Sharma, Ahmed Halawa, Faculty of Health and Life Science, Institute of Learning and Teaching, University of Liverpool, Liverpool L69 3BX, United Kingdom

Ajay Sharma, Consultant Transplant Surgeon, Royal Liverpool University Hospitals, Liverpool L7 8XP, United Kingdom

Ahmed Halawa, Department of Transplantation, Sheffield Teaching Hospitals, Sheffield S10 2JF, United Kingdom

Corresponding author: Ahmed Halawa, FRCS (Gen Surg), MD, MSc, Surgeon, Department of Transplantation, Sheffield Teaching Hospitals, Glossop Rd, Sheffield S10 2JF, United Kingdom. ahmed.halawa@liverpool.ac.uk

Abstract

BACKGROUND

Post-transplant nephrotic syndrome (PTNS) in a renal allograft carries a 48% to 77% risk of graft failure at 5 years if proteinuria persists. PTNS can be due to either recurrence of native renal disease or *de novo* glomerular disease. Its prognosis depends upon the underlying pathophysiology. We describe a case of post-transplant membranous nephropathy (MN) that developed 3 mo after kidney transplant. The patient was properly evaluated for pathophysiology, which helped in the management of the case.

CASE SUMMARY

This 22-year-old patient had chronic pyelonephritis. He received a living donor kidney, and human leukocyte antigen-DR (HLA-DR) mismatching was zero. PTNS was discovered at the follow-up visit 3 mo after the transplant. Graft histopathology was suggestive of MN. In the past antibody-mediated rejection (ABMR) might have been misinterpreted as *de novo* MN due to the lack of technologies available to make an accurate diagnosis. Some researchers have observed that HLA-DR is present on podocytes causing an anti-DR antibody deposition and development of *de novo* MN. They also reported poor prognosis in their series. Here, we excluded the secondary causes of MN. Immunohistochemistry

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was suggestive of IgG1 deposits that favoured the diagnosis of *de novo* MN. The patient responded well to an increase in the dose of tacrolimus and angiotensin converting enzyme inhibitor.

CONCLUSION
Exposure of hidden antigens on the podocytes in allografts may have led to subepithelial antibody deposition causing *de novo* MN.

Key Words: Post-transplant nephrotic syndrome; Recurrent membranous nephropathy; Secondary membranous nephropathy; Alloimmunity; Cryptic antigens; Case report

Core Tip: This is a case presentation of a patient who developed post-transplant nephrotic syndrome 3 mo after transplantation and was diagnosed with *de novo* membranous nephropathy (MN). He had received a well-matched living donor kidney. According to the literature, the most common causes of *de novo* MN include secondary causes and antibody mediated injury, which we ruled out. This patient was treated with increased dosage of tacrolimus and an angiotensin converting enzyme inhibitor, which resulted in a good recovery. We favoured a new concept of pathogenesis of *de novo* MN, which requires the identification of the causative antigens.

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INTRODUCTION

The development of proteinuria after kidney transplantation is not uncommon, with 3% to 14% of recipients presenting with post-transplant nephrotic syndrome (PTNS). The risk of allograft loss with persistent proteinuria at 5 years is around 48% to 77% [1]. This may be due to either a recurrence or new (*de novo*) development of glomerular disease. It is rather difficult to differentiate between these two possibilities because only 15% to 20% of native kidneys are subjected to biopsy before transplantation[2]. Factors, such as immunosuppression, donor specific anti-human leukocyte antigen (HLA) antibodies (DSA), acute rejection, hypertension and infection, might pose a diagnostic dilemma in regard to the clinical picture and histopathology of the graft. We hereby present a case of a kidney transplant patient who developed PTNS in the early period following transplantation.

CASE PRESENTATION

Chief complaints

There were no chief complaints. Abnormal signs were observed at the 3-mo follow-up after renal transplantation.

History of present illness

A 22-year-old male patient was diagnosed with end-stage kidney disease due to chronic pyelonephritis and received dialysis for 8 mo. He received a live donor kidney transplant from his 42-year-old mother in August 2020. HLA-A, B and DR mismatches were 1-1-0. He was not given induction therapy and was maintained on triple immunosuppression (tacrolimus, mycophenolate mofetil and prednisolone). He was discharged on day 7 with a serum creatinine of 0.9 mg/dL (normal: 0.7-1.2 mg/dL). His graft duplex scan was normal, and tacrolimus 12-h trough level was maintained at 10 ng/mL. At the time of discharge, his urine protein was normal. At the 3-mo follow-

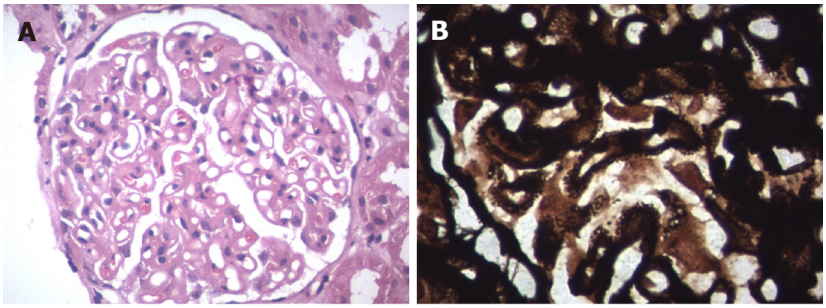

Figure 1 Light microscopy. A: Haematoxylin and eosin staining (40 × magnification) showed diffuse thickening of the glomerular basement membrane; B: Periodic acid-Schiff silver methenamine stain (100 × magnification) showed membrane thickening.

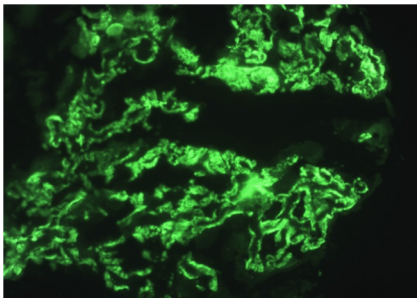

Figure 2 Immunofluorescence microscopy showed granular IgG deposits in the glomerular basement membrane.

up, he had signs of mild pedal oedema.

History of past illness

The patient had a history of end-stage kidney disease due to chronic pyelonephritis treated with a renal transplantation 3 mo prior. A bilateral ureteric re-implantation for vesicoureteral reflux had been performed at the age of 6 years.

Personal and family history

No significant personal and family history.

Physical examination

We observed mild pedal oedema, which was pitting in nature.

Laboratory examinations

His urine showed + 4 proteinuria, and urine protein/creatinine ratio was 4.6 mg/mg (normal: < 0.2 mg/mg) with stable serum creatinine. We recorded a serum albumin level of 3 gm/dL and total cholesterol of 295 mg/dL, suggestive of PTNS.

Imaging examinations

Allograft biopsy was performed and subjected to light, immunofluorescence and electron microscopy to rule out secondary causes of PTNS. Light microscopy revealed a thickening of the basement membrane and spikes at high power magnification with periodic acid-Schiff silver methenamine stain (Figures 1A and 1B). Immunofluorescence microscopy showed IgG deposits along the glomerular basement membrane in a granular pattern (Figure 2), suggesting membranous nephropathy (MN).

EVALUATION AND DIFFERENTIAL DIAGNOSIS

This was a case of PTNS that was histologically suggestive of MN. We conducted further investigations to identify secondary causes of MN, antibody-mediated rejection (ABMR), and differentiation of recurrence *vs de novo* MN.

This patient's serology was negative for hepatitis B virus, hepatitis C virus and hepatitis E virus. Cytomegalovirus was also undetected by polymerase chain reaction.

Antiphospholipase A2 receptor antibody testing was negative. There was no evidence of post-transplant malignancy upon clinical assessment and detailed investigations. Secondary causes of MN were ruled out.

In this recipient, the donor class II HLA was fully matched. When he developed proteinuria, DSA was negative. His biopsy did not show any changes of ABMR. Electron microscopy did not show duplication of peritubular capillaries or glomerular basement membrane (Figure 3). The C4d stain was also negative (Figure 4). These findings ruled out ABMR in our case.

The biopsy revealed positive IgG1 deposits and scarcity of IgG4 after immunohistochemistry (Figures 5A and 5B).

FINAL DIAGNOSIS

Post kidney transplant *de novo* MN.

TREATMENT

The patient's tacrolimus 12-h trough level at the time of development of PTNS was 5.9 ng/mL. The dose of tacrolimus was increased to achieve a level of 9-12 ng/mL. Ramipril was commenced and optimized to 5 mg twice a day. Serum creatinine and potassium were checked on day 10 and remained unchanged. The dose of ramipril was kept tolerable to avoid hypotension.

OUTCOME AND FOLLOW-UP

At 6 mo after the biopsy, his urine protein creatinine ratio decreased to 0.6 mg/mg. His graft function remained stable with a serum creatinine level of 0.94 mg/dL.

DISCUSSION

Recurrence of idiopathic MN after renal transplant is seen in 25%-40% of cases. A diagnosis of *de novo* MN is reported in 1%-2% of post-transplant adults and up to 9% in paediatric renal transplant recipients[3]. The exact incidence is difficult to ascertain due to variability in pretransplant biopsies to confirm diagnosis[2,4].

New onset hepatitis virus infection, particularly hepatitis C virus and hepatitis B virus, is a common secondary cause of *de novo* MN[2,3,5]. Taton *et al*[5] reported a probable association of hepatitis E virus infection with post renal transplant *de novo* MN. Teixeira *et al*[6] reported a case of cytomegalovirus infection and its relationship to *de novo* MN. Risk factors such as post-transplant malignancy, ureteral obstruction and renal infarction have also been found to cause *de novo* MN[2]. Prasad *et al*[7] reported a case of *de novo* MN in a patient having Alport's syndrome as a native kidney disease. It has been reported that *de novo* MN is more common in patients with IgA nephropathy[2,3,7]. We ruled out all the secondary causes of MN in our patient.

Sometimes, a recurrence of MN may be misdiagnosed as *de novo* MN due to undiagnosed native kidney disease[2,4]. Pathology findings of *de novo* MN are like those of idiopathic MN, except for mesangial proliferation, focal and segmental distribution of subepithelial deposits, and simultaneous presence of different stages of disease in *de novo* MN[3]. Anti-phospholipase A2 receptor antibodies have been identified in most cases of idiopathic MN, whereas anti-phospholipase A2 receptor antibodies are absent in *de novo* MN because of other causative antigens that remain unidentified[2,3,8-10]. Different IgG subtype depositions have been reported in cases of primary/recurrent MN and *de novo* MN. IgG4 was commonly deposited in recurrent MN, whereas IgG1 was observed in *de novo* MN. In our case, there was an absence of anti-phospholipase A2 receptor antibodies and IgG1 deposition in the kidney biopsy, which confirmed the diagnosis of *de novo* MN.

Schwarz *et al*[11] published a retrospective observational study of renal transplant subjects transplanted between 1970 and 1992 who developed *de novo* MN. They observed histopathological features of acute vascular rejection in 17 out of 21 recipients and interstitial rejection in 12 out of 21 recipients. During this period, the

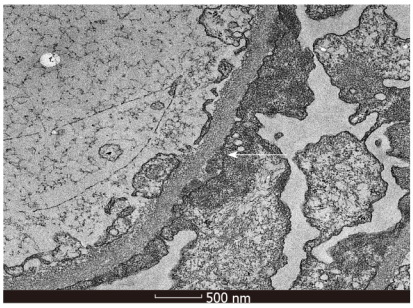

Figure 3 Electron microscopy showed subepithelial electron dense deposits (× 13500).

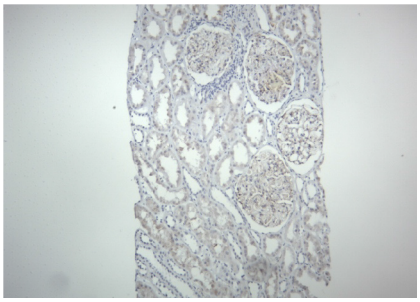

Figure 4 Immunohistochemistry (10 × magnification) was negative for C4d stain.

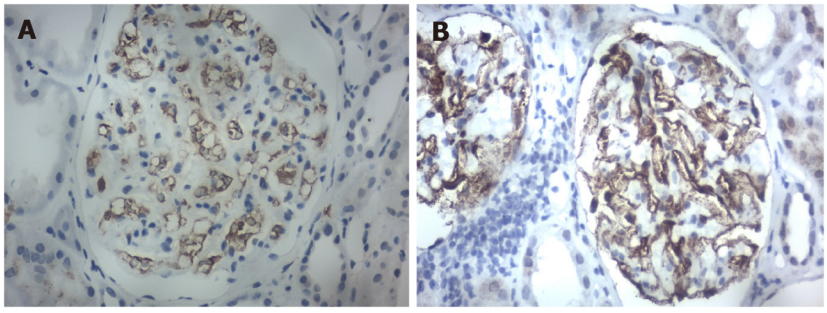

Figure 5 Immunohistochemistry staining (40 × magnification). A: IgG4 was negative; B: IgG1 was positive.

availability of DSA measurement techniques and knowledge of diagnosing ABMR may have been limited. Other investigators have reported a possible relationship of donor-specific alloantibodies in the development of *de novo* MN[12]. Wen *et al*[13] reported the presence of HLA-DR on podocytes of recipients who developed *de novo* MN; they also reported a higher incidence of peritubular capillaritis, intimal arteritis and C4d deposits in post-transplant MN in comparison to recurrence of idiopathic MN in the renal allograft. There are also reports of poor prognoses in patients who had *de novo* MN possibly related to ABMR[11,12]. Interestingly, Bansal *et al*[14] reported a case of *de novo* MN following a renal transplant between conjoined twins. Even in our case, the mother was the donor, with fully matching HLA-DR. The biopsy of our patient confirmed that there were no changes suggestive of acute or chronic ABMR.

There may be another pathophysiological mechanism precipitating in the development of *de novo* MN. It is likely that immunological, viral, mechanical or ischemic injury to the graft may expose the podocyte cryptic antigens to the recipient immune system. This may trigger an activation of innate immunity, resulting in production of auto- or alloantibodies against the antigens on the podocyte. This antigen-antibody complex develops at subepithelial sites and causes activation of complement and membrane injury[9].

There is lack of consensus in the published literature about the optimal management of *de novo* MN. Schwarz *et al*[11] reported no response to methylprednisolone bolus and a high graft loss. El Kossi *et al*[12] hypothesized that *de novo* MN was an atypical manifestation of ABMR. If a secondary cause, such as viral infection or malignancy, is

identified, then the treatment of the underlying cause might treat MN. Cyclophosphamide or rituximab has been tried, as in the treatment of idiopathic MN[8]. In our case, we optimized the dose of tacrolimus and started an angiotensin converting enzyme inhibitor; the proteinuria was significantly reduced, and graft function was stable after 6 mo, suggesting a good prognosis.

CONCLUSION

De novo MN, a rare disease in renal allografts, may be due to exposure of a hidden antigen on the podocytes that is recognized by the immune system of the recipient. The causative antigens still need to be identified. The reported poor prognosis of *de novo* MN may be due to misdiagnosed ABMR, as it was in an era prior to routine availability of DSA by the Luminex platform (Bio-Rad Laboratories, Hercules, CA, United States) and recognition of C4d for an ABMR diagnosis. Proper evaluation and targeting of the pathophysiological processes may help in the management of these patients.

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Associate Editor of *World Journal of Transplantation*, Sanem Guler Cimen, MD, MSc, Associate Professor, Director, Surgeon, Department of General Surgery, Health Sciences University, Ankara 6500, Turkey. s.cimen@dal.ca

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LETTER TO THE EDITOR

Immunosuppressive regimens and outcomes of inflammatory bowel disease patients requiring kidney transplantation

Urvashi Singh, Baljit Singh, Maria Irene Bellini

ORCID number: Urvashi Singh 0000-0003-2176-5750; Baljit Singh 0000-0001-9713-0247; Maria Irene Bellini 0000-0003-0730-4923.

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Urvashi Singh, Department of Surgery, Wythenshawe Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester M23 9LT, United Kingdom

Baljit Singh, Department of Colorectal Surgery, University Hospitals Leicester, Leicester LE1 5WW, United Kingdom

Maria Irene Bellini, Department of Surgical Sciences, Sapienza University, Roma 00161, Italy

Corresponding author: Urvashi Singh, MBBS, MSc, Department of Surgery, Wythenshawe Hospital, Manchester University Hospitals NHS Foundation Trust, Southmoor Road, Manchester M23 9LT, United Kingdom. usingh01@qub.ac.uk

Abstract

Patients with inflammatory bowel disease (IBD) can develop extra-renal complications and as a result, suffer from end stage renal failure requiring kidney transplantation (KT). A brief review of available literature revealed that IBD patients undergoing KT have shorter overall survival rates compared to their controls. Literature reporting steroid regimens and survival outcomes specific to IBD and post kidney transplant are scarce and these studies have small sample sizes thus making it difficult to draw accurate conclusions. Further research is required in the form of a randomized controlled study to clarify the effect and mechanism of steroid immunosuppression on the prognosis of renal transplant recipients and explore new treatment schemes.

Key Words: Inflammatory bowel disease; Kidney transplantation; Steroids; Immunosuppression; Kidney failure; Ulcerative colitis; Crohn's disease

Core Tip: Patients with inflammatory bowel disease (IBD) can develop extra-renal complications and as a result, suffer from end stage renal failure requiring kidney transplantation (KT). A brief review of available literature revealed that IBD patients undergoing KT have shorter overall survival rates compared to their controls. We highlight through our paper, previously reported survival outcomes and immunosuppressive regimens used in this cohort of patients through a brief literature review.

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TO THE EDITOR

The recent systematic review published by Aref *et al*[1] titled 'Does steroid-free immunosuppression improve the outcome in kidney transplant recipients compared to conventional protocols?' provided thought provoking insight into the impact of steroid-free immunosuppression on the outcome of kidney transplant recipients. Further to the authors conclusions in their paper, we aim to highlight the effect of steroids and steroid free regimens on the outcomes of inflammatory bowel disease (IBD) patients who were kidney transplant receipts.

IBD is comprised of Crohn's disease (CD) and ulcerative colitis (UC). Patients with IBD can develop extra-intestinal manifestations. These include peripheral arthritis, oral aphthous ulcers, erythema nodosum, episcleritis, pyoderma gangrenosum, primary sclerosing cholangitis and uveitis[2]. Patients with IBD can develop renal manifestations of the disease, including nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, and secondary amyloidosis[3]. A study reported that the incidence of end stage renal disease (ESRD) in patients with CD was 5 times higher than cross matched controls[3]. Kidney injury can also result from dehydration, long term malnutrition and side effects of IBD medical therapy. These can all contribute to chronic kidney disease and eventually ESRD warranting kidney dialysis and transplantation[3].

Studies reporting IBD patients requiring kidney transplantation (KT) are scarce. However, existing literature discussing IBD, and post KT outcomes reports similar survival rates for IBD patients post transplantation. In a recent detailed study, in which 12 IBD patients (7 CD patients and 5 UC patients) underwent KT due to immunoglobulin A (IgA) nephropathy and polycystic kidney disease, the estimated survival of IBD patients was reported to be 80.8% *vs* 96.8% in patients without IBD (P = 0.001)[4]. Treatment with infliximab or a dalimumab resulted in stable disease or improvement in kidney transplant patients affected by mild to moderate IBD. Eleven out of 12 patients were on maintenance immunosuppression with low dose corticosteroids (5 mg prednisolone daily), calcineurin inhibitors (tacrolimus), and antimetabolite (mycophenolic acid in nine and mycophenolate mofetil in two); the twelfth patient was kept on low-dose corticosteroids and tacrolimus only. IBD course remained stable in the whole transplant group, but resulted in an increased risk of mortality and hospitalization, due to a higher infection rate[4].

Data on immunosuppression and steroid regimens specific to IBD and the post-KT period remains poorly reported. In a study, six patients (5 CD patients and 1 UC patient) out of 1537 patients with IBD, underwent KT for kidney failure secondary to amyloidosis, IgA nephropathy, oxalate nephropathy, haemolytic uraemic syndrome, and chronic kidney failure of unknown origin[5]. Five of the six patients received steroid therapy after transplantation, yet specific immunosuppressive regimens are not reported pre and post transplantation. The study discusses the outcomes of IBD patients post liver transplantation together with KT, hence it is not possible to comment on the post KT alone. However, the study does report an 84% survival rate during a total follow up of 103.0 mo and median follow up of 33 mo after solid organ transplantation. One male patient also developed papillary renal cell carcinoma in the transplanted kidney in this study. No graft rejection was reported[5]. In a different prospective cohort study that followed 26 patients with IBD and systemic ascorbic acid (AA) amyloidosis between 1989 and 2010, an 83% survival rate 15 years post transplantation was reported. In this study all patients had renal dysfunction as result of AA amyloidosis[6]. However, only six patients required renal transplantation due to ESRD. Four patients had deceased donor transplants and two patients had live-related transplants. There were five functioning grafts at census 0.8, 3.2, 4.2, 20.1 and 24.6 years after transplantation. One graft failure was reported at 14.5 years after renal transplantation due to recurrence of amyloidosis and sustained chronic inflammatory activity. The study notes that patients were provided with steroid regimens however does not provide specific details about whether these regimens were supplemented with other immunosuppressants[6]. Specific reporting regarding immunosuppressive regimens is warranted for IBD patients before and after KT.

In conclusion, IBD is an immunomediated disease that is associated with kidney disease and can cause ESRD in patients. From the available literature, it is suggested that patients with IBD that undergo KT have shorter overall survival rates compared to their controls. Reported data is scarce and inconclusive due to the small patient cohort sizes. Further research is required in the form of a randomized controlled study to clarify the effect and mechanism of steroid immunosuppression on the prognosis of renal transplant recipients and explore new treatment schemes.

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LETTER TO THE EDITOR

Assessment of advanced age candidates for liver transplantation warrants more caution

Alessandro Parente, Vincenzo Ronca

ORCID number: Alessandro Parente 0000-0001-5506-224X; Vincenzo Ronca 0000-0003-0761-1333.

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Alessandro Parente, Vincenzo Ronca, Liver Unit, Queen Elizabeth Hospital University Hospital Birmingham NHS Foundation Trust, Birmingham B15 2TH, United Kingdom

Vincenzo Ronca, Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy University of Birmingham, Birmingham B15 2TT, United Kingdom

Corresponding author: Alessandro Parente, FEBS, MD, Surgeon, Liver Unit, Queen Elizabeth Hospital University Hospital Birmingham NHS Foundation Trust, Mindelsohn Way, Birmingham B15 2TH, United Kingdom. aleparen@gmail.com

Abstract

For patients with fulminant liver failure and end-stage liver disease, liver transplantation remains the only effective treatment. Over the years, as a result of the ageing population, the average age of liver transplant donors and recipients has increased and currently about one quarter of patients receiving transplantation in the United States are above the age of 65. Recently, a study reported that patients aged 65 years or older had lower one-year survival compared to a younger cohort. Herein, we express our opinion about this interesting publication.

Key Words: Liver transplantation; Elderly patients; Age in liver transplantation; Frailty; Transplant assessment; Liver transplant outcomes

Core Tip: As a result of the ageing population, the average age of liver transplant candidates has increased over the years and about one quarter of recipients receiving transplantation in the United States are over 65 years of age. The study reported that patients aged 65 years or older had lower survival at one year compared to a younger cohort. In addition, they have identified congestive heart failure to be strongly associated with poor outcomes in elderly. In this letter to the editor, we express our opinion about these interesting findings.

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TO THE EDITOR

We read with great interest the study from Kleb *et al*[1]. The authors analysed the outcome of 260 elderly patients (65 years old) undergoing liver transplantation (LT) with the aim of identifying features associated with futility, defined as death within 90 d post transplantation. In this retrospective study, Kleb *et al*[1] demonstrated that congestive heart failure (CHF) is strongly associated with futility of LT in elderly patients. Furthermore, patients aged 65 years or older had even when adjusting for severity of liver disease and comorbidities.

LT is a life-saving procedure and it is the only efficient treatment for chronic liver diseases and acute liver failure. However, organ shortage is one of the main challenges that the transplant community continues to face. Indeed, donor availability is becoming an increasing problem globally, limiting the wider spread of LT. As a result of the ageing population, average age of donors and recipients has increased throughout the decades and about one quarter of LT recipients in the United States are over the age of 65[2]. In addition to the standard transplant assessment, when considering patients in this age group, close attention should be paid to cardiovascular diseases, frailty and performance status. Commonly, elderly recipients have more medical conditions, higher waitlist and post-transplant mortality as opposed to a younger cohort.

In a large study it has been demonstrated that, in recipients without hepatocellular carcinoma, advanced age at registration has been shown to be a considerable risk factor behind patients being too unwell to undergo transplantation and it has been linked with higher waitlist mortality[3]. With a competing risk analysis, Su *et al*[3] have shown interesting results with regards to age and transplantation. In fact, patients aged 64 to 69 years displayed higher waiting list mortality with an adjusted hazard ratio of 1.73 as opposed to 2.04 for those aged ≥ 70. In addition, age was linked to less likelihood of LT, with an adjusted hazard ratio of 0.89 and 0.86 in patients aged 64 to 69 years and ≥ 70 years, respectively.

This is one of several studies which highlight the relation between advanced age and LT outcomes. Interestingly, the authors identified CHF to be strongly associated with poor outcomes. Although the results by Kleb *et al*[1] are compelling, they need to be interpreted with caution. The data presented have been retrospectively reviewed, but some important indexes to estimate frailty and comorbidities, such as the Charlston Comorbidity Index[4] and Liver Frailty Index[5] have not been calculated. This would add a more precise evaluation of the pre-transplant status and comorbidities of the recipients that can influence outcomes. Secondly, the causes of death within 90 d from LT have not been reported. Therefore, it is difficult to estimate the clear relation between advanced age alone and futility, as death could be related to post-operative complications such as graft dysfunction, infection, or immunosuppression rather than recipient age itself. Thirdly, the cohort for this study is from a single-centre, hence as yet we cannot translate this to a broader population.

By way of conclusion, the authors have to be congratulated for their work. They have demonstrated with a well-conducted analysis that recipients aged 65 years and older had increased mortality at one year compared to patients below the age of 65. This finding is of great interest and warrants a thorough assessment of potential recipients with advanced age. In particular, as underlined also by other authors[6], a meticulous pre-transplant cardiological evaluation appears to be of high importance in elderly. Identifying additional pre-operative factors that can guide the decision-making to select low-risk patients in a wider population would be of great interest.

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REVIEW

Innovative immunosuppression in kidney transplantation: A challenge for unmet needs

Maurizio Salvadori, Aris Tsalouchos

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Maurizio Salvadori, Department of Renal Transplantation, Careggi University Hospital, Florence 50139, Italy

Aris Tsalouchos, Division of Nephrology, Santa Maria Annunziata Hospital, Florence 50012, Italy

Corresponding author: Maurizio Salvadori, MD, Professor, Department of Renal Transplantation, Careggi University Hospital, Largo Palagi 1, Florence 50139, Italy. maurizio.salvadori1@gmail.com

Abstract

Due to the optimal results obtained in kidney transplantation and to the lack of interest of the industries, new innovative drugs in kidney transplantation are difficult to be encountered. The best strategy to find the new drugs recently developed or under development is to search in the sections of kidney transplantation still not completely covered by the drugs on the market. These unmet needs are the prevention of delayed graft function (DGF), the protection of the graft over the long time and the desensitization of preformed anti human leukocyte antigen antibodies and the treatment of the acute antibody-mediated rejection. These needs are particularly relevant due to the expansion of some kind of kidney transplantation as transplantation from non-heart beating donor and in the case of antibody-incompatible grafts. The first are particularly exposed to DGF, the latter need a safe desensitization and a safe treatments of the antibody mediated rejections that often occur. Particular caution is needed in treating these drugs. First, they are described in very recent studies and the follow-up of their effect is of course rather short. Second, some of these drugs are still in an early phase of study, even if in well-conducted randomized controlled trials. Particular caution and a careful check need to be used in trials launched 2 or 3 years ago. Indeed, is always necessary to verify whether the study is still going on or whether and why the study itself was abandoned.

Key Words: New drugs; Unmet needs in kidney transplantation; Delayed graft function; Long-term outcomes; Kidney inflammation; Anti-human leukocyte antigen antibodies

Core Tip: Finding new innovative drugs for kidney transplantation is not easy but looking for unmet needs it is possible to find new interesting drugs and opportunities to use in kidney transplantation. Many of these drugs are just at the beginning of their process toward the approval and should be careful checked until the finish of their path. Principal unmet needs are treatment and prevention of delayed graft function, improve the long-term outcomes, desensitization and treatment of acute antibody-mediated rejection. Finding new drugs in these fields results extremely important to face new kind of transplantation as transplant from non-heart beating donor and transplant in ABO incompatibles pairs.

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INTRODUCTION

Little progress has been made over the past decade in the development of new therapeutic measures in clinical kidney transplantation, chiefly because of a lack of interest by industries and providers and because most centers have reached optimal outcomes with the drugs used today[1]. However, a strategy may be adopted to identify new immunosuppressant drugs in kidney transplantation.

New immunosuppressant drugs may be found looking for identified unmet therapeutic needs.

These new drugs may also be adopted as new immunosuppressive treatments or new strategies for special kidney transplantation scenarios such as ABO incompatibility, non-heart-beating donor (NHBD) transplantation and transplantation from high-risk donors.

Drugs for unmet therapeutic needs

These drugs may be categorized as follows: (1) Therapy for ischemia-reperfusion injury (IRI) that results in delayed graft function (DGF); (2) Therapy to preserve optimal kidney function over the long-term; and (3) Therapy for desensitization and antibody-mediated rejection (ABMR).

THERAPY FOR DGF

DGF refers to acute kidney injury (AKI) occurring in the first week of transplantation that cannot not be ascribed to acute rejection[2].

DGF is associated with increased immune activation, complement activation and release of damage-associated molecular patterns, such as hypomethylated DNA, hyaluronic acid, heparin sulfate, fibrinogen and heat shock proteins. Consequently, nuclear factor κB is activated and induces inflammatory cytokines such as interleukin (IL)-1, IL-6, tumoral necrosis factor alpha and interferon beta[3].

Due to this complex mechanism, although several drugs to treat DGF have been tried, many of them failed to prove their effectiveness. Indeed, DGF has also been called the graveyard of drugs for transplantation.

However, new drugs have recently emerged and they are still in randomized controlled trials (RCTs) to control DGF.

Anti-apoptotic strategies

Apoptosis plays an important role in shaping DGF. Indeed, the pro-apoptotic gene p53 is activated by hypoxia and induces cell cycle arrest and apoptosis[4].

QPI-1002 also known as 15 NP, is a short interfering RNA that inhibits the expression of p53. The results of a phase I/II clinical trial in kidney transplant recipients demonstrated beneficial effects on IRI/DGF in humans[5]. Additionally, two studies reported good results in mice[6,7]. However, the RCT was terminated in 2018 without positive results because of a lack of documented efficacy.

Pegylated carboxyhemoglobin

Carbon monoxide (CO) is involved in regulating endothelial cell survival and proliferation. It also plays roles in protecting against DGF through IRI, vessel relaxation and inhibition of proinflammatory responses[8-10]. The infusion of pegylated carboxyhemoglobin delivers CO to organs. CO is a very powerful anti-apoptotic substance and has anti-inflammatory effects. In animal studies, CO is extremely effective in both cold and warm ischemia.

The use of pegylated carboxyhemoglobin is currently the object of a phase 2/3 study to analyze the efficacy and safety of SANGUINATE for reducing the DGF rate in patients receiving a kidney transplant

[11,12]. In a recent study by Thuillier *et al*[13], 3 oxygen transporters, HBOC-201, BbV and M101, were tested in organ preservation[13-15].

Relaxin

In DGF, relaxin (RLX) has an anti-inflammatory effect by reducing the expression of intracellular adhesion molecule 1, inducing the expression of Notch 1 in macrophages and reducing neutrophil adhesion through increased synthesis of nitric oxide[16-18]. Additionally, RLX causes vasodilatation through increased NO production and inhibition of endothelin 1 production[19]. Two studies[18,20] documented improved renal function, histologic improvement in damaged tissue after DGF, and a reduced number of apoptotic cells.

Hepatocyte growth factor

ANG-3777, formerly BB3, is a hepatocyte growth factor mimetic that binds to its transmembrane tyrosine kinase receptor, cMET[21]. In preclinical studies, ANG-3777 was renoprotective in a variety of animal models of AKI, exerting anti-inflammatory and regenerative effects and preventing tubular cell apoptosis, epithelial to mesenchymal transition and fibrosis[22,23]. In a randomized, placebo-controlled phase 2 trial on oliguric patients after kidney transplantation, patients treated with ANG-3777 had a larger increase in urine output, a greater reduction in C reactive protein and neutrophil gelatinase-associated lipocalin and a higher estimated glomerular filtration rate (eGFR)[24]. More recently, Vincenti *et al*[25] started the Graft Improvement Following Transplant (GIFT) trial, which is a phase 3 trial on the hepatocyte growth factor mimetic ANG-3777 in kidney transplant recipients with DGF. The aim of GIFT is to generate data to advance the treatment of DGF. In addition, the authors stress that a significant factor is that ANG-3777 may also be effective when administered after AKI-related DGF.

Complement inhibition

Complement activation plays a significant role in IRI, which causes and precedes DGF. The most studied among the complement inhibitor drugs to minimize DGF has been Mirocept (APT 070), which inhibits C3/C5 convertases and C1 esterase inhibitors.

Mirocept, still in a phase 1 trial (ISRCTN49958194)[26], is a potent membrane-localizing complement inhibitor and may be administered *ex vivo* to the donor kidney prior to transplantation. However, a recent dose finding study in animals[27] documented that a high dose of Mirocept might be needed to achieve adequate complement inhibition. More promising results have been obtained with C1 esterase inhibition.

This drug may also be administered as a donor pretreatment strategy in high-risk recipients (NCT02435732)[28], but the trial results are still unknown. Better results have been obtained by administering C1 esterase inhibitors to recipients of kidneys from high-risk donors or in the case of donation after circulatory death (DCD)[29-31]. A recent study from Huang *et al*[32] studied the three-year outcomes of patients treated with C1 esterase inhibitors to avoid DGF in a randomized controlled study. The study found that the treatment was associated with a lower incidence of graft failure.

Table 1 summarizes representative drugs in the categories described above used to prevent DGF and their targets.

Improving perfusion techniques

Improving perfusion techniques is not drugs in the sense of the word but rather a different strategy to prevent IRI and DGF by improving kidney perfusion at the time of kidney transplantation.

In a recently published study, Urbanellis *et al*[33] documented that continuous normothermic *ex vivo* kidney perfusion significantly improved early kidney function compared with hypothermic anoxic machine perfusion and static cold storage (SCS) in a porcine kidney auto-transplantation model.

A more interesting study was performed by Niemann *et al*[34]. The authors documented that reducing the body temperature by 2 °C of the deceased donor achieved a significant reduction in DGF rates and that the effect was more significant in the extended criteria donors.

Finally, in a recent review[35], it was documented that active oxygenation during hypothermic machine perfusion is the most beneficial in cases involving the use of DCD kidneys when applied starting from kidney procurement until transplantation. Active oxygenation improves preservation and subsequent early graft function.

THERAPY TO PRESERVE RENAL FUNCTION

These drugs may be divided into the following categories: (1) Therapy to avoid nephrotoxicity, usually by elimination of calcineurin inhibitors (CNIs); (2) Therapy to control inflammation and fibrosis (principally when inflammation overlaps fibrosis); and (3) Therapy to prevent donor-specific antibodies (DSAs) and treat chronic ABMR (cABMR).

Table 1 Therapies targeting delayed graft function in kidney transplantation

Drug	Molecular target	Mechanism of action
15NP or QPI-1002	p53	Inhibition of apoptosis
Pegylated carboxyhemoglobin	Cytochrome C oxidase; cytochrome P450; HMGB-1; P38 MAPK pathway	Inhibition of oxidative injury, inflammation, and apoptosis
Relaxin	ICAM-1; neutrophil adhesion	Vasodilatation; inhibition of apoptosis
ANG-3777 (BB3)	Tyrosine kinase receptor cMET	Antinflammation; inhibition of epithelial to mesenchymal transition
Mirocept (APT 070)	Inhibition of C3/C5 convertase	Inhibition of complement activation
C1 esterase inhibitor	C1 esterase	Inhibition of complement activation

HMGB-1: High mobility group protein box-1; MAPK: Mitogen-activated protein kinases; ICAM 1: Intercellular adhesion molecule 1.

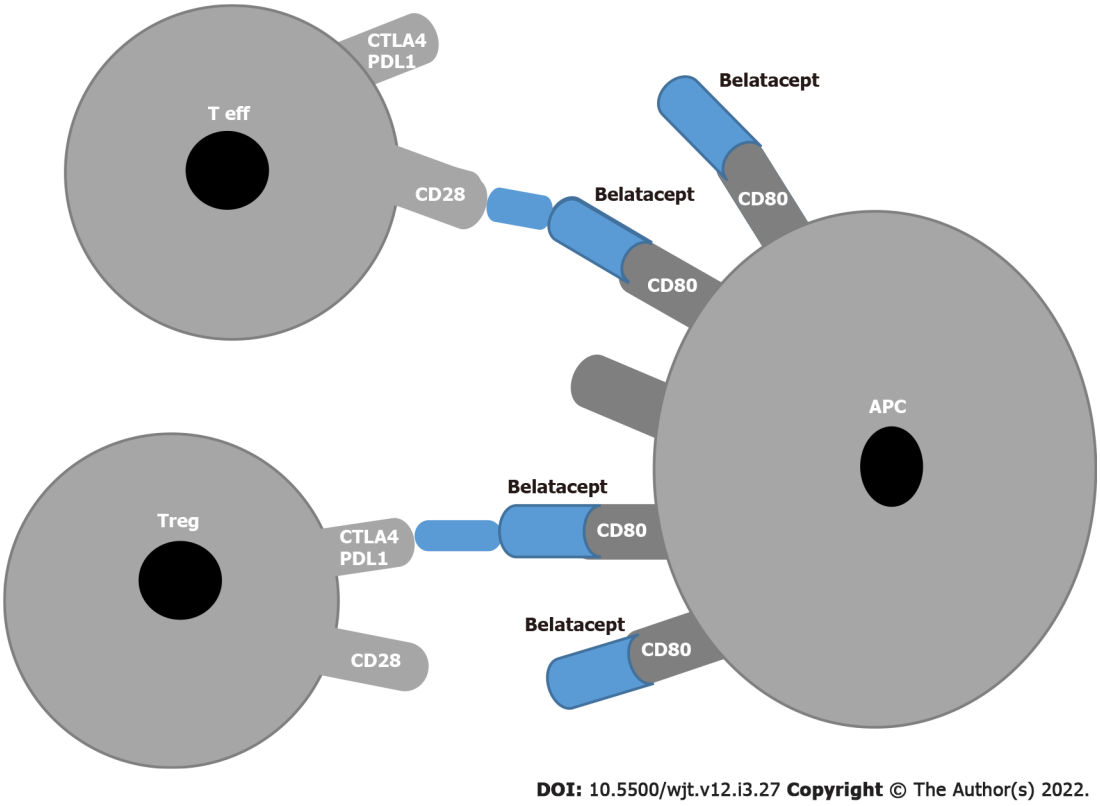

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Figure 1 Block of co-stimulation with Belatacept. APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.

Therapy to avoid nephrotoxicity induced by CNIs

Until recently and even today, the two main strategies for a CNI-free regimen have been as follows: Mammalian target of rapamycin inhibitor-based immunosuppression; belatacept based immunosuppression.

Several studies have documented the efficacy of everolimus therapy in conjunction with low-dose CNIs[36-39]. The study by Pascual *et al*[36] "the Advancing renal TRANSplant eFficacy and safety Outcomes with eveRoliMus based regimen (TRANSFORM)" was a randomized open label, two-arm study with 2037 *de novo* kidney transplant recipients recruited in 186 centers worldwide. Everolimus efficacy was demonstrated, but the administration of low-dose tacrolimus (TAC) was needed.

The complete withdrawal of CNIs is difficult to achieve and is only appropriate for low-risk patients and donors and for living donors, and in the absence of DSAs[40].

The use of belatacept or other agents blocking the costimulatory pathways is the other method to avoid CNIs.

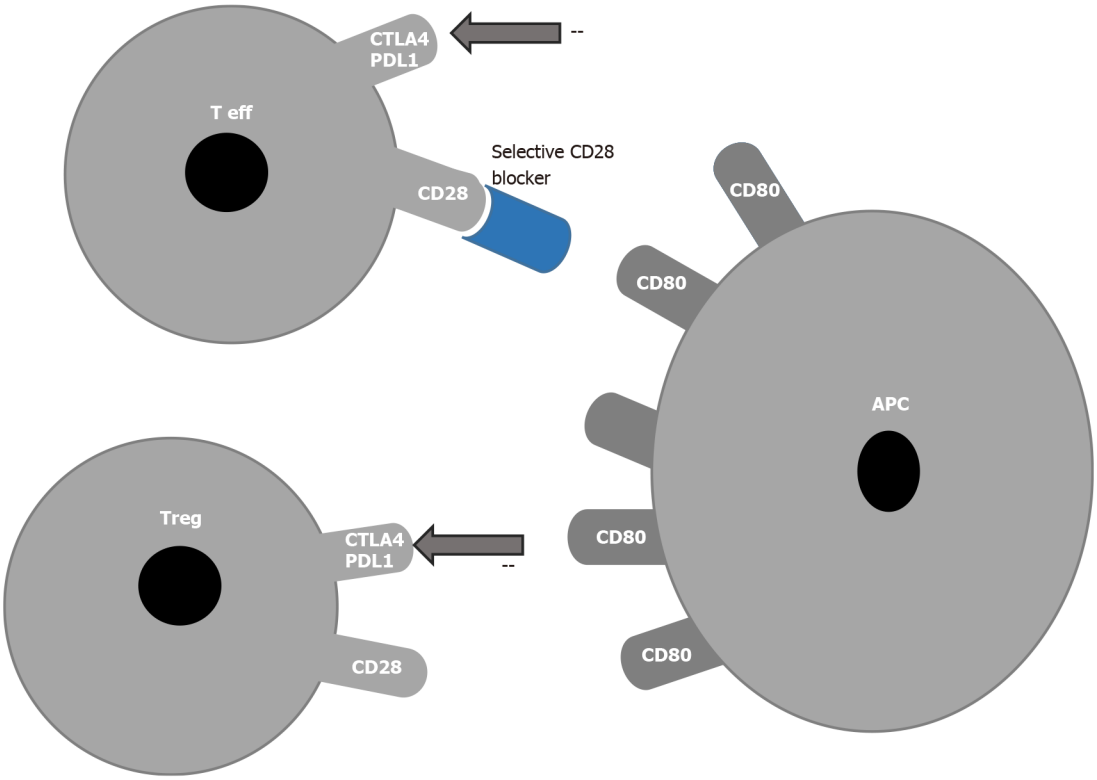

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Figure 2 Block of co-stimulation with anti CD28. APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.

The blockade of CD28/cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T effector lymphocytes and CD80/CD86 on antigen presenting cells (APCs) was the first pathway to be targeted in the trials BENEFIT and BENEFIT-EXT[41,42] . Independent of well-preserved kidney function, the use of belatacept in a subset of patients was associated with an increased number of severe rejections[43, 44] and an increased number of opportunistic infections[45] , including cytomegalovirus[46]. In addition a correlation between the incidence of post-lymphoproliferative disease and Epstein-Barr virus seronegative patients in the belatacept group was found[47].

These drawbacks are related to the fact that belatacept, which binds to CD80 and CD86 on APCs, blocks not only the T effectors that represent the positive signal but also the regulatory T (Tregs) that constitute the inhibitory signal (Figure 1).

In 2015, a report showed that the blockade of CD28 on effector T cells without inhibition of Treg cells prolonged survival in a nonhuman primate kidney transplant model. In this way, effector cells can be inhibited without inhibiting Tregs because selective CD28 blockade allows inhibitory signals *via* CTLA-4 and programmed cell death ligand-1 to remain intact while blocking T cell activation by CD28[48] (Figure 2).

Selective targeting of the CD28 antigen on T cells might be a more effective immunosuppressive therapy than belatacept, since this blockade leaves the inhibitory signal of CTLA-4 intact and may preserve Treg functions[49-51].

Currently, two monovalent antibodies, FR104 and lulizumab-pegol are under development for clinical application. These antibodies have antagonistic activity against CD28 alone[52,53]. To date, an RCT has been conducted at the University of California to modulate Tregs with combinatorial treatment with CD28 and IL-6 receptor antagonists[54] (Figure 3). The addition of an IL-6 receptor antagonist (tocilizumab) aims to further stimulate Treg cells and exert an anti-inflammatory effect. In the CTOT24 trial, after induction with thymoglobulin, steroids are administered from the beginning, lulizumab is started at the beginning and then continued weekly through day 77, belatacept is started on day 84 and administered every 4 wk, tocilizumab is started at the beginning and continued every 2 wk through day 168, and everolimus is started on day 14 and administered twice daily.

A different way to block costimulation is to block the interaction between CD40 and CD40 L. A first attempt was made to block the CD 40 receptor, but the studies were interrupted because of a number of thromboembolic complications[55,56]. This was because CD40 L is also expressed on platelets, which causes thromboembolic complications.

In 2014, Okimura *et al*[57] reported that ASKP 1240, a fully human antibody targeting human CD40, had a potent immunosuppressive effect that did not interfere with platelets.

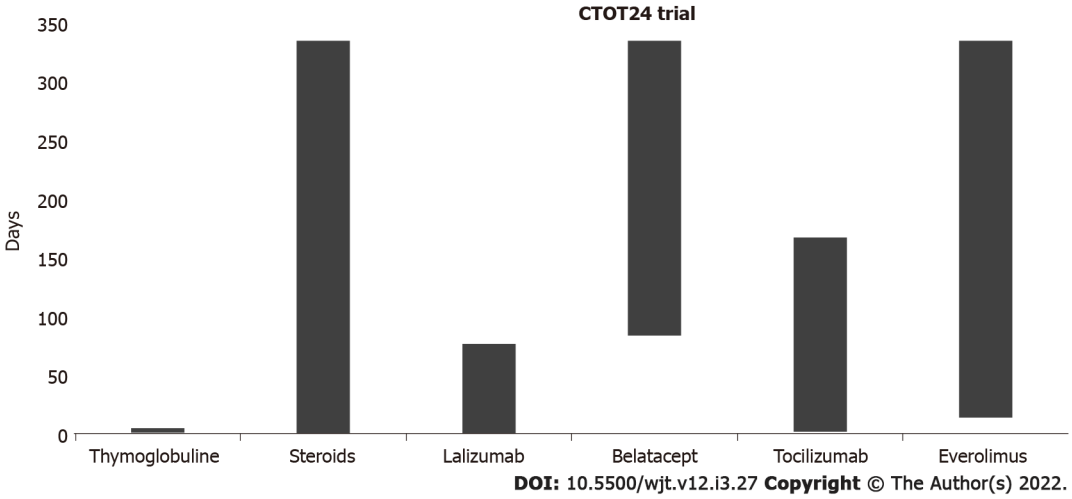

Figure 3 CTOT24 trial.

Recently, in a phase 1b study, the safety and efficacy of bleselumab, a fully human anti-CD40 monoclonal antibody, was documented by Vincenti *et al*[58]. The results were confirmed by a phase 2, randomized, open label, noninferiority study by Harland *et al*[59].

Novartis claimed to have developed another anti-CD40 monoclonal antibody (CFZ-533, Iscalimab). The antibody was characterized by several studies[60,61] . The antibody is the object of an RCT in *de novo* renal transplantation[62] to demonstrate comparable efficacy to and better renal function than TAC in *de novo* CNI-free kidney transplantation.

Until recently, it was believed that the main cause of kidney injury over time after transplantation was primarily due to CNI nephrotoxicity.

The first study questioning this opinion was the DeKAF study by Gaston *et al*[63] . The study documented that the decline in kidney function was not only due to CNI nephrotoxicity but also due primarily to the presence in the recipient of DSAs and the consequent activation of the humoral response[64]. Indeed, long-term graft survival was lower in patients with DSAs in the serum and C4d, a marker of immune response activation on the glomerular capillary wall. The role of DSAs and ABMR was further documented by Sellarés *et al*[65] and Lefaucheur *et al*[66]. A separate study documented that both *de novo* and pre-existing DSAs caused ABMR and reduced graft survival[67].

A more recent study by Stegall *et al*[68] examined 575 surveillance biopsies of kidney transplants from living donors on low-dose TAC therapy and found that 82% of patients whose grafts survived 10 years were affected by inflammatory lesions not related to CNI toxicity or to immunological mechanisms.

Preserving renal function requires other therapies in addition to safely reducing or withdrawing CNIs.

Therapy to control inflammation and fibrosis not related to immunological causes

Several factors, such as hyperuricemia, glucose intolerance, arterial hypertension, dyslipidemia and infection, may induce an inflammatory state in kidney transplant patients[69]. In addition, chronic hypoxia mediated by IL-1 and IL-6, angiotensin II and transforming growth factor beta may result in the accumulation of extracellular matrix, which can lead to interstitial fibrosis. In particular, several studies [70-72] document that IL-6 leads to allograft injury by acute inflammation, adaptive cellular/humoral responses, innate immunity and fibrosis. All these studies indicate that IL-6 is a mainstay in inducing inflammation and allograft injury.

Several drugs have been proposed to control the graft inflammatory state, including low-dose aspirin, statins, renin-angiotensin inhibitors, and xanthine-oxidase inhibitors, but no prospective trial with these drugs has been conducted in kidney transplantation. The only drug object of an RCT is the IL-6R inhibitor.

Currently, available agents for IL-6 signaling inhibition include monoclonal antibodies against IL-6 or IL-6R and Janus kinase inhibitors. The most often studied is tocilizumab, an IL-6R blocker. In a study conducted by Chandran *et al*[73], IL-6 blockade with tocilizumab increased Tregs and reduced T effector cytokines in renal graft inflammation. Tocilizumab-treated patients showed an improved tubulointerstitial Banff score and an increased Treg frequency.

Therapy to control chronic humoral rejection

Important advances have been made in the treatment of ABMR, but less effective treatments are available to control cABMR, which is a slowly progressing disease in which grafts are primarily injured

by *de novo* DSAs[74].

Until recently, attempts to treat cABMR had been limited to a combination of plasmapheresis and intravenous immunoglobulins (IVIGs)[75] and rituximab (RTX)[76,77]. Recently, proteasome inhibitors such as bortezomib[78] and carfilzomib[79] have also been studied, but these drugs were not as effective as anticipated.

In addition, complement inhibitors such as C1 inhibitors (C1-INH) and eculizumab, failed to control cABMR[80,81] probably because antibodies may injure the endothelium in a complement-independent pathway. Better results have been obtained with the use of IL-6R or IL-6 inhibitors.

In a previous study, Shin *et al*[82] documented the efficacy of tocilizumab in blocking monocyte activation in an *in vitro* model, to inhibit the inflammatory cascade induced by alloantibodies. In a more recent study, Shin *et al*[83] documented a beneficial effect of tocilizumab on cABMR owing to a reduction in antibody production by B cells.

Similarly, Choi *et al*[84] documented a reduction in DSAs and cABMR and stabilization of renal function in patients with cABMR, DSAs and transplant glomerulopathy treated with tocilizumab. A phase 4 RCT in patients with cABMR was recently designed[85].

Clazakizumab is a humanized monoclonal antibody directed against IL-6. In a study by Dobere *et al*[86], clazakizumab reduced DSAs and demonstrated beneficial effects on cABMR and renal function.

THERAPY FOR DESENSITIZATION AND ACUTE ABMR

Desensitization and treatment of ABMR are the two faces of the same coin. It has already been discussed how DSAs play a relevant role in inducing AKI and graft failure. DSAs may already be present before transplantation, or they may appear *de novo* after kidney transplantation. In both conditions, they may cause ABMR.

Desensitization is the treatment to reduce or, when possible, completely eradicate DSAs before or at the time of transplantation. Treatment of ABMR includes powerful drugs aimed at controlling this severe complication.

To better understand the mechanism of action of these drugs, Figure 4 represents how DSAs are formed and where the immunosuppressant drugs may act[87]. Naïve CD4+ T cells recognize the antigen presented by APCs. Activated CD4+ cells process antigens, which are presented to naïve B cells. Costimulatory molecules mediate the presentation through CD80/86 and CD28. B cell maturation and development into B-memory cells and plasma cells (PCs) is regulated by cytokines (principally IL-6 and IL-21), B cell activating factor (BAFF) and a proliferation-inducing ligand that interact with B cell maturation antigen. PCs produce antibodies that bind to donor-specific human leukocyte antigen (HLA) molecules, activate complement and initiate injury leading to ABMR. Agents capable of interfering with this complex system are numerous and act at different levels.

Several studies and reviews have described the drugs used in desensitization and in the treatment of ABMR[88-93].

Novel agents will be discussed in this chapter. New agents acting on costimulatory signals have already been discussed[48,49,57,59]. Similarly, anti-IL-6/IL-6R agents have been discussed[83-86].

Obintuzumab is a type 2 anti-CD20 antibody that induces more robust B cell depletion than RTX. To date, the drug has been evaluated in a phase 1b study to induce desensitization[94].

Belimumab belongs to the anti BAFF family. The drug is effective in treating systemic lupus erythematosus[95] but less effective in treating ABMR[96] due to possible infective complications. Proteasome inhibitors such as bortezomib and carfilzomib act on PCs, but are not as effective as anticipated. Carfilzomib has been studied in desensitization in a nonhuman primate model[97].

Drugs acting directly on PCs target CD38. Several studies or case reports have documented the efficacy of daratuzumab in the treatment of ABMR[98-100]. Isatuximab is effective on PCs and other immune cells, such as Tregs and Bregs. This fact may limit its applicability in the treatment of ABMR [101].

Inebilizumab is a humanized anti-CD19 monoclonal antibody approved for neuromyelitis optica [102].

An RCT with inebilizumab for pretransplant desensitization[103] was suspended due to the coronavirus disease pandemic.

Finally, another fully human monoclonal antibody, anti-CD38, is the object of an RCT for the treatment of ABMR[104].

In ABMR, the activation of the complement cascade is triggered by ligation of the C1 complex to HLA antigens that are bound by DSAs. Several drugs are capable of blocking complement activation (Figure 5). The C1 complex is activated upon antibody binding. The humanized monoclonal antibody BIVV009 (sutinlimab) targets its enzymatic subcomponent C1 s and this therapy blocks C4 and C2 cleavage and the formation of C3 convertase.

A phase 1 study with this drug[105] was concluded, and Eskandary *et al*[80] studied 10 kidney transplant recipients with ABMR. Repeated biopsies documented a reduction in C4d deposition even if DSA levels and microvascular inflammation were unchanged.

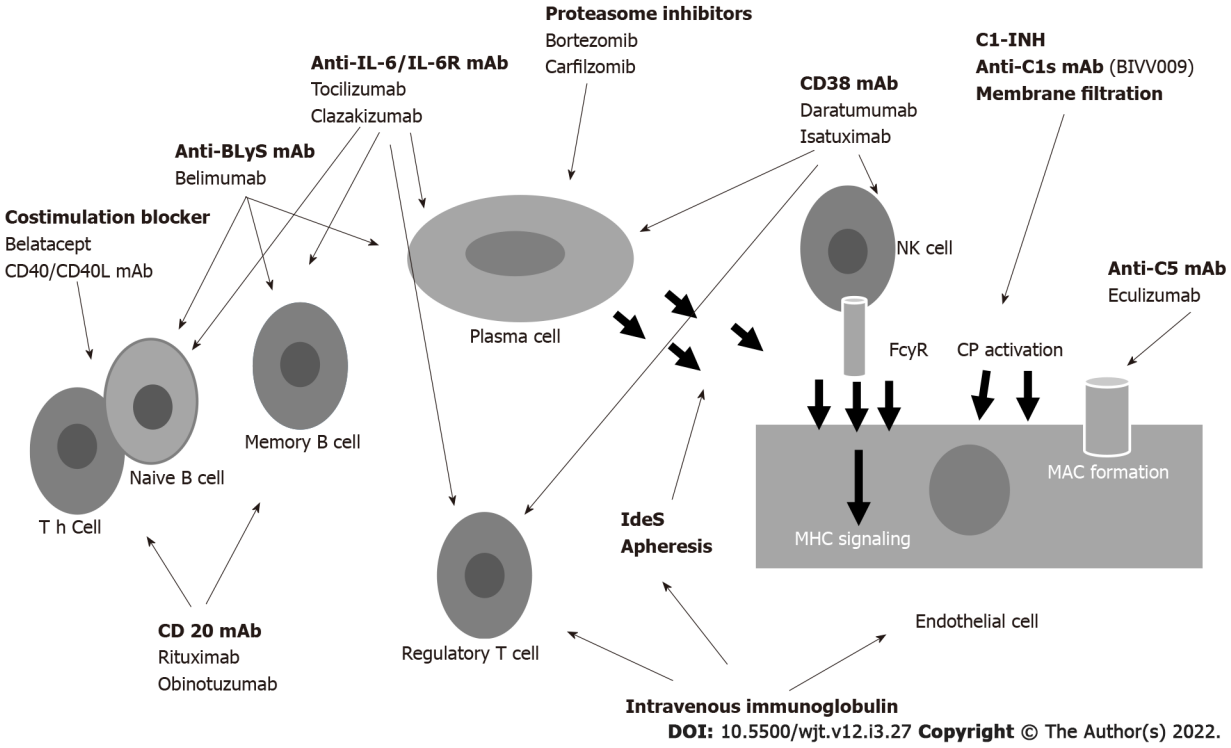

Figure 4 Drugs acting at different levels to control the antibody formation. BLyS: B Lymphocyte stimulating factor; mAb: Monoclonal antibody; C1-INH: C1 inhibitors; NK: Natural killer; Cp: Complement; FcyR: FcyReceptor; MAC: Membrane attacking complex; MHC: Major histocompatibility complex; IL: Interleukin.

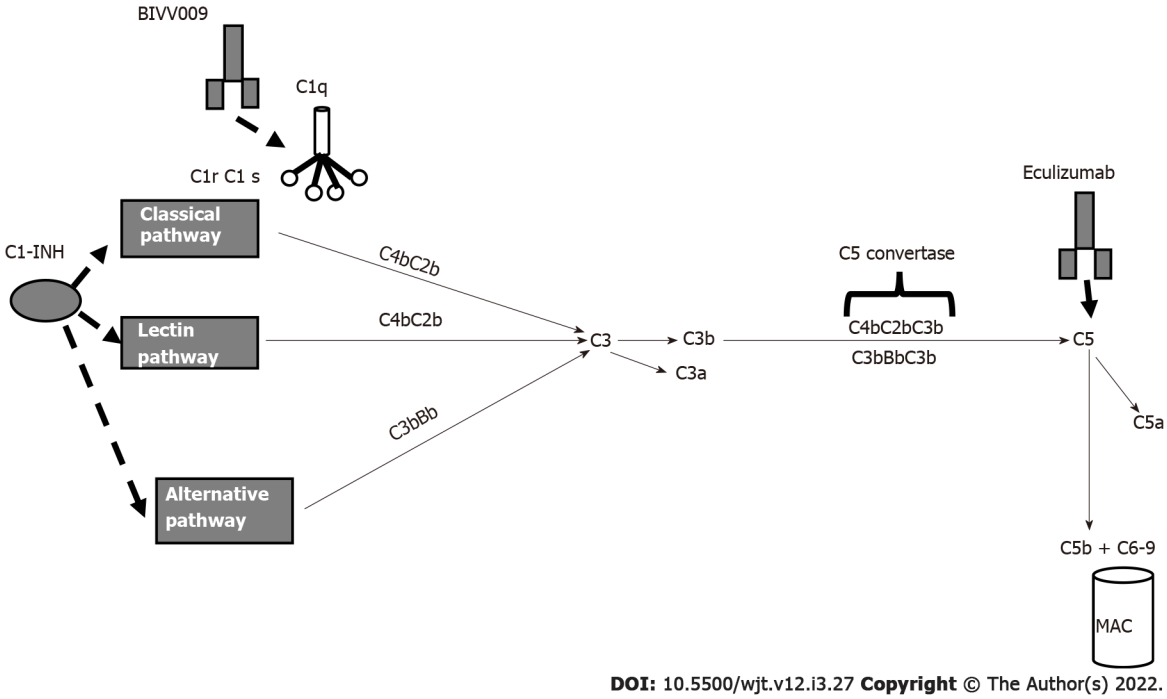

Figure 5 Principal drugs affecting complement. C1-INH: C1 inhibitor; MAC: Membrane attacking complex.

C1-INH regulates several pathways that contribute to complement activation and cause ABMR.

In 2015, in a phase I/II placebo-controlled trial, Vo *et al*[106] reported the efficacy of C1-INH in the prevention of ABMR in HLA-sensitized patients. Later, Montgomery *et al*[107] in a randomized controlled pilot study, documented the efficacy of C1-INH in controlling ABMR. More recently, two more studies are ongoing to document the efficacy of human plasma C1 esterase inhibition as an addition to the standard of care for the treatment of ABMR[108,109].

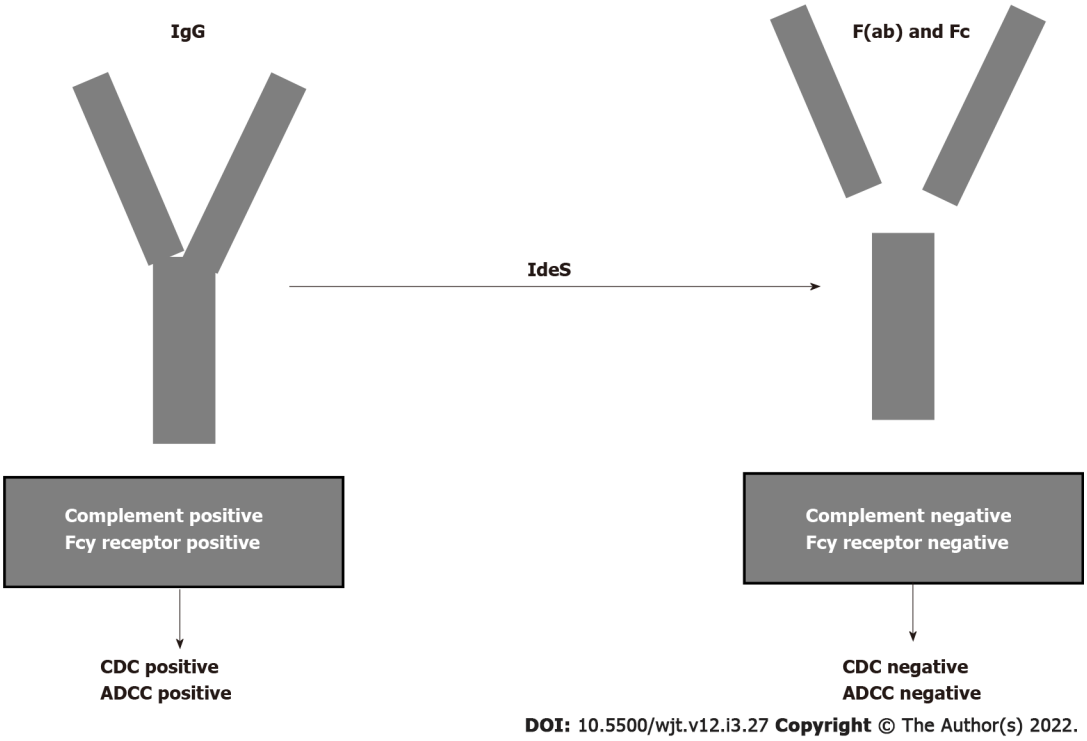

Figure 6 Cleaving intact immunoglobulin G by imlifidase. CDC: Complement dependent cytotoxicity; ADCC: Antibody dependent cell cytotoxicity; F(ab): Fragment ab; Fc: Fragment c; Ides: Imlifidase; IgG: Immunoglobulin G.

The humanized monoclonal antibody eculizumab binds to C5 with high affinity and prevents C5 convertase-mediated cleavage to C5a and C5b. In the past, several studies documented the efficacy of eculizumab in treating ABMR[110-112]. Recently, other studies documented the efficacy of eculizumab in treating and preventing ABMR[113,114]. Antibody removal is another therapeutic technique that may be applied primarily to desensitize patients with preformed DSAs before transplantation. Until recently, antibody removal and/or inhibition have been performed by plasmapheresis and IVIGs. Recently, it was documented that imlifidase (IdeS), a recombinant cysteine protease derived from Streptococcus pyogenes, rapidly cleaves IgG in the lower hinge region to a Fab fragment and a dimeric Fc fragment [115] (Figure 6). In addition to eliminating HLA antibodies, Ge *et al*[116] demonstrated that IdeS is a potent inhibitor of antibody-dependent cell cytotoxicity. A drawback of IdeS treatment is antibody recurrence after the interruption of the treatment. Incorporation of plasmapheresis and RTX to this treatment may overcome this drawback.

An international phase 2 trial was conducted in five transplant centers[117] for desensitization of cross-match-positive, highly sensitized kidney transplant recipients. Antibody rebound occurred 3-14 d after lipopolysaccharide administration, but graft survival at six months was 88.9%. The study conclusion was that IdeS converted positive cross matches to negative cross matches and achieved the transplantation of high-sensitized patients with optimal results at 6 mo.

In a more recent study, Kjellman *et al*[118] documented that lipifidase treatment administered to 39 cross-match-positive patients accomplished a 3-year graft survival of 93% with an ABMR incidence of 38% in the first month post-transplantation.

CONCLUSION

Lack of interest by industries and optimal outcomes reached by the drugs used to date has resulted in little progress in finding new drugs. However, examining unmet needs in the field of kidney transplantation may help us to find new drugs. Needs not optimally covered by current drugs are control of DGF, improvement of the long-term immunosuppression with graft outcomes reduced by chronic damage and the control of desensitization and ABMR. The control of these needs is of outmost importance, considering the expanding numbers of new kinds of kidney transplantation as transplantation from older donors and from NHBDs and transplantation from antibody-incompatible donors.

In the first kind, controlling or reducing DGF is essential; in the latter kind, the reduction of antibodies against HLA is essential.

DGF may be controlled either with optimal management of the donor before or during kidney removal or with drugs attempting to target one of the multiple pathways involved in causing the IRI that is conducive to DGF.

New drugs are also emerging to control or reduce the antibody serum level. Several steps are involved in antibody generation and for each of those steps new drugs will be found.

In addition, drugs are able to reduce the nephrotoxicity induced by the long-term use of CNIs and to control kidney inflammation that may contribute to a worse graft outcome.

The majority of these drugs have been very recently found and are still in RCTs. Therefore, trials with novel agents require a careful approach and these new agents in transplantation face many challenges, but may provide a hopeful pipeline in this issue.

FOOTNOTES

Author contributions: Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, performed the last revision and provided answers to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

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Country/Territory of origin: Italy

ORCID number: Maurizio Salvadori 0000-0003-1503-2681; Aris Tsalouchos 0000-0002-8565-4059.

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MINIREVIEWS

New onset hypertension after transplantation

Mahmoud Nassar, Nso Nso, Sofia Lakhdar, Ravali Kondaveeti, Chandan Buttar, Harangad Bhangoo, Mahmoud Awad, Naveen Siddique Sheikh, Karim M Soliman, Most Sirajum Munira, Farshid Radparvar, Vincent Rizzo, Ahmed Daoud

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Mahmoud Nassar, Nso Nso, Sofia Lakhdar, Ravali Kondaveeti, Chandan Buttar, Harangad Bhangoo, Vincent Rizzo, Department of Medicine, Icahn School of Medicine at Mount Sinai (NYC Health and Hospitals: Queens), New York, NY 11432, United States

Mahmoud Awad, Department of Medicine, The Memorial Souad Kafafi University Hospital, 6th of October - Giza 0000, Egypt

Naveen Siddique Sheikh, Department of Physiology, CMH Lahore Medical College and Institute of Dentistry, Lahore - Punjab 0000, Pakistan

Karim M Soliman, Department of Medicine, Medical University of South Carolina, Charleston, SC 29425, United States

Most Sirajum Munira, Farshid Radparvar, Division of Cardiology, Department of Medicine, Icahn School of Medicine at Mount Sinai (NYC Health and Hospitals: Queens), New York, NY 11432, United States

Ahmed Daoud, Department of Medicine, Kasr Alainy Medical School, Cairo University, Cairo 11211, Egypt

Corresponding author: Ahmed Daoud, MBChB, MD, MSc, PhD, Lecturer, Staff Physician, Department of Medicine, Kasr Alainy Medical School, Cairo University, Kasr Alainy Street, Cairo 11211, Egypt. ahmed.daoud84@yahoo.com

Abstract

It has been reported that up to 90% of organ transplant recipients have suboptimal blood pressure control. Uncontrolled hypertension is a well-known culprit of cardiovascular and overall morbidity and mortality. In addition, rigorous control of hypertension after organ transplantation is a crucial factor in prolonging graft survival. Nevertheless, hypertension after organ transplantation encompasses a broader range of causes than those identified in non-organ transplant patients. Hence, specific management awareness of those factors is mandated. An in-depth understanding of hypertension after organ transplantation remains a debatable issue that necessitates further clarification. This article provides a comprehensive review of the prevalence, risk factors, etiology, complications, prevention, and management of hypertension after organ transplantation.

Key Words: New onset; Hypertension; Organ; Transplantation; Renal

Core Tip: This article provides a comprehensive review of the prevalence, risk factors, etiology, complications, prevention and management of hypertension after organ transplantation.

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INTRODUCTION

The systolic blood pressure of more than 130 mmHg or diastolic blood pressure of above 80 mmHg leads to the development of hypertension requiring medical management *via* antihypertensive medications[1]. The primary and secondary blood pressure elevations potentially increase the risk of various cardiovascular complications. Secondary hypertension develops under the impact of several morbidities and comorbidities. Organ transplantation based on heart, kidney, lung, bone marrow, and liver predisposes 70%-90% of the treated patients to hypertension that potentially impacts their overall survival[2]. The development of posttransplant hypertension also leads to graft-related complications. The systematic prevention and control of organ transplant-related hypertension are paramount to reducing the risk of morbidity/mortality. This review elaborates on the complications, etiology, risk factors, prevalence, incidence, and medical management of hypertension occurring after organ transplantation.

KIDNEY TRANSPLANTATION

Most of renal transplant recipients are already hypertensive before transplant. The prevalence of hypertension in end stage renal disease is around 70%-80%. Hypertension improves in some patients after renal transplantation with the improvement of the renal functions, many patients continue to have renal transplantation related hypertension after transplantation[3].

The renal transplantation-related hypertension prevalence among 47%-82% of children and 50%-80% adults potentially deteriorate their prognostic outcomes. However, the variations in hypertension prevalence between the patient populations potentially deteriorate their medical management and treatment outcomes. More than 27.6% of patients experience hypertension within one year of their organ transplantation. The utilization of immunosuppressants, organ rejection, graft dysfunction, long surgery duration, and advanced donor age are the significant factors that increase the risk of organ transplantation-related hypertension[4]. Other predisposing factors include post-biopsy arteriovenous fistula, post-transplantation glomerulonephritis/renal artery stenosis, and family history of hypertension among organ donors[5].

HEART TRANSPLANTATION

Seventy percent of patients who receive heart transplants experience hypertension and its clinical complications[6]. The elderly hypertensive patients with heart transplant status often experience a marked reduction in estimated glomerular filtration rate and elevation in serum creatinine levels. The findings by United Network for Organ Sharing database indicate hypertension predisposition among heart transplant recipients with age sixty years or above compared to other age groups[7]. The clinical studies reveal a reduction in hypertension incidence among patients who undergo heterotrophic cardiac transplants[8]. The patients who receive an orthotopic heart transplant, however, experience a high risk for hypertension. The obese patients undergoing heart transplantation also remain highly predisposed to hypertensive heart disease. The dependence on steroids, calcineurin inhibitors, and other immunosuppressants further increase the risk of hypertension among heart transplant recipients. Medical literature correlates 70%-90% incidence of hypertension with the use of calcineurin inhibitors among heart transplant patients[9].

LUNG TRANSPLANTATION

A reportable number of patients develop new-onset/episodic hypertension after undergoing lung transplantation. Medical literature confirms the cumulative prevalence of new-onset hypertension among 45% (at one year), 56% (at two years), and 63% (at three years) of lung transplant recipients. These patients frequently develop comorbidities, including diabetes mellitus and hypercholesterolemia [10]. The lung transplant patients who receive cyclosporine treatment or encounter blood pressure elevation (before transplant) also develop hypertension in many clinical scenarios[11].

LIVER TRANSPLANTATION

Liver transplantation is the gold standard in a patient with end-stage liver disease. Immunosuppressive therapy is required to reduce rejection after transplantation[12]. Unfortunately, more than half of the liver transplant patients develop hypertension that impacts their prognosis and treatment outcomes six months after surgery. In addition, post-transplant hypertension develops among liver transplant patients based on their calcineurin inhibitor/steroid use, family history of hypertension, obesity, and older age. However, the tacrolimus use, and race of liver transplantation patients do not increase their risk for episodic hypertension[13].

BONE MARROW TRANSPLANTATION

Approximately 2.4% of bone marrow transplant recipients develop pulmonary hypertension that potentially deteriorates their quality of life, life expectancy, and quality-adjusted life-years[14]. The progressive elevation in pulmonary vascular resistance often triggers right ventricular dysfunction and mortality among bone marrow transplant patients. Hemopoietic cell transplantation among adults and children predisposes them to systemic hypertension during the initial two years of their recovery. Sixty-one percent of adults/children experience new-onset hypertension within one month of their hemopoietic cell transplant[15,16].

Etiology

The surgical interventions, immunosuppressive therapy/immune system deterioration, and recipient/donor factors potentially impact the hypertension etiology in patients with organ transplant status.

Donor factors

Hypertension among organ transplant patients also develops under the impact of deceased donor renal graft[17]. Medical literature provides inclusive findings concerning the impact of donor hypertension on the hypertension predisposition of organ transplant patients; however, it independently increases the risk for renal allograft failure[18]. The donor's age often determines the post-transplant hypertension risk of the organ transplant candidates[19]. The kidney transplant patients whose donors exhibit a history of familial hypertension experience ten times greater risk of blood pressure elevation than the patients whose donors do not report a family history of hypertension[12]. The differences between the donors' age and body surface area and their organ recipients also predispose them to episodic hypertension. The nephron underdosing due to reduced recipient/donor body weight ratio potentially triggers chronic inflammation among organ transplant patients, which eventually predisposes them to diabetes mellitus, post-transplant hypertension, and chronic rejection of transplanted organs[20].

Recipient factors

The clinical studies provide inconclusive evidence concerning the impact of behavioral patterns of organ transplant patients on their hypertension predisposition. However, alcohol consumption, smoking, salt intake, and obesity deteriorate the clinical outcomes of organ transplant patients and increase their risk of hypertension compared to the general population. The organ transplant candidates with pretransplant hypertension and obesity experience a high risk of posttransplant hypertension[17-22]. Stable kidney transplant patients with hypovolemia experience a high risk of elevated mean arterial/diastolic/systolic blood pressures[23]. Post-transplant hypertension also develops under the impact of comorbidities (including endocrine tumors and obstructive sleep apnea) and the age of the recipients.

Transplant renal artery stenosis

The development of transplant renal artery stenosis (TRAS) under the impact of renal artery stenosis reduces the vascular supply to the allograft. TRAS triggers hypertension among 1%-5% of renal transplant recipients[24,25]. The initial six months to two years after organ transplant predispose the treated patients to TRAS-related complications[26]. TRAS manifests with transplant dysfunction,

water/salt retention, renal function deterioration, and refractory hypertension. The organ transplant patients eventually experience acute pulmonary edema and hypertensive crisis[26]. TRAS-induced hypoperfusion triggers renin-angiotensin-aldosterone system (RAAS) that potentiates renovascular hypertension in patients with organ transplant status[26]. The potential causes of transplant renal artery stenosis include immune-mediated endothelial deterioration, recipient/donor artery trauma, suturing techniques, donor artery atheroma, and renal artery lesions[27]. TRAS assessment relies on conventional angiography; however, TRAS correction and enhancement of blood pressure/renal perfusion warrants renal vascularization *via* PCTA (percutaneous transluminal coronary angioplasty)[26].

Acute rejection and chronic allograft injury

Hypertensive crisis in organ transplant patients correlates with acute and chronic allograft injury. However, clinical studies provide inconclusive evidence concerning a causal relationship between hypertension and allograft deterioration[22].

Acute rejection

The cases of acute organ rejection warrant diagnostic assessment concerning post-transplant hypertension. The therapeutic management of acute organ rejection often corrects the systolic and diastolic blood pressure elevations in organ transplant patients. These outcomes substantiate the acute organ rejection attribution of hypertension in organ transplant scenarios[22].

Chronic graft injury

The chronic renal allograft injury emanates from recurrent glomerular disease, thrombotic microangiography, tubular atrophy, interstitial fibrosis, and chronic antibody-mediated organ rejection. The focal segmental glomerulosclerosis predominantly associates with hypertension in patients with organ transplant status. The current body of evidence provides inconclusive evidence concerning the cause-and-effect relationship between renal allograft dysfunction and hypertensive crisis among organ transplant patients. However, the findings from a preclinical study advocate the potential of hypertension to cause allograft deterioration in organ transplant scenarios[28].

Immunosuppressive drugs

The toxic effects of immunosuppressive drugs often elevate the risk of hypertension among organ transplant patients.

Steroids

The organ rejection prevention protocol concerning transplantation scenarios relies on the systematic administration of methylprednisolone and prednisone. Corticosteroid maintenance therapy potentially triggers a range of morbidities and comorbidities among patients with organ transplant status. It also increases their risk of hypertension to multiple folds. A plausible mechanism concerning steroid-induced hypertension attributes to volume expansion/sodium retention due to mineralocorticoid receptor overstimulation in organ transplant patients. The exclusion of steroids from the immunosuppressive therapy to mitigate the risk of hypertension could, however, trigger organ rejection and its fatal complications. A recently reported meta-analysis confirmed a 48% incidence of acute organ rejection in patients who did not receive steroids with their immunosuppressive therapies compared to 30% organ rejection incidence among patients who received steroid-controlled immunosuppressive treatments[29].

Calcineurin inhibitors

The multifactorial characteristics of calcineurin inhibitor-induced hypertension are widely debated in the medical literature. The calcineurin inhibitors impact the function of the sodium-potassium pump/sympathetic nervous system and vascular tone that eventually triggers a hypertensive crisis in patients with organ transplants. They further induce nitric oxide metabolism by triggering nicotinamide adenine dinucleotide phosphate oxidase-induced angiotensin-II release in the context of intrarenal renin-angiotensin system activation[30]. Furthermore, renal/systemic vasoconstriction often develops under the impact of cyclosporine therapy[31]. The endothelial receptor type A across preglomerular arteries triggers endothelin production that eventually leads to renal vasoconstriction in organ transplant recipients[29,32]. The clinical studies demonstrated cardioprotective effects of tacrolimus compared to cyclosporin in the setting of organ transplantation[33]. They also reveal the superiority of tacrolimus over cyclosporin in controlling blood pressure elevations among organ transplant patients [21]. Research evidence confirms blood pressure elevation in organ transplant recipients on cyclosporin treatment after increasing their dietary sodium intake. This increase in blood pressure indicates the incidence of sodium-dependent hypertension among patients after their organ transplantation[34]. However, the clinical studies do not provide conclusive evidence related to the sodium retaining effects of calcineurin inhibitors in organ transplant scenarios[35]. However, the medical literature indicates the potential of cyclosporin inhibitors in elevating the activity of sodium-potassium chloride/sodium chloride cotransporters for maximizing sodium reabsorption in organ transplant patients[36]. The clinical studies also emphasize the possibility of replacing calcineurin inhibitors with sirolimus based on

its safety profile and least impact on the 24 h systolic blood pressures of patients with organ transplant status.

PREVENTION MEASURES

Organ transplant-related hypertension prevention warrants the mitigation of risk factors that potentially aggravate systolic and diastolic blood pressures in the treated patients. These risk factors include native kidneys, donor hypertension, smoking, drug use, obstructive sleep apnea, and obesity[37,38]. The findings from various clinical studies recommend lifestyle/behavioral modifications and weight reduction strategies for organ transplant recipients to minimize their risk of postprocedural hypertension. They also advocate the need for evaluating suprarenal masses based on their hypertension attribution[39].

The long-term use of calcineurin inhibitors, including tacrolimus and cyclosporine among organ transplant patients, clinically correlates with their hypertensive crises. The clinical studies reveal a reduced impact of tacrolimus (compared to cyclosporine) on the blood pressure levels of organ transplant patients[40]. The organ transplant recipients who receive tacrolimus also exhibit a limited dependence on antihypertensive drugs for managing their blood pressure levels[37]. The clinicians accordingly recommend tacrolimus over cyclosporine for the medical management of organ transplant patients. The medical literature alternatively recommends the selective T-cell co-stimulation blocker (Belatacept) to control T cell proliferation and cytokine production in renal transplant patients for effectively managing their episodic hypertension[41].

The clinical studies further advocate the deleterious impact of corticosteroids on the blood pressure management of organ transplant patients. They provide substantial evidence concerning the dose-dependent relationship between corticosteroid utilization and hypertensive crisis in organ transplant scenarios. The clinicians accordingly recommend minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing their risk for episodic hypertension[42].

The worsening of hypertension in kidney transplant patients clinically correlates with their antibody-mediated and acute cellular organ rejection[43]. The subsequent administration of immunosuppressive therapy (based on thyroglobulin, immunoglobulins, and steroids for reversing organ rejection) further exacerbates the hypertensive crisis[44]. These findings necessitate the development of comprehensive treatment protocols to minimize hypertensive crisis without compromising the outcomes of immunosuppressive therapies in organ transplantation scenarios.

The clinical studies reveal the impact of expanded criteria donor recipient status on worsening cardiovascular complications and hypertensive crises in patients with organ transplant status[45]. Organ transplant patients prevalently develop diabetes, chronic rejection, and hypertension under the impact of reduced donor/recipient body weight ratio[20]. Posttransplant hypertension also triggers under the impact of aortorenal donor atheroma in various clinical scenarios[19]. The medical literature accordingly recommends selecting young and normal-weight donors without a confirmed diagnosis of hypertension or atherosclerosis to minimize the risk of hypertension among organ transplant patients.

A range of genetic factors contributes to the development of hypertensive crises in organ transplant patients. The presence of apolipoprotein L-1 variants in deceased African American donors potentiates early graft dysfunction and eventual blood pressure elevation in the recipients of transplanted organs. The polymorphisms in CYP3A5, ABCC2, and ABC1 transporters further attribute to posttransplant hypertension and poor graft survival in organ transplant scenarios[46,47]. The assessment of these genetic mechanisms and factors is paramount to minimizing the risk of posttransplant hypertension among organ transplant patients.

Post-transplant hypertension also develops under the impact of transplanted renal artery stenosis following kidney transplantation[48]. The clinical studies reveal substantial improvements in blood pressure levels of organ transplant patients after the medical management of their renal artery stenosis [49]. These findings substantiate early diagnosis and therapeutic management of renal artery stenosis to reduce the incidence of posttransplant hypertension and its critical complications.

The therapeutic management of posttransplant hypertension relies on the systematic administration of calcium channel blockers, beta-blockers, and loop diuretics (for volume optimization). The normalization of serum potassium levels and enhancement of kidney function of organ transplant patients further depends on angiotensin receptor blockers and angiotensin-converting enzyme inhibitors[38].

The hypertension risk factors among liver transplant recipients include new-onset hepatic steatosis, alcoholic cirrhosis, and rapamycin use[50]. These findings advocate the need for monitoring organ transplant patients on mTOR inhibitor therapies to reduce their incidence of hypertensive crises.

The patients with allogenic hematopoietic stem cell/bone marrow transplant experience a high risk of hypertension based on several factors including graft *vs* host disease, mycophenolate/calcineurin inhibitor therapies, and lymphoma/Leukemia history[51]. Other hypertension predisposing factors concerning stem cell transplant scenarios include serum creatinine elevation, sinusoidal obstruction syndrome, amphotericin-B therapy, and the young age of the patients in pediatric hematopoietic stem

cell transplant[15]. The clinical studies accordingly advocate consistent monitoring of the bone marrow transplant patients based on their dependence on amphotericin-B, mycophenolate, and calcineurin inhibitors.

DIAGNOSTIC PARAMETERS

The diagnostic assessment of hypertension in organ transplant scenarios relies on 24 h ambulatory/home/office blood pressure monitoring interventions. The office blood pressure assessment warrants the recording of three consecutive blood pressure readings and calculation of their mean value. The home blood pressure monitoring requires averaging two blood pressure readings obtained at home within a tenure of 4 days. The 24 h ambulatory blood pressure assessment relies on averaging various blood pressure readings obtained within a day's duration *via* a digital blood pressure monitor[1]. The 24 h blood pressure evaluation also helps categorize systolic/diastolic blood pressure levels based on their reverse dipping, dipping, and non-dipping patterns.

The clinical studies emphasize marked differences between clinical blood pressure monitoring, home blood pressure assessment, and ambulatory blood pressure monitoring. These studies also advocate the requirement of practicing care and caution while measuring the blood pressure levels of organ transplant patients. The clinical findings prioritize the use of ambulatory blood pressure monitoring for investigating the occurrence of whitecoat/masked/nocturnal hypertension to rule out the risk of cardiovascular complications[52].

The medical literature reveals a substantial increase in night-time systolic blood pressure following kidney transplantation[53]. The 24 h ambulatory blood pressure monitoring effectively tracks nocturnal blood pressure variations in organ transplant patients[54]. This blood pressure evaluation approach is the method of choice for tracking posttransplant hypertension and is recommended over home/office blood pressure monitoring interventions[55].

The diagnostic affirmation of posttransplant hypertension thoroughly relies on the appropriate use of blood pressure recording interventions. The blood pressure monitored at the physician's office may not give an accurate outcome based on the risk of masked/whitecoat hypertension and circadian variation/diurnal rhythm. Masked hypertension could increase the risk of native kidney disease among renal transplant patients[56]. However, clinical studies do not provide conclusive findings determining the impact of masked hypertension on the outcomes of renal transplant patients. These diagnostic intricacies warrant the use of automated electronic devices for blood pressure monitoring to minimize the risk of masked hypertension and the whitecoat effect in organ transplant scenarios[57].

The medical literature advocates optimizing blood pressure cutoff limits to accurately identify the existence or absence of hypertension and initiate antihypertensive therapies for organ transplant patients. The diagnostic parameters for assessing hypertension in posttransplant scenarios rely on the following parameters[4]: Office blood pressure reading of greater than 140/90 mmHg.

An ambulatory blood pressure reading of greater than 135/85 mmHg (awake state) and 120/70 mmHg (sleeping state) The recommendations by KDIGO (Kidney Disease Improving Global Outcomes) advocate the need to administer antihypertensive therapies to kidney transplant patients following their blood pressure elevation above 130/80 mmHg[58].

MAJOR COMPLICATIONS

Approximately 50%-80% of adult organ transplant recipients develop hypertension and its clinical complications. The past medical history of hypertension further increases the incidence of post-transplant hypertension. Additionally, the old age of donors, elevated body mass index, male gender, and African American race include the significant demographic factors attributing to the development of hypertension among organ transplant patients[43].

Types of complications

Medical literature reports a 50% prevalence of hypertensive among patients with organ transplant status[43]. Posttransplant hypertension predominantly triggers graft dysfunction and cardiovascular events in organ transplant patients that eventually lead to their renal failure. The cardiovascular complications related to posttransplant hypertension include coronary artery disease and congestive heart failure. Uncontrolled hypertension in the setting of kidney transplants potentially disrupts cardiorenal outcomes by impacting the overall functions of the heart and renal allograft[21,59].

Cardiovascular complications due to post-transplant hypertension

The recipients of kidney transplants experience a 3%-5% incidence of non-fatal/fatal cardiovascular episodes. They further experience a 50-fold predisposition to cardiorenal complications compared to the general population[60]. Posttransplant mortality often attributes to critical cardiovascular complications

emanating from hypertensive crises. The cardiovascular compromise develops under the impact of posttransplant hypertension and elevates the incidence of morbidity/mortality among the treated patients. The cardiovascular episodes attribute to forty percent of patient deaths in the setting of a kidney transplant[4]. The predominant cardiovascular complications emanating from posttransplant hypertension include stroke, arterial narrowing, coronary artery disease, congestive heart failure, and ischemic heart disease. The kidney transplant scenarios also report a high incidence of diastolic dysfunction, left atrial enlargement and left ventricular hypertrophy. Heart failure with decreased left ventricular ejection fraction potentially increases the mortality risk among organ transplant patients. The clinical studies reveal a strong association between nocturnal hypertension and left ventricular hypertrophy in various organ transplant scenarios[4].

Graft dysfunction due to post-transplant hypertension

The graft dysfunction in posttransplant scenarios predominantly develops under the impact of hypertensive crisis. The deterioration in renal function also correlates with blood pressure elevation in the setting of organ transplants. The renal allograft injury triggered by posttransplant hypertension-induced kidney failure further aggravates episodic hypertension and its potential manifestations[43]. The clinical studies continue to examine the relationship between independent allograft survival and blood pressure levels of organ transplant patients.

The retrospective study by Opelz *et al*[61] (1998) based on 29571 renal transplant recipients revealed the adverse impact of posttransplant hypertension on the renal allograft injury patterns[61]. Another clinical study indicated improvements in cardiovascular mortality and renal allograft function after therapeutic management of systolic blood pressure of patients within 1-3 years of their kidney transplantation[22]. The study outlined positive clinical outcomes in organ transplant recipients with a marked reduction in systolic blood pressure (below 140 mmHg).

A clinical study revealed improvements in renal transplant survival rates among patients with reduced diastolic pressures (ranging between 89-99 mmHg). The study findings advocated the need for monitoring mean arterial/diastolic/systolic blood pressures of the renal transplant patients until one year after transplantation to enhance their allograft survival. The study outcomes further correlated the risk of allograft failure for every 10 mmHg diastolic/systolic blood pressure elevation[61]. The clinical studies also indicate blood pressure reduction is a protective factor for kidney transplant recipients during the initial year of their recovery[4,22]. The evidence-based findings clinically correlate graft failure/chronic allograft nephropathy, renal failure, and cardiovascular compromise with posttransplant hypertension. Organ transplant patients with hypertension accordingly experience a high risk of morbidity and mortality[61].

MEDICAL MANAGEMENT

The treatment guidelines for managing posttransplant hypertension do not differ from the therapeutic protocols adopted for treating hypertension/blood pressure elevation among patients with a high risk for cardiovascular complications (Table 12-3). The clinical studies reveal the impact of diabetes/proteinuria and cardiovascular conditions on the blood pressure elevation in organ transplant patients. The maintenance of systolic/diastolic blood pressure below 140/90 mmHg is highly necessary to reduce the risk of posttransplant hypertensive crisis. The multifactorial origin of posttransplant arterial hypertension in renal transplant cases warrants its systematic monitoring and medical management. Posttransplant hypertension/hypertensive crisis further intensifies under the impact of allograft nephropathy and immunosuppressive therapies. The diagnostic interventions to track and evaluate the causative factors of posttransplant hypertension include assessing 24 h urinary sodium, proteinuria, 24 h urine clearance, renal function tests, and hepatic panel. The candidates for kidney transplantation qualify for renal ultrasound in the context of evaluating their urinary tract blockage and renal artery stenosis.

The pretransplant hypertension of kidney transplant recipients warrant antihypertensive therapy. The clinical studies reveal rare cases (concerning kidney transplantation) that achieve normotensive status in the absence of antihypertensive therapy. These outcomes necessitate pharmacological management of hypertension of kidney transplant patients to reduce the risk of their cardiovascular complications[22]. The non-pharmacological approaches for hypertension management in kidney transplant scenarios rely on lifestyle modification, stress reduction, weight management, smoking cessation, low-salt diet, and exercise management. Clinical studies need to explore the complex interplay between pharmacodynamics and pharmacokinetics of antihypertensive medications to optimize their use in organ transplant scenarios. They also need to investigate drug-drug interactions and their impact on comorbidities and hypertension management of organ transplant patients[62].

The renal transplant scenarios report a high incidence of hypertension emanating from corticosteroid therapy. The novel organ transplantation protocols advocate the exclusion of corticosteroid treatment to minimize the risk of hypertensive crises or episodic hypertension[22]. However, the clinical studies provide inconclusive evidence concerning the discontinuation timings of steroid therapies for renal

Table 1 Management for hypertension following renal transplantation

Blood pressure management	Interventions	Comments
Non-pharmacological management	Dietary sodium restriction; Weight reduction; Exercise; Smoking cessation; Stress reduction	
Pharmacological therapy	Antihypertensive medications: -Diuretics; -Calcium channel blockers; -Beta-blockers; -Renin-angiotensin aldosterone system blockade; -Alpha1 antagonists; -Alpha 2 agonists	Medication choice depends on patient characteristics, adverse effects, tolerability
Invasive interventions	-Transplant renal artery angioplasty +/- stenting; -Continuous positive airway pressure; -Bilateral native nephrectomy; -Native renal denervation	-Transplant renal artery stenosis; -Obstructive sleep apnea; -Failed native kidney; -Sympathetic overactivity
Adjustment of Immunosuppressive Medication	-Steroid withdrawal protocol; -Minimize dose of calcineurin inhibitors; -Replace CsA by using less hypertensive and less nephrotoxic drugs	Other drugs that can be used: -MMF: Mycophenolate mofetil; -Tacrolimus; -Sirolimus

Table 2 Target Blood pressure guideline for kidney transplant recipients

Medical Society/Guideline	Recommended BP target
ACC/AHA[65]	< 130/80 mm Hg
JNC 8 (2014)[66]	Not defined
Kidney disease outcomes quality initiative (KDOQI)[67]	-Goal of 125/75 mm Hg for transplant recipients with proteinuria. -Goal of 130/85 in the absence of proteinuria
Kidney disease: Improving Global outcomes (KDIGO)[68]	< 130/80
European Best Practice Guidelines for Renal Transplantation 2002[19]	Target BP ≤ 125/75 mm Hg in proteinuria patients
Canadian Society of Nephrology[69]	Patients with significant proteinuria; Target Blood pressure is < 130/80 mm Hg
British Renal Association[70]	< 130/80 mm Hg

A reasonable target blood pressure is < 140/90 mmHg for transplant recipients who do not develop proteinuria. (Are you sure about the recommended first line agents?)

transplant patients. The researchers continue to debate regarding the early or late withdrawal of steroid treatments in organ transplant scenarios. Few clinical studies alternatively negate the contention related to the impact of steroid therapies on the hypertensive crisis of organ transplant patients[37].

The medical literature provides some evidence concerning the need for manipulating the currently deployed immunosuppressive therapies to optimize the hypertension management of patients with organ transplant status. This belief reciprocates with the adverse impact of immunosuppressive treatments on posttransplant hypertension. Clinical studies showed that cyclosporine increases the risk of posttransplant hypertension compared to tacrolimus[63]. Furthermore, clinical studies also confirm a marked reduction in systolic/diastolic blood pressures following the dose reduction of cyclosporine or its replacement with tacrolimus in organ transplant scenarios[41]. These findings warrant investigation concerning the hypertension induction effect of cyclosporine in organ transplant patients. The impact of cyclosporine on renal sodium retention probably triggers vasoconstriction of glomerular arterioles leading to posttransplant hypertension[43].

Posttransplant hypertension management primarily relies on first-line therapies based on dihydropyridine calcium channel blockers since they effectively minimize calcineurin-induced vasoconstriction. The beta-blocker therapies further improve the survival rate of organ transplant recipients irrespective of their predisposition to cardiovascular complications[64]. The antihypertensive therapies in organ transplant scenarios must exclude ACE (angiotensin-converting enzyme) inhibitors during the initial 3-6 mo based on the risk of hyperkalemia, anemia, and reduction in glomerular filtration rate[2].

The medical literature provides evidence concerning the development of posttransplant hypertension despite administering antihypertensive therapies. The evidence-based findings elaborate on the necessity for renal arteriography to rule out renal artery stenosis in organ transplant patients. The patients who develop more than 80% renal arterial stenosis qualify for percutaneous transluminal angioplasty. Renal denervation is another viable therapy with the potential to manage refractory hypertension in organ transplant scenarios[4].

Table 3 Studies regarding the management of posttransplant hypertension

	Study type	Title	Ref.	Intervention	Outcome	Conclusion
1	Four cross-sectional Retrospective analysis	Treatment of Hypertension in Renal Transplant Recipients in Four Independent Cross-Sectional Analysis	Kuxmiuk-Glembin *et al*[64], 2018	-Beta-blockers 80%); -Calcium channel blockers (53%); -Diuretics (37%); -Alpha-blockers (35%); -Angiotensin-converting enzyme inhibitors (ACEi) (32%); -ARB (7%)	Blood pressure controlled using BB (43.9 controlled, 56.1 not controlled P = 0.007); -Number of antihypertensive agents: 2.43 +/- 1.3 (controlled BP); 1.88 +/- 1.5 (Uncontrolled BP) P < 0.001. -ACEI &/ARB: Yes: 57.1 (controlled, 42.9 (Uncontrolled); No ACEI/ARB: 48 (Controlled), 52 (uncontrolled) P = 0.08	The commonly used monotherapy agents:-BB followed by CCB. -Use of ACEI, diuretics, and alpha-blockers was about the same. -ARB therapy was least utilized. -Significant increase was observed in the mean number of antihypertensive drugs per patient in subsequent years
2	Randomized controlled trials systemic review	Antihypertensive treatment for kidney transplant recipients	Cross *et al* [71], 2009	60 studies involving 3802 recipients. -29 studies (2262 participants) compared calcium channel blocker to placebo/no treatment. -10 studies (445 participants) compared ACEi to placebo/no treatment. -7 studies (405 participants) compared CCB to ACEi	-CCB compared to placebo/no treatment reduced graft loss (RR 0.75, 95%CI: 0.57-0.99) and improved glomerular filtration rate (GFR), (MD, 4.45 mL/min, 95%CI: 2.22-6.68). -ACEi versus placebo/no treatment were inconclusive for GFR (MD -8.07 mL/min, 95%CI: -18.57-2.43) and variable for graft loss, precluding meta-analysis. -Direct comparison with CCB, ACEi decreased GFR (MD -11.48 mL/min, 95%CI: -5.75 to -7.21), proteinuria (MD -0.28 g/24 h, 95%CI: -0.47 to -0.10), hyperkalaemia (RR 3.74, 95%CI: 1.89-7.43)	CCB may be used as first-line agents for hypertensive kidney transplant recipients. ACEi have few detrimental effects in kidney transplant recipients
3	Double-blind, randomized, placebo-controlled trial.	Angiotensin II blockade in kidney transplant recipients.	Ibrahim *et al*[72], 2013	-The effect of losartan compared to placebo and initiated within three months of transplantation	Doubling of renal cortical volume – Measure of interstitial fibrosis/tubular atrophy	-Use of losartan tended to be protective, with an odds ratio (OR) of 0.39 (95%CI: 0.13–1.15, P = 0.08). -Losartan had no significant effect on time to a composite of ESRD, death, or doubling of creatinine level. The mean time to doubling of serum creatinine was longer in the losartan group, compared with placebo (1065 versus 450 d [hazard ratio (HR) 7.28, 95%CI: 2.22–32.78])
4	Prospective Controlled Trial	Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants	Mourad *et al*[73], 1993	-6 mo after transplantation, patients were randomly allocated to treatment by the angiotensin-converting enzyme inhibitor lisinopril (ACEI, alone or associated with frusemide; n = 14), or the calcium antagonist, nifedipine (CA, alone or associated with atenolol; n = 11)	-Before initiation of antihypertensive therapy, the two groups had similar mean arterial pressures and GFRs. -Both ACEI and CA treatments were associated with no change in renal function, a similar change in mean arterial pressure (ACEI -18 +/- 3; CA -13 +/- 5 mm Hg), and identical trough blood levels cyclosporine	In cyclosporine-treated transplant recipients, satisfactory control of hypertension was obtained by ACEIs based on their potential to minimize arterial pressures
5	Prospective Randomized Trial	Randomized trial of steroid withdrawal in kidney recipients treated with mycophenolate mofetil and cyclosporine	Pellitier *et al*[74], 2006	-121 patients were randomized either to discontinue or remain on steroids (60 patients per group)	There were no significant differences in patient and graft survival rates at 1 year or at last follow-up (approximate 3.7y). -Incidence of acute and chronic rejection as well as graft function were the same within 1 yr	Steroid withdrawal in low-risk kidney transplant recipients is safe and ameliorates many of the unwanted side effects of steroid use
6	Retrospective study	Lack of long-term benefits of steroid withdrawal in renal transplant recipients	Sivaram *et al*[75], 2001	-Retrospective review identified 58 patients administered cyclosporine, azathioprine, and prednisone who underwent complete steroid withdrawal	-Post-steroid withdrawal follow up: 7.6 +/- 1.9 years; -9 patients restarted therapy; 3 patients lost their graft (2 of which are those who restarted prednisone therapy). -2 died with functioning grafts	When prednisone dosage was tapered from 10 mg/d to 10 mg every other day, clinically significant improvements were seen in weight, systolic and diastolic blood pressures, glycosylated hemoglobin levels, and diabetes-related outcomes

CONCLUSION

Posttransplant hypertension increases the risk of graft-related complications in patients with a known history of (pretransplant) hypertension. Steroids, cyclosporine, calcineurin inhibitors, and other immunosuppressive drugs further increase the predisposition of organ transplant patients to hypertension. Hemopoietic cell transplantation predominantly adds to the 2-year risk of systemic hypertension in children and adults. The donor factors for episodic hypertension attributes to the donors' age and body surface area. The recipient factors, however, include hypovolemia and pre-existing comorbidities. TRAS-induced hypoperfusion triggers RAAS that potentiates renovascular hypertension in organ transplant patients. Posttransplant hypertension is a significant cause of cardiovascular complications and graft dysfunction. The 24 h blood pressure monitoring is, therefore, necessary to effectively manage hypertensive crises in organ transplant recipients. The evaluation also helps categorize systolic/diastolic blood pressure levels based on their reverse dipping, dipping, and non-dipping patterns.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Mahmoud Nassar 0000-0002-5401-9562; Nso Nso 0000-0002-0340-169X; Sofia Lakhdar 0000-0001-5320-2990; Ravali Kondaveeti 0000-0003-2335-5296; Chandan Buttar 0000-0003-4777-5439; Harangad Bhangoo 0000-0001-8893-3005; Mahmoud Awad 0000-0002-9243-3449; Naveen Siddique Sheikh 0000-0002-8549-2029; Karim M Soliman 0000-0002-0960-2644; Most Sirajum Munira 0000-0002-4691-1550; Farshid Radparvar 0000-0001-9631-9208; Vincent Rizzo 0000-0002-5530-447X; Ahmed Daoud 0000-0001-6311-3887.

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MINIREVIEWS

In memoriam of Thomas Earl Starzl, the pioneer of liver transplantation

Sezai Yilmaz, Sami Akbulut

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Sezai Yilmaz, Sami Akbulut, Surgery and Liver Transplant Institute, Inonu University, Malatya 44280, Turkey

Corresponding author: Sami Akbulut, MD, PhD, Professor, Surgery and Liver Transplant Institute, Inonu University, Elazig Yolu 10. Km, Malatya 44280, Turkey.
akbulutsami@gmail.com

Abstract

Starzl's nearly 3000 publications that contribute to the science of transplantation in every field have been the most important resources for every scientist working in this field. For those of us who work in the liver transplant field, his contributions throughout his life have shaped our career and passion, even for those who have never met, spoken to, or worked with him. If we are able to help patients with liver failure today by offering them the chance of transplantation, it is because of Starzl's passionate work and efforts. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life. It has been an honor for us to write this article about Professor Starzl.

Key Words: Liver transplantation; Thomas Earl Starzl; Pioneer of liver transplantation

Core Tip: Starzl's nearly 3000 publications that contribute to the science of transplantation in every field have been the most important resources for every scientist working in this field. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life thanks to this legacy. It has been an honor for us to write this article about Professor Starzl.

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INTRODUCTION

Thomas Earl Starzl was born March 11, 1926, in LeMars, Iowa[1]. He received his medical degree from Northwestern University[1]. He worked at the University of Colorado as a surgeon from 1962 until 1981. Thomas Earl Starzl, MD, PhD, a surgeon who was a pioneer of liver transplantation (LT) died at the age of 91 years on Saturday, March 4, 2017 at his home in Pittsburgh, Pennsylvania[1,2]. Starzl is called "the Father of Modern Transplantation"[1-3]. Starzl's death deeply saddened all liver transplant surgeons around the world. A better understanding Professor Starzl, requires mentioning his biography and the first liver transplant.

He performed the world's first liver transplant in Denver on March 1, 1963 in a child, named Bennie Solis[4,5]. Bennie Solis belonged to a Spanish American family, and suffered from biliary atresia. Bennie's donor was another child who died during open heart surgery. The donor was already on a heart-lung machine for artificial circulation and the body temperature was cooled for organ preservation until the family gave consent for donation of the liver. Starzl and colleagues had performed nearly two hundred LTs in dogs. It took several hours just to make the incision and enter the abdominal cavity. Dissection was very difficult due to high-pressure venous collaterals as a result of portal hypertension. Previous operations resulted in highly vascularized and rough scar tissue that encased the liver. Bennie also had severe coagulopathy. Pharmaceutical or other human-derived factors that should have been used to prevent hemorrhage and deficiency of coagulation factor were not easily available. Bennie bled to death as Starzl tried everything to stop the hemorrhage. The transplantation could not be performed. Despite the fact that Bennie was three years old, he spent every day of his short life in agony. When his wound was closed and his body was washed and prepared the surgical team burst into tears. Starzl and his team remained in the operating room for a long time without saying a word. Starzl has always stated "it was not the last time that I would see this scene, both in my dreams and in reality". Ever since, I have not heard anybody describe it as a case of Solis or the first human LT.

The efforts made during the process of initiating kidney transplants in research laboratories should now be made for LT which is a more difficult procedure. The main lesson to be learned from Bennie Solis's surgery was dealing with the clotting problems in severe liver disease. An expert named Von Kaulla who was working on the coagulation pathway at the time was recruited to the team. Von Kaulla made important contributions such as the definition of fibrinolysis and recommending the use of epsilon amino caproic acid and specific coagulation agents in LT[6]. Moreover, the prompt transplantation of a well-functioning liver graft was essential.

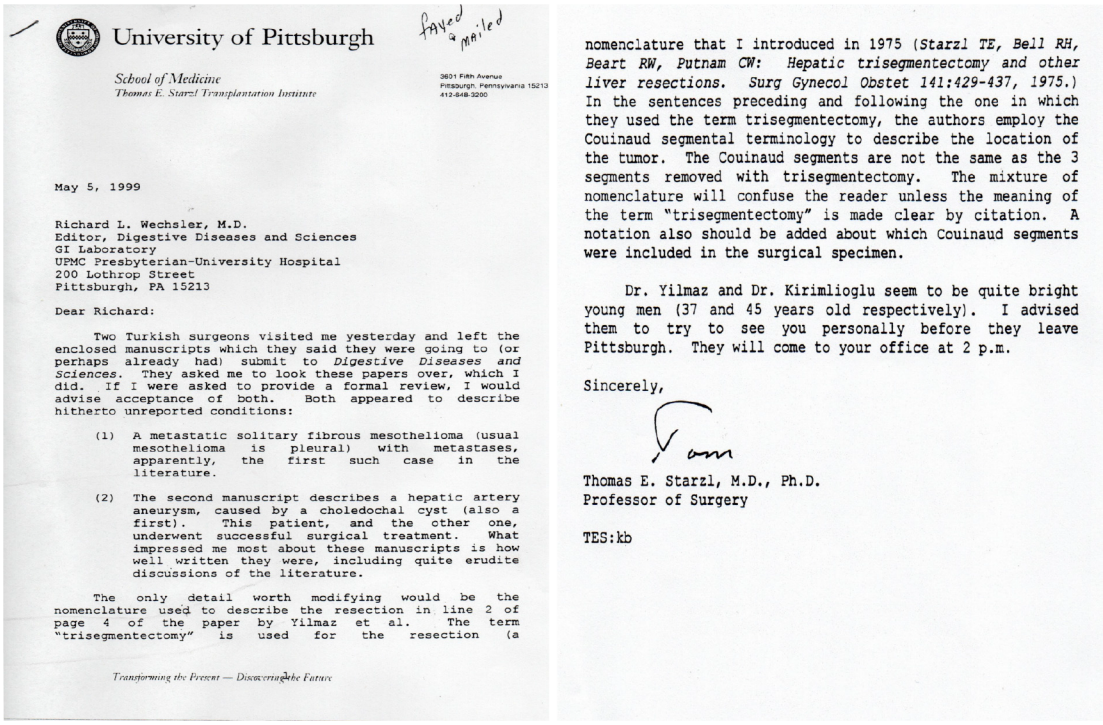
After the first 7 unsuccessful liver transplants (5 were performed by Starzl), a voluntary moratorium was declared that lasted for 3.5 years. Starzl then performed the first successful liver transplant in 1967 with long-term survival, after having experienced this battle many times and having been defeated in each time[7]. An 19-mo-old girl named Julie Rodriguez underwent LT for hepatoblastoma. Julie lived 400 d and unfortunately passed away due to metastatic recurrence of her tumor.

In 1968, the liver transplant program at the University of Colorado was bolstered by the liver transplant program initiated by Roy Calne at Cambridge University. Starzl particularly emphasized the following statements "the fate of liver transplantation would depend on an unspoken transatlantic alliance between Cambridge and Denver". Calne has made undeniable contributions related to the use of 6-mercaptopurine, azathioprine, and cyclosporine in transplantation[8,9].

Professor Starzl then went to the University of Pittsburgh which became the busiest transplant center in the world. In 1996, the transplant institute was renamed in Starzl's honor. Starzl combined azathioprine and prednisone as a strategy that made renal allograft transplantation possible. He repeated the same steroid strategy to improve the success of LT. Starzl pioneered the use of cyclosporine in the 1970s and tacrolimus in the 1990s[10-12]. The success of these treatments has revolutionized all organ transplants. Starzl performed baboon-to-human liver xenotransplantation in 1992[13]. This patient lived 72 d. It was also a milestone for future generations. Thomas Starzl's worked on organ preservation, abdominal multi-visceral transplantation, chimerism or immunotolerance are all revolutionary advances in the field of transplantation[14]. Thanks to his work, the National Institutes of Health's consensus report stated that liver transplant is now an acceptable treatment for end-stage liver disease.

Special comment (Professor Sezai Yilmaz)

I would like to briefly talk about my story regarding Professor Starzl. In the last months of 1998, I was assigned to University of Pittsburgh Medical Center (UPMC) as a visiting research fellow to initiate the LT program at Inonu University as a general and gastrointestinal surgery specialist. The director of the UPMC Thomas Starzl Transplantation Institute at that time was Professor John Fung. I received great help from Professor John Fung and transplantation surgery fellow Dr Daniel Katz during the registration and initial periods of my clinical work. This is how I met Starzl: Dr Vedat Kirimlioglu, my colleague from Malatya Inonu University had come to Pittsburgh for a period of one month. We made an appointment with Starzl's secretary and went to visit him. It was actually a courtesy visit. Dr Kirimlioglu presented embroidered copper gifts to Professor Starzl, which were local art items he had brought from Turkey. I presented the dried apricots and pistachios that I planned to give to Starzl and Fung on my way from Malatya. In his 2-storey wooden office located on Fifth Avenue, opposite UPMC



University of Pittsburgh

faxed & mailed

School of Medicine
Thomas E. Starzl Transplantation Institute

3601 Fifth Avenue
Pittsburgh, Pennsylvania 15213
412-648-9200

May 5, 1999

Richard L. Wechsler, M.D.
Editor, Digestive Diseases and Sciences
GI Laboratory
UPMC Presbyterian-University Hospital
200 Lothrop Street
Pittsburgh, PA 15213

Dear Richard:

Two Turkish surgeons visited me yesterday and left the enclosed manuscripts which they said they were going to (or perhaps already had) submit to *Digestive Diseases and Sciences*. They asked me to look these papers over, which I did. If I were asked to provide a formal review, I would advise acceptance of both. Both appeared to describe hitherto unreported conditions:

(1) A metastatic solitary fibrous mesothelioma (usual mesothelioma is pleural) with metastases, apparently, the first such case in the literature.

(2) The second manuscript describes a hepatic artery aneurysm, caused by a choledochal cyst (also a first). This patient, and the other one, underwent successful surgical treatment. What impressed me most about these manuscripts is how well written they were, including quite erudite discussions of the literature.

The only detail worth modifying would be the nomenclature used to describe the resection in line 2 of page 4 of the paper by Yilmaz et al. The term "trisegmentectomy" is used for the resection (a nomenclature that I introduced in 1975 (*Starzl TE, Bell RH, Beart RW, Putnam CW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429-437, 1975.*) In the sentences preceding and following the one in which they used the term trisegmentectomy, the authors employ the Couinaud segmental terminology to describe the location of the tumor. The Couinaud segments are not the same as the 3 segments removed with trisegmentectomy. The mixture of nomenclature will confuse the reader unless the meaning of the term "trisegmentectomy" is made clear by citation. A notation also should be added about which Couinaud segments were included in the surgical specimen.

Dr. Yilmaz and Dr. Kirimlioglu seem to be quite bright young men (37 and 45 years old respectively). I advised them to try to see you personally before they leave Pittsburgh. They will come to your office at 2 p.m.

Sincerely,

Thomas E. Starzl, M.D., Ph.D.
Professor of Surgery

TES:kb

Transforming the Present — Discovering the Future

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Figure 1 Letter from Professor Starzl to the editor of Digestive Diseases and Sciences (original version).

Presbyterian Hospital, he welcomed us with his secretary and his dog. We spent a very long and pleasing time together that day. He offered us coffee. We even talked about the Bosnian War, which was taking place in those years. Afterwards, we sat outside on the terrace and even took pictures there with the three of us and his dog. Later, I stated that I had prepared two medical articles and wanted to get his comments on them. Starzl took the printed-out articles and said he would evaluate them. We said goodbye to him and left. Early the next day, while I was at my home, I received a phone call from Starzl's secretary who said that Starzl was waiting for me in the office at 1:00 pm. I was so surprised. I quickly got ready and went first to the hospital and then to Starzl's office. He greeted me again with a smile and said that he liked my articles. He told me that I needed to make some corrections regarding hepatectomy terminology. He gave me a letter and asked me to forward it to Richard Wechsler at the Gastrointestinal Laboratory a few hundred yards away. I left after thanking him. The envelope was open. The letter consisted of 2 separate pages and had 2 copies. He probably made a copy for me. It was there that I learned that Richard L. Wechsler was the editor of Digestive Diseases and Sciences. When I got to Wechsler's office, he immediately accepted me. I realized that Starzl had already talked to Wechsler about me. I handed him the letter and had a coffee then left. I read the letter line by line without missing a word. I would like to summarize Starzl's statements.

"Two Turkish surgeons visited me yesterday and left the enclosed manuscripts. They asked me to review these papers, which I did. If I were asked to provide a formal review, I would advise acceptance of both. Both appeared to describe hitherto unreported conditions (metastatic solitary fibrous tumor of liver and hepatic artery aneurysm caused by choledochal cyst). Dr Yilmaz and Dr Kirimlioglu seem to be quite bright young men (37 and 45 years old, respectively)" (Figure 1). Both these articles were published in the first issue of Digestive Diseases and Sciences[15,16]. This was an unforgettable moment for me and I was faced with the image of an exemplary scientist-mentor. Later, I met Starzl several times while visiting his transplant ward and at interesting coffee shops in Pittsburgh during those years. I have always seen his kind, loving and affectionate personality.

CONCLUSION

In conclusion, Professor Starzl's nearly 3000 publications that contribute to the science of transplantation in every aspect and has been the most important resources for every scientist working in this area. For those of us who work in the liver transplant field, his lifetime contributions have defined our career and passion. Even for those individuals who have never met, talked to, or worked with him are affected by this work and efforts. If we can help patients with liver failure today by offering them the chance of LT, this is because of the passionate work and efforts of Starzl. Thanks to Starzl's scientific legacy, hundreds of scientists serve humanity and thousands of patients can hold on to life. It has been an honor for us to

write this article about Professor Starzl.

FOOTNOTES

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ORCID number: Sezai Yilmaz 0000-0002-8044-0297; Sami Akbulut 0000-0002-6864-7711.

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MINIREVIEWS

Autoimmune hepatitis and liver transplantation: Indications, and recurrent and *de novo* autoimmune hepatitis

Murat Harputluoglu, Ali Riza Caliskan, Sami Akbulut

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Murat Harputluoglu, Department of Gastroenterology and Transplant Hepatology, Inonu University Faculty of Medicine, Malatya 44280, Turkey

Ali Riza Caliskan, Department of Gastroenterology, Adiyaman Education and Research Hospital, Adıyaman 04120, Turkey

Sami Akbulut, Liver Transplant Institute, Inonu University, Malatya 44280, Turkey

Corresponding author: Sami Akbulut, MD, PhD, Professor, Liver Transplant Institute, Inonu University, Elazig Yolu 10. Km, Malatya 44280, Turkey. akbulutsami@gmail.com

Abstract

Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. Liver transplantation may be required for patients with acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma. Recurrence is defined as development of the same disease in the allograft following liver transplantation. Autoimmune hepatitis recurs in 36%-68% of the recipients 5 years after liver transplantation. *De novo* autoimmune hepatitis is the development of autoimmune hepatitis like clinical and laboratory characteristics in patients who had undergone liver transplantation for causes other than autoimmune hepatitis. Diagnostic work up for recurrent and *de novo* autoimmune hepatitis is similar to the diagnosis of the original disease, and it is usually difficult. Predniso(lo)ne with or without azathioprine is the main treatment for recurrent and *de novo* autoimmune hepatitis. Early diagnosis and treatment are vital for patient prognosis because *de novo* autoimmune hepatitis and recurrent autoimmune hepatitis cause graft loss and result in subsequent retransplantation if medical treatment fails.

Key Words: Liver transplantation; Autoimmune hepatitis; Recurrence autoimmune hepatitis; *De novo* autoimmune hepatitis

Core Tip: Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. Liver transplantation may be required for patients with acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma. *De novo* autoimmune hepatitis and recurrent autoimmune hepatitis are known causes of late graft dysfunction following liver transplantation which should be included in the differential diagnosis.

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INTRODUCTION

Autoimmune hepatitis is a chronic inflammatory disease of the liver that is characterized by circulating autoantibodies and elevated serum globulin levels. This disease may manifest as elevated liver transaminases, acute hepatitis, cirrhosis or acute liver failure[1]. Autoimmune hepatitis is classified into types 1 and 2. Patients with positive antinuclear antibody (ANA) and/or anti-smooth muscle antibody (anti-SMA) are classified as type 1, whereas type 2 is defined by the presence of anti-liver-kidney microsomal type 1 antibody (anti-LKM-1) or anti-liver cytosol type 1 antibody (anti-LC-1) positivity. Autoimmune hepatitis is mainly treated with immunosuppressive drugs such as glucocorticoids and azathioprine (AZA). In this review, indications for liver transplantation in patients with autoimmune hepatitis and the diagnosis and treatment of recurrent autoimmune hepatitis after liver transplantation are discussed. Additionally, *de novo* autoimmune hepatitis, which can be seen in patients who have received liver transplantation for indications other than autoimmune hepatitis, are discussed.

Indications for liver transplantation for patients with autoimmune hepatitis

Liver transplantation may be indicated for patients with autoimmune hepatitis if one of the following conditions are present: (1) Acute liver failure; (2) Decompensated cirrhosis (Model for End-Stage Liver Disease score ≥ 15); or (3) Hepatocellular carcinoma. Liver transplantation may be required if there is a failure to diagnose and treat autoimmune hepatitis, inadequate response or intolerance to immunosuppressive therapy, or if the patients are not compliant with the treatment. Ultimately, 10%-20% of patients with autoimmune hepatitis eventually need liver transplantation[2,3].

Autoimmune hepatitis accounts for approximately 5% and 2%-3% of liver transplants in the United States and Europe, respectively[4,5]. The frequency of acute and chronic rejection after liver transplantation for autoimmune hepatitis is more frequent compared to other liver diseases[6]. Five-year patient and graft survivals for autoimmune hepatitis are reported to be 80%-90% and 72%-74%, respectively[7].

Clinical manifestations associated with autoimmune hepatitis after liver transplantation

Recurrence of autoimmune hepatitis after liver transplantation: Recurrence is defined as reappearance of the disease in the liver allograft. Autoimmune hepatitis recurs in 8%-12% of patients within the first year and 36%-68% within 5 years following liver transplantation[6]. Recurrent autoimmune hepatitis frequency is not significantly affected by the graft type (either living related or cadaveric)[8]. Diagnostic workup of recurrent autoimmune hepatitis is similar to diagnosing the original disease and it is equally challenging. The main reason for the complexity in diagnosis is the absence of a specific marker for diagnosis. In addition, immunosuppressive therapy may mask some features of the original disease. The disease progression may differ and may lead to an atypical presentation. Transplant recipients with recurrence of autoimmune hepatitis usually have elevated transaminases, fever, fatigue, jaundice, abdominal pain, skin rash, and joint pain upon presentation[9]. Nevertheless, the presentation of recurrence of autoimmune hepatitis is not specific and can be seen in other complications of liver transplantation. Hypergammaglobulinemia is defined as increased serum IgG levels, and together with positivity of ANA and SMA, make up the serological findings of the disease. The pathophysiology of recurrent autoimmune hepatitis is not comprehensively understood and is similar to the mechanisms involved in the development of classical autoimmune hepatitis. The main histopathological feature of recurrent autoimmune hepatitis is prominent lymphocytic interface activity with or without plasma cell infiltration. Other pathological findings are acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells, pseudo-rosetting of hepatocytes, perivenular lymphoplasmacytic inflammation, and confluent and bridging necrosis with lymphoplasmacytic infiltration (severe inflammatory activity)[10]. Cellular and antibody-mediated forms of cytotoxicity are involved in the pathogenesis of the disease. These features may be less evident or absent in certain instances. The differential diagnoses include rejection, drug hepatotoxicity, *de novo* steatohepatitis, and viral hepatitis,

including hepatitis E. The diagnosis is performed by excluding other possible etiologies.

Many risk factors such as the effects of immunosuppressive therapy as well as recipient- and donor-related factors play an important part in the recurrence of autoimmune hepatitis in the liver allograft. Early corticosteroid withdrawal for reasons such as nonadherence or physician recommendation, high titers of autoantibodies at the time of liver transplantation, coexisting autoimmune disorders, association of human leukocyte antigen (HLA)-DR3 and HLA-DR4 mismatch, and severe necroinflammatory activities in the explant liver at the time of liver transplantation are some of the reported risk factors of recurrence[9]. Figure 1 summarizes the factors implicated in the development of recurrent autoimmune hepatitis.

Recurrent autoimmune hepatitis needs prompt treatment because nearly half of cases are resistant to therapy and result in graft failure. Treatment is usually empirical. In mild cases, only increasing compliance with immunosuppressive therapy and increasing immunosuppressive doses are sufficient. In severe cases, predniso(lo)ne (30 mg/d) and AZA (1-2 mg/kg/d) are required. The combination of corticosteroids and mycophenolate mofetil (MMF) may also be the initial therapeutic approach[6]. When laboratory values improve, the dose of corticosteroids is tapered to 5-10 mg within 1-2 mo[9,11]. Patients who do not respond to this combination are considered for other immunosuppressive agents such as calcineurin inhibitors or inhibitors of mammalian target of rapamycin. In cases with severe liver failure, retransplantation may be required. It has been reported that retransplantation is required in 33%-60% of patients with recurrent autoimmune hepatitis[6,12,13].

***De novo* autoimmune hepatitis:** *De novo* autoimmune hepatitis is the development of autoimmune hepatitis in patients who underwent liver transplantation for reasons other than autoimmune hepatitis. In its latest update, the Banff Working Group for liver allograft pathology proposed replacing the term *de novo* autoimmune hepatitis with plasma cell-rich rejection[14]. *De novo* autoimmune hepatitis is more common in children than in adults (5%-10% *vs* 1%-3%)[6,11]. Clinical findings in *de novo* autoimmune hepatitis are similar to those observed in recurrent autoimmune hepatitis and autoimmune hepatitis. Serum aspartate aminotransferase, alanine aminotransferase, and IgG levels are high. One of the most striking features of *de novo* autoimmune hepatitis is detection of newly developed autoantibodies. Patients with *de novo* autoimmune hepatitis may have ANA, antimitochondrial antibody, anti-SMA antibodies and also anti-LKM-1, anti-LC, antibodies to gastric parietal cells, and atypical anti-liver/kidney cytosolic antibody targeting the antigen glutathione-S-transferase T1 (GSTT1) may be positive. The main histological feature in *de novo* autoimmune hepatitis is interface hepatitis with lymphocytes and plasma cells. Other histopathological features are spotty necrosis, portal fibrosis, and bile duct injury[15].

Older donors, the mismatch of GSTT1 genotype of donor and recipient, the use of antilymphocyte antibodies, treatment with tacrolimus or MMF are associated with a higher risk of *de novo* autoimmune hepatitis[16]. Cyclosporine A and granulocyte colony-stimulating factor treatment is reported to be protective against *de novo* autoimmune hepatitis. The pathogenesis of *de novo* autoimmune hepatitis is still unknown. Although it has been suggested that antibodies against GSST1 antigen may play a role in the development, it may also develop in the absence of these antibodies. Therefore, the role of antibodies against GSST1 antigens in pathogenesis is not fully established. One of the possible mechanisms for the development of *de novo* autoimmune hepatitis is the release of autoantigens from the damaged tissue during reperfusion which exacerbates the autoimmune response after liver transplantation. Other possibilities are due to molecular similarities; in other words, exposure to microorganisms that share amino acid sequences with autoantigens causing crossreactive immunity. In fact, viral infections (which are common after transplantation) can cause autoimmunity by various mechanisms[17]. In addition, interferons used for hepatitis C have potent immunomodulatory effects and can trigger autoimmune disorders in immunosuppressive patients. Today, since interferon-free treatment regimens are used in the treatment of hepatitis C after liver transplantation, hepatitis C patients are now safer in terms of the risks of interferon after transplantation.

While the results of treatment of *de novo* autoimmune hepatitis are promising, poor outcomes such as cirrhosis and graft loss can be seen if these patients are not treated properly. Therefore, early diagnosis and treatment of this disease has paramount importance. Predniso(lo)ne with or without AZA continues to be the mainstay of treatment for *de novo* autoimmune hepatitis. If there is no response to these agents, then MMF can be given instead of AZA[11].

Long-term use of corticosteroids after liver transplantation

The risk of acute and chronic rejection in patients undergoing liver transplantation for autoimmune hepatitis is higher than in patients who are transplanted for other indications. Corticosteroids may prevent development of rejection or relapse on the long term however, usually they are tapered to reduce the risk of infections and adverse effects of steroids. Corticosteroids have many side effects, including infection, depression, osteoporosis, diabetes, hypertension and adrenal suppression, which significantly affect the quality of life in recipients following liver transplantation[18]. The issue of how long corticosteroids should be given to prevent rejection and relapse in patients with autoimmune hepatitis remains a controversial issue. There have been few studies on the long-term administration of corticosteroids after transplantation in autoimmune hepatitis patients. In a study involving 73 patients

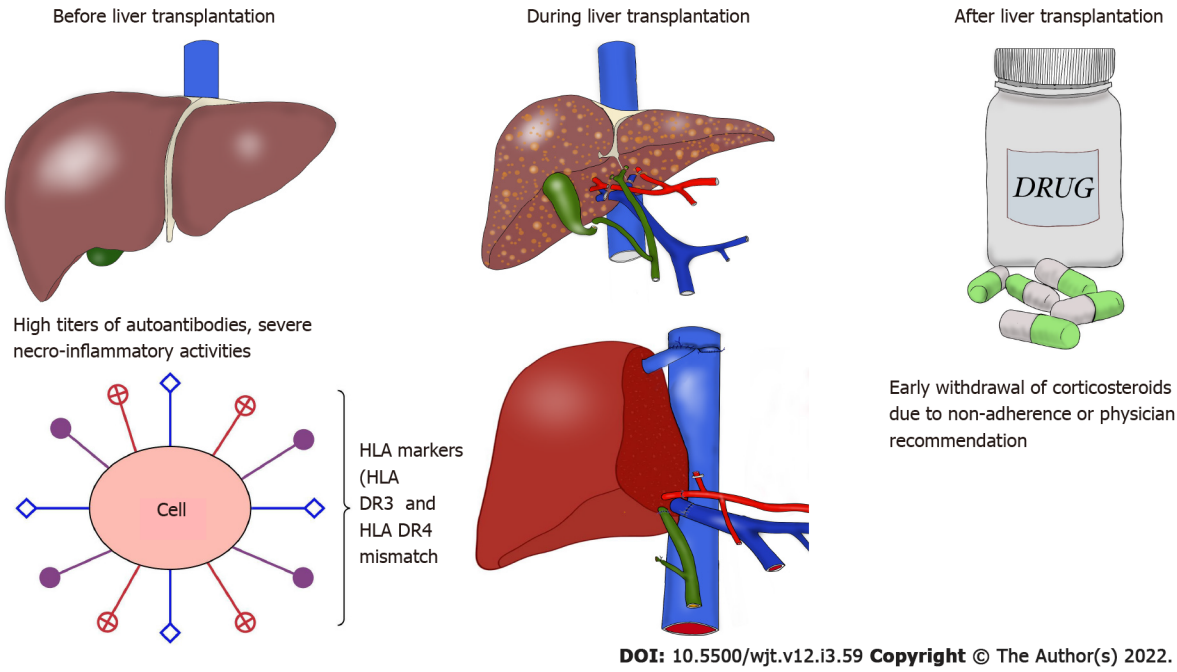

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Figure 1 Summary of the factors implicated in the development of recurrent autoimmune hepatitis after liver transplantation. HLA: Human leukocyte antigen.

with autoimmune hepatitis who underwent liver transplantation, it has been shown that long-term treatment with low-dose corticosteroid in combination with other immunosuppressive medication reduced recurrence rates of autoimmune hepatitis[19]. The recent American Association for the Study of Liver Diseases (AASLD) guidelines emphasize that the data supporting the long-term administration of corticosteroids to prevent post-transplant rejection, graft loss and recurrent autoimmune hepatitis are limited and the treatment is not justified. Therefore, AASLD suggested corticosteroids should be gradually tapered in following liver transplantation[6]. The latest European Association for the Study of the Liver guidelines regarding autoimmune hepatitis do not provide a clear recommendation on how long corticosteroids should be given after transplantation[20].

Another alternative approach is meticulous selection of patients that are at high risk of recurrence and who may benefit from intensified immunosuppression. This group of patients should receive long-term steroids. Steroids should be tapered gradually with close follow-up, if the risk of recurrence is low and long-term steroid administration would cause additional problems in the patients such in patients with diabetes, hypertension, hyperlipidemia and osteoporosis[21].

Until a specific marker is developed or standardization of the diagnosis of recurrent or *de novo* autoimmune hepatitis is developed, steroids will always be an important part of treatment and duration of steroid use will always be a matter of debate.

CONCLUSION

De novo autoimmune hepatitis and recurrent autoimmune hepatitis are known causes of late graft dysfunction in pediatric and adult liver transplantation. In liver transplant recipients with graft dysfunction, recurrent or *de novo* autoimmune hepatitis should always be considered in differential diagnosis. Early diagnosis and intervention are vital in *de novo* and recurrent autoimmune hepatitis because they cause graft loss and subsequent re-transplantation if they are not treated properly.

FOOTNOTES

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Country/Territory of origin: Turkey

ORCID number: Murat Harputluoglu 0000-0002-9415-147X; Ali Riza Caliskan 0000-0003-3187-8548; Sami Akbulut 0000-0002-6864-7711.

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Peer Reviewer of *World Journal of Transplantation*, Ahmed M Halawa, MD, MSc, PhD, FRCSEd, FRCS (Gen), Associate Professor, University of Liverpool, Institute of Life Course and Medical Science, School of Medicine, Liverpool L69 3GE, United Kingdom. ahmed.halawa@liverpool.ac.uk

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CASE REPORT

Renal transplantation in gigantism: A case report

Jeevan Prakash Gopal, Sotirios Charalampidis, Jinpo Xiang, Frank J M F Dor, Vassilios E Papalois

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Jeevan Prakash Gopal, Sotirios Charalampidis, Frank J M F Dor, Vassilios E Papalois, Imperial College Renal and Transplant Center, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, United Kingdom

Jinpo Xiang, Imperial College School of Medicine, Imperial College, London W12 0HS, United Kingdom

Frank J M F Dor, Vassilios E Papalois, Department of Surgery and Cancer, Imperial College, London W12 0HS, United Kingdom

Corresponding author: Jeevan Prakash Gopal, MBBS, MS, Surgeon, Imperial College Renal and Transplant Center, Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London W12 0HS, United Kingdom. jeevan.gopal@nhs.net

Abstract

BACKGROUND

Gigantism, characterized by excessive growth and height is due to increased secretion of growth hormone, most commonly from a pituitary adenoma. In addition to the surgical and anesthetic complexity, the extreme stature of these patients presents a unique challenge for kidney transplantation in deciding whether to proceed with a single or dual kidney transplantation. The lack of relevant literature further adds to the dilemma.

CASE SUMMARY

A 45-year-old patient with untreated gigantism and end stage renal failure on renal replacement therapy was waitlisted for a deceased donor dual kidney transplantation due to the extreme physical stature (Height-247 cm and weight-200 kg). He was offered 2 kidneys from a 1-0-1 HLA mismatched 24-year-old DCD donor (Height-179 cm and weight-75 kg), and was planned for a bilateral retroperitoneal implantation into the recipient external iliac vessels. The immunosuppression consisted of alemtuzumab induction (50 mg) and steroid-free maintenance with tacrolimus. The donor's right kidney was uneventfully implanted extra-peritoneally into the right external iliac vessels. On contralateral exposure, the left common and external iliac arteries were ectatic and frail. A complex vascular reconstruction was not preferred in order to preserve the arterial supply to the left lower limb, to minimise the cold ischemia time and prevent additional warm ischemic insult to the second kidney. Hence, it was decided not to proceed with dual transplantation. Amidst concerns of nephron mass insufficiency, the graft function was remarkable with a serum creatinine of 120 μmol/L within a month from transplantation and 94 μmol/L at 1-year post transplantation, and without proteinuria.

CONCLUSION
To our knowledge, this is the first case report on kidney transplantation in gigantism. Although it is believed that dual kidney transplantation is ideal, a single kidney transplantation from an appropriately selected donor can provide sufficient functioning nephron mass in patients with gigantism.

Key Words: Gigantism; Giantism; Renal transplantation; Kidney transplantation; Pituitary adenoma; Case report

Core Tip: We report a patient with untreated pituitary gigantism with end stage renal failure due to IgA nephropathy with secondary focal segmental glomerular sclerosis who underwent a successful deceased donor kidney transplantation. We have described the intra-operative challenges in deciding whether to proceed with a single kidney transplantation or dual kidney transplantation. To the best of our knowledge this is the first case report on kidney transplantation in gigantism.

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INTRODUCTION

Gigantism is a disorder resulting from increased growth hormone secretion before the fusion of growth plate, most often due to a pituitary adenoma and is characterized by excessive growth and height. In addition to the surgical and anesthetic complexity, the extreme stature of these patients presents a particular challenge for kidney transplantation in deciding whether to proceed with a single or dual kidney transplantation. So far there is no literature on kidney transplantation in patients with gigantism. To our knowledge, we are the first to report a patient with untreated pituitary gigantism characterized by uniquely extreme physical size and stature who underwent a successful kidney transplantation for end stage renal failure and discuss the dilemmas involved in his management.

CASE PRESENTATION

Chief complaints

Our patient, a 45-year-old African male presented with end stage renal failure and was awaiting a kidney transplant.

History of present illness

The end stage renal failure was due to IgA nephropathy which was biopsy proven and with secondary focal segmental glomerular sclerosis. He was established on haemodialysis.

History of past illness

He was diagnosed in his early teenage years to have pituitary gigantism but was left untreated.

Personal and family history

There were no relevant histories.

Physical examination

His physical stature [Height = 247 cm, weight = 200 kg, body mass index (BMI) was 33 kg/m^2, and body surface area (BSA) with the DuBois formula = 3.7 m^2], was twice than the normal upper limit.

Laboratory examinations

The laboratory investigations were not relevant apart from deranged kidney function due to end stage renal failure.

Imaging examinations

A pre-transplant computed tomography (CT) scan of the abdomen and pelvis showed normal iliac vessels bilaterally.

Multidisciplinary expert consultation

There was a therapeutic dilemma as to whether a single kidney transplantation would be sufficient for a patient of his body surface to alleviate his kidney failure to a degree that would not require further renal replacement therapy. With the above dilemma into consideration the patient was added to the United Kingdom deceased donor kidney transplant waiting list for dual kidney transplantation from a single deceased donor after discussion in our multidisciplinary team (MDT) meeting and approval by the NHS Blood and Transplant's Kidney Advisory Group.

Transplant characteristics

Less than a year after being waitlisted and after having received a few offers from extended criteria donors that were deemed unsuitable, the patient received and accepted a deceased donor dual kidney transplant offer from a 24-year-old male donation after circulatory death (DCD) donor who suffered irreversible hypoxic brain injury following a road traffic accident. The donor's past medical history was insignificant and had normal kidney function. His height was 179cm, weight was 75kgs, BMI was 23 kg/m^2, and BSA with the DuBois formula was 1.9 m^2 (almost half of our prospective recipient). Furthermore, there was a 1-0-1 HLA mismatch between the donor and recipient, the latter of which had a calculated reaction frequency of 0% (and therefore only a virtual crossmatch was performed). Immunosuppression consisted of induction with a depleting monoclonal antibody, alemtuzumab (50 mg) and steroid-free maintenance with tacrolimus as the only immunosuppressant. The organ retrieval in the donor hospital was uneventful.

Customised anaesthetic protocol

For the recipient, a customised anaesthetic protocol was implemented based on previous general anaesthetic experience with the patient. He was ventilated using a large (size 6) oropharyngeal airway and a large (size 6) face mask. A long Macintosh blade and size 10 endotracheal tube was used for intubation. Patient was anaesthetized on a hover mattress to enable safe transfer to the operating table, which can take up to 300 kgs body weight. The only issue was the patient's height; two table extensions were added to the operating table on either side and an instrument trolley was used to support the feet (Figure 1).

FINAL DIAGNOSIS

A bilateral extraperitoneal implantation in to the recipient's external iliac vessels was chosen as the preferred implantation technique. Initially the patient's right external iliac vessels were exposed and an uneventful implantation of the donor's right kidney was successfully completed with intraoperative urine production from the transplanted kidney. The cold ischemia time was 9 h and 52 min. On subsequent exposure of the recipient's contralateral iliac fossa, the left common and external iliac arteries were noted to be significantly ectatic and frail, which was not apparent from the pre-operative CT scan. In addition there were abnormal intraoperative Doppler signals (monophasic signals).

TREATMENT

Implanting the donor's left kidney in to the right common/internal iliac vessels was one of the options, but it would involve clamping the right common iliac artery which would potentially add an additional ischemic insult to the transplanted kidney. Implanting the donor's left kidney into the left internal iliac vessels or intra-peritoneal implantation into the aorta/inferior vena cava were the other options. In order not to further extend the duration of the procedure and the resultant cold ischemia time by performing a complex vascular reconstruction/implantation with potential compromise to the arterial supply of the recipient's left lower limb and in view of the already completed successful single kidney implantation of the donor's right kidney, the decision was made to not to proceed with the dual kidney implantation. The donor kidney was of average size without having taken proper measurements. According to the national allocation policy of NHS Blood and Transplant, the donor's left kidney was subsequently offered to another patient on the waiting list.

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Figure 1 Operating table with extensions on either side and an instrument trolley at both the foot end and head side.

OUTCOME AND FOLLOW-UP

The patient was extubated at the end of the operation and was cared in intensive care unit for one day and subsequently stepped down to our high dependency unit. There was primary graft function and following an overall uneventful recovery, he was discharged from the hospital at day 15, with an improving estimated glomerular filtration rate (eGFR) of 44 mL/min/1.73 m^2. Following discharge, his serum creatinine continued to improve to 120 μmol/L within a month from the procedure. His serum creatinine remained stable throughout the first year post-transplant and without proteinuria (Figure 2).

DISCUSSION

Although giants are depicted in literature as individuals with lionized capabilities, the description of patients with gigantism in medical literature is very limited due to the rarity of the condition. Overproduction of growth hormone by a pituitary adenoma or pituitary hyperplasia can lead to pituitary gigantism. They can be either sporadic or can occur as a part of several genetic disorders such as multiple endocrine neoplasia type 1, McCune-Albright syndrome and carney complex[1-5]. There is no bibliographic report of pituitary gigantism patients that required renal transplantation for end stage renal failure.

The underlining challenge in such patients with extreme stature is to ensure that the physiological capacity and the functioning nephron mass of the donor organ can meet the increased metabolic needs of this unique recipients so to alleviate their need for renal replacement therapy and have a significant positive impact on their overall health, quality of life, and life expectancy. Recent studies have confirmed that the graft kidney volume/recipient BSA ratio along with the donor age and recipient's gender are independent predictors of recipient GFR in the early post-transplant period[4-6]. Considering the above concern, the option of synchronous dual deceased kidney transplantation in such extreme stature patients seems reasonable and needs to be considered at the time of wait listing them for a deceased donor kidney transplant and weighted against depriving the second graft from another potential recipient given the current scarcity of deceased donor organs.

Although there are some variations between jurisdictions in the allocation policy of kidneys for dual kidney transplantation, the common theme is to allocate kidneys from extended criteria donors for dual transplantation[7]. There was a special consideration for our patient due to his body habitus following MDT discussions and discussions in the national kidney advisory group of NHS Blood and Transplant, and hence was listed for dual kidney transplantation and ultimately received an offer from a young donor. Various implantation techniques have been described for dual kidney transplantation[7]. Although it has been reported that the complication rates for bilateral and unilateral placement of kidneys are similar[8,9], a bilateral extraperitoneal approach was chosen based on the operating surgeon's preference.

Vascular calcifications and atherosclerosis are well established complications of end stage renal failure[10], but it is unusual for isolated arterial aneurysm or ectasia to occur due to renal failure. Despite the intra-operative finding of ectasia and frailty of the left common and external iliac arteries, we still had several options for proceeding with dual kidney transplantation. Implanting the donor's left kidney in to the right common/internal iliac vessels was one of the options, but it would involve clamping the right common iliac artery which would potentially add an additional ischemic insult to the transplanted kidney. Implanting the donor's left kidney into the left internal iliac vessels or intraperitoneal implantation into the aorta/inferior vena cava were the other options. In order not to further extend the duration of the procedure and the resultant cold ischemia time by performing a complex

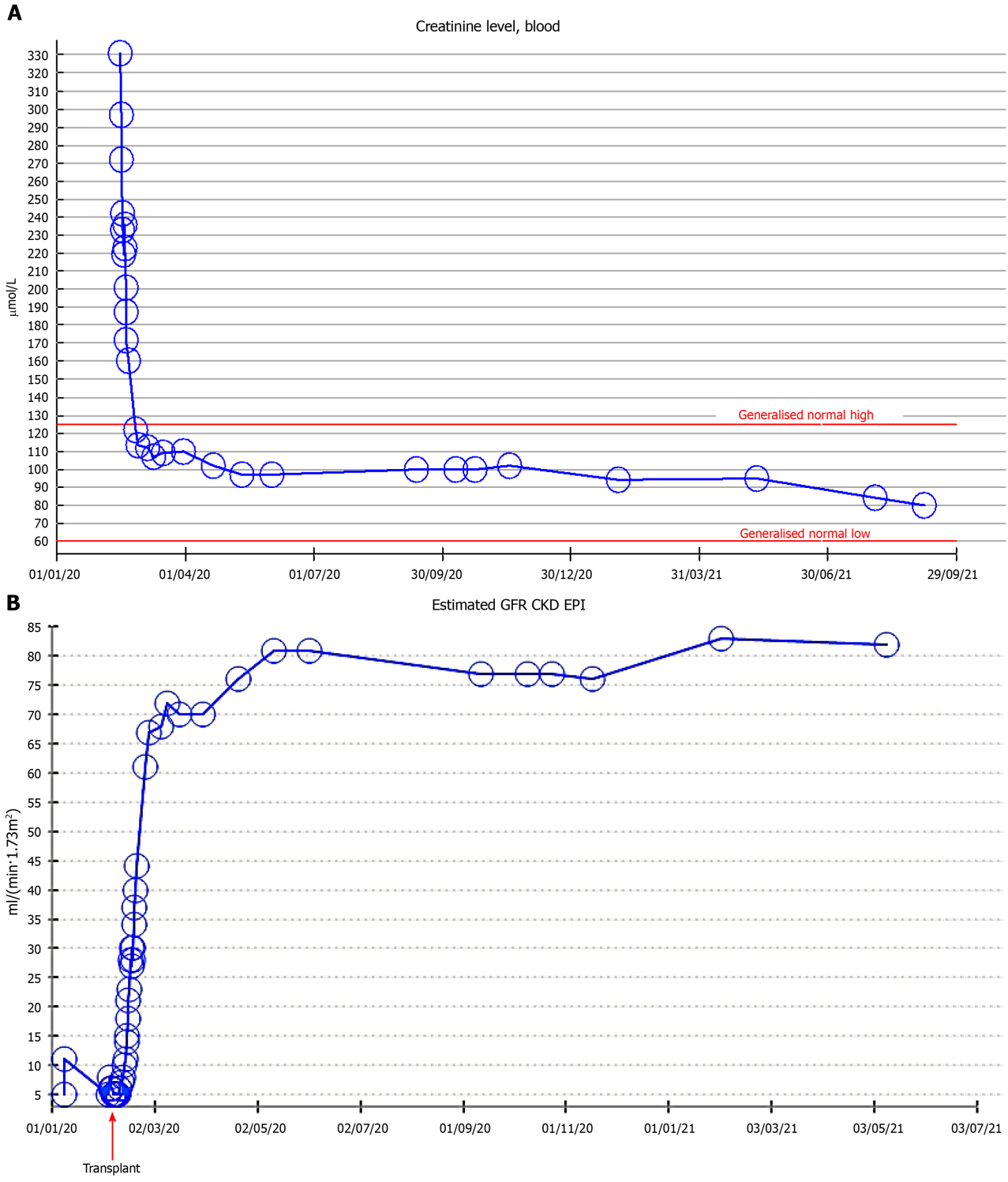

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Figure 2 Serum creatinine and estimated glomerular filtration rate trend post-transplant. A: Serum creatinine; B: Estimated glomerular filtration rate. GFR: Glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration.

vascular reconstruction/implantation with potential compromise to the arterial supply of the recipient's left lower limb and in view of the already completed successful single kidney implantation of the donor's right kidney, the decision was not to proceed with the dual kidney implantation.

Although it has been reported that transplanting small kidneys in to large recipients (donor kidney weight/recipient body weight < 2 g/kg) causes hyperfiltration and results in decreased creatinine clearance and proteinuria 6-months after transplantation[11], in our patient, the single kidney graft has proved sufficient enough to keep him off renal replacement therapy and with normal serum creatinine levels as noted at 1-year post-transplant, and without proteinuria. Additionally, the second kidney from the same deceased donor was eventually implanted to a different recipient in our centre who benefited

from an equally good graft function.

Especially in rare cases such that of our patient with extreme physical stature and significant comorbidities one cannot overemphasize the importance of a detailed preoperative assessment and preparation. There are a few general considerations for people with gigantism undergoing transplantation such as a thorough multidisciplinary work up including anaesthetic pre-assessment before wait listing, the design of a customised anaesthesia protocol, modification of the operating table, and arranging an appropriately sized bed post-operatively. Furthermore, every individual organ offer needs to be assessed for suitability in regards to the donor's past medical history, renal function, age, as well as the body mass index and potentially total kidney volume calculated through any appropriate donor imaging available at the time.

CONCLUSION

This is the first case report on kidney transplantation in gigantism. Although it is believed that dual kidney transplantation is ideal for such patients based on body surface area, a single kidney transplantation from an appropriately selected donor can provide sufficient functioning nephron mass in patients with gigantism.

FOOTNOTES

Author contributions: Gopal JP, Charalampidis S and Xiang J wrote the manuscript; Gopal JP revised the manuscript; Papalois VE performed the transplant; Papalois VE and Dor FJMF made critical corrections to the manuscript; all the authors reviewed and approved the final version.

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Country/Territory of origin: United Kingdom

ORCID number: Jeevan Prakash Gopal 0000-0001-9637-1268; Sotirios Charalampidis 0000-0001-5998-2940; Jinpo Xiang 0000-0001-7612-9028; Frank JMF Dor 0000-0003-2448-7362; Vassilios E Papalois 0000-0003-1645-8684.

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CASE REPORT

Potential importance of early treatment of SARS-CoV-2 infection in intestinal transplant patient: A case report

Mathias Clarysse, Laurens J Ceulemans, Lucas Wauters, Nicholas Gilbo, Viktor Capiau, Gert De Hertogh, Wim Laleman, Chris Verslype, Diethard Monbaliu, Jacques Pirenne, Tim Vanuytsel

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Mathias Clarysse, Nicholas Gilbo, Diethard Monbaliu, Jacques Pirenne, Department of Abdominal Transplant Surgery & Transplant Coordination, University Hospitals Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Mathias Clarysse, Laurens J Ceulemans, Lucas Wauters, Nicholas Gilbo, Diethard Monbaliu, Jacques Pirenne, Tim Vanuytsel, Leuven Intestinal Failure and Transplantation Center (LIFT), University Hospitals Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Mathias Clarysse, Nicholas Gilbo, Diethard Monbaliu, Jacques Pirenne, Laboratory of Abdominal Transplant Surgery, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Laurens J Ceulemans, Department of Thoracic Surgery, University Hospitals Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Laurens J Ceulemans, Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Lucas Wauters, Wim Laleman, Chris Verslype, Tim Vanuytsel, Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Lucas Wauters, Tim Vanuytsel, Translational Research Center for Gastrointestinal Disorders (TARGID), Department Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Viktor Capiau, Gert De Hertogh, Department of Pathology, University Hospitals Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Gert De Hertogh, Laboratory of Translational Cell & Tissue Research, KU Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Chris Verslype, Laboratory of Clinical Digestive Oncology, Department of Digestive Oncology, KU Leuven, Leuven 3000, Vlaams-Brabant, Belgium

Corresponding author: Tim Vanuytsel, MD, MSc, PhD, Associate Professor, Doctor, Senior Researcher, Leuven Intestinal Failure and Transplantation Center (LIFT), University Hospitals Leuven, Herestraat 49, Leuven 3000, Vlaams-Brabant, Belgium. tim.vanuytsel@uzleuven.be

Abstract

BACKGROUND

Predispositions for severe coronavirus disease 2019 (COVID-19) are age, immunosuppression, and co-morbidity. High levels of maintenance immunosuppression render intestinal transplant (ITx) patients vulnerable for severe COVID-19. COVID-19 also provokes several gastroenterological pathologies which have not been discussed in ITx, so far.

CASE SUMMARY

During the second European COVID-19 wave in November 2020, an ITx recipient was admitted to the hospital because of electrolyte disturbances due to dehydration. Immunosuppression consisted of tacrolimus, azathioprine, and low-dose corticosteroids. During hospitalization, she tested positive on screening COVID-19 nasopharyngeal polymerase chain reaction swab, while her initial test was negative. She was initially asymptomatic and had normal inflammatory markers. Tacrolimus levels were slightly raised, as Azathioprine was temporarily halted. Due to elevated D-dimers at that time, prophylactic low-molecular weight heparin was started. Seven days after the positive test, dyspnea, anosmia, and C-reactive protein increase (25 mg/L) were noted. Remdesivir was administered during 5 d in total. High stomal output was noted in two consecutive days and several days thereafter. To exclude infection or rejection, an ileoscopy and biopsy were performed and excluded these. Four weeks later, she was discharged from the hospital and remains in good health since then.

CONCLUSION

Early eradication of severe acute respiratory syndrome coronavirus 2 in ITx recipients may be warranted to prevent acute rejection provocation by it.

Key Words: COVID-19; Intestinal transplantation; Outcome; SARS-CoV-2; Treatment; Case report

Core Tip: Acute rejection is often seen in intestinal transplant (ITx) recipients due to the high immunogenicity of the intestinal graft. However, it might also be provoked by latent presence of viruses, due to the high immunosuppression needs. Recently, chronic latency of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the intestine has been shown. Hence, early recognition, eradication, and follow-up on intestinal biopsies in ITx recipients might be warranted to prevent the potential acute rejection provocation of the intestinal graft by SARS-CoV-2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), provoked by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a major challenge in intestinal transplantation (ITx) due to the high immunogenicity of the graft, requiring high levels of immunosuppression. In the early phase of the pandemic, patients were treated with hydroxychloroquine[1]. The treatment of SARS-CoV-2 in transplant patients was altered over time in favor of dexamethasone, antivirals, or only supportive therapy[2-4]. Next to this, it is known that SARS-CoV-2 provokes gastroenterological manifestations, due to its invasion of the enterocytes[5]. It has recently been shown that SARS-CoV-2 remained latent present in the upper gastrointestinal tract, as well as in the small intestine, until at least 3 mo post-COVID-19 positivity[6]. Several other latent gastrointestinal tract viruses are known to be able to provoke acute rejection of the intestinal graft, due to the high immunosuppression needs in these ITx recipients[7,8]. To our knowledge, the influence of SARS-CoV-2-related gastroenterological manifestations in ITx patients or the provoked risk for rejection have not been elucidated so far.

CASE PRESENTATION

Chief complaints

We recently encountered a SARS-CoV-2 infection in a 41-year-old female ITx-recipient, acquired during hospitalization for dehydration and electrolyte disturbances, during the second European COVID-19 wave in November 2020.

History of present illness

She underwent an isolated intestinal re-transplantation, combined with a kidney, in August 2019 for chronic allograft enteropathy. After her re-ITx, she underwent a conversion of her terminal ileostomy to a low ileorectal anastomosis with protective loopileostomy on September 29, 2020.

History of past illness

Her first isolated ITx was in December 2004 for chronic intestinal pseudo-obstruction with recurrent catheter sepsis. In between the two ITx procedures, she was in good health and never encountered an acute rejection, until she developed chronic allograft enteropathy for which she was back on parenteral nutrition since February 2019.

Personal and family history

Negative.

Physical examination

On admission, on October 28, 2020, she was on tacrolimus (3.5 mg bidaily, target trough level: 7-8 μg/L), azathioprine (50 mg/d), and methylprednisolone (4 mg/d). She had no fever, respiratory issues, nor recent contact with a potential COVID-19 positive patient.

Laboratory examinations

She tested negative on SARS-CoV-2 on a nasopharyngeal polymerase chain reaction (PCR)-test (Figure 1). Her lab values revealed an acute deterioration of kidney function and electrolyte disturbances. Six days after admission, on November 3, 2020, she tested positive for SARS-CoV-2 on a screening PCR-test.

Imaging examinations

There were no clinical nor biochemical signs of infection or chest X-ray alterations.

FINAL DIAGNOSIS

The final diagnosis of this presented case is mild COVID-19.

TREATMENT

Azathioprine was temporarily halted, and tacrolimus levels slightly raised towards target trough levels of 8-9 μg/L. Prophylactic low-molecular weight heparin was started as D-dimers measured 4110 ng/mL (normal ≤ 500 ng/mL). She was transferred to the COVID-19 low-care ward of our hospital. Five days later, on November 8, 2020, her stomal output increased with 227% up to 2830 mL/24 h. As rejection was suspected, ileoscopy *via* the stoma was performed on November 9, 2020, and ileal biopsies were taken (Figure 2). These excluded inflammation or rejection. That same day, anosmia and mild dyspnea with normal oxygen saturation developed. Body temperature increased until 37.8 °C and C-reactive protein level was 25 mg/L (normal < 5 mg/L). Remdesivir was intravenously administered for 5 d with 200 mg as loading dose and 100 mg daily thereafter. After the remdesivir treatment was finished, azathioprine was restarted, and tacrolimus trough levels lowered to standard levels.

OUTCOME AND FOLLOW-UP

Weekly SARS-CoV-2 PCR remained positive, until a cycle threshold (Ct)-value of 39.22 was found, 4 wk after her first positive test, on November 30, 2020, and she was removed from the COVID-19 ward as the internal hospital protocol states when the Ct-value is > 29. Stomal output kept fluctuating for 1 mo, with several days of high output (> 1200 mL/24 h). With adequate fluid replacement, renal function remained stable, and the patient could be discharged on December 2, 2020 remaining in good health since then. SARS-CoV-2 PCR remained negative since then, and 3 mo after discharge from the hospital

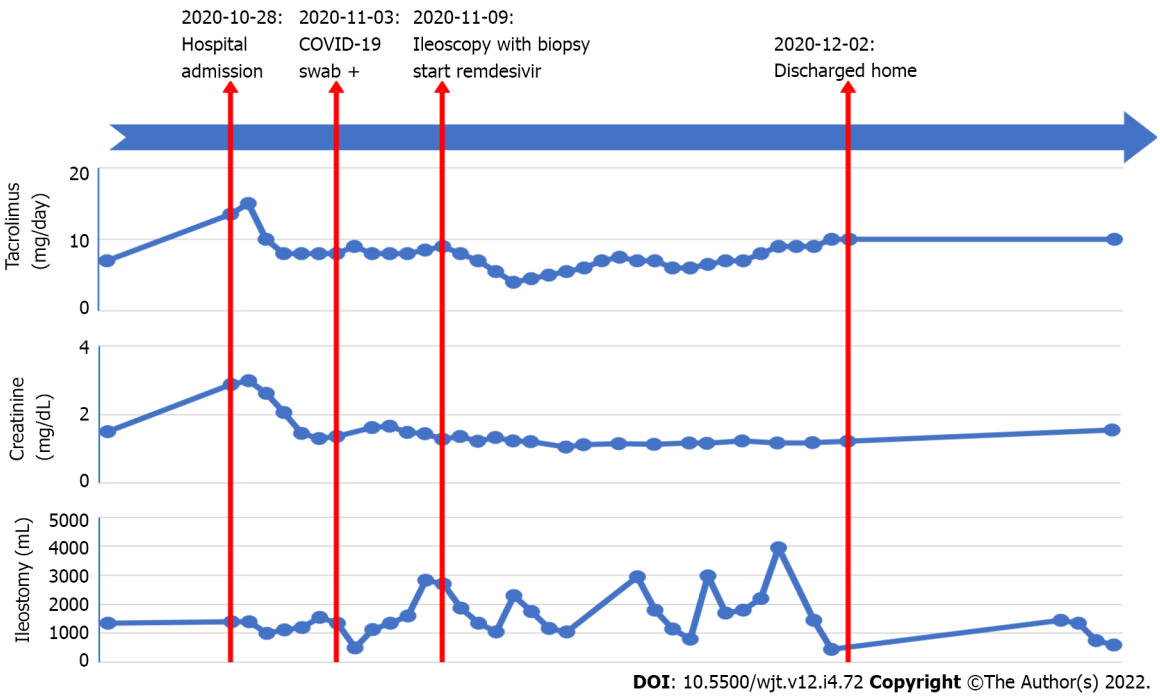

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Figure 1 Timeline of case report, with immunosuppressive regimen (total daily tacrolimus dosage; bidaily administration), serum creatinine (kidney function), and stomal output evolution. COVID-19: Coronavirus disease 2019.

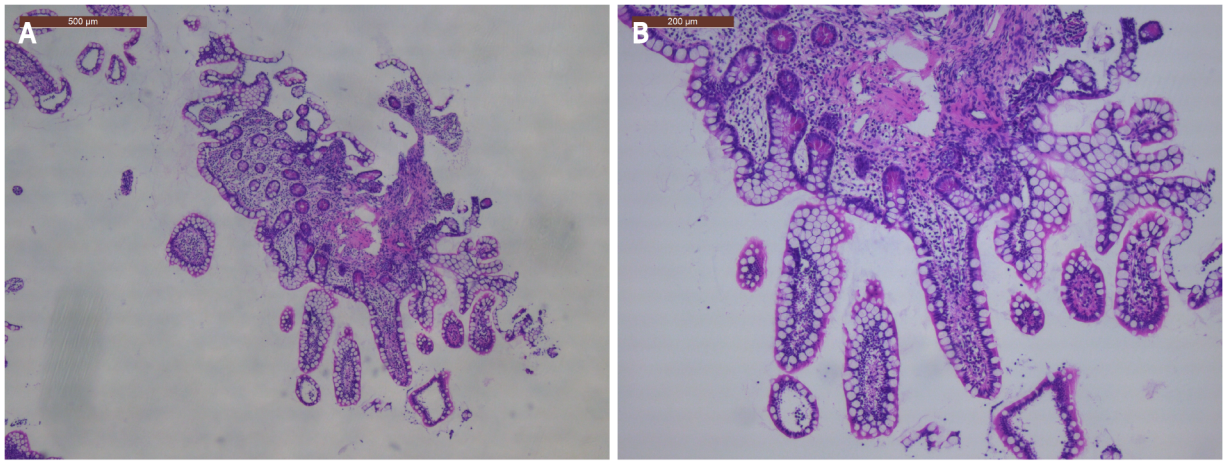

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Figure 2 Histology of the intestinal transplant biopsy showing normal intestinal mucosa, without arguments for rejection or infection. A: 500 µm; B: 200 µm.

SARS-CoV-2 immunoglobulin G (IgG) nucleocapsid antigen was negative. The patient gave informed consent, and ethical approval from the institutional review board was obtained (S64844).

DISCUSSION

We present the first report, to our knowledge, of mild COVID-19 in an ITx-patient treated with remdesivir, prophylactic low-molecular weight heparin, and temporary interruption of azathioprine. As according to the currently available evidence in transplant recipients, azathioprine was halted and tacrolimus slightly raised in return[9,10]. However, it has recently been shown that solid organ transplant recipients can also be successfully treated without adjustment of immunosuppressive therapy and without any antiviral treatment[4]. Our patient was preemptively treated with remdesivir as antiviral treatment. Up till now, there is not much yet known about remdesivir treatment in solid organ transplant recipients[11]. Recent reports have shown its tolerability and safety in kidney

transplant recipients, without effects on kidney or liver function[12,13]. However, it is strongly advised to monitor regularly liver biochemistry in patients treated with remdesivir, as hepatotoxic side effects have been described[11,14].

Although gastroenterological manifestations, including diarrhea, nausea, vomiting, and loss of appetite, are commonly seen in COVID-19 patients, symptomatology was mild in our case and limited to high stomal output[5,15,16]. These clinical symptoms might also be suggestive for an acute rejection in ITx recipients, which should be treated with an increase of immunosuppression or pulse corticosteroids, which is opposite in the case of an gastroenterological infectious process[8]. This symptomatic overlap renders the cause of the gastroenterological manifestations more difficult and hence influences the treatment strategy. If not treated promptly, acute rejection might eventually lead to intestinal graft loss[17]. Only endoscopic evaluation with histopathologic confirmation of acute rejection on biopsy can make a clear differentiation. A recent study showed that D-dimers > 1850 ng/mL, which was the case in our patient (up to 4110 ng/mL), is the best discriminator to find major intestinal mucosal abnormalities at endoscopy in COVID-19 positive patients[18].

It is known that viral entrance of SARS-CoV-2, by the angiotensin-converting enzyme 2 receptor, which is abundantly present in the enterocytes of the gastrointestinal tract, plays a major role[5,6,18]. This viral entrance provokes an acute inflammatory response, which coincides with ischemic damage due to the procoagulant state and endothelialitis, which has also been observed in ITx rejection[17,18]. Several other viruses have already been shown to mimic intestinal graft rejection by crypt apoptosis, such as cytomegalovirus, Epstein-Barr virus, adenovirus, and norovirus[7,8]. Close monitoring, during the postinfectious period of these viruses, is also important as the infection might provoke acute rejection of the intestinal graft[8]. For SARS-CoV-2, such a correlation has not been shown so far. However, as shown by Gaebler *et al*[6], SARS-CoV-2 can remain latent present in even asymptomatic patients at least 3 mo post-COVID-19[6]. As SARS-CoV-2 is able to enter the enterocytes by the angiotensin-converting enzyme 2-receptor and provoke an acute inflammatory response, it is hypothetically possible that SARS-CoV-2 might mimic or provoke acute rejection of the intestinal graft in ITx recipients as well. As such, follow-up of SARS-CoV-2 antigen on routine or screening , re-jection/infection suspicion, biopsies of the intestinal allograft might be performed in previous, current or suspected COVID-19 positive ITx recipients, as is currently the case for cytomegalovirus[7]. Early treatment and eradication of intestinal SARS-CoV-2 may be warranted to prevent the potential acute rejection mimicry or provocation.

SARS-CoV-2 nucleocapsid (N) antibodies assay, on the Abbott Architect system, was negative in our patient, despite SARS-CoV-2 positive PCR 3 mo earlier. However, it has been shown that SARS-CoV-2 IgG anti-N are positive in only 62% of SARS-CoV-2 PCR positive transplant recipients 1-2 mo post-infection, whilst these are decreasing towards only 55% at 3-4 mo and even 38% at 5-7 mo post-infection. This decline in anti-N is mainly seen in mild disease form[19]. SARS-CoV-2 spike (S) antibodies, on the contrary, are more durable with IgG anti-S present in 92% at 1-2 mo, 84% at 3-4 mo, and even 76% at 6-7 mo post-infection in transplant recipients[4]. Next to this, the analysis was run on the Abbott Architect system, of which it has been shown that it is less sensitive in transplant recipients, in comparison to non-transplant recipients and in comparison to other assets, due to a different targeting antigen[20]. It is proposed that the spike antigen is more immunogenic than the nucleocapsid antigen in immunosuppressed patients[20]. On top of that, there is evidence that spike antibodies may provide functional immunity information, as there is a correlation between spike antibodies and neutralizing antibodies[21,22]. As such, analyzing the anti-S might be clinically more relevant than the anti-N in immunosuppressed patients[20].

CONCLUSION

Early treatment of SARS-CoV-2 should be considered in ITx recipients in order to eradicate the virus and to prevent acute rejection mimicry or provocation and potential graft loss. SARS-CoV-2 antigen determination on ileal biopsies of ITx recipients might be routinely performed to screen for the hypothesis of SARS-CoV-2 acute rejection mimicry or provocation.

FOOTNOTES

Author contributions: Clarysse M contributed review of the clinical case, review of literature, and drafting of the article; Ceulemans LJ contributed critical review of literature and the article; Wauters L, Gilbo N, Capiau V, and De Hertogh G contributed review of clinical case and critical review of article; Verslype C, Laleman W, Monbaliu D, and Pirenne J contributed critical review of the article; Vanuytsel T contributed review of the clinical case, review of literature, and review of the article; All authors issued final approval for the version to be submitted.

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Country/Territory of origin: Belgium

ORCID number: Mathias Clarysse 0000-0002-2875-9516; Laurens J Ceulemans 0000-0002-4261-7100; Lucas Wauters 0000-0002-3195-4996; Nicholas Gilbo 0000-0001-6456-7071; Viktor Capiau 0000-0002-3116-1742; Gert De Hertogh 0000-0001-8494-7725; Wim Laleman 0000-0002-0842-7813; Chris Verslype 0000-0003-3857-466X; Diethard Monbaliu 0000-0002-0506-1609; Jacques Pirenne 0000-0002-8147-8801; Tim Vanuytsel 0000-0001-8728-0903.

Corresponding Author's Membership in Professional Societies: The Transplantation Society, No. 27551; Intestinal Rehabilitation and Transplant Association, No. 27551; International Pediatric Transplant Association, No. 27551; The International Society of Experimental Microsurgery; The European Society for Organ Transplantation, No. 12825.

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LETTER TO THE EDITOR

Can adequate hemodynamic management of brain-dead donors improve donor organ procurement?

Myat Soe Thet, Alessandra Verzelloni Sef, Davorin Sef

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Myat Soe Thet, Department of Cardiac Surgery, St Bartholomew's Hospital, London EC1A 7BE, United Kingdom

Myat Soe Thet, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London & Imperial College Healthcare NHS Trust, London W2 1NY, United Kingdom

Alessandra Verzelloni Sef, Department of Anaesthesia and Critical Care, Harefield Hospital, Royal Brompton and Harefield Hospitals, Part of Guy's and St Thomas' NHS Foundation Trust, London UB9 6JH, United Kingdom

Davorin Sef, Department of Cardiothoracic Surgery and Transplant Unit, Harefield Hospital, Royal Brompton and Harefield Hospitals, Part of Guy's and St Thomas' NHS Foundation Trust, London UB9 6JH, United Kingdom

Corresponding author: Davorin Sef, MD, PhD, Surgeon, Department of Cardiothoracic Surgery and Transplant Unit, Harefield Hospital, Royal Brompton and Harefield Hospitals, Part of Guy's and St Thomas' NHS Foundation Trust, Hill End Road, London UB9 6JH, United Kingdom. davorin.sef@gmail.com

Abstract

There is increasing evidence that adequate donor management with a goal of optimization of organ function is essential to maximize the number of organs that can be procured. Therefore, identification of the cause of hemodynamic instability is crucial in order to direct the right therapy. Several donor management goals for better hemodynamic management including serial echocardiography can guide hemodynamic management in potential donors to increase both number and quality of donor hearts.

Key Words: Brain-dead donors; Hemodynamic; Management; Organ procurement

Core Tip: There is increasing evidence that adequate donor management with a goal of optimization of organ function is essential to maximize the number of organs that can be procured. Early identification of potential donors and adequate donor management are essential in order to expand the donation pool and improve transplantable organ quality. The authors have summarized the available evidence on therapeutic strategies for hemodynamic management and monitoring.

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TO THE EDITOR

In the complex donation process, early identification of potential donors and adequate donor management are essential in order to expand the donation pool and improve transplantable organ quality[1,2]. Lack of evidence from randomized controlled trials still remains one of the main issues regarding the management strategies in donation after brainstem death (DBD) along with acceptance of more marginal donors with comorbidities and worldwide variability in donor management strategies due to various constraints. Most of the current guidelines are based on pathophysiological explanations, observational data and standard critical care practice[3]. Lazzeri *et al*[4] should be congratulated for aiming to summarize the available evidence regarding hemodynamic management of DBD in the era of consistently increased donor organ demand. In their article, authors focused especially on vasoactive-drug support and therapeutic goals[4]. The authors emphasized a loss of up to 20% of DBD organs due to inadequate intensive care management as one of the key concerns, which can be prevented with active donor management in intensive care[4]. Brain death can be often accompanied with considerable physiological instability, which, can induce deterioration in organ function before retrieval if not managed carefully[2]. In addition to a well-known rule of 100, the authors discussed several more donor management goals for better hemodynamic management including: (1) Invasive arterial pressure monitoring aiming mean arterial pressure ≥ 65 mmHg; (2) Urine output ≥ 1 mL/kg/h; (3) Central venous pressure monitoring (aiming 8-10 cm H_2O); (4) Lactate measurements; (5) Mixed venous oxygenation saturation; and (6) Serial echocardiography[4,5]. There is increasing evidence that adequate donor management with a goal of optimization of organ function is essential to maximize the number of organs that can be procured[5-7]. Therefore, identification of the cause of hemodynamic instability is crucial in order to direct the right therapy.

In this context, the role of pulmonary artery catheters (PAC) is not clearly described; whether the routine placement of PAC is warranted or not, since PAC insertion is not without risk of injury to the donor heart, including ventricular arrhythmias, bundle branch blocks, and even cardiac or pulmonary artery perforation[8]. However, appropriate hemodynamic monitoring is a prerequisite in assessment of volume status and response to therapy; therefore, the authors should have addressed the role of initial intravascular volume replacement and the need for assessment of volume status. Pathophysiological changes in DBD donors make the clinical assessment of volume status even more challenging, hence appropriate monitoring is of paramount importance in guiding fluid replacement. Recent guidelines suggest that the primary therapeutic goal should be to maintain euvolemia while isotonic crystalloid solutions should be the preferred when considering fluid replacement[9].

Serial echocardiography monitoring is suggested, yet it is not defined clearly whether we should rely on transthoracic echocardiography (TTE) or we should use more often TEE[3]. Interestingly, in a large study of 472 donor hearts, Casartelli *et al*[10] performed exclusively TTE for evaluation of ejection fraction. On the other hand, we would like to highlight that TEE can provide therapeutic benefits over TTE in critically ill, mechanically ventilated patients, even when the views with TTE are deemed adequate[11]. Importantly, serial echocardiography should be performed to evaluate recovery of function in neurogenic stunned myocardium and guide hemodynamic management in potential donors to improve availability and quality of donor hearts[3]. It is again highlighted that the benefits of the use of dopamine in renal transplant patients are not directly translated to donor hearts in heart transplantation[4]. Among vasopressor drugs, norepinephrine (NE) is the mainstay of cardiovascular support with the addition of vasopressin in cases of higher vasopressors requirements, and this is in line with current practices in many of the centers, as highlighted by the authors[4]. However, recent guidelines propose rather dopamine as the catecholamine of choice, and judicious NE usage due to concerns that it can increase both afterload and pulmonary capillary permeability and stimulate coronary vasoconstriction[9]. These guidelines recommend the use of dopamine as a first line therapy, with addition of NE when the requirement of dopamine exceeds 10 mcg/kg/min. However, the data on this is variable with a retrospective analysis stating otherwise[12]. Furthermore, NE may be associated

with worse cardiac graft function and worse post-transplant survival[13]. Moreover, vasopressin with its action on the V2 receptor will treat diabetes insipidus at the same time. It is also not evident whether it would require further therapy with selective V2 receptor therapy. However, as the authors did not perform systematic review, this could lead to extrapolation bias. Lastly, while there are many reasons why a significant number of potential organs are not donated and successfully transplanted, hemodynamic instability of the donor is an essential and modifiable factor.

FOOTNOTES

Author contributions: Thet MS, Verzelloni Sef A and Sef D designed the research study; Thet MS wrote the original draft of the manuscript; Thet MS, Verzelloni Sef A and Sef D analyzed the literature and edited the draft of the manuscript; and all authors have read and approve the final manuscript.

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Country/Territory of origin: United Kingdom

ORCID number: Myat Soe Thet 0000-0002-2741-0339; Alessandra Verzelloni Sef 0000-0002-5049-7559; Davorin Sef 0000-0001-5053-3815.

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The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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EDITORIAL

Multiorgan retrieval and preservation of the thoracic and abdominal organs in Maastricht III donors

Daniel Casanova, Federico Castillo, Eduardo Miñambres

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Daniel Casanova, Federico Castillo, Department of Surgery, University Hospital Marqués de Valdecilla University Cantabria, Santander 39008, Cantabria, Spain

Eduardo Miñambres, Intensive Care Unit, Transplant Office, University Hospital Marques de Valdecilla University of Cantabria Medical School, Santander 39008, Cantabria, Spain

Corresponding author: Daniel Casanova, FRCS (Hon), MD, PhD, Full Professor, Professor, Surgeon, Department of Surgery, University Hospital Marqués de Valdecilla University Cantabria, Chairman Board Europeo de Trasplante, President Section Surgery UEMS, Servicio de Cirugía General y Digestiva Hospital Universitario Marqués de Valdecilla, Santander 39008, Cantabria, Spain. daniel.casanova@unican.es

Abstract

This editorial describes the indications and technical aspects of the simultaneous retrieval of thoracic and abdominal organs in Maastricht III donors as well as the preservation of such organs until their implantation.

Key Words: Multiorgan retrieval; Abdominal organs; Thoracic organs; Maastricht III; Preservación; Transplantation

Core Tip: Every year approximately 100000 transplants are performed worldwide, which together with good success rates and the improvement of immunosuppressive medication means that indications for transplant are continually increasing. However, the imbalance between supply and demand of organs for transplantation means that the existing number of donors is insufficient for the large number of patients on waiting lists. Donation of organs after death needs to become an integral consideration as part of end-of-life care.

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INTRODUCTION

Organ transplantation is one of the most important advances in modern medicine, making it possible to increase the longevity and quality of life of transplant recipients, with patient and graft survival rates that were unimaginable just a few decades ago.

Every year approximately 100000 transplants are performed worldwide, which together with good success rates and the improvement of immunosuppressive medication means that indications for transplant are continually increasing. However, the imbalance between supply and demand of organs for transplantation means that the existing number of donors is insufficient for the large number of patients on waiting lists. Donation of organs after death needs to become an integral consideration as part of end-of-life care.

In Spain, due to efficient organization and public trust in the system and management of available resources, donation rates stand at 49 per million population (the highest in the world), although this supply still does not meet existing needs. There is, therefore, a need to further optimize the management of donation by tapping into new sources of organs. Currently, the most common type of donor for transplantation is the brain-dead donor, although in some centres, living donor transplantation programmes have been developed as an alternative, primarily for the kidney and liver.

Currently, we are witnessing renewed interest in organ procurement from donors after cardiocirculatory arrest. This type of donor was not previously accepted by most transplant teams due to the prolonged periods of ischaemia after cardiac arrest resulting in significant cell damage due to hypoxia. It should be remembered that before the brain death law was implemented in 1968, many organ donors were of this type, as it was necessary to wait for cardiocirculatory arrest to occur before harvesting organs.

In the 1980s transplant groups, especially in the United States and northern European countries, began including donation after cardiocirculatory arrest into their programmes. Kidneys were obtained either from living donors or from donors in asystole, who in English-language terminology have been called Non Heart Beating Donors, Donors after Cardiac Death or more recently and due to considerations related to the diagnosis of death Donors after the Circulatory Determination of Death (DCDD). Controlled Donation after Circulatory Determination of Death (cDCDD) is gradually becoming an important source of organs in countries with active programmes[1-4]. In Spain from 2010-2019, cDCDD accounted for up to 28% of total organ procurement activity[5].

In 1995, the first symposium on donation after cardiocirculatory arrest was held in Maastricht (The Netherlands), where three fundamental aspects were agreed upon: (1) Classification of donors after cardiac arrest (Non Heart Beating Donors) into four categories (Table 1); (2) Criteria for determining death after irreversible cardiac arrest; and (3) The period of time to wait between cardiac arrest and the start of organ harvesting.

In 1998, the United States Institute of Medicine published the consensus on transplantation with donors in irreversible cardiac arrest, recommending a non-touch time of 5 min, which became the standard time period for most groups[6]. However, a "no-touch period" attempts and varies widely between countries-protocols, ranging from 5 to 20 min[7].

Therefore, potential type III asystole donors are those patients with no apparent contraindications for donation who due to their admission pathology and subsequent evolution are expected to go into cardiorespiratory arrest after withdrawal of life-support measures within a period of time compatible with organ donation. The selection of donors is decided jointly with the family.

MAJORITY OF POTENTIAL MAASTRICHT TYPE III DONORS

The majority of potential Maastricht type III donors are patients with severe neurological pathology with a catastrophic functional prognosis and in whom progression to brain death is not foreseeable. Other patients may come from respiratory and/or cardiological medical pathologies with unfavourable evolution and prognosis, in whom the therapeutic measures applied have proved ineffective. There is no absolute age limit for controlled asystole donation, but it tends to be more restrictive than for brain death donation. In general, it depends on the organ to be transplanted, but a limit of 65-70 years has been established, although this limit is likely to be re-evaluated as experience is gained with this type of donation.

Current protocol recommendations are that the time elapsed between extubation and cardiorespiratory arrest should not exceed 2 h, although this time is debatable, as the haemodynamic and respiratory conditions of the patient after extubation are potentially more important.

The medical criteria for organ selection do not differ from the general criteria for brain death donation, although they are usually more restrictive. With regard to family consent, specific consent must be obtained for femoral vessel cannulation, heparin administration as well as administration of organ preservation drugs prior to death. Once mechanical ventilation has been withdrawn, periods of hypotension, hypoxia or anuria should be recorded. Sedation should be administered as necessary to ensure the patient's comfort and well-being, in accordance with recommendations on the management

Table 1 Donors after Cardiac Death Maastricht classification

Category	Type	Circumstances
1	Uncontrolled	Dead on arrival
2	Uncontrolled	Unsuccessful resuscitation
3	Controlled	Cardiac arrest follows planned withdrawal of life sustaining treatments
4	Either	Cardiac arrest in a patient who is brain dead

of the critically ill patient at the end of life from the relevant bioethics committee.

The death of the patient will be confirmed by a doctor responsible for the Critical Care Unit where the patient is admitted and who is not involved in the donation process, after confirming the absence of a curve in the arterial monitoring, the absence of breathing and the absence of response to stimuli for a period of 5 min. International recommendations on the type III donation procedure have recently been published that help define and clarify the most debated aspects of this type of donation[8].

In many hospitals, the multiorgan harvesting of abdominal organs in cDCDD is performed using a rapid harvesting technique. However, in recent years, the procurement of organs from asystole has developed significantly in Spain. Several centres are now pioneering the use of abdominal normothermic regional perfusion (NRP) with extracorporeal membrane oxygenation (ECMO) devices as a strategy for in situ blood reperfusion in both controlled and uncontrolled Donors after Cardiac Death [9-11]. Simultaneous thoracic and abdominal organ harvesting in controlled asystole type III donors is based on normothermic ECMO technology. NRP has the potential to decrease or ameliorate ischaemic injury and facilitate the testing of graft viability, reducing the percentage of organs discarded before transplantation.

One of the important advantages of the Spanish system is that it is legally authorised to initiate anticoagulation manoeuvres and placement of cannulae with consent.

Functional warm ischaemia time for abdominal grafts is defined as the time from systolic blood pressure < 60 mmHg to the onset of NRP (5 min of non-contact period included). For functional warm ischaemia time, an upper time limit of 30 min is set for the liver, pancreas and heart and 60 min for lungs and kidneys. In the intensive care unit, heparin administration (300-500 units/kg) and cannulation of the femoral vessels is performed prior to withdrawal of life support therapies. The femoral artery and femoral vein are cannulated, and an aortic balloon occlusion is placed in the contralateral groin to prevent cerebral and coronary perfusion during NRP. The goal of performing abdominal NRP is to maintain a pump flow of 2.0-2.4 L/min. A continuous pressure of 60-65 mmHg and a temperature of 37 °C should be maintained at the femoral arterial cannula; bicarbonate is administered after NRP is initiated to maintain a pH of 7.35-7.45, and a haematocrit > 25% is targeted.

Whilst NRP appears to be the ideal method for abdominal grafts, the lungs are removed from the donor in controlled asystole using the rapid extraction technique, by lowering the lung temperature with topical cooling as quickly as possible. This combined method was first described in the United Kingdom[12]. Our group has proposed a variant of the technique with premortem interventions, in which the risk of possible trans-diaphragmatic cooling of the liver is minimized[13]. However, there is still some reluctance among practitioners to combine the lung cooling and rapid retrieval technique with NRP for abdominal grafts. This method increases the complexity of the procurement procedure and might injure the grafts due to double temperature (low temperature affecting the liver and normothermia affecting the lungs) or due to inadequate perfusion pressure in the pump as a result of bleeding in the thorax after removal of the cardiopulmonary block or after vena cava clamping. From a technical point of view, once death is determined and NRP is initiated, a rapid sternotomy is performed. At the same time, the donor is reintubated and ventilated 5 min after NRP with 100% oxygen and a positive end-expiratory pressure of 5 cm H2O. The pulmonary artery is cannulated for cold lavage perfusion with Perfadex® (50 mL/kg). One litre of saline at 4 °C is administered in both hemithoraces for topical cooling, and the superior vena cava is ligated to separate the thoracic and abdominal compartments. Once the lungs are preserved with Perfadex® solution, lung extraction is performed using the same technique as for Donors after Cardiac Death donors.

To avoid low blood flow in the pump due to the absence of venous return from the thorax and head, 1.0-1.5 L of saline are administered to the cDCDD donor just before ligation of the vena cava. After perfusing the pulmonary artery with preservation solution, a laparotomy is performed to assess the appearance of the abdominal grafts by placing a cannula in the inferior mesenteric vein. After 2 h of NRP, the ECMO device is stopped, and a rapid dual cold organ perfusion is performed.

The retrieval of the kidneys, pancreas and liver is performed in the conventional way with the same surgical technique used in brain death donation, as haemodynamic stabilisation due to perfusion with NRP allows a completely controlled sequence of dissection and extraction. Perfusion with preservation solutions allows the kidneys, pancreas and liver to be obtained in optimal conditions for implantation.

Blood samples are taken from the ECMO device immediately after starting the NRP and at least every 30 min. Biochemistry, serum lactate levels and haematocrit are analysed. If alanine transaminase or aspartate transaminase exceed four times the upper limit of normal during NRP, the liver and pancreas are ruled out, even with a normal macroscopic appearance. Lactate levels are also monitored during NRP.

Ethical questions have been raised about the use of abdominal NRP and premortem interventions in cDCDD such as the possibility of restoring cerebral circulation after declaration of death if the aortic balloon occlusion technique fails. A specific methodology to avoid restoration of cerebral circulation after determination of death when using NRP and antemortem cannulation has recently been described and validated in a multicentre study[14]. This approach avoids the aforementioned ethical concern by guaranteeing the absence of cerebral resuscitation.

In the last 5 years the use of thoraco-abdominal NRP (TA-NRP) has made heart transplantation feasible and allows practitioners to assess heart function before organ procurement without any negative impact on the preservation of abdominal organs. The combined retrieval of lungs, heart and abdominal grafts using TA-NRP has been performed successfully in our centre. The use of TA-NRP in cDCDD heart donors in conjunction with cold storage following retrieval can eliminate the need to use *ex situ* machine perfusion devices, making cDCDD heart transplantation economically possible in other countries[15-17].

CONCLUSION

In summary, the use of TA-NRP for heart, lung and abdominal grafts or the combined approach (rapid recovery of the lungs and NRP for abdominal grafts) offers a remarkable recovery rate and is safe for thoracic organs (heart and lungs). Furthermore, abdominal grafts can benefit from the use of NRP as a preservation procedure. As this is a promising initial experience, further studies are needed to confirm our findings in the combined thoracic and abdominal procurement procedure.

FOOTNOTES

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Country/Territory of origin: Spain

ORCID number: Daniel Casanova 0000-0003-3863-5039; Federico Castillo 0000-0002-5092-8830; Eduardo Miñambres 0000-0002-0466-044X.

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MINIREVIEWS

Pediatric transplantation during the COVID-19 pandemic

Christos Dimitrios Kakos, Ioannis A Ziogas, Georgios Tsoulfas

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Christos Dimitrios Kakos, Ioannis A Ziogas, Surgery Working Group, Society of Junior Doctors, Athens 15123, Greece

Ioannis A Ziogas, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, United States

Georgios Tsoulfas, Department of Transplantation Surgery, Aristotle University School of Medicine, Thessaloniki 54622, Greece

Corresponding author: Georgios Tsoulfas, FACS, FICS, MD, PhD, Professor, Department of Transplantation Surgery, Aristotle University School of Medicine, 66 Tsimiski Street, Thessaloniki 54622, Greece. tsoulfasg@gmail.com

Abstract

Children infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seem to have a better prognosis than adults. Nevertheless, pediatric solid organ transplantation (SOT) has been significantly affected by the unprecedented coronavirus disease 2019 (COVID-19) pandemic during the pre-, peri-, and post-transplant period. Undoubtedly, immunosuppression constitutes a real challenge for transplant clinicians as increased immunosuppression may prolong disease recovery, while its decrease can contribute to more severe symptoms. To date, most pediatric SOT recipients infected by SARS-CoV-2 experience mild disease with only scarce reports of life-threatening complications. As a consequence, after an initial drop during the early phase of the pandemic, pediatric SOTs are now performed with the same frequency as during the pre-pandemic period. This review summarizes the currently available evidence regarding pediatric SOT during the COVID-19 pandemic.

Key Words: Pediatric; Transplantation; SARS-CoV-2; COVID-19; Immunosuppression

Core Tip: Pediatric patients experience milder symptoms of coronavirus disease 2019 (COVID-19). Pediatric solid organ transplantation during the COVID-19 pandemic represents a real challenge not only for the solid organ transplantation candidates and recipients but also for the transplant clinicians. Immunosuppression increases the risk of COVID-19 but may also provide a benefit against possible infection, as it lowers the risk of a catastrophic hyperinflammatory response from the host. We herein review the currently available evidence regarding pediatric solid organ transplantation during the COVID-19 pandemic.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has impacted all people worldwide and particularly people with chronic underlying comorbidities. Specifically, people with weakened immunity either due to an underlying disease or due to immunosuppression are at high risk. Although children represent just 2%-10% of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostic cases and seem to have less severe disease when compared with adults[1], pediatric solid organ transplantation (SOT) candidates and recipients have been significantly afflicted by the pandemic. The aim of this review is to summarize and discuss the currently available data regarding pediatric SOT during the COVID-19 pandemic.

CHILDREN AND COVID-19

It is well known now that children experience milder COVID-19 when compared with adults and a lower proportion of children require hospitalization[2,3]. The most frequently reported symptoms are cough and fever, while some pediatric patients may also present with gastrointestinal symptoms[4]. Although fatalities are rare in the pediatric population, 2%-8% of children with COVID-19 will eventually require admission to an intensive care unit[5]. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 is a post-infectious consequence of pediatric SARS-CoV-2 infection presenting with gastrointestinal, cardiac, renal, or neurologic manifestations[6].

There has been excessive research on why adults experience a more severe form of COVID-19. A key concept is the difference between the pediatric and adult immune systems. Except for the most severe SARS-CoV-2 cases, children appear to preserve CD8+ cytotoxic response[6-8], as they do not face the immunosenescence that normally occurs with aging. Data have also shown that children might have more powerful adaptive immunity[9]. For example, pediatric SARS-CoV-2 patients do not present with either lymphopenia or high neutrophil/lymphocyte ratio[6]. In addition, adults have higher levels of circulating proinflammatory cytokines [interleukin-1β (IL-1β), IL-6, IL-10, IL-12, interferon-γ, tumor necrosis factor-α (TNF-α), C-reactive protein] than pediatric SARS-CoV-2 patients[10-12]. Although in a study from New York City, IL-6 and TNF-α values did not differ from adults[13].

A finding that needs further investigation is the potential role of angiotensin-converting enzyme 2 (ACE2) receptor, which is the main binding protein of SARS-CoV-2 on host cells[14]. ACE2 has been described as an anti-fibrotic and anti-inflammatory agent against pulmonary leak and inflammation, thus higher expression of ACE2 that has been observed in children may contribute to the fact that children are more resistant to SARS-CoV-2[7].

Furthermore, the fact that children typically do not have significant comorbidities, such as arterial hypertension, diabetes mellitus, or congestive heart failure, may contribute to the milder cases of COVID-19 observed. Associated factors that predispose a negative outcome in children with SARS-CoV-2 have not been well defined[15]. Nevertheless, previous studies have identified obesity, hypoxemia at clinical presentation, asthma, congenital heart disease, inherited metabolic syndrome, chromosomal disorders, and ethnicity as risk factors for severe SARS-CoV-2 infection in children[16-19]. Last but not least, another theory suggests that common childhood infections (respiratory syncytial virus, mycoplasma pneumoniae) can carry out cross protection, so children who have recently recovered from these infections may have higher immunoglobin G titers than adults[20,21].

SARS-COV-2 AND HEPATIC/RENAL MANIFESTATIONS IN CHILDREN

SARS-CoV-2 enters the liver parenchyma through the ACE2 receptor. However, the liver is only rarely affected seriously by the disease, most probably due to its tolerogenic environment[22,23]. The most common hepatic manifestation is an elevation of hepatic transaminases in 6%-27% of pediatric cases and a mild elevation of γ-glutamyl transferase, alkaline phosphatase, and total bilirubin, yet their clinical significance remains unclear[24]. The liver damage may be directly caused by viral infection of the liver cells from medications like remdesivir or lopinavir/ritonavir or from chronic hypoxia[25-27]. High levels of IL-6 and IL-10 are associated with severe SARS-CoV-2 infection but not with SARS-CoV-2-related abnormal liver enzymes[28].

A cohort study from the United States and the United Kingdom demonstrated that adults with chronic liver disease and cirrhosis are prone to increased risk of adverse outcomes following SARS-CoV-2[29]. A study from northern Italy also noted that adults and children with autoimmune liver disease maintained satisfactory health status despite their imbalanced immune system[30]. Another Italian multicenter study that included both cirrhotic and non-cirrhotic liver disease patients demonstrated that 84% of children with chronic liver disease remained healthy during the outbreak[9]. It remains unclear whether children with chronic liver disease experience more severe symptoms.

SARS-CoV-2 can also present with renal manifestations, while several studies suggest that kidney transplantation should be continued during the COVID-19 pandemic under certain precautions[31-34]. Acute kidney injury is mostly associated with immune alterations and direct cytopathic lesions by SARS-CoV-2[35]. Acute tubular injury is also a common yet typically mild manifestation[36]. Comorbidities, such as diabetes mellitus and cardiovascular disease, can delay recovery from acute kidney injury[37]. A multicenter study from Turkey revealed that the incidence of SARS-CoV-2 is higher in pediatric patients on dialysis or after kidney transplantation, yet the authors reported that regional factors, such as the high population, the crowded households, and socioeconomic status in Istanbul, may have contributed to this particular observation in that cohort[38]. They also found that the hospitalization rate was higher in dialysis patients compared with kidney transplantation recipients, potentially due to a higher proportion of asymptomatic disease in kidney transplantation recipients[38].

IMPACT OF SARS-COV-2 ON PEDIATRIC TRANSPLANTATION

It was inevitable that the COVID-19 pandemic would affect the transplant activity worldwide. A multicenter analysis of the European Reference Network on Pediatric Transplantation showed a substantial reduction of pediatric transplants across Europe[39]. This was related to the precautions and measures to minimize SARS-CoV-2 transmission, the shortage of hospital beds and staff, the restrictions in operation room availability, and a notable decline in the recovery of deceased donor organs, especially during the early phase of the pandemic[40]. Additionally, United States data from the Scientific Registry of Transplant Recipients showed an initial decrease in pediatric kidney transplants from both deceased and living donors by 47% and 82%, respectively[41]. Subsequently, there was a continual increase with numbers reaching the expected pre-pandemic levels by May 2020[41]. The authors also reported a 189% increase in waitlist removal due to mortality or deterioration[41]. Kemme *et al*[42] used the same registry studying pediatric liver transplantation. They found a decrease in waitlist addition by 25% between March and May of 2020, with Black candidates being affected the most. During the early phase of the pandemic there was a 38% reduction in pediatric liver transplantation, with Black children experiencing an 81% decline in living donor liver transplantation in contrast to White children who faced no change in this category. Overall, White children had a 30% drop in liver transplantation during the pandemic[42]. Figure 1 depicts the number of pediatric kidney and liver transplants performed in the United States between January 1, 2020 and January 1, 2022.

PEDIATRIC TRANSPLANTATION DURING THE COVID-19 PANDEMIC

Except for universal recommendations from transplant societies worldwide, there are no mandatory guidelines specific to pediatric SOT during the pandemic. The decision for SOT depends on the urgency of the need for a new organ and the risk-to-benefit ratio. Both pediatric SOT candidates and living donors should follow prevention strategies to reduce potential exposure to SARS-CoV-2 in the pretransplant period. Self-quarantine for 14 d prior to living donation is important, while a negative swab test for both the candidate and the donor upon admission to the hospital should also be required. Particularly in cases of pediatric SOT, the caregiver should also be asymptomatic and have a negative swab test prior to transplant. Further, most transplant societies strongly mandate universal SARS-CoV-2 screening of potential deceased donors before organ procurement[43].

There is no consensus about the optimal time for transplantation when the potential donor had a SARS-CoV-2 infection. In general, it is recommended to avoid grafts from donors with active SARS-CoV-2 infection[44], while there are different acceptance criteria for donors who have recently recovered

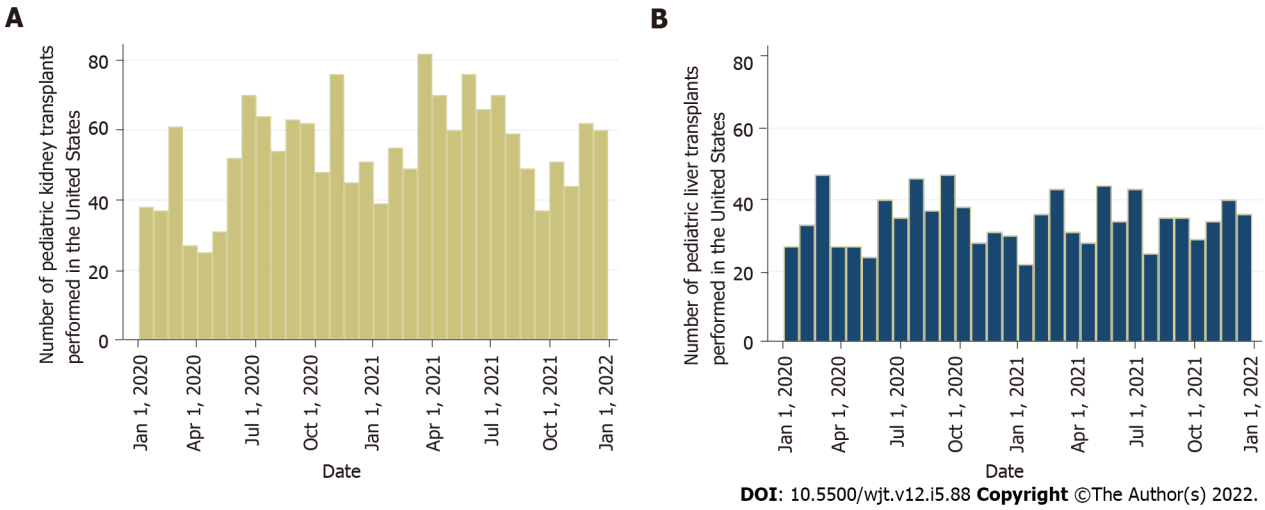

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Figure 1 Number of pediatric transplants performed in the United States between January 1, 2020 and January 1, 2022 (data from the United Network for Organ Sharing database). A: Kidney transplants; B: Liver transplants.

from the infection[43]. Some transplant societies recommend using a graft from a living donor at least 28 d after symptom resolution irrespective of real-time reverse transcriptase polymerase chain reaction (RT-PCR) positivity. Due to the pulmonary and renal dysfunction associated with SARS-CoV-2 infection, additional considerations may be appropriate when the procedure involves transplantation of lungs or kidneys from a previously infected donor.

There is a scarcity of data regarding the optimal time of SOT if a pediatric candidate is infected by SARS-CoV-2. Ideally, the candidate should be both asymptomatic and have a negative test. Notably, Goss *et al*[45] reported an uncomplicated liver transplantation in a child positive for SARS-CoV-2 on a nasopharyngeal swab test just 4 wk before transplant. The immunoglobin G specific antibodies persisted for 6 wk after liver transplantation, with unaltered immunosuppression per the center's standard protocol[45]. Until additional data are available, the risk of the procedure must always be weighed against the risk of deferring SOT.

On another note, technology overall has significantly changed the way people communicate during the COVID-19 pandemic, and thus telemedicine can have a pivotal role on transplant follow-up as it facilitates the general rules for social distancing[46]. However, a German study showed that most young adults who underwent liver transplantation in childhood were afraid to attend medical appointments and 40% reported lower appointment adherence[47]. Additionally, although video consultations might be helpful for follow-up, their acceptance by liver transplantation recipients was lower than expected [47]. It is important that pediatric patients adhere to follow-up appointments after SOT, and their parents should notify the transplant provider of any suspected or proven SARS-CoV-2 exposure and discuss whether additional measures are needed. Careful hand hygiene and avoidance of crowds during the period of high immunosuppression are key strategies for prevention of a possible infection [48].

Finally, several studies have evaluated the SARS-CoV-2 vaccine safety and efficacy in SOT recipients and children, with nearly all of them supporting that the administration of at least two vaccine doses in these patients is safe and efficient[49-55]. There is also an ongoing study approved by Johns Hopkins University examining the levels of SARS-CoV-2 antibodies in children who are organ transplant candidates or recipients before and after they get the SARS-CoV-2 vaccine (IRB00248540).

MANAGEMENT OF SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

A confirmed SARS-CoV-2 case requires laboratory evidence of viral detection. The testing strategies vary by geographical location and testing capacity. A nasopharyngeal RT-PCR test is the recommended gold standard. However, a negative RT-PCR test does not definitively exclude SARS-CoV-2 infection, and the reported rates of false negative results vary between 2%-29%[56]. If symptoms persist, a second nasopharyngeal RT-PCR test should be performed after 48-72 h. Depending on the time of the year, an evaluation for other respiratory viruses should be considered. An alternative diagnosis would reduce but not eliminate the possibility of COVID-19, while the detection of another respiratory pathogen may require additional management (*e.g.*, antiviral treatment in case of influenza infection).

Antibody tests should not be used to diagnose acute SARS-CoV-2 infection, while their application to assess the host response after an infection is an area under investigation. It is unknown if pediatric SOT recipients mount a robust serologic response to SARS-CoV-2, and even if they have protective

antibodies, the length of this protection is unknown[53-55]. Single center studies from Saudi Arabia and Brazil have shown a relatively high seroprevalence of SARS-CoV-2 in the pediatric kidney transplantation population[57,58]. However, there are concerns for possible false positive antibody results due to cross-reactivity with other coronaviruses[59].

The management of a confirmed case of SARS-CoV-2 in a pediatric SOT recipient is mainly supportive, with supplemental oxygen, nonsteroidal anti-inflammatory drugs, remdesivir, dexamethasone, and SARS-CoV-2 convalescent plasma being the only proven measures that can significantly affect the outcome[26,60,61]. Lopinavir, ritonavir, and hydroxychloroquine have not shown any significant benefit in mortality and morbidity, including the need for mechanical ventilation[60].

A crucial aspect in this group of patients is immunosuppression, which is generally considered a double-edged sword[62]. Increased immunosuppression may increase the viral load and delay recovery, whereas low immunosuppression may contribute to severe COVID-19 forms due to a more robust immune response[63]. In fact, SARS-CoV-2-induced pulmonary injury is mainly driven by excessive activation of the innate immune inflammatory response of the host[64]. Despite that notion, it has been proposed that immunosuppression in immunocompromised children may not actually increase the risk for severe SARS-CoV-2 disease[65]. On the contrary, SOT recipients may benefit from immunosuppressive drugs, as they will dampen the cytokine storm[66,67]. Immunosuppression has not been reported as a stronger risk factor than obesity, chronic comorbidities, or increased age. One possible explanation is that in SARS-CoV-2, unlike other viral agents (*e.g.*, adenovirus, rhinovirus, norovirus, influenza), the host immune response is the main driver of lung tissue damage during infection[65]. Interestingly, a systematic review showed that immunosuppressed patients have a lower incidence of SARS-CoV-2 infection when compared with the general population, and they may exhibit relatively favorable outcomes as compared to other comorbidities[68].

The impact of immunosuppression on COVID-19 severity in pediatric SOT recipients remains unclear. Although complete withdrawal of immunosuppression might not be the optimal approach, individual modifications may be necessary in cases of moderate-to-severe SARS-CoV-2 infection[69]. It seems that some immunosuppression may allow for control of the dysregulated immune response, which is commonly observed in severe SARS-CoV-2 infection[65,69]. Comparative data on immunosuppression management strategies are not yet available. Some authors recommend decreasing or discontinuing cell cycle inhibitors and cautiously reducing calcineurin inhibitors (*i.e.*, cyclosporine, tacrolimus) in moderate-to-severe COVID-19 in adult SOT recipients, while others recommend continuing calcineurin inhibitors and steroids and stopping anti-proliferative medication[70]. It is also thought that calcineurin inhibitors might exert an antiviral effect and inhibit IL-6 and IL-10 pathways, which are involved in the immune dysregulation observed in COVID-19 patients[71]. In addition, certain immunosuppression therapies like mammalian target of rapamycin inhibitors may even have biologic activity against SARS-CoV-2[72].

Transplant centers follow their own strategies based on their institutional experiences. Although the data for pediatric patients are scarce, Colmenero *et al*[73] observed no adverse outcome with the use of calcineurin inhibitors and mammalian target of rapamycin inhibitors in adult patients. On the other hand, mycophenolate mofetil was associated with severe SARS-CoV-2 infection in a dose-dependent manner[74]. This can be explained by its mechanism of action, as mycophenolate mofetil produces a cytostatic effect on activated lymphocytes[74]. It is well known that SARS-CoV-2 is associated with lymphopenia, so mycophenolate mofetil may exert a synergic and deleterious effect on depleting peripheral lymphocytes[74]. On the contrary, mammalian target of rapamycin inhibitors increase the quality and functionality of memory T cells and reduce the replication of multiple viruses including cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus[75]. Regarding calcineurin inhibitors, some studies have shown *in vitro* antiviral effects against coronaviruses and that they can ameliorate the cytokine storm[76]. Randomized clinical trials comparing the different immunosuppressive schemas would help us guide management of both adult and pediatric SOT recipients.

If there is strong suspicion for bacterial superinfection, the administration of antibiotics, such as moxifloxacin, levofloxacin, ceftriaxone, vancomycin, or amikacin, can be considered[77-79]. Azithromycin should be used with caution in SOT recipients as it can increase the levels of tacrolimus [80]. These medications have been prescribed mainly in unresponsive cases, which precludes us from deducing meaningful conclusions in the absence of high-quality data.

OUTCOMES IN SARS-COV-2 POSITIVE PEDIATRIC TRANSPLANT RECIPIENTS

There are several recent reports of pediatric SOT recipients who have been infected by SARS-CoV-2 (Table 1)[38,57,58,66,77-79,81-98]. For example, Heinz *et al*[81] reported mild symptoms in a 6-mo-old recipient just 4 d after liver transplantation, while the infection was probably transmitted from the mother-donor. Neither the donor nor the recipient were tested pretransplant due to low availability of rapid testing at the early phase of the pandemic[81]. A multicenter study documented no mortality due to COVID-19 but a high rate of acute liver injury in pediatric liver transplantation recipients[83]. Morand *et al*[82] reported a coinfection of SARS-CoV-2 and Epstein-Barr virus in a pediatric liver

Table 1 Pediatric solid organ transplantation recipients with severe acute respiratory syndrome coronavirus 2 infection in 25 previously published studies

Ref.	Organ	Number of recipients	Diagnosis method	Center	Outcome	Cause of death
Sin *et al*[83]	Liver	110	N/A	International	All alive	N/A
Kehar *et al*[88]	Liver	47	RT-PCR test: 39. Serum antibodies: 8	International	All alive	N/A
Fonseca *et al*[89]	Liver	12	RT-PCR test	Hospital Sírio-Libanês, São Paulo, Brazil	All alive	N/A
Yuksel *et al*[90]	Liver	10	RT-PCR test	Koç University Hospital, Istanbul, Turkey	All alive	N/A
Ali Malekhosseini *et al*[84]	Liver	4	RT-PCR test or chest computed tomography scan	Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran	All died	Liver failure
Duvant *et al*[79]	Liver	1	Serum antibodies	Hospital Timone Enfants, Marseille, France	Alive	N/A
Heinz *et al*[81]	Liver	1	RT-PCR test	Columbia University Vagelos College of Physician and Surgeons, New York, United States	Alive	N/A
Morand *et al*[82]	Liver	1	RT-PCR test	La Timone Children Hospital, Marseille, France	Alive	N/A
Nikoupour *et al* [78]	Liver	1	RT-PCR test	Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran	Dead	Multiorgan failure
Soin *et al*[91]	Liver	1	RT-PCR test	Medanta the Medicity, Gurgaon, Delhi, India	Alive	N/A
Petters *et al*[85]	Liver	1	RT-PCR test	Baylor College of Medicine, Houston, United States	Alive	N/A
Canpolat *et al*[38]	Kidney	29	RT-PCR test	Multicenter, Turkey	All alive	N/A
Varnell *et al*[92]	Kidney	24	RT-PCR test	Multicenter (United States)	All alive	N/A
Alshami *et al*[57]	Kidney	9	RT-PCR test	King Fahad Specialist Hospital Dammam, Saudi Arabia	All alive	N/A
Berteloot *et al*[86]	Kidney	5	RT-PCR test	Hospital Universitaire Necker Enfants Maladies, Paris, France	All alive	N/A
Singer *et al*[93]	Kidney	5	RT-PCR test	Cohen Children Medical Center, New York, United States	All alive	N/A
Solomon *et al*[94]	Kidney	4	RT-PCR test	Maria Fareri Children's Hospital, New York, United States	All alive	N/A
Levenson *et al*[87]	Kidney	1	RT-PCR test	Louisiana State University Health Sciences Center, New Orleans, Louisiana, United States	Alive	N/A
Bush *et al*[77]	Kidney	1	RT-PCR test	University of Florida, Gainesville, United States	Alive	N/A
Bock *et al*[95]	Heart	20	RT-PCR test	Loma Linda Children's Hospital, California, United States	All alive	N/A
Lee *et al*[96]	Heart	4	RT-PCR test: 3. Serum antibodies: 1	Columbia University Irving Medical Center, New York, United States	All alive	N/A
Russell *et al*[97]	Heart	1	RT-PCR test	UCLA, California, United States	Alive	N/A
Goss *et al*[66]	Liver, kidney, heart, lung	26	RT-PCR test	Multicenter (United States)	All alive	N/A
Cleto-Yamane *et al*[58]	Liver, kidney	25	RT-PCR test	Hospital Estadual da Crianca, Rio de Janeiro, Brazil	All alive	N/A
Talgam-Horshi *et al*[98]	Liver, kidney, combined (liver and pancreas)	25	RT-PCR test	Schneider Children's hospital of Israel, Tel Aviv, Israel	All alive	N/A

N/A: Not applicable; RT-PCR: Real-time reverse transcriptase polymerase chain reaction.

transplantation recipient that was managed with slight reduction of tacrolimus. Nikoupour *et al*[78] reported a fatal outcome in a 3-year-old liver transplantation recipient after multiorgan failure and cardiorespiratory arrest. Results from the same transplant center reported a 100% death rate in 4 pediatric liver transplantation recipients due to liver failure, implying an increased mortality risk in children[84]. A case report from Texas described a case of multisystem inflammatory syndrome with features of Kawasaki disease in a 3-year-old African American female liver transplantation recipient [86]. The patient did not require transfer to the intensive care unit and was effectively managed with tacrolimus titration[85].

There are also some interesting findings in pediatric kidney transplantation recipients. Berteloot *et al* [86] presented 9 pediatric cases, 7 of whom developed graft arterial stenosis during early follow-up after kidney transplantation. It was reported as immune post viral graft vasculitis triggered by SARS-CoV-2 [86]. Levenson *et al*[87] reported acute kidney injury in an adolescent male kidney transplantation recipient following SARS-CoV-2 infection, with biopsy showing segmental glomerulosclerosis on a background of chronic active antibody-mediated rejection. The case was treated with an overall reduction of immunosuppression, along with anti-inflammatory treatment, which proved to be effective in preserving allograft function while attaining recovery[87]. Finally, a multicenter, multiorgan case series from five transplant centers across the United States demonstrated favorable outcomes in pediatric SOT recipients with COVID-19, which may mirror those of immunocompetent children, with infrequent hospitalizations and minimal additional treatment requirements[66].

CONCLUSION

Pediatric transplantation is a complex process that requires a combination of resources and specialized professionals and has been significantly impacted by the COVID-19 pandemic. Overall, there was a substantial decrease in pediatric SOT during the early phase of the pandemic, yet recent findings show that pediatric SOT outcomes during the pandemic were favorable. The results on the safety and efficacy on vaccines have been promising, yet further research is required to draw more solid conclusions on the optimal immunosuppressive management of pediatric SOT recipients.

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FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Christos Dimitrios Kakos 0000-0002-2269-9014; Ioannis A Ziogas 0000-0002-6742-6909; Georgios Tsoulfas 0000-0001-5043-7962.

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ORIGINAL ARTICLE

Observational Study

Simultaneous nephrectomy during kidney transplantation for polycystic kidney disease does not detrimentally impact comorbidity and graft survival

Tom Darius, Sébastien Bertoni, Martine De Meyer, Antoine Buemi, Arnaud Devresse, Nada Kanaan, Eric Goffin, Michel Mourad

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Tom Darius, Sébastien Bertoni, Martine De Meyer, Antoine Buemi, Michel Mourad, Surgical and Abdominal Transplantation Unit, University Clinics Saint Luc, Brussels 1200, Belgium

Arnaud Devresse, Nada Kanaan, Eric Goffin, Division of Nephrology, University Clinics Saint Luc, Brussels 1200, Belgium

Corresponding author: Tom Darius, FRCS (Gen Surg), MD, PhD, Doctor, Professor, Surgeon, Surgical and Abdominal Transplantation Unit, University Clinics Saint Luc, Avenue Hippocrate 10, Brussels 1200, Belgium. tom.darius@uclouvain.be

Abstract

BACKGROUND

The lack of space, as an indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other autosomal dominant polycystic kidney disease-related symptoms, remains controversial.

AIM

To evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease.

METHODS

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

RESULTS

Creation of space for future graft positioning was the main reason (n = 74, 96.1%) for associated ipsilateral nephrectomy. No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed between the two study groups. The incidence of primary nonfunction and delayed graft function was comparable

in both groups [0% and 2.6% (P = 0.497) and 9.1% and 16.9% (P = 0.230), respectively, in the KTA and KTIN group]. The 1- and 5-year graft survival were 94.8% and 90.3%, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168).

CONCLUSION

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease does not negatively impact surgical comorbidity and short- and long-term graft survival.

Key Words: Autosomal dominant polycystic kidney disease; Complications; Kidney transplantation; Graft survival; Unilateral nephrectomy; Surgical comorbidity

Core Tip: The associated surgical comorbidity and graft survival of an ipsilateral nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease was evaluated. One hundred and fifty-four patients were retrospectively evaluated, of which 77 did and 77 did not undergo associated ipsilateral nephrectomy during the transplantation. In a long-term follow-up, we observed no negative impact on surgical comorbidity and graft survival of a simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most frequent causes of renal failure in Europe and the USA and may affect 2.5% to 10% of dialysis patients. Renal failure is the result of the development and progressive expansion of multiple bilateral cysts in the renal parenchyma, leading to a progressive decline in renal function owing to compression of normal functioning parenchyma by enlarging cysts[1-3].

Clear indications for nephrectomy before transplantation include intractable pain and discomfort, ongoing hematuria, recurrent severe cyst infections, gastrointestinal symptoms such as early satiety, recurrent nephrolithiasis and risk of malignancy[1,2,4]. Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of increased surgical comorbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation. However, many controversies still exist concerning the indication and timing of a unilateral nephrectomy to create space for graft positioning in an asymptomatic kidney transplant candidate suffering from massive enlarged polycystic kidney[3,5,6].

Therefore, this retrospective study aimed to evaluate the surgical comorbidity and the impact on early and late graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in ADPKD patients. Based on these results a symptom-based algorithm is proposed to decide the timing and necessity of a unilateral or bilateral nephrectomy in ADPKD candidates waiting for, or during transplantation.

MATERIALS AND METHODS

Donor and recipient demographics

Figure 1 illustrates the selection flowchart of this retrospective study. Between January 1 2007 and January 1 2019, a total of 1026 kidney transplantations were performed at the University Clinics Saint-Luc (Brussels, Belgium) of which 154 patients underwent isolated kidney transplantation for ADPKD.

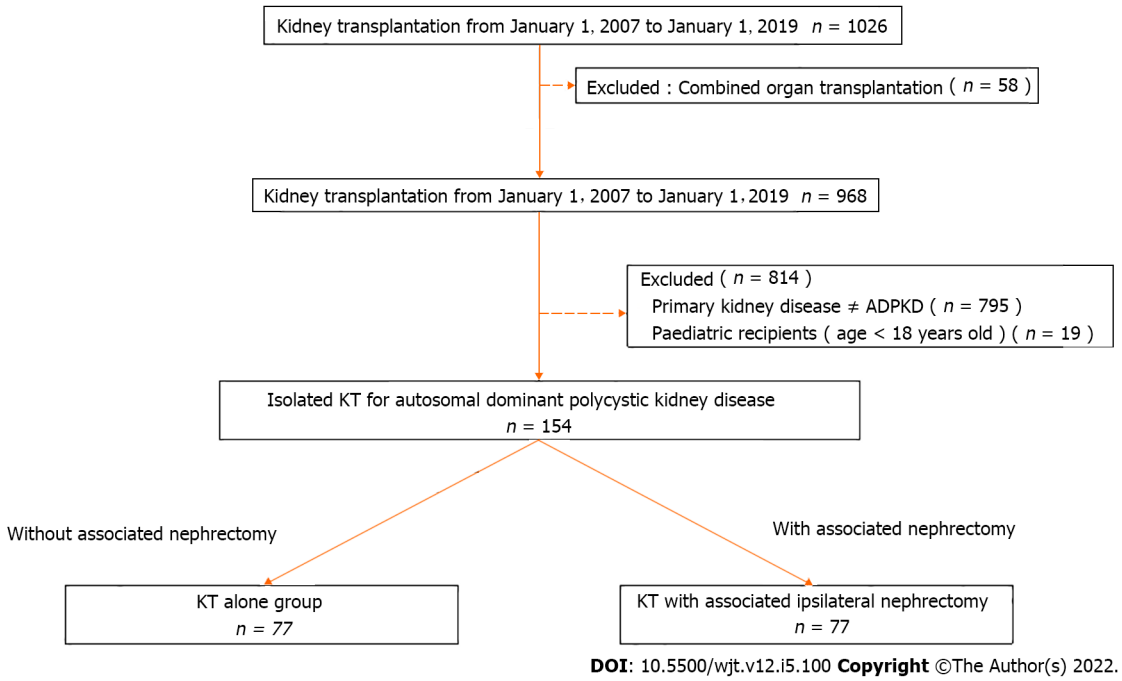

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Figure 1 Selection flowchart of this retrospective study. ADPKD: Autosomal dominant polycystic kidney disease; KT: Kidney transplantation.

This selection was obtained using the following inclusion criteria: isolated kidney transplant recipient, ADPKD as a primary cause of renal failure, age greater than 18 years old. The exclusion criteria were the following: multi-organ recipients, ADPKD not the primary kidney disease and pediatric recipients. No patients were lost from follow-up. From these 154 ADPKD patients, 77 underwent a kidney transplantation alone (KTA group) and 77 kidney transplantation with associated native ipsilateral nephrectomy (KTIN group) and were retrospectively reviewed. This study was approved by the institutional ethical committee. The following donor characteristics were analyzed: Age, gender, type of donor (living *vs* deceased) and type of deceased donor (donation after brain death or donation after circulatory death) and cytomegalovirus status. Recipient characteristics included: age, gender, body mass index (BMI), rank of transplant, time on dialysis and residual diuresis before transplantation, Human Leucocyte Antigen (HLA) mismatching, hemoglobin and albumin level before transplantation. Donor and recipient characteristics are presented in Table 1. Combined organ transplantation and ABO incompatible transplantations were excluded.

Surgical technique

A standard kidney transplant procedure was performed by a hockey stick incision with a classical vascular reconstruction on the iliac vessels and a ureterovesical anastomosis achieved according to the extravesical approach described by Lich-Gregoir[7-9]. A ureter stent was not routinely used but only according to the surgeon's preference and indication. An associated native ipsilateral nephrectomy was performed, if indicated, before implantation of the kidney graft with cranial extension up to the costal margin of the hockey stick incision by a retroperitoneal approach. Perioperative drainage of multiple renal cysts was frequently performed to facilitate surgical resection. The following surgical characteristics were collected: indications for associated ipsilateral native nephrectomy, total surgical time, anastomosis time (defined as the time from the start of vascular anastomosis to reperfusion of the kidney), cold ischemia time (defined as the time from the start of *in situ* cold perfusion of the kidney in the deceased donor or *ex vivo* cold perfusion of the kidney in a living donor to the start of *in situ* vascular anastomosis in the recipient) and weight of the removed native polycystic kidney.

Posttransplant immunosuppression

A triple-drug protocol consisting of tacrolimus (Advagraf, Astellas Pharma BV, Brussels, Belgium), methylprednisolone (Medrol, Pfizer NV, Brussels, Belgium) and mycophenolate mofetil (Cellcept, 2x500 mg/d, NV Roche SA, Brussels, Belgium) was used during the whole study period in all except one patient. Induction therapy with basiliximab (Simulect, Novartis Pharma GmbH, Neurenberg, Germany) on day 0 and 4 and thymoglobuline 1.25 mg/kg (Thymoglobulin, Sanofi Genzyme Europe B.V., Amsterdam, The Netherlands) day 1 until day 4 after transplantation was used in recipients of a living donor graft and a donor after circulatory death, respectively. Plasmapheresis was applied in highly immunized recipients until one month after transplantation. Tacrolimus trough levels (T_0) were between 10 and 14 ng/mL, 7 and 10 ng/mL and 5 and 7 ng/mL, during the first month, between the second and

Table 1 Donor and recipient characteristics of 154 kidney transplant recipients suffering from autosomal dominant polycystic kidney with or without associated ipsilateral nephrectomy during isolated kidney transplantation in a single center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P* value
Donor characteristics			
Age, yr	46.23 ± 14.94	47.40 ± 14.86	NS
Gender, male/female, *n* (%)	42/35 (54.5/45.5)	37/40 (48.1/51.9)	NS
CMV status, negative/positive, *n* (%)	32/43 (55.2/47.8)	26/47 (35.6/64.4)	NS
Type of donor, living/deceased donor, *n* (%)	6/71 (7.8/92.2)	21/56 (27.3/72.7)	[a]
Type of deceased donor, DBD/DCD, *n* (%)	54/17 (76.1/23.9)	38/18 (67.9/32.1)	NS
Recipient characteristics			
Age, yr	57.40 ± 9.89	53.40 ± 9.12	NS
Gender, male/female, *n* (%)	48/29 (62.3/37.7)	47/30 (61.0/38.9)	NS
Body mass index, kg/m²	25.69 ± 4.00	25.33 ± 3.76	NS
Blood group, *n* (%)			NS
A	33 (42.9)	42 (54.5)	NS
B	5 (6.5)	4 (5.2)	NS
AB	0 (0)	3 (3.9)	NS
O	39 (50.6)	28 (36.4)	NS
Pretransplant dialysis versus preemptive kidney transplant, *n* (%)	65/12 (84.4/15.6)	55/22 (71.4/28.6)	NS
Residual urine diuresis before transplant, mL	1057.75 ± 852.84	1188.42 ± 818.65	NS
Rank of transplant			NS
First transplant, *n* (%)	73 (94.8)	76 (98.7)	NS
Second transplant, *n* (%)	3 (3.9)	1 (1.3)	NS
Third transplant, *n* (%)	1 (1.3)	0 (0)	NS
Time on dialysis before transplantation, d	1105 ± 1198	720 ± 757	NS
HLA Mismatching (MM), *n* (%)			NS
0 MM	11 (14.3)	6 (7.8)	
1 MM	8 (10.4)	7 (9.1)	
2 MM	30 (39.0)	16 (30.8)	
3 MM	23 (29.9)	30 (39)	
4 MM	2 (2.6)	7 (9.1)	
5 MM	3 (3.9)	6 (7.8)	
6 MM	0 (0.0)	5 (6.5)	
Hemoglobin before transplantation, g/dL	12.47 ± 1.72	12.69 ± 1.18	NS
Albumin before transplantation, g/dL	4.32 ± 0.40	4.24 ± 0.41	NS
Peritransplant plasmapheresis treatment, *n* (%)	14 (18)	3 (4)	[a]

[a]$P < 0.05$. Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; CMV: Cytomegalovirus; DBD: Donation after brain death; DCD: Donation after circulatory death; HLA: Human leukocyte antigen; KT: Kidney transplantation; MM: Mismatching; NS: No significance.

third month and from 3 mo after transplantation, respectively. Methylprednisolone was started immediately after transplant at 16 mg/d and tapered (minus 4 mg every 2 wk) to a fixed dose of 4 mg for all recipients at long-term. Co-trimoxazole prophylaxis was given to all patients during the first 6 mo after transplantation. Valganciclovir prophylaxis (900 mg/d for normal kidney function) was given to

Table 2 Surgical data of 154 recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during isolated kidney transplantation in a single-center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P value*
Indications for associated nephrectomy, *n* (%)			
Creating space for graft positioning, *n* (%)		74 (96.1)	
Pain, *n* (%)		29 (37.7)	
Recurrent urinary tract infections, *n* (%)		11 (14.3)	
Hematuria, *n* (%)		30 (39.0)	
Digestive symptoms, *n* (%)		3 (3.9)	
Lithiasis, *n* (%)		9 (11.7)	
Anastomosis time[1], min	39.61 ± 9.782	36.96 ± 10.10	NS
Cold ischemia time, min	827.56 ± 446.12	767.87 ± 436.81	NS
Total surgical time, min	169.07 ± 44.31	223.29 ± 71.96	[a]
Weight of removed native kidney, g		2073.94 ± 1197.89	

[1]Time from kidney out of ice water until moment of *in vivo* blood reperfusion.

[a]$P < 0.05$. Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; NT: Not significant; KT: Kidney transplantation; NS: No significance.

all patients during the first 6 mo after transplantation with the exception of cytomegalovirus donor seronegative/recipient seronegative patients. Biopsy-proven acute cellular rejection and humoral rejections were treated with methylprednisolone boluses for 3 d and plasmapheresis, respectively.

Follow-up

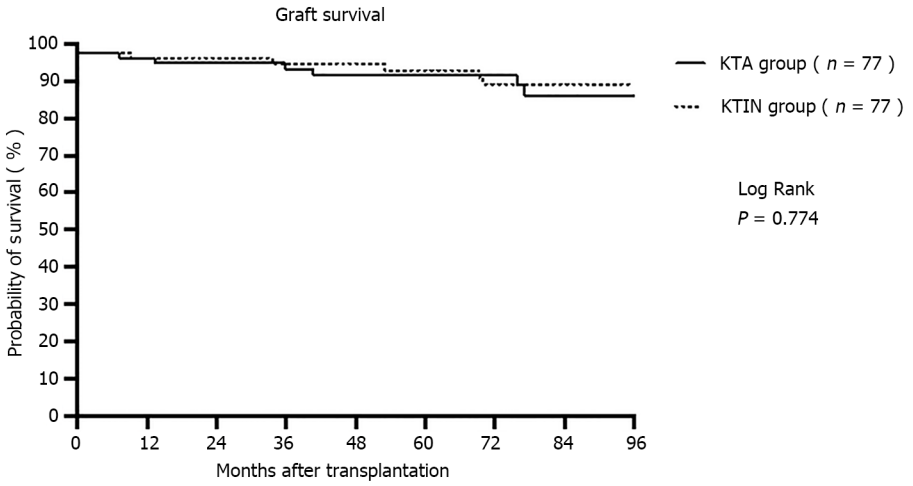
During the transplant hospitalization, the patients were monitored daily to evaluate comorbidity and kidney function was evaluated by serum creatinine and urine analysis. If primary nonfunction (PNF), delayed graft function (DGF) or vascular problems of the kidney graft were suspected, an urgent ultrasound was performed. Otherwise, a baseline ultrasound was performed at the end of the transplant hospitalization. Ambulatory follow-up of the kidney graft function (measured by serum creatinine and urine analysis) and surgical comorbidity was performed according to local center practice. No protocol, only indication biopsies of the kidney graft were performed after the preceding ultrasound. Every year after transplantation, an ultrasound of the kidney graft and the native kidneys was performed. If malignancy of the native kidneys was suspected, nuclear magnetic resonance was carried out.

Endpoints

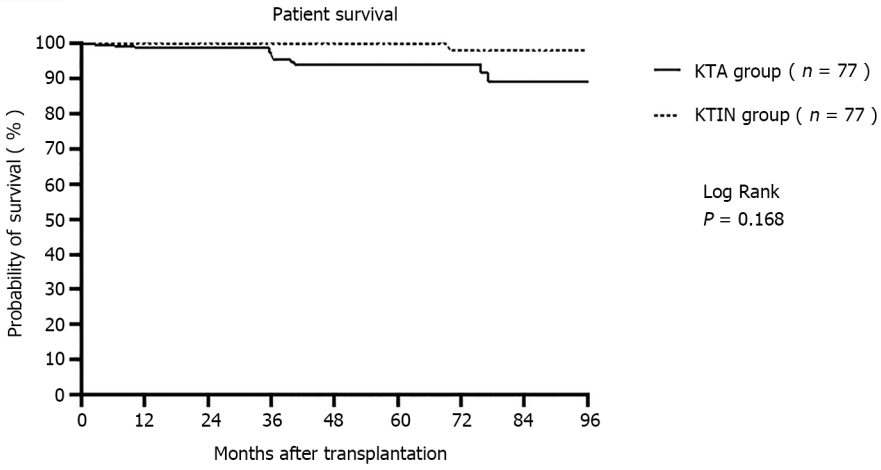
The primary endpoint was surgical comorbidity, measured as the incidence of postoperative lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for peritransplant (during and after transplantation) blood transfusion, pulmonary embolism, total hospital stay, readmission rate and surgical complications classified according to the Dindo Clavien classification [10]. Secondary endpoints were the incidence of PNF, DGF (defined as the need for dialysis during the first week after transplantation), venous or arterial kidney graft thrombosis, acute rejection incidence and type of rejection (cellular *vs* humoral) during the first year after transplantation and the 1- and 5-year patient- and graft survival rate.

Statistical analysis

Characteristics of the donor, the recipient and the transplant outcome were compared using the chi-square test for categorical variables and the t-test for continuous variables. Continuous variables are provided as means and standard deviations. Log-rank statistics were used with the Kaplan-Meier product-limit method to evaluate the associations of individual covariates with allograft survival. $P < 0.05$ was considered statistically significant. Statistical analysis and plots were accomplished with SPSS 24.0 statistical software (SPSS, Chicago, IL, USA) and Prism 8.2.0 (Graphpad Software, San Diego, CA, USA).



	Months after transplantation	12	24	36	48	60	72	84	96
KTA group (*n* = 77)	Graft survival rate (%)	94.8	93.5	92	90.3	90.3	90.3	85	85
	Patients at risk (*n*)	73	67	58	48	43	37	30	21
KTIN group (*n* = 77)	Graft survival rate (%)	96	96	94.6	94.6	92.8	89.2	89.2	89.2
	Patients at risk (*n*)	74	72	62	55	51	47	42	34



	Months after transplantation	12	24	36	48	60	72	84	96
KTA group (*n* = 77)	Graft survival rate (%)	100	98.7	97	93.8	93.8	93.8	88.7	88.7
	Patients at risk (*n*)	77	71	61	50	44	40	32	22
KTIN group (*n* = 77)	Graft survival rate (%)	100	100	100	100	100	98	98	98
	Patients at risk (*n*)	77	75	66	59	56	52	46	38

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Figure 2 The graft and patient survival of 154 isolated kidney transplant recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during transplantation performed in a single center transplant program from January 2007 until January 2019. KT: Kidney transplantation.

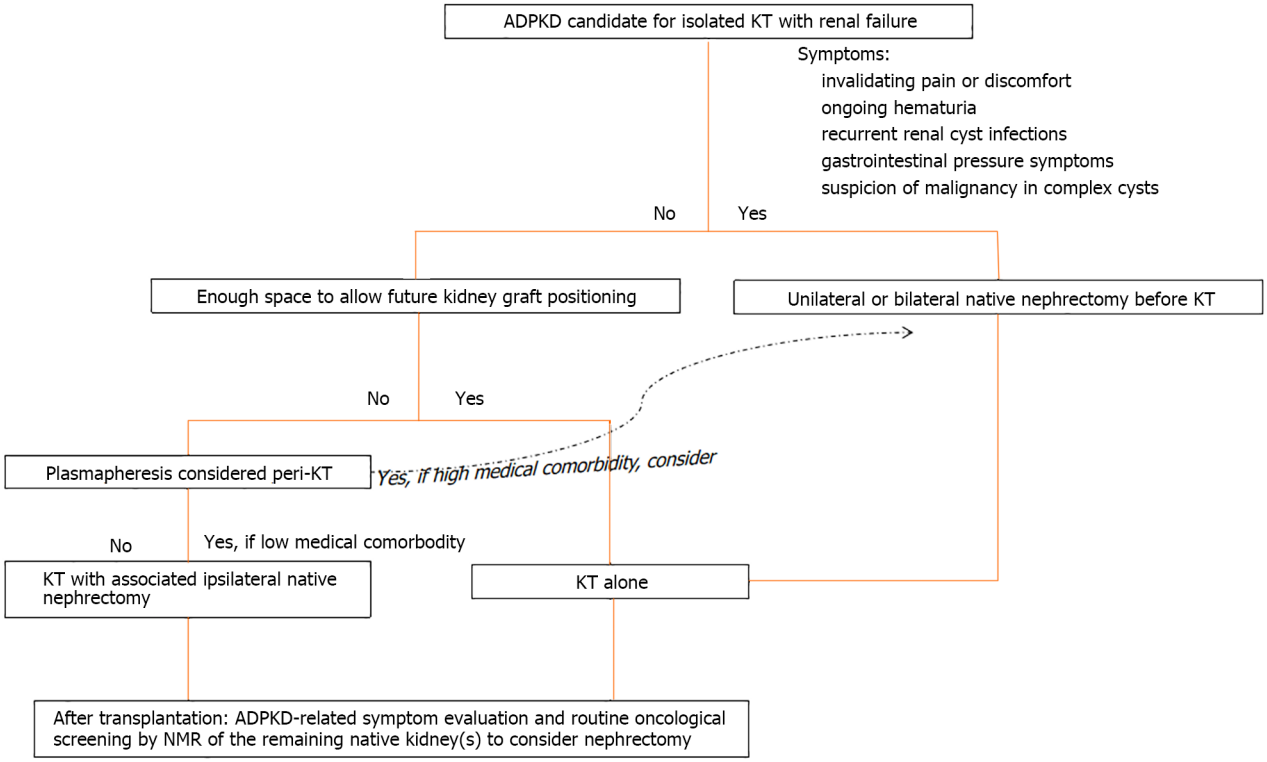
RESULTS

Donor and recipient characteristics

Donor and recipient characteristics of both study groups were comparable, with the exception of the incidence of living donation, which was significantly higher in the KTIN group compared with the KTA group [21 (27.3%) *vs* 6 (7.8%), *P* = 0.003] (Table 1). Peritransplant plasmapheresis was performed in 14 (18%) and 3 (4%) immunized recipients in the KTA and the KTIN group, respectively (*P* = 0.008).

Operative data

The main indications for performing an associated ipsilateral native nephrectomy at the same site as the kidney transplantation were lack of space for graft positioning (*n* = 74; 96.1%), pain (*n* = 29; 37.7%) and



DOI: 10.5500/wjt.v12.i5.100

Figure 3 Clinical algorithm to decide the optimal timing of a native nephrectomy in patients with autosomal dominant polycystic kidney disease, candidate for isolated kidney transplantation. ADPKD: Autosomal dominant polycystic kidney disease; NMR: Nuclear magnetic resonance; KT: Kidney transplantation.

hematuria (n = 30; 39.0%). Pain, as the only reason for ipsilateral nephrectomy, was present in 3 (3.9%) patients. The decision not to perform an associated ipsilateral native nephrectomy was taken by the surgeon during the transplant procedure if enough space for graft positioning in combination with the absence of other ADPKD-related symptoms was estimated at the moment of transplantation. No difference in anastomosis and cold ischemia time was observed between the two study groups (Table 2). The total surgical time was significantly longer in the KTIN group as compared with the KTA group (223.29 ± 71.96 *vs* 169.07 ± 44.31, respectively; P = 0.005). The mean weight of the removed polycystic kidney was 2073.94 ± 1197.89 g.

Comorbidity after transplantation

No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, pulmonary embolism, urinary infection, need for peritransplant blood transfusion, hospitalization stay, readmission rate and Dindo Clavien classification) was observed between the two study groups (Table 3).

Graft function and patient survival

The incidence of PNF and DGF was comparable in both groups [0% *vs* 2.6% (P = 0.497) and 9.1% *vs* 16.9% (P = 0.230), respectively, in the KTA and KTIN group] (Table 3). No significant difference in renal artery and vein thrombosis of the kidney graft was observed between the two study groups. In addition, the incidence of acute rejection within one year after transplantation was comparable among the groups.

The 1- and 5-year graft survival were 94.8% and 90.3, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774) (Figure 2). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168) (Figure 2).

DISCUSSION

This retrospective single-center study is one of the largest series to demonstrate the absence of a negative impact on surgical comorbidity and short- and long-term kidney graft function following an associated ipsilateral native nephrectomy to create space for graft positioning during isolated kidney transplantation in ADPKD patients compared with ADPKD kidney transplant recipients without simultaneous nephrectomy.

Table 3 Surgical comorbidity and clinical outcomes of 154 isolated kidney transplant recipients suffering from autosomal dominant polycystic kidney disease with or without associated ipsilateral nephrectomy during transplantation in a single center transplant program from January 2007 until January 2019

	KT alone group (*n* = 77)	KT with associated ipsilateral nephrectomy (*n* = 77)	*P* value
Surgical comorbidity			
Lymphocele, *n* (%)	5 (6.5)	7 (9.1)	NS
Wound infection, *n* (%)	6 (7.8)	2 (2.6)	NS
Incisional hernia, n%)	0 (0)	3 (3.9)	NS
Wound hematoma, *n* (%)	6 (7.8)	3 (3.9)	NS
Pulmonary embolism, *n* (%)	1 (1.3)	0 (0)	NS
Urinary infection, *n* (%)	14 (18.2)	8 (10.4)	NS
Need for blood transfusion, *n* (%)	22 (28.6)	34 (44.2)	NS
Hospital stay after transplantation, d	15.22 ± 6.662	14.81 ± 6.44	NS
Readmission rate during whole follow-up, *n* (%)	42 (46.2)	49 (63.6)	NS
Dindo Clavien classification			NS
Class I	36 (46.8)	33 (42.9)	NS
Class II	22 (28.6)	32 (41.6)	NS
Class III	7 (9.1)	3 (3.9)	NS
Class IV	12 (15.6)	9 (11.7)	NS
Clinical outcomes			
Primary nonfunction, *n* (%)	0 (0)	2 (2.6)	NS
Delayed graft function, *n* (%)	7 (9.1)	13 (16.9)	NS
Renal artery thrombosis of kidney graft, *n* (%)	2 (2.6)	0 (0)	NS
Renal vein thrombosis of kidney graft, *n* (%)	2 (2.6)	0 (0)	NS
Acute rejection episode within 1 year after transplantation, *n* (%)	5 (6.5)	5 (6.5)	NS
Cellular, *n* (%)	5 (100)	2 (40)	
Humoral, *n* (%)	0 (0)	3 (60)	

Data are given as the mean ± SD. ADPKD: Autosomal dominant polycystic kidney disease; NT: Not significant; KT: Kidney transplantation; NS: No significance.

The lifetime nephrectomy rate of at least one kidney is approximately 20-30% for patients with ADPKD[11,12]. Maintaining native kidneys in ADPKD transplant candidates may help to prevent renal osteodystrophy, anemia, uremia, fluid overload, congestive heart failure, and hyperkalemia[4,13,14]. The advantage of maintaining total native urine output is important for dialysis comfort in patients on the waiting list for transplantation and confers some survival benefits on the waiting list[15]. Even today, the indications and timing for a native unilateral or bilateral nephrectomy in ADPKD candidates for isolated kidney transplantation remain controversial and are quite often center-dependent and based on historical routine and experience. Clear indications for unilateral or bilateral native nephrectomy before transplantation are: (1) Invalidating pain and discomfort; (2) Ongoing hematuria; (3) Recurrent renal cyst infections and gastrointestinal pressure symptoms (*e.g.*, early satiety); (4) recurrent nephrolithiasis (rare); (5) The suspicion of malignancy in those with complex cysts; and (6) Combined liver and kidney transplantation. In the absence of these clear indications, the lack of space for positioning a future kidney graft remains controversial as an indication for performing a unilateral native nephrectomy before transplantation. We agree that a simultaneous ipsilateral nephrectomy to create space during isolated kidney transplantation can be technically challenging, even in the hands of an experienced surgeon. A review of the literature, as illustrated in Table 4, does not demonstrate a significant negative impact of an associated ipsilateral or bilateral nephrectomy during isolated kidney transplantation on surgical comorbidity and early and late allograft and patient survival[16-20]. The advantage of performing the nephrectomy simultaneous with the transplantation is the avoidance of an

Table 4 Overview of studies investigating the surgical comorbidity of a simultaneous native unilateral or bilateral nephrectomy during isolated kidney transplantation for autosomal dominant polycystic kidney disease

Ref.	Study group (n)	Type of donor	Isolated KT with simultaneous native bilateral or unilateral nephrectomy		KT alone	Study conclusions
			Bilateral	Unilateral		
Nunes P *et al*[13], 2007	1 (143)	LD (6%) + DD (94%)		+		Comparable overall complication rate and graft survival after 5 years if unilateral nephrectomy is performed for creation of space for a renal allograft
	2 (16)	LD (2%) + DD (98%)			+	
Kramer A *et al*[14], 2009	1 (20)	LD (100%)	+			Minimal morbidity of an associated bilateral nephrectomy during transplantation and graft and patient survival of 100% during 5-year follow-up
Skauby MH *et al*[15], 2012	1 (79); 2 (78)	LD (100%)	+		+	Associated bilateral nephrectomy results in a longer hospital stay and more postoperative complications. No difference in 1- and 5-year patient and graft survival
Neeff HP *et al*[16], 2013	1 (100)	LD (38%) + DD (62%)		+		Routine ipsilateral nephrectomy, independent of volume of polycystic kidney, during transplantation is a safe procedure without endangering patient or graft survival. The death of 3 patients in the first year post-transplant is a concern
Ahmad SB *et al*[17], 2016	1 (66)	LD (100%)	+			In symptomatic patients with ADPKD, the combined procedure is advantageous, especially in terms of patient satisfaction
	2 (52)				+	
Current study	1 (77)	LD (7.8%) + DD (92.2%)		+		Comparable surgical comorbidity and 1- and 5-year patient and graft survival
	2 (77)	LD (27.3%) + DD (72.7%)			+	

ADPKD: Autosomal dominant polycystic kidney disease; DD: Deceased donor; LD: Living donor; KT: Kidney transplantation.

extra anesthetic/surgical procedure and possible oliguria when performed before transplantation during the time on the waiting list. In line with these previous studies, the risk of losing a kidney graft, in relation to native nephrectomy is extremely low.

The proposed algorithm to decide the optimal timing of a native nephrectomy in candidates for isolated kidney transplantation is mainly based on ADPKD-related symptoms (Figure 3). In general, we do not perform a native nephrectomy to create space for graft positioning in the absence of ADPKD-related symptoms before transplantation but by preference during the transplantation. Patients with a pretransplant clinical examination showing a polycystic kidney below the level of the umbilicus or a radiological image showing a polycystic kidney extending into the iliac fossa, are very likely to need an ipsilateral native nephrectomy during transplant. Our center policy is to add peritransplant plasmapheresis to the standard immunosuppressive therapy in all high-immunized patients. Therefore, only for high-immunized patients with an expected long waiting time on the transplant list and high associated medical comorbidity, we consider a unilateral nephrectomy to create space for future kidney graft positioning before transplantation with the aim to decrease the risk of plasmapheresis-related surgical complications (bleeding, incisional hernias, blood transfusions, ...) during transplantation. This might explain the difference in the numbers of patients receiving peritransplant plasmapheresis in favor of the KTA group in our study. For high-immunized patients with low associated medical comorbidity, our preference is to perform the associated nephrectomy during the transplantation.

Also, our strategy is to avoid an unnecessary nephrectomy after transplantation. Today, it is unusual for ADPKD patients to require nephrectomies for complications related to their native kidney (< 20%) after transplantation[5]. Nuclear magnetic resonance of the abdomen is routinely performed after transplantation to screen for malignancies in the native polycystic kidney(s). Conflicting data exists regarding the risk of renal cell carcinomas in ADPKD-affected kidneys. While case studies report the occurrence of renal cell carcinomas in ADPKD-affected kidneys[21,22], these tumors may be partly due to acquired renal cystic disease resulting from long-term dialysis[23]. In contrast, data from the Scientific Registry of Transplant Recipients observed a lower cancer risk in polycystic kidney disease recipients. This might be explained by the ADPKD mutations causing clear cyst formation, but it is also possible that these mutations trigger protective cellular mechanisms that prevent cells from undergoing malignant transformation[24]. Ward CJ *et al*[25] demonstrated that germline mutations in polycystic kidney and hepatic disease 1 were protective against colorectal cancer. However, the observed lower

risk of renal cancer in the Scientific Registry of Transplant Recipients can also be explained by the higher incidence of nephrectomies in ADPKD recipients in contrast with their non-ADPKD counterparts[24].

We recognize some limitations in the present study. First, this a retrospective study. Second, in recipients with associated nephrectomy during isolated kidney transplantation, the lower incidence of peritransplant plasmapheresis and higher incidence of living donors could have underestimated the surgical comorbidity in this study group.

CONCLUSION

In conclusion, simultaneous native ipsilateral nephrectomy to create space for graft positioning during kidney transplantation in ADPKD patients does not detrimentally impact surgical comorbidity and short- and long-term graft survival.

ARTICLE HIGHLIGHTS

Research background

The lack of space, as an indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other autosomal dominant polycystic kidney disease (ADPKD)-related symptoms, remains controversial.

Research motivation

Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of increased surgical comorbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation.

Research objectives

To evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with ADPKD.

Research methods

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

Research results

No significant difference in surgical comorbidity (lymphocele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed between the two study groups. The 1- and 5-year graft survival were 94.8% and 90.3%, and 100% and 93.8%, respectively, in the KTA and KTIN group (P = 0.774). The 1- and 5-year patient survival were 96.1% and 92.9%, and 100% and 100%, respectively, in the KTA and KTIN group (P = 0.168).

Research conclusions

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with ADPKD does not negatively impact surgical comorbidity and short- and long-term graft survival.

Research perspectives

More kidney transplant candidates suffering from ADPKD when activated on the waiting list should be proposed for an associated ipsilateral nephrectomy during the transplantation instead of routinely programmed pretransplant nephrectomy.

FOOTNOTES

Author contributions: Darius T and De Meyer M designed the research; Bertoni S, De Meyer M and Darius T performed the research; Darius T analyzed the data; Darius T wrote the paper.

Institutional review board statement: This study was approved by the Institutional Board of our University Hospital on July 6, 2020.

Informed consent statement: All study participants provided informed written consent regarding personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at tom.darius@uclouvain.be

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ORCID number: Tom Darius 0000-0002-8151-4286; Sébastien Bertoni 0000-0001-8066-0639; Martine De Meyer 0000-0003-2002-6163; Antoine Buemi 0000-0001-9341-7902; Arnaud Devresse 0000-0003-4943-788X; Nada Kanaan 0000-0001-7903-8631; Eric Goffin 0000-0001-9242-7148; Michel Mourad 0000-0002-0372-275X.

Corresponding Author's Membership in Professional Societies: Belgian Transplant Society; European Society for Organ Transplantation; The Transplantation Society.

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OPINION REVIEW

Tolerance protocol of living kidney transplant for developing countries through basic strategy of lymphocyte depletion

Sufi M Suhail

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Sufi M Suhail, Department of Renal Medicine, Singapore General Hospital, Singapore 169856, Singapore

Sufi M Suhail, Department of Clinical Research, Duke-NUS Graduate Medical School, Singapore 169856, Singapore

Corresponding author: Sufi M Suhail, FRCP, MBBS, MRCP, Assistant Professor, Department of Renal Medicine, Singapore General Hospital, Block 6, Level 6, Outram Road, Singapore 169856, Singapore. grmsms@sgh.com.sg

Abstract

End-stage kidney failure (ESKD) is a global issue where kidney replacement therapy imposes enormous economic burden to people of developing countries, in addition to the severe limitations to the availability of hemodialysis and peritoneal dialysis technique. The best option of kidney transplantation also requires lifelong combination immunosuppressive medicines, the cost of which is equally comparable to lifelong dialysis. A strategy of achieving transplant tolerance that requires minimum immunosuppressive medicines, although in experimental stage, also requires state-of-art technology with costly medicines and interventions. This is evidently beyond the reach of ESKD patients of developing countries. Hence, globally in developing countries, a need for an innovative but cost-effective tolerance protocol is a burning need for a successful transplant program. In brief, transplant tolerance is defined as a state of donor-specific unresponsiveness to the allograft antigens without the need for ongoing pharmacologic immunosuppression or with a minimal need. Current state-of-art techniques involves: (1) A state of hematological chimera, for complete tolerance; (2) Prope or partial tolerance where immune-reactive T-lymphocytes are inhibited using monoclonal antibodies; and (3) Chimeric antigen receptor for T-regulatory (T-reg) cell therapy using genetically engineered T-reg cells targeting specific T-lymphocyte receptors for inducing anergy. From our real-world experience in transplant management in post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. We recently published a case study on a real-world experience transplant case where we explained a partial or prope tolerance that developed after lymphocyte ablation therapy, following which the allograft was maintained with low dose dual standard immunosuppressive medicines. Based on this publication, we propose here an innovative tolerance protocol for living related low risk kidney transplantation for

developing countries, in this opinion review.

Key Words: Renal allograft; B and T lymphocytes depletion; Tolerance protocol; Immunosuppressive medicines; Living renal transplant

Core Tip: In this opinion review that is based on our recent publication, the core tip concentrates on achieving a partial or prope tolerance in renal allograft through sequential B and T lymphocyte depletion in an approved and in-practice strategy, for living related and low risk kidney transplantation. The allograft would require a half dose dual immunosuppressive therapy subsequently.

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INTRODUCTION

Renal allograft, unlike autograft or isograft, would invoke rejection process through cellular and humoral immune mechanism by the nonself-antigen mediated alloimmune response. This results in rejection of the grafted organ unless immunosuppressive medicines targeting the donor/recipient T and B lymphocytes are in place. As opposed to the rejection process, tolerance is a state of unresponsiveness to the allograft, where the graft can be maintained without or with minimal immunosuppression. This is achieved by the use of effective innovative and aggressive immunosuppressive protocols[1].

Even though, safe and reliable strategies of achieving transplant tolerance are not in place, anecdotal reports and experimental animal studies targeting T and B lymphocyte ablation, offer hope[2]. However, these need cost and state-of-art infrastructures which are beyond the reach of end-stage renal failure patients in developing countries. Finding an innovative but cost-effective tolerance protocol remains an allusive goal for a successful transplant program for low economic zones.

In real-world experience (RWE) of transplant management when transplanted patients develop post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. Recently we published a case study of a living kidney transplant who achieved immunologic tolerance requiring low dose calcineurin inhibitor (CNI) with minimal prednisolone after the patient was treated by lympho-ablative therapy for Lymphoma that developed during the post-transplant period[3]. Based on this publication and our RWE with PTLD cases management[3], we would propose in this opinion review a partial or prope tolerance protocol that can be achieved through depletion of lymphocytes pre-emptively in low risk kidney transplant recipients. The added advantages being considered are the reduced requirements of stat-of-the-art technologies and reduced cost that are needed for achieving current desensitization and immunosuppressive protocols required for tolerance.

WHAT ARE THE CURRENT EVIDENCES OF TOLERANCE IN ALLOGRAFT?

In anecdotal case reports, complete tolerance was achieved in subsequent renal allograft where bone marrow transplant was done in case of Multiple Myeloma (MM) patients with lymphocyte ablation done by radiation and chemotherapy prior to kidney transplantation from the marrow donor. The grafted kidney did not require immunosuppressive medicines afterward[4]. This is a kind of tolerance obtained because of a form of hematologic chimera thus developed during treatment of MM through allogeneic bone marrow transplant where host immune system was replaced by donor marrow.

WHAT ARE THE MECHANISMS OF TOLERANCE AND REJECTION?

A brief outline of gross immunology physiology in fetal life and life after birth is presented in Figure 1A. Immune reactive cells undergo apoptosis on exposure of fetal self-antigens, thus leaving behind the cells which are naïve to any other foreign antigens. In life after birth, immune response shifts to proliferation and activation state in contrast to fetal state of apoptosis[5].

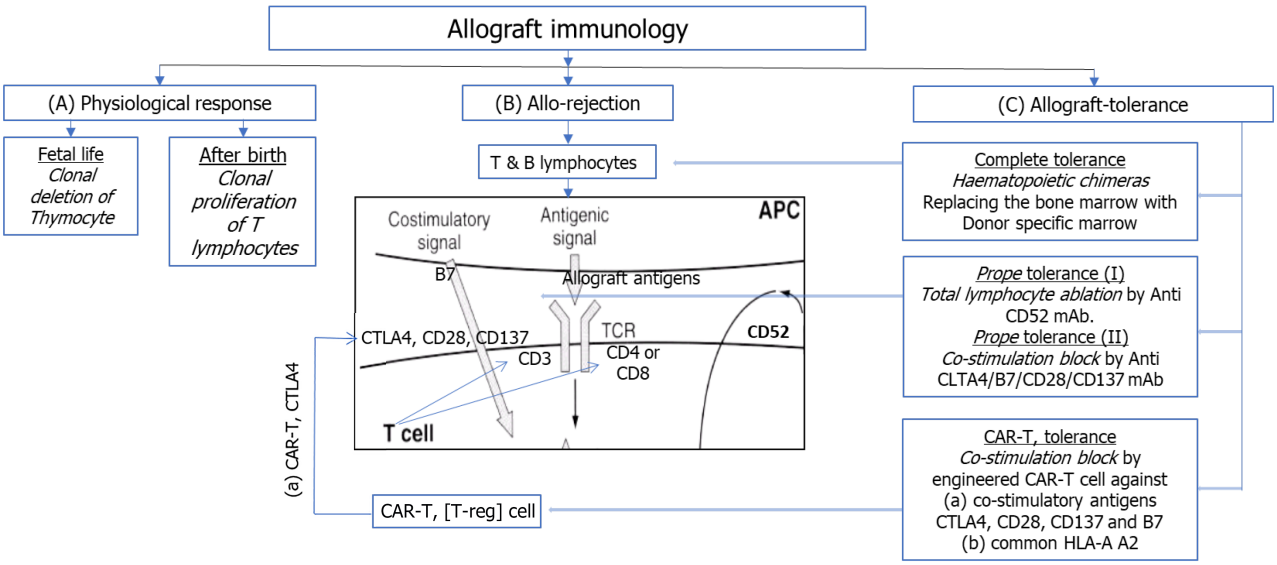

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Figure 1 The mechanisms of tolerance and rejection. A: In fetal life, T-lymphocyte response as the clonal deletion of auto reactive T-lymphocytes in the thymus to the fetal antigens so that the organism is rendered self-tolerant to self-antigens, whereas after birth these changes to the state of clonal proliferation on exposure to exogenous antigens; B: In presence of allograft the immune reactive T-lymphocytes and subsequently B-lymphocytes, carry out the process of immune response and rejection as carried out by hematologic immune cells. Suppression of this mechanism leads to graft maintenance; C: Possible tolerance inducing strategies. APC: Antigen presenting cell; CD: Cluster differentiation; T-eff: T-effector; T-reg: T-regulator lymphocyte; CTLA4: Cytotoxic T-lymphocyte associated antigen 4; mAb: Monoclonal antibody; CAR-T: Chimeric antigen receptor encoded T-reg cell.

Thus immune cells show immune response by proliferating and reacting to foreign antigens and allograft, as shown in Figure 1B. This induces T-cell proliferation, and results in cell mediated cytotoxicity and inflammation that results in acute rejection unless immunosuppressive therapies are imposed[6].

Figure 1C summarizes the current research-based adoptable protocols for achieving anergy (tolerance). Firstly, achieving a state of hematologic chimera, in other ward, complete tolerance; Second, a state of partial or prope tolerance, where immunoreactive T-lymphocytes are depleted or suppressed; and third, the newer, CAR-T (Chimeric Antigen Receptor for T-reg therapy). T-reg cells are genetically manipulated to express co-stimulatory receptors on their surfaces, that results in blocking of co-stimulatory signal-2. This causes ablation of T-cell immunoreactivity resulting in anergy or tolerance.

WHAT ARE THE CURRENT PRACTICES OF TOLERANCE PROTOCOLS IN RENAL ALLOGREAFT?

Road to complete tolerance has not opened yet because of lack of available protocols.

Transplantation among monozygotic twins does not require immunosuppressive medications, hence is an example of complete tolerance[7].

Partial or prope tolerance is available using Campath-1H where allograft could be maintained with minimal immunosuppression with Low dose Cyclosporine-A (CSA) alone. CAMPATH-1H is monoclonal antibody (mAb) against CD52 antigen present on surface of all lymphocytes. Anti-CD52 mAb administration causes ablation of all lymphocytes that lasts for long period. The new lymphocytes that are subsequently produced from lymphoreticular tissues are naïve to the grafted kidney, inducing tolerance[8]. This was demonstrated in 3C, INTAC and other studies, showing promising evidences to tolerance[9]. This is costly and requires infrastructures where infections and patient safety protocols can be monitored. In many low economic zones, expected to be not feasible.

Current approach to tolerance is focused on inducing anergy to the reactive host or graft T-lymphocytes by blocking the co-stimulatory signal to CD-3 T-lymphocytes either by unique mAb against receptors for T-lymphocyte co-stimulation [CTLA-4 (cytotoxic T-lymphocyte associated antigen 4), CD28, B7, CD137]—the so called signal-2 co-stimulation, inducing T-lymphocyte anergy, or by CAR-T therapy targeting T-regulatory lymphocyte's CTLA-4 antigen, to block co-stimulation of CD3 T-lymphocytes, inducing tolerance (anergy) for all T-lymphocytes.

BENEFIT study used Belatacept, a selective co-stimulation blocking mAb against CTLA-4 mentioned above for inducing anergy, to show a partial tolerance[10]. But the results were not promising.

Most recently, research on CAR-T therapy targeting CTLA-4 co-stimulatory receptor on the CD-3 T-lymphocytes for induction of T-lymphocyte anergy, produced promising results in pancreatic islet cell graft, as well as cutaneous graft[11,12]. Furthermore, these therapies are exceedingly costly.

HOW RECIPIENT AND DONOR FACTORS AFFECT IMMUNOSUPPRESSION AND TOLERANCE?

Highly sensitized recipients and marginal donors would impact the outcome of immunosuppression and concepts of tolerance.

A higher immunosuppressive protocol for graft survival is required for recipients with preformed antibodies against donor antigens that includes pre-transplant desensitization[13]. ABO incompatible recipient and recipient with donor specific antibodies requires desensitization protocol. Recipients with multiple blood transfusion recipients, multigravida, cases of repeat transplant, are highly immunogenic showing frequent cross-match positive results for both B and T-lymphocytes[14]. Consequently, tolerance protocols may not be appropriate for these groups of highly immunogenic recipients.

Organ donors with high immunogenicity are ABO incompatible and HLA mismatch donors, deceased donors, and harvested kidney with long cold ischemia time. These require increased immunosuppression[15,16]. In addition, may require desensitization protocol with cascade plasmapheresis and immuno-adsorbtion techniques. This is combined with use of various anti-lymphocyte antibodies and combination of potent immunosuppressive medicines. These protocols are available to be practised in targeted high risk kidney transplantation. Obviously achieving a successful protocol of tolerance could be a matter of ingenuity here.

HOW SHOULD BE THE PARADIGM SHIFT TO TOLERANCE FROM CONVENTIONAL IMMUNOSUPPRESSION?

The objectives of tolerance protocol are: (1) Minimum acute rejections; (2) minimum use of immunosuppressive medicines; (3) normal graft function; and (4) reduced short term and long term complications.

Shift to tolerance from conventional immunosuppression should be planned for minimally and normally immunogenic kidney donors and recipients, as described above. ABO compatible, better HLA matching, closer family members and matching body parameters are important considerations. All other donor recipient relationships are not appropriate for any tolerance protocol.

Available protocols for partial tolerance involve depletion of lymphocytes at the initial period of transplant surgery. The examples are, 3C, INTAC studies, where lymphocyte depletion was achieved using CAMPATH-1H mAb[8,9]. Sadly, lack of generalization and limiting factors of higher incidences of sepsis and malignancy limit their application[10]. Use of CAR-T therapy against T-lymphocyte receptors is also in infancy for renal transplantation[11,12]. For low socio-economic zones, nonetheless, they are irrelevant.

WHAT COULD BE THE TOLERANCE PROTOCOL FOR DEVELOPING COUNTRIES WHERE BURDEN OF END-STAGE KIDNEY FAILURE ALSO EQUALLY HIGH?

In RWE cases of PTLD, the point to note is depletion of lymphocytes with use of R-CHOP cycles for PTLD as mentioned in earlier sections. Profound lymphocytopenia and neutropenia that resulted from these R-CHOP therapy, required withdrawal of some immunosuppression like Mycophenolate Mofetil (MMF). The grafted kidney was subsequently maintained with a small dose of prednisone and a low dose of CSA[3].

Thus we summarize the protocol in Figure 2 as follows: The protocol starts with selection of donor and recipient, as shown in Figure 2A—the donor would be living ABO compatible donor with maximum possible HLA match and negative for B and T-lymphocyte cross match. The recipient needs to be of low immunologic risk with Panel Reactive Antibody titer less than 26%.

The subsequent steps are shown in Figure 2B as follows: First step is elective bone marrow suppression with a few R-CHOP cycles as described, each cycle consisted of IV Rituximab, IV Cyclophosphamide, IV Doxorubicin and IV Vincristine. This is followed by oral Prednisolone 50 mg daily for 5 days. This cycle is repeated 3 to 6 times till the desired depletion of Lymphocytes is achieved as mentioned earlier[3].

Second step: For low risk renal transplant, induction with Anti-CD25 mAb along with MMF, CNI and IV Hydrocortisone (or Solumedrol) at standard doses till stable graft function is achieved. We used 2 doses of IV Basiliximab as anti-CD25 mAb 20 mg IV at interval of 4 d at induction. We used CSA as CNI with a target Peak level of 1000 to 1200 μg/L at the beginning with reduction to 600 to 800 μg/L at

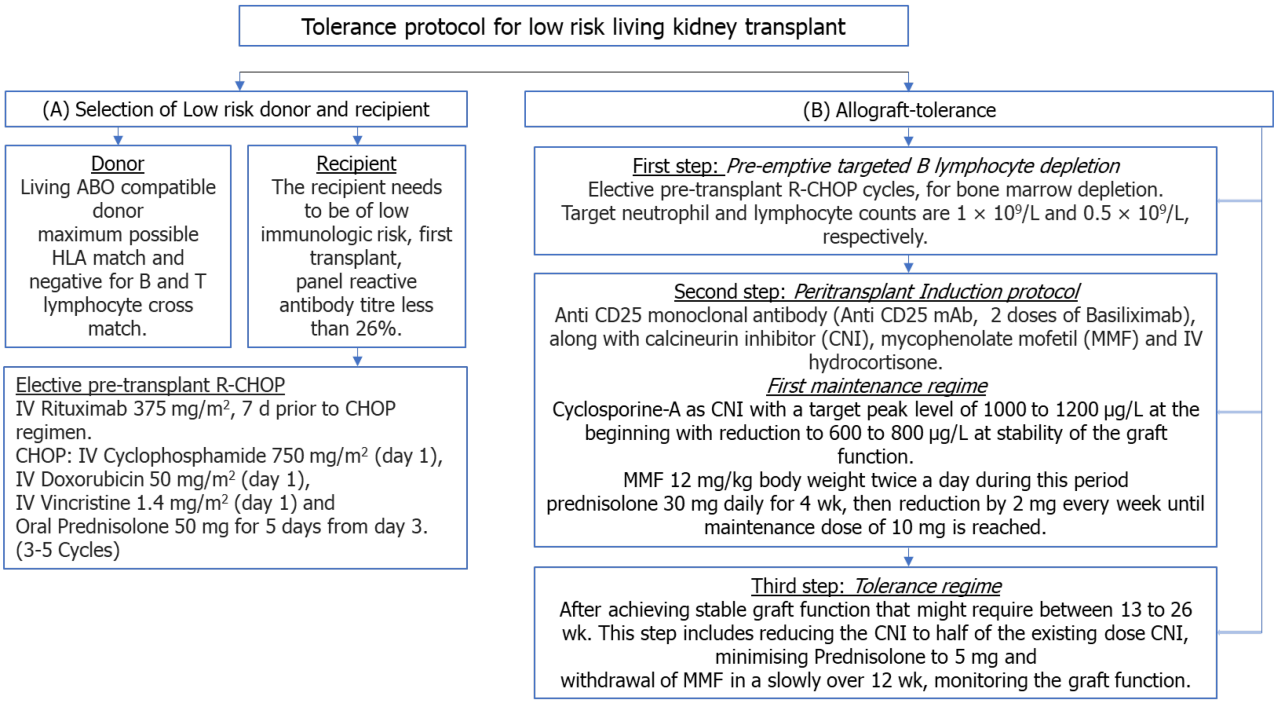

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Figure 2 The tolerance protocol methodology for low immunogenic living kidney transplantation. A: Selection of Living donor and low immunogenic recipient; B: Sequence of peri-transplant protocol for B lymphocyte depletion, followed by transplantation and induction of immunosuppression. Subsequently, migration to tolerance regime.

stability of the graft function. MMF was used at 12 mg/kg body weight twice a day during this period. We used Prednisolone 30 mg daily for 4 wk, then reduction by 2 mg every week until maintenance dose of 10 mg is reached.

Third step: After achieving stable graft function that might require between 13 to 26 wk, to reduce CNI to half of the existing dose (target peak level and trough levels, 300 and 50 µg/L respectively). Over time, Prednisolone to be reduced to 5 mg daily and MMF to be withdrawn slowly over 12 wk, monitoring the graft function[17].

HOW COULD THIS TOLERANCE PROTOCOL FOR LOW RISK LIVING TRANSPLANT BE VALIDATED?

Firstly, the use of R-CHOP therapy is validated as B-lymphocyte depleting treatment in Lympho-proliferative diseases as a standard therapy[3]. This was used in the RWE scenario for treating the PTLD that developed later. Subsequently, the allograft was maintained with low dose dual immunosuppression with stable graft function for long time. Following this practical experience, use of this B-lymphocyte depletion regime is aimed to achieve predominant B-lymphocyte depletion prior to transplant surgery. Subsequently following the transplant of the allograft, the recipient's marrow would produce B-lymphocytes (now new host B-lymphocytes) that are naïve to the renal allograft antigens (resident antigens). Consequently, as the new host B-lymphocytes are naïve to the grafted resident antigens, it would not display humoral immune response against the graft tissue.

Secondly, the validity for using MMF and CNI at the beginning is to avoid incidence of acute cellular rejection by depleting resident and host T-lymphocytes at the engraftment period post-transplant[18]. New batch of T-lymphocytes are produced by lymphoreticular system that are naïve to the renal graft. Thus, the newer lymphocytes (host T-lymphocytes), appear to take the allograft antigens (resident antigens) as self, thus do not cause cellular immune rejection.

Thirdly, B-lymphocyte depletion in a sequential manner as above before transplant surgery followed by immediate post-transplant T-lymphocyte depletion by anti CD25 mAb with CSA and MMF, enables the host acquire a state of prope tolerance to the renal allograft that was observed in the RWE scenario. The dual immunosuppressive medicines at lower dose maintain the graft and avoids long and short term complications of currently used medicines[19].

Lastly, risk of infection post-lymphocyte depletion, as described, would be similar to current existing strategies used in high risk renal transplant programs as well as same as lymphocyte ablative therapies used in Lymphoma. Paradoxically, the risk of infection would be rather reduced following the cycle of

lymphocyte depletion strategy as mentioned, because the strategy is time limited. This therapy would be followed by rather a reduced and dual immunosuppressive low CNI trough level therapy to maintain the renal graft. In practical situations of Lymphoma treatment, infection and recurrent malignancies are rather infrequent. In the RWE case and several other similar situations, recurrent malignancies and infections were not of frequent impediments.

HOW WILL THIS TOLERANCE PROTOCOL IMPACT CURRENT TRANSPLANT PROGRAM?

Current transplant protocols with newer monoclonal antibodies, desensitization procedures and newer drugs, may impact disastrously in many programs of transplantation[18]. Nevertheless, kidney transplant is considered best renal replacement therapy in End-stage kidney failure (ESKD).

For a sustainable transplant program guideline-based immunosuppressive regimens and opinion based protocols are required for highly immunogenic donor-recipient relationship. The parody lies in the disparity of the economics and infrastructures for provision, and extent of ESKD cases in developing regions. In such situation, an alternative approach may be considered.

This tolerance protocol could be suitable and applicable in RWE situations for low risk transplant scenario. In developing countries ethics committee may contribute to the feasibility of low risk living renal transplantation for maintaining a reasonable transplant program to reduce the burden of ESKD at lower cost and feasible infrastructures.

HOW THIS TOLERANCE PROTOCOL DIFFERS FROM EXISTING TOLERANCE PROTOCOLS?

We aimed at a sequential lymphocyte depletion therapy rather than an ablative therapy. The sequence starts with B lymphocyte depletion with cycles of R-CHOP therapy to achieve the target Neutrophil and lymphocyte levels, pre-transplant. Following living kidney donation (LKD) transplant with a low immunogenic donor-recipient risk-relation, standard triple immunosuppressive protocol with CNI, MMF and prednisolone will resume for achieving stable graft function. This will be followed by step wise and monitored reduction of immunosuppression to a half trough level CNI and minimum alternate day Prednisolone regimen. Thus, episodes of immediate acute rejections are minimized and a prope or partial tolerance with low dose dual immunosuppressive strategy is achieved.

The strategy of CNI half trough level as described, and alternate day low dose prednisolone is described as prope or partial tolerance. The monitoring of this tolerance would be the regular monitoring of graft function by serum creatinine levels and hematuria and proteinuria levels. In essence, it is the equivalent monitoring of a standard graft kidney.

This strategy to induce partial or prope tolerance, even though is meant for facilitating low risk LKD transplant in developing countries for reasons explained in the epilog, in fact, it will benefit the recipients world-wide. I would rather think that developed countries are better equipped with ancillary supportive infrastructure to consider this proposed protocol.

In the abstract, a detailed background introduction was mentioned in order to simplify the understanding of issues related to scope of transplant needs, especially in developing countries with marked limitations in infrastructure, finance, and scarcity of dialysis facilities for an increasing population of ESKD. To maintain a universal understanding of different stakeholders of chronic kidney disease, the article did a little elaboration before focusing on the strategy of partial tolerance.

CONCLUSION

In our recent publication[3], we discussed the real world experience scenario renal transplant case who achieved prope or partial tolerance requiring a low dose dual immunosuppression following B lymphocyte depletion therapy for PTLD. In this opinion review, we extrapolate that B lymphocyte depletion protocol to living kidney transplant of low immunogenic risk. Considering the impact of ESKD burden in developing nations, respective transplant societies with their corresponding ethics committee, would consider this proposed protocol for low risk living kidney transplant program.

ACKNOWLEDGEMENTS

We felt impulse for attracting relevant transplant organizations in particular, in the developing nations, where discrepancy in the availability of infrastructure for state-of-the-art technology for immunosup-

pressive protocols and the ESKD burden, makes a successful transplant program, difficult. With that view in mind we progressed to this opinion review based on our recent publication on this subject[3]. The opinion and conclusion of this opinion review are those of the author only.

FOOTNOTES

Author contributions: Suhail SM has contributed to the opinion and conclusion of this opinion review solely. He based this opinion review based on his recent publication with a view to confer generalizability of the protocol for the greater interest of ESKD patients of developing countries with an intention to attracting relevant transplant organizations there, where the ESKD burden is high and the availability kidney transplant program is low. The planning of contents of the review and the designs of the figures were done by the author based on the existing information in transplant medicine.

Conflict-of-interest statement: This opinion review is done based on our recent publication with a view to confer generalizability of the protocol for the greater interest of ESKD patients of developing countries.

Country/Territory of origin: Singapore

ORCID number: Sufi M Suhail 0000-0001-9514-475X.

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ORIGINAL ARTICLE

Retrospective Study

Reduced upper limb lean mass on dual energy X-ray absorptiometry predicts adverse outcomes in male liver transplant recipients

Penelope Hey, Rudolf Hoermann, Paul Gow, Timothy P Hanrahan, Adam G Testro, Ross Apostolov, Marie Sinclair

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Penelope Hey, Paul Gow, Timothy P Hanrahan, Adam G Testro, Ross Apostolov, Marie Sinclair, Liver Transplant Unit, Austin Health, Heidelberg 3084, Australia

Penelope Hey, Rudolf Hoermann, Paul Gow, Adam G Testro, Ross Apostolov, Marie Sinclair, Department of Medicine, University of Melbourne, Melbourne 3052, Australia

Corresponding author: Penelope Hey, FRACP, MBBS, Research Fellow, Staff Physician, Liver Transplant Unit, Austin Health, 145 Studley Road, Heidelberg 3084, Australia.
penny.hey@austin.org.au

Abstract

BACKGROUND

Pre-transplant muscle wasting measured by computed tomography has been associated with adverse clinical outcomes after liver transplantation including increased rates of sepsis and hospitalisation days. Upper limb lean mass (LM) measured by dual-energy X-ray absorptiometry (DEXA) was recently identified as a novel predictor of sarcopenia-associated mortality in men waitlisted for transplantation.

AIM

To investigate the use of DEXA LM in predicting gender-stratified early post-transplant outcomes.

METHODS

Liver transplant recipients who underwent pre-transplant DEXA body composition imaging between 2002 and 2017 were included. Endpoints included post-transplant mortality and graft failure, bacterial infections, acute cellular rejection (ACR) and intensive care and total hospital length of stay.

RESULTS

Four hundred and sixty-nine patients met inclusion criteria of which 338 were male (72%). Median age was 55.0 years (interquartile range 47.4, 59.7) and model for end-stage liver disease (MELD) score 16. Median time from assessment to transplantation was 7 mo (3.5, 12). Upper limb LM was inversely associated with bacterial infections at 180 d post-transplant (hazard ratio = 0.42; 95% confidence interval: 0.20-0.89; P = 0.024) in males only. There was a negative correlation between upper limb LM and intensive care (τ_b = -0.090, P = 0.015) and total

hospital length of stay (τ_b = -0.10, P = 0.0078) in men. In women, neither MELD nor body composition parameters were associated with post-transplant adverse outcomes or increased length of stay. Body composition parameters, MELD and age were not associated with 90-d mortality or graft failure in either gender. There were no significant predictors of early ACR.

CONCLUSION
Sarcopenia is an independent and potentially modifiable predictor of increased post-transplant bacterial infections and hospital length of stay in men with cirrhosis. DEXA upper limb LM provides a novel measure of muscle wasting that has prognostic value in this cohort. The lack of association in women requires further investigation.

Key Words: Dual-energy X-ray absorptiometry; Sarcopenia; Body composition; Liver transplantation; Survival

Core Tip: Pre-transplant sarcopenia as measured by single-slice computed tomography has prognostic value in predicting outcomes in liver transplant recipients. In this retrospective study, we explore the association of pre-transplant dual-energy X-ray absorptiometry (DEXA) body composition analysis with early post-transplant outcomes. Low upper limb lean mass (LM) was a predictor of 180-d post-transplant bacterial infections and longer hospital and intensive care length of stay in men but not women. Upper limb LM was superior to other measures of LM including appendicular LM in predicting adverse outcomes. There was no association between pre-transplant body composition and post-transplant mortality, graft failure or early acute cellular rejection. In conclusion, pre-transplant sarcopenia is associated with adverse outcomes in men after liver transplantation. Upper limb LM provides a novel measure of muscle mass that is superior to other measures of LM on DEXA in predicting early post-transplant outcomes.

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INTRODUCTION

Sarcopenia is a syndrome defined by decreased muscle mass and reduced strength or function[1]. It is estimated to affect between 40% and 70% of patients waitlisted for liver transplantation depending on the modality used to measure muscle mass[2]. Sarcopenia is a predictor of waitlist mortality, independent of model for end-stage liver disease (MELD) score[3]. Muscle wasting measured using the cross-sectional muscle area at the third lumbar vertebrae on computed tomography (CT) is associated with longer hospital length of stay and increased risk of post-operative complications following liver transplantation[4,5].

There is emerging evidence for the role of dual-energy X-ray absorptiometry (DEXA) body composition to quantify muscle mass in cirrhosis. DEXA provides whole body compartmentalised measurements of bone mineral content, fat mass and lean tissue. It has the advantage of being a simple, reproducible, low-cost technique that can be performed easily on outpatients being worked up for transplantation. Results are readily available without the need for further analysis or dedicated software. The major limitation for the use of DEXA in cirrhosis is that it can be influenced by hydration status including the presence of ascites and oedema. To reduce the impact of ascites, appendicular lean mass (APLM), the sum of LM in arms and legs corrected for height is the preferred measure for sarcopenia in cirrhosis.

We recently identified that upper limb LM was a novel, independent predictor of sarcopenia-associated mortality in men waitlisted for transplantation[6]. Upper limb LM rather than total APLM has the advantage of being unaffected by peripheral oedema. This study aims to describe the associations between pre-transplant gender-specific body composition measurements and early post-transplant outcomes.

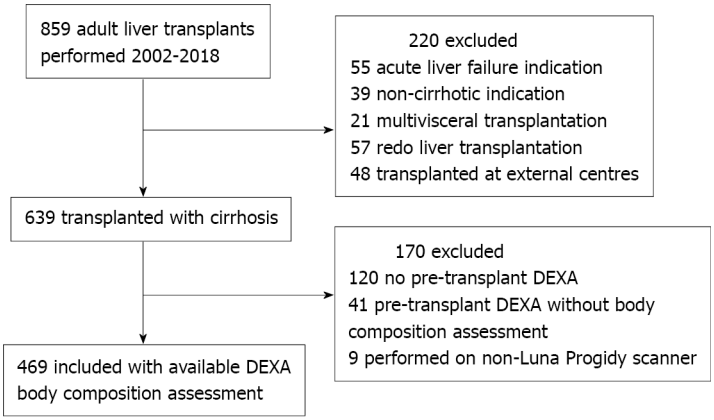

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Figure 1 Flowchart of inclusion and exclusion of patients undergoing liver transplantation. DEXA: Dual-energy X-ray absorptiometry.

MATERIALS AND METHODS

Study design

This study retrospectively analysed data of all adult patients (> 18 years) who underwent liver transplantation at a tertiary centre in Melbourne, Australia, between January 2002 and July 2018. Exclusion criteria included transplantation for non-cirrhotic indications, redo liver transplantation, multi-visceral transplants and those missing DEXA body composition data at transplant assessment. Approval was obtained by the Austin Health Human Ethics Research Committee.

Clinical and laboratory assessments

Baseline demographics including age and aetiology of liver disease were recorded at transplant assessment. Clinical examination findings including presence of hepatic encephalopathy and ascites were recorded by a transplant hepatologist. Ascites was graded as requiring no treatment, diuretic therapy alone or paracentesis. Body mass index was calculated at the time of the DEXA. Biochemistry and haematology were measured at transplant assessment, all within 6 wk of the DEXA scan. Laboratory assessments included bilirubin, serum creatinine, international normalized ratio and serum albumin to enable calculation of MELD and Child Pugh Scores. Operative data at the time of liver transplantation was collected including cold and warm ischaemic time (minutes), operative time (minutes), and blood transfusion requirement (units).

Body composition assessment

DEXA body composition analysis was performed at the time of transplant assessment using a Lunar Prodigy DEXA scanner (GE Healthcare, Madison, WI. United States). This quantified compartmentalised total body composition including LM, fat mass and bone mass. Variables analysed included appendicular, upper limb, lower limb and total LM and fat mass. All measurements were corrected for height^2. Sarcopenia was defined by previously reported cut-off values for APLM from the European Working Group on Sarcopenia in older people (males < 7.26 kg/m^2, females < 5.5 kg/m^2)[7,8].

Clinical endpoints

Clinical endpoints were examined at 90 d, 180 d and 12 mo post transplantation and included mortality, graft failure, bacterial infections, and acute cellular rejection (ACR). Graft failure was defined as graft loss requiring re-transplantation or due to patient death. Bacterial infections required the identification of a causative pathogen treated with systemic antimicrobial therapy. ACR was biopsy proven, defined as a rejection activity index ≥ 4 based on Banff criteria. Other outcomes included post-transplant intensive care stay (hours), hospital length of stay (days) and discharge destination (discharge to home or subacute care). Length of stay data excluded patients who died within the early post-operative period, within 48 h of transplantation.

Peri-operative and early post-operative management

Orthotopic liver transplantation was performed according to unit protocol and included both donation after brain death and donation after cardiac death. Organ allocation was based on the MELD scoring system. Protocolised immunosuppression comprised intravenous corticosteroids administered from day 0 to day 5 post-transplantation followed by a weaning course of oral corticosteroids. A combination of oral calcineurin inhibitors (cyclosporin or tacrolimus) and either mycophenolate mofetil or azathioprine were initiated early post-transplantation. A gradual switch from azathioprine to mycophenolate mofetil

was made following Therapeutic Goods Administration approval of the latter medication in Australia in 2012. Intravenous basiliximab was administered at day 0 and 5 in patients with impaired renal function to allow delayed commencement of calcineurin inhibitors.

Statistical analysis

Continuous variables were expressed as a median and interquartile range (25th and 75th percentile). Chi squared and fisher's exact tests were used for categorical variables. Continuous variables were compared using students *t* test (normal distribution) or Mann-Whitney *U* test (without normal distribution). Kendall Rank correlations were used to assess correlations between pre-transplant variables and post-transplant intensive care and hospital length of stay.

Survival analysis was used to follow patients after liver transplantation until they had died, experienced a complication such as bacterial infection or graft failure, or their status had last been audited. Univariate Cox proportional hazard regression analysis was used to identify predictors of 90-d and 12-mo post-transplant mortality and graft failure. Univariate and multivariate Cox regression analyses were used to identify predictors of 90 and 180-d post-transplant bacterial infections and 90-d ACR. Two-sided $P < 0.05$ conferred significance for all tests. The statistical software package R 4.1.2 for Mac with the survival package 3.2-13 was used for the analyses[9,10].

RESULTS

Baseline patient characteristics

Between January 2002 and December 2018, 859 adults underwent liver transplantation (Figure 1). Four-hundred and sixty-nine patients had available pre-transplant DEXA body composition data and met the inclusion criteria. Three-hundred and thirty-eight (72%) were male. The median age was 55.0 years (interquartile range 47.4, 59.7) and MELD score 16 (Table 1). The most common indications for liver transplantation were decompensated cirrhosis caused by viral hepatitis (n = 138, 29%) and alcohol (n = 51, 11%). Hepatocellular carcinoma in the context of cirrhosis was the primary indication for transplantation in 122 patients (26%). At transplant assessment, 259 (55%) patients had ascites, of which 137 (29%) had required recent paracentesis. A history of hepatic encephalopathy was reported in 220 patients (47%). The median time from assessment to transplantation was 7 mo (3.5, 12).

Body composition assessment

Using DEXA body composition assessment, the median APLM was 7.91 kg/m^2 (7.15, 8.71) for males and 6.50 kg/m^2 (5.87, 7.36) for females. Based on previously reported cut-off values[7], 95 men (28%) and 19 women (15%) were sarcopenic (Table 1). Women had higher fat mass, 7.56 kg/m^2 (5.48, 9.95) compared to men, 6.41 kg/m^2 (4.70, 9.31), P = 0.018.

Mortality and graft failure

At 90 d and 12 mo post transplantation, 15 (3.2%) and 33 (7.0%) of patients respectively had died. 12-mo post-transplant survival increased in the latter half of the period examined from 90% in 2002-2009 to 96% in 2010-2018. Pre-transplant body composition parameters, MELD and age were not associated with 90-d or 12-mo post-transplant mortality in men. Higher total LM but no other LM parameters was associated with 12-mo mortality in women [hazard ratio (HR) = 1.22; 95% confidence interval (CI): 1.04-1.44; P = 0.017]. Peri-operative blood transfusion requirements was associated with 90-d and 12-mo mortality in both men (HR = 1.21; 95%CI: 1.06-1.39; P = 0.006) and women (HR = 1.24; 95%CI: 1.10-1.40, P = 0.006). Of the 15 patients who died within 90 d of transplantation, only 3 met previously reported DEXA-based gender-specific diagnostic criteria for sarcopenia using APLM[7].

At 90 d and 12 mo post transplantation, 22 (4.6%) and 43 (9.2%) of patients respectively had graft failure. Body composition parameters, MELD and presence of ascites at workup were not associated with 90-d or 12-mo graft failure in men. Higher intra-operative blood transfusion requirement was associated with 90-d graft failure in both genders. Longer operative time was also associated with 90-d graft failure in men only (HR = 1.004; 95%CI: 0.001-1.008; P = 0.017).

Post-transplant bacterial infection

At 90 d and 180 d post-transplant, 59 (17.5%) and 73 (21.6%) men respectively had suffered a bacterial infection. Reduced upper limb LM was associated with bacterial infections in men at 180 d only, HR = 0.42; 95%CI: 0.20-0.89 (Table 2). The presence of ascites at transplant assessment was associated with 90-d and 180-d post-transplant bacterial infection in men only. Body composition parameters, MELD score, ascites and operative variables did not show an association with 90-d or 180-d bacterial infections in women.

ACR

At 90 d post transplantation, 105 patients (22.4%) had an episode of moderate to severe ACR. In men,

Table 1 Baseline patient characteristics based on gender and presence of sarcopenia defined by low appendicular lean mass[8]

	Non-sarcopenic (*n* = 355, 75.7%)	Sarcopenic (*n* = 114, 24.3%)	*P* value
Age, indication for transplantation	55 (48, 60)	54 (46, 58)	0.253
Viral hepatitis	106 (30%)	32 (28%)	0.715
Alcohol	30 (8%)	21 (18%)	0.003[a]
Hepatoma	96 (27%)	26 (23%)	0.370
PBC/PSC/AIH	66 (19%)	18 (16%)	0.497
Bilirubin (μmol/L)	57 (28, 114)	47.5 (25, 91.5)	0.324
Albumin (g/L)	29 (24, 33)	30 (25, 25)	0.172
INR	1.4 (1.2, 1.7)	1.4 (1.2, 1.6)	0.786
Ascites	188 (53%)	71 (62%)	0.082
Encephalopathy	163 (46%)	57 (50%)	0.401
MELD score	16 (12, 20)	16 (12, 19)	0.934
Operative data			
Total operative time (min)	465 (397, 534)	445 (291, 510)	0.162
Peak ALT	884 (509, 1525)	933 (496, 1494)	0.991
Cold ischaemic time (min)	381 (318, 479)	384 (303, 473)	0.530
Warm ischaemic time (min)	45 (39, 52)	44 (38, 50)	0.212
RBC transfusions (units)	2 (0, 4)	2 (0, 5)	0.008[a]

[a]*P* value < 0.05.

PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; AIH: Autoimmune hepatitis; INR: International normalized ratio; MELD: Model for end stage liver disease; ALT: Alanine transaminase; RBC: Red blood cell.

Table 2 The association of pre-transplant variables and 180-d post-transplant sepsis

	Males (*n* = 338)		Females (*n* = 131)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
MELD	1.04 (1.00, 1.08)	0.051	1.06 (0.99, 1.12)	0.074
APLM	1.03 (0.87, 1.21)	0.76	0.93 (0.70, 1.24)	0.63
Upper limb LM	0.42 (0.20, 0.89)	0.024[a]	0.74 (0.19, 2.95)	0.67
Lower limb LM	1.09 (0.92, 1.30)	0.33	0.93 (0.67, 1.28)	0.66
Total LM	1.07 (0.99, 1.15)	0.08	0.89 (0.76, 1.03)	0.12
Total fat mass	0.98 (0.91, 1.05)	0.50	0.99 (0.90, 1.08)	0.76
Ascites	2.18 (1.32, 3.59)	0.002[a]	2.14 (0.95, 4.82)	0.06

[a]*P* value < 0.05.

MELD: Model for end stage liver disease; APLM: Appendicular lean mass; LM: Lean mass; HR: Hazard ratio; CI: Confidence interval.

90-d ACR was negatively associated the presence of ascites (HR = 0.93; 95%CI: 0.89-0.97, *P* = 0.0021) and MELD sore (Table 3). Similarly, lower total lean mass (TLM) was associated with higher 90-d ACR (HR = 0.83; 95%CI: 0.75-0.92; *P* < 0.001) whereas APLM and upper limb mass were not. 90-d ACR was not associated with body composition parameters, MELD or the presence of ascites in women. Peri-operative blood transfusion requirement was negatively associated with 90-d ACR in men but not women (HR = 0.89; 95%CI: 0.81-0.99; *P* = 0.026). Other operative data was not associated with ACR in either gender.

Length of stay

The median intensive care stay following liver transplantation was 66 and hospital length of stay was 15

Table 3 The association of pre-transplant variables and acute cellular rejection within ninety days of liver transplantation

	Males (*n* = 338)		Females (*n* = 131)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
MELD	0.93 (0.89, 0.97)	0.002	1.04 (0.99, 1.09)	0.14
APLM	0.87 (0.72, 1.05)	0.16	1.10 (0.87. 1.4)	0.43
Upper limb LM	1.34 (0.67, 2.68)	0.41	0.43 (0.12, 1.51)	0.19
Lower limb LM	0.80 (0.63, 1.01)	0.063	1.17 (0.90, 1.52)	0.23
Total LM	0.83 (0.74, 0.92)	< 0.001[a]	1.05 (0.95, 1.17)	0.32
Total fat mass	0.93 (0.87, 1.00)	0.062	1.03 (0.95, 1.12)	0.50
BMI	0.91 (0.86, 0.96)	< 0.001[a]	1.02 (0.97, 1.08)	0.45
Ascites	0.43 (0.26, 0.70)	< 0.001[a]	1.51 (0.76, 3.00)	0.24

[a]*P* value < 0.05.

MELD: Model for end stage liver disease; APLM: Appendicular lean mass; LM: Lean mass; BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

d in men but not women, upper limb LM was inversely associated with longer intensive care stay (τ_b = -0.090, *P* = 0.015) and hospital length of stay (τ_b = -0.10, *P* = 0.0078) (Figure 2 and Table 4). The presence of ascites at transplant assessment was associated with longer intensive care and hospital stay in men (median 15 d *vs* 4 d, *P* = 0.024) but not women (Figure 3). In men only, a higher peak alanine transaminase also correlated with longer intensive care stay (τ_b = 0.13, *P* < 0.001), but not total hospital length of stay. There was no significant difference in intensive care or hospital length of stay in patients who were classified as sarcopenic based on gender-specific cut offs for APLM.

Interaction between MELD, ascites and DEXA body composition parameters

Pre-transplant MELD and the presence of ascites at work up showed differing relationships with DEXA body composition parameters.

MELD and body composition: Upper limb LM negatively correlated with increasing MELD score in men but not women (men: τ_b = -0.14, *P* < 0.001, women; τ_b = -0.077, *P* = 0.20). Increasing TLM and lower limb LM correlated with higher MELD score in both genders (Table 5).

Ascites and body composition: Compared to those without, ascites was associated with lower upper limb LM in men [median 1.83 kg/m^2 (1.63, 2.03) *vs* 2.02 kg/m^2 (1.86, 2.20), *P* < 0.001). Conversely, TLM was higher in those with ascites [median 20.0 kg/m^2 (18.4, 22.1) *vs* 18.7 kg/m^2 (17.2, 20.2), *P* < 0.001]. In women, the presence of ascites was associated with TLM only [median 16.9 kg/m^2 (15.7, 19) *vs* 16.2 kg/m^2 (14.4, 17.3), *P* = 0.004].

Ascites and MELD: With rising MELD, the prevalence of ascites increased (risk ratio for ascites 4.79 ± 0.58, *P* < 0.001).

DISCUSSION

This study investigates the impact of pre-transplant DEXA body composition on outcomes after liver transplantation. We identified reduced upper limb LM as a novel predictor of adverse outcomes including bacterial infections and longer hospital stay in men only. We did not find any significant association between body composition and post-transplant graft-failure or mortality, which suggests that prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without a negative impact on post-transplant survival[6].

Previous studies investigating the impact of pre-transplant sarcopenia on post-transplant survival have shown conflicting outcomes[5,11,12]. This disparity may relate to differing definitions of sarcopenia, modalities used for muscle mass assessment, severity of liver disease and inadequate power of some studies to adequately assess mortality. In this study, we describe excellent patient and graft survival of 93% and 91% respectively at 12 mo post-transplant. Era of transplantation may also be a factor as advancements in peri-operative care and immunosuppressive agents have improved post-transplant survival in the modern era. The higher 12-mo post-transplant survival observed in the latter half of the period likely reflects improvements in medical care, despite the increasing medical complexity and older age of transplant recipients. Further large-scale multi-centre studies using

Table 4 Correlation of variables at transplant assessment with post-transplant total hospital and intensive care length of stay

	Males (*n* = 338)				Females (*n* = 131)			
	Correlation[1] (τ_b)	*P* value[1]	Correlation[2] (τ_b)	*P* value[2]	Correlation[1] (τ_b)	*P* value[1]	Correlation[2] (τ_b)	*P* value[2]
Age	< -0.001	0.98	0.055	0.14	0.084	-0.18	0.047	0.44
Total APLM	-0.027	0.48	-0.004	0.91	-0.029	0.65	-0.012	0.84
Upper limb LM	-0.10	0.0078[a]	-0.090	0.015[a]	-0.079	0.21	0.019	0.75
Lower limb LM	< 0.001	0.99	0.017	0.64	-0.018	0.76	-0.018	0.76
Total LM	0.32	0.037[a]	0.055	0.13	-0.012	0.84	-0.012	0.84
Total fat mass	0.036	0.33	0.048	0.20	0.039	0.53	0.039	0.53
MELD	0.078	0.045[a]	0.0087	0.058	-0.037	0.56	0.087	0.17

[a]*P* value < 0.05.
[1]Correlation of variables at transplant assessment with post-transplant total hospital length of stay.
[2]Correlation of variables at transplant assessment with post-transplant intensive care length of stay.
APLM: Appendicular lean mass; LM: Lean mass; MELD: Model for end stage liver disease.

Table 5 Correlation of model for end stage liver disease score and body composition parameters

	Males (τ_b)	*P* value	Females (τ_b)	*P* value
APLM	0.071	0.056	0.15	0.01[a]
Upper limb LM	-0.14	< 0.001[a]	-0.077	0.20
Lower limb LM	0.12	< 0.001[a]	0.18	0.0024[a]
Total LM	0.22	< 0.001[a]	0.18	0.0036[a]
Fat mass	-0.04	0.27	-0.097	0.11

[a]*P* value < 0.05.
APLM: Appendicular lean mass; LM: Lean mass.

reproducible measures of sarcopenia that incorporate muscle function and potential deterioration on the waitlist are required to better elucidate the impact of pre-transplant sarcopenia on post-transplant survival. This will help to determine whether prioritising sarcopenic patients is appropriate and whether a threshold exists below which these patients are indeed too sick for transplantation.

Pre-transplant sarcopenia, as defined by CT imaging, has been consistently reported to be associated with increased post-transplant sepsis. In keeping with this, our study found that upper limb LM was associated with bacterial infections in men at 180-d post-transplant. No significant association was found at 90-d post-transplant, likely reflecting our relatively low infection rate of 21% at this time point as compared to other studies[13]. Our definition of bacterial infections, requiring the identification of a causative pathogen, may result in a lower incidence of early post-transplant bacterial infection leading to inadequate power to detect an association with pre-transplant muscle parameters. The influence of pre-transplant sarcopenia and frailty on early post-transplant ACR is also uncertain with conflicting reports in the literature[14,15]. This study found no association between pre-transplant sarcopenia and early ACR. This provides reassurance that optimising sarcopenia pre-transplant does not appear to result in higher rates of ACR.

While muscle area measured on transverse abdominal CT is often considered gold standard for quantifying muscle mass in cirrhosis, practice guidelines recommend against the use of CT for the sole purposes of sarcopenia assessment due to high radiation doses[16]. In addition to CT, DEXA and bioelectrical impedance are recommended by the European Working Group for Sarcopenia in Older People for assessment of muscle mass[1]. DEXA has advantages over CT due to its reproducibility, low cost and radiation and no requirement for further analysis. However, the inability of DEXA to differentiate fluid and lean tissue is particularly problematic in decompensated cirrhosis where the occurrence of ascites and peripheral oedema are high.

Current guidelines recommend the use of APLM for defining sarcopenia using DEXA with cut-off values extrapolated from non-cirrhotic cohorts for both men and women[1,7]. In a small prospective series of men with cirrhosis, APLM did not change following large volume paracentesis suggesting this is not confounded by ascites[17]. However, the influence of peripheral oedema in this population has

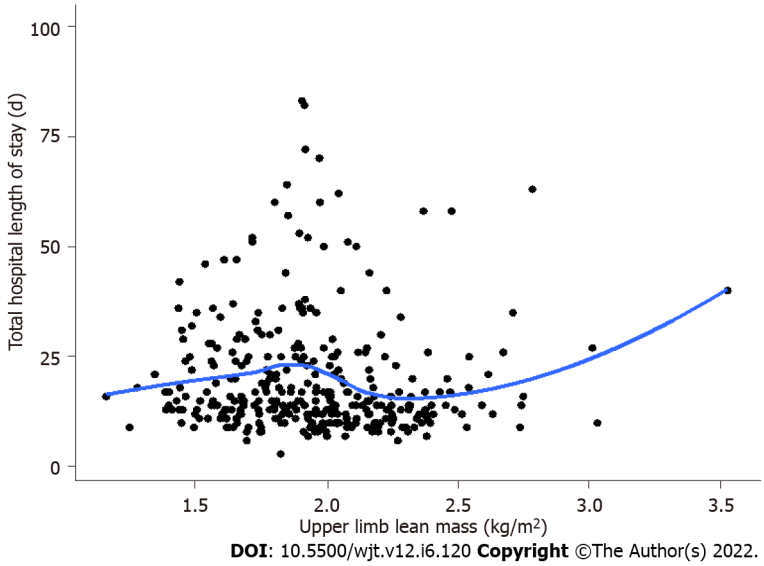

Figure 2 Correlation of upper limb lean mass and hospital length of stay in men. Correlations are given in the text.

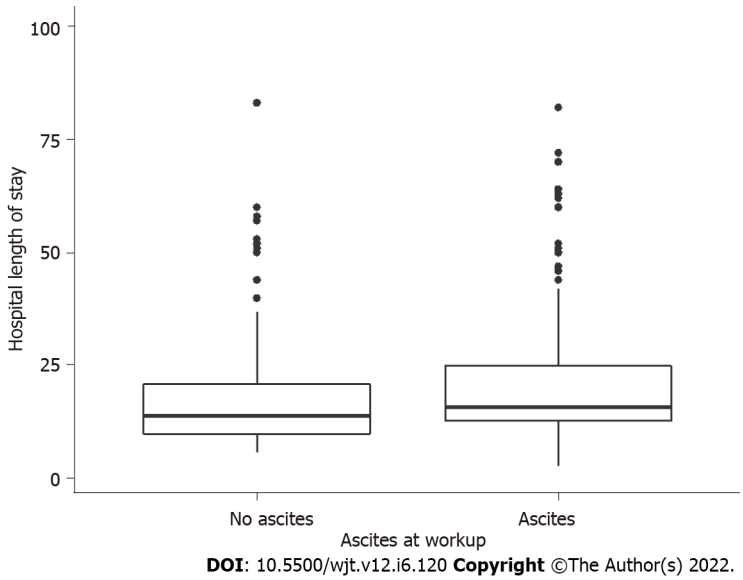

Figure 3 The presence of ascites at transplant assessment and the impact on hospital length of stay in men. *P* values are given in the text.

not been well described. Similar to our prior work[6], this study demonstrates the superiority of upper limb LM in predicting post-transplant outcomes in patients with cirrhosis when compared to APLM, lower limb LM and TLM. As MELD rose, upper limb LM decreased whereas lower limb LM and TLM increased. This suggests that in decompensated cirrhosis, upper limb LM more accurately reflects true muscle mass as it is not confounded by peripheral oedema or ascites. A cut-off of upper limb LM of < 1.6 kg/m^2 was the best predictor of waitlist mortality in a single-centre cohort of men with cirrhosis[6]. This cut-off requires validation in multicentre cohorts and as yet no definitions for sarcopenia using upper limb LM have been proposed for women.

A major finding in this study is the lack of association of pre-transplant muscle parameters with post-transplant outcomes in women. This remains an unanswered question in the literature. While a sex-stratified approach to diagnose sarcopenia is required, most studies fail to report on gender-specific mortality analyses. Like most studies in the field of cirrhosis, women accounted for less than a third of patients transplanted for cirrhosis in this cohort. This may lead to inadequate power to detect significant associations between sarcopenia and outcomes.

It is possible that muscle mass has greater prognostic significance in men than women. The pathogenesis of sarcopenia in cirrhosis is a complex interplay between multiple factors. Testosterone, a potent promoter of muscle growth, plays a particularly important role in the development of sarcopenia in men. Testosterone levels fall with progression of liver disease and correlate with muscle mass in men

with cirrhosis[18,19]. Furthermore, there is a clear association between testosterone levels in cirrhotic men and the adverse outcomes of hepatic decompensation, need for liver transplantation and death [20]. This may explain the higher prevalence of low muscle mass in men waitlisted for transplantation compared to women[21].

Functional measures of muscle such as handgrip strength and the liver frailty index may carry better prognostic utility in women. A multi-centre study of patients waitlisted for liver transplantation in the United States found that women had higher frailty scores than men and that increased frailty was associated with higher waitlist mortality[22]. A major limitation of this study is that muscle strength was not included due to the lack of available data over the timeframe described. Larger studies describing sarcopenia-related outcomes in cirrhotic and liver transplant cohorts need to include functional measures of sarcopenia and provide gender-stratified analyses so we can better understand the role of muscle in predicting outcomes in each gender.

CONCLUSION

In conclusion, this study is the first to comprehensively describe the association of reduced muscle mass as measured by DEXA on post-liver transplant outcomes providing gender-stratified analyses. We identify upper limb LM as a novel measure of sarcopenia that is associated with adverse outcomes post-liver transplant in men, without a corresponding increase in mortality. Larger multi-centre studies that provide gender-stratified monitoring of muscle mass and function serially on the waitlist are required to assess the full impact of sarcopenia on post-transplant outcomes. This will help determine whether prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without compromising post-transplant survival.

ARTICLE HIGHLIGHTS

Research background

Pre-transplant sarcopenia defined by reduced skeletal muscle index measured by transverse abdominal computed tomography (CT) is associated with adverse outcomes after liver transplantation. These include increased rates of sepsis, longer hospital length of stay and a possible increase in post-transplant mortality.

Research motivation

CT is not recommended for use solely for the purpose of diagnosing sarcopenia given the high radiation doses. Dual-energy X-ray absorptiometry (DEXA) body composition assessment provides a low radiation and reproducible alternative for measuring muscle mass with prognostic utility in the pre-transplant setting. Upper limb lean mass (LM) has recently been identified as a novel assessment of sarcopenia using DEXA.

Research objectives

This study investigates the use of DEXA body composition assessment in predicting gender-stratified early post-transplant outcomes.

Research methods

This study retrospectively analysed liver transplant recipients who underwent pre-transplant DEXA body composition imaging between 2002 and 2017 at a single-centre. DEXA variables analysed included appendicular LM (APLM), total, upper and lower limb LM and fat mass corrected for height^2. Endpoints included post-transplant mortality and graft failure, bacterial infections, acute cellular rejection and intensive care and total hospital length of stay (days).

Research results

Four hundred and sixty-nine patients met inclusion criteria of which 338 were male (72%). Upper limb LM was inversely associated with bacterial infections at 180 d post-transplant in males only. There was a negative correlation between upper limb LM and intensive care and total hospital length of stay in men. In women, neither model for end-stage liver disease (MELD) nor body composition parameters were associated with post-transplant adverse outcomes or increased length of stay. Body composition parameters, MELD and age were not associated with 90-d mortality or graft failure in either gender.

Research conclusions

Upper limb LM measured on DEXA is a novel measure of sarcopenia with better prognostic value compared to APLM in predicting adverse outcomes after liver transplantation. Reduced upper limb LM

was a predictor of post-transplant bacterial infection and longer length of stay in men only, but was not associated with increased mortality or graft failure. The lack of association in women requires further investigation.

Research perspectives

Larger multi-centre studies that provide gender-stratified analysis of muscle mass and function serially on the waitlist are required to assess the full impact of pre-transplant sarcopenia on post-transplant outcomes. This will help determine whether prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without compromising post-transplant survival.

FOOTNOTES

Author contributions: All authors have contributed to this manuscript and have agreed on the content; Hey P and Sinclair M were involved in the study design; Hey P and Hanrahan TP performed data collection; Hoermann R performed statistical analysis; Hey P, Gow P, Testro AG, Apostolov R and Sinclair M, were involved in data interpretation, drafting and revising the work; and all authors provided approval of the final version to be published.

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Country/Territory of origin: Australia

ORCID number: Penelope Hey 0000-0002-5219-0382; Rudolf Hoermann 0000-0002-1326-4270; Paul Gow 0000-0001-6505-7233; Timothy P Hanrahan 0000-0003-0657-3048; Adam G Testro 0000-0001-6776-3115; Ross Apostolov 0000-0002-4827-8795; Marie Sinclair 0000-0003-0657-3115.

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SYSTEMATIC REVIEWS

Risk factors of extraneural spreading in astrocytomas and oligodendrogliomas in donors with gliomas: A systematic review

Serena Ammendola, Valeria Barresi, Elena Bariani, Ilaria Girolami, Antonia D'Errico, Matteo Brunelli, Massimo Cardillo, Letizia Lombardini, Amedeo Carraro, Ugo Boggi, Owen Cain, Desley Neil, Albino Eccher

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Serena Ammendola, Valeria Barresi, Elena Bariani, Matteo Brunelli, Section of Pathology, Department of Diagnostics and Public Health, University of Verona, Verona 37134, Italy

Ilaria Girolami, Division of Pathology, Central Hospital, Bolzano 39100, Italy

Antonia D'Errico, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna 40138, Italy

Massimo Cardillo, Letizia Lombardini, National Transplant Center, Istituto Superiore di Sanità, Rome 00161, Italy

Amedeo Carraro, General Surgery and Liver Transplant Unit, Verona University Hospital, Verona 37126, Italy

Ugo Boggi, Division of General and Transplant Surgery, Pisa University Hospital, Pisa 56126, Italy

Owen Cain, Desley Neil, Department of Cellular Pathology, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW, United Kingdom

Albino Eccher, Department of Pathology and Diagnostics, Verona University Hospital, Verona 37126, Italy

Corresponding author: Serena Ammendola, MD, Doctor, Section of Pathology, Department of Diagnostics and Public Health, University of Verona, P.le L.A. Scuro 10, Verona 37134, Italy. serena.ammendola88@gmail.com

Abstract

BACKGROUND

Patients with a history of primary brain tumors can be eligible for organ donation under extended criteria. The risk assessment of tumor transmission *via* organ transplant in primary brain tumors is primarily based on the assessment of tumor histotype and grade. Previous surgeries, chemo-/radiotherapy, and ventriculo-peritoneal shunt placement can lead to a disruption of the blood-brain barrier, concurring to an increase in the transmission risk.

AIM

To investigate the role of tumor transmission risk factors in donors with oligodendrogliomas and astrocytomas.

METHODS

We searched PubMed and EMBASE databases for studies reporting extraneural spreading of oligoden-drogliomas and astrocytomas and extracted clinical-pathological data on the primary tumor histotype and grade, the elapsed time from the diagnosis to the onset of metastases, sites and number of metastases, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or ventriculo-peritoneal shunt placement, and the presence of isocitrate dehydrogenase 1/2 mutation and 1p/19q codeletion. Statistical analysis was performed using R software. Statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-central nervous system metastases was analyzed using χ^2 and Fischer exact test. The Kaplan-Meier method was used to evaluate the presence of a correlation between the metastasis-free time and: (1) Localization of metastases; (2) The occurrence of intracranial recurrences; and (3) The occurrence of multiple metastases.

RESULTS

Data on a total of 157 patients were retrieved. The time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo in patients with oligodendrogliomas and 0 to 267 mo in those with astrocytomas. Respectively, 19% and 39% of patients with oligodendroglioma and astrocytoma did not receive any adjuvant therapy. The most frequent metastatic sites were bone, bone marrow, and lymph nodes. The lungs and the liver were the most commonly involved visceral sites. There was no significant correlation between the occurrence of multiple metastases and the administration of adjuvant chemo-/radiotherapy. Patients who developed intracranial recurrences/metastases had a significantly longer extraneural metastasis-free time compared to those who developed extraneural metastases in the absence of any intra- central nervous system spread.

CONCLUSION

A long follow-up time does not exclude the presence of extraneural metastases. Therefore, targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors.

Key Words: Metastatic gliomas; Extra-central nervous system metastases; Tumor transmission; Expanded donor; Risk factors; Transplantation

Core Tip: Recognized risk factors of tumor transmission from donors with a history of primary brain tumors are previous surgery, chemotherapy,and radiotherapy. We performed a systematic review of the literature on oligodendroglioma and astrocytomas with extraneural metastases, aiming to clarify the role of tumor transmission risk factors. We searched PubMed and EMBASE databases for studies reporting extraneural spreading of these gliomas. Performed treatments do not seem to impact on the timing of metastatic spread, and a long follow-up time does not exclude extraneural spread. Targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors.

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INTRODUCTION

The transplant community has been struggling with the chronic shortage of donor's organs for transplantation. In order to increase the donor pool, criteria for donation have been expanded[1,2], accepting as donors individuals with a history of malignancies of low metastatic potential. However, transplantation from these donors carries a risk of cancer transmission that should be carefully assessed for each tumor type[1-4].

Organs from donors with a history of a primary brain tumor (PBT) may be considered eligible for transplantation under extended criteria since these tumors have a low propensity to metastasize outside the central nervous system (CNS). These patients represent a relevant subgroup of donors that can increase the number of transplants performed, reducing times on the waiting list[5]. According to the 7th

edition of the guidelines on quality and safety of organ transplantation, the risk of transmission for patients with a history of PBT is mainly influenced by the tumor histotype and grade[6]. The risk of tumor transmission in donors with a history of CNS tumors is graded as minimal, low to intermediate, and high or unacceptable; in detail, donors with World Health Organization (WHO) grade I and II PBTs are considered at minimal risk of tumor transmission, while grade III tumors are now considered at low to intermediate risk in the absence of any recognized risk factors, such as previous surgical resections, ventriculo-peritoneal (VP) or ventriculo-atrial shunt placement, and/or chemotherapy/radiotherapy that increase the risk from intermediate to high[6]. These procedures disrupt the blood-brain barrier, increasing the risk of hematogenous and lymphovascular spread of these tumors[7]. Extra-CNS metastases from PBTs do however occur, with a reported prevalence of up to 4.3%[7], and metastases mainly occur in patients with a history of high-grade gliomas and, in particular, of glioblastoma[8-10]. Ventriculo-atrial and VP shunts have also been reported as risk factors for tumor spread[11].

However, the studies on PBT transmission after solid organ transplantation often include limited data on the tumor histological features and the patients' clinical management[9-13]. In the United Network for Organ Sharing registry, among 642 patients who received organs from a donor with a PBT, three died due to the transmission of a glioblastoma[8,13]. However, no cases of transmission were reported among 96 recipients in the Australian and New Zealand Organ Donation Registry[14], 89 recipients from the Czech Republic registry[15], and 448 recipients from the United Kingdom registry[16]. More recently, Lee *et al*[17] reported that none of 87 transplant recipients had tumor transmission from 28 donors with PBTs.

To date, there are no reports of transmission of oligodendroglioma to organ transplant recipients, while donor-to-recipient transmission of grade III/IV astrocytic tumors have been previously reported [6]. Though the metastatic potential of these tumors in the context of transplantation needs to be clarified and kept up-to-date. Oligodendrogliomas are CNS diffuse gliomas mainly occurring in adulthood, with a peak incidence in the fourth and fifth decade and a slight male predominance (1.3:1), preferentially arising in the cerebral hemispheres and mostly in the frontal lobe[18]. According to the WHO, oligodendroglioma is defined by the co-occurrence of isocitrate dehydrogenase 1/2 (*IDH1/2*) mutation and chromosome 1p/19q whole arm codeletion and classified into grade II and grade III (anaplastic oligodendrogliomas) based on the presence of histologic features of anaplasia, such as microvascular proliferation and/or brisk mitotic activity[18].

Tumors of astrocytic lineage, contrary to oligodendrogliomas, have a four-tiered grading system that encompasses a wide spectrum of clinical entities, from grade I tumors characterized by a benign clinical course to grade IV tumors carrying a dismal prognosis[18]. About 5% of all PBTs with extra-CNS metastatic spread are reported to be oligodendrogliomas, while astrocytomas account for about 10% of extraneural metastatic PBTs[19]. However, data on extraneural metastatic spread mostly come from case reports or small case series, and there is no systematic appraisal of the risk factors or patterns of metastatic spread.

In this study, we performed a systematic review of the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases with the aim of identifying clinical or pathological factors that can be helpful to predict the tumor transmission risk and guide decision making in organ transplantation from donors with these tumors.

MATERIALS AND METHODS

Search strategy

This literature review was performed in accordance with the PRISMA. A literature search without language restrictions was carried out in the electronic databases MEDLINE-PubMed and EMBASE until December 2020. The search terms were: "oligodendroglioma", "anaplastic oligodendroglioma", "astrocytoma", "anaplastic astrocytoma" "oligodendroglial tumours", "diffuse glioma" "extracranial metastasis" "oligodendroglioma metastatic to", "astrocytoma metastatic to", "extraneural metastases" "primary brain tumours", "metastatic oligodendroglioma", "metastatic astrocytoma". Screening of article titles and abstracts was independently performed by three investigators using Rayyan QCRI reference manager web application[20]. Some references for Journal articles also were searched from (*RCA*), an artificial intelligence technology-based open citation analysis database (https://www.referencecitationanalysis.com, Baishideng Publishing Group Inc., Pleasanton, CA, United States).

Inclusion criteria and data extraction

The full texts of the articles fulfilling the initial screening criteria were retrieved and reviewed (Supplementary Table 1); disagreement was resolved *via* consensus. Inclusion criteria were: Case reports, case series, and literature reviews reporting on patients with a history of oligodendroglioma or astrocytoma that subsequently metastasized outside the CNS. Articles with limited data were included if they at least reported the histologic diagnosis of primary and metastatic tumors (Table 1; Supplementary Table 1). We included articles mentioning different tumor histotypes only if findings of each case were further detailed. We excluded articles reporting metastatic disease not histologically

Table 1 Clinical-pathological features of the study populations

Clinical features	Oligodendroglioma (%)	Astrocytoma (%)
Patients	90 (100)	67 (100)
Sex		
Male	52 (58)	39 (58)
Female	32 (35)	27 (40)
Undisclosed	6 (7)	1 (2)
Age in yr	1.5-74.0 (mean: 44.5; median: 46)	0-82.0 (mean: 31.0, median: 26)
Location		
Frontal lobe	34 (38)	7 (11)
Parietal lobe	8 (9)	2 (3)
Temporal lobe	5 (6)	11 (16)
Spine	1 (1)	6 (9)
NA	22 (24)	2 (3)
Other sites	20 (22)	39 (58)
Surgery		
Yes	79 (88)	48 (71)
No	2 (2)	16 (24)
Multiple surgeries		
Yes	44 (49)	24 (36)
No	35 (39)	41 (61)
Radiotherapy		
Yes	60 (67)	49 (73)
No	14 (15)	15 (22)
Chemotherapy		
Yes	33 (37)	16 (23)
No	37 (41)	48 (72)
VA/VP shunt		
Yes	3 (3)	20 (30)
No	26 (29)	34 (50)
Metastatic sites		
Bone	48 (53)	30 (44)
Bone marrow	30 (33)	6 (8)
Lymph nodes	27 (30)	24 (30)
Cervical	16 (17)	14 (17)
Retroperitoneal	3 (3)	2 (3)
Axillary	2 (2)	-
Other	6 (7)	7 (10)
Lung	10 (11)	11 (17)
Liver	8 (9)	8 (11)
Scalp	8 (9)	8 (11)
Pleura	5 (6)	6 (8)
Parotid gland	5 (6)	3 (4)

Breast	3 (3)	-
Chest wall	3 (3)	1 (1)
Peritoneum	3 (3)	10 (14)
Kidney	-	3 (4)
Retroperitoneum	2 (2)	1 (1)
Soft tissues	1 (1)	11 (15)
Pericardium	1 (1)	-
Pancreas	1 (1)	1 (1)
Spleen	1 (1)	-
Thymus/mediastinum	1 (1)	1 (1)
Adrenal gland	1 (1)	-
Muscles	3 (3)	2 (3)
Intra-CNS metastases/recurrence		
Yes	43 (48)	37 (55)
No	19 (21)	26 (39)
Non-conclusive	1 (1)	3 (6)
Time from the diagnosis to metastatic spread	0-324 (mean: 53.7; median: 36)	0-276 (mean: 31.0; median: 13)

NA: Not available; VA/VP: Ventriculo-atrial/ventriculo-peritoneal; CNS: Central nervous system.

confirmed and those concerning only animal models or cell cultures. Articles reporting extracranial metastases from primary glioblastomas were also excluded. Finally, from the included articles we extracted data on: Author and publication year, country, type of paper, sex and age of the patients at metastatic spread, tumor histotype and grade, synchronous or metachronous malignancies, intracranial recurrence, intra-axial spreading, tumor progression, time between the diagnosis and the onset of metastases, sites and number of metastases, tumor progression of the primary neoplasm preceding extracranial extra-CNS spread, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or VP shunt placement, *IDH1/2* mutation and 1p/19q codeletion in both the primary and metastatic tumors.

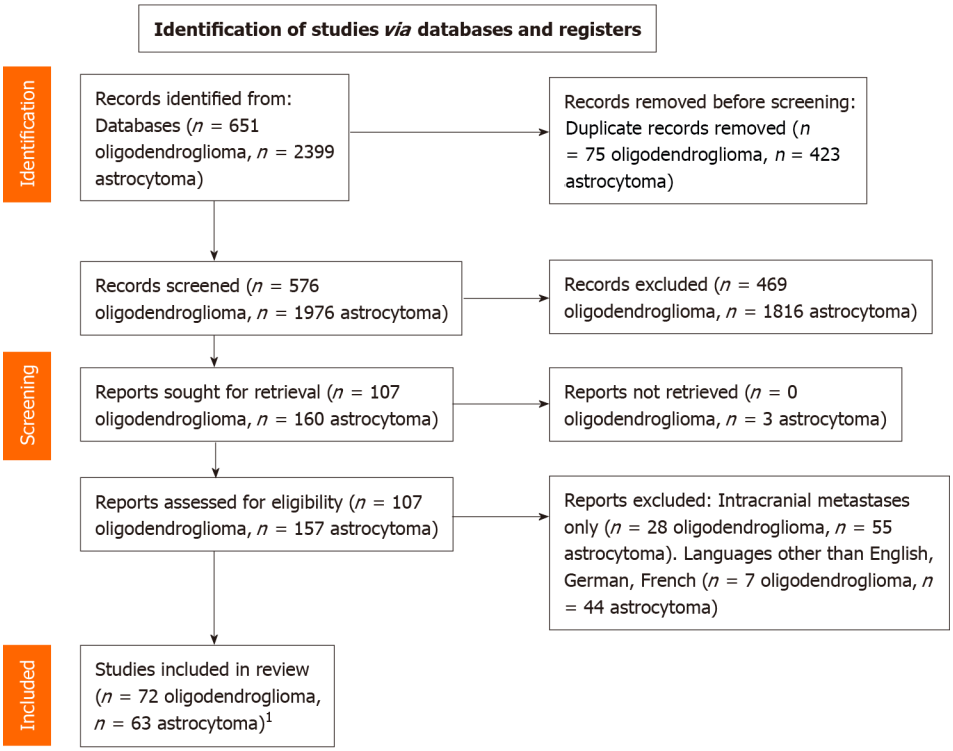
Statistical analysis

Statistical analysis was performed using open-source software R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with RStudio 1.4.1106 environment (RStudio Inc, Boston, Massachusetts, United States). The statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-CNS metastases was analyzed using χ^2 and Fischer exact test. Kaplan-Meyer method was used to investigate the correlation between metastasis-free time and metastatic sites, presence/absence of intracranial recurrence, and the occurrence of multiple metastases. A *P*-value less than 0.05 was considered statistically significant. No institutional review board approval was needed, as no ethical issue is raised by literature reviews.

RESULTS

The results are summarized in Table 1 and detailed in Supplementary Table 1. A total of 2675 articles were identified after duplicate removal. After an initial screening on titles and abstracts, we considered 267 articles as potentially relevant to our study. We excluded 3 articles with unavailable full text and 83 reporting only intracranial or spinal drop metastases; 51 articles were excluded due to language restrictions. A PRISMA flow diagram of the literature screening and article exclusion is shown in Figure 1.

The 130 articles included were case series, case reports, and literature review articles reporting data on a total of 90 patients (52 males, 32 females, and 6 with undisclosed sex) with extra-CNS metastases from oligodendroglial tumors and 67 patients with extra-CNS metastatic astrocytoma (39 males, 27 females, and 1 with undisclosed sex) (Table 1; Supplementary Table 1). Age at metastatic spread ranged between 1.5 years to 74.0 years (mean: 44.7; median: 46) in patients with oligodendrogliomas and between 8 mo and 84.0 years (mean: 31.3; median: 26) in patients with astrocytoma.



DOI: 10.5500/wjt.v12.i6.131 **Copyright** ©The Author(s) 2022.

Figure 1 PRISMA flow diagram. [1]Three articles included in the systematic review reported cases of extraneural metastases from both oligodendrogliomas and astrocytomas.

Among patients with metastatic oligodendrogliomas, 11 (12%) progressed from grade II to III in the intracranial relapse or in the metastasis, and 1 anaplastic oligodendroglioma recurred as a secondary glioblastoma; 2 cases diagnosed as oligoastrocytomas at the initial diagnosis were reported as oligodendrogliomas at recurrence. Twenty-one astrocytic tumors also displayed tumor progression, and 15 patients received a diagnosis of secondary glioblastoma at the time of recurrence or at microscopic evaluation of the metastasis. Time from the initial diagnosis to metastatic spread of oligodendrogliomas ranged from 0 to 325 mo (mean: 54; median: 36) and from 0 to 276 mo for astrocytic tumors (mean: 31; median: 13) (Table 1). One patient with oligodendroglioma and 10 patients with astrocytic tumors were found with extraneural metastatic disease at the time of the first diagnosis.

Two patients with oligodendroglioma and 8 patients with astrocytic tumors did not undergo any surgical resection before metastatic spread. In 7 cases a diagnostic stereotactic biopsy was performed without open craniotomy; the remaining cases received an autoptic diagnosis. Sixty-three (70%) patients with oligodendroglioma and 51 (76%) patients with astrocytoma received radiation therapy, chemotherapy, or both before metastases occurred, while 12 patients with oligodendroglioma and 8 with astrocytoma did not receive any adjuvant therapy. Twenty patients with astrocytoma underwent VP shunt placement, while among patients with oligodendroglioma, only three required VP shunt placement. Forty-three patients with oligodendroglioma (48%) and 37 patients with astrocytomas (55%) had at least one intracranial recurrence and/or intra-CNS metastatic disease before extra-CNS metastases.

Among oligodendrogliomas, metastases were mainly localized at the bone (n = 48), bone marrow (n = 30), and lymph nodes (n = 27), with cervical stations being the most affected (n = 16). Metastases to the scalp were present in 8 cases. The most common visceral metastatic sites were the lung (n = 10), liver (n = 8), and pleural cavity (n = 5). Kidneys were always spared (Table 1). The most common extra-CNS metastatic sites of astrocytoma were instead bone (n = 30) and lymph nodes (n = 24), and in more than half of the cases the cervical nodal stations were affected (n = 14). The scalp was involved in 8 cases and the soft tissues in 11 cases. Visceral metastases were localized to the lungs (n = 11), liver (n = 8), and kidney (n = 3) (Table 1).

There was a significantly shorter metastasis-free time in patients with astrocytoma than in those with oligodendrogliomas (P = 0.0042), and median time from the diagnosis of the primary tumor to metastatic spread was 36 mo [95%confidence interval (CI): 29-48] in patients with oligodendroglioma and 13 mo in patients with astrocytic tumors (95%CI: 15-41) (Figure 2). There was no significant correlation between timing of metastatic spread and metastatic sites (bone and lymph nodes *vs* visceral metastases) for both oligodendrogliomas (P = 0.98) and astrocytomas (P = 0.93).

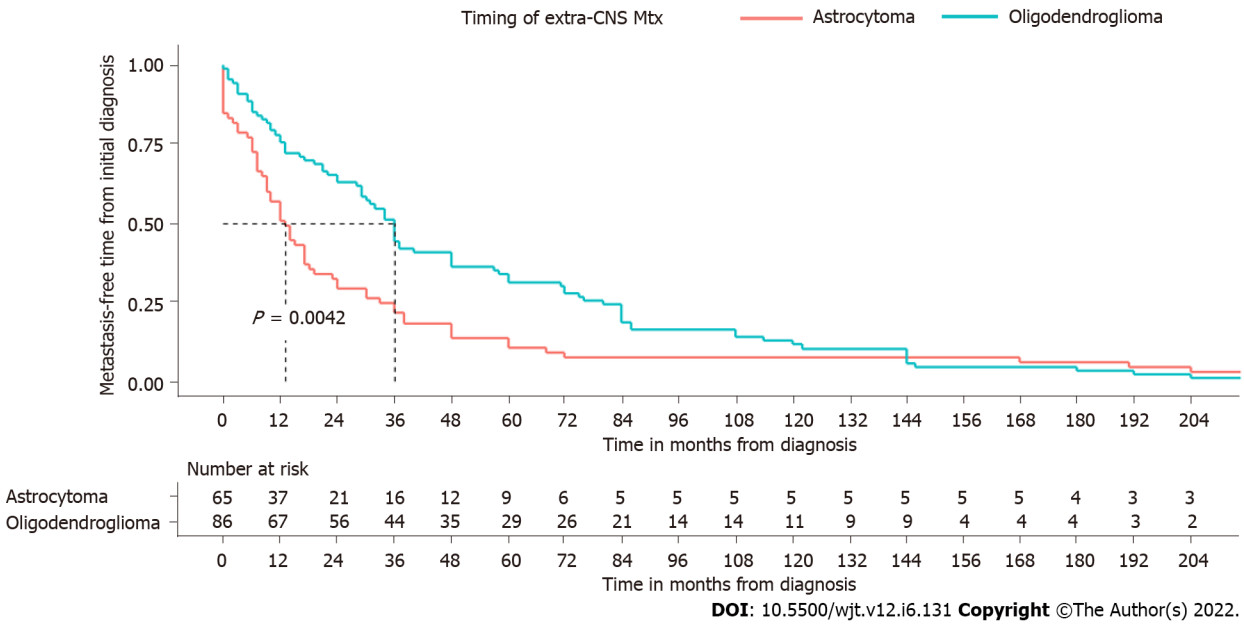


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Figure 2 Survival analysis of patients with extra-central nervous system metastases of oligodendroglioma and astrocytoma. CNS: Central nervous system; Mtx: Metastasis.

Considering: (1) Surgical procedures; (2) Radiotherapy/chemotherapy; and (3) VP shunt as risk factors for extracranial metastatic spread, in the astrocytoma cohort, 7 patients had extra-CNS metastases without any recognized risk factor, 6 patients displayed only one risk factor, 29 of them had two risk factors, and only 3 patients received all the above-mentioned treatments. All patients with metastatic oligodendroglioma had instead at least one risk factor for extracranial metastatic spread.

Patients with intracranial recurrence or intra-CNS dissemination of oligodendroglioma had a significantly longer extra-CNS free-time interval (median: 59.8 mo; 95%CI: 36-84) than those who had no local recurrences (median: 24.0 mo; 95%CI: 9-37) (P = 0.014) (Figure 3). The same correlation was present when considering patients with astrocytomas. There is indeed a significant correlation between the presence of intracranial metastases and a longer time before extra-CNS metastatic spread (P = 0.04) (Figure 3).

DISCUSSION

In this study, we reviewed the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases. Based on the present review, extra-CNS metastasis of these tumor entities may occur, independently from the grade of the primary neoplasm. Indeed, the reported cases of extra-CNS metastases were roughly similar in lower and higher grade oligodendrogliomas. This distinction appears to be less sharp taking into account extraneural metastases from astrocytomas since in many articles the tumor grade is not specified, while terms such as "low grade", "aggressive" or "malignant" are used as substitutes of the grading system. Indeed, it should be noted that the criteria for tumor grading changed substantially over the past decades. As an example, the tumor reported by James and Pagel[21] in 1951 as oligodendroglioma showed areas of necrosis and moderately conspicuous mitotic activity, which are nowadays considered diagnostic criteria of a higher grade oligodendroglioma. These limitations are partly shared by many transplantation registry data, whose reports cover a wide timespan and in the past were often incomplete, not providing data on donors' tumor histotypes or the interval between performed treatments and donation[22,23]. According to the Disease Transmission Advisory Committee, recurrence-free survival can be used as a surrogate for transmission risk and donors, with a history of neoplasm diagnosed 5 or more years earlier and with a probability of cure of > 99% are considered at low risk for tumor transmission, while neoplasms with a probability of cure between 90% and 99% are considered at intermediate risk of transmission[24].

According to this literature review, while the extraneural spread of PBT appears to be an earlier event in astrocytic tumors, in oligodendrogliomas it can occur after more than 10 years from the primary diagnosis in a non-negligible number of patients. Indeed, the interval between diagnosis and metastatic spread varied widely among patients, and many of them underwent multiple treatments that have possibly interfered with the natural history of the tumor[25]. Therefore, the possibility of metastatic spread even after many years should be carefully considered when selecting eligible donors for organ transplantation. In light of these findings, taking into account that diffuse gliomas preferentially

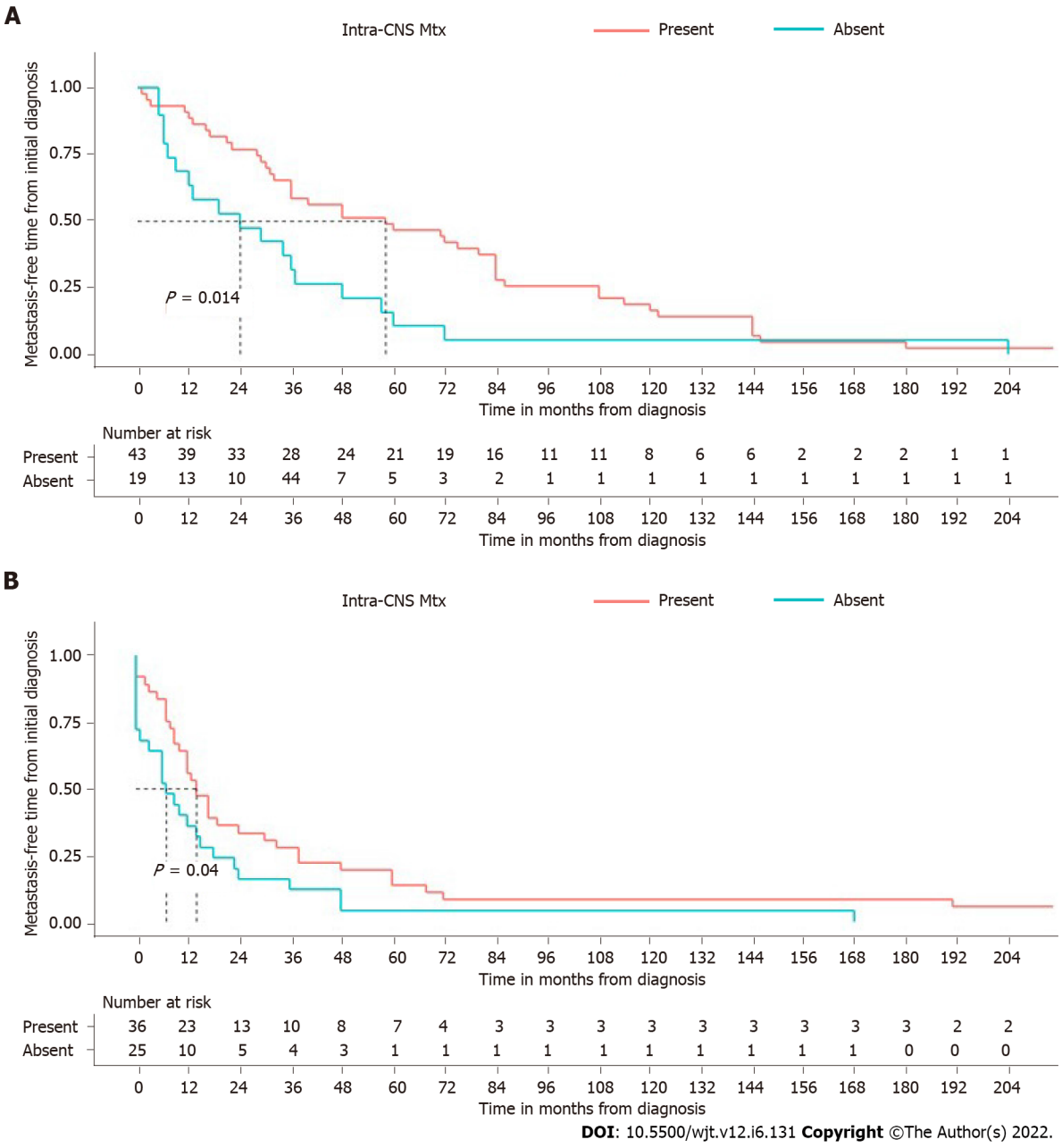

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Figure 3 Time from initial diagnosis to metastatic spread in patients with and without intra-central nervous system recurrences/metastases. A: Oligodendrogliomas; B: Astrocytomas. CNS: Central nervous system; Mtx: Metastasis.

metastasize to the bone and cervical lymph nodes, we suggest that protocols for potential donors with a present or past history of oligodendroglioma should include ultrasound imaging of the head and neck and/or computerized tomographic scan of the skeleton. A minority of patients also had metastases in transplantable organs such as lungs, liver, and pancreas, while metastases to kidney and heart were not reported in oligodendrogliomas, suggesting that these organs are relatively spared from metastatic spread. This is in accordance with two studies on donors with glioblastoma that described a better outcome in recipients of kidneys than in those with lung or liver grafts and worse outcomes in patients with liver metastases compared to those with other extracranial metastatic sites[9,26].

Of note, patients with intracranial tumor relapse had a significantly longer interval between the initial diagnosis and the metastatic spread. Additionally, we found that patients who had multiple surgeries for intra-CNS relapses or metastases developed extra-CNS disease after a longer time interval than those who had a single surgery. We may speculate that patients with intracranial relapses or metastases have tumors with a lower biological aggressiveness and that acquire "visceral" metastatic potential only in a later stage.

The present review has several limitations. First, we did not include in the literature search articles reporting extracranial metastases from primary glioblastomas, currently classified as grade IV tumors according to the WHO[18]. Moreover, the selected literature covers a wide timespan, and inevitably the

changes in the classification of tumor entities and in grading systems represent a limitation to every systematic review on this topic. It should be noted, indeed, that most of the articles included in this review were published before the 2016 update of the WHO classification of CNS tumors and do not always include data on 1p19q codeletion and *IDH1/2* mutations[18].

CONCLUSION

In conclusion, despite the relatively low propensity to metastasize outside the CNS of oligodendrogliomas and astrocytomas, findings in this review confirm the theoretical possibility of tumor transmission when transplanting organs from these donors and that a long interval between tumor diagnosis and donor death does not exclude the possibility of metastases. Tumor grade does not seem to be the main feature influencing the metastatic potential, with the caveat that recent diagnostic advances may add useful information in the future. Kidneys and hearts seem to be relatively resistant to metastases compared with lungs and livers. Finally, we suggest that imaging of the skeleton and cervical lymph nodes could be helpful to identify metastatic disease in donors with a past or present history of these gliomas.

ARTICLE HIGHLIGHTS

Research background

Under extended criteria, patients with a history of primary brain tumor can be eligible for organ donation. Tumor histotype and tumor grade are considered the main risk factors of tumor transmission, and previous surgeries, chemo-/radiotherapy, and ventriculo-peritoneal shunt placement concur to increase the transmission risk.

Research motivation

Most of the literature on the extraneural metastatic spread of diffuse gliomas is based on case reports and case series, and there is a lack of systematic appraisal of patterns of metastatic spread- and on factors concurring to increase the risk of extraneural spreading.

Research objectives

We aimed to collect and analyze the existing literature on extraneural spreading of oligodendroglial and astrocytic tumors in order to identify clinical or pathological factors that could help clinicians to assess the risk of tumor transmission from donors with a history of these gliomas and guide decision making in organ transplantation.

Research methods

We performed a systematic review of the literature in accordance with the PRISMA guidelines. A literature search without language restrictions was performed in the electronic databases MEDLINE-PubMed and EMBASE, searching for articles, case reports, and case series reporting data on extra-central nervous system metastases of oligodendrogliomas and astrocytomas.

Research results

Elapsed time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo and from 0 to 276 mo for oligodendrogliomas and astrocytic tumors, respectively. The most common metastatic sites were bone and lymph nodes for both tumors, while the most common visceral sites were the lungs and the liver in patients with oligodendrogliomas and lungs, liver, and kidneys in patients with astrocytomas. Among patients with astrocytomas, 7 did not undergo surgery, chemo-/radiotherapy or ventriculo-peritoneal shunt placement before the onset of metastases.

Research conclusions

A long interval between the tumor diagnosis and the donor's death does not exclude the possibility of extraneural spreading of these tumors. Bone and lymph nodes are the most common metastatic sites; the lungs and the liver are instead the preferential visceral sites of metastatic spread. Follow-up imaging of the skeleton and cervical lymph nodes could be useful to identify metastatic disease in donors with a history of these gliomas.

Research perspectives

The diagnostic advances made recently in tumor classification and targeted follow-up protocols could improve the knowledge on the factors involved in extraneural spreading of gliomas, with repercussions on the tumor transmission risk assessment of potential donors.

FOOTNOTES

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REVIEW

Cardiac risk stratification of the liver transplant candidate: A comprehensive review

Sanjana Nagraj, Spyros Peppas, Maria Gabriela Rubianes Guerrero, Damianos G Kokkinidis, Felipe I Contreras-Yametti, Sandhya Murthy, Ulrich P Jorde

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Sanjana Nagraj, Maria Gabriela Rubianes Guerrero, Department of Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, New York City, NY 10461, United States

Spyros Peppas, Department of Gastroenterology, Athens Naval Hospital, Athens 115 21, Greece

Damianos G Kokkinidis, Section of Cardiovascular Medicine, Yale University School of Medicine, Yale New Haven Hospital, New Haven, CT 06510, United States

Felipe I Contreras-Yametti, Department of Medicine, Wellstar Atlanta Medical Center, Atlanta, GA 30312, United States

Sandhya Murthy, Ulrich P Jorde, Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, New York City, NY 10467, United States

Corresponding author: Sanjana Nagraj, MBBS, Doctor, Department of Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, 1400 Pelham Parkway S, New York City, NY 10461, United States. sanjana94nagraj@gmail.com

Abstract

Cardiovascular diseases (CVD) form a principal consideration in patients with end-stage liver disease (ESLD) undergoing evaluation for liver transplant (LT) with prognostic implications in the peri- and post-transplant periods. As the predominant etiology of ESLD continues to evolve, addressing CVD in these patients has become increasingly relevant. Likewise, as the number of LTs increase by the year, the proportion of older adults on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve with parallel increases in their CVD risk profiles. The primary goal of cardiac risk assessment is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability. This review focusses on cardiac assessment of LT candidates in a stepwise manner with special emphasis on preoperative patient optimization. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

Key Words: Cardiovascular risk; Liver transplantation; End stage liver disease; Liver cirrhosis; Cardiovascular diseases; Cardiovascular diagnostic techniques

Core Tip: Liver transplantation is high-risk invasive procedure with an increased likelihood of cardiovascular mortality in the perioperative and postoperative periods. As the predominant etiology of end-stage liver disease and attributes of transplant candidates continue to evolve, cardiac risk stratification of these patients is becoming increasingly relevant. This review aims to reach providers seeking to learn about the current state of cardiac assessment of liver transplant candidates, commonly encountered cardiovascular conditions, preoperative diagnostic testing, and patient optimization. We also highlight areas requiring further investigation.

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INTRODUCTION

Patients with end-stage liver disease (ESLD) often have multiple comorbidities, of which cardiovascular diseases (CVD) form a principal consideration with prognostic implications in the peri- and post-transplant periods[1]. Nearly 36000 liver transplants (LTs) per million population were performed globally in 2019, a 5% increase since 2018, and an additional 13000 patients were added to the waiting list[2]. CVD which is a well-established risk factor of increased mortality in both the early and late periods after LT, accounts for > 40% of deaths in the first 30 d after transplant[3-5]. Additionally, CVD is the leading cause of death at 1-yr follow-up[3-5].

As the predominant etiology of ESLD continues to shift towards non-alcoholic steatohepatitis (NASH) with corroborating increases in obesity (body mass index ≥ 30 kg/m^2 in 40% of LT recipients) and diabetes mellitus (30% of LT recipients), addressing CVD in these patients has become increasingly relevant[6-9]. Likewise, as the number of LTs increase by the year, the proportion of older adults (age ≥ 65 years old) on the waiting list with competing comorbidities increase, and the demographics of LT candidates evolve, they parallel increases in their CVD risk profiles. Therefore, cardiac risk stratification and timely management of CVD is important to ensure favorable outcomes in LT candidates.

The primary goal of cardiac risk assessment in patients awaiting LT is to preemptively reduce the risk of cardiovascular morbidity and mortality that may arise from hemodynamic stress in the peri- and post-transplant periods. Currently, there exist no validated models to predict cardiovascular mortality in LT recipients. The complex hemodynamics shared by ESLD patients in the pre-transplant period with adverse cardiovascular events occurring in only some of these recipients continue to challenge currently available guidelines and their uniform applicability[8]. Moreover, there is a paucity of guidelines for adverse cardiac events unrelated to perioperative myocardial ischemia in LT recipients[10]. Recognizing these limitations, this review aims to reach providers seeking to learn about the current state of cardiac assessment of LT candidates. We hope that this will reinforce the importance of cardiovascular optimization prior to LT, prevent futile LT in those with advanced CVD beyond the stage of optimization, and thereby use the finite resources prudently.

HEMODYNAMIC CHANGES DURING LT

Significant hemodynamic alterations occur during the LT procedure and invasive hemodynamic monitoring is necessary to guide intraoperative management[11]. The most significant periods of hemodynamic instability arise while clamping the portal vein and inferior vena cava (IVC) during the anhepatic stage, and again at the time of reperfusion of the donor graft called the neohepatic stage[12, 13]. During the anhepatic stage, an abrupt cessation of blood flow to the native liver results in a significant reduction in the preload and subsequently, in the cardiac output predisposing to cardiac dysfunction[12]. In anticipation of this complication, intravenous administration of fluids is recommended prior to vessel clamping to prevent sudden reductions in intravascular volume. Alternative options include partially occluding the IVC or creating a temporary portocaval shunt[11,14].

During the neohepatic stage, reperfusion of the donor graft predisposes to post-reperfusion syndrome (PRS), defined as a > 30% decline in mean arterial pressure that lasts for at least 1 min and occurs within 5 min of reperfusion of the donor liver[15]. PRS complicates 8%-30% of LT and manifests as dramatic reductions in the heart rate, cardiac output and systemic vascular resistance, leading to systemic hypotension, and in some cases dysrhythmias or even cardiac arrest[16]. Although the pathogenesis of PRS remains unclear, different mechanisms have been implicated with most important being the rapid release of vasoactive substances and pro-inflammatory cytokines [tumor necrosis factor (TNF)-1α, interleukin (IL)-6] from both the donor graft and the recipient's immune system[16,17].

A subset of patients undergoing LT develop an abnormal cardiac response characterized by a decrease in stroke work despite an increase in preload[18]. This is associated with a longer post-operative intubation time and poor surgical outcomes[18,19]. Although these cardiovascular complications can be anticipated, the cardiac response during LT tends to vary significantly between individuals depending on competing comorbidities and presence of preexisting cardiomyopathy[20]. Therefore, careful monitoring of hemodynamic parameters during LT is essential to lower the risk of perioperative adverse outcomes and increase the likelihood of graft survival. Similarly, recognition of underlying CVD and optimization prior to LT is imperative in reducing the risk of perioperative complications and mortality. A comprehensive review of CVD encountered in LT candidates, including their pathophysiology, pretransplant evaluation, and management is detailed below and outlined in Table 1.

CLINICAL ENTITIES

Coronary artery disease

Epidemiology: Patients with ESLD and concomitant coronary artery disease (CAD) undergoing LT have higher morbidity and mortality rates compared to recipients without CAD[21,22]. The incidence of CAD in LT candidates varies widely, ranging 2%-38% depending on the etiology of ESLD, investigation modality used for diagnosis, criteria for significant CAD used in different studies (defined as either ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels *vs* ≥ 70% stenosis), and heterogeneity of the surveyed populations[4,10,21,23]. Among ESLD patients without symptoms of CAD, prevalence of obstructive CAD (defined as ≥ 50% diameter stenosis of ≥ 1 major epicardial vessels) is similar to that of the general population[24]. Besides the well-established implications of obstructive CAD, nonobstructive CAD plays an important role in LT candidates. Patients with ESLD have a significantly higher prevalence of silent nonobstructive CAD in comparison with matched subjects without liver disease[21,24]. This is relevant as any degree of CAD, obstructive or non-obstructive, has been associated with a significantly higher risk of major adverse cardiac events (MACE) after transplant[21,24,25]. Additionally, the prevalence of CAD in ESLD from NASH/cryptogenic etiology is higher compared to other etiologies of ESLD and parallels the increased risk of postoperative myocardial ischemia in this subset of transplant recipients[4].

Pathophysiology: Patients with ESLD may not manifest symptoms of CAD due to the mal-adaptive hemodynamic changes that occur in liver disease[26]. Splanchnic vasodilation in response to high portal pressures reduce the peripheral vascular resistance and increases the cardiac output. The resulting hyperdynamic circulation leads to increased blood flow through systemic and pulmonary circulations [26]. Therefore, in the presence of a reduced afterload from a low peripheral vascular resistance, both CAD and cirrhotic cardiomyopathy may remain silent for prolonged durations. As described previously, intraoperative hemodynamic changes during LTs are significant and impose immense stress on the cardiovascular system, wherein a sudden reduction in preload, precipitated by acute blood loss or clamping of the portal vein and IVC, a reduction in the cardiac output, and an increase in systemic vascular resistance can rapidly precipitate overt myocardial ischemia in patients with preexisting CAD [23].

Pre-operative evaluation: The rationale behind screening for CAD in LT candidates is to determine the ability of the cardiovascular system to handle hemodynamic stress peri- and post-transplant without sustaining ischemic damage. Therefore, screening helps with cardiac risk stratification and identification of those patients who would benefit from pre-operative optimization, including revascularization of their CAD[27]. Considering the high prevalence of CAD in these patients, basic cardiac workup consisting of an electrocardiogram (ECG), chest X-ray, and transthoracic echocardiogram should be obtained routinely in all LT candidates, with further workup pursued on a case-specific basis[28]. As per American Heart Association (AHA) guidelines, screening for CAD should be pursued only if diagnosis would change management with a discernable improvement in patient outcomes[8]. Specifically, screening asymptomatic individuals should take into consideration patient eligibility for downstream intervention(s) if indicated, cost of the screening procedure and intervention, and the likelihood of preventing adverse cardiac events in the context of LT. However, decision to screen and treat asymptomatic patients is often challenging as predicting which subset will develop intraoperative or postoperative complications is difficult. Therefore, a detailed history and examination that explore

Table 1 Preoperative assessment of common cardiac diseases and relationship with liver transplant outcomes

	Pretransplant	During transplant	Post-transplant
Coronary artery disease	Prevalence 2%-38%. Screening: DSE (high NPV), SPECT myocardial perfusion, conventional coronary angiography (gold standard)		Cumulative 3-yr post-LT MACE incidence: 37.5%. All-cause mortality: 13%
Cirrhotic cardiomyopathy	Prevalence 40%-50%. TTE is the preferred method for the diagnosis of systolic or diastolic dysfunction preoperatively	23% abnormal cardiac response	Pretransplant diastolic dysfunction increase the risk for acute graft rejection or failure, and all-cause mortality
Valvular heart disease	27.5% with cardiac valve dysfunction. Routine TTE screening is recommended prior to LT	Severe aortic stenosis associated with 31% risk of perioperative complications	Pretransplant AV replacement or AS increase the likelihood for significant cardiac complications 1-3 yr post-LT
Portopulmonary hypertension	Prevalence 5%-8.5%. Preoperative screening with TTE is recommended to all LT candidates. Patients with RVSP > 45 mm Hg needs confirmation with RHC	MPAP > 50 mm Hg: 100% mortality. MPAP 35-50 mm Hg: Increased morbidity and mortality. MPAP < 35 mm Hg and MPAP > 35 mm Hg due to volume overload or hyperdynamic state: No increase in mortality	
Conduction abnormalities	Routine ECG should be performed in all LT candidates independently of a cardiac abnormality history		AF is the most common MACE in the first 90 d post-transplant (-43%). AF is an independent risk factor for MACE 30- and 90-d after LT
QTc prolongation	Common ECG finding in ESLD patients with CCM; no sex-based differences exist as in general population. Reversible causes of QTc prolongation should be identified and corrected preoperatively		Conflicting data exist regarding QTc prolongation as an independent predictor of mortality and its reversibility post-LT

LT: Liver transplantation; DSE: Dobutamine stress echocardiogram; NPV: Negative predictive value; SPECT: Single-photon emission computerized tomography; MACE: Major adverse cardiac events; TTE: Transthoracic echocardiogram; AV: Aortic valve; AS: Aortic stenosis; RVSP: Right ventricular systolic pressure; RHC: Right heart catheterization; MPAP: Mean pulmonary arterial pressure; ECG: Electrocardiogram; AF: Atrial fibrillation; ESLD: End-stage liver disease; CCM: Cirrhotic cardiomyopathy; QTc: Corrected QT.

the presence of both traditional and non-traditional risk factors of CAD, and presence of CAD equivalents such as peripheral artery disease should be obtained in all patients to determine the need of screening and the choice of investigation. Presence of ≥ 1 risk factors of CAD has been found to be highly predictive of angiographically significant stenosis and can be used to guide decision-making[24,25]. Similarly, the absence of CAD risk factors serves as a reliable clinical marker in ruling out significant CAD[24]. Specifically, age > 60 years, hypertension, left ventricular hypertrophy, diabetes, smoking, dyslipidemia, prior history of CAD, and high model for ESLD scores have been identified as significant risk factors of CAD in LT candidates[4,8]. Non-traditional risk factors of CAD pertinent to LT candidates should also be identified and integrated into decision-making. These include familial amyloid polyneuropathy, hereditary hemochromatosis, and NASH, each of which is associated with CAD apart from causing ESLD[29,30].

Despite studies reporting the presence one or more risk factors of CAD to be highly predictive of angiographically significant stenosis, there is a lack of consensus between guidelines on the number of risk factors needed to pursue noninvasive testing and the role of functional status in determining the need for screening for CAD. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend noninvasive testing in the presence of more than two risk factors of CAD and poor functional capacity while the AHA/American College of Cardiology (ACC) guidelines consider three or more risk factors to warrant testing irrespective of patients' functional status[8,31]. Generally, candidates should be perceived as high risk in the presence of a prior history of CAD, diabetes mellitus or ≥ 2 risk factors of CAD.

Noninvasive testing: Noninvasive testing which has a well-established role in detecting CAD in the general population is unfortunately suboptimal in patients with ESLD who tend to have a higher pre-test probability. In these patients, noninvasive tests are further limited by the hemodynamic changes of liver disease, poor coronary flow reserve, microvascular dysfunction, and carry a poor sensitivity[32-34]. However, they have been found to accurately predict development of adverse cardiac events in the post-transplant period[32-34]. Patients with nondiagnostic or abnormal noninvasive testing should undergo coronary angiography (CAG) to corroborate findings, determine the need for intervention, and whether revascularization will improve LT outcomes on an individual basis.

Noninvasive testing with stress echocardiography, typically dobutamine stress echocardiography (DSE) is a class 1B recommendation of the American Society of Transplantation for routine evaluation of CAD in all LT candidates[27]. Cardiac catheterization is recommended if DSE is nondiagnostic or abnormal. Over the years, conflicting data regarding the sensitivity and predictive value of noninvasive stress tests have been reported. In a meta-analysis evaluating the diagnostic accuracy of DSE for detecting CAD in ESLD patients awaiting LT, DSE demonstrated a poor sensitivity (32%) but excellent negative predictive value (NPV) (98%) for perioperative and long-term cardiac events[33]. Multiple other studies have found DSE to have a low sensitivity and positive predictive values and intermediate to high NPVs[4,34-36]. A frequently encountered limitation of DSE in patients with ESLD is the inability to achieve target heart rates and thereby rate-pressure products.

Myocardial perfusion imaging with single positron emission tomography (SPECT) is another modality with established role in diagnosing CAD in the general population. However, its diagnostic accuracy in ESLD patients is unclear due to conflicting results reported by different studies[28,37,38]. A high number of false positives may be secondary to the chronic vasodilatory state characteristic of ESLD and a low coronary flow due to microvascular dysfunction rather than epicardial vessel stenosis, encountered frequently in patients with NASH cirrhosis[28,37,38].

Coronary computed tomography (CT) is another option with excellent diagnostic accuracy for detect significant CAD in the general population and can serve as a viable option in ESLD patients as well[39]. Considering the questionable sensitivity of stress tests and specificity of perfusion testing such as SPECT, coronary CT can serve as an accurate and noninvasive alternative. However, there are limitations associated with it just like any other test. As per the 2018 American Society of Transplantation Liver and Intestinal and Thoracic and Critical Care Community of Practice guidelines, coronary CT maybe considered as an alternative to CAG in patients with ESLD who are able to tolerate lying flat, do not have severely impaired renal function, have low heart rates without irregularities in the rhythm, although newer gating techniques allow interpretation of coronary CT even in patients with atrial fibrillation (AF)[40,41].

Invasive testing: CAG is the gold standard diagnostic modality for detecting coronary artery stenosis and is relatively safe in patients with ESLD[28,40]. It is indicated in patients with a prior history of CAD, myocardial infarction, or a coronary intervention, in those with high pre-test probability of CAD, and in patients with abnormal or nondiagnostic noninvasive test results. On detecting significant stenosis, the decision to revascularize should be guided by whether it will improve transplant outcomes. Notably, the study conducted by Snipelisky *et al*[42] showed that patients with severe CAD continued to have an elevated cardiac mortality after LT despite revascularization preoperatively, thus questioning the benefit of pre-transplant coronary interventions. However, revascularization should be pursued if obstructive CAD is the primary precluding factor for LT[28,43]. Studies investigating the feasibility of percutaneous coronary intervention and stenting in LT candidates have found it to be feasible with a preference for bare metal stents considering the shorter dual antiplatelet therapy compared to drug eluting stents[44,45].

Cirrhotic cardiomyopathy

Epidemiology: Impaired cardiac contractility secondary to sympathetic stress and altered diastolic function in patients with ESLD is termed cirrhotic cardiomyopathy[26,46,47]. Although there are limited data citing the prevalence of cirrhotic cardiomyopathy, attributable in part to the indolent nature of the disease, nearly 40%-50% of ESLD patients have cardiac changes consistent with cardiomyopathy[48,49]. This is relevant as nearly 20% of mortality in LT recipients over a 20 years post-transplant follow up period and 40% of early postoperative deaths after LT are cardiovascular-related[50].

Pathophysiology: Cirrhotic cardiomyopathy predisposes to reduced survival, and complications such as renal failure and hepatorenal syndrome in patients undergoing LT[47]. Cardiac dysfunction in ESLD occurs secondary to maladaptive alterations in the systemic and splanchnic circulations leading to an increased cardiac output and heart rate[51,52]. Pooling of blood in the splanchnic vascular bed leads to a lower central blood volume termed “central” or “effective” hypovolemia. This results in baroreceptor-induced activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)[47]. SNS stimulation leads to overactivation of the β-adrenergic system resulting in receptor desensitization and cardiac dysfunction[53].

Systolic dysfunction: At rest, systolic dysfunction in patients with ESLD remains subclinical due to a reduced afterload and low systemic vascular resistance. However, it manifests overtly when the cardiovascular system is challenged with stressors such us LT, TIPS, and exercise[26,46,47,53]. Four possible mechanisms have been proposed to explain the systolic dysfunction in patients with ESLD: (1) Impaired beta-adrenergic receptor signaling secondary to sympathetic hyperactivity, which has also been shown to cause direct myocyte damage; (2) Decreased cardiac contractility and increased cardiomyocyte apoptosis mediated by endocannabinoids, levels of which have been shown to be increased in murine cirrhotic hearts; (3) The presence of cardio-depressant substances such as nitric oxide and carbon monoxide; and (4) Abnormalities of the sodium/calcium (Na/Ca) exchanger that result in the excess Ca influx leading to cardiomyocyte apoptosis[26,53].

Diastolic dysfunction: Diastolic dysfunction in patients with ESLD occurs due to an increased stiffness of the myocardial wall from a combination of myocardial hypertrophy, fibrosis and subendothelial edema. Activation of RAAS has been implicated in myocardial hypertrophy, myocardial fibrosis and development of diastolic heart failure in patients with portal hypertension irrespective of the presence of cirrhosis[54]. Additionally, increased levels of plasma aldosterone, a byproduct of RAAS activation have been associated with a reduced ratio of early to late (atrial) phases of ventricular filling (E:A ratio) in ESLD[54]. Therefore, it is likely that activation of RAAS leads to diastolic dysfunction by multiple direct and indirect pathophysiologic mechanisms[55-58]. Other proposed mechanisms for diastolic dysfunction in ESLD involve alteration in collagen configuration and sodium retention[59,60].

Pretransplant evaluation: Patients with ESLD can be screened for cirrhotic cardiomyopathy through biological markers and imaging modalities, wherein they supplement data obtained from history and physical examination[61]. Imaging appears to provide maximum diagnostic value when used in the appropriate clinical context.

Biological markers: Biomarkers for subclinical and clinical heart failure (HF) include brain natriuretic peptide (BNP), propeptide, N-terminal pro-BNP (NT-proBNP), and cardiac troponins[53,62,63]. BNP and NT-proBNP have been associated with the severity of ESLD and portal hypertension. Henriksen *et al*[64] demonstrated a significant correlation between proBNP and BNP levels and Child score. Moreover, they reflect the severity of diastolic and systolic cardiac abnormalities as well as mortality in clinical HF and in cirrhotic cardiomyopathy (CCM)[63,65,66]. A major consideration and limitation to setting cut-off values for any biomarker including BNP and NT-proBNP is the heterogeneity in assays used across institutions, timing of measurement, and the different thresholds/cut-offs used by individual labs. Therefore, at this time there are no cut-off points for biomarkers indicating that the patient should be removed from the transplant waiting list.

Cardiac remodeling may be measured by levels of galectin-3 and soluble suppression of tumorgenicity-2 (ST-2), member of the IL-1 family, directly interacting with cardioprotective IL-33. These markers have been shown to reflect cardiac inflammatory and fibrotic remodeling[67,68]. However, galectin-3, and soluble ST-2 are also markers for liver inflammation and fibrosis, which may limit their applicability to CCM[69]. In addition to highly sensitive C-reactive protein associated with cardiac disease (and other inflammatory conditions), other inflammatory markers have been studied in HF and CCM including IL-6, IL-8, TNF-α, lipopolysaccharide binding protein, vascular endothelial growth factor, and soluble urokinase-type plasminogen activator receptor, some of which may worsen the circulatory dysfunction of portal hypertension[47,53,61,63].

Imaging

Transthoracic echocardiography: Transthoracic echocardiography (TTE) is the preferred imaging modality although cirrhotic cardiomyopathy is largely a clinical diagnosis and there are no specific TTE features distinguishing a cirrhotic etiology[47]. Systolic dysfunction is characterized by either left ventricular ejection fraction (LVEF) ≤ 50% or global longitudinal strain (GLS) < 18% even in the presence of a normal LVEF[47,53]. Some studies have recommended a higher a cut-off value of LVEF 55%-60% in patients with ESLD due to the decreased afterload and increased preload, which could falsely normalize the LVEF in this subset[61]. GLS is particularly useful as the longitudinally oriented subendocardial fibers are highly susceptible to damage making longitudinal left ventricular function the first manifestation of cardiac impairment[53]. Diastolic dysfunction characterized by TTE should meet three or more of the following diagnostic criteria: (1) Diastolic tissue velocity of mitral annulus (septal E′ velocity) < 7 cm/s; (2) Ratio of velocity of the left ventricle inflow during early, rapid passive filling (E wave) compared to E′ (E/E′ ratio) ≥ 15. E:E′ ratio has been found to reflect left ventricular filling pressure, and this ratio increases as diastolic function worsens; (3) Left atrial volume index > 34 mL/m^2; and (4) Tricuspid regurgitation velocity > 2.8 m/s[47,53,61]. Tissue doppler imaging is a well validated imaging technique for diastolic dysfunction evaluation[61].

Cardiac magnetic resonance imaging: Structural changes in cirrhotic cardiomyopathy as seen on cardiac magnetic resonance imaging (MRI) appear similar to those of myocarditis with a non-specific patchy distribution[70]. Considering the non-specific changes, the practical applicability of cardiac MRI for diagnosing cirrhotic cardiomyopathy is low[61]. However, it can be used to visualize edema and myocardial fibrosis seen as late gadolinium enhancement, especially pronounced in patients with alcoholic liver cirrhosis, to measure LVEF and chamber volumes[39,61,71,72].

Management and prognosis: Currently there exist no guidelines for the diagnosis and treatment of cirrhotic cardiomyopathy. Management of heart failure in patients with ESLD is built on principles similar to that of non-cirrhotic patients, consisting of strict sodium and fluid restriction, use of diuretics to decongest, and afterload reduction[26]. However, afterload reduction in patients with ESLD can be challenging as they have arterial hypotension at baseline[26]. Additionally, the benefit of beta-blockers in ESLD patients is not as clear as in other groups. While nonselective beta-blockers can help improve electromechanical coupling, data from clinical trial report a reduction in cardiac output which can have

detrimental consequences during periods of stress such as infection[73].

LT remains the gold standard treatment as it normalizes hepatic metabolism and reduces the adverse effects of hyperdynamic circulation, thus improving cardiac function[53,74]. Despite undergoing LT, recipients seldom remain complication free as the presence of cirrhotic cardiomyopathy increases their likelihood of acute graft rejection and mortality. This unfavorable effect of cirrhotic cardiomyopathy on post-transplant outcomes was illustrated in a study by Mittal *et al*[75] of 970 LT recipients evaluated over a mean duration of 5.3 years. Patients with diastolic dysfunction pretransplant had a significantly higher risk of acute cellular rejection [hazard ratio (HR) = 10.56; P = 0.0001)], graft failure (HR = 2.09; P = 0.007), and all-cause mortality (HR = 1.52; P = 0.01) compared to recipients without cardiac dysfunction. Notably, the risk of complications increased with worsening diastolic dysfunction. Although point-based scoring systems such as the cardiovascular risk in orthotopic liver transplantation score to predict adverse cardiovascular events after LT have been proposed, till date there exist no validated and standardized models to quantitatively risk-stratify patients based on their risk of developing perioperative cardiac complications[76].

Portopulmonary hypertension

Epidemiology and pathophysiology: Portopulmonary hypertension (PoPH) is the presence of pulmonary arterial hypertension associated with portal hypertension of hepatic or extrahepatic origin and is currently classified as World Health Organization group 1 PH[77,78]. Prospective studies evaluating PoPH have reported a prevalence of 5 to 8.5% in patients awaiting LT[78-80]. No specific etiology of portal hypertension or chronic liver disease is associated consistently with the development of PoPH[81,82]. Similarly, the severity of liver disease has not been found to be predictive of PoPH[81,82]. However, presence of severe PoPH has been associated with a worse prognosis in patients undergoing LT compared to recipients without PoPH[83,84]. Although the pathophysiology of PoPH remains unclear, the most widely accepted mechanism is an imbalance of vasoconstrictive and vasodilatory mediators, wherein humoral substances such as endothelin-1 bypass hepatic metabolism and reach the pulmonary circulation through portosystemic shunts, leading to pulmonary arterial hypertension[85,86].

Preoperative evaluation and management: PoPH most commonly presents with exertional dyspnea but symptoms may be absent or subtle in the initial stages[87,88]. Currently, the ESC and ERS recommend echocardiographic assessment for PH in symptomatic patients with chronic liver disease or portal hypertension and in all LT candidates (Class I/Grade B)[89]. Screening with TTE is geared at estimating the right ventricular systolic pressure (RVSP). Additional information obtained from TTE include right ventricular dilatation or dysfunction and presence and severity of tricuspid regurgitation[90,91]. Patients with RVSP > 45-50 mmHg should be evaluated further with right heart catheterization (RHC) which is the gold standard investigation for diagnosing PoPH. The updated RHC criteria for diagnosing PoPH are: Mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary vascular resistance (PVR) ≥ 240 dyne $s^{-1} \cdot cm^{-5}$ or 3 Wood Units (WU) and pulmonary capillary wedge pressure ≤ 15 mmHg[92]. Importantly, PoPH with severe hemodynamic impairment (*i.e.*, mPAP > 45-50 mmHg or PVR > 3 WU) is associated with excessive mortality and is considered an absolute contraindication for LT[93,94]. Patients with mPAP ranging from 35-50 mmHg should be referred to a PoPH specialist for pulmonary arterial hypertension-specific-therapy with the goal of lowering mPAP to < 35 mmHg and becoming eligible for LT in the future[93,94]. It is important to note that mPAP may be elevated in conditions other than PoPH such as volume overload and a hyperdynamic state encountered in ESLD patients. Therefore, optimization of volume status is important and a complete assessment during RHC to ensure PVR is > 3 WU is necessary to diagnose PoPH[95,96].

Hypertension: Systemic hypertension is not a common finding among patients with ESLD who most often have low arterial blood pressure (BP), pathognomonic of splanchnic vasodilation and portal hypertension in liver cirrhosis[97,98]. The release of vasodilators and SNS-mediated vasodilation of splanchnic vessels lead to reductions in the afterload and systemic vascular resistance[97,99]. Also, patients with ESLD have a blunted response to vasopressors, and an increased arterial compliance, all of which result in low systemic BPs[99]. Often, patients with arterial hypertension become "normotensive" during the course of developing chronic liver disease. In clinical practice, determining the etiology of an inappropriately normal BP should take into consideration secondary causes of hypertension such as severe renovascular disease, a previous history of arterial hypertension, and mechanisms counteracting vasodilation. In ESLD, release of nitric oxide, calcitonin gene-related peptide, and adrenomedullin results in splanchnic vasodilation, while counteractive activation of renin angiotensin aldosterone system leads to vasoconstriction and an increase in BP[97,98]. Additionally, these counteractive mechanisms are influenced by agents such as beta blockers and aldosterone antagonists which are often used in these patients to mitigate other manifestations of ESLD and also provide antihypertensive effects.

Valvular diseases: The prevalence of valvular heart disease in patients with ESLD is currently unknown and there is a paucity of literature and guidelines about management of structural heart disease in LT

candidates[100]. The presence of valvular diseases such as severe aortic stenosis can pose a prohibitive risk to live transplant due to an increased risk of intraoperative complications and a risk of perioperative mortality greater than 30%[101,102]. Similarly, the hemodynamics of ESLD can preclude candidacy for valve surgery making these patients extremely high-risk for both procedures[101]. Additionally, the severity of aortic stenosis has been found to correspond with perioperative mortality in patients undergoing noncardiac surgery[102]. Additionally, patients with uncorrected severe aortic stenosis undergoing LT have been found to have a higher rate of cardiac complications, including cardiac death, myocardial infarction, and requirement of aortic valve replacement in the post-transplant period compared to patients without valvular disease[101,103]. As per the AHA/ACC 2014 guidelines, elevated-risk elective noncardiac surgery is reasonable to perform in patients with either severe asymptomatic aortic stenosis, mitral regurgitation, or severe asymptomatic aortic regurgitation with normal LVEF[104]. Since exercise tolerance is often poor in patients with ESLD, assessment of severity of valvular heart disease is primarily made based on imaging. However, a detailed history of symptoms of valvular heart disease or heart failure, clinical examination including cardiac examination for murmurs, and transthoracic echocardiogram is recommended routinely in all LT candidates to detect ESLD valvular heart disease, determine its severity, and assess left ventricular function[100,104,105]. This allows for risk stratification and timely planning of valvular intervention if indicated based on clinical or radiological findings.

Conduction abnormalities: A routine 12-lead ECG should be performed irrespective of a history of cardiac disease in all patients undergoing evaluation for LT[8,27].

AF: AF has a prevalence of around 10% in patients with ESLD and is the most common arrhythmia after liver transplantation[106]. It has been found to be associated with a poor prognosis, especially higher in-hospital mortality, length of hospital stay, increased perioperative cardiac complications, and MACE after liver transplantation[106-109]. Presence of AF in the pre-transplant period is a strong independent predictor of MACE at both 30- and 90-d after LT. In LT recipients, it is also the most common major adverse cardiac event in the first 90 d after transplant and constitutes nearly half of MACE (43%) in these patients[107]. Therefore, detection of AF with 12-lead ECG, telemetry monitoring, or ambulatory monitoring devices in those with a suspicion of paroxysmal AF is important as a part of cardiac evaluation of LT candidates.

QT interval prolongation: QT interval prolongation, considered a hallmark of cirrhotic cardiomyopathy, occurs in 30%-50% of patients with ESLD[110-112]. The mechanism for QT prolongation in ESLD can be multifactorial but only the Child-Pugh score has been found to be an independent predictor, with changes in plasma norepinephrine contributing to corrected QT (QTc) interval variability[110,113]. Individual components of the Child-Pugh score have not been found to prolong QTc interval significantly[110,112]. Sex-specific differences in the duration of QT interval which are well-established in the general population do not exist in patients with ESLD, whereby a QTc ≥ 440 ms is considered elevated in both women and men[112,113]. The lack of sex-based differences in the duration of QTc interval in patients with ESLD persists in the post-transplant period[113]. Although men with ESLD have a relative androgen deficiency, levels of sex hormones have not been found to correlate with durations of QTc interval in men and women in the pre-transplant period[113]. Assessment and management of prolonged QTc interval is important as it has been associated with an increased risk of mortality, especially in alcoholic liver cirrhosis, and in Child-Pugh Class A patients with any etiology of ESLD[110,114]. However, conflicting data have been reported on the effect of prolonged QT interval on mortality and its reversibility with LT[110,112,114]. Ko *et al*[112] their study of LT candidates did not find an association between QTc interval prolongation and mortality or complications in the post-transplant period. In this study, patients who underwent LT demonstrated a significant rise in QTc intervals in the early-post transplant period followed by a significant reduction within the first six months of LT. On the contrary, Kim *et al*[114] did not find significant reversibility of the QTc interval after LT, and rather found it to be an independent predictor of mortality. Also, the threshold value set for usually defined in the general population and the investigators found male sex to be an independent predictor of prolongation. This is contrary to the study by Adigun *et al*[113] who found no sex-based differences in QTc prolongation among patients with ESLD and did not find male gender to be independently associated with the duration of the QT interval.

A QT interval of ≥ 500 ms has been found to be associated with a greater risk of developing torsade de pointes in the general population but there exists no established cut-off threshold below which a prolonged QT interval confers freedom from a risk of arrhythmias in both LT recipients and the general population[115]. There is also a lack of consensus on the cut-off threshold warranting drug discontinuation in drug-induced QT prolongation[115]. Beta blockers which are frequently used in patients with ESLD have been found to shorten the QT-interval in those with prolonged durations and increase the duration of QT-interval without prolonging it in those with normal values at baseline[116,117]. Although prolonged QTc interval is prevalent in LT candidates, reversible causes such as QT-interval prolonging medications and electrolyte abnormalities should be sought and corrected promptly due to the possibility of life-threatening ventricular arrhythmias. Also, a prolonged QTc interval is not a

contraindication to LT.

Pericardial diseases

Pericardial effusion: Pericardial effusions can occur both before and after LT and require careful evaluation to detect tamponade. Hepatitis C infection with or without cryoglobulinemia has been associated with pericardial effusions both in patients with ESLD and in transplant recipients[118-120]. Although cryoglobulinemia is a well-established complication of hepatitis C infection, pericardial effusions and myopericarditis occurring as a multiorgan manifestations of cryoglobulinemia are rare with only a few reported cases worldwide[120]. Physical examination and bedside TTE should be performed to exclude tamponade. Presence of tamponade or significant pericardial effusion requires timely pericardiocentesis or pericardial window prior to LT and follow-up with repeat echocardiogram to evaluate for recurrence[28].

Constrictive pericarditis: In the context of patients with ESLD awaiting LT, constrictive pericarditis occurs as an etiology of chronic liver disease whereby longstanding hepatic congestion can lead to cardiac cirrhosis. A high degree of clinical suspicion is required as symptoms of constrictive pericarditis such as ascites, hepatomegaly and peripheral edema are often misdiagnosed as primary chronic liver disease[121]. TTE with doppler is the initial recommended test which may reveal characteristics suggestive of constrictive pericarditis such as ventricular septal shift with respiration, variation in mitral annular inflow velocity, a thickened pericardium, and rapid early diastolic filling[122]. Cardiac MRI and cardiac catheterization provide additional information to aid with diagnosis. Management involves pericardiectomy but cannot reverse ESLD, which in turn renders this procedure very high risk due to coagulopathy[123].

CONCLUSION

Comprehensive and yet patient-directed cardiovascular assessment consisting of risk factor evaluation, clinical examination, diagnostic testing with laboratory parameters, imaging, and invasive testing when medically indicated is essential for risk stratifying patients being considered for LT. Considering the high-risk nature of this invasive procedure, limited number of donor grafts available, and the high likelihood of cardiovascular mortality in the postoperative period, identifying those at highest risk of adverse events who will also benefit from preoperative optimization is imperative. This will help maximize the chances of a successful LT and avoid futile transplants in those with severe CVD not amenable to mitigation or repair. Routine cardiac workup consisting of basic tests is indicated in all LT candidates. Further workup should be guided by clinical judgement and results of the preliminary workup. Despite the high prevalence of CVD among patients with ESLD, current guidelines fall short of meeting clinical need. Areas of future research include developing validated predictive models for cardiac risk stratification in patients with ESLD, improving the diagnostic accuracy of noninvasive tests for evaluation of CAD, and development of standardized guidelines for nonischemic CVD in patients with ESLD.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Sanjana Nagraj 0000-0002-6230-7214; Spyros Peppas 0000-0002-2661-978X; Maria Gabriela Rubianes Guerrero 0000-0002-7412-5354; Damianos G Kokkinidis 0000-0002-1381-4754; Felipe I Contreras-Yametti 0000-0003-0799-4805; Sandhya Murthy 0000-0002-9337-329X; Ulrich P Jorde 0000-0002-9476-6466.

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MINIREVIEWS

Gut microbiome dysbiosis in the setting of solid organ transplantation: What we have gleaned from human and animal studies

Aparna Sharma, Emmanouil Giorgakis

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Aparna Sharma, Department of Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR 72223, United States

Emmanouil Giorgakis, Department of Surgery, University of Arkansas for Medical Sciences, Little Rock, AR 72223, United States

Corresponding author: Aparna Sharma, MD, Assistant Professor, Department of Nephrology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Little Rock, AR 72223, United States. asharma@uams.edu

Abstract

The human gut microbiome refers to all of the microorganisms present throughout the length of the gastrointestinal tract. Gut flora influence host metabolic and immune processes in myriad ways. They also play an important role in maturation and modulation of the immune system. Dysbiosis or a pathologic alteration in gut flora has been implicated in a number of diseases ranging from metabolic, autoimmune and degenerative. Whether dysbiosis has similar implications in organ transplant has been the focus of a number of pre-clinical and clinical studies. Researchers have observed significant microbiome changes after solid organ transplantation in humans that have been associated with clinical outcomes such as post-transplant urinary tract infections and diarrhea. In this article, we will discuss the available data regarding pathologic alterations in gut microbiome (dysbiosis) in solid organ transplant recipients as well as some of challenges in this field. We will also discuss animal studies focusing on mouse models of transplantation that shed light on the underlying mechanisms that explain these findings.

Key Words: Dysbiosis; Gut microbiome; Innate immunity; Short chain fatty acids; Toll like receptors; Tolerance

Core Tip: The human gut microbiome refers to all of the microorganisms present throughout the length of the gastrointestinal tract. Gut flora influence host metabolic and immune processes in myriad ways. Gut microbiota alterations have been described in solid organ recipients. In this review we discuss available human studies about changes in gut flora in solid organ transplant such as kidney, liver and small bowel.

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INTRODUCTION

The human gut microbiota refers to all of the microorganisms present throughout the length of the gastrointestinal tract and include bacteria, viruses, protozoa, and fungi. The term microbiome is used to describe these microorganisms along with their collective genetic material. In this article, the terms microbiome/microbiota will be used interchangeably. We now know that there are over 100 trillion microbes in the human gut alone, with the majority being found in the colon[1].

Most of these microorganisms consist of bacteria, along with smaller numbers of viruses, fungi, and protozoa. Previous studies of gut microbiota relied heavily on culture methods and could reliably detect only a small minority of organisms. Advances in molecular technology with methods such culture independent RNA and meta-genomic sequencing have revolutionized our understanding of the composition and function of gut flora and ways they influence host metabolism, immunity and inflammation.

The importance of gut flora in maintaining a healthy physiologic state cannot be understated. Research studies have shed light on the fact that a multitude of host processes depend on microbial function. These include maintaining the integrity of gut epithelial cells and thereby the epithelial barrier, modulation of immune system[2], nutrient processing and regulating systemic inflammation and metabolism through production of chemical messengers[3,4]. One example of these messengers are short chain fatty acids (SCFAs) that are produced by bacterial fermentation of dietary fiber in the gut lumen and circulate in the bloodstream with resultant downstream organ effects[5]. Due to their enormous contribution to the host, researchers have referred to the gut microbiome as the "second human genome". Dysbiosis is defined as a pathologic alteration in the microbiota that has adverse consequences for the host. This could manifest either as bloom of pathogenic organisms, loss of commensals or loss of diversity. Both animal and human studies have described the association between dysbiosis and diseases as diverse as such as coronary artery disease, chronic kidney disease[6], liver cirrhosis, diabetes mellitus and autoimmune conditions like systemic lupus erythematosus and rheumatoid arthritis[7-9].

The advent of modern immunosuppressive drugs has revolutionized transplant outcomes in the short term due to a dramatic reduction in the incidence of acute rejection. However long-term allograft survival remains sub-optimal[10]. It has been noted that allograft outcomes vary according to the type of organ transplanted. For instance, lung and intestine grafts that are considered colonized with microorganisms have poorer graft outcomes than heart and kidney grafts (not colonized)[11]. Gut bacteria play an important role in maturation and "setting the tone" of the host immune system[2]. Given their pivotal role in shaping immunologic responses, gut microbiome can possibly affect graft outcomes in transplantation. In this review we discuss the available data regarding pathologic alterations in gut microbiome (dysbiosis) in solid organ transplant recipients. We will also explore data from preclinical studies on mouse models of transplantation that shed light on the possible mechanisms behind these findings.

METHODOLOGY

Literature search was conducted on PubMed using Mesh database for papers until March 2021. We also cite high-quality articles in Reference Citation Analysis (https://www.referencecitationanalysis.com). Only studies published in English were considered. Search terms on Mesh database consisted of "Dysbiosis", "Gut microbiome", "Kidney transplantation", "Liver transplantation", "heart transplantation", "Heart lung transplantation" and "Lung transplantation".

Organ transplantation is associated with changes in gut microbiome

Solid organ transplant recipients are exposed to a variety of factors that can affect gut flora. These include, but are not limited to, antibiotics used for treatment or prophylaxis of infections, immunosup-

pressive medications as well as other classes of medications such as antihypertensives. Numerous studies have shed light on gut microbiome changes in hematopoietic stem cell transplant recipients. In regards to the setting of solid organ transplantation, these studies are still limited and consist mostly of cross-sectional or longitudinal observational correlation studies.

Studies in liver transplant recipients

Bajaj *et al*[12] looked at liver transplant recipients and noted that they have increase in microbial diversity and decrease in endotoxin levels compared to pre-transplant cirrhotic levels. Pathogenic genera such as *Enterobacteriaceae* (*Escherichia*, *Shigella*, *Salmonella*) were decreased compared to baseline cirrhotic state while relative abundance of potentially beneficial commensals *Lachnospiraceae* and *Ruminococcaceae* were increased. Kato *et al*[13] looked at liver transplant patients and found that *Enterobacteriaceae*, *Streptococcaceae* and *Bifidobacteriaceae* were increased whereas *Enterococcaceae*, *Lactobacillaceae*, *Clostridiaceae*, *Ruminococcaceae,* and *Peptostreptococcaceae* were decreased in patients with allograft rejection. A study by Sun *et al*[14] showed that microbiota of cirrhotic patients awaiting liver transplant surgery was significantly different than controls, however in this study no significant difference was noted between post-transplant and control groups. A similar study showed that compared to healthy controls, liver transplantation was associated with decrease beneficial bacteria such as bifibacteria and lactobacillus and increased pathogenic bacteria such as *Enterobacteriaceae*[15].

Studies in kidney transplant recipients

The phylum bacteroides is dominant in normal humans as shown by the human microbiome project. In a study of kidney transplant recipients, Swarte *et al*[16] found that gut microbiome composition was significantly different from that of healthy controls, and had a lower diversity. Use of mycophenolate mofetil (MMF) correlated to a lower diversity of gut flora as well. Lee *et al*[17] in a study looking at 26 kidney transplant recipients found that instead of bacteroides the dominant phylum was *firmicutes*. The same group also showed significant differences in gut bacteria between kidney transplant patients that had post-transplant complications such as diarrhea, acute rejection and *Enterococcal* urinary tract infections *vs* those that did not. Similar findings were noted in pediatric kidney transplant recipients [18].

In a study of intestinal transplant patients, ileal microbial diversity as measured by Shannon indices were not different between patients with and without allograft rejection however patients with acute graft rejection had significantly higher relative abundance of *Proteobacteria* and lower abundance of *firmicutes*[19]. In a study by Yuzefpolskaya *et al*[20], stool samples of patients who had received a heart transplant within the past 6 mo showed a decrease in microbial diversity.

Metabolic changes after solid organ transplant and changes in gut microbiome: New onset diabetes after transplant

New onset Diabetes after transplant (NODAT) is a frequent complication in solid organ transplant recipients. Microbiota changes have been described in these patients that were non diabetic pre transplant. In a study of kidney transplant recipients, the relative abundance of *Akkermansia muciniphila* decreased significantly after transplant in NODAT and in initially diabetic patients but not in controls [21].

Viral infections after transplant

In a study of 168 kidney transplant recipients, Lee *et al*[22] showed that patients with high levels of butyrate producing gut (BPG) bacteria in their stool had a significantly decreased risk for development of respiratory viral infections such as rhinoviral and coronavirus infections and influenza at 6 mo, 1 year and 2 years post transplantation. It was also noted in the study that the higher BPG bacteria group had a decreased risk for development of cytomegalovirus viremia at 1 year post kidney transplantation.

The above-described studies have a number of limitations. These include small sample size and patient heterogeneity. The timing of sample collection after transplant also varied between studies. Hence the pivotal question of whether dysbiosis is merely associated with rather than directly causing post-transplant adverse outcomes remains unanswered.

Evidence from animal models of transplantation

Mice with allogenic skin grafts have been studied to understand immune processes during transplantation. It has been shown that considerable immune defects are detectable in germ-free mice that lack gut flora[23]. In these mice, smaller Peyer's patches are noted and the number of $CD4^+$ T cells and immunoglobulin A producing plasma cells are found to be reduced. This highlights the important role that gut microorganisms play in maturation and development of host immunity. In a landmark study, Lei *et al*[24] found that both germ-free and antibiotic-pre-treated mice exhibit decreased allo-immunity and had increase in survival of skin grafts. This phenomenon was associated with reduction in type I interferon and nuclear factor-κB pathway activation in dendritic cells. In the same study when these germ-free mice had gastric inoculation of gut bacteria from conventional mice, accelerated skin graft rejection occurred.

Pre-clinical studies show that both innate and adaptive immune responses are affected by gut flora [25,26]. Intestinal epithelial cells express surface toll-like receptors on their surface and these are activated by binding to microbial ligands also called microbe associated molecular patterns MAMP. This binding suppresses the inflammatory response and promotes tolerance to normal microbiota components by the host immune cells. Gut flora also stimulates Treg cells which are known to play a role in graft tolerance. Depending on whether gut flora prime or quiesce the immune system of a mouse model, changes in allograft outcomes can be seen. If gut bacteria activate inflammatory pathways, this can hasten allograft rejection. On the other hand, induction of inhibitory pathways can dampen the immune response and induce tolerance. A study by Emal *et al*[27] showed that microbiome inflammation and acute kidney injury after ischemia-reperfusion *via* maturation of macrophages. Conversely, depletion of the microbes significantly attenuated renal damage, dysfunction, and remote organ injury and maintained tubular integrity after ischemia-reperfusion.

A number of chemical messengers are produced in the gut lumen by microbial activity. These include SCFAs comprising butyrate, acetate, and propionate. Butyrate has been found to induce Tregs and increase interleukin-10 production and decrease proinflammatory cytokine production by colonic macrophages[28]. In a mouse study, antibiotics to alter gut microbiota increased rate of acute rejection of skin grafts[29]. This indicates that disruption of the gut microbiota during early life development may have persistent effects on immune regulation.

The concept of molecular mimicry

Infections occurring prior to transplant can result in several T cell receptors (TCRs) that can cross-react with donor self-peptides/allo-major histocompatibility complex. In other words, microbial antigens can mimic allo-antigens from the graft. These have the potential to generate memory T cells that can subsequently cause injury to the transplanted organ. Infections contracted after transplantation can influence ongoing allo-immunity by influencing both native and memory alloreactive T cells independently of TCR cross-reactivity. This can lead to Th1 differentiation and heralds the onset of acute rejection[30].

Therapeutic trials of modifying microbiome in a mouse model seem promising. Supplementation with the SCFAs sodium acetate or sodium butyrate decreased dysbiosis and afforded protection against allograft rejection. This protection was dependent on the G protein-coupled receptor GPR43 and T regulatory cells. This study could prompt future clinical trials exploring prebiotic and dietary modifications in solid organ transplant recipients as a means to facilitate better long-term graft survival[31].

Microbiome and immunosuppressive drugs: A bidirectional relationship

The gut microbiome can influence pharmacokinetics of immunosuppressive medications causing either activation or inactivation of the drug[32,33]. Drug elimination can also be impacted by interference in the enterohepatic circulation by de-conjugation of liver-produced drug metabolites. Studies have shown that human gut bacteria are capable of metabolizing tacrolimus and MMF, the two most commonly used medications in solid organ transplantation. Additionally, Guo *et al*[34] showed that bacterial species belonging to the *Clostridiales* order convert tacrolimus into a less active metabolite. The same research group found that *Faecalibacterium prausnitzii*, a member of the *Clostridiales* order, was found in greater levels in the gut of 5 kidney transplant patients in need of higher tacrolimus doses. Gut microbes can also alter the expression of metabolic liver enzymes (*e.g.*, cytochrome P450s). It is a commonly seen phenomenon that diarrhea in transplant patients can elevate tacrolimus levels. This effect is thought to be related to downregulation of intestinal cytochrome P4503A4 and P-glycoprotein activity.

Discussion

Both animal and human studies conducted thus far indicate an association between gut microbiome changes and distinct clinical consequences in solid organ transplant recipients. However, association does not imply causation and further studies are needed in this direction. The complex crosstalk between gut flora and immune cells of solid organ transplant recipients needs to be better elucidated in order to develop newer and better therapeutic strategies to improve long term graft outcomes. There remain challenges in designing and executing methodologically rigorous microbiome studies including patient heterogeneity, financial cost and distinguishing between cause, effect, and coincidental association.

CONCLUSION

It is clear from both animal and human studies conducted thus far that gut microbiome changes are associated with distinct clinical consequences in solid organ transplant recipients. The complex crosstalk between gut flora and immune cells of solid organ transplant recipients needs to be better elucidated in order to develop newer and better therapeutic strategies to improve long term graft outcomes. There remain significant challenges in designing and executing methodologically rigorous microbiome studies due to patient heterogeneity, financial cost and distinguishing between cause, effect, and coincidental

association.

FOOTNOTES

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ORCID number: Aparna Sharma 0000-0001-9805-4848; Emmanouil Giorgakis 0000-0002-5019-5497.

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MINIREVIEWS

Robot-assisted kidney transplantation: Is it getting ready for prime time?

Vincenzo Li Marzi, Alessio Pecoraro, Maria Lucia Gallo, Leonardo Caroti, Adriano Peris, Graziano Vignolini, Sergio Serni, Riccardo Campi

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Vincenzo Li Marzi, Alessio Pecoraro, Maria Lucia Gallo, Graziano Vignolini, Riccardo Campi, Department of Minimally Invasive and Robotic Urologic Surgery, Careggi University Hospital, University of Florence, Florence 50134, Italy

Leonardo Caroti, Nephrology Unit, Careggi Hospital, Florence 50134, Italy

Adriano Peris, Intensive Care Unit and Regional ECMO Referral Centre, Careggi Hospital, Florence 50134, Italy

Sergio Serni, Department of Minimally Invasive and Robotic Urologic Surgery, University of Florence, Florence 50134, Italy

Sergio Serni, Riccardo Campi, Department of Experimental and Clinical Medicine, University of Florence, Florence 50134, Italy

Corresponding author: Vincenzo Li Marzi, MD, Surgeon, Department of Minimally Invasive and Robotic Urologic Surgery, Careggi University Hospital, University of Florence, Largo Brambilla 3, Florence 50134, Italy. limarzi2012@gmail.com

Abstract

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis. Despite the progress in the medical management of KT patients, from a purely surgical standpoint, KT has resisted innovations during the last 50 years. Recently, robot-assisted KT (RAKT) has been proposed as an alternative approach to open surgery, especially due to its potential benefits for fragile and immuno-compromised recipients. It was not until 2014 that the role of RAKT has found value thanks to the pioneering Vattikuti Urology Institute-Medanta collaboration that conceptualized and developed a new surgical technique for RAKT following the Idea, Development, Exploration, Assessment, Long-term follow-up recommendations for introducing surgical innovations into real-life practice. During the last years, mirroring the Vattikuti-Medanta technique, several centers developed RAKT program worldwide, providing strong evidence about the safety and the feasibility of this procedure. However, the majority of RAKT are still performed in the living donor setting, as an "eligible" procedure, while only a few centers have realized KT through a robotic approach in the challenging scenario of cadaver donation. In addition, despite the spread of minimally-invasive (predominantly robotic) surgery worldwide, many KTs are still performed in an

open fashion. Regardless of the type of incision employed by surgeons, open KT may lead to non-negligible risks of wound complications, especially among obese patients. Particularly, the assessment for KT should consider not only the added surgical technical challenges but also the higher risk of postoperative complications. In this context, robotic surgery could offer several benefits, including providing a better exposure of the surgical field and better instrument maneuverability, as well as the possibility to integrate other technological nuances, such as the use of intraoperative fluorescence vascular imaging with indocyanine green to assess the ureteral vascularization before the uretero-vesical anastomosis. Therefore, our review aims to report the more significant experiences regarding RAKT, focusing on the results and future perspectives.

Key Words: Deceased donors; Living donors; Kidney transplantation; Minimally invasive surgery; Robotics

Core Tip: Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis. Despite the progress in the medical management of KT patients, from a purely surgical standpoint KT has resisted innovations during the last 50 years. Recently, robot-assisted KT (RAKT) has been proposed as an alternative approach to open surgery especially thanks to its potential benefits for fragile and immunocompromised recipients. Therefore, our review aims to report the more significant experiences regarding RAKT, focusing on the results and future perspectives.

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INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease, providing a better survival rate and quality of life compared to dialysis[1]. Despite the progress in the medical management of KT patients, from a purely surgical standpoint, KT has resisted innovations during the last 50 years[2]. Indeed, open surgery remains the gold standard approach for KT according to the latest European Association of Urology (EAU) guidelines[3]. Recently, minimally invasive surgery (MIS) [and in particular robot-assisted KT (RAKT)] has been proposed as an alternative approach to open surgery, particularly due to its potential benefits for fragile and immunocompromised recipients in terms of peri- and postoperative outcomes, length of hospital stay, postoperative pain, wound infection rate, and cosmetic results[4]. While the spread of a pure laparoscopic approach was limited by the complexity of the procedure and by long learning curves, robotic surgery in this setting helps overcome these limitations thanks to the three-dimensional vision, high magnification, elimination of hand tremor, and the opportunity to take advantage from the Endo-wrist technology.

In 2021, RAKT has become a reality at selected referral centers worldwide in the setting of KT from living donors (LD), with several reports showing favorable outcomes at a short- and mid-term follow-up. Yet, expanding the indications for RAKT from deceased donors (DD) is still challenging due to specific technical and logistical issues[5]. Herein we provide a comprehensive overview of the history of RAKT, focusing on the evolution of the techniques proposed by different groups worldwide, as well as on the specific challenges associated with the expansion of this approach for KT from DDs.

RAKT: A HISTORICAL PERSPECTIVE

During the last decades, selected referral centers have implemented MIS in the field of KT from LDs. As such, a pure laparoscopic approach and subsequently RAKT were performed as progressive steps to minimize the surgical morbidity of KT while ensuring favorable functional and perioperative outcomes. Rosales *et al*[6] reported their first experience with a pure laparoscopic approach, introducing the kidney through a Pfannenstiel incision and using topical ice slush and cold saline to keep a low graft temperature. KT was completed with a median overall operative time of 240 min (53 min for vascular sutures), with a blood loss of 300 cm^3 and a hospital stay of 14 d. No surgical complications were reported.

Then, Modi *et al*[7] published a larger experience of 72 patients treated with laparoscopic KT from LDs. The authors described the use of a Pfannenstiel incision and four left-sided abdominal ports, and compared laparoscopic KT to open KT. The authors found that laparoscopic KT was associated with a longer overall operative time [223.8 min *vs* 175.7 min (P = 0.07), respectively] and a similar estimated glomerular filtration rate (eGFR) value at 3, 6, 12, and 18 mo. The mean wound length was 5.5 and 17.8 cm (P = 0.0001) and the analgesic requirement was 1.4 and 3.2 mg morphine equivalent in first 24 h (P = 0.005) in the laparoscopic KT and open KT groups, respectively. While other groups have attempted to use a laparoscopic approach to perform KT from LDs, the spread of a pure laparoscopic approach among transplant centers was limited by several issues, such as the prolonged rewarming time (that could negatively impact graft outcomes), the complexity of surgical procedure, and the longer learning curve for surgeons, which represents a barrier to the widespread adoption of the technique across centers.

Therefore, thanks to the progressive spread of robotic surgery for the treatment of urological diseases [8], and given the persistence of the unmet clinical need of introducing MIS in the field of KT, the technique of RAKT was progressively codified and developed by selected centers in United States, India, and Europe[9-13] as shown in Table 1. In particular, Hoznek *et al*[14] performed the first KT assisted by a robot using an open incision and taking advantage of the robotic arms to perform the vascular anastomoses. For the first time, this experience demonstrated that vascular anastomoses for KT could be performed through the robotic platform.

While the first preliminary experience with a purely robotic KT was reported by Giulianotti *et al*[15], it was not until 2014 that the role of RAKT has been valued thanks to the pioneering Vattikuti Urology Institute-Medanta collaboration that conceptualized and developed a new surgical technique for RAKT following the Idea, Development, Exploration, Assessment, Long-term (IDEAL) follow-up recommendations for introducing surgical innovations into real-life practice[9-11,16].

Such a technique, described in detail in the following sections of the review, allowed to overcome the main limitations of a pure laparoscopic approach (*i.e.*, long exposure of the graft to high temperatures during vascular anastomosis; technical challenges associated with performance of anastomoses laparoscopically leading to long learning curves, *etc*). This experience provided robust evidence showing the advantages of the robotic technology for minimally-invasive KT, and the foundation for the spread of a structured step-by-step technique for robotic KT to other referral KT centers worldwide[9,10].

A further major step in this direction was made by the EAU Robotic Urology Section (ERUS), which created a specific working group to prospectively collect data from patients undergoing RAKT from LDs at several European Institutions[12]. Breda *et al*[12] reported the results of a large multicenter prospective study by the ERUS-RAKT working group, confirming the feasibility and safety of RAKT and highlighting the reproducibility of the procedure by multiple surgeons with experience in both open KT and robotic urologic surgery. In this study, excellent perioperative and functional outcomes of RAKT were reported. An updated analysis from the ERUS-RAKT prospective registry including almost 300 patients provided evidence on the favorable mid-term outcomes of RAKT from LDs[17]. Lastly, the feasibility and safety of RAKT from DDs were explored by the team of the University of Florence[5]. This preliminary experience raised the bar for RAKT and led to a renowned enthusiasm for this technique also in the broader setting of DDs. In fact, the University of Florence experience confirmed that RAKT can be successfully performed in the complex setting of DDs despite specific logistical and technical challenges. Of note, expanding the indications for RAKT to DDs is a key unmet need for the transplant community, aiming to increase the number of recipients who may benefit from MIS.

SURGICAL TECHNIQUE FOR RAKT

The Vattikuti-Medanta technique RAKT from LDs

IDEAL phase 0-1: The introduction of the Vattikuti-Medanta technique for RAKT with regional hypothermia following the IDEAL recommendations represents a milestone for the development and spread of RAKT worldwide[16]. The IDEAL phase 0-1 involved the preliminary ideation of a new procedure/technique that could provide benefits for patients. After this, authors could use animal models or cadavers to evaluate and modify the initial procedure to optimize results during real clinical cases[9].

First, to reduce the exposure of the graft to longer ischemia time, the authors tested a new technique to keep the graft temperature low within the pelvis, introducing 240-300 mL of ice slush in the abdomen during > 300 robot-assisted laparoscopic radical prostatectomies. In addition, based on previous experiences in robot-assisted laparoscopic radical prostatectomy and robotic partial nephrectomy, they employed the GelPOINT® device (Applied Medical Resources Corp, Rancho Santa Margarita, CA, United States) to provide an easy access to the intraperitoneal environment, allowing safe positioning of the graft into the surgical field, as well as of the ice slush to achieve renal hypothermia[18]. Later, to simulate a real procedure, four autotransplantations with such a robotic approach were performed in two cadavers. During the first procedure, the authors replicated the Giulianotti technique, highlighting relevant difficulties in performing the ureterovesical anastomosis without undocking the robot platform

Table 1 Overview of the main steps for development and implementation of robot-assisted kidney transplantation programs worldwide

Ref.	Topic
Hoznek *et al* [14], 2002	First procedure performed through da Vinci robot (Intuitive Surgical, Inc., Mountain View, California) to complete vascular dissection and anastomosis as well as ureterovesical anastomosis
Rosales *et al* [6], 2010	First laparoscopic transplantation of a kidney from a living, related donor, performed April 16, 2009
Boggi *et al* [13], 2011	First European robotic kidney transplantation
Giulianotti *et al*[15], 2010	First robotic kidney transplant in a morbidly obese patient
Menon *et al* [9], 2014	First standardization of RAKT according to IDEAL principals. Phase 0 (simulation) studies included the establishment of techniques for pelvic cooling, graft placement in a robotic prostatectomy model, and simulation of the robotic kidney transplantation procedure in a cadaveric model. Phase 1 (innovation) studies began in January 2013 and involved treatment of a highly selective small group of patients (n = 7), using the principles utilized in the phase 0 studies, at a tertiary referral center
Menon *et al* [10], 2014	Prospective study of 50 consecutive patients who underwent live-donor RAKT at Medanta Hospital following a 3-yr planning/simulation phase at the Vattikuti Urology Institute according to IDEAL principals
Sood *et al*[11], 2014	Monitoring patient safety during the learning phase of RAKT and determine when it could be considered learned using the techniques of statistical process control
Breda *et al* [12], 2018	First multicenter prospective observational study performed by the ERUS RAKT working group
Vignolini *et al* [5], 2019	Report of the development of the first RAKT program from deceased donors
Territo *et al* [29], 2018	Update of the multicenter prospective observational study performed by the ERUS RAKT working group
Campi *et al* [26], 2019	Report of a monocentric RAKT experience with extraperitonelization of the graft according to the Vattikuti-Medanta technique, allowing a safe access for diagnostic and therapeutic percutaneous procedures during the postoperative period
Gallioli *et al* [19], 2020	Analyse of the learning curve for RAKT. At least 35 cases are needed to achieve reproducibility in terms of timing, complications, and functional results
Vignolini *et al* [25], 2019	First preliminary experience with 6 patients operated from January 2017 to April 2018 using indocyanine green fluorescence videography to assess graft and ureteral reperfusion
Musquera *et al*[17], 2021	The results of the RAKT experience performed in 10 European centers by members of the ERUS-RAKT group

ERUS: European Robotic Urology Section; IDEAL: Idea, Development, Exploration, Assessment, Long-term; RAKT: Robot-assisted kidney transplantation.

[15]. As such, for the following procedures, the cadaver was placed in a lithotomic position with a 15°-20° Trendelenburg tilt, and the robot was positioned between the patient's legs mirroring the configuration for robot-assisted laparoscopic radical prostatectomy[9].

IDEAL phase 2A: Patient and trocar positioning: The ideal phase 2A aimed to evaluate the safety and the efficacy of the new procedure in a few patients in a small prospective study[16]. The absolute contraindications were the presence of significant atherosclerosis plaques at the level of the iliac vessels, prior bilateral KTs, previous major abdominal surgery, second transplant, simultaneous dual or multiple organ transplant, and second transplantation. After confirming the feasibility of RAKT in a cadaver model with the introduction of specific technical nuances, Menon *et al*[10] reported their first experience with RAKT from LDs in carefully selected patients.

In particular, the recipient was positioned as previously described[9]. A 4-5 cm periumbilical incision was performed for the GelPOINT® device. The port configuration included: (1) One 12-mm port for the camera and one 8-mm port for the assistant, placed within the GelPOINT device (to minimize the abdominal incisions); (2) Three 8-mm ports for the robotic arms; and (3) One 12-mm assistant port placed in the right iliac fossa. The da Vinci robotic platform (Intuitive Surgical, Sunnyvale, CA, United States) was docked between the patient's legs. After skeletonization of external iliac vessels, the surgeon created an extraperitoneal pouch over the psoas muscle to allocate the graft after completion of the vascular anastomoses. The graft was placed in a gauze jacket filled with ice and then introduced into the pelvis using the GelPOINT device. Subsequently, 180-240 mL of ice slush were introduced in the pelvis through modified Toomey syringes to achieve adequate regional hypothermia.

A distal bulldog clamp followed by a proximal clamp was placed on the external iliac vein. Then, a longitudinal venotomy with cold scissors was performed, and an end-to-side anastomosis between the graft renal vein and the external iliac vein was completed in an end-to-side fashion using a running ePTFE suture (Gore-Tex CV-6; W. L. Gore & Associates Inc, Flagstaff, AZ, United States)[10]. Before the

suture had been finished, the lumen of the external iliac vein was flushed with heparinized solution through a 4.8 Fr ureteric catheter introduced through the assistant port. In the end, the graft vein was clamped, and the previously placed bulldog clamps were released and positioned proximally and then distally on the external iliac artery. Initially, the arteriotomy was made with cold scissors; thereafter, a laparoscopic aortic punch (Teleflex-Medical Inc, Research Triangle Park, NC, United States) was employed to create a circular hole. A continuous end-to-side anastomosis was realized between the external iliac and the graft artery using the Gore-Tex CV-6 suture.

At completion of the arterial anastomosis, the graft renal vessels were clamped and the external iliac artery declamped. If no signs of bleeding were observed, all clamps were removed to revascularize the graft. The graft was inspected for color, turgor, and on-table diuresis, and gently placed in the extraperitoneal pouch (closed by approximating the previously prepared peritoneal flaps) taking care not to stretch the vascular anastomoses. Lastly, the uretero-vesical anastomosis was performed according to a modified Lich-Gregoire technique using a 4-0 polydiaxone suture (Ethicon Inc, Cincinnati, OH, United States). A 6 Fr, 16-cm double-J stent, introduced through the assistant port, was placed into the ureter before completing the anastomosis. During this phase, developing an adequate detrusor tunnel was relevant to provide an anti-reflux mechanism. The stent was generally removed 3 wk after RAKT in the outpatient clinic.

ERUS-RAKT technique for RAKT from LDs

In 2018 the ERUS RAKT working group reported their first multicenter prospective study on RAKT from LD enrolling 120 enrolled patients[12]. All European centers followed a standardized operative protocol based on the Vattikuti-Medanta experience with the introduction of a few technical nuances. The patient was placed in a lithotomy position with a 20°-30° Trendelenburg tilt. After the introduction of the GelPOINT through a linear periumbilical incision of 6 cm, the other four ports were placed, in the same position reported by Menon *et al*[10]. However, in 4 female recipients, the introduction of the graft was provided through a transvaginal GelPOINT. In all cases, a 2 cm incision of the GelPOINT cap was made to guarantee the introduction of ice slush with a modified Toomey tip syringe. After placing the clamp on the external iliac vein and the realization of the venotomy using Potts scissors, an end-to-side anastomosis between the graft vein and the external iliac vein was made with a 6/0 Gore-Tex® CV-6 TTc-9 or THc-12 needle. The suture was tied to secure the posterior wall of the anastomosis at the proximal angle and then it was completed until the distal to avoid stenosis. For the artery, the bulldog clamps placement on the external iliac artery were finalized to perform a preliminary incision with cold scissors, completed using a laparoscopic aortic punch. In the beginning, both vascular anastomoses require passing the needle in the external iliac vessel in an outside-inside direction and then inside-outside through the graft vessel. However, while during the venous anastomosis the knot was tied immediately, and only then the needle was passed outside-inside through the renal vein to start the running suture, during the artery anastomosis, the knot was created to a loop left outside after the passage of the needle through the graft vessel outside-inside. Finally, the vesicoureteral anastomosis was realized following the principles of the Lich-Gregoir technique over a pre-placed 4.8-Fr, 12-cm double-J stent[12].

During the procedure, an adequate management of vascular anastomosis was mandatory to reduce the risk of severe postoperative complications. In particular, avoiding intimal injury through a careful manipulation of graft vessels was a key step during RAKT. In addition, as suggested by Gallioli *et al* [19], a complete learning curve could be useful to achieve reproducible intra- and postoperative outcomes. Finally, the exclusion criteria to perform RAKT have been modified during the last years, but the main issues are currently represented by severe calcification at the level of the iliac vessels and previous bilateral KT[17].

Technical nuances for RAKT from DD: The University of Florence experience

After the development of RAKT from LD, some centers tried to widen the indications for RAKT, including grafts from DDs[20]. The main contraindications in these series were: (1) The presence of atherosclerotic plaques at the level of the iliac vessels; (2) Previous multiple major abdominal surgery; (3) Absolute contraindications for robotic surgery; and (4) Previous bilateral KT. In this context, the transplant multidisciplinary team must deal with specific issues from both organizational and technical standpoints due to the "emergency scenario" and the time-dependent nature of the intervention. To the best of our knowledge, the largest experience of RAKT from DD was reported by our group proposing specific technical nuances to improve surgical technique while ensuring maximal patient and graft safety[5,19].

Bench surgery

The harvesting procedure is performed according to established protocol[21]. In case of grafts from donors after circulatory death, a hypothermic machine perfusion device is employed for graft preservation before RAKT. During the bench surgery, the graft is perfused with Celsior® solution. Then, the anterior margin of the vein is shaped by cutting a small part of venous tissue to provide better visualization of its posterior margin. In addition, if a right-sided graft is available, increasing the length of the

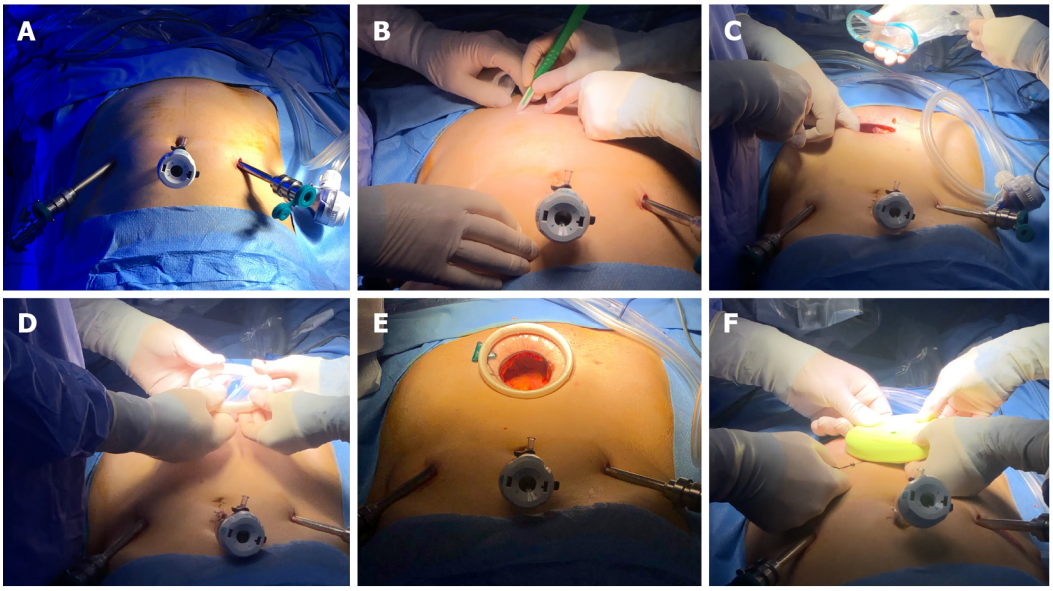

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Figure 1 Overview of the main steps for Alexis® Wound Protectors/Retractors placement through Pfannestiel incision according to the University of Florence technique for robot-assisted kidney transplantation. A: After ports placement; B and C: A Pfannestiel incision is performed; D-F: The Alexis® device is placed through Pfannestiel incision.

right vein using an inferior vena cava patch is always considered; yet, RAKT using right-sided grafts from DDs appears feasible even without a caval patch thanks to the advantages of the robotic platform, as demonstrated for RAKT in LD setting[22].

Of note, if severe atherosclerotic plaques are observed at the level of the aortic Carrel's patch, the surgeon may remove them, realizing the arterial anastomosis without the patch. In case of multiple vessels, the surgeon usually reconstructs them to perform a single anastomosis (*i.e.*, using a side-to-side anastomosis between two renal arteries in a "pantaloon" fashion), as shown in several experiences[23, 24]; alternatively, a small polar artery can be anastomosed to the inferior epigastric artery with a separate arterial anastomosis[10]. When the kidney is prepared, it is placed into a gauze jacket filled with ice to provide less traumatic handling and to maintain graft hypothermia. Finally, a 5-Fr, 12-cm double-J stent is routinely pre-placed into the ureter during bench surgery to facilitate the subsequent uretero-vesical anastomosis.

Surgical technique for RAKT from DDs

At our institution, all RAKTs followed the principles of the Vattikuti-Medanta technique with the progressive introduction of specific nuances during the learning curve[10]. Specifically: (1) A Pfannestiel rather than a periumbilical incision is used for the GelPOINT® (or the Alexis® Wound Protectors/Retractors, Applied Medical Resources Corp, United States) placement improving the aesthetic results and providing closer access to the iliac vessels (Figure 1); (2) The GelPOINT® device is placed only after adequate preparation of iliac vessels, bladder, and extraperitoneal pouch to reduce the potential risk of bladder injury; (3) The venotomy is realized with curve scissors and then a two-continuous suture is completed for the posterior and anterior plate of the venous anastomosis. First, the anterior part is performed from 12 to 6 o'clock position knotting at 6 o'clock, and then the posterior one is completed from 6 to 12 o'clock position; and (4) The arteriotomy is realized with cold scissors without the use of a laparoscopic aortic punch. In addition, considering the higher risk of atherosclerotic plaques at the level of the external iliac arteries for recipient in DD setting, the anastomosis is performed using two running sutures (in Gore-Tex 5/0 instead of 6/0). After the realization of the posterior plate using a running suture from 12 to 6 o'clock position, without knotting at the end, the anterior wall is completed with another running suture from 6 to 12 o'clock position. Then, the two ends are tied together at 6 o'clock. This technique establishes the correct tension of the anastomosis considering the characteristics of both the graft and iliac vessels. If the Carrel's patch is suitable, it can be removed, mirroring the anastomosis during RAKT in LD setting.

Regarding the assessment of graft and ureter reperfusion, our group proposed the use of intraoperative indocyanine green fluorescence videography to complement the intraoperative visual and ultrasound-based evaluation of the graft after completion of the vascular anastomoses[25]. In any case, the graft is allocated in the previously prepared extraperitoneal pouch by reapproximating the two peritoneal flaps prepared at the beginning of the procedure (Figure 2): This step has been shown to offer a safe access for diagnostic and therapeutic percutaneous procedures during the postoperative period,

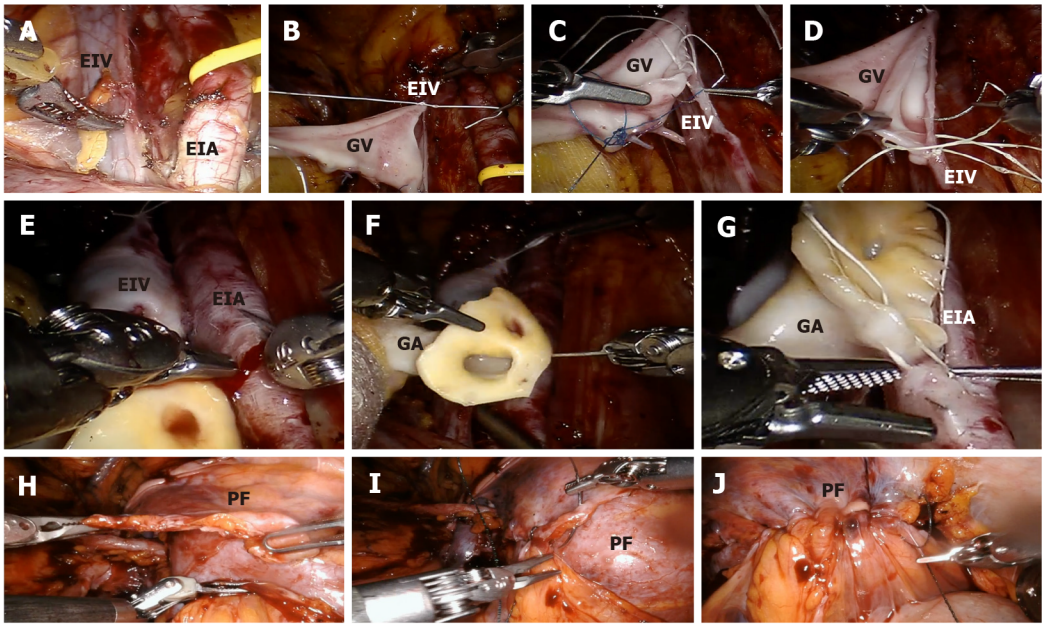

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Figure 2 Intraoperative snapshots showing the main phases of isolation of the vascular and uretero-vesical anastomoses during robot-assisted kidney transplantation from deceased donors. A: After skeletonization of external iliac vessels, the surgeon created an extraperitoneal pouch over the psoas muscle to allocate the graft after completion of the vascular anastomoses. A distal bulldog clamp followed by a proximal clamp was placed on the external iliac vein; B-D: A longitudinal venotomy with cold scissors was performed, and an end-to-side anastomosis between the graft renal vein and the external iliac vein was completed in an end-to-side fashion using a running suture; E: The previously placed bulldog clamps were released and positioned proximally and then distally on the external iliac artery. After the realization of the arteriotomy; F and G: A continuous end-to-side anastomosis was performed between the external iliac and the graft artery. Subsequently, the uretero-vesical anastomosis was performed according to a modified Lich-Gregoire technique; H-J: The graft is allocated in the previously prepared extraperitoneal pouch by reapproximating the two peritoneal flaps prepared at the beginning of the procedure. EIA: External iliac artery; EIV: External iliac vein; GA: Graft artery; GV: Graft vein; PF: Peritoneal flap.

as reported by Campi *et al*[26] without any type of postprocedural complications.

OUTCOMES OF RAKT FROM LD SETTING

During the last 10 years, several studies have been reported showing the feasibility and safety of RAKT in the LD setting. Menon *et al*[10] published their experience of the first 25 RAKTs, reporting a mean console, warm ischemia, arterial, and venous anastomotic times of 135 min, 2.4 min, 12 min, and 13.4 min, respectively. In addition, no delayed graft function (DGF) or early surgical postoperative complications were observed, while at 6 mo of follow-up two patients underwent re-exploration, and one patient died of congestive heart failure. Subsequently, Sood *et al*[27] published a preliminary comparison of 50 and 175 patients who had undergone RAKT and open KT, respectively. No difference in terms of early postoperative functional outcomes was reported (median creatinine 1.2 and 1.3 mg/dL, in RAKT and open KT group, respectively). No DGF was observed, while one patient in the RAKT group and four in the open KT underwent post-transplant dialysis. In addition, during the early follow-up, three deaths were observed (one in the RAKT group and two in the open KT, respectively). Recently, the final results of this experience (IDEAL phase 2B) have been published[28]. Particularly, 126 patients undergone RAKT and 378 open KT (1:3 matched cohort) were included, reporting a lower rate of wound infections (0% *vs* 4%, $P = 0.023$), symptomatic lymphoceles at 36 mo (0% *vs* 7%, $P = 0.003$), DGF (0% *vs* 2.3%, $P = 0.081$), and reduced postoperative pain with the robotic approach. At a median follow-up of 24.7 and 23.2 mo, for RAKT and open KT group respectively, no differences in terms of graft survival were observed {95.2% [95% confidence interval (CI): 86-99.3] *vs* 96.3% (95%CI: 93.1-99.4), $P = 0.266$}.

Another relevant experience was reported by Breda *et al*[12], presenting the preliminary results of ERUS RAKT working group from 120 patients who underwent RAKT. In this multicenter prospective observational study, the median operative and vascular suture time was 250 and 38 min, respectively. The median estimated blood loss was 150 mL and no major intraoperative complications were reported. Two patients needed open conversion and in five cases (4.2%), surgical management was requested for intraperitoneal hematoma. The median eGFR was 58.0 mL/min on postoperative day 30. Territo *et al*[29] updated this study, reporting the results of 291 RAKTs from LD and highlighting a shorter operative time after the first 120 cases (265 min *vs* 230 min, $P = 0.005$). The mean overall surgical and re-warming

time was 244 (70.5) and 53.16 (15.27) min, respectively. In all, five (2%) were lost due to thrombosis and one due to acute rejection. Two patients had arterial stenosis, three had incisional hernias, six had ureteric stenosis, and nine had lymphoceles. Finally, Musquera *et al*[17] described the mid-terms outcomes of 291 RAKT from LDs procedures. Overall, 22 cases of early major postoperative complications (defined as Clavien-Dindo Complication > 2) were recorded, while after more than 90 d from RAKT, 16 cases of major postoperative complications were observed, including one patient who died for pulmonary thromboembolism, two cases of arterial stenosis, three of incisional hernias, two of ureteric stenosis, one of angioplasty, and seven of lymphoceles. However, regarding the functional outcomes, the authors reported a progressive improvement of the eGFR (60 mL/min/1.73 m^2 at last follow-up). The median hospital stay ranged between 7 and 14 d[12,17], but it could be influenced by several items, such as hospital policies and patient-related factors. Despite the favorable results, several issues still limit the spread of RAKT from living (and deceased) donors worldwide, including the technical and logistical complexity of the procedure, as well as limited evidence regarding its learning curve. Sood *et al*[11] analyzed the learning curve of RAKTs with regional hypothermia from LDs, stratifying the recipients into three groups according to the robotic and open KT experience of the surgeons. Of note, they observed that the learning curve for RAKT was minimal for surgeons who had prior robotic and KT experience. These results were confirmed by Ahlawat *et al*[30] who described a short learning curve in RAKT for experienced surgeons in KT and robotic surgery, achieving optimal skills within ten cases. However, the authors suggested that further improvements could be observed for the first 20-25 cases.

Later, Gallioli *et al*[19] published the results of a multicenter study, including the five highest-volume centers of the ERUS RAKT working group. They demonstrated that the Trifecta, defined as no major intra/postoperative complications, no delayed graft function, and rewarming time < mean + 2 SD (= 48.6 min), was achieved in 75% of cases after a minimum of 35 procedures. Notably, all graft losses took place during the first ten RAKTs, raising concerns regarding potential technical errors during the very first cases of the robotic series, and highlighting the need of proper modular training for surgeons wishing to start their experience with RAKT. In brief, the authors suggested that at least 35 procedures could be necessary to achieve reproducibility in surgical time, complications rate, and functional results. In conclusion, while further prospective studies are needed to define the differences in the learning curve of open and robotic KT (adjusting for all patient- and provider-specific factors), centers that are interested in developing RAKT programs may benefit from existing courses on RAKT (*i.e.*, Orsi Academy, Belgium) and from the expertise gained by multicenter collaborations such as the ERUS-RAKT working group. Standardized proficiency-based training curricula are warranted.

RAKT FROM DECEASED-DONORS: CHALLENGES AND PRELIMINARY RESULTS

Since its inception, RAKTs has been primarily developed as an "elective" procedure in the LD setting. Considering the limited available evidence, as well as several logistical challenges, many teams might have concerns regarding the feasibility and safety of RAKT in a more complex scenario, such as that of DDs. Indeed, RAKT from DDs is a challenging procedure, demanding great efforts from organizational standpoints and with only few preliminary experiences worldwide[15,17,19,31-33]. Particularly, Vignolini *et al*[5] published the results of their structured RAKT program, based on a previous solid experience in open KT and RAKT from LDs.

The authors defined 5 essential phases to determine the technical and logistical feasibility of performing RAKT in case of DDs. Initially, the availability of the dedicated surgical team must be ensure, while the recipient is admitted to the Nephrology Unit to perform careful anesthesiologic and preoperative work-up. Then, the availability of the robotic operating room must be verified, aiming to start RAKT within 16 h from the organ procurement surgery, in order to keep the overall ischemia time < 24 h[34]. Finally, a careful graft evaluation on the bench is critical to individualize the indication for RAKT (*i.e.*, open KT is preferred in case of multiple vessels which cannot be reconstructed to perform a single vascular robotic anastomosis).

Despite these specific challenges, preliminary experiences coming from selected referral centers worldwide provided the proof of the concept that RAKT (in experienced hands) can be safely perform from DDs, with favorable short- and mid-term outcomes, even during the pandemic[5,19,35,36]. To the best of our knowledge, our experience represents the largest series so far on RAKT from unselected DDs [19,37]. At a median follow-up of 16 mo [interquartile range (IQR): 7-22], recipients showed good functional results with a median eGFR of 57 mL/min/1.73 m^2 (IQR: 45-76); only two patients needed dialysis treatment at the last follow-up. The safety profile of RAKT from DDs in terms of major (Clavien-Dindo grade ≥ 3) surgical complications was also promising. These favorable preliminary findings were confirmed by an updated analysis comparing RAKT and open KT from DDs at our center [37]. Overall, there were no significant differences between the RAKT and open KT cohorts in terms of baseline donor-, graft- and recipient-related characteristics, except for a significantly higher proportion of pre-emptive recipients in the RAKT cohort (40.0% *vs* 4.9%, $P = 0.0001$), a significantly lower American Society of Anesthesiologists score among patients undergoing RAKT (2 *vs* 3, $P = 0.033$). The re-warming and the vascular anastomosis time did not significantly differ between RAKT and open KT (47 min *vs* 28

min, P = 0.2; 15 min *vs* 18 min, P = 0.2, respectively).

There were no significant differences between RAKT and open KT in terms of median hospital stay (13 d) as well as the major postoperative complication rate. However, the RAKT group was associated with a significantly lower blood transfusion rate (14.3% *vs* 22.2%, P = 0.008). At the last follow-up, no differences were observed between the two groups in terms of mid-term graft function. Despite lack of randomization, our experience provides further evidence supporting the non-inferiority of RAKT as compared to open KT from DDs, provided careful patient selection, adequate surgical training, and availability of a framework allowing performance of RAKT even in "non-elective" conditions (*i.e.*, weekends, night, *etc*). However, our technique is not devoid of limitations. In particular, all candidates for RAKT are evaluated with a computed tomography (CT) scan before surgery to identify atherosclerotic plaques at the level of the external iliac vessels; that remains an absolute contraindication for the procedure. In addition, in case of atherosclerotic lesions of the renal vessels, the characteristics of polypropylene needle could provide advantages compared to Gore-Tex, but it is not suitable for robotic surgery. For these reasons, a carefully preoperative evaluation of patients is needed to tailor the surgical approach taking into consideration the patients' characteristics, especially when the procedure will be carried out as an emergency.

DISCUSSION OF THE EVIDENCE AND FUTURE PERSPECTIVES

Despite the development and spread of minimally invasive (predominantly robotic) surgery worldwide, many KTs are still performed in an open fashion. Regardless of the type of incision employed by surgeons, open KT may lead to non-negligible risks of wound complications[38], especially among obese patients. In addition, considering the fragility of KT recipients, there is certainly a window of opportunity for new surgical techniques to minimize the morbidity of KT allowing faster recover and better patient-reported outcomes[39]. As such, RAKT has the potential to reduce specific KT-related surgical complications, such as wound dehiscence/infection, symptomatic lymphoceles, postoperative pain, as well as to minimize the length of hospitalization. RAKT might also improve the cosmetic result of KT. All these potential advantages of RAKT are most promising for overweight/obese recipients[40], who represent a patient population at a higher risk of postoperative adverse events. As universally known, the obese "pandemic" is nowadays spread in developed countries, affecting a large part of the population. Although obesity is not considered an absolute contraindication for KT, European and United States data have shown that this condition is associated with a reduced chance of receiving transplantation[12]. The assessment of obese recipients for KT should consider not only the added surgical technical challenges but also the higher risk of postoperative complications, while remaining the best treatment option[41,42]. In this context, robotic surgery could offer several benefits, providing a better exposure of the surgical field and a better instrument maneuverability.

However, the optimal indications as well as the ideal body mass index (BMI) to perform RAKT is still under debate. Recently, some experiences regarding the outcomes for obese patients and morbidity obese ones (BMI ≥ 30 and 35 kg/m^2, respectively) have been reported, highlighting benefits in terms of postoperative wound infection if compared to open KT[40-43]. In addition, Spaggiari *et al*[44] have recently published the results about the simultaneous realization of RAKT and sleeve-gastrectomy, improving the patients' compliance and outcomes. The available evidence suggests potential advantages, even in terms of learning curve. As previously reported, a surgeon's background has a limited impact on his ability to perform RAKT; what really matter is the previous surgeons' exposure to robotic surgery and open KT[11]. However, considering the major exposure to minimally invasive surgery and expertise in ureteral diseases, urologists may have advantages, if compared to other specialties (*e.g.*, general surgeons, transplant surgeons), as well as the skills to manage significant postoperative complications (*e.g.*, ureteral stricture).

On this regard, while Musquera *et al*[17] reported two patients treated through open ureteral reimplantation for stenosis, Campi *et al*[37] reported two cases of endoscopic management for ureteral complications in a DD setting. Therefore, the best surgical approach to treat urological complications should be evaluated in light of patients' and related-problems characteristics (endoscopic, minimally invasive surgery, or an open approach). Despite the fact that the development of a RAKT program from DD could be extremely challenging from both a technical and organizational standpoint, Campi *et al*[37] proposed the realization of a dedicated pathway, avoiding any impact on donors' management from both a clinical and organizational standpoint, even in the DD setting. To move the field forward, specific challenges of RAKT (especially in the DD setting) must be overcome. These include the need of a dedicated, highly qualified surgical team (trained in robotic surgery), and higher direct costs as compared to open KT. While an estimated increased cost of 15000 USD per RAKT has been reported if compared to open approach[31], the higher availability of platforms will hopefully reduce the costs of robotic technology, mitigating the financial downside of RAKT in the future. This might potentially allow a more significant penetrance of the robotic technology among KT centers in Europe and worldwide.

CONCLUSION

In conclusion, the vast majority of RAKTs so far have been performed using grafts from LDs in carefully selected recipients and have been shown to achieve optimal early and mid-term outcomes (which are at least non-inferior to those of open KT based on the current literature). Yet, to date, no randomized controlled trial has been conducted comparing RAKT to the gold-standard open approach. As such, several clinical and research questions (such as the reproducibility of RAKT outside referral high-volume centers) remain unanswered. In addition, only a few preliminary experiences have been reported on the outcomes of RAKT from DDs. In this scenario, critical steps need to be taken to implement the technique and the logistics aiming to increase the number of recipients who may benefit from minimally invasive surgery and "making RAKT ready for the prime time". Large randomized prospective multicenter studies are eagerly warranted to address these unmet clinical needs, defining the best indications and limits of robotic surgery for KT.

FOOTNOTES

Author contributions: Li Marzi V and Campi R conceptualized and designed the study; Gallo ML collected data; Pecoraro A and Campi R wrote the manuscript and made the figures and table; Serni S, Vignolini G, Li Marzi V, Peris A, and Caroti L revised the manuscript for important intellectual content.

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Country/Territory of origin: Italy

ORCID number: Vincenzo Li Marzi 0000-0002-6328-7980; Alessio Pecoraro 0000-0002-0667-1468; Maria Lucia Gallo 0000-0002-1305-9904; Leonardo Caroti 0000-0002-0612-3517; Adriano Peris 0000-0003-0724-4422; Graziano Vignolini 0000-0002-8327-6859; Sergio Serni 0000-0002-8699-985X; Riccardo Campi 0000-0001-5237-0888.

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MINIREVIEWS

How and when of eyelid reconstruction using autologous transplantation

Giovanni Miotti, Marco Zeppieri, Agostino Rodda, Carlo Salati, Pier Camillo Parodi

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Giovanni Miotti, Pier Camillo Parodi, Department of Plastic Surgery, University Hospital of Udine, Udine 33100, Italy

Giovanni Miotti, Agostino Rodda, Department of Medical, Surgical and Health Sciences, Plastic and Reconstructive Surgery Unit, University of Trieste, Trieste 34123, Italy

Marco Zeppieri, Carlo Salati, Department of Ophthalmology, University Hospital of Udine, Udine 33100, Italy

Corresponding author: Marco Zeppieri, BSc, MD, PhD, Doctor, Department of Ophthalmology, University Hospital of Udine, p.le SM Misericordia, Udine 33100, Italy.
markzeppieri@hotmail.com

Abstract

Reconstructive surgery of the eyelid after tumor excision, trauma or other causes can be challenging, especially due to the complexities of the anatomic structures and to the necessity of both functional and aesthetic successful outcomes. The aim of this minireview was to investigate the use of tissue transplantation in eyelid reconstruction. Surgical procedures are various, based on the use of both flaps, pedicled or free, and grafts, in order to guarantee adequate tissue reconstruction and blood supply, which are necessary for correct healing. Common techniques normally include the use of local tissues, combining non-vascularized grafts with a vascularized flap for the two lamellae repair, to attempt a reconstruction similar to the original anatomy. When defects are too wide, vast, deep, and complex or when no adjacent healthy tissues are available, distant area tissues need to be recruited as free flaps or grafts and paired with mucosal layer reconstruction. With regards to the anterior lamella, full thickness skin grafts are commonly preferred. With regards to the reconstruction of posterior lamella, there are different graft options, which include conjunctival or tarsoconjunctival, mucosal or palatal or cartilaginous grafts usually combined with local flaps. Free flap transplantation, normally reserved for rare select cases, include the use of the radial forearm and anterolateral flaps combined with mucosal grafts, which are surgical options currently reported in the literature.

Key Words: Eyelid reconstruction; Graft transplantation; Flap transplantation; Eyelid lamella grafts; Cartilage grafts; Dermis grafts; Mucosa grafts

Core Tip: Transplantation tends to be a viable option in eyelid reconstruction surgery. The most commonly used technique involves the use of grafts for the reconstruction of one or both eyelid structures. The use of free flaps are seldom used and are reserved for cases of extensive tissue lost. In these cases, favorable flaps considered are those that are anatomically thin and pliable.

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INTRODUCTION

Eyelid reconstruction tends to be complex and difficult and can be needed after oncological surgery or trauma. There are also cases, which are not frequent, in which reconstructive surgery is needed to repair damage caused by aesthetic surgery, such as lagophthalmos post-blepharoplasty or scarring eyelid retraction. In patients with invasive and relatively large eyelid tumors, the need to perform complete oncologic excision with margins adapted to tumor type may result in the removal of an important part of this anatomical structure that encompasses both aesthetic and functional properties[1].

The eyelid consists of an anterior and posterior lamella. The anterior portion of the lid is composed of skin and orbicularis muscles, while the posterior portion includes the posterior tarsal plate, retractors (in the lower eyelid), and conjunctiva[2]. In most eyelid reconstruction surgical procedures, both lamellae need to be replaced. At least one lamella needs to include a functioning blood supply and therefore has to be pediculated, otherwise the reconstructed tissue cannot properly grow and heal, resulting in poor and/or no wound closure[3].

Several surgical techniques are currently available for lower eyelid reconstruction; the choice of the technique and postoperative results mainly depend on the preference and experience of the surgeon and on the etiology of the eyelid defect. Most surgical techniques combine different flaps and grafts in order to reconstruct both lamellae. The most commonly used reconstructive techniques are based on local flaps, which are widely described in the literature[4-6], and possible grafts to complete lid reconstruction. The main objectives of surgery include obtaining postsurgical outcomes that reflect the normal eyelid in terms of anatomy, aesthetics, and function. The aim of our minireview was to present a brief overview of reconstructive techniques based on autologous tissue transplantation for eyelid reconstruction surgery, including the use of grafts and/or free flaps, which have been reported in the literature in the past 10 years.

MATERIALS AND METHODS

We conducted a search of the literature published between January 1, 2011 to November 1, 2021 using MEDLINE (PubMed). The database was first searched using the key words "eyelid reconstruction, eyelid reconstruction AND grafts, free flaps, tissue transplantation, autologous grafts, autologous tissues". We considered only studies in English and those referring to humans and with an abstract, thus reducing the count to 1473 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. The research of articles was preformed using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (https://www.referencecitation-analysis.com).

Only articles with an abstract were considered. After excluding all works in which only local flaps were used for reconstruction, 63 studies were analyzed. A quality score was calculated for each article using a check list from the American Society of Plastic Surgeons guideline for therapeutic studies[7]. Each study was independently assessed by at least two reviewers (Miotti G and Zeppieri M), and rating decisions were based on the consensus of the reviewing authors. The results of the most relevant studies are shown in Table 1.

GENERAL NOTIONS REGARDING RECONSTRUCTIVE EYELID SURGERY

The particular eyelid anatomy must always be considered when reconstructing it. In doing so, we must always remember the presence of two lamellae that constitute the two eyelids. Full thickness defects larger than a third of the eyelid should be reconstructed in two planes, which correspond to the posterior and anterior lamellae. In order to avoid necrosis of the reconstruction, at least one lamella

Table 1 Studies in literature regarding reconstructive eyelid surgery

What	Where	Type of tissue transplant	Ref.	Conclusions
Grafts	Bilamellar reconstruction	Skin graft + tarsoconjunctival graft with orbicularis oculi muscle advancement	Doxanas[11], 1986, Kakizaki *et al*[10], 2009	Orbital part muscle mobilization allows full thickness eyelid reconstruction using two grafts due to its vascular support
		Skin graft + tarsal graft	Bortz *et al*[12], 2020	Reconstruction of lower eyelid defects with a free tarsal graft and overlying free skin graft resulted in an acceptable functional and aesthetic lower eyelid suggesting that retention of or provision of vascular support in either the anterior or posterior lamella may not be necessary
	Anterior lamella	Skin graft	Alghoul *et al*[9], 2013	Anterior lamellar defects can be reconstructed with a full-thickness skin graft. Split-thickness skin grafts should not be used
		Skin graft	Shorr *et al*[14], 2003	Upper eyelid skin grafting can be performed with good cosmetic results to address corneal decompensation in patients who have acquired lagophthalmos from anterior lamellar insufficiency
	Posterior lamella	Tarsoconjunctival graft	Hawes *et al*[17], 2011	Essential component of eyelid reconstruction as it provides an anatomically similar tissue for the inner layer of reconstructed eyelids. Patients receiving a free tarsoconjunctival graft were less likely to require surgery to repair eyelid margin erythema than those receiving a Hughes tarsoconjunctival flap
			Yazici *et al*[23], 2020	Lateral periorbital bilobed flap with tarsoconjunctival graft can be a good alternative for the single-stage reconstruction of large upper eyelid defects
			Bengoa-González *et al*[24], 2019	Reconstruction of upper eyelid defects secondary to malignant tumors with a newly modified Cutler-Beard technique with tarsoconjunctival graft gives stability to the new upper eyelid, avoiding retraction caused by scarring
		Hard-palate mucoperiosteal	Yue *et al*[26], 2020, Ito *et al*[27], 2007	HPM may be considered the optimal choice for reconstructing the posterior lamella of the eyelids because it has similar histological composition and texture to the tarsoconjunctiva
			Hendriks *et al*[28], 2020	The use in upper eyelid reconstruction is controversial because hard-palate mucosa is composed of keratinized, stratified squamous epithelium, which can irritate the cornea. Despite this, excellent results were reported for its use in upper eyelid posterior lamellar reconstruction
		Chondromucosal graft	Yamamoto *et al*[33], 2017	Ear cartilage is useful because it is easy to harvest and fabricate, has suitable flexibility, and provides adequate support. Chondromucosal grafts from the nasal septum consist of highly supportable tissue. It lacks softness and flexibility, and harvesting is limited
			Suga *et al*[34], 2016	Ear cartilage fits well to bulbar surface. It has lower complication rate, while in the nose septal perforation and more bleeding can occur
			Hendriks *et al*[28], 2020	The use of alar or triangular cartilage provides a thinner but smaller sized sample, with good adaptability in eyelid reconstruction but raised the problem of donor site morbidity
		Scapha chondrocutaneous graft	Uemura *et al*[36], 2016	The scapha cartilage graft with small skin, round and soft with a shape similar to that of the lower lid, affords a good fit to the eye globe
		Dermis fat graft	Kuzmanović Elabjer *et al*[39], 2018	Provides stiffness, additional surface area, and a scaffold. Helps with vascularization and decreases fat tissue atrophy. It can be flat or domed
		Venous graft	Barbera *et al*[40], 2008	VGs obtained by propulsive venous vessels are the most suitable for this reconstruction because of their thinness, texture, and anatomical structure
			Tomassini *et al*[41], 2012	By properties of elasticity, smoothness, and concavity, the VG conforms to the globe without inducing a chronic inflammatory reaction on the bulbar conjunctiva or on the cornea
			Scevola *et al*[42], 2015	Safe, fast, and easily reproducible compared with chondroseptal graft
		Galea or pericranium graft	Ibáñez-Flores *et al*[43], 2019	Pericranial graft provides enough tissue to cover large defects, with an appropriate volume and a non-painful postoperative period
		Buccal mucosa graft	Grixti and Malhotra[44], 2018, Jin and Cao[45], 2021	It lacks structural integrity. It is too weak and small to support the lower eyelid, shrinking substantially during the postoperative period, so it should be used in combination with cartilage
Flaps	Bilamellar reconstruction	Neurovascular free flap from the first web space of the foot	Chait *et al*[46], 1980	

Free flap based on the second metacarpal artery	Yap *et al*[47], 1997	
Free dorsalis pedis flap	Thai *et al*[48], 1999	Free flap used for outer lamella and conjunctival flap for inner lamella
Free forearm flap	Kushima *et al*[49], 2003	Entire upper eyelid reconstruction and a hard palate graft for the posterior one
	Ghadiali *et al*[50], 2016	Upper and lower eyelid total reconstruction where an extensive tissue loss of the ipsilateral forehead and temple. Tarsal plate of the eyelids was rebuilt by palmaris tenon grafts
	Iwanaga *et al*[51], 2019	2 cases of functional upper eyelid defect reconstruction. They used a free flap elevated with palmaris longus tenon split into two strips: One fixed to the frontalis muscle to achieve the opening function and the second to the medial palpebral ligament and the lateral orbicularis muscle to achieve the closing function
ALT flap	Rubino *et al*[52], 2008	Upper and lower eyelid unilateral full thickness reconstruction with ALT free flap in a patient with no available adjacent tissues, involved in extended burns, and no possibility of using RFF

ALT: Anterolateral; HPM: Hard-palate mucoperiosteal; RFF: Radial forearm flap; VGs: Venous grafts.

should have an intact blood supply. The association of two grafts is therefore not recommended. The two planes must thus consist of the association of either two flaps or a flap and a graft[1]. Most studies reported in the literature follow this common idea; however, some authors have also proposed the use of only grafts.

The association of two flaps is the safest combination regarding vascular supply and postoperative recovery. However, the use of two flaps can lead to a thick reconstructed eyelid, which can be limited if each flap is comprised exclusively of the exact missing layer. For this reason, the use of a flap and a graft is the best option for satisfactory aesthetic result. The final choice of the surgical technique depends on several factors, which include the preference and experience of the surgeon, etiology of the eyelid defect, and the availability of flaps and grafts[8]. The quality of local tissues can also modify this choice. History of radiotherapy, previous or planned in the postoperative period, can guide the reconstruction. By determining a reduction of the vascularization of the treated tissues, well vascularized tissue are preferred to repair the defects[3,5]. Local flaps certainly represent a common reconstructive choice and are preferable to grafts, especially for previously irradiated sites. The aim of our study, however, was to assess a narrower and more specific field of literature, to concentrate on studies regarding eyelid reconstruction surgery based on tissue transplantation, to include grafts or free flaps.

GRAFT TRANSPLANTATION

Graft transplantation in eyelid reconstruction is perhaps the most commonly used procedure in routine clinical settings. Various tissues can be transplanted to complete the eyelid reconstruction. Both lamellae can be restored with grafts; however, the anterior lamella is the most common segment that tends to be repaired. As a basic rule, grafts should be used when there is an adequate vascular bed to enhance post-transplanted survival. Grafts can also be used in irradiated tissues when needed; however, these types of grafts generally need to be associated with local flaps to enhance the vascularization and guarantee graft survival. Radiotherapy on engrafted areas could cause ulceration or delay the wound healing[9]. Commonly used techniques combine a non-vascularized graft for one lamella with a vascularized flap for the other[9].

As mentioned above, usually only one lamella can be reconstructed with a graft, but techniques to reconstruct both have also been described. Kakizaki *et al*[10] reported bilamellar graft reconstruction with orbicularis muscle mobilization between grafted areas ("sandwich flap"), first described by Doxanas[11] in 1986. The orbicularis oculi muscle provides an excellent blood supply to grafted tissues in these cases, in addition to enhancing the mobility of the reconstructed lid. In 2020, Bortz *et al*[12] published a clinical series in which full-thickness lid defects were restored using free tarsal grafts for the posterior lamella and free skin grafts for the anterior lamella. The authors reported this method as an alternative to the "classic" Hughes flap for lower eyelid reconstruction, especially when the occlusion of the eye could be a problem (vision deficit, elderly patients, *etc*). The evidence reported by Tenland *et al*[13] led the authors to propose this type of reconstruction. The study showed that tarsoconjunctival (TC) tissue survival does not seem to be dependent on a conjunctival flap, and thus free TC grafts or composite grafts might be considered as viable alternatives.

Anterior lamella grafts

Anterior lamella is often reconstructed with a full-thickness skin graft[10-14]. Other possibilities of

tissue transplantation include tissue cultured autograft, tissue cultured allograft, skin bank allograft, acellular dermal replacement, and xenograft[15]. Ideal donor sites include upper and lower eyelid skin and posterior auricular, preauricular, or supraclavicular skin. Split-thickness skin grafts should not be used, with the exception of cases of extensive burns in which the donor site is limited[9].

Posterior lamella grafts

Grafts or flaps are viable options for posterior lamellar reconstruction[10]. Grafts include conjunctival or TC grafts, hard palate (or palate) graft, cartilage (auricular or nasal septal) grafts, mucoperichondrium grafts, dermis fat grafts (DFGs), venous grafts (VGs), galea or pericranium grafts, mucosal membrane (buccal or labial) grafts, and temporalis fascia grafts. For lower eyelid reconstruction, for example, single or tandem composite skin muscle TC eyelid grafts from the upper lids or contralateral lower lid may be an option[10].

TC grafts: TC grafts are an excellent choice for posterior lamellar reconstruction considering that this structure reflects the features of a normal eyelid[9]. Tarsal grafts alone, taken from the healthy eyelid, can be used in association with local flaps for anterior lamella reconstruction[16]. TC grafts and flaps are essential components of eyelid reconstruction since these alternatives provide anatomically similar tissues for the inner layer of reconstructed eyelids[17]. First described in 1918 by Blaskovics[18] for lower eyelid reconstruction, autogenous TC grafts have found widespread use, as described by Hughes [19], Leone *et al*[20], and several others in the literature[21,22]. Hawes *et al*[17] proposed guidelines for the use of TC flaps and grafts to repair lower eyelid defects.

Free grafts are preferred in most cases in which the defect is from one-third to three-quarters of the eyelid length. TC flaps are advantageous when the defects are large (entire lower eyelid loss) and when poor healing can be expected. Usually, this type of reconstruction is completed by a local flap for the anterior lamella and is not limited only to the lower eyelid. Yazici *et al*[23] recently described the association of a TC graft with a bilobed local flap for the upper eyelid. Bengoa-González *et al*[24] described the use of the graft to complete and modify the Cutler-Beard technique for the upper eyelid. The TC graft gives stability to the new upper eyelid, avoiding retraction caused by scarring. From a technical point of view, it is fundamental to also avoid complications in the donor site, which usually heals spontaneously by secondary intention[9]. Almost 3-4 mm of tarsus must be maintained to allow donor eyelid stability, and Müller's muscle should be conserved. To avoid entropion or ectropion to reconstructed eyelid, the tarsal graft should be snug and no wider than the smallest dimension of the defect[17]. Figure 1 shows an example of our patient that underwent left lower eyelid reconstruction after tumor excision using a TC graft (from the left upper eyelid) for the posterior lamella and a local flap for the anterior one.

Hard-palate mucoperiosteal grafts: Hard-palate mucoperiosteal (HPM) grafts, described for the first time by Siegel[25] in 1985, can be used to replace the posterior lamella due to the ability of this graft to provide structural support and mucosal lining[9]. HPM may be considered the optimal choice for reconstructing the posterior lamella of the eyelids because it has similar histological composition and texture to the tarsoconjunctiva, and an adequately sized graft can easily be acquired[26,27]. HPM tends to be one of the preferred choices for most lower eyelid reconstructions in routine clinical settings[26]. The use of HPM in upper eyelid reconstruction is controversial because hard-palate mucosa is composed of keratinized, stratified squamous epithelium, which can irritate the cornea, especially when the defect is adjacent to the middle part of the cornea[9,28]. Despite this, excellent results without complications have been reported in studies when used in upper eyelid posterior lamellar reconstruction[28,29].

The reconstruction of the anterior lamella requires the use of flaps. Palatal mucosal grafts provide good structural support to the eyelid. This is essential for the inferior eyelid, especially when the graft is combined with a heavy flap such as the Mustardé or the orbito-nasogenien flap. The graft is and remains stiff. The shrinkage is minimal, thus providing a stable, free eyelid margin and limiting ectropion or entropion[28]. Limits of this technique, in addition to the aforementioned corneal irritation, are the described pain and delayed healing at the donor site observed when periosteum is included in the graft[30].

Auricular and nasoseptal cartilage grafts: Auricular and nasoseptal cartilage can also be useful alternatives when considering graft tissues for reconstructive surgery[28,31,32]. In some cases, this graft may prove to be too thick and too stiff to match with the eye convexity, thus needing to be thinned without compromising the supportive strength. Ear cartilage is useful because it is easy to harvest and fabricate, has suitable flexibility, and provides adequate support[33]. The spherical surface fits well with the shape of the external bulbar surface[34]. Chondromucosal grafts from the nasal septum consist of highly supportable tissue. Caution must be taken when harvesting a chondroseptal graft to avoid damage to the remaining mucosa surrounding the vast perforation. Considering this tissue is composed of hyaline cartilage, it lacks softness and flexibility. This may result in difficulty with fabrication and unsuitable contact with the bulbar conjunctiva. In addition, the harvestable size is limited[33]. The use of alar or triangular cartilage provides a thinner but smaller sized sample, with good adaptability in eyelid reconstruction but raises the problem of donor site morbidity[28]. Suga *et al*[34] published in 2016 a

comparison between ear and nasal septum grafts. The study reported that both tissues provide good options for reconstructing an inner layer of the lower eyelid. The authors stressed that the main difference lies on postoperative outcomes at the donor site. Ear cartilage tends to have lower complication rates, while harvesting nose grafts can cause important septal perforation and vast bleeding.

Another option for cartilaginous reconstruction of the posterior lamella of the lower eyelid is a scapha chondrocutaneous graft, first proposed by Yanaga and Mori[35]. Further studies reported by Uemura *et al*[36] described interesting results with the use of this graft combined with a local propeller flap. The scapha cartilage graft is an interesting alternative because it has a thin coat of skin and is round and soft with a shape similar to that of the lower lid. This tissue can provide a good fit with the eye globe and can be harvested quickly without severe complications.

DFGs: DFGs can provide useful replacement tissue for eyelid and orbit reconstruction. The DFG is composed of a dermis button, obtained by removing the overlying epidermis with the underlying subcutaneous fat. The dermis provides stiffness, additional surface area, and a scaffold. Moreover, the dermis helps with vascularization and decreases fat tissue atrophy. This tissue can be flat or domed shaped[37]. This graft option tends to be considered primarily for socket reconstruction in the context of anophthalmia, either congenital or acquired[38]. Secondary indications are eyelid reconstruction, socket contraction, eyelid contraction (used as spacer[39]), or implant exposure.

VGs: Barbera *et al*[40] first proposed VGs as a reconstructive possibility in 2008. The study reported that VGs obtained by propulsive venous vessels are the most suitable for this type of surgical reconstruction because of the tissue thinness, texture, and anatomical structure. Moreover, due to the properties of elasticity, smoothness, and concavity, the venous graft conforms to the globe without inducing a chronic inflammatory reaction on the bulbar conjunctiva or on the cornea[41]. Scevola *et al*[42] showed that VG is a good technique for palpebral reconstruction because it is safe, fast, and easily reproducible when compared with a chondroseptal graft.

Galea and pericranium grafts: Galea and pericranium grafts represent a secondary choice in eyelid reconstruction. These tissues represent a reconstructive possibility in cases of severe periocular trauma, wide tumor resections, or in socket reconstruction[35]. Ibáñez-Flores *et al*[43] published a series of cases in which pericranium grafts were used. The authors concluded that pericranial grafts provided a sufficient amount of tissue to cover large defects, thus providing appropriate substitutional volume without painful postoperative healing.

Buccal mucosa graft: Buccal mucosa graft is a good lining option[9]. Oral mucosa has similar biological properties to conjunctiva, thus making it a viable alternative to restore the ocular surface[44]. This tissue, however, lacks structural integrity and tends to be too weak and small to support the lower eyelid. Moreover, postoperative shrinking can be substantial during the follow-up period, thus it should be used in combination with cartilage[43,45]. It is important to note that buccal mucosa graft harvesting and postoperative healing tend to be rather painful for most patients.

FLAP TRANSPLANTATIONS FROM DISTANT SITES

When defects are too complex to be reconstructed with local flaps or grafts or when no adjacent tissues are available, the operation is challenging, and transplantation of tissues from distant areas is necessary. Mechanical support and mobility for reconstructive surgery can seldom be found in tissues from a distant region, combining thin and pliable skin with mucosal layer reconstruction. The flap needs to provide characteristics that are appropriate both from a functional and an aesthetic prospective. Free flaps are normally not frequently considered in reconstructive surgery. In addition, reconstructions with free flaps have several possible complications. The effect of possible radiotherapy on the recipient site (which is frequent in advanced tumors) is one of the elements that can determine the failure of autologous microsurgical reconstruction. The harmful effects on tissues and blood vessels are well known. There are only a few studies reported in the literature that are based on this surgical option for complete or partial eyelid reconstruction.

One of the first attempts of periocular region reconstruction using free flaps was described by Chait *et al*[46] who used a neurovascular free flap from the first web space of the foot after exenteration. An alternative distant surgical flap was described in a case report by Yap *et al*[47] in 1997 in which the eyelids were rebuilt using a free flap based on the second metacarpal artery. Thai *et al*[48] proposed a free dorsalis pedis flap for the outer lamella and a local conjunctival flap for the inner one for total eyelid surgical reconstruction after deep facial burn in a study published in 1999.

One of the main problems in periocular region reconstruction is represented by the extreme thinness of the tissues that compose it. This represents a limit for the reconstructive techniques due to the thickness of the tissues generally used to cover the defects. This limit is highlighted when the reconstructive choice is a free flap. For this reason, it is quite difficult to find a viable flap that can

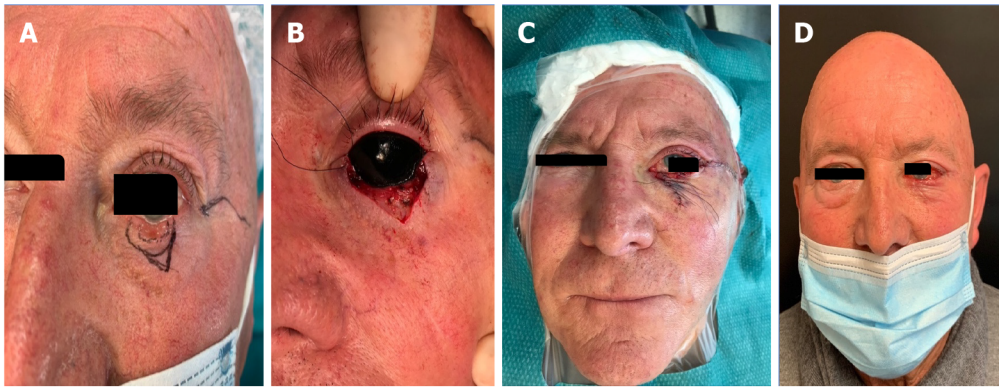

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Figure 1 A patient that underwent left lower eyelid reconstruction after tumor excision using a tarsoconjunctival graft (from the left upper eyelid) for the posterior lamella and a local flap for the anterior one. A: Basal cell carcinoma of left lower eyelid with preoperative markings; B: Lid after surgical removal; C: Postoperative reconstruction with Tenzel flap + tarsoconjunctival graft from the left upper eyelid; D: Clinical presentation 2 wk after surgery.

provide satisfactory surgical reconstruction outcomes. Kushima *et al*[49] described an entire upper eyelid reconstruction using a free radial forearm flap for the anterior lamella and a hard palate graft for the posterior one. This flap, thanks to its flexibility and thinness, is considered the ideal solution.

The same flap has been used by Ghadiali *et al*[50] in a case of upper and lower eyelid total reconstruction in which the patient had extensive tissue loss of the ipsilateral forehead and temple. In this specific case, there were no local tissues available for reconstruction. The authors used a 5 cm × 11 cm radial flap to reconstruct the entire area, followed by a fenestration of the flap 4 mo later. The tarsal plate of the eyelids was rebuilt by palmaris tenon grafts. As a result, the patient obtained a visually useful eye, which remained intact after the trauma[50]. Radial forearm flap was also used by Iwanaga *et al*[51] in 2 cases of functional upper eyelid defect reconstruction surgeries. The authors used a free flap elevated with palmaris longus tenon in a fascinating way. The palmaris longus tenon was split into two strips, in which one strip was fixed to the frontalis muscle to achieve the opening function and the second to the medial palpebral ligament and the lateral orbicularis muscle to achieve functioning closing lids.

Another feasible free flap, especially in thin or super-thin forms, is the anterolateral flap. In 2008, Rubino *et al*[52] described a case of upper and lower eyelid unilateral full thickness reconstruction with anterolateral free flap in a patient with no available adjacent tissues, who had extensive burns and no possibility of using a radial forearm flap. In this patient, the blepharoraphy was opened after 3 mo from the first surgery, obtaining good skin coverage but incomplete closure of the eye.

CONCLUSION

Eyelid reconstruction remains extremely complex and fascinating, especially considering that the main aims of surgery include re-establishing the anatomy, providing protection of the eye globe, favoring the sight, and guaranteeing the aesthetics of the face. It is clear that each surgical procedure requires experience, careful planning, and personalized surgical options tailored for each patient. From the analysis of the current literature in this field, it appears significantly advantageous to exploit periocular tissues when possible. However, other options including non-traditional flaps and grafts can prove to be viable alternatives in specific cases, especially when there is extensive damage to the lids and/or neighboring tissues are scarce and not feasible options. Stem cell harvesting and new transplanted autologous tissues can pave the way to future surgical techniques in reconstructive lid surgery.

FOOTNOTES

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ORIGINAL ARTICLE

Randomized Controlled Trial

Metabolic and functional effects of exercise training in diabetic kidney transplant recipients

Vassiliki Michou, Maria Nikodimopoulou, Asterios Deligiannis, Evangelia Kouidi

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Vassiliki Michou, Asterios Deligiannis, Evangelia Kouidi, Sports Medicine Laboratory, School of Physical Education & Sport Science, Aristotle University, Thessaloniki 57001, Greece

Maria Nikodimopoulou, Transplant Surgery Clinic of Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Corresponding author: Evangelia Kouidi, Doctor, PhD, Professor, Sports Medicine Laboratory, School of Physical Education & Sport Science, Aristotle University, Laboratory Building (3rd Floor), Thessaloniki 57001, Greece. kouidi@phed.auth.gr

Abstract

BACKGROUND

Physical activity levels are significantly lower in kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear, and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients.

AIM

To investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels and lipid profile of diabetic KT patients.

METHODS

In total, 21 type II diabetic KT recipients were randomly assigned into two groups: Exercise (n = 11, aged 52.9 ± 10.1 years) and control (n = 10, aged 53.01 ± 9.5 years). All participants at baseline and the end of the study underwent biochemical tests for fasting plasma glucose levels, glycated hemoglobin and lipid profile and cardiopulmonary exercise testing for maximum oxygen uptake [$(VO_2)_{peak}$] estimation. The exercise group followed a 6-mo supervised home-based aerobic and progressive resistance exercise program of moderate intensity 3 times per week, while the control group continued to receive usual care.

RESULTS

At the end of the 6-mo study, the exercise group had significantly lower values in fasting plasma glucose by 13.4% (from 120.6 ± 28.9 mg/dL to 104.8 ± 21.9 mg/dL, P = 0.01), glycated hemoglobin by 1.5% (from 6.7% ± 0.4 to 6.6% ± 0.4, P = 0.01) and triglycerides by 8.5% (from 164.7 ± 14.8 mg/dL to 150.8 ± 11.6 mg/dL, P < 0.05) and higher values in high-density lipoprotein by 10.2% (from 51.4 ± 8.8

mg/dL to 57.2 ± 8.7 mg/dL, $P < 0.05$) and $(VO_2)_{peak}$ by 4.7% (from 22.7 ± 3.3 to 23.8 ± 4.2, $P = 0.02$) than the control group. There were statistically significant differences between the two groups at the end of the study for fasting plasma glucose (decreased by 9.6%, $P < 0.05$), triglycerides (decreased by 4.5%, $P = 0.04$) and $(VO_2)_{peak}$ (increased by 4.4%, $P = 0.01$). Finally, after training, there was a moderate, positive linear relationship between $(VO_2)_{peak}$ and glycated hemoglobin in the exercise group ($r = 0.408$, $P = 0.03$).

CONCLUSION

The results demonstrated that a 6-mo home-based mixed type exercise training program can improve the functional capacity, levels of glucose and lipid profile of diabetic KT recipients.

Key Words: Renal transplant recipients; Diabetes mellitus; exercise; Lipid profile; Glucose control; Functional capacity

Core Tip: Physical activity levels are significantly lower in kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear, and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients. This randomized controlled trial aimed to investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels and lipid profile of diabetic KT patients. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients.

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INTRODUCTION

Renal transplantation is an effective treatment option for end-stage kidney disease patients and aims to improve quality of life and reduce mortality. Kidney transplant (KT) patients are dealing with many non- or modifiable risk factors after the transplantation surgery, especially due to the use of maintenance immunosuppression[1,2]. Dyslipidemia, abnormal glucose tolerance, hypertension, anemia and nephrotoxicity are common immunosuppressive therapy side effects in KT patients[2,3]. Unfavorable alterations in lipid and glucose profiles contribute to high cardiovascular risk[4], while low functional capacity due to comorbidities, corticosteroids and inactivity is common among these patients [5].

Diabetes mellitus incidence among the KT patient population is also high. Regular physical exercise can be an adjunct therapeutic modality for patients with diabetes mellitus, as it reduces the risk of cardiovascular disease, increases insulin sensitivity[5], leads to better glucose control and reduces lipid disorders[1]. High cardiovascular disease risk in KT patients is strongly associated with low physical activity levels[6-8]. Despite physical exercise benefiting KT patients' general health, only a few patients include physical activity in their daily routine[9]. This may be due to the non-normalized physical fitness after transplantation and comorbidities[10,11].

Although most of the studies on KT recipients have previously evaluated functional capacity and metabolic profile compared to healthy individuals, only a few studies have investigated the effects of structured exercise programs on glucose levels and lipid profile. Results from the few studies on functional capacity in KT recipients have shown that physical inactivity is a risk factor contributing to a patient's low physical fitness, which increases the risk of morbidity and mortality[5,9].

By increasing physical activity levels during their daily life KT recipients show favorable results, such as improvements in their cardiovascular fitness[6], even though the exact type, frequency or intensity recommended is not yet clear. Home-based exercise programs have previously largely been applied in hemodialysis and patients undergoing cardiovascular rehabilitation[4,12], while only two studies have so far provided home-based exercise rehabilitation programs for KT recipients[13,14]. This study aimed to examine the effects of a 6-mo home-based exercise training program on glycemic control, lipid profile and functional capacity of diabetic KT recipients.

MATERIALS AND METHODS

Patients

Twenty-eight adult KT recipients with type 2 diabetes (T2D) mellitus were recruited from the Transplant Surgery Clinic of the Hippokration General Hospital of Thessaloniki, Greece. Exclusion criteria included age older than 70 years, body mass index over 40 kg/m^2, presence of autoimmune disorders (such as systemic lupus erythematosus, multiple sclerosis, ulcerative colitis, Crohn's disease or rheumatoid arthritis), history of recent coronary heart disease (CHD) (myocardial infarction, unstable angina) within the previous 6 mo, serious musculoskeletal problems that may limit the patient's participation in this study, non-compliance with diabetes medication and previous participation in an exercise training program.

Study design

Initially, all patients who met the inclusion criteria underwent clinical examination {electrocardiography, hemodynamic [blood pressure and heart rate (HR)] and anthropometric (weight and height) measurements}, blood sampling and cardiorespiratory testing for their physical fitness estimation. After baseline measurements, patients were randomly assigned by simple randomization (drawing lots) to either an exercise group or a control group. Participants in the control group were asked to maintain their regular lifestyle and their current physical activity level during the study period. At the end of the 6-mo study, all patients underwent the same assessment. All tests were conducted by the same researcher, who was blinded to group allocation. Patients' medications were asked to remain unchanged during the study period. This randomized controlled trial protocol was approved by the Ethics Committee of the Aristotle University of Thessaloniki (Protocol number: 117461/2019). All participants received all the necessary study information before the enrollment and provided written informed consent. The clinical trial started in September 2019 and ended in February 2020.

Functional capacity assessment

To assess patient functional capacity, patients underwent a symptom-limited cardiopulmonary exercise testing on a treadmill using a Bruce protocol[15] during morning hours (9:00-11:00 am). Breath-by-breath gas exchange was measured by the Med Graphics Breeze Suite CPX Ultima (Medical Graphics Corp, MN, United States). The electrocardiogram was continuously monitored throughout each test, and the blood pressure was measured at every stage. The endpoint was set as the respiratory exchange ratio ≥ 1.10. From each test, the peak oxygen uptake [$(VO_2)_{peak}$], pulmonary ventilation, ventilatory equivalents for oxygen (pulmonary ventilation/VO_2), carbon dioxide (pulmonary ventilations/VCO_2) and the ratio between VO_2 and maximum HR (VO_2/HR_{max}) were measured.

Lipid and glucose profile assessment

At baseline and the end of the study, blood samples were taken from the brachial artery between 7:00-9:00 am, after a 12-h fast by the same blinded microbiologist at the Hippokration General Hospital of Thessaloniki. Blood samples were drawn from each group to determine by photometric method hematocrit, by computational method hemoglobin, by ion-selective electrode method serum concentrations of sodium, potassium, calcium, magnesium and electrolytes (potassium, sodium, calcium, phosphorus, magnesium), by enzymatic colorimetric method fasting plasma glucose (FPG) (mg/Dl), serum triglycerides (TG) and hemoglobin A1c (HbA1c) and by enzymatic method serum total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Results were analyzed through biochemical auto-analyzer devices.

Exercise program design

Participants in the exercise group received a home-based exercise program for 6 mo. The exercise program included aerobic exercise and muscle strengthening exercises, 3 times per week for 60-90 min, with moderate intensity, *i.e.*, 60%-80% of the maximum HR reached during cardiopulmonary exercise testing. Training intensity was increased gradually throughout the study according to each patient's capacity and adaptations. Each exercise session started with a 10-min warm-up and finished with a 10-min recovery (upper and lower limp stretching).

The aerobic part of each exercise session consisted of walking through going up and down stairs or cycling on a stationary bike, initially for 15 min, with a consequent gradual increase of time by 5 min every 2 wk, reaching 40 min in the last 2 wk before the end of the program. After a 5 min break, patients continued with the strengthening part of the exercise program. Patients were asked to perform six dynamic muscle strengthening exercises using just their body weight at the beginning. During the first week, each patient had three familiarization sessions with a physical education teacher experienced in exercise rehabilitation for patients with chronic disease, who also gave him/her an information booklet with exercise instruction images and a detailed description of the strengthening part of the program. Strengthening exercises were performed in 2 sets of 8-10 repetitions (with a 1-min passive break between the sets), in a progressive sequence from sitting to standing position. The exercise prescription included three strengthening exercises for the upper limbs (such as shoulder press, bicep curl and

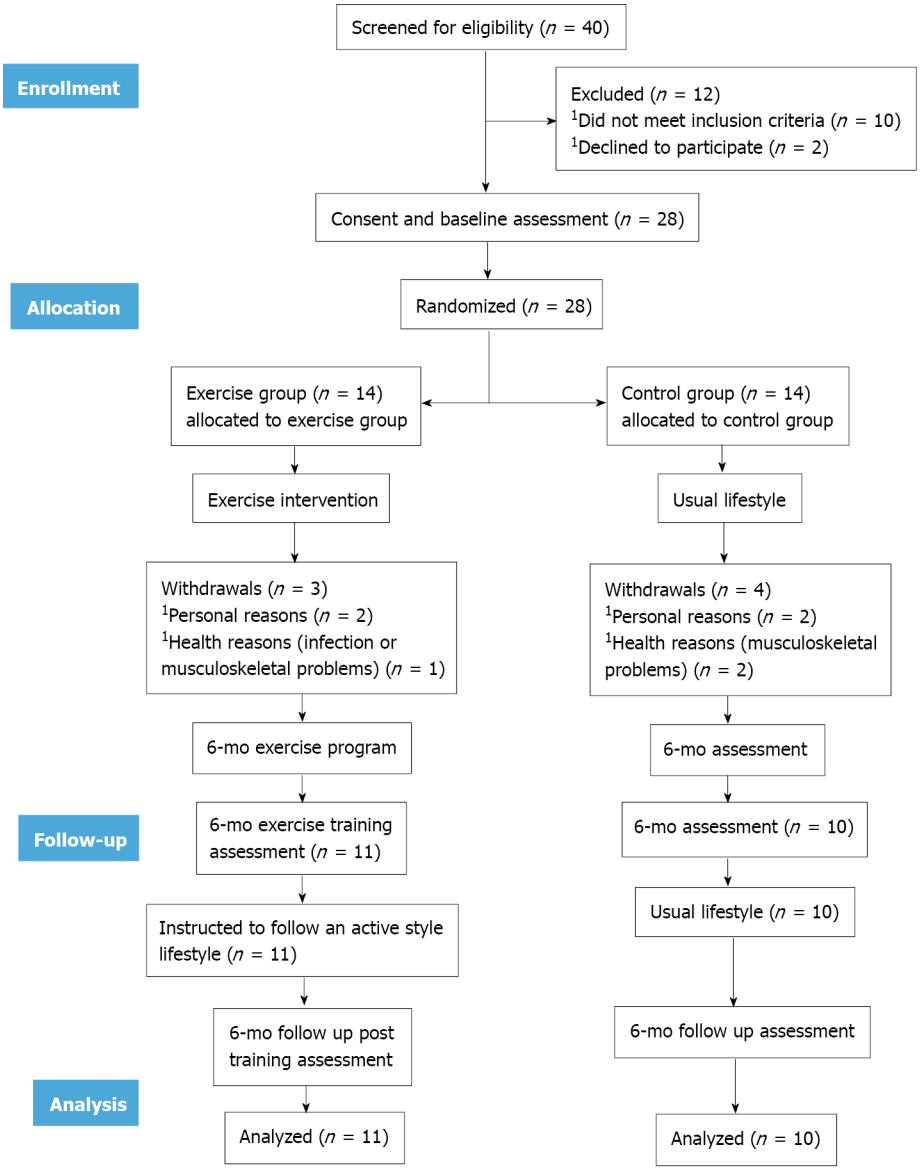

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Figure 1 Flow chart diagram of the study design. [1]Flowchart of participants was based on recommendations from the Consolidated Standards of Reporting Trials. EX: Exercise; C: Control.

triceps extension) and three for the lower limbs (such as leg flexion-extension). Progressively they were asked to perform the same exercises using rubber bands, balls and dumbbells (1 kg). Patients were advised to first perform 2 sets (8-10 repetitions) of upper limb strengthening exercise with balls and 2 sets with the 1 kg dumbbells (8-10 repetitions) in a sitting position. Second, patients were asked to place the rubber bands on their feet, tie them to the bottom of their bed or chair and do strengthening exercises in a sitting position (2 sets, 8-10 repetitions). Last, patients were asked to place the dumbbells on their feet in a standing position and move their legs back and forth, right and left of their torso, with hands placed in the middle of their body.

To ensure each patient's autonomy, the interventional 6-mo home-based exercise program was individualized, while the progress and adherence to the program were monitored by telephone every week and a home visit every month to control improvement and possible modification of the program by the researcher. To enhance compliance, participants were asked to fill in individual diaries, describing the type, frequency and duration of each exercise session and significant notes, which were collected every week through telephone communications. Moreover, researchers contacted patients for possible modifications or recommendations for exercise prescription.

Furthermore, it was essential for patients to measure before each exercise session (at least 30 min before) their blood glucose, blood pressure and HR levels and note the results in their diary. If glucose concentration was below 70 mg/dL or above 130 mg/dL, patients were advised to avoid starting exercise. Moreover, intake of a small number of carbohydrates (10-15 g) before exercise or having a carbohydrate snack available, in case of signs of hypoglycemia, was an important preventive measure.

Patients were also informed about the area of insulin injection that should be done in the abdominal cavity and not in the exercised limbs.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS 27.0 for Windows, Chicago, IL, United States) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to evaluate variables' normality of distribution. Mean differences within time and between the two groups were analyzed using two-way analysis of variance with repeated measures. Linear regression was used to study the association between variables that revealed statistically significant changes over time. Data were expressed as mean ± SD for normally distributed variables. The two-tailed *P*-values < 0.05 were considered statistically significant.

RESULTS

Patient demographic data and characteristics

At baseline, 40 KT patients were screened for eligibility; 28 were included in our study and randomized to either exercise or control group. During the 6 mo, 3 patients from the exercise group and 4 patients from the control group withdrew from the study due to health reasons (such as infection or musculoskeletal problems) or personal reasons (such as lack of time). Therefore, 21 patients completed the study (exercise group: $n = 11$; control group: $n = 10$). The flowchart of participants was based on recommendations from the Consolidated Standards of Reporting Trials (Figure 1). There was no statistically significant difference between the two groups' demographic and clinical data (Table 1). There were no exercise-induced musculoskeletal, cardiovascular, renal or other complications during the study.

Lipid and glucose profile results

After the 6-mo home-based exercise program, a statistically significant reduction of FPG by 13.4% ($P = 0.01$), TG by 8.5% ($P < 0.05$) and HbA1c by 1.5% ($P = 0.01$) as well as a significant increase in HDL by 10.2% ($P < 0.05$) compared to the baseline values in the exercise group was noted. In contrast, there was no statistically significant difference in any biochemical parameter studied in the control group at the end of the study (Table 2). Concerning changes between groups at the end of the study, the mean concentrations of FPG and TG were decreased by 9.6% ($P < 0.05$) and 4.5% ($P = 0.04$), respectively.

Functional capacity results

Exercise group results from the cardiopulmonary exercise testing revealed a statistically significant increase in $(VO_2)_{peak}$ by 4.7%, ($P = 0.02$) at the end of the study (Table 3). At baseline, there was no statistically significant difference between groups, but at the end of the study, there was only a significant intergroup difference in $(VO_2)_{peak}$, which was increased by 4.4% ($P = 0.01$) in the exercise group compared to controls.

Correlations

Lastly, linear regression analysis showed that there was a moderate, positive correlation only between $(VO_2)_{peak}$ and HbA1c after training in the exercise group ($r = 0.408$, $P = 0.03$) (Figure 2).

DISCUSSION

The results of the present study demonstrated that a home-based aerobic and strengthening exercise training program improved serum lipids by lowering the TG and increasing the HDL levels and glucose metabolism, as reflected by fasting glucose and HbA1c levels in diabetic KT patients. Moreover, the improved cardiorespiratory fitness observed in the exercise patients was found to be linearly related to the improved HbA1c.

Randomized controlled trials on exercise training programs in KT patients are few, and so little is known about their positive or negative effects or the type, frequency or intensity of exercise in this population. Painter *et al*[13] was the first that studied the clinical effects of exercise training on CHD risk profile through the first year of renal transplantation. Results showed that even though exercise led to a statistically significant increase in HDL and decreased high TC-HDL ratio, which categorized patients at high CHD risk, exercise as the only modifiable parameter did not significantly reduce CHD risk in KT patients. Pooranfar *et al*[16] showed that a 10-wk, non-pharmaceutical, aerobic (at 45%-65% of maximum HR) and resistance exercise program statistically decreased TG, TC and LDL, while HDL remained unchanged.

A few years ago Juskowa *et al*[17] assessed the effects of early rehabilitation on the musculoskeletal system and blood atheromatic indices and found that after daily 30 min of exercise, FPG and HDL levels were statistically improved in the exercise group, while TC-HDL ratio was unchanged. There was also a

Table 1 Patients' baseline demographic and clinical data

	Exercise group	Control group	*P* value
Sex (male/female)	8/3	8/2	0.52
Age (yr)	52.9 ± 9.5	53.0 ± 13.1	0.51
Height (cm)	1.6 ± 0.5	1.6 ± 0.0	0.34
Weight (kg)	70.8 ± 12.2	72.1 ± 6.7	0.77
BMI (kg/m^2)	24.4 ± 2.6	25.6 ± 2.0	0.23
Place of residence			
Rural area	27.2% (3/11)	40.0% (4/10)	0.69
Urban area	72.7% (8/11)	60.0% (6/10)	0.42
Education			
Primary education	54.5% (6/11)	40.0% (4/10)	0.33
Secondary education	18.1% (2/11)	10.0% (1/10)	0.68
Higher education	9.0% (1/11)	20.0% (2/10)	0.65
No education	18.1% (2/11)	30.0% (3/10)	0.70
Employment status			
Employed	18.1% (2/11)	10.0% (1/10)	0.71
Unemployed	54.5% (6/11)	40.0% (4/10)	0.53
Retired	27.2% (3/11)	50.0% (5/10)	0.38
Smoking	18.1% (2/11)	10.0% (1/10)	0.74
eGFR-CKD-EPI equation (mL/min)	61.0 ± 7.3	59.5 ± 8.2	0.53
Stage of diabetic nephropathy			
Stage 3	81.8% (9/11)	90.0% (9/10)	0.77
Stage 4	18.1% (2/11)	10.0% (1/10)	0.64
Time after KTx (mo)	47.4 ± 18.3	47.8 ± 18.1	0.68
Primary causes of ESKD			
Diabetes mellitus	54.5% (6/11)	50.0% (5/10)	0.64
Hypertension	27.2% (3/11)	20.0% (2/10)	0.56
Polycystic kidney disease	18.1% (2/11)	10.0% (1/10)	0.56
Glomerulonephritis	9.0% (1/11)	10.0% (1/10)	0.72
Nephrosclerosis	9.0% (1/11)	0.0% (0/10)	0.55
Reflux nephropathy	0.0% (0/11)	10.0% (1/10)	0.61
Others	0.0% (0/11)	10.0% (1/10)	0.59
Medication			
Statins	100.0% (11/11)	100.0% (10/10)	0.53
Calcium channel blockers	36.3% (4/11)	50.0% (5/10)	0.23
Oral antidiabetic drugs	18.1% (2/11)	30.0% (3/10)	0.51
Angiotensin II receptor blockers/angiotensin converting enzyme blockers	54.5% (6/11)	50.0% (5/10)	0.66
Slow and/or intermediate acting insulin	81.9% (9/11)	70.0% (7/10)	0.47
Immunosuppression therapy (corticosteroid, tacrolimus, mycophenolate mofetil)	100.0% (11/11)	100.0% (10/10)	0.74
Adherence to medication	90.9% (10/11)	100.0% (10/10)	0.82

Hematocrit (%)	42.1 ± 4.6	39.8 ± 4.5	0.63
Hemoglobin (g/dL)	14.1 ± 1.0	13.1 ± 1.6	0.16
Na^+ (mg/dL)	139.8 ± 2.5	140.3 ± 4.3	0.90
K^+ (mg/dL)	4.1 ± 0.3	4.3 ± 0.5	0.15
Ca^{2+} (mg/dL)	10.1 ± 0.5	9.7 ± 0.9	0.94
P (mg/dL)	2.9 ± 0.5	3.4 ± 0.4	0.09
Mg^+ (mg/dL)	1.6 ± 0.1	1.6 ± 0.3	0.50
Fe^+ (mg/dL)	89.8 ± 23.2	87.9 ± 16.6	0.54
Urea (mg/dL)	42.2 ± 8.7	48.1 ± 16.7	0.90
Creatinine (mg/dL)	1.1 ± 0.2	1.2 ± 0.5	0.16
Alkaline phosphatase (mg/dL)	72.1 ± 27.2	62.5 ± 10.4	0.17
Uric acid (mg/dL)	5.7 ± 1.1	5.9 ± 1.2	0.23
24-h urine albumin level (mg/dL)	106.4 ± 25.1	115.6 ± 20.9	0.25

Paired-sample *t*-test for continuous variables. Significant at the 0.05 level ($P < 0.05$). BMI: Body mass index; KTx: Kidney transplantation; eGFR: Estimated glomerular filtration rate; ESKD: End-stage kidney disease; CKD-EPI: Chronic kidney disease epidemiology collaboration equation; Na: Sodium; P: Potassium; Ca: Calcium; Mg: Magnesium; P: Phosphorus; Fe: Iron.

Table 2 Lipid and glucose profile at the beginning and the end of the 6-mo clinical trial

	Exercise group			Control group			Exercise *vs* control group	
	Baseline	After 6-mo	*P* value	Baseline	After 6-mo	*P* value	Pre	Post
FPG (mg/dL)	120.6 ± 28.9	104.8 ± 21.9	0.01	116.1 ± 33.2	115.4 ± 33.9	0.38	0.47	< 0.05
TC (mg/dL)	224.8 ± 30.4	224.0 ± 30.1	0.11	229.7 ± 28.8	230.8 ± 27.8	0.60	0.41	0.48
TG (mg/dL)	164.7 ± 14.8	150.8 ± 11.6	< 0.05	165.4 ± 19.0	165.2 ± 20.5	0.67	0.11	0.04
HDL (mg/dL)	51.4 ± 8.8	57.2 ± 8.7	< 0.05	51.1 ± 7.9	51.3 ± 12.6	0.43	0.56	0.06
LDL (mg/dL)	119.6 ± 11.4	119.4 ± 10.9	0.27	119.4 ± 17.0	119.5 ± 16.4	0.33	0.78	0.45
HbA1c (%)	6.7 ± 0.4	6.6 ± 0.4	0.01	6.5 ± 1.0	6.5 ± 1.1	0.25	0.20	0.36

Data are expressed as mean ± SD. $P > 0.05$: Baseline *vs* 6 mo follow-up; $P > 0.05$ and $P < 0.05$: Exercise *vs* control group. FPG: Fasting plasma glucose; TC: Total cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HbA1c: Hemoglobin A1c.

positive correlation between improved graft function and muscle strength in the intervention group. The results of our study showed that a 6-mo mixed type exercise program led to a significant decrease in TG, FPG and HbA1c and an increase in HDL, without affecting the TC and LDL levels.

Interestingly, a 6-mo combined exercise program in our diabetic KT recipients led to a significantly improved lipid and glucose profile, while their functional capacity was enhanced, too. These results are very important, as cardiovascular mortality in KT patients is almost 10 times higher than in the general population[18], and the T2D prevalence according to global estimates will increase by 3.0%-6.0% at the end of 2025, with approximately 3 million T2D patients[19]. According to our results, combined exercise training in diabetic patients seems to be the most dominant choice.

De Feyter *et al*[20] showed that after a 5-mo progressive resistance training with high-intensity interval training, T2D patients under regular diabetes medication, had lower FPG and HbA1c levels, while HDL, LDL and TG did not statistically improve. Furthermore, Yavari *et al*[21] in a 52-wk aerobic, resistance or combined training program in 80 T2D patients found that aerobic or combined exercise statistically reduced TG, but the long-term combined exercise was associated with higher reductions both in HbA1c and TG levels compared to the aerobic or resistance training groups. Similarly, Cauza *et al*[22] compared the effects of short-term (4 mo) and long-term (8 mo) strength and endurance training on glucose and lipid control in 20 T2D patients. Results showed that HbA1c, TC, LDL and TG were statistically decreased in the group of the 8-mo combined training program, while the group in the 4-mo exercise program developed after the end of the exercise training an atherogenic lipid profile and did not improve glycemic control compared to those who continued exercising.

Table 3 Functional capacity and respiratory responses at the beginning and the end of the 6-mo clinical trial

	Exercise group			Control group			Exercise *vs* control group	
	Baseline	After 6-mo	*P* value	Baseline	After 6-mo	*P* value	Pre	Post
$(VO_2)_{peak}$ (mL/kg/min)	22.7 ± 3.3	23.8 ± 4.2	0.02	21.9 ± 4.1	21.8 ± 3.2	0.34	0.43	0.01
RER_{max}	1.1 ± 0.0	1.2 ± 0.1	0.53	1.1 ± 0.0	1.1 ± 0.2	0.75	0.73	0.48
VO_2/HR_{max}	12.6 ± 3.3	13.0 ± 3.0	0.23	12.7 ± 2.9	12.8 ± 2.6	0.69	0.63	0.51
$VE/(VO_2)_{max}$	37.2 ± 5.0	36.3 ± 2.2	0.54	37.4 ± 4.8	37.3 ± 4.5	0.56	0.54	0.62
$VE/V(CO_2)_{max}$	33.0 ± 4.4	32.4 ± 4.3	0.60	32.9 ± 4.1	33.2 ± 3.8	0.33	0.38	0.43

Data are expressed as mean ± SD. $P > 0.05$: Baseline *vs* 6 mo follow-up; $P > 0.05$ and $P < 0.05$: Exercise *vs* control group. HR: Heart rate; RER: Respiratory exchange ratio; VO_2/HR_{max}: Ratio between VO_2 and maximum heart rate; VE: Pulmonary ventilation; $VE/(VO_2)_{max}$: Ventilatory equivalents for oxygen; $VE/V(CO_2)_{max}$: Ventilatory equivalents for carbon dioxide; $(VO_2)_{peak}$: Maximum oxygen consumption.

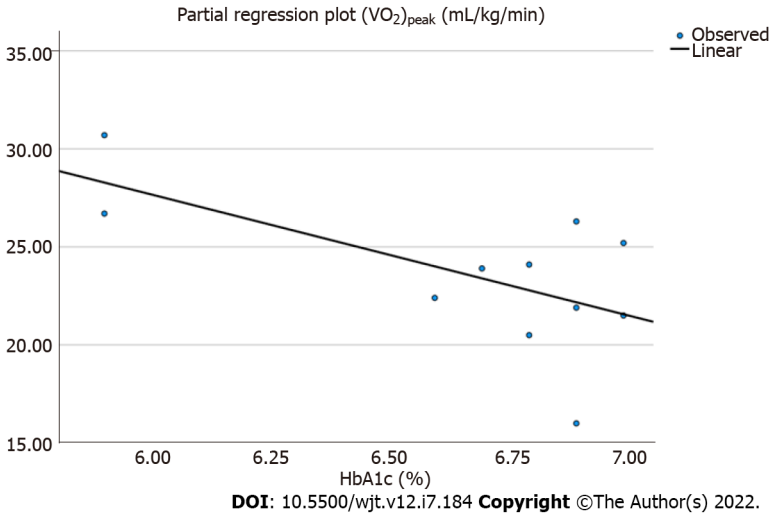

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Figure 2 Linear regression analysis between the peak oxygen uptake and glycated hemoglobin (%) after 6 mo in exercise group (r = 0.408, P = 0.03). HbA1c: Hemoglobin A1c; $(VO_2)_{peak}$: Maximum oxygen consumption.

Our study revealed statistical differences between groups after a 6-mo combined exercise program in FPG and TG levels under stable diabetic medication for both groups, similarly to the above-mentioned studies. Maintenance of diabetic medication therapy is important to understand glycemic control and lipid profile relationship and to exact results towards effects of exercise on dyslipidemia without the impact of drugs[23].

According to a recent systematic review[24], structured exercise programs for KT patients have shown short-term improvements in aerobic capacity and muscular strength, while De Smet and Van Craenenbroeck[1] mentioned that exercise towards long-term effects is only slightly investigated. Improving functional capacity is very important for KT patients, with or without diabetes. According to Calella *et al*[24], exercise training improves the cardiovascular fitness of KT patients. However, $(VO_2)_{peak}$ improvements were observed only after aerobic exercise training. In a recent randomized controlled trial, O'Connor *et al*[14] showed that $(VO_2)_{peak}$ values have notably increased after a 12-wk non-supervised moderate-intensity aerobic exercise program and that after a 9-mo follow up there were statistically significant differences in the $(VO_2)_{peak}$ values between the exercise and control groups.

On the contrary, Riess *et al*[25] showed that a supervised endurance and strength exercise program did not improve the cardiovascular disease score, although it improved the aerobic capacity and muscle strength of the KT recipients, who were taking statins and immunosuppression medication. Moreover, in a previous study of ours a 15.8% increase in $(VO_2)_{peak}$ after a 6-mo aerobic exercise training on KT patients was also noted[26]. At the end of the study, we found a statistically significant increase of 4.7% in $(VO_2)_{peak}$ of the exercise group and a significant intergroup difference in $(VO_2)_{peak}$.

This study has some limitations that need to be taken into consideration. Firstly, the sample size was small, which may decrease the power of our findings. However, this study included a 6-mo

intervention, which is a considerably long period for patients. Secondly, the biochemical tests were performed only at baseline and after 6 mo. Unfortunately, there was neither an assessment in the middle of the study nor a follow-up. Thus, larger randomized controlled trials should be implemented in the specific population to confirm the favorable effects of exercise on their metabolic profile.

CONCLUSION

In conclusion, long-term aerobic and strengthening exercise training in diabetic KT patients was found to have many beneficial effects on patients' metabolic profiles and functional capacities. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients. It is a major challenge to change their daily routine into active living to sustain their physical fitness and the benefits achieved by systemic exercise training.

ARTICLE HIGHLIGHTS

Research background

According to the existing literature, kidney transplant (KT) recipients with diabetes mellitus seem to have low physical activity levels, while dyslipidemia and abnormal glucose profile are common cardiovascular risk factors.

Research motivation

As little is known about the effects of systematic exercise on the metabolic profile and cardiovascular risk of KT patients, we believe that this study will positively contribute to the literature gap.

Research objectives

This study aimed to investigate the effects of a mixed type 6-mo exercise program on functional capacity, glucose and lipid profile of KT patients with diabetes mellitus.

Research methods

KT patients were randomly divided into two groups. Both exercise and control groups underwent biochemical blood analysis, in order to determine lipid and glucose levels, at baseline and at the end of the study. Cardiopulmonary exercise testing was also done to assess functional capacity.

Research results

At the end of the 6-mo study, fasting plasma glucose, glycated hemoglobin, triglycerides, high-density lipoprotein and the peak oxygen uptake [$(VO_2)_{peak}$] were statistically improved in the exercise group, while a positive linear relationship between peak oxygen uptake and glycated hemoglobin was also found (r = 0.408, P = 0.03).

Research conclusions

According to the results, a 6-mo home-based mixed type exercise training program can significantly improve the metabolic profile and functional capacity of diabetic KT recipients.

Research perspectives

It is crucial for future larger randomized controlled trials to explore the side effects of exercise on the metabolic profile and respiratory responses of diabetic KT recipients.

FOOTNOTES

Author contributions: Michou V designed this study and collected and analyzed the data; Michou V, Koudi E and Deligiannis A drafted the manuscript and gave final approval of the version to be published; Michou V and Koudi E took part in this study as cardiopulmonary exercise testing operators or assistants; Nikodimopoulou M recruited diabetic kidney transplant recipients to participate to the study.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Aristotle University of Thessaloniki (Protocol number:117461/2019).

Clinical trial registration statement: This study is registered at Laboratory of Sports Medicine, Aristotle University of Thessaloniki, TEFAA.

Informed consent statement: All study participant received all the necessary study information before the study enrollment and provided written informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORCID number: Vassiliki Michou 0000-0002-7097-2927; Maria Nikodimopoulou 0000-0003-2961-7066; Asterios Deligiannis 0000-0001-7765-1897; Evangelia Kouidi 0000-0002-5023-2542.

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SYSTEMATIC REVIEWS

Enhanced recovery after surgery in liver transplantation: Challenges and feasibility

Georgios Katsanos, Konstantina-Eleni Karakasi, Nikolaos Antoniadis, Stella Vasileiadou, Athanasios Kofinas, Antonios Morsi-Yeroyannis, Evangelia Michailidou, Ioannis Goulis, Emmanouil Sinakos, Olga Giouleme, Ilias Marios Oikonomou, George Evlavis, Georgios Tsakiris, Eleni Massa, Eleni Mouloudi, Georgios Tsoulfas

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Georgios Katsanos, Konstantina-Eleni Karakasi, Nikolaos Antoniadis, Stella Vasileiadou, Athanasios Kofinas, Antonios Morsi-Yeroyannis, Ilias Marios Oikonomou, Georgios Tsakiris, Georgios Tsoulfas, Department of Transplantation, Medical School, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Evangelia Michailidou, Eleni Massa, Eleni Mouloudi, Intensive Care Unit, National Health System, Hippokration General Hospital, Thessaloniki 54642, Greece

Ioannis Goulis, Emmanouil Sinakos, Fourth Department of Internal Medicine, Hippokration General Hospital, Medical School of Aristotle University, Thessaloniki 54642, Greece

Olga Giouleme, Second Propaedeutic Department of Internal Medicine, Hippokratio General Hospital, Aristotle University Thessaloniki, Thessaloniki 54642, Greece

George Evlavis, Nursing Department, National Health System, Department of Transplantation, Hippokration General Hospital, Thessaloniki 54642, Greece

Corresponding author: Georgios Tsoulfas, FACS, FICS, MD, PhD, Associate Professor, Department of Transplantation, Medical School, Aristotle University of Thessaloniki, Hippokration General Hospital, Konstantinoupoleos 49, Thessaloniki 54642, Greece. tsoulfasg@gmail.com

Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) started a revolution that changed age-old surgical stereotypical practices regarding the overall management of the surgical patient. In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. One of the last remaining fields, given its significant complexity and intricate nature, is liver transplantation (LT).

AIM

To investigate the existing efforts at implementing ERAS in LT.

METHODS

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical

primary endpoints, namely length of hospital stay.

RESULTS
All studies demonstrated a considerable decrease in length of hospital stay, with no readmission or negative impact of the ERAS protocol applied to the postoperative course.

CONCLUSIONS
ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT.

Key Words: Enhanced recovery; Enhanced recovery after surgery; Recovery; Liver transplantation; Liver

Core Tip: Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. The benefits of ERAS in liver transplantation seem promising, and further studies should be conducted to validate its application in properly selected patients.

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INTRODUCTION

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery[1]. Since its introduction in 1997 by Kehlet *et al*[2], initially destined for and subsequently established in colorectal surgery, the concept of ERAS was validated and has since evolved and spread to a multitude of surgical disciplines[3] including solid organ transplantation[4].

Although the concept of enhanced recovery was explored in liver transplantation (LT) before its official introduction by Kehlet *et al*[2] as early as 1990 in the form of early extubation yielding encouraging results[5], it was done so without the classic multimodal approach, focusing and highlighting on the importance of anesthesia management in these patients[6]. Over the years, independent studies have validated the significance and efficiency of other classic ERAS parameters such as preoperative nutrition, early mobilization, early feeding, and optimal analgesia of patients undergoing LT. Nevertheless, the medical literature is scarce in studies that combine all of the above parameters in a classic large-scale ERAS approach specific for LT. This narrative review paper will investigate existing efforts at implementing ERAS in LT, as well as try to identify the existing challenges and future potential developments in the field.

This review paper investigates existing efforts at implementing ERAS in LT and identifies the existing challenges and future potential developments in the field.

MATERIALS AND METHODS

Our goal was to identify the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay. Medline, Embase, OVID, and the Cochrane library were searched in the English language using the search terms (ERAS OR "enhanced recovery" OR "fast track" AND "liver transplantation") from years 1990 to 2021 and after independent assessment from three reviewers, three articles were selected. PRISMA flow chart is presented in Figure 1.

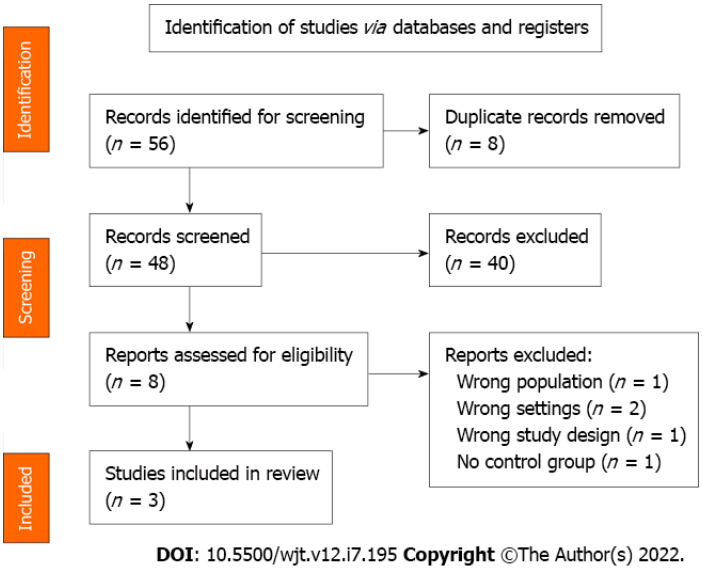

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Figure 1 PRISMA flowchart.

RESULTS

There was a small number of studies identified, which were limited scale non-randomized single-center observational studies, with the exception of the work of Rao *et al*[7], who presented a prospective single-blinded randomized study including 128 patients divided in two groups: ERAS (n = 54) and control (n = 74). The ERAS group was analyzed by logistic stepwise regression analysis and displayed a decreased intensive care unit and hospital stay, without significant difference in the postoperative complication rate between the two groups and no readmissions or postoperative mortality during the follow-up period. Brustia *et al*[8] conducted a small-scale feasibility study with 10 patients treated prospectively with an ERAS protocol who were compared with 20 matched patients treated by the same team in previous years. They designed an elaborate 26-point ERAS protocol and observed a 47% reduction in the total length of stay compared to the control arm. There were no readmissions or postoperative mortality during the follow-up period.

Xu *et al*[9] reported a cohort of 93 patients, 40 in the ERAS group and 53 in the control group, and found a significant reduction of postoperative hospital stay in favor of the ERAS group (14.5 *vs* 16 d; P < 0.001). No difference in postoperative complication rate between the two groups and no readmissions or postoperative mortality were noted.

Common inclusion criteria used in the aforementioned studies are presented in Table 1. As expected, patients' Model for End-Stage Liver Disease (MELD) scores were low in all four studies, as they reflect patient status[10]. All studies included patients with a MELD score well below 25. Patients with no previous history of LT were also selected for the ERAS group in all three studies. A considerable number of patients for ERAS LT had a hepatocellular carcinoma (HCC)-related indication in all three studies (Brustia 90%, Xu 42.5%, Rao 33.3%).

Given the lack of a standardized ERAS protocol, each team designed its own protocols, based on previous experience from existing literature on other surgical fields. Table 2 depicts a comparison of the preoperative, intraoperative and post-operative characteristics between the three studies. All of the studies applied multimodal measures in the three distinct phases of classic ERAS protocols: preoperative, intraoperative and postoperative phase. In Table 3, measures applied by all three authors are depicted in capital letters. Of the 26 points proposed by Brustia *et al*[8], 11 (42.3%) were observed by all three authors.

All three studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocol applied in the postoperative course (Table 2). From the above-mentioned publications, we meta-analyzed the primary endpoint, postoperative hospital stay. The variable was continuous, and the results were summarized using median and 25%-75% values (because the data were skewed). The sample mean and standard deviations were calculated using the formula of Wan *et al*[11]. The random-effects model was applied for the meta-analysis, as high heterogeneity was expected among the studies with regard to study populations and diagnostic procedures. The presence of between-study heterogeneity was quantitatively reflected with the I^2 index, considering I^2 of > 50%, indicative of statistically significant heterogeneity. R studio version 4.0.2 software was used to perform all of the statistical analyses, employing the packages "meta" and "metaphor." A comparison of total hospital stay showed a statistically significant difference in both groups (n = 251; MD- 5.79; 95% confidence interval (CI), 10.89 to 0.69; I^2 = 89%; P < 0.01). Nevertheless,

Table 1 Common inclusion criteria (with incorporation of exclusion criteria)

Inclusion criteria	Brustia *et al*[8]	Xu *et al*[9]	Rao *et al*[7]
Meld score < 25	√	[1]	[1]
HCC	√	√	√
The first liver transplantation	√	√	√
Age > 18	√	> 16	> 16

[1]All patients included in the three studies had a MELD score < 25. HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease.

great heterogeneity was observed between the samples (Figure 2). A similar meta-analysis of the MELD score showed that there was no statistically significant difference in both groups (n = 251, MD -0.25, 95%CI, -1.36 to 0.85; I^2 0%; P = 0.62) (Figure 3). As aforementioned, all patients were low MELD patients with a mean MELD well below 20.

DISCUSSION

The scarcity of strong evidence in the widespread application of ERAS programs in LT may reflect the reluctance of teams to implicate such protocols in a cohort of patients that are generally perceived as a frail, high-risk group, undergoing a major surgical procedure of a life-threatening nature. The evolution of LT on the other hand, is a successful story, evolving from an experimental and innovative procedure to a more "standard" one over the last several decades, and especially when performed in high volume centers with experienced multidisciplinary teams. Throughout the years, LT has proved its life saving nature as an operation and the morbidity and mortality plummeted, offering patients excellent survival and quality of life[12]. The major incentives in applying ERAS in LT came from the successful application of Enhanced Recovery Programs in Liver Surgery[13] and the subsequent publication of suggested guidelines for ERAS in Liver Surgery[14]. Although ERAS with its multimodal approach pattern did not appear in the literature until recently, the concept of multimodal clinical pathways in LT was raised as early as 2011 by Pavlakis *et al* of the Beth Israel Deaconess Medical Center team[15], characterizing the transplantation domain as an "*ideal forum for successful implementation of clinical pathways*" and highlighting their importance and potential in reducing length of stay, morbidity, costs, as well as improving patient satisfaction. Piñero *et al*[16] introduced in 2015 the concept of the early discharge from hospital following LT focusing on healthcare costs and proposed an early discharge prediction model based on MELD points (exception MELD points were deemed a favorable prognostic factor), length of surgery (time < 4 h), transfusion of less than 5 units of packed red blood cells, and early respirator weaning. The author concluded that early discharge from the hospital following LT is feasible, without a negative impact on patient or graft survival, nor did it increase short-term rehospitalization. A recent publication of Brustia *et al*[18] in Paris reinforced the basis for further developing ERAS in LT. Although it is a small-scale single-center observational study, the authors reported a 47% reduction of length of hospital stay with no safety issues in a small but well-designed protocol. This conclusion was corroborated by all three publications mentioned above, demonstrating that ERAS in LT could be possible in a larger scale and should be further studied. Rodríguez-Laiz *et al*[17] presented a cohort of 236 patients who were treated with a comprehensive multistep ERAS protocol that is the product of lessons and experiences emanating from liver surgery and other disciplines aiming to evaluate its value as a proof-of-concept. In this study, the authors identified 133 patients who were discharged early and they retrospectively defined them as the ERAS group. However, their study, with extremely short lengths of stay, was inherently flawed, as the authors pointed out, by a lack of a traditional control group; for this reason, their article was not included in our final selection. In 2021 Brustia *et al*[18] drafted the "*Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations,*" after a systematic review by a wide international panel of experts and the application of the Delphi method. The authors of the manuscript recognized the lack of current strong evidence in ERAS in LT but laid a solid foundation and precious scaffold, which can serve as the basis for large studies in the definitive validation of ERAS in LT.

ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT. The majority of studies analyzing ERAS in LT use a cohort of low MELD highly selected patients that might not represent the majority of patients that benefit from LT; an issue that has to be addressed. The overall majority of patients in the three studies analyzed were low MELD HCC patients, and this type of selection might harbor an inherent bias in evaluating ERAS in LT. However it is a first step and understandably first steps must be careful. The encouraging results

Table 2 Preoperative, intraoperative, and post-operative characteristics

Preoperative	Brustia *et al*[8]		Xu *et al*[9]		Rao *et al*[7]	
	ERAS group, *n* = 10	CONTROL group, *n* = 20	ERAS group, *n* = 40	CONTROL group, *n* = 53	ERAS group, *n* = 54	CONTROL group, *n* = 74
Gender						
Male	8	17	35	46	40	58
Female	2	3	5	7	1	16
Age, yr	60.1 (52.5-66.1)	58.2 (52.6-65.3)	49.5 (40-56.8)	53 (47-59)	52.4 + 15.2	55.8 + 14.3
Primary cause						
Alcohol	7 (70%)	9 (45%)	7	3	6 (11.1)	10 (13.5)
Viral cirrhosis	7 (70%)	10 (50%)	11	16	30 (55.6)	40 (54.1)
HBV	2 (20%)	4 (20%)	NA	NA	NA	NA
HCV	6 (60%)	8 (40%)	NA	NA	NA	NA
Metabolic syndrome	2 (20%)	4 (20%)	NA	NA	NA	NA
Biliary disease	0	3 (15%)	NA	NA	NA	NA
HCC	9 (90%)	9 (45%)	17	24	18 (33.3)	24 (32.4)
MELD score	7 (6-10)	7 (6-9)	14 (9-22)	17 (14-19)	7.7 + 3.2	7.9 + 4.6
Intraoperative						
Operative time	6.0 (5.9-8.4) h	6.7 (5.7-8.2) h	443.7 + 85.3min	453.5 + 62.3min	265 (215-360) min	325 (275-455) min
Anhepatic period	NA	NA	44.3 + 5.2 min	42.7 + 4.2 min	45 (35-70) min	60 (50-75) min
Blood loss	NA	NA	775 (525-1000) mL	800 (600-1000) mL	1100 (300-4200) mL	2900 (1600-7000) mL
Hypothermia during the operation (*n*, %)	NA	NA	0	12%	0	0
Postoperative						
Early extubation (h)	2 (0-2)	7.5 (4.5-13.0)	0	6 (5.5-8)	NA	NA
ICU stay (d)	3 (2-4)	4.5 (3.0-8.3)	2 (2-3)	4 (4-5)	2 (1-7)	5 (3-15)
Complications (*n*, %)	5 (50%)	16 (80%)	9 (22.5%)	26 (49.1%)	10 (18.5%)	20 (27%)
Pain score after operation	3 (1.0-4.0) POD	4.5 (2.7-6.) POD	2.45+ 0.54	3.02+0.44	NA	NA
Postoperative hospital stay (d)	9.5 (9.0-10.5)	18 (14.3-24.3)	14.5 (12-17)	16 (15-18)	18 (15-32)	28 (23-35)
Readmission within 30 d after discharge	NA	NA	0	0	0	0

Categorical variables are reported using percentages; continuous variables are summarized using median and 25%-75% percentiles. ERAS: Enhanced recovery after Surgery; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICU: Intensive care unit; MELD: Model for end-stage liver disease.

presented, along with the observed benefit of a well-designed ERAS protocol in these patients mandates further exploration and expansion of inclusion criteria in these types of protocols. After all, an earlier discharge might be the result of a better overall patient management in all aspects of their journey through the hospital and not necessarily the primary endpoint.

One of the key factors in implementing ERAS protocols is the understanding of the philosophy behind ERAS by both patients and caregivers and although this might seem simple or a given, studies indicate that this might not be the case[19,20]. As ERAS is new to the field of LT, similar issues are expected to occur. In the first years of the implementation of ERAS in colorectal surgery, many issues arose concerning patient and physician capability of correctly implementing and accepting what proved to be a validated protocol for better patient recovery[21,22] including the complexity of these multimodal pathways[23], the need for teamwork along with the difficulty of eradicating old surgical stereotypes of traditional care. Agrafiotis *et al*[24], along with the first author of the present review, have

Table 3 Experimental "fast trans" protocol items

Preoperative	Brustia *et al*[8]	Xu *et al*[9]	Rao *et al*[7]
1 Outpatient counseling and information	√	√	√
2 Preoperative carbohydrate loading	√	√	√
3 Absence of preanesthetic medication (anxiolytic)	√		
Intraoperative			
4 Antimicrobial prophylaxis and skin preparation	√		
5 Prevention of intraoperative hypothermia	√	√	
6 Incision	√		
7 Adapted IV filling	√	√	√
8 Temporary portocaval anastomosis	√		
9 No prophylactic nasogastric intubation	√		√
10 No prophylactic abdominal drainage	√		√
11 Prevention of postoperative nausea and vomiting	√		
12 Antithrombotic prophylaxis and/oranti-aggregation	√	√	
13 Early extubation (< 6 h after the endof lt)	√	√	√
Postoperative			
14 Early mobilization (POD1)	√	√	√
15 Patient-controlled analgesia	√	√	
16 Gastric probe removal POD1	√	√	
17 Clear liquid per OS POD1	√	√	√
18 Enteral feeding per OS POD1	√	√	√
19 Stop IV fluids POD1	√	√	
20 Per OS analgesia (POD2)	√	√	
21 Abdominal drain removal POD2	√		
22 Urinary probe removal POD2	√	√	√
23 Stop IV analgesia POD3	√	√	
24 Independent mobilization POD3	√	√	√
25 Daily revision of discharge criteria	√	√	√
26 Audit	√	√	√

ICU: Intensive care unit; IV: Intravenous; LT: Liver transplantation; POD: Post-operative day; PONV: Post-operative nausea and vomiting.

explored in 2013 the efficacy of a "soft" non-strict fast-track protocol in a cohort of 92 patients undergoing colorectal surgery. The conclusion was that even without a strict ERAS protocol, enhanced recovery and accelerated safe patient discharge are possible, pointing out among others[25] that *"length of stay should not be an aim in itself within an enhanced recovery protocol. The main object of these programs ought to be the enhancement of patient recovery and not earlier discharge."* This statement is endorsed by our team, in the Transplantation Department of a public Medical School part of a public healthcare system with significant challenges, who tried to evaluate the implementation of a non-strict ERAS protocol in selected LT patients in a small cohort of patients trying to replicate the results of Brustia *et al*[8]. In a small feasibility and safety study, we observed a 56% decrease in hospital stay in the ERAS group without any safety issues (unpublished data). These encouraging results might indicate that ERAS, when implemented in the right way, can be beneficial to patients even in small volume transplant centers and their implementation should be encouraged. We also noted the lack of estimation of the importance of every point in the proposed ERAS protocols towards the final endpoint, which hinders the simplification of these protocols, as we do not currently know which one of the steps – if any - could be omitted without a significant compromise in the outcome.

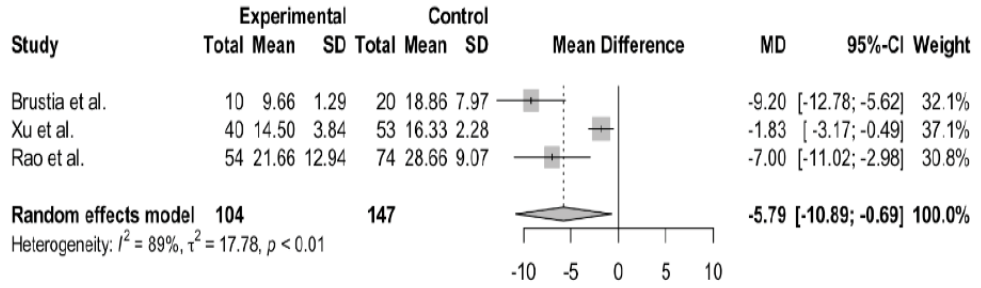

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Figure 2 Forest plot of postoperative hospital stay in days.

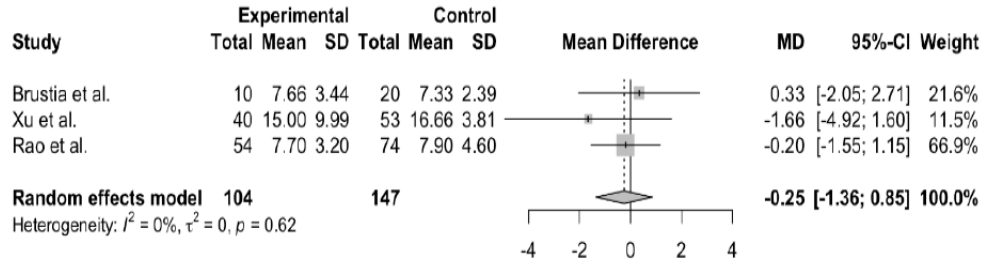

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Figure 3 Forest plot of model for end-stage liver disease scores.

Henric Kehlet pointed out the delay of the development of ERAS: "*there is an urgent need for better implementation of the current established scientific evidence for ERAS practices in order to fill the still very present gap between knowing and doing*" and has been advocating for many years the concept of "stress free, pain free" operations[26], which might seem an impossible task for operations of the magnitude of a LT. However, as the term "fast-track" was gradually replaced by the more correct term "enhanced recovery," the concept of "*first better, then faster*" had to be reappraised[27,28].

CONCLUSION

Enhanced recovery means better recovery and its value should be further exploited for liver transplant patients. After all, ERAS is not about the type of operation; ERAS is about the patient.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery.

Research motivation

In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. Orthotopic Liver Transplantation (LT) remains one of the last frontiers in the application of ERAS.

Research objectives

To evaluate existing data on the use of ERAS in orthotopic LT.

Research methods

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay.

Research results

All studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocols in the postoperative period.

Research conclusions

Enhanced recovery can be safely applied in selected LT patients and its value should be further exploited.

Research perspectives

The future widespread use of ERAS in selected LT patients seems promising.

FOOTNOTES

Author contributions: Katsanos G, Karakasi KE, and Tsoulfas G wrote the manuscript; Morsi-Yeroyannis A and Sinakos E conducted the statistics; Goulis I, Giouleme O, and Vasileiadou S, reviewed the articles; Oikonomou IM and Mochailidou E proofread the manuscript; Tsoulfas G, Katsanos G, and Mouloudi E designed the review; Antoniadis N, Massa E, Tsakiris G, and Evlavis G conducted the bibliographic research and analyzed the results; All authors read and approved the final manuscript.

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ORCID number: Georgios Katsanos 0000-0002-5845-8175; Konstantina-Eleni Karakasi 0000-0003-2448-556X; Nikolaos Antoniadis 0000-0002-3988-4515; Stella Vasileiadou 0000-0001-9143-6085; Athanasios Kofinas 0000-0002-3180-1930; Antonios Morsi-Yeroyannis 0000-0002-6579-9488; Evangelia Michailidou 0000-0002-6508-3295; Ioannis Goulis 0000-0002-2765-4157; Emmanouil Sinakos 0000-0003-0923-050X; Olga Giouleme 0000-0003-0176-3598; Ilias Marios Oikonomou 0000-0003-3620-4462; George Evlavis 0000-0003-1432-990x; Georgios Tsakiris 0000-0001-6440-5726; Eleni Massa 0000-0003-4594-3259; Eleni Mouloudi 0000-0003-0079-2012; Georgios Tsoulfas 0000-0001-5043-7962.

Corresponding Author's Membership in Professional Societies: American College of Surgeons; American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society of Transplant Surgeons; American Society of Transplantation.

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CASE REPORT

Portal vein-variceal anastomosis for portal vein inflow reconstruction in orthotopic liver transplantation: A case report and review of literature

Aviad Gravetz

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Aviad Gravetz, Department of Transplantation, Rabin Medical Center, Beilinson Hospital, Petach-Tikva 4941492, Israel

Corresponding author: Aviad Gravetz, MD, Surgeon, Department of Transplantation, Rabin Medical Center, Beilinson Hospital, 39 Jabotinsky Street, Petach-Tikva 4941492, Israel. agravetz@gmail.com

Abstract

BACKGROUND

Portal vein thrombosis (PVT) is a frequent complication occurring in 5% to 26% of cirrhotic patients candidates for liver transplantation (LT). In cases of extensive portal and or mesenteric vein thrombosis, complex vascular reconstruction of the portal inflow may become necessary for a successful orthotopic LT (OLT).

CASE SUMMARY

A 54-year-old male with history of cirrhosis secondary to schistosomiasis complicated with extensive portal and mesenteric vein thrombosis and severe portal hypertension who underwent OLT with portal vein-left gastric vein anastomosis.

CONCLUSION

We review the various types of PVT, the portal venous inflow reconstruction techniques.

Key Words: Portal vein thrombosis; Portal inflow reconstruction; Orthotopic liver transplantation; Splanchnic varices; Left gastric varix; Case report

Core Tip: The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. Herein we review the various types of portal vein thrombosis, the portal venous inflow reconstruction techniques and describe an extraordinary case of portal vein-left gastric vein anastomosis for the portal inflow reconstruction during orthotopic liver transplantation.

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INTRODUCTION

Portal vein thrombosis (PVT) is a frequent and serious complication in patients with cirrhosis, with a prevalence ranging from 5% to 26%[1-4]. Patients with PV and/or mesenteric vein thrombosis while awaiting liver transplantation (LT) pose a significant surgical challenge for the reconstruction of the liver portal inflow, an essential step for successful orthotopic LT (OLT)[5-6]. While an end-to-end donor to recipient portal vein anastomosis is fashioned in the majority of liver transplant recipients, approximately 2% of recipients will require a complex vascular reconstruction due to inadequate recipient portal vein inflow[7,8].

The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. Herein we review the various types of PVT, the portal venous inflow reconstruction techniques and describe an extraordinary case of portal vein-left gastric vein (LGV) anastomosis for the portal inflow reconstruction during OLT.

CASE PRESENTATION

Chief complaints

A 54-year-old male of Ethiopian origin who presented back in 1993 with variceal bleeding leading to a subsequent diagnosis of non-cirrhotic portal hypertension with splenomegaly and PVT with cavernous transformation.

History of present illness

The presence of granulomas and periportal fibrosis with preserved hepatic architecture on liver biopsy, together with positive serologic tests for antischistosomal antibodies and the patient origin suggested the diagnosis of hepatosplenic schistosomiasis. Further work up revealed protein C deficiency. Whether the patient received anthelmintic therapy upon diagnosis is unclear, however, prior to transplant no specific prophylactic treatment was administered as there was no evidence of active hepatic or systemic disease.

History of past illness

The patient in 1993 with variceal bleeding leading to a subsequent diagnosis of non-cirrhotic portal hypertension with splenomegaly and PVT with cavernous transformation.

Personal and family history

The patient has none personal and family history.

Physical examination

Medical management of portal hypertension complications included diuretics, beta-blockers and periodic upper endoscopy with sclerotherapy and esophageal varices ligation. The patient eventually presented with severe decompensation and model for end-stage liver disease score of 25 necessitating LT.

Laboratory examinations

His physical examination revealed signs of cachexia, jaundice, abdominal distention, umbilical hernia, caput medusa and impression of moderate to large volume ascites. Laboratory results showed total white blood cell count of 2.67 × 10^9/L, hemoglobin levels of 8 g/dL, platelet count of 33 × 10^9/L, international normalized ratio 2.43, total bilirubin of 7.5 mg/dL (and direct bilirubin of 3.6 mg/dL), serum

sodium 140 mEq/L, serum creatinine 1.1 mg/dL and albumin levels of 2.5 gr/dL.

Imaging examinations

Preoperative esophagogastroduodenoscopy showed grade III esophageal varices and portal hypertensive gastropathy. Imaging revealed liver cirrhosis, extensive portal and mesenteric vein thrombosis with cavernous transformation, splenomegaly, with the spleen measuring 20 cm in diameter, and splanchnic varices comprising a large left gastric varix (Figure 1).

FINAL DIAGNOSIS

Over the years the patient gradually developed compensated liver fibrosis and cirrhosis as seen on various imaging modalities and worsening liver synthetic function.

TREATMENT

The patient underwent OLT on April 2021 with piggyback venous outflow reconstruction and a portal vein-left gastric varix anastomosis for portal inflow. During the procedure the LGV was carefully dissected cephalad at the level of the mid lesser curvature of the stomach. Adequate venous flow was confirmed prior to creation of end-to-side porto-LGV anastomosis performed using polypropylene 5-0 suture (Figure 2A). Postoperative Doppler sonography documented patent anastomosis with adequate flow (Figure 2B), a finding which was confirmed by a contrast abdominal computed tomography performed on postoperative day 16 (Figure 2C).

OUTCOME AND FOLLOW-UP

The patient had a relatively benign postoperative course characterized by mild to moderate ascites, as anticipated, controlled initially with drainage and medical treatment and eventually resolved prior to discharge. Ten months post-operatively the patient is doing well with excellent liver function.

DISCUSSION

Schistosomiasis (bilharzia) is a chronic parasitic entero-pathogenic disease caused by a genus of trematodes commonly known as blood flukes[1]. Hepatic schistosomiasis represents the best known form of chronic disease and represents the most important cause of non-cirrhotic portal hypertension in Latin America, Africa, and Asia[2]. The pathogenesis of schistosomiasis is related to the host cellular immune response. This leads to granuloma formation and neo-angiogenesis with subsequent irreversible periportal fibrosis and, consequently, severe portal hypertension manifesting with splenomegaly and esophageal varices[3,4]. Traditionally the diagnosis of Schistosoma infection is based upon demonstration of parasite eggs in patient secretions or tissues. However, in the case of liver disease, detection of ova often fails and the diagnosis is established using serologic tests along with DNA amplification techniques and characteristic liver biopsy findings[5-7]. Praziquantel is the drug of choice to treat laboratory-proven Schistosoma infection[8]. The effect of antischistosomal treatment on disease manifestations varies by stage. Early liver involvement is known to resolve after anthelmintic therapy, but late manifestations, such as fibrosis, do not change and treatment is focused on tempering portal hypertension manifestations[9]. LT represents a curative option for patients who develop severe hepatic fibrosis and portal hypertension secondary to hepatic schistosomiasis[10], and no specific treatment is indicated for the recipients[11].

PVT is a frequent and serious complication in patients with cirrhosis, with a prevalence ranging from 5% to 26%[12-17]. Patients with cirrhosis presenting with or developing PV and/or superior mesenteric vein (SMV) thrombosis while awaiting LT pose a significant surgical challenge for the reconstruction of the liver portal inflow, an essential step for successful OLT[18,19]. Although PVT has long been considered an absolute contraindication to OLT, it is currently regarded as a relative contraindication, depending on the patient clinical status, type of PVT and collateral venous flow, and the surgeon's experience[20,21]. While an end-to-end donor to recipient portal vein anastomosis is fashioned in the majority of liver transplant recipients, approximately 2% of recipients will require a complex vascular reconstruction due to inadequate recipient portal vein inflow[22,23].

The type of PVT is classified according to the nature of the occlusion (complete *vs* partial) and the extension in the portal vein, the venous confluence and its contributories - the SMV and the splenic vein (SV). Various classification systems of PVT have been proposed with the Yerdel classification being

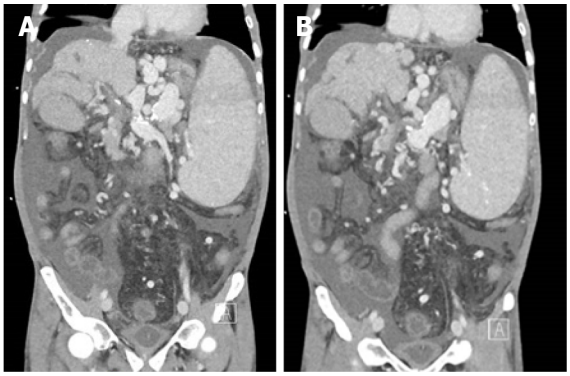

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Figure 1 Preoperative abdominal computed tomography. A: Extensive portal vein thrombosis; B: Superior mesenteric vein thrombosis.

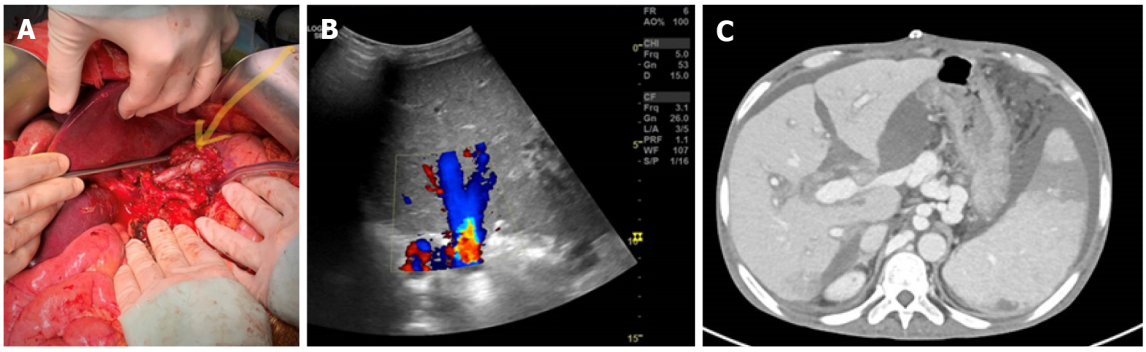

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Figure 2 Treatment imaging. A: End-to-side portal vein-left gastric vein anastomosis upon completion; B: Postoperative Doppler sonography documenting patent anastomosis with adequate flow; C: Abdominal computed tomography showing patent portal vein-left gastric vein anastomosis.

widely used because it correlates thrombus extent and surgical management[24-28]. Yerdel's classification defines grade I as partial PVT (< 50% of the lumen) with or without minimal extension into the SMV, grade II as partial PVT (> 50% of the lumen), grade III - complete thrombosis of both PV and proximal SMV and grade IV with complete PV and both proximal and distal SMV.

For the reconstruction of the liver portal inflow in the presence of PV-SMV thrombosis there are 3 main strategies: Anatomical (and physiological), physiological (non-anatomical) and non-physiological [19,29]. For Yerdel grades I to III, an anatomical reconstruction may be achieved; operative techniques include thrombectomy, whether the thrombus is removed *en-bloc* with the liver or through an intraoperative PV/SMV thrombectomy, followed by direct porto-portal anastomosis or indirect using an interposition venous graft.

For more complex cases of complete occlusion or proximal extension of the thrombus, such as in Yerdel's grade IV and some grade III cases, alternative approaches should be used to redirect the portal venous flow into the graft[29,30]. Some of those extraordinary cases of extensive thrombosis may be considered as a contraindication to transplant. However, when evaluated by highly experienced transplant centers, a complex vascular reconstruction may be attempted or else, a multivisceral transplant may be considered. That is, for Yerdel's grade IV and some grade III cases, a physiological (non-anatomical) or non-physiological (inflow achieved by reno-portal anastomosis, cavo-portal hemitransposition or portal vein arterialization), approach may be used.

The portal vein-variceal anastomosis is a challenging physiological non-anatomical technique of portal vein inflow reconstruction used and described rarely. In those procedures, enlarged splanchnic varices[31-34], LGV[35-38], or pericholedochal varix[39,40] is used. Use of a splanchnic varix such as a dilated LGV necessitates a meticulous and very careful dissection in a hostile surrounding of other dilated fragile varices. Furthermore, length of the donor's liver portal vein should be sufficient or else an interposition venous graft may be used for the anastomosis. From the functional standpoint, adequate portal flow should be assessed, using direct (needle- transducer) or indirect (ultrasound Doppler) method. In the occurrence of slow venous flow, proximal ligation of the varix may be considered in order to divert splanchnic venous drainage towards the neo-liver and to avoid the siphon effect of the peri-gastric varices and SV. In cases of extensive SMV thrombosis there is also a concern for inadequate venous intestinal drainage, despite a successful and functional anastomosis, and a as result refractory ascites.

Although challenging, good outcomes are possible in patients with extensive PV/SMV thrombosis undergoing LT. Meticulous patient selection, preoperative imaging planning and highly experienced surgical team are crucial for a successful transplantation and reconstruction of the portal inflow in those complex clinical scenarios. This case shows the feasibility of this unusual approach, using a dilated left gastric varix for the reconstruction of the liver portal inflow, giving a patient in an extreme condition access to life-saving LT.

CONCLUSION

Although challenging, good outcomes are possible in patients with extensive PV/SMV thrombosis undergoing LT. Meticulous patient selection, preoperative imaging planning and highly experienced surgical team are crucial for a successful transplantation and reconstruction of the portal inflow in those complex clinical scenarios. This case shows the feasibility of this unusual approach, using a dilated left gastric varix for the reconstruction of the liver portal inflow, giving a patient in an extreme condition access to life-saving LT.

FOOTNOTES

Author contributions: Gravetz A contributed to the manuscript drating.

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REVIEW

Hypertension in kidney transplant recipients

Maria-Eleni Alexandrou, Charles J Ferro, Ioannis Boletis, Aikaterini Papagianni, Pantelis Sarafidis

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Maria-Eleni Alexandrou, Aikaterini Papagianni, Pantelis Sarafidis, Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Charles J Ferro, Department of Renal Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2WB, United Kingdom

Ioannis Boletis, Department of Nephrology, Laiko General Hospital, National and Kapodistrian University, Athens 11527, Greece

Corresponding author: Pantelis Sarafidis, MD, MSc, PhD, Associate Professor, Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Konstantinoupoleos 49, Thessaloniki 54642, Greece. psarafidis11@yahoo.gr

Abstract

Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients (KTRs) than in the general population. Hypertension is highly prevalent in KTRs and represents a major modifiable risk factor associated with adverse cardiovascular outcomes and reduced patient and graft survival. Proper definition of hypertension and recognition of special phenotypes and abnormal diurnal blood pressure (BP) patterns is crucial for adequate BP control. Misclassification by office BP is commonly encountered in these patients, and a high proportion of masked and uncontrolled hypertension, as well as of white-coat hypertension, has been revealed in these patients with the use of ambulatory BP monitoring. The pathophysiology of hypertension in KTRs is multifactorial, involving traditional risk factors, factors related to chronic kidney disease and factors related to the transplantation procedure. In the absence of evidence from large-scale randomized controlled trials in this population, BP targets for hypertension management in KTR have been extrapolated from chronic kidney disease populations. The most recent Kidney Disease Improving Global Outcomes 2021 guidelines recommend lowering BP to less than 130/80 mmHg using standardized BP office measurements. Dihydropyridine calcium channel blockers and angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers have been established as the preferred first-line agents, on the basis of emphasis placed on their favorable outcomes on graft survival. The aim of this review is to provide previous and recent evidence on prevalence, accurate diagnosis, pathophysiology and treatment of hypertension in KTRs.

Key Words: Hypertension; Kidney transplantation; Epidemiology; Diagnosis; Physiopathology; Therapy

Core Tip: Kidney transplantation is considered the treatment of choice for end-stage kidney disease patients. However, the residual cardiovascular risk remains significantly higher in kidney transplant recipients than in the general population. This article summarizes available evidence on prevalence, abnormal blood pressure phenotypes and diurnal patterns as well as on the association of hypertension with target organ damage and clinical outcomes in kidney transplantation. The complex pathophysiology, treatment goals and recent data on therapeutic options for management of hypertension in kidney transplant recipients are also discussed.

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INTRODUCTION

Kidney transplantation is considered the optimal choice for renal replacement therapy in end-stage kidney disease due to improved survival and quality of life compared to dialysis modalities; this survival benefit has been attributed to kidney function improvement and delay of progression of cardiovascular disease[1]. Nevertheless, cardiovascular disease remains the leading cause of death in these patients in the early (< 10) post-transplant years[2]. Among traditional cardiovascular disease risk factors, hypertension represents the most prominent comorbidity post transplantation and a major cause of allograft dysfunction and adverse patient outcomes[3]. The diagnosis and treatment of hypertension in kidney transplantation has been traditionally based on office blood pressure (BP) measurements; BP control therefore remains suboptimal due to high rates of resistant and masked hypertension and abnormal diurnal BP patterns[4]. Controversies over BP targets and optimal antihypertensive regimen remain unresolved and should be further explored in well-designed randomized clinical trials (RCTs) in order to optimize hypertension management in this population.

EPIDEMIOLOGY OF HYPERTENSION IN KIDNEY TRANSPLANT RECIPIENTS

Prevalence of hypertension and abnormal BP phenotypes by the various metrics and definitions

The prevalence of hypertension is particularly high among kidney transplant recipients (KTRs) with previously reported rates between 70%-90%[5] and more recently even exceeding 95% of this population [6]. The source of variability in estimates of prevalence, control and different phenotypes of hypertension among KTRs is attributed to differences in the definitions used for hypertension diagnosis and in the type of BP measurement used (in office *vs* out-of-office setting) across various studies. Defining the diagnostic threshold for hypertension based on office and ambulatory BP measurements has been a matter of intense debate in chronic kidney disease (CKD) patients and more specifically in KTRs[7], with the two major existing hypertension guidelines producing confusion[8].

The cutoff values for hypertension diagnosis proposed by the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for office and ambulatory BP monitoring (ABPM) measurements were ≥ 130/80 mmHg and ≥ 125/75 mmHg, respectively[9] (Table 1), while those proposed by the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines were office BP ≥ 140/90 mmHg and ABPM ≥ 130/80 mmHg[10]. In the more recent 2021 Kidney Disease Improving Global Outcomes BP guidelines (Table 1), hypertension was defined as office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg[11], in agreement with the 2017 ACC/AHA guidelines.

Taking into consideration all the above, studies assessing the epidemiology of hypertension have previously reported the presence of this disease in > 80.0% of patients based on the office 140/90 mmHg cutoff value[12] and in 89.5% based on the office 130/80 mmHg cutoff value, with control rates among hypertensive subjects at 45.5%[13]. The prevalence of resistant hypertension in this population (office BP ≥ 130/80 mmHg) has been previously reported in 17.5%[13] and 23.5%[14] of patients, despite intake of ≥ 1 and ≥ 3 antihypertensive drugs, respectively.

Recent guidelines recommend the use of out-of-office BP measurements as a complementary tool for improving the management of hypertension. In KTRs the wider use of ABPM has led to the recognition of abnormal diurnal BP patterns and BP phenotypes[11,15]. The rates of non-dipping status have been reported to range between 36%-95%[16-18] and that of nocturnal hypertension between 69%-77%

Table 1 Summary of guidelines for the management of hypertension in kidney transplant recipients

Ref.	Threshold for pharmacological treatment	Target blood pressure	Recommendations on 24-h ABPM	Recommendations for KTRs
Whelton *et al*[9], 2018	≥ 130/80 mmHg for primary prevention if estimated 10-yr ASCVD risk ≥ 10% and for secondary prevention if known CVD; ≥ 140/90 mmHg for primary prevention if no history of CVD and estimated 10-yr ASCVD risk < 10%	< 130/80 mmHg	Advised to exclude white coat and masked hypertension	In the absence of trials comparing different BP targets in KTRs, treatment targets for BP should probably be similar to the general CKD population; CCBs recommended as first line therapy on the basis of improved GFR and kidney survival; RAASi reserved for subset of patients with other comorbidities (proteinuria or heart failure)
KDIGO Blood Pressure Work Group[11], 2021	≥ 130/80 mmHg using standardized office BP measurement	< 130/80 mmHg using standardized office BP measurement	Out-of-office BP measurements with ABPM or home BP monitoring recommended to complement standardized office BP readings (2B)	Use of a dihydropyridine CCB or an ARB recommended as the first-line antihypertensive agent in adult KTRs (1C)

ABPM: Ambulatory blood pressure monitoring; ARB: Angiotensin receptor blocker; ASCVD: Atherosclerotic cardiovascular disease; BP: Blood pressure; CCB: Calcium channel blocker; CKD: Chronic kidney disease; CVD: Cardiovascular disease; GFR: Glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; KTRs: Kidney transplant recipients; RAASi: Renin-angiotensin-aldosterone system inhibitor.

(according to the nighttime ABPM > 120/70 mmHg cutoff value for both)[18,19]. In an Italian cohort of 260 KTRs followed-up for 3.9 years, the agreement between 785 paired office and 24-h ABPM measurements was assessed, revealing significant discordance in 37% of all visits (κ-statistics = 0.25, indicating poor agreement)[19]. In 12% of all visits, patients were misclassified as hypertensive according to the office BP > 140/90 mmHg criterion while 24-h ABPM was normal according to the < 130/80 mmHg criterion (white-coat hypertension); in 25% of all visits patients were classified as normotensive according to the office criterion, while 24-h ABPM was > 130/80 mmHg (masked hypertension). In a cross-sectional study from Spain with 868 KTRs, the prevalence of white-coat and masked hypertension was 12% and 20%, respectively, applying similarly the ESC/ESH criteria[14]. Absence of systolic BP (SBP) dipping pattern was evidenced in 80% of patients. In a retrospective study, prevalence of white-coat and masked hypertension was estimated to be at 3% and 56%, respectively, with the office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg thresholds[20].

In a recently published cross-sectional study with 205 KTRs[6], the prevalence of hypertension and the diagnostic performance of the two existing office BP thresholds for defining hypertension (adopted by the ESC/ESH and ACC/AHA guidelines mentioned above) was comparatively assessed. Prevalence of hypertension was 88.3% and 92.7% according to the ESC/ESH with ACC/AHA definitions for office BP measurements and 94.1% and 98.5% according to the respective ABPM thresholds. Moderate to fair agreement between office BP and 24-h ABPM was shown for both thresholds (κ-statistics = 0.52, P < 0.001; κ-statistics = 0.32, P < 0.001, respectively). Prevalence of white coat and masked hypertension was 6.7% and 39.5% using the office BP ≥ 140/90 mmHg and 5.9% and 31.7% using the office BP ≥ 130/80 mmHg threshold. Notably, ABPM revealed significantly lower control rates among hypertensive patients compared to office BP measurements using both definitions (69.6% for office *vs* 38.3% for ABPM measurements with the ESC/ESH thresholds; 43.7% *vs* 21.3% respectively with ACC/AHA thresholds).

In a sub-analysis of this study investigating presence of sex differences, the prevalence of hypertension was similar between the two genders with the office BP ≥ 130/80 mmHg threshold (93.4% for men *vs* 91.3% for women, P = 0.589) but significantly higher in men with the ABPM ≥ 125/75 criterion (100% *vs* 95.7%, P = 0.014, respectively). Prevalence of white-coat hypertension (5.1% *vs* 7.6%, P = 0.493) and masked hypertension (35.3% *vs* 24.2%, P = 0.113) did not differ significantly between men and women. The above findings underline the need for more extensive use of 24-h ABPM in KTRs, similarly to what is currently being increasingly recommended for the general population.

Association of hypertension with target organ damage

In KTRs, abnormal dipping status (non-dipping and reverse-dipping) independently predicts kidney function deterioration[21,22], while nighttime BP and night-day ratio are strongly associated with carotid-intimal media thickness[18]. Increased urinary albumin and protein excretion have been associated with hypertension in KTRs and are both independent predictors of graft loss[23-26]. Several longitudinal studies have reported an association of hypertension with left ventricular hypertrophy in KTRs, while significant reduction in left ventricular mass index (LVMI) and regression of left ventricular hypertrophy have been observed in the first 2-3 years following kidney transplantation[27,28]. However, this regression may be compromised by persistence of hypertension, high pulse pressure[27] and high sodium intake[28].

Moreover, reversal of uremic cardiomyopathy has been recently questioned according to the results of a recent meta-analysis where no difference in LVMI was detected following kidney transplantation after pooling data from four studies with 236 participants [standardized mean difference = 0.07, 95% confidence interval (CI): 0.41-0.26][29]. Masked or sustained hypertension were independent predictors for left ventricular hypertrophy in a cohort of 221 children and young adults with kidney transplant [30]. A negative association between brachial flow-mediated dilation, a marker of endothelial function, with 24-h BP and indices of BP variability has also been reported[31]. In a recently published meta-analysis pooling data from 22 studies (2078 participants), 24-h ABPM was found to be a stronger predictor of renal function decline and outperformed office BP with regards to LVMI, carotid-intimal media thickness and endothelial dysfunction markers[32]. Abnormal dipping status also identified a subgroup of KTRs at risk for target organ damage.

Prognostic impact of hypertension for adverse clinical outcomes

Hypertension in KTRs has been consistently shown to be associated with a higher incidence of kidney function decline, poor graft survival[33-38] and worse patient survival[3,34,38,39]. In the Collaborative Transplant Study, a retrospective cohort that evaluated the impact of hypertension on long-term kidney function in 29751 KTRs, a strong graded relationship between post-transplant BP and subsequent graft failure, even when patient death was censored, was reported for the first time[35]. In a subsequent sub-analysis of the Collaborative Transplant Study with data from 24404 patients, the same authors showed that SBP values consistently lower than 140 mmHg during the first 3 years post transplantation were associated with the best 10-year graft and patient outcomes; moreover successfully lowering SBP to ≤ 140 mmHg even by the 3rd year was associated with better 10-year graft and death-censored survival (but not with total patient survival) compared to persistently uncontrolled BP[3].

With regards to different causes of death, changes in SBP were significantly associated with the risk of cardiovascular death only in the subgroup of patients < 50-years-old but not in older KTRs. In another retrospective cohort of 1666 patients, each rise in SBP by 10 mmHg was associated with a 12% higher risk for graft failure [relative risk (RR) = 1.12, 95%CI: 1.08-1.15], a 17% higher risk for death-censored graft failure (RR = 1.17, 95%CI: 1.12-1.22) and an 18% higher risk for death (RR = 1.18, 95%CI: 1.12-1.23), even after adjusting for acute rejection and decreased kidney failure that were previously reported to trigger BP increases and therefore further supported the independent beneficial effect of BP control[34]. Microalbuminuria and macroalbuminuria, both markers of target organ damage associated with hypertension, have been similarly shown to be independent predictors of death compared to normoalbuminuria [odds ratio (OR) = 5.55, 95%CI: 2.43-12.66; OR = 4.12, 95%CI: 1.65-10.29, respectively] [25].

With regards to specific cardiovascular events in KTRs, their burden remains high; a fact that is partly attributed to accumulation of traditional cardiovascular risk factors[40]. In a French retrospective cohort of 17526 KTRs and 3288857 non-transplanted non-dialysis participants with a 5-year follow-up, an increased incidence of myocardial infarction in the former compared to the latter (5.8% *vs* 2.8%) was shown [hazard ratio (HR) = 1.45, 95%CI: 1.35-1.55][41]. KTRs experiencing an myocardial infarction were more likely to be hypertensive than their non-KTR counterparts (76.0% *vs* 48.1%, $P < 0.0001$). Hypertension is an independent predictor of death from ischemic heart disease and major ischemic heart events, with a reported increase by 20% in the risk for death from ischemic heart disease per 10 mmHg SBP increments, during a follow-up of 5 years[39].

PATHOPHYSIOLOGY OF HYPERTENSION IN KTRS

The underlying mechanisms for development of hypertension in KTR include: (1) Traditional risk factors; (2) Those that are associated with kidney function decline; and (3) Those that are related to the kidney transplantation procedure.

Traditional risk factors

Factors considered to be associated with an increased risk of hypertension in the general population, including age, male sex, smoking status, obesity, insulin resistance and syndrome of obstructive sleep apneas, are also present in patients undergoing kidney transplantation and may be aggravated, further contributing to new-onset or worsening hypertension[42-46].

Factors associated with impaired kidney function

The same risk factors that are present in CKD populations and that are inherent to kidney function decline are also applicable in KTRs. Among those, impaired homeostatic mechanisms handling sodium and water excretion are considered a hallmark of CKD, leading to extracellular volume accumulation, hypervolemia and increased BP[5,47]. Renal sodium retention may be worsened by the use of immunosuppressive regimens, mainly corticosteroids[48] and calcineurin inhibitors (CNIs)[49] as well as during episodes of acute rejection, probably indicating ischemic allograft damage[50]. Dysregulation of the renin-angiotensin-aldosterone system[51] and sympathetic nerve overactivity, driven in the early

post transplantation period by the native kidneys (since the graft is initially denervated before becoming later re-innervated[52]), also lead to increased peripheral vascular resistance and development of hypertension[5,53,54]. Increased arterial stiffness, endothelial dysfunction and imbalance between vasoconstrictive and vasodilating agents are also pertinent to CKD and further contribute to increased BP[55,56].

Factors associated with kidney transplantation

Immunosuppressive regimens: Most current protocols for prevention of transplant rejection include as maintenance therapy a combination of a CNI (cyclosporine or tacrolimus) with either a purine pathway inhibitor that subsequently blocks lymphocyte proliferation (mycophenolate mofetil or azathioprine) or a mammalian target of rapamycin inhibitor (everolimus or sirolimus), with or without corticosteroids [57]. While mycophenolate mofetil and mammalian target of rapamycin inhibitors are considered low risk agents, corticosteroids and CNIs potentially trigger hypertension and other major comorbidities in KTRs[58,57].

The burden of long-term corticosteroid exposure on corticosteroid-related adverse events and healthcare economic costs has been previously explored in the general population, as well as in KTRs, with prevalence of corticosteroid-induced hypertension estimated to exceed 30% of the total population [59] and hospitalization costs to be 2.2-fold higher in the steroid-maintenance group than in the steroid-free group 1-year post living-donor kidney transplantation[60]. According to the results of a meta-analysis (34 studies, 5637 patients), complete steroid avoidance or withdrawal reduces the risk of incident hypertension and diabetes with no significant effect on graft or patient survival[61]. The main cause of corticosteroid-induced hypertension is associated with partial activation of mineralocorticoid receptors by cortisol causing urinary sodium and water retention and therefore volume expansion[5]. This mechanism has been however called into question, and a similarly important role of glucocorticoid receptors in vascular smooth cells has been proposed[62], leading to an increase in peripheral vascular resistance through attenuation of vascular response to vasodilators (nitric oxide) and upregulation of the angiotensin II receptor[48].

The mechanisms of CNI-induced hypertension are multifactorial and involve impaired sodium and water excretion, upregulation of vasoconstrictive agents (prostaglandins, thromboxane, endothelin-1), downregulation of vasodilating prostaglandins and alterations in regulation of intracellular calcium ions, leading to vasoconstriction of afferent arteriole, a decrease in glomerular filtration rate (GFR) and an increase in peripheral vascular resistance[49,63-66]. Tacrolimus has been associated with a lower incidence of hypertension[67,68] but a higher risk for new-onset diabetes compared to cyclosporine[69, 70].

After complete withdrawal of CNIs was abandoned due to an increased risk of biopsy-proven acute rejection episodes[71], reduction of their dose was explored in an attempt to minimize their toxic effects. In an open-label RCT, 1645 KTRs were randomly allocated to receive standard-dose cyclosporine (target trough level 150-300 ng/mL for the first 3 mo; 100-200 ng/mL thereafter), low-dose cyclosporine (target trough level 50-100 ng/mL throughout the study), low-dose tacrolimus (target trough level 3-7 ng/mL throughout the study) or low-dose sirolimus (target trough level 4-8 ng/mL throughout the study) for 12 mo[72]. Patients in all treatment groups received mycophenolate mofetil and corticosteroids; those randomized to low-dose regimens followed a 2-mo induction treatment with daclizumab. At study-end, patients in the low-dose tacrolimus group had the highest estimated GFR (65.4 mL/min) and highest rates of allograft survival (94.2%), followed by low-dose cyclosporine (93.1%), standard-dose cyclosporine (89.3%) and low-dose sirolimus (89.3%) (P = 0.02), therefore providing further evidence in favor of low-dose tacrolimus regimens.

Accordingly, it is usually recommended to use minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing the risk for hypertension[42]. Belatacept is another biologic immunosuppressive agent that acts by inhibiting T cell co-stimulation, approved by the United States Food and Drug Administration since 2011 on the basis of evidence of non-inferiority in preventing acute rejection in KTRs provided from three RCTs comparing belatacept to cyclosporine[69,73,74]. According to a meta-analysis (5 studies, 1535 participants), use of belatacept has been associated with lower BP levels and reduced incidence of chronic kidney scarring compared to CNIs[75].

Donor/recipient factors: Donor's age represents a major risk factor for development of post-transplant hypertension[23], along with considerable discrepancies in somatometric characteristics between donors and graft recipients (female to male transplantation, pediatric to adult transplantation, low donor/recipient body weight ratio), leading to a phenomenon of "underdosing" due to reduced donor nephron mass compared to recipient needs[76,77]. These differences result in hyperfiltration, glomerular hypertrophy and increased intraglomerular pressure.

Pre-existing donor hypertension is also associated with an increased risk for post transplantation hypertension and allograft dysfunction[23,78]. Transplant recipients from donors with a family history of hypertension face a 10-fold higher risk of requiring antihypertensive treatment compared to recipients from a normotensive family[79]. Recipients of transplants from expanded criteria donors (age > 60 or 50-59 with two of the following: History of hypertension; serum creatinine > 1.5 mg/dL;

cerebrovascular death) also experience a higher risk for hypertension post transplantation[80].

Other factors related to donors, predisposing to delayed graft function and increased nephrotoxicity, that could be possibly associated with development of hypertension in KTRs include the presence of genetic variants that affect the expression of cytochrome P450 3A5, apolipoprotein L1, P-glycoprotein and multidrug resistance protein 2[81-83]. With regards to recipient factors, the presence of native kidneys may further contribute to BP increments probably due to renin secretion[84]. Moreover, longstanding hypertension may be present in many recipients before transplantation, as progression of CKD is associated with atheromatosis of middle-sized conduit arteries and most importantly with reduced compliance and arterial stiffness of the aorta and the large arteries[85]. This vascular remodeling may not be fully reversible after kidney transplantation.

Transplant renal artery stenosis: Prevalence of transplant renal artery stenosis (TRAS) reportedly ranged in the past between 1%-23%, with a significant increase noted in diagnosed cases with the use of non-invasive imaging techniques[86]. Refractory hypertension and worsening kidney function are the main clinical manifestations of TRAS, which usually develops 3-24 mo post transplantation and is associated with an increased risk of graft loss[84].

With regards to the anatomic site, the stenosis can be: (1) Anastomotic (due to vascular damage at the time of surgery); (2) Proximal (due to recipient's atherosclerosis); and (3) Distal (with a non-fully elucidated pathogenesis related to mechanical and immunological factors)[87]. Since the recipient's iliac artery and not the abdominal aorta is the most common site of donor renal artery anastomosis, this connection between smaller arteries is prone to narrowing and subsequent development of TRAS pathophysiology, involving impediment of blood flow, renal hypoperfusion and activation of the renin-angiotensin-aldosterone system[84].

Immunological factors leading to TRAS include immune-mediated vascular endothelial injury[88] and development of *de novo* class II donor-specific antibodies[89]. The association between TRAS and cytomegalovirus infection[90], as well as ischemia/reperfusion injury, has also been reported[91]. In the absence of an RCT comparing endovascular angioplasty with or without stenting *vs* surgical vascularization in KTRs, angioplasty is the preferred treatment of TRAS with reported rates of clinical success (improvements in BP or kidney function) between 65.5%-94.0% and of technical success > 90%[92].

Acute and chronic kidney dysfunction: Kidney function decline, whether in the context of an episode of acute cellular and antibody rejection or due to chronic allograft nephropathy, has been associated with new or worsening hypertension, with the evidence of a cause-effect relationship still inconclusive [42,84,93,94]. Acute rejection may trigger new-onset hypertension, probably *via* activation of the renin-angiotensin system according to the patient's volume status. In this case, treatment of rejection is accompanied by improvement in BP levels, whereas hypertension that is not associated to acute rejection would be further deteriorated with modifications in doses of immunosuppression[94].

Recurrence of the primary glomerular disease, tubular atrophy, interstitial fibrosis, chronic antibody-mediated organ rejection, development of non-HLA agonistic anti-angiotensin-II type 1 receptor antibodies and thrombotic microangiopathy are the major contributors to chronic allograft injury leading to sudden rises of BP[5,84,94,95]. Patients with positive angiotensin-II type 1 receptor antibodies represent a subset of those with antibody-mediated rejection in whom kidney dysfunction is associated with malignant hypertension and acute vascular lesions on biopsy. A clinicopathological entity including seizures on top of malignant hypertension and vasculopathy has also been described, bearing resemblance to pre-eclamptic syndromes where angiotensin-II type 1 receptor antibodies have been previously reported[95].

HYPERTENSION TREATMENT IN KTRS

Targets of BP therapy

Historically, no universal agreement has been achieved with regards to BP targets in CKD and more particularly in kidney transplantation, similarly to the heterogeneity observed in different BP thresholds used for diagnosis of hypertension[7-11]. In the absence of specific focus on KTRs, the BP targets of CKD population were expected to be endorsed; according to the 2018 ESC/ESH guidelines in patients with CKD the respective recommendation was lowering BP to < 140/90 mmHg and towards 130/80 mmHg [10]. However in the latest 2017 ACC/AHA and 2021 Kidney Disease Improving Global Outcomes guidelines specific recommendations targeting BP less than 130/80 mmHg have been provided for KTRs[9,11].

Non-pharmacological measures

In the absence of evidence focused on KTRs, lifestyle modifications should be adopted as a first-line approach on the basis of recommendations applied in the general population since these interventions provide general health benefits that extend beyond BP control[96]. Low sodium intake (< 2 g/d), moderate-intensity physical activity (≥ 150 min/wk), adoption of a balanced diet and maintenance of

body mass index and waist circumference within normal range (18.5 and 24.9 kg/m^2 and < 102 cm, respectively), reduction in alcohol consumption and smoking cessation are encompassed by most hypertension guidelines[5,9-11,97].

Pharmacological measures

In CKD populations, use of an angiotensin-converting enzyme inhibitors (ACEi) or an angiotensin receptor blocker (ARB) has been established as first-line treatment, followed by combinations with a calcium channel blocker (CCB) and/or diuretic[98]. In KTRs, the use of a dihydropyridine CCB is commonly advocated notably in the early post transplantation period because of their demonstrated efficacy in improving graft function and minimizing the vasoconstrictive effects of CNIs[15,93,99]. To support this choice, CCBs have been uniformly associated with improved patient and graft outcomes in several studies[99-103]. In contrast, the use of ACEis/ARBs in KTRs was considered a source of controversy for many years[4]. Treatment with an ACEi/ARB led to impressively better patient (HR = 0.57; 95%CI: 0.40-0.81) and graft (HR = 0.56; 95%CI: 0.40-0.78) survival rates in a retrospective cohort with 2031 KTRs[104] but not in a subsequent analysis of data from 17208 KTRs[105].

According to the results of an RCT with 154 hypertensive KTRs allocated to receive nifedipine 30 mg or lisinopril 10 mg 3 wk post transplantation, no differences were noted in BP control. Nevertheless, a significant increase was observed in measured GFR for nifedipine compared to lisinopril (mean between-group difference 9.6 mL/min, 95%CI: 5.5-13.7 mL/min) at 1 year, an improvement that was maintained at 2 years[106]. The results of a 2009 Cochrane systematic review claimed that patients receiving ACEis were exposed to a higher risk of hyperkalemia and anemia and that in direct comparison with CCBs their use was associated with worse kidney function (mean between-group difference for estimated GFR -11.48 mL/min, 95%CI: -15.75 to -7.21).

Data on graft loss were available from only one study showing no significant differences (RR = 7.37, 95%CI: 0.39-140.35)[100]. Among the main limitations of this meta-analysis was the fact that data for head-to-head comparisons were pooled from six studies with only 296 participants; four of them had a follow-up between 4 wk and 6 mo[25,107-109], two of them were published after the year 2000[25,106], and no one compared ARBs to CCBs directly. In a more recent meta-analysis conducted by Pisano *et al* [99] pooling data from 71 RCTs and providing evidence on both ACEis and ARBs, a significant reduction in the risk for graft loss was observed by 42% with CCBs (16 studies, 1327 participants) and by 38% with ACEi/ARBs (9 studies, 1246 participants).

When pooling results from head-to-head comparisons between CCBs and ACEis/ARBs, an increase in GFR (11.07 mL/min, 95%CI: 6.04-16.09) was noted for CCBs, along with a reduction in serum potassium levels (-0.24 mEq/L, 95%CI: -0.38 to -0.10). In the 2021 Kidney Disease Improving Global Outcomes guidelines, use of a dihydropyridine CCB or an ARB has received a grade 1C recommendation for first-line treatment in KTRs, with potential benefits on graft survival (RR for graft loss compared to placebo: Dihydropyridine CCBs 0.62, 95%CI: 0.43-0.90; ARBs: 0.35, 95%CI: 0.15-0.84) outweighing side effects related to each class of agent[11]. No significant effect on mortality or cardiovascular events was detected with either of these classes.

CONCLUSION

The accurate diagnosis of hypertension and adequate BP control in KTRs remains an area of controversy among different guidelines, with BP thresholds and treatment goals mostly extrapolated from CKD populations. The diagnostic performance of office measurements has been recently questioned, with more recent studies using ABPM suggesting a higher prevalence of uncontrolled, masked and nocturnal hypertension in KTRs than previously believed that is further increased when the new lower BP thresholds are applied. Recent analyses provide evidence that 24-h ABPM outperforms office BP measurements with regards to markers of target organ damage, including LVMI, carotid-intimal media thickness and flow-mediated dilation, and represents an independent predictor of kidney function decline and graft loss.

Except from pre-existing or *de novo* traditional risk factors and factors associated with CKD, immunosuppressive drugs, donor-recipient mismatches, TRAS, recurrence of primary glomerular disease, presence of native kidneys as well as episodes of acute and chronic allograft injury contribute to development of hypertension post transplantation. Recent guidelines recommend the use of dihydropyridine CCBs[15], as they exhibit a favorable profile due to their vasodilatory effects counteracting vasoconstriction induced by CNIs and their favorable effects on outcomes, or ARBs due to their favorable effects on graft survival, despite previously reported undesirable effects on risk of hyperkalemia and anemia. High-quality large-scale RCTs comparatively assessing the effect of different antihypertensive agents on mortality and major cardiovascular events are warranted to provide definite evidence.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Maria-Eleni Alexandrou 0000-0003-3526-261X; Aikaterini Papagianni 0000-0003-0437-5208; Pantelis Sarafidis 0000-0002-9174-4018.

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MINIREVIEWS

Acute kidney injury and the compensation of kidney function after nephrectomy in living donation

Kenji Okumura, Holly Grace, Hiroshi Sogawa, Shigeyoshi Yamanaga

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Kenji Okumura, Hiroshi Sogawa, Department of Surgery, Westchester Medical Center/New York Medical College, Valhalla, NY 10595, United States

Holly Grace, Department of Surgery, New York Medical College, Valhalla, NY 10595, United States

Shigeyoshi Yamanaga, Department of Surgery, Japanese Red Cross Kumamoto Hospital, Kumamoto 861-8520, Japan

Corresponding author: Kenji Okumura, MD, Doctor, Department of Surgery, Westchester Medical Center/New York Medical College, 100 Woods Road, Valhalla, NY 10595, United States. kenji.okumura@wmchealth.org

Abstract

Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. After nephrectomy, all the patients have decreased kidney function with AKI and recover from AKI. However, the characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors that have been identified as being associated with kidney recovery in donors including age, sex, body mass index, remnant kidney volume, estimated glomerular filtration rate, and various comorbidities.

Key Words: Acute kidney injury; Kidney transplant donor; Compensation; Kidney function

Core Tip: Acute kidney injury (AKI) incidence is growing rapidly, and AKI is one of the predictors of inpatient mortality. The characteristic and behavior of AKI is different from usual AKI and compensatory kidney function has been well known in the postoperative setting, especially in living donors. In this review, we have focused on the compensation of kidney function after nephrectomy in living donors. We discuss factors of compensation of kidney function after nephrectomy.

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INTRODUCTION

The incidence of acute kidney injury (AKI) is growing rapidly in many situations[1]. Despite advances in medical care, AKI remains an independent predictor of in-hospital mortality[2]. While the nature of kidney is the organ to recover, it is well established that AKI, especially when severe, is a risk factor for incident and progressive chronic kidney disease (CKD) and eventually leading to progressive nephron loss and end-stage renal disease (ESRD)[3,4].

Kidney transplantation has been considered a preferred treatment for patients with ESRD and offers a better quality of life than dialysis[5,6]. While a previous study showed that showed that living donation of kidney is safe in a large cohort, nephrectomy is a major procedure which is associated with potential risks for the donor, including increased cardio-vascular risks and progression to ESRD in the long-term [7]. After donation of the kidney, it has been well known that all patients have hemodynamic changes associated with AKI and have compensated kidney function with the contralateral kidney after donation[6,8-12]. The degree of contralateral kidney function has been reported to be around 60%-70 % on average in previous studies[13,14], however, the degree of compensatory kidney function varies in each donor. In this review, we have discussed the topics related to the clinical factors of compensation and the mechanism of recovery after kidney donation.

CLINICAL FACTORS

Many variables are involved in the clinical settings for kidney recovery after kidney donation (Table 1, Figure 1). Age is one of the significant factors which affects the extent of recovery. Younger age is associated with favorable outcomes in many studies[6,8,15-19] and this is supported by the facts that aging is associated with underlying abnormalities and structural changes such as nephrosclerosis and nephron hypertrophy[16]. The rate of glomerular density has an inverse correlation with aging[20]. The number of nephrons decreases with aging and affects the function of the kidney[20]. Denic *et al*[21] investigated the risk factors associated with kidney abnormalities, and they demonstrated that mild hypertension and aging are associated with underlying abnormalities. They showed the changes of the volumes of kidney, cortex and medulla in living kidney donors[22].

Hypertension is also one of the significant factors which affect the extent of recovery in kidney function[6]. It is known that prevalence of hypertension increases with age. Hypertension was previously regarded as contraindication for living kidney donation, however, living donor donation was reported to be safe if hypertension is under controlled with medication[22]. On understanding of kidney aging, kidney function in people with advanced age have less reserve when they tend to develop CKD and have also higher risk of AKI[23]. As people get old, the prevalence of hypertension also increases, and glomerular hypertrophy has been identified as an integral feature of hypertensive nephropathy and seems to precede rather than to compensate for glomerulosclerosis[24].

Gender is another significant factor for kidney compensation and prognosis. Male gender is associated with poor prognosis in kidney donation[6,8,15], however, this is controversial since many studies showed that gender did not reach to conclusion as one of the independent factors[17,25,26]. This might be more related to the fact that male gender has a higher rate of smoking, which is one of the factors affecting the kidney function and is associated with hypertension.

Metabolic syndrome has been defined by the National Cholesterol Education Program Adult Treatment Panel III if three or more of the following five criteria are met: Waist circumference over 40 inches (men) or 35 inches (women); blood pressure over 130/85 mmHg; fasting triglyceride level over 150 mg/dL; fasting high-density lipoprotein cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women); fasting blood sugar over 100 mg/dL[27]. Metabolic syndrome has been shown to have a negative impact on remnant kidney function after nephrectomy since metabolic syndrome is associated with a high incidence of hypertension, obesity, hyperglycemia, and hyperuricemia[17,28,29].

The impact of serum uric acid level has been an emerging topic on the residual kidney function in living kidney donors. The total 4650 living-donor cohort study showed that donors with post-donation gout had higher risk of developing AKI and progression to CKD[30]. Other living-donor studies from Turkey and Korea also suggested that preoperative hyperuricemia are associated with impaired postoperative renal function at 6 and 12 mo[31-33]. It was also reported that preoperative hyperuricemia was strongly associated with suboptimal renal compensatory function or recovery at one year after renal donation[34]. Furthermore, hyperuricemia had 1.76-fold higher adjusted risk of adverse events

Table 1 Clinical factors associated with kidney recovery in living donors

Ref.	Significant factors		
Ohashi *et al*[17]	Age	Presence of metabolic syndrome	Chronic histological changes
Ibrahim *et al*[8]	Age	Sex	BMI
Rook *et al*[11]	Age	BMI	
Denic *et al*[21]	Age	HTN	
Shiraishi *et al*[15]	Age	Sex	BMI
	HTN		
Nishida *et al*[34]	Hyperuricemia	Chronic histological changes	
Yakoubi *et al*[25]	Age	BSA adjusted RKV	Preoperative eGFR
Shinoda *et al*[26]	BMI	RKV/BSA	
Okumura *et al*[6]	Age	Sex	History of HTN
	RKV/Wt		
Zabor *et al*[18]	Age	Sex	History of HTN
Lee *et al*[19]	Age	Sex	History of HTN
	BMI	History of DM	Preoperative eGFR
	RKV		
Vaz *et al*[42]	Age	Sex	

BMI: Body mass index; HTN: Hypertension; BSA: Body surface area; RKV: Remnant kidney volume; eGFR: Estimated glomerular filtration rate; CrCl: Creatinine clearance; mGFR: Measured glomerular filtration rate; Wt: Weight; DM: Diabetes.

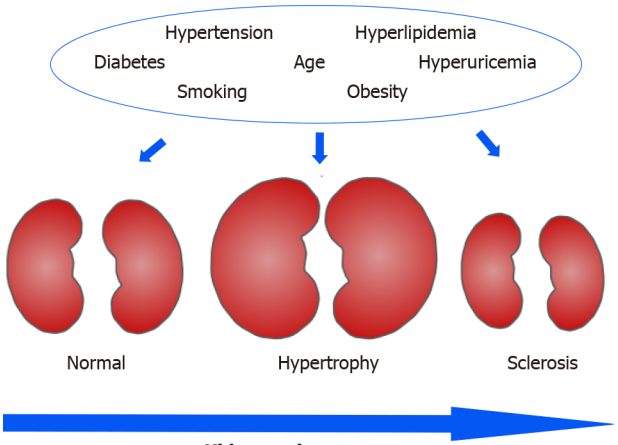

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Figure 1 Clinical factors associated with kidney compensation.

within 5 years after donation, such as cardiovascular events, initiation of dialysis, and *de novo* prescriptions for hypertension, hyperuricemia, diabetes, and dyslipidemia as well as lower estimated glomerular filtration rate (eGFR)[35].

The size of kidney is one of the important factors affecting the donor/recipient outcomes in kidney transplantation[36,37]. Since larger size of the kidney is associated with better renal function, it is recommended to choose the smaller kidney for donation to fulfil the principle of leaving the "better" kidney in donor if there is a more than 10% volume difference between kidneys in donor. The reasons to select suboptimal side of kidneys in donation, were cysts or tumors (46.5%), arterial abnormalities (22.7%), inferior size or function (19.8%), and anatomic abnormalities (11.0%), and those kidneys showed worse long-term overall graft survival regardless of the reasons[38].

Remnant kidney volume (RKV) in living donor is one of the important factors to determine the kidney recovery after donor nephrectomy[6,19]. Shinoda *et al*[26] showed the ratio of RKV to body

surface area (BSA) ratio has an independent factor to predict renal function or compensation after kidney donation. Yakoubi *et al*[25] also showed BSA adjusted with RKV was an independent predictor of kidney recovery after donation. With respect to recipient outcomes, the ratio of donated kidney volume to body weight (Wt) has been suggested as an important factor related to allograft function[39].

The ratio of RKV to Wt (RKV/Wt) was reported to be one of the significant associated factors in eGFR at 1 year after kidney donation[6]. Although it has been thought that a lower RKV/Wt can cause hyperfiltration and subsequent proteinuria[40], Song *et al*[41] suggested that a ratio of RKV/Wt less than 2.0 mL/kg did not affect the eGFR in donors but was associated with more severe proteinuria at 1 year after donor nephrectomy. There was no significant difference in the RKV/Wt ratio in the study [41], but they suggested the "deterioration" of kidney function since the donors were associated with presence of proteinuria at 1 year after donation. Thus, a lower RKV/Wt ratio might be associated with hyperfiltration and subsequently decrease "renal reserve".

Laterality of the donated kidney is another factor to evaluate when considering donor and recipient outcomes in kidney transplantation. Vaz *et al*[42] studied the outcomes of hand assisted laparoscopic donor nephrectomy (HALDN) of the left and the right kidney among 739 donors. This study concluded that, although most transplant centers and surgeons prefer performing left nephrectomies because of having a longer vein, right HALDN nephrectomy is a safe procedure with similar outcomes to left HALDN. Gunseren *et al*[43] compared right and left side laparoscopic donor nephrectomy outcomes and found that they had similar intraoperative outcomes. These authors noted, however, that dissection of lymphatic structures during left laparoscopic donor nephrectomy may cause chylous drainage and prolong hospitalization time compared to right-sided nephrectomy. Zeuschner *et al*[44] evaluated left and right pure laparoscopic donor nephrectomies and found a higher rate of complications for recipients of right grafts, but long-term function and graft survival were equivalent.

PATHOLOGICAL CHANGES OF NEPHRECTOMY

After the nephrectomy, the compensation of contralateral kidney function has been well known. Immediately after nephrectomy, an approximately 40% increase in renal plasma flow and glomerular filtration rate is measured in the remaining kidney[9,45]. This leads to developing glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly. The glomerulomegaly from hyperfiltration also occurs in response to nephron loss. In addition to glomerulomegaly, hyperfiltration leads to tubular hypertrophy and hyperplasia. Prolonged hyperfiltration and glomerular hypertension causes glomerular sclerosis and decreased glomerular density (Figure 2).

Once glomerular size reaches a certain threshold, glomerularsclerosis, hypertension, proteinuria, and renal failure may develop[46]. This pathological process was associated with kidney function, blood pressure and metabolic conditions: Metabolic syndrome, hypertension, hyperglycemia and hyperuricemia[17,20,34,47,48]. However, these histological changes might not always be seen in donors since donors were in a relatively good state of health and the unaffected nephrons would respond with compensation[48]. Studies showed that donors who had hyperuricemia, had chronic histological changes such as intestinal fibrosis, tubular atrophy and arterial hyalinosis in the donated kidney[34]. Intestinal fibrosis and tubular atrophy have significant impacts on long term graft function[49]. It is thought that arteriosclerosis has a significant relationship with intestinal fibrosis and tubular atrophy since the chronic ischemic condition caused by arteriosclerosis induces histological changes such as intestinal fibrosis, tubular atrophy and glomerular sclerosis[50].

Rule *et al*[20] showed that increased GFR, body mass index and uric acid level and a family history of end stage renal disease were independent predictors of decreased glomerular density. The size of individual nephrons can reflect important elements of metabolic regulation. After living kidney donation, donors can develop glomerular hypertension and increased single-nephron filtration with compensatory glomerulomegaly[51-53]. Polichnowski *et al*[54] showed that contralateral nephrectomy is associated with kidney recovery from ischemic kidney injury and prevent tissue atrophy with capillary repair and tubule redifferentiation. This result supports that remnant kidney is not vulnerable but sustainable after kidney donation. However, we emphasize that the best strategy for AKI is prevention. It is rare to perform living donation in the setting of AKI, however, in deceased donors, Cima *et al*[55] reported that kidney transplant could be performed from donors with AKI depending on the histological grading score with glomerulosclerosis, tubular atrophy, intestinal fibrosis, vascular damage and acute tubular necrosis[55,56].

MOLECULAR CHANGES OF NEPHRECTOMY

At present, the specific mechanism after nephrectomy remain unclear. However, several hypotheses have been proposed and it has shown that endothelial injury and recovery have an important role in the pathogenesis of kidney injury[57]. As discussed above, renal blood flow and GFR significantly increased after nephrectomy. This has been a critical role of upstream factors responsible to recruit dormant

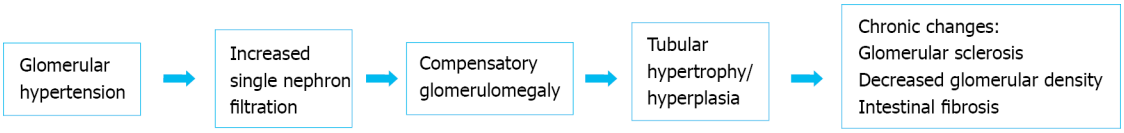

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Figure 2 Changes in kidney after nephrectomy.

nephrons and subsequently to improve in GFR. As renal blood flow increases and renal glomerular filtrate rate increases, it would lead to increase oxygen consumption and cause tissue hypoxia. It induces hypoxia-inducible factor 1 alpha and induces vascular endothelial growth factor. Hypoxia also induces phosphatase and tension homolog in tubules which causes tubule redifferentiation and repair [54].

In another way, renal tubular epithelial cells, which are surviving from ischemic injury, undergo differentiation[58]. These surviving epithelial cells express vimentin (an intermediate filament protein, which is found in undifferentiated mesenchymal cells but not in differentiated kidney cells), and proliferating cells nuclear antigen (a marker of mitogenesis), in contrast, damaged cells do not express either vimentin or proliferating cell nuclear antigen[59]. The molecular drivers in the process of intrinsic repair remain indeterminate, but the transcription factor Sox9 has been shown to be a critical part of the cellular repairing pathway in surviving renal tubular epithelial cells[60].

Oliver *et al*[60] reported that there are renal specific stem cells, which have been identified in the renal tubules as well as the papilla, however, the contribution of these cells still remains under investigation. Many recent studies have looked into the progenitor cell or bone marrow derived mesenchymal stem cells in renal repair[61]. The mesenchymal stem cell, which are derived from renal specific or bone marrow, may accelerate the process of repairing the injured tubules by direct proliferation or through paracrine effects. In transplant kidney, some studies suggest that the recipient derived cells may repopulate injured tubule[62,63], however, mesenchymal stem cells may predominantly play a role in their beneficial effects *via* paracrine mechanisms[64]. The mesenchymal stem cells may release microvesicles to communicate between cells and protect renal injury in addition to releasing cytokines [65].

CONCLUSION

We have performed living donor kidney transplant safely, however, a large cohort study showed that being a donor increased cardiovascular risk and progression to ESRD in the long term[7]. Since the degree of recovery from AKI affects the prognosis of kidney function[66], we believe that it is important to identify the risk of patients without compensation of kidney function of the contralateral kidney to predict the long term risk.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Kenji Okumura 0000-0002-7751-2624; Holly Grace 0000-0003-2585-2675; Hiroshi Sogawa 0000-0003-3724-9005; Shigeyoshi Yamanaga 0000-0002-4372-0011.

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MINIREVIEWS

Kidney disease in non-kidney solid organ transplantation

Kurtis J Swanson

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Kurtis J Swanson, Division of Nephrology and Hypertension, University of Minnesota, Minneapolis, MN 55414, United States

Corresponding author: Kurtis J Swanson, MD, Assistant Professor, Division of Nephrology and Hypertension, University of Minnesota, 717 Delaware Street SE, Suite 353, MMC 1932, Minneapolis, MN 55414, United States. kjswanson88@gmail.com

Abstract

Kidney disease after non-kidney solid organ transplantation (NKSOT) is a common post-transplant complication associated with deleterious outcomes. Kidney disease, both acute kidney injury and chronic kidney disease (CKD) alike, emanates from multifactorial, summative pre-, peri- and post-transplant events. Several factors leading to kidney disease are shared amongst solid organ transplantation in addition to distinct mechanisms unique to individual transplant types. The aim of this review is to summarize the current literature describing kidney disease in NKSOT. We conducted a narrative review of pertinent studies on the subject, limiting our search to full text studies in the English language. Kidney disease after NKSOT is prevalent, particularly in intestinal and lung transplantation. Management strategies in the peri-operative and post-transplant periods including proteinuria management, calcineurin-inhibitor minimization/sparing approaches, and nephrology referral can counteract CKD progression and/or aid in subsequent kidney after solid organ transplantation. Kidney disease after NKSOT is an important consideration in organ allocation practices, ethics of transplantation. Kidney disease after SOT is an incipient condition demanding further inquiry. While some truths have been revealed about this chronic disease, as we have aimed to describe in this review, continued multidisciplinary efforts are needed more than ever to combat this threat to patient and allograft survival.

Key Words: Acute kidney injury; Chronic kidney disease; Solid organ transplant; Native kidneys; Calcineurin inhibitor toxicity; Renal replacement therapy; Kidney after solid organ transplant

Core Tip: Kidney disease in the non-kidney solid organ transplant population occurs at significantly higher rate than the general population. Pre-transplant morbidity as well as peri-/post-transplant events contribute to this prevalence. Management strategies throughout the journey of non-renal solid organ transplantation are being studied, including transplantation after native kidney failure to help offset the morbidity/mortality of chronic kidney disease and maximize the benefit of non-kidney solid organ transplantation.

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INTRODUCTION

Chronic kidney disease (CKD), most commonly defined as decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or markers of kidney damage persistent at least 90 d per Kidney Disease Improving Global Outcomes (KDIGO) criteria, is a frequently observed post-transplant complication for non-kidney solid organ transplantation (NKSOT) recipients and is associated with adverse outcomes[1-3]. While quantifying the prevalence of CKD in any population is daunting, several studies have noted an incidence of CKD in NKSOT ranging between 6%-21%[2,3]. Notably, this is derived *via* CKD definition as GFR < 30 mL/min/1.73 m^2. In one study of liver transplant recipients, approximately 57% had a GFR between 30-59 mL/min/1.73 m^2[2,3]. This is compared to the estimated CKD rate of 15% in the general population[1].

Intuitively, end-organ disease compelling transplantation often leads to impaired kidney function, stemming from recurrent acute kidney injury (AKI) and subsequent CKD. Furthermore, the post-transplant milieu portends CKD through injurious transient and persistent insults, leading to the well described disproportionately high burden of kidney disease in SOT recipients[2-4]. The goal of this review is to condense the current literature in this field to: (1) Illustrate the scope of the problem; (2) Examine mechanisms leading to CKD in this population; and (3) Identify potentially modifiable risk factors and discuss management/treatment of CKD after NKSOT. In the following sections, we will discuss common factors driving AKI and CKD and then describe kidney disease after NKSOT in the following distinct contexts: Pancreas, liver, heart, lung, and intestinal transplantation.

KEY DEFINITIONS

AKI

While several definitions exist, we will use those endorsed by the KDIGO work group whereby AKI is defined as at least a 0.3 mg/dL increase in creatinine within 48 h or at least 1.5-1.9 times baseline increase in creatinine within 1 wk or decrease in urine output of at least 0.5 mL/kg/h for at least 6 h[1].

CKD

As in AKI, KDIGO has defined CKD, which is identified by markers of kidney damage, estimated GFR (eGFR) < 60 mL/min/1.73 m^2, and degree of albuminuria given the well described relationship between proteinuric kidney disease and CKD progression[1]. Unless otherwise stated, we will use these criteria to define CKD.

SCOPE OF CKD AFTER NKSOT

How common is CKD after NKSOT? This is an important question many have sought to answer given the well documented deleterious impact CKD has on cardiovascular and survival outcomes[2]. As described by Bloom *et al*[3] in their landmark review, historically varied CKD definitions as well as the reliance of estimating equations based on serum creatinine (SCr), of which their distinct strengths/weaknesses/limitations has made the assessment of CKD prevalence enigmatic at best. An oft-cited key study by Ojo *et al*[2] notes the following rates of 5-year post-transplant CKD: 21.3% among intestinal transplant (IT) recipients, 18.1% among liver transplant recipients, 15.8% among lung transplant recipients, 10.9% among heart transplant recipients, and 6.9% among heart-lung transplant recipients. Whereas this study offers a reference point, they utilized a stringent definition of CKD [GFR < 30 mL/min per 1.73 m^2, *via* four variable Modification of Diet in Renal Disease Study (MDRD)

equation]. While such conservative criteria lead to underestimation of CKD prevalence (as most patients with CKD fall in the eGFR 30-60 mL/min/1.73 m^2 range), shared patient characteristics of low muscle mass/malnutrition accentuate the already flawed estimating creatinine-based equations. Moreover, the paucity of proteinuria measurements performed clinically and/or analyzed in studies is a major contributor to the underestimation of CKD in NKSOT recipients.

Several studies have helped improve our understanding of CKD prevalence in NKSOT recipients which will be highlighted below. In their recent study, Shaffi *et al*[5] compared 26 eGFR equations in NKSOT recipients [*n* = 3622, including recipients of kidney (53%), liver (35%), and other or multiple organs (12%)] to measured GFR (mGFR) either *via* urinary iothalamate clearance or plasma iohexol clearance. They found that the proportion of absolute percent error < 30% (P_{30}) and mean absolute error for the CKD Epidemiology Collaboration equation (CKD-EPI) and the MDRD Study equations were 78.9% [99.6%, 95% confidence interval (CI): 76.9%-80.8%] for both and 10.6 (99.6%, 95%CI: 10.1-11.1) *vs* 11.0 (99.6%, 95%CI: 10.5-11.5) mL/min/1.73 m^2. Compared to the other 24 estimating eGFR equations the authors examined, the CKD-EPI and MDRD equations were significantly more accurate ($P < 0.001$). In their study examining 1135 pancreas transplant alone (PTA) recipients in Scientific Registry of Transplant Recipients (SRTR), Kim *et al*[6] observed that about 25% of the cohort had an eGFR below 61.3 mL/min/1.73 m^2. Gonwa *et al*[7] *via* prospective study serially measuring iothalamate clearance in 1447 liver transplant recipients observed the following: At 3 mo, 1 year, and 5 years post-transplant, the mean mGFR was 59.5 ± 27.1 mL/min, 62.7 ± 27.8 mL/min, and 55.3 ± 26.1 mL/min. Interestingly, the mean mGFR at the time of initial evaluation was 90.7 ± 40.5 mL/min. In their analysis of risk factors for CKD after heart transplantation, Hamour *et al*[8] observed that CKD post-heart transplant is common, noting probabilities of eGFR < 45 mL/min/1.73 m^2 were the following: 45% at year 1, 71% at year 5 and 83% at year 10. In their review which included 186 lung transplant recipients, Ishani *et al*[9] showed that CKD was commonly observed at 1 year post transplant and progressed henceforth: From a mean pre-transplant SCr of 0.88 ± 0.19 mg/dL to 1.22 ± 0.82 mg/dL at one month 1.67 ± 0.88 mg/dL at 12 mo and to 1.98 ± 1.1 mg/dL at three years post-transplant. Kidney disease after NSKOT appears to be common, progressive and is likely substantially underestimated due to patient factors as well as understated albuminuria.

MECHANISMS LEADING TO CKD IN NON-KIDNEY SOT

Across NSKOT, both shared and organ-specific factors give rise to CKD onset and progression. Comorbidities directly related to primary end-organ failure *e.g.*, diabetes mellitus, liver failure, heart failure, lung failure in addition to common baseline demographic characteristics (advancing age, female gender, diabetes mellitus, hypertension, hepatitis C virus infection, drug-induced nephrotoxicity) as well as transplant specific factors, namely perioperative AKI, as well as calcineurin inhibitor (CNI) use, all contribute to the development of CKD[2-4].

The perioperative setting is a crucial shared risk factor impacting kidney function both short and long term. Hypotension, hypoperfusion, fluid shifts, nephrotoxic agents, sepsis in the perioperative period all spur AKI[3,10]. In a fashion similar to pre-transplant organ dysfunction leading to kidney impairment, marginal allograft function begets renal decompensation and vice versa[3,10]. CNI use and its impact on renal function after NKSOT is a controversial topic. While CNI use is an oft-implicated cited reason for post SOT kidney disease, it does not tell the entire story[10]. In a recent study, Ojo *et al*[10] noted that CNI use constitutes the majority of histologic lesions observed on kidney biopsy, ranging from between 46%-60% of cases. Non-CNI related pathology, as illustrated in their description of orthotopic heart and liver transplant recipients in their cited figures, is also an important player and has been observed in 27%-40% of kidney biopsies. Importantly, histologic findings must be interpreted cautiously as these biopsies were subject to having multiple concurrent histologic patterns.

Kubal *et al*[11] expounded on this, conducting their own histologic study of 62 nonrenal SOT recipients with kidney biopsies, where they showed that only 35.5% (*n* = 22) of those biopsied had predominant features consistent with chronic CNI toxicity. Hypertensive nephropathy [43.5% (*n* = 27)], not without its own disputes, was the most common diagnosis. Nearly 20% (*n* = 12) of the cohort had biopsies showing alternative pathology including acute tubular necrosis (*n* = 5), mesangioproliferative glomerulonephritis (*n* = 2), diabetic nephropathy (*n* = 1), post infectious glomerulonephritis (*n* = 1), and membranous nephropathy (*n* = 1)[11].

In a recent review, Wiseman[12], as adapted from Schwarz *et al*[13], describes the clinical characteristics and histology of biopsy proven kidney disease after liver, lung and heart transplantation. Of note, primary glomerulonephritis was 26% in liver transplant recipients and acute tubular injury were the most commonly observed histologic patterns in lung and heart recipients. In addition to shared mechanisms leading to CKD, distinct factors inherent to the various subtypes of organ transplant exist. These have been suitably defined in the literature and will be discussed in the following sections[10]. Though SOT recipients may recover from these early post-transplant kidney perturbations, often AKI, irrespective of renal replacement therapy (RRT) need, in addition to a "pro-nephrotoxic" environment with ongoing insults (post-transplant diabetes, hypertension, hyperlipidemia, CNI use, transplant organ

dysfunction, cardiovascular disease, infection, malignancy) in addition to pre-existing kidney dysfunction contribute to progressive CKD[2,3,14,15].

KIDNEY DISEASE AFTER PANCREAS TRANSPLANTATION

PTA is a novel transplant option for non-uremic diabetic patients. Interestingly, there is evidence that PTA may be renoprotective *via* proteinuria reduction and reversal of diabetic kidney lesions[16,17]. Despite this, kidney disease often progresses for PTA recipients. The following studies detail some of the contributing factors leading to kidney disease.

Kim *et al*[6], in their study examining 1135 adult PTA recipients, showed that kidney function prior to transplantation is a strong predictor of end stage kidney disease (ESKD): PTA recipients with pre-transplant eGFR < 60 and 60-89.9 mL/min/1.73 m^2 were 7.74 (95%CI: 4.37-13.74) and 3.25 (95%CI: 1.77-5.97) times more likely to develop ESKD than patients with eGFR ≥ 90 mL/min/1.73 m^2. Smail *et al*[18] also found that a pre-transplant eGFR < 60mL/min/1.73 m^2 was associated with an end stage renal disease (ESRD) incidence at 1, 3, 5 years of 0%, 28.6% and 61.9% compared to those with an eGFR > 60 mL/min/1.73 m^2 (P = 0.006). Younger age, female sex, and duration of diabetes predicted the development of ESRD (all P < 0.05). However, there was no difference in patient survival based on pre-transplant eGFR (P = 0.73). Gruessner *et al*[19] examined 513 PTAs transplanted from 1966 to 2006. They observed a 5 year post-transplant ESKD rate of 13% and found that SCr > 1.5 mg/dL at time of transplant and age < 30 predicted kidney failure. Odorico *et al*[20] performed a retrospective analysis comparing PTA recipients (n = 27) and pancreas after kidney transplant (PSK) recipients (n = 61) to assess changes in kidney function. They observed that pre-transplant eGFR < 60 mL/min/1.73 m^2 was associated with CKD progression. Fascinatingly, 67% PTA patients showed an increase (> 10%) in their SCr from baseline *vs* 34% PAK patients (P = 0.035). PTA transplant was considered mildly protective in terms of progression of CKD, though this finding was not significant [hazard ratio (HR) = 0.29, 95%CI: 0.04-2.37, P = 0.182). Chatzizacharias *et al*[21] in their risk analysis of progression to kidney failure after pancreas transplant found that tacrolimus levels > 12 mg/dL at 6 mo post-transplant were associated with declining kidney function (HR = 14.3, 95%CI: 1.3-161, P = 0.03). Surprisingly, pre-transplant proteinuria (urine protein creatinine ratio > 100 mg/mmol) and low eGFR, which they defined as ≤ 45 and ≤ 40 mL/min/1.73 m^2, were not significantly associated with worsening CKD. Marchetti *et al*[22] in their inquiry of 28 PTA recipients observed stable native kidney function comparing pre-transplant to post-transplant (0.95 ± 0.2 *vs* 0.96 ± 0.22, P > 0.05). However, this follow up was only at 3 mo post-transplant. Coppelli *et al*[17] showed that at 1 year follow up, 32 PTA recipients did not have significantly different creatinine pre-and post-transplant (0.95 ± 0.25 mg/dL *vs* 1.00 ± 0.19 mg/dL, P > 0.05). They observed improvement in lipid levels, blood pressure as well as albuminuria. Genzini *et al*[23] in their single center retrospective review followed 45 PTA recipients. After stratifying by 24 h creatinine clearance (CrCl) post PTA [group 1 = CrCl ≤ 70 mL/min; (n = 20); group 2 = CrCl > 70; (n = 25)], they observed significant decreases in native kidney function at 1 year in both groups (group 1 CrCl pre- *vs* post-transplantation = 57.3 ± 9 *vs* 34.8 ± 32 mL/min, P = 0.003); (group 2 CrCl pre- *vs* post-transplantation = 107.1 ± 25 *vs* 81.0 ± 23 mL/min, P = 0.008). In group 1, 10/20 patients (50%) ended up with a CrCl < 30 mL/min, 5/20 (25%) initiated on hemodialysis, and 3/20 (15%) underwent kidney after pancreas transplantation. No patients in group 2 ended up with significantly decreased kidney function. Scalea *et al*[24] looked at PTA recipients over 14 years retrospectively and saw that 88% of patients had eGFR decrease with a mean decrement of 32.1 mg/min/1.73 m^2. Mean eGFR pre-transplantation was 88.9 *vs* 55.6 post-transplantation (P < 0.0001) with mean follow-up of 3.68 years. Donor demographics, immunosuppression, human leukocyte antigen mismatch were not significantly associated with progressive CKD in their analysis.

Studies on kidney function after PTA are limited in terms of sample size and duration of follow up. However, it would appear that the presence of pre-transplant CKD with eGFR < 60 mL/min/1.73 m^2 tends to associate with cumulative CKD. While more robust studies are needed to better characterize kidney function in this population, it would appear that pre-transplant native kidney function is an important predictor of progressive CKD for pancreas transplant recipients and ought to inform organ allocation practices as well as evaluation for kidney after pancreas transplantation. These results are summarized in Table 1.

KIDNEY DISEASE AFTER LIVER TRANSPLANTATION

Kidney disease is common for patients with liver failure, due to hemodynamic changes associated with portal hypertension as well as disease processes impacting both organs *e.g.*, viral hepatitis, hepatorenal syndrome, secondary immunoglobulin A nephropathy, oxalosis[2,3]. Although hepatitis C as a primary diagnosis of liver failure is declining, as described by the Organ Procurement Transplant Network/SRTR (OPTN/SRTR) 2019 annual data report, it still constitutes 12.6% of liver registrations [25]. In addition to its associations with glomerulonephritis, hepatitis C has been shown to increase the

Table 1 Kidney disease after pancreas transplant alone

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Kim *et al*[6]	1135	Pre-transplant eGFR < 60 mL/min/1.73 m^2. Pre-transplant eGFR 60-89.9 mL/min/1.73 m^2	PTA recipients with pre-transplant eGFR < 60 and 60-89.9 mL/min/1.73 m^2 were 7.74 (95%CI: 4.37-13.74) and 3.25 (95%CI: 1.77-5.97) times more likely to develop ESKD than patients with eGFR ≥ 90 mL/min/1.73 m^2
Smail *et al*[18]	43	Pre-transplant eGFR < 60mL/min/1.73m^2 was associated with a ESRD incidence at 1, 3, 5 yr of 0, 28.6% and 61.9% compared to those with an eGFR > 60 mL/min/1.73 m^2 1, 3, 5 yr incidence of 0.82, and 12.5% (P = 0.006); age, female sex, duration of diabetes pre-PTA (all P < 0.05)	The risk of progression to ESRD after PTA may be increased in patients with pretransplant eGFR below 60 mL/min/1.73 m^2, younger patients and in women
Gruessner *et al*[19]	513	SCr > 1.5 mg/dL at transplant, age < 30	5 yr post-transplant ESKD rate of 13%
Odorico *et al*[20]	27 PTA, 61 PAK	Pre-transplant eGFR < 60 mL/min/1.73 m^2	67% PTA patients showed an increase (> 10%) in their SCr from baseline *vs* 34% PAK patients (P = 0.035). PTA transplant was considered mildly renoprotective; this finding was not significant (HR = 0.29, 95%CI: 0.04-2.37, P = 0.182)
Chatzizacharias *et al*[21]	24	Tacrolimus levels > 12 mg/dL at 6 mo post-transplant	Tacrolimus levels, but not pre-transplant proteinuria or low eGFR < 45 mL/min/1.73 m^2 were associated with CKD progression
Marchetti *et al*[22]	28		Stable native kidney function comparing pre-transplant to post-transplant (0.95 ± 0.2 *vs* 0.96 ± 0.22, P > 0.05); limited follow up of 3 mo
Coppelli *et al*[17]	32		32 PTA recipients did not have significantly different creatinine pre- and post-transplant (0.95 ± 0.25 mg/dL *vs* 1.00 ± 0.19 mg/dL, P > 0.05); PTA lead to improvement in lipids, BP, and albuminuria
Genzini *et al*[23]	45; 20-group 1 CrCl ≤ 70 mL/min; 25-group 2 CrCl > 70 mL/min	CrCl < 70 mL/min	Kidney function at 1-yr: Group 1 CrCl pre- *vs* post-transplantation = 57.3 ± 9 *vs* 34.8 ± 32 mL/min, P = 0.003); (group 2 CrCl pre- *vs* post-transplantation = 107.1 ± 25 *vs* 81.0 ± 23 mL/min, P = 0.008). In group 1, 10/20 patients (50%) ended up with a CrCl < 30 mL/min, 5/20 (25%) initiated on hemodialysis, and 3/20 (15%) underwent kidney after pancreas transplantation. No patients in group 2 ended up with significantly decreased kidney function
Scalea *et al*[24]	123		88% of patients had eGFR decrease with a mean decrement of 32.1 mg/min/1.73 m^2. Mean eGFR pre-transplantation was 88.9 *vs* 55.6 post-transplantation (P < 0.0001) with mean follow-up of 3.68 yr. Donor demographics, immunosuppression, HLA mismatch were not significantly associated with progressive CKD in their analysis

PTA: Pancreas transplant alone; ESKD: End stage kidney disease; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; SCr: Serum creatinine; PAK: Pancreas after kidney transplant; HR: Hazard ratio; CI: Confidence interval; BP: Blood pressure; CrCl: Creatinine clearance; HLA: Human leukocyte antigen; CKD: Chronic kidney disease.

risk of developing diabetes mellitus[3]. As previously mentioned, CKD is often underreported in this group of NKSOT recipients due to liver failure mediated sarcopenia and malnutrition[26]. Here we will explore recent studies describing kidney function after liver transplantation. Ojo *et al*[2] utilizing SRTR data, observed that in 36849 liver transplant recipients at 1 year follow up, 8% had advanced CKD (CKD stage IV or V) and at 60 mo, 18.1% do. Key risk factors associated with chronic renal failure (CRF) after liver transplantation were pre-transplant GFR, particularly that of ≤ 29 mL/min/1.73 m^2 [relative risk (RR) = 3.78], post-operative renal failure (RR = 2.11), pre-transplant dialysis (RR = 1.45), hepatitis C (RR = 1.22), and pre-transplant diabetes mellitus (RR = 1.39).

Given the dilemmas associated with creatinine/eGFR interpretation in liver disease, several groups have attempted to evaluate kidney function after liver transplantation by serially following mGFR as summarized below. Cohen *et al*[27] looked at 353 liver transplant recipients with pre- and post-transplant mGFR *via* iothalamate clearance. Mean age at transplant was 50.3 years, with mean follow up of 6.8 years. 41% of their liver transplant recipients were transplanted due to cholestatic liver disease. Tacrolimus (51.7%) was the most common CNI used. At 3 years and 5 years in both the entire group (n = 353) and intensive follow-up group (n = 191), mean mGFR was > 50 mL/min/body surface area at 3 (56.5 and 56.4) and 5 years (56.6 and 53.9). Although mGFR at listing did not correlate well with 3 year mGFR in the intensive follow up group (correlation coefficient, r = 0.35). 1 year mGFR correlated relatively well with 3 year mGFR (r = 0.72). The authors reported a near doubling of transplant recipients with mGFR < 40 at 3 years posttransplant (39/191, 20.4%) *vs* pre-transplant (10/191, 10.5%). In the entire cohort of 353 orthotopic liver transplant (OLT) recipients, 15 patients (4.2%) developed

ESKD. Mean time to ESKD was 7.5 years after transplant (range = 2.5-11.3 years). In Kaplan-Meier analysis, the incidence of ESKD within 10 years was 10% ± 3%, 95%CI: 3%-15%.

In their study of 152 OLT recipients at least 5 years post-liver transplant, Herlenius *et al*[28] set out to describe the prevalence of CKD by linking early mGFR to late mGFR and to determine risk factors leading to CKD after liver transplant. At 5 years, 8 (5%) of the patients were on dialysis. GFR decreased by 36% at 5 years and 42% at 10 years. The authors observed that baseline mGFR had a weak correlation with 5-year mGFR (Pearson correlation coefficient, R^2 = 0.27). Stronger correlation was observed between 3 mo and 5 year mGFR [0.67 and R^2 = 0.46 (2-tailed P < 0.001) and 1 year and 5 year mGFR (0.72 and R^2 = 0.52 (2-tailed P < 0.001)]. They also conducted a multivariate logistic regression analysis on risk factors for developing advanced kidney disease (CKD IV, V) at 5 years post-liver transplant and found that only mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 was predictive (P = 0.03).

The following studies describe kidney disease after liver transplantation using eGFR: Wilkinson and Pham[29] reported the following rates in terms of incidence and mortality rate from AKI and CKD: 17%-95% rate of AKI with a mortality rate of 25%-74% in those on RRT *vs* 52% not requiring RRT; 10%-20% incidence of CKD, 2%-8% rate of ESRD with a mortality rate between 25%-50%. AKI risk factors included delayed graft function, poor liver allograft function, body mass index, use of cyclosporine-A and pre-transplant AKI. CKD risk factors included the following: AKI, need for hemodialysis, hepatorenal syndrome, CNI use, diabetes mellitus, hepatitis C, and age. Gonwa *et al*[30] inspected 834 liver transplant recipients which they stratified into 3 groups: Controls (n = 748), CRF [defined as sustained SCr > 2.5 mg/dL, (n = 41)], and ESRD (n = 45). They observed an incidence of "severe renal dysfunction", CRF + ESRD in 18.1% of OLT recipients after 13 years of follow up. In multivariate stepwise logistic regression analysis, increased creatinine by 1 mg/dL above the average of the group conferred the following risk for CRF or ESRD: Creatinine at 4 wk (odds ratio (OR) = 1.598, 95%CI: 1.076-2.372), creatinine at 3 mo (OR = 2.254, 95%CI: 1.262-4.025), and 1 year creatinine (OR = 2.582, 95%CI: 1.633-4.083). Survival was markedly decreased at year 13 in the ESRD group (28.2%) compared to the control group without significant kidney disease (54.6%). The authors also noted decreased survival after ESRD onset for those who did not receive a subsequent kidney transplant: 6 years after the onset of ESRD, patients receiving HD without a transplant had a survival of only 27% compared with 71.4% in the kidney transplant group (P = 0.04). O'Riordan *et al*[26], in their study of 230 OLT recipients, observed that at 5 years post-liver transplant, 71% had CKD with GFR < 60 mL/min. Pre-transplant factors associated with progression to ESRD included age, female gender, liver transplant from cytomegalovirus (CMV) positive donor to CMV positive recipient, and pre-liver transplant diabetes in univariate analysis (all P < 0.05). Though pre-OLT proteinuria was missing in 53% of patients, more than 40% of those with measurements had > 150 mg/L/d. Mean pre-transplant proteinuria = 0.21 ± 0.29 g/L (range = 0.00-2.09) and was significantly associated with CKD progression (OR = 5.36, 95%CI: 1.41-20.45, P = 0.01). In multivariate analysis for factors impacting CKD progression to stage 5 disease, pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive. In multivariate Cox regression analysis, GFR < 30 mL/min (HR = 3.05, 95%CI: 1.21-7.70, P = 0.02) was meaningfully associated with reduced patient survival. Similarly, survival was significantly decreased for those with GFR < 30 mL/min compared to those with GFR > 30 mL/min in Kaplan-Meier analysis (log rank P = 0.04). Wyatt and Arons[31] observed significant mortality in 358 liver transplant recipients who sustained AKI, irrespective of whether they required RRT or not: AKI without RRT [adjusted OR (aOR) = 8.69, 95%CI: 3.25-23.19, P < 0.0001]; AKI requiring RRT (aOR = 12.07, 95%CI: 3.90-37.32, P < 0.0001). Bahirwani *et al*[32] retrospectively reviewed 40 OLT recipients with CKD prior to transplant, which they defined as SCr ≥ 2 mg/dL for 90 d. Notable demographics included median eGFR of 24 mL/min (range 16-33), mean age of 56.5 years [interquartile range (IQR) = 52-60.5], 21 (53%) of the group had liver failure from hepatitis C, median Model of End Stage Liver Disease (MELD) of 26 (range = 22-31) and 19 (48%) of the recipients had pre-transplant diabetes. Interestingly, they observed the following median eGFR at 1, 2, and 3 years post-transplant 35 mL/min (IQR = 27-47), 34 mL/min (IQR = 20-51), and 37 mL/min (IQR = 22-55). 53% of recipients developed CKD stage 4 at 3 years. At a median follow up of 1.21 years post-transplant, 12 (30%) of recipients were on RRT. On univariate analysis, pre-transplant diabetes (HR = 4.23, 95%CI: 1.12-15.93, P = 0.03) and African American race (HR = 3.44, 95%CI: 1.04-11.35, P = 0.04) significantly predicted post-transplant RRT. This association was not significant on multivariate analysis. Interestingly, hypertension, hepatitis C, pre-transplant RRT, MELD score, pre transplant eGFR were not predictive of post-transplant RRT on univariate analysis (all P > 0.05). Cabezuelo *et al*[33] analyzed 184 OLTs for both early postoperative acute renal failure (> 50% increase in SCr within 1 wk of transplant) and late postoperative acute renal failure (similar increase in creatinine two to four weeks post-transplant). 12% of the cohort required RRT. Predictors of early acute renal failure were pre-transplant acute renal failure (OR = 10.2, P = 0.025), serum albumin (OR = 0.3, P = 0.001), duration of dopamine treatment (OR = 1.6, P = 0.001), and grade II-IV dysfunction of the liver graft (OR = 5.6, P = 0.002). Late postoperative risk factors were: Re-operation (OR = 3.1, P = 0.013) and bacterial infection (OR = 2.9, P = 0.017). Pham *et al*[34] in their review of AKI in NKSOT refer to a study whereby renal recovery after liver transplantation in recipients who were on dialysis at transplant was related to pre-transplant dialysis vintage: The percentage of renal function recovery for those who were on dialysis for ≤ 30 d 31-60 d, and 61-90 d were 71%, 56%, and 24%. They also note that in an analysis of the Canadian Organ Replacement

Register database by Al Riyami *et al*[35], despite a low incidence of ESRD (2.9%) in their cohort, the unadjusted mortality rate for those with AKI requiring dialysis compared to those who did not was 49.2% *vs* 26.8%, respectively ($P < 0.001$)[34,35].

A particularly interesting study by Kollmann *et al*[36] investigated whether donor type [donation after circulatory death (DCD) ($n = 57$) *vs* donation after brain death (DBD) ($n = 446$) or living donor liver transplantation (LDLT) ($n = 178$)] impacted AKI rates. They observed that perioperative AKI (defined as AKI within the first 7 postoperative days) was observed more often in the DCD group (61%; DBD, 40%; and LDLT, 44%; $P = 0.01$) and was associated with significantly higher peak aspartate aminotransferase levels ($P < 0.001$). DCD patients also had a significantly higher peak SCr ($P < 0.001$) and a trend toward higher rates of AKI stage 3 per Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease criteria (DCD, 33%; DBD, 21%; LDLT, 21%; $P = 0.11$). AKI recovery (DCD, 77%; DBD, 72%; LDLT, 78%; $P = 0.45$) and progression to CKD (DCD, 33%; DBD, 32%; LDLT, 32%; $P = 0.99$) were similar across groups. Patient survival was significantly lower in OLT recipients who received DCD or DBD organs and required perioperative RRT in multivariate analysis (HR = 7.90; 95%CI: 4.51-13.83; $P < 0.001$).

While a plethora of studies exist examining kidney function after liver transplantation exist, this appears to be representative of the body of work, including both studies using measured and eGFR to assess kidney function. As is the case of longitudinal studies, impaired kidney function definitions and immunosuppression eras have changed over time, rendering comparison difficult. Clearly AKI and CKD are adverse outcomes that lead to adverse outcomes including ESKD and patient mortality. While some risk factors are unmodifiable (age, sex, ethnicity), potentially modifiable risk factors, such as diabetes, hypoalbuminemia, proteinuria, and donor type were observed in these studies. Perhaps these modifiable risk factors can be diagnosed and managed as part of pre-transplant care to optimize before transplantation, especially in those with lower baseline kidney function. Moreover, these studies support the use of mGFR in select candidates and recipients both in the pre- and post-transplant contexts to better identify kidney disease. These studies are abbreviated in Table 2.

KIDNEY DISEASE AFTER HEART TRANSPLANTATION

With kidney and heart function intricately related, disease in one organ precipitates disease in the other; the same comorbidities (hyperlipidemia, hypertension, diabetes, metabolic syndrome, *etc*) lead to kidney and heart disease[2,10,37]. While heart failure can arise from kidney-sparing, acute conditions, *de novo* heart failure in CKD is a common occurrence, with rates cited between 17%-21%[38]. Estimating pre-heart transplant kidney disease can be challenging in waitlisted heart transplant candidates due to underestimated eGFR stemming from cardiac cachexia/poor nutrition. Moreover, thoracic transplantations (heart and lung) are complex, high-risk surgeries with high rates of AKI due to aortic cross-clamping, cardiopulmonary bypass, aggressive diuresis and fluid shifts[3]. The following studies describe kidney disease after heart transplantation: Ojo *et al*[2] described a perioperative acute renal failure rate of 20%-30% of heart transplant recipients with a 10.9% CKD IV/V rate at 60 mo post-transplant. In addition to shared mechanisms, they noted systemic atherosclerosis, renal hypoperfusion from cardiorenal disease as organ specific risk factors leading to kidney dysfunction[10].

In their retrospective cohort study of 233 orthotopic heart transplant (OHT) recipients, Cantarovich *et al*[39] observed that early renal dysfunction predicts poor long-term kidney function: A 30% decline in CrCl between 1 mo and 3 mo independently predicted the need for chronic dialysis ($P = 0.04$) and time to first CrCl < 30 mL/min at > 1 year after transplant ($P = 0.01$). Rubel *et al*[40] studied 370 OHT recipients with up to 10 year follow up looking for early GFR decline as well as ESKD. They found mean eGFR fell 24% at year one, 23% of patients developed a 50% reduction in GFR by year 3, and that 20% of the cohort developed ESRD at 10 years post-transplant. Significant predictors of post-transplant ESRD in Cox multivariate analysis included the following: GFR < 50 mL/min (HR = 3.69, $P = 0.024$); high mean cyclosporine trough in the first 6 mo (HR = 5.10, $P = 0.0059$); and presence of diabetes (HR = 3.53, $P = 0.021$). Lindelöw *et al*[37] investigated kidney outcomes in 151 of their OHT recipients with 9 year follow up. The average preoperative GFR (66 ± 17 mL/min per 1.73 m^2) declined to 52 ± 19 ($P < 0.0001$) at 1 year. From 2 years to 9 years after heart transplantation, overall kidney function remained fairly stable (all $P > 0.05$). There was no significant correlation between the preoperative GFR and postoperative renal function or survival. Recipient age predicted post heart transplant renal function. Boyle *et al*[14] set out to determine risks and consequences of post-heart transplant AKI in their study of 756 OHT recipients. They observed an AKI rate of 5.8% (44 of 756). Significant AKI risk factors were insulin dependent diabetes ($P = 0.019$) and prior cardiac surgery ($P = 0.014$). OHTs with AKI had higher preoperative SCr, lower preoperative GFR, lower preoperative albumin, lower preoperative hematocrit, increased cardiopulmonary bypass time, and increased blood transfusion needs compared to those without AKI (all $P < 0.01$). They observed a 50% (22/44) mortality rate in OHTs with AKI requiring dialysis compared to those who did not have AKI (1.4%, 10/712).

In their analysis of CKD risk factors after heart transplantation, Hamour *et al*[8] evaluated 352 OHT recipients. They found that the cumulative probability of eGFR < 45 mL/min/1.73 m^2 over time was the

Table 2 Kidney disease after liver

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	36849	Pre-transplant GFR ≤ 29 mL/min/1.73 m^2 (RR = 3.78), post-operative renal failure (RR = 2.11), pre-transplant dialysis (RR = 1.45), hepatitis C (RR = 1.22), and pre-transplant diabetes mellitus (RR = 1.39)	8% with CKD IV/V at 1 yr; 18.1% at 5 yr. Pre-transplant GFR, particularly that of ≤ 29 mL/min/1.73 m^2, post-operative renal failure, pre-transplant dialysis, hepatitis C, and pre-transplant diabetes mellitus associated with CKD
Cohen *et al* [27]	353	1 yr mGFR correlated with 3 yr mGFR (r = 0.72)	At 3 and 5 yr in both the entire group (n = 353) and intensive follow-up group (n = 191), mean mGFR was > 50 mL/min/BSA at 3 (56.5 and 56.4) and 5 yr (56.6 and 53.9). Near doubling of transplant recipients with mGFR < 40 at 3 yr posttransplant (39/191, 20.4%) *vs* pre-transplant (10/191, 10.5%). 15 patients (4.2%) developed ESKD. Mean time to ESKD was 7.5 yr after transplant (range = 2.5-11.3 yr). The incidence of ESKD within 10 yr was 10% ± 3%, 95%CI: 3%-15%
Herlenius *et al*[28]	152	mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 predicted CKD IV, V (P = 0.03)	At 5 yr, 8 (5%) of the patients were on dialysis. GFR decreased by 36% at 5 yr and 42% at 10 yr. mGFR 3 mo post-liver transplant below 30 mL/min/1.73 m^2 predicted CKD IV, V (P = 0.03)
Wilkinson and Pham [29]		AKI risk factors: Delayed graft function, poor liver allograft function, BMI, use of cyclosporine-A and pre-transplant AKI; CKD risk factors: Acute kidney injury, need for hemodialysis, hepatorenal syndrome, calcineurin inhibitor use, diabetes mellitus, hepatitis C, and age	17%-95% rate of AKI with a mortality rate of 25%-74% in those on RRT *vs* 52% not requiring RRT; 10%-20% incidence of CKD, 2%-8% rate of ESRD with a mortality rate between 25%-50%
Gonwa *et al* [30]	834	Cr by 1 mg/dL above the average of the group conferred the following risk for CRF or ESRD: Cr at 4 wk (OR = 1.598, 95%CI: 1.076-2.372), Cr at 3 mo (OR = 2.254, 95%CI: 1.262-4.025), and 1 yr Cr (OR = 2.582, 95%CI: 1.633-4.083)	"severe renal dysfunction", CRF + ESRD in 18.1% of (OLTx) recipients after 13 yr of follow up; 6 yr after the onset of ESRD, patients receiving HD without a transplant had a survival of only 27% compared with 71.4% in the kidney transplant group (P = 0.04)
O'Riordan *et al*[26]	230	Univariate: Age, female gender, liver transplant from CMV positive donor to CMV positive recipient, and pre-liver transplant diabetes, pre-transplant proteinuria. Multivariate: Pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive	5 yr post-liver transplant, 71% had CKD; pre-OLT total urinary protein (OR = 7.48, 95%CI: 1.04-53.97) and female gender (OR = 7.84, 95%CI: 2.04-30.08, P < 0.005) were the most predictive of CKD progression. In multivariate Cox regression analysis, GFR < 30 mL/min (HR = 3.05, 95%CI: 1.21-7.70, P = 0.02) was associated with patient survival. Similarly, survival was significantly for those with GFR < 30 mL/min compared to those with GFR > 30 mL/min in Kaplan-Meier analysis (log rank P = 0.04)
Wyatt and Arons[31]	358		Mortality in 358 liver transplant recipients who sustained AKI, irrespective of whether they required RRT or not: AKI without RRT (aOR = 8.69, 95%CI: 3.25-23.19, P < 0.0001); AKI requiring RRT (aOR = 12.07, 95%CI: 3.90-37.32, P < 0.0001)
Bahirwani *et al*[32]	40	Univariate: Pre-transplant diabetes (HR = 4.23, 95%CI: 1.12-15.93, P = 0.03) and African American race (HR = 3.44, 95%CI: 1.04-11.35, P = 0.04). Multivariate: No significant predictors of CKD	53% of recipients developed CKD stage 4 at 3 yr. At a median follow up of 1.21 yr post-transplant, 12 (30%) of recipients were on RRT
Cabezuelo *et al*[33]	184	Early acute renal failure: Pretransplant acute renal failure (OR = 10.2, P = 0.025), serum albumin (OR = 0.3, P = 0.001), duration of dopamine treatment (OR = 1.6, P = 0.001), and grade II-IV dysfunction of the liver graft (OR = 5.6, P = 0.002). Late postoperative risk factors: Re-operation (OR = 3.1, P = 0.013) and bacterial infection (OR = 2.9, P = 0.017)	12% of the cohort required RRT
Pham *et al* [34]			The percentage of renal function recovery for those who were on dialysis for ≤ 30 d, 31-60 d, and 61-90 d were 71%, 56%, and 24%
Al Riyami *et al*[35]	4186		Despite a low incidence of ESRD (2.9%) in their cohort, the unadjusted mortality rate for those with AKI requiring dialysis compared to those who did not was 49.2% *vs* 26.8%, respectively (P < 0.001)
Kollman *et al*[36]	681; 57 DCD, 446 DBD; 178 LDLT	Perioperative AKI (defined as AKI within the first 7 postoperative days) was observed more often in the DCD group (61%; DBD, 40%; and LDLT, 44%; P = 0.01)	Perioperative AKI associated with DCDLT. No significant differences in stage 3 AKI per RIFLE, AKI recovery, and progression to CKD. Patient survival was significantly lower in OLTx recipients who received DCD or DBD organs and required perioperative RRT in multivariate analysis (HR = 7.90; 95%CI: 4.51-13.83; P < 0.001)

GFR: Glomerular filtration rate; RR: Relative risk; CKD: Chronic kidney disease; mGFR: Measured glomerular filtration rate; BSA: Body surface area; ESKD: End stage kidney disease; CI: Confidence interval; AKI: Acute kidney injury; BMI: Body mass index; RRT: Renal replacement therapy; ESRD: End stage renal disease; Cr: Creatinine; CRF: Chronic renal failure; CI: Confidence interval; OR: Odds ratio; OLTx: Orthotopic liver transplant; CMV:

Cytomegalovirus; HR: Hazard ratio; aOR: Adjusted odds ratio; DCD: Donation after circulatory death; DBD: Donation after brain death; LDLT: Living donor liver transplantation; DCDLT: Donation after circulatory death liver transplantation; RIFLE: Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease.

following: 45% at year 1, 71% at year 5 and 83% at year 10. In their multivariable logistic regression model for decrease in eGFR to < 45 mL/min/1.73 m^2 at 3 years, they found the following significant risk factors: Post-operative RRT for AKI, P < 0.001; pre-transplant diabetes (P = 0.005); increasing recipient age, (P < 0.001); female recipient (P = 0.029) and female donor (P = 0.04). Interestingly cyclosporine regimen was not significantly associated with CKD development progression. In their analysis of the Planning and Research Cooperative database, which included 141 OHTs, Wyatt and Arons[31] observed that postoperative AKI, especially that requiring RRT, was associated with increased mortality (aOR = 8.96, 95%CI: 1.75-45.80, P = 0.008).

As previously described, progressive CKD is common after heart transplantation. Similar to other NKSOT, perioperative/early AKI incites CKD and increased mortality. Modifiable risk factors exist in addition to those inherent to heart failure and subsequent transplantation. Though studies have mixed results, recipient age (as modified by selection/organ allocation), pre-transplant diabetes, as well as elevated CNI levels are potentially modifiable. Moreover, several of the risk factors described by Boyle *et al*[14] such as low pre-transplant albumin, lower preoperative hematocrit are perhaps biomarkers of frailty, malnutrition and may suggest a role for "pre-habilitation" to bolster nutrition, frailty, anemia preoperatively in hopes of abating AKI and future adverse renal and patient outcomes in heart transplantation. These studies are abridged in Table 3.

KIDNEY DISEASE AFTER LUNG TRANSPLANTATION

Lung transplantation shares many parallels with heart transplantation in terms of kidney disease. For one, end stage lung disease is a debilitating, profound state of illness rendering GFR estimations difficult due to the toll chronic lung disease exerts. As described previously, characteristics inherent to thoracic transplantation predispose lung transplant recipients to AKI[3]. Below are studies chronicling kidney disease after lung transplantation.

In their examination of SRTR, Ojo *et al*[2] observed a 2.9% incidence of CKD IV/V at 12 mo and 15.8% incidence of GFR < 30 mL/min/1.73 m^2 at 5 years post lung transplant. Rocha *et al*[41] examined 296 lung transplant recipients whereby they observed an overall AKI rate of 56% (n = 166). 8% of those with AKI required RRT (n = 23). AKI predictors included the following in multivariate analysis: Baseline GFR (OR = 0.98, 95%CI: 0.96-0.99, P = 0.012), pulmonary diagnosis other than chronic obstructive pulmonary disease (OR = 6.80, 95%CI: 1.5-30.89, P = 0.013), mechanical ventilation > 1 d (OR = 6.16, 95%CI: 1.70-22.24, P = 0.006) and parenteral amphotericin B use (OR = 3.04, 95%CI: 1.03-8.98, P = 0.045). Patient survival was significantly impacted both by AKI and AKI requiring RRT with one-year patient survival of 92.3%, 81.8% and 21.7% in the no AKI, AKI sans RRT and AKI requiring RRT subgroups, respectively (P < 0.0001). This relationship was observed at 5 (61%, 58% and 13%) and 10 years (59%, 55% and 13%) as well. Single lung transplant (HR = 1.78, 95%CI: 1.24-2.55, P = 0.0018) and AKI requiring RRT (HR = 6.77, 95%CI: 4.00-11.44, P < 0.0001) were independent variables associated with increased mortality in multivariate Cox proportional-hazards regression. In their prospective trial examining mGFRs in lung transplant recipients, Broekroelofs *et al*[42] identified an association between pulmonary diagnosis and GFR loss. A nearly 50% decrease in mGFR at 36 mo post transplantation (100 mL/min pre-transplant *vs* 51 mL/min at 36 mo post-transplant) was observed in lung transplant recipients. The highest median loss of GFR occurred in cystic fibrosis (CF) recipients (-10 mL/min/year, range -14 to -6 mL/min/year), compared to those who were transplanted for emphysema (-6 mL/min/year, range -27 to +12 mL/min/year) and pulmonary hypertension (-1 mL/min/year, range -6 to +7 mL/min/year). This is a relatively consistent finding as described in other studies with CF lung transplant recipients having more severe kidney complications than lung transplant recipients with lung failure from pulmonary hypertension[34,43].

Mason *et al*[44] retrospectively reviewed their 425 lung transplant recipients to describe dialysis after transplantation. In examining need for dialysis, they determined a prevalence 0.6%, 4%, 9%, 13%, 16% and 19%, at 30 d and 1, 3, 5, 7 and 9 years post-transplant. Significant risk factors associated with dialysis were the following: Lower creatinine clearance (P = 0.03) and greater recipient height (P = 0.0002). Notably, donor blood type O (P = 0.001) and head trauma as donor cause of death (P = 0.01) decreased risk for dialysis need. Mortality risk after ESRD was 100%, 17% and 3.1% per year at 3 mo, 1 year and 3 years, respectively. Median survival after starting dialysis was 5 mo. In their single center retrospective study, Canales *et al*[45] examined 186 lung transplant recipients (plus 33 heart-lung transplant recipients), looking for predictors of time to doubling SCr and ESKD. A major takeaway observed from their trial was the prevalence of CKD, particularly advanced CKD at 1 and 7 years compared to the NHANES III cohort. At 1 and 7 years, the prevalence of CKD IV (81 and 95 times) and

Table 3 Kidney disease after heart

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	24024	Systemic atherosclerosis, renal hypoperfusion from cardiorenal disease	Perioperative acute renal failure rate of 20%-30% of heart transplant recipients with a 10.9% CKD IV/V rate at 60 mo post-transplant
Cantarovich *et al*[39]	233	30% in CrCl between 1 mo and 3 mo independently predicted the need for chronic dialysis (P = 0.04) and time to first CrCl < 30 mL/min at > 1 yr after transplant (P = 0.01)	Early renal dysfunction predicts poor long term kidney outcomes
Rubel *et al*[40]	370	Multivariate analysis: GFR < 50 mL/min (HR = 3.69, P = 0.024); high mean cyclosporine trough in the first 6 mo (HR = 5.10, P = 0.0059); and presence of diabetes (HR = 3.53, P = 0.021)	Mean eGFR fell 24% at year one, 23% of patients developed a 50% reduction in GFR by year 3, and that 20% of the cohort developed ESRD at 10 yr post-transplant
Lindelöw *et al*[37]	151	Age	The average preoperative GFR of 66 ± 17 mL/min per 1.73 m^2 declined to 52 ± 19 (P < 0.0001) at 1 yr. From 2 yr to 9 yr after heart transplantation, overall kidney function remained fairly stable (all P > 0.05)
Boyle *et al*[14]	756	Insulin dependent diabetes (P = 0.019) and prior cardiac surgery (P = 0.014)	AKI rate of 5.8% (44 of 756); they observed a 50% (22/44) mortality rate in OHTs with AKI requiring dialysis compared to those who did not have AKI (1.4%, 10/712)
Hamour *et al*[8]	352	Post-operative RRT for AKI, P < 0.001; pretransplant diabetes (P = 0.005); increasing recipient age, (P < 0.001); female recipient, (P = 0.029) and female donor (P = 0.04) associated for progression to eGFR < 45. CSA not associated	Cumulative probability of eGFR < 45 mL/min/1.73 m^2 over time was the following: 45% at year 1, 71% at year 5 and 83% at year 10
Wyatt and Arons[31]	141		Postoperative AKI, especially that requiring RRT, was associated with increased mortality (aOR = 8.96, 95%CI: 1.75-45.80, P = 0.008)

CKD: Chronic kidney disease; CrCl: Creatinine clearance; GFR: Glomerular filtration rate; HR: Hazard ratio; eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; AKI: Acute kidney injury; OHT: Orthotopic heart transplant; RRT: Renal replacement therapy; CSA: Cyclosporine; CI: Confidence interval; aOR: Adjusted odds ratio.

V (10 and 20 times) were substantially higher in the lung, heart-lung transplant recipients than the general population as described by NHANES III. In their multivariate step model, older age, lower 1 mo GFR and CSA use in the first 6 mo were associated with faster doubling of SCr (all P < 0.05). AKI episodes (RR = 1.6, 95%CI: 1.2-2.0, P < 0.001), and older age at transplant (RR = 1.02, 95%CI: 1.008-1.04), P = 0.004) were significant predictors of death. Ishani *et al*[9] in their study of lung, heart-lung transplant recipients found that diastolic blood pressure greater than 90 mmHg (RR = 1.30, 95%CI: 1.05-1.60, P = 0.02), 1 mo post-transplant creatinine (RR = 1.28, 95%CI: 1.02-1.70, P =0.03) were associated with increased risk to time to doubling baseline SCr. Cause of lung failure, age at transplant, nor rejection were significantly associated. Tacrolimus use in the first 6 mo after transplant was associated with a decreased in the risk for doubling time of SCr (RR = 0.38, 95%CI: 0.19-0.79, P = 0.0009). Paradela de la Morena *et al*[46] retrospectively evaluated 161 lung transplant recipients at their center. They found that 68.6% of the cohort developed CKD. On multivariate analysis, older age (OR = 2.0; P < 0.001) and CMV infection (OR = 2.2; P = 0.045) were associated with CKD development. CKD at 1 year was associated with increased mortality compared to those without CKD (P = 0.001).

Kidney disease, both in terms of AKI and CKD, is common in lung transplant recipients. There appear to be certain risk factors associated with CKD development, namely lower pre- and early post-transplant creatinine, AKI, end stage lung disease from CF, and older recipient age. There appears to be a subset of lung transplant recipients at higher risk for progressive CKD. Early transplant nephrology referral may be of benefit for these patients. Despite CKD commonly manifesting post-lung transplant, modifiable/preventable risk factors including diastolic blood pressure and CMV infection are potential targets in terms of blood pressure optimization and prophylaxis strategies to mitigate CKD development. In summary, early multidisciplinary care and co-management from transplant pulmonology and nephrology is vital for appropriate patient selection and continued management of kidney disease in lung transplant recipients. These studies are summarized in Table 4.

KIDNEY DISEASE AFTER INTESTINAL TRANSPLANTATION

Kidney disease after IT is understudied due to the rarity of IT. As described in OPTN/SRTR annual report, 104 ITs were performed in 2018[47]. We will highlight pertinent studies in the field of intestinal

Table 4 Kidney disease after lung

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Ojo *et al*[2]	7644		2.9% incidence of CKD IV/V at 12 mo and 15.8% incidence of GFR < 30 mL/min/1.73 m^2 at 5 yr post lung transplant
Rocha *et al*[41]	296	AKI: Baseline GFR (OR = 0.98, 95%CI: 0.96-0.99, *P* = 0.012), pulmonary diagnosis other than COPD (OR = 6.80, 95%CI: 1.5-30.89, *P* = 0.013), mechanical ventilation > 1 d (OR = 6.16, 95%CI: 1.70-22.24, *P* = 0.006) and parenteral amphotericin B use (OR = 3.04, 95%CI: 1.03-8.98, *P* = 0.045)	AKI rate of 56% (*n* = 166). Patient survival by AKI and AKI requiring RRT with one-year survival no AKI = 92.3%, AKI w/o RRT = 81.8% and AKI w/RRT 21.7% (*P* < 0.0001). At 5 (61%, 58% and 13%) and 10 yr (59%, 55% and 13%). Single lung transplant (HR = 1.78, 95%CI: 1.24-2.55, *P* = 0.0018) and AKI requiring RRT (HR = 6.77, 95%CI: 4.00-11.44, *P* < 0.0001) associated with mortality
Broekroelofs *et al*[42]	57	Highest median GFR in the CF recipients (-10 mL/min/year, range -14 to -6 mL/min/year), compared to those w/emphysema (-6 mL/min/year, range -27 to +12 mL/min/year) and pHTN (-1 mL/min/year, range -6 to +7 mL/min/year)	Nearly 50% decrease in mGFR at 36 mo post transplantation (100 mL/min pre-transplant *vs* 51 mL/min at 36 mo post-transplant)
Mason *et al*[44]	425	Lower creatinine clearance (*P* = 0.03) and greater recipient height (*P* = 0.0002)	HD prevalence = 0.6%, 4%, 9%, 13%, 16% and 19%, at 30 d and 1, 3, 5, 7 and 9 yr post-transplant. Mortality risk after ESRD was 100%, 17% and 3.1% per year at 3 mo, 1 yr and 3 yr, respectively. In other words, median survival after starting dialysis was 5 mo
Canales *et al*[45]	186	Older age, lower 1 mo GFR and CSA use in the first 6 mo were associated with faster doubling of serum creatinine (all *P* < 0.05)	At 1 and 7 yr, the prevalence of CKD IV (81 and 95 times) and V (10 and 20 times) were substantially higher in the lung, heart-lung transplant recipients than the general population as described by NHANES III; AKI episodes (RR = 1.6, 95%CI: 1.2-2.0, *P* < 0.001), and older age at transplant (RR = 1.02, 95%CI: 1.008-1.04), *P* = 0.004) were significant predictors of death
Ishani *et al*[9]	186	DBP than 90 mmHg (RR = 1.30, 95%CI: 1.05-1.60, *P* = 0.02), 1 mo post-transplant Cr (RR = 1.28, 95%CI: 1.02-1.70, *P* =0.03) were associated with increased risk to time to doubling baseline SCr	Cause of lung failure, age at transplant, nor rejection were significantly associated with doubling of Cr. Tacrolimus use in the first 6 mo after transplant was associated with a decreased in the risk for doubling time of SCr (RR = 0.38, 95%CI: 0.19-0.79, *P* = 0.0009)
Paradela de la Morena *et al*[46]	161	Older age (OR = 2.0; *P* < 0.001) and CMV infection (OR = 2.2; *P* = 0.045)	68.6% of the cohort developed CKD; CKD at 1 yr was associated with increased mortality compared to those without CKD (*P* = 0.001)

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; Cr: Creatinine; COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; OR: Odds ratio; AKI: Acute kidney injury; RRT: Renal replacement therapy; HR: Hazard ratio; CF: Cystic fibrosis; pHTN: Portal hypertension; mGFR: Measured glomerular filtration rate; ESRD: End stage renal disease; CSA: Cyclosporine; AKI: Acute kidney injury; RR: Relative risk; CI: Confidence interval; DBP: Diastolic blood pressure; SCr: Serum creatinine; CMV: Cytomegalovirus.

transplantation discussing kidney disease. Huard *et al*[48] in their evaluation of SRTR data of 843 IT recipients, assessed incidence, risk factors, and impact on survival of severe CKD, which they defined as GFR < 30 mL/min/1.73 m^2 in IT recipients. They observed a cumulative incidence of severe CKD of 3.2%, 25.1%, and 54.1% 1, 5 and 10 years after IT, respectively. Female sex (HR = 1.34), older age (HR = 1.38/10 year increment), catheter-related sepsis (HR = 1.58), steroid maintenance immunosuppression (HR = 1.50), graft failure (HR = 1.76), acute cellular rejection (HR = 1.64), prolonged requirement for IV fluids (HR = 2.12) or total parenteral nutrition (HR = 1.94), and diabetes (HR = 1.54) were associated with severe CKD. Individuals with higher GFR at the time of IT (HR = 0.92 for each 10 mL/min/1.73 m^2 increment), and those receiving induction therapies (HR = 0.47) or tacrolimus (HR = 0.52) showed lower hazards of severe CKD. In adjusted analysis, severe CKD was associated with a significantly higher hazard of death (HR = 6.20). Herlenius *et al*[28] studied 10 patients after IT *via* serial measurements of GFR. They performed measurements at baseline, 3 mo post transplantation, and yearly thereafter. Median follow-up time for the cohort was 1.5 years (0.5-7.8 years). Tacrolimus was discontinued in four patients because of impaired renal function. These four patients were switched to sirolimus at 11, 18, 24, and 40 mo post transplantation. Median baseline GFR was 67 (22-114) mL/min/1.73 m^2 (22-114). In the adult patients, GFR 3 mo post transplantation had decreased to 50% of the baseline. At 1 year, median GFR in the adult patients was reduced by 72% (*n* = 5). Two patients developed renal failure within the first year and required hemodialysis. Notably, eGFR *via* MDRD formula consistently overestimated GFR by approximately 30% compared with the mGFR. Ueno *et al*[49] examined 24 adult IT recipients with at least 2 years survival in the tacrolimus-based era. They measured kidney function *via* 6 mo averages of SCr along with calculating creatinine clearance per the Cockcroft-Gault formula. Post-transplant mean CrCl was significantly lower at 2 years compared to baseline (49.6 mL/min/1.73 m^2 *vs* 114 mL/min/1.73 m^2, *P* < 0.0001). The authors also evaluated the role of tacrolimus by cumulative level, which they defined as the sum of weekly average tacrolimus levels (ng·day/mL). They found that

recipients with cumulative tacrolimus levels > 4500 ng ng·day/mL had significantly decreased CrCl at 2 years compared to those with cumulative tacrolimus levels less than 4500 ng ng·day/mL (P = 0.006).

Kidney disease after IT is understudied. Even so, there are key takeaways that can be derived from the data to date. In this moribund population, perhaps mGFR and/or cystatin C could be used adjunctively with typical estimating equations to better characterize kidney function and guide nephrology referral/management. One can surmise that a subset of patients *i.e.*, older, diabetic IT recipients, with persistent IV fluid needs could benefit from early transplant nephrology care. These results are described in Table 5.

DIAGNOSIS AND MANAGEMENT OF CKD POST NON-KIDNEY SOT

Uncertainty regarding kidney function is an overarching theme surrounding kidney disease in NKSOT. While mGFR would be the ideal, most accurate/precise test of function, it is impractical, expensive, and not widely available. As previously described, CKD-EPI and MDRD in some contexts appear to be acceptable eGFR equations that can aid in screening for and diagnosis of CKD. Bloom *et al*[3] endorse using MDRD, acknowledging that it is conservative *i.e.,* would be sensitive in that it has better capture of SOT recipients with permissible false-positivity. As with any test, patient selection is of utmost importance, in both a macro and micro sense *i.e.,* a test primarily based on clearance of a muscle waste product will be flawed in those with significant malnutrition, sarcopenia.

Nephrologists are aptly suited to manage kidney disease in NKSOT as the modifiable risk factors leading to progressive CKD are shared across SOT recipients and the general public alike. As is well described in Bloom *et al*'s seminal work, CKD management after NKSOT is founded on the same tenets of CKD management generally[3]. Fundamentally, CKD after NKSOT is CKD management + CNI considerations. In other words, the same diseases processes that effect native kidney function remain relevant after SOT. The literature/guidelines describing CKD management are well described and summarizing them is beyond the scope of this review[1,12,50]. The impact of therapies and management strategies for risk factors leading to CKD in NKSOT is understudied. In the following sections, we will highlight salient points on CKD management.

Proteinuria

Renin angiotensin aldosterone system (RAAS) blockade for proteinuria management in transplant recipients is extrapolated from the non-transplant CKD literature with limited direct evidence. Most research in this domain has occurred in kidney transplant. Knoll *et al*[51] attempted to answer this question in the context of kidney transplant with a randomized controlled trial. However, as is aptly put by Toto[52] in his comment from Nature Reviews Nephrology, this study did not "settle the controversy surrounding the use of RAAS blockade in the renal transplant population". Though proteinuria management in non-kidney SOT is understudied, RAAS blockade appears to be a reasonable approach not only for treating proteinuria, but also for those with significant risk factors for heart disease given their cardioprotective benefit[53,54].

CNI use/minimization strategies

With CNIs as possible potentiators of CKD, CNI-sparing/minimizing maintenance immunosuppression regimens have been proposed as a renoprotective management strategy. There is a large body of evidence examining CNI minimization in NKSOT, which we will discuss below. With the advent of tacrolimus and results of ELITE-SYMPHONY, tacrolimus has ousted cyclosporine CNI-wise, as tacrolimus appears to have a less nephrotoxic profile[55]. Mechanistically, this may be due to less renal vasoconstriction as has been demonstrated in both *in vivo* and *in vitro* studies[3,56,57]. Pancreas transplant wise, limited evidence exists supporting CNI minimization or sparing. While Kandula *et al*[58] compared tacrolimus-sirolimus based regimen to tacrolimus-mycophenolate immunosuppression in PTA recipients, mean tacrolimus levels were similar across groups at all time points.

In the context of liver transplantation, there is an expansive body of literature supporting the use of CNI-sparing or minimization therapy with sirolimus and mycophenolate[59-64]. For heart transplant recipients, CNI minimization/sparing has been shown as a viable immunosuppression approach. Cornu *et al*[65] in their systematic review and meta-analysis of eight studies on CNI minimization showed that creatinine clearance was preserved in individuals with impaired renal function, which they defined as eGFR < 60 mL/min, at 6 mo [+12.23 (+5.26, +18.82) mL·min^{-1}, P = 0.0003). Although longer term benefit was not shown in this study, CNI minimization strategies were not associated with increased rejection, mortality or adverse events compared to the standard CNI regimen approach (all P > 0.05). As is aptly described by Zuckermann *et al*[66], the use of induction in OHT recipients has "provided immunosuppressive cover" to allow for the following approaches: CNI minimization and delayed CNI introduction whilst kidney function is recovering post- heart transplantation[66-70].

In lung transplant recipients, evidence exists supporting the use of CNI sparing/minimization regimens. Högerle *et al*[71] in their recent review describe a following approaches including basiliximab induction, which showed favorable short term renal outcomes. They also noted CNI minimization

Table 5 Kidney disease after intestinal

Ref.	Total number of patients, *n*	Risk factors associated with kidney disease	Study conclusion
Huard *et al* [48]	843	Female sex (HR = 1.34), older age (HR = 1.38/10 yr increment), catheter-related sepsis (HR = 1.58), steroid maintenance immunosuppression (HR = 1.50), graft failure (HR = 1.76), ACR (HR = 1.64), prolonged requirement for IV fluids (HR = 2.12) or TPN (HR = 1.94), and diabetes (HR = 1.54)	Cumulative incidence of severe CKD of 3.2%, 25.1%, and 54.1% 1, 5 and 10 yr after intestinal transplant; in adjusted analysis, severe CKD was associated with a significantly higher hazard of death (HR = 6.20)
Herlenius *et al*[76]	10		In the adult patients, GFR 3 mo post transplantation had decreased to 50% of the baseline. At 1 yr, median GFR in the adult patients was reduced by 72% (n = 5). Two patients developed renal failure within the first year and required hemodialysis
Ueno *et al* [49]	24	Cumulative tacrolimus levels > 4500ng ng·day/mL associated with significantly decreased creatinine clearance at 2 yr (P = 0.006)	Post-transplant mean creatinine clearance was significantly lower at 2 yr compared to baseline (49.6 mL/min/1.73 m^2 *vs* 114 mL/min/1.73 m^2, P < 0.0001)

HR: Hazard ratio; ACR: Acute cellular rejection; TPN: Total parenteral nutrition; CKD: Chronic kidney disease; GFR: Glomerular filtration rate.

approaches with tacrolimus/mammalian target of rapamycin (mTOR) inhibitor combinations which showed improved renal function with comparable allograft/patient survival. Notably, mTOR use was associated with increased wound complications, proteinuria, hypertension, post-transplant diabetes and dyslipidemia. They also highlighted CNI minimization approaches with mTOR use instead of anti-metabolite immunosuppression. Strueber *et al*[72] examined 190 lung transplant recipients randomized to everolimus or mycophenolate mofetil 1 mo post-transplant. Though results limited due to lack of completion of the study protocol, rejection and infectious complications were lower in the everolimus group of whom 20%-28% of recipients were also on reduced CNI doses. In a 3-year multicenter randomized prospective study, Glanville *et al*[73] did not show significant differences in creatinine at 3 years comparing lung transplant recipients on mycophenolate sodium *vs* everolimus. While the authors stated that they utilized reduced 2-h post-dose CSA levels in the everolimus group and that "most levels measured were within pre-specified target ranges", granular data describing CNI levels in these cohorts is lacking. Further in support of CNI minimization/sparing is a study by Stephany *et al*[74], who observed improved GFR durable out to 18 mo for lung transplant recipients converted to sirolimus-based immunosuppression, with the greatest benefit incurred to lung transplant recipients without proteinuria.

In IT recipients, the benefit of CNI minimization/sparing strategies appears to be limited in terms of preserving renal function. Rutter *et al*[75] in their single center study demonstrated significant decline in renal function irrespective of tacrolimus exposure. Herlenius *et al*[76], in their study of 10 IT recipients, noted that 4 patients were switched from CNI to sirolimus based regimen. Of these, one developed renal failure leading to hemodialysis, one died due to hemorrhage with CKD IV at the time of death, and the other 2 had "stable GFR" at 2 and 3 years post conversion without developing rejection or intestinal allograft failure. Based on the initial successes of the BENEFIT and BENEFIT-EXT trials comparing belatacept to cyclosporine in kidney transplant recipients, belatacept in lieu of CNI or with CNI minimization has been proposed as a novel immunosuppression strategy for NKSOT[77,78]. There is mounting research describing CNI-minimizing or sparing approaches using belatacept in OHT recipients[79], lung transplant recipients[80], and PTA recipients[81,82]. More robust studies *e.g.*, randomized control trials with longer follow-up are needed to better understand outcomes related to belatacept in NKSOT as these early studies are limited in design (case-series, retrospective studies) and follow up.

An important caveat to belatacept use is that of liver transplantation. As demonstrated by Klintmalm *et al*[83] in their phase II trial and Schwarz *et al*[84], concerns exist regarding allograft function and safety with belatacept. Though results from a study conducted by LaMattina *et al*[85] were more favorable, these are limited due to small numbers as well as the patients being converted back to a CNI-based regimen. Thus, belatacept use in liver transplantation is at most controversial. Additional studies sufficiently powered are needed to determine efficacy and safety of belatacept in liver transplant recipients.

Approaches to minimize CNI use *via* induction/maintenance immunosuppression appear promising in terms of preserving renal function. While these often incur adverse effects related to specific therapies *e.g.*, mTOR inhibitors, in several instances, they have not lead to decreased allograft or patient survival. Appropriate, sufficient CNI minimizing immunosuppression tailored to preserve renal function while also staving off rejection is achievable *via* multidisciplinary collaboration and dialogue between transplant experts across nonrenal organ systems and transplant nephrology.

Hypoalbuminemia

Low serum albumin appears to impact kidney function in NKSOT recipients. As described in their review, Kim *et al*[86] note that hypoalbuminemia may indicate poor nutritional state, impact pharmacokinetics/pharmacodynamics, and/or represent an increased inflammatory state. As a relatively inexpensive, trackable biomarker, perhaps albumin and a goal albumin *e.g.*, greater than 3.0 g/dL could be a pre-transplant goal for the multi-disciplinary team including nutritionist/dieticians to help patients with pre-transplant CKD with high risk for progression.

Nephrology referral/management considerations

The integration of nephrology care into dedicated NKSOT care throughout various stages of pre-, peri-, and post-transplantation is critical for diagnosis and management of kidney disease. Wiseman[12], in his recent review, provides substantive recommendations on timing/appropriateness of nephrology referral, based on KDIGO guidelines, and management considerations across transplant timepoints in tabular form. As has been described throughout this study, SOT recipients are a unique subset of patients with CKD that often progresses to ESKD necessitating RRT. This has led to the growing demand for kidney transplantation (KT) after solid organ transplantation which will be discussed subsequently.

KIDNEY AFTER SOLID ORGAN TRANSPLANTATION

Kidney after NKSOT is an emerging RRT for the SOT community[87]. Though this is a relatively comorbid population, they have: (1) Overcome perioperative risks associated organ transplantation; and (2) Tolerated prior induction/maintenance immunosuppression. For patients deemed candidates, KT is a viable therapy for advanced kidney disease after solid organ transplantation. Cassuto *et al*[88], in their study examining the survival benefit of KT for kidney after heart (KAH), kidney after lung (KALu), and kidney after liver (KALi) in addition to repeat KT recipients. While they observed a survival benefit for kidney after SOT compared to the waitlist population as whole for prior heart, liver recipients, this was not the case for KALu recipients who had a 61% greater risk of death *vs* those on the waitlist for KT generally (HR = 1.61, 95%CI: 1.09-2.38, P = 0.017)[86]. El-Husseini *et al*[89] examined outcomes in their 15 year analysis of national data from the United Network of Organ Sharing (UNOS) database whereby they showed inferior median graft survival (7.8 years, 95%CI: 7.3-8.2) and patient survival (8.3 years, 95%CI: 7.9-8.3) compared to primary kidney (graft survival 10.7, 95%CI: 10.6-10.8; patient survival 12.2, 95%CI: 12.1-12.3) and repeat kidney (graft survival 10.5, 95%CI: 10.2-10.7; patient survival 13.2 years, 95%CI: 12.9-13.5) (P < 0.001). In subgroup analysis, the graft and patient median survival time and 1, 5, and 10 year survival rates for KALi, KAH, and KALu were comparable. After adjustment, KALu transplant was associated with increased risk of graft loss compared to primary KT (HR = 2.123, 95%CI: 1.516-2.974, P < 0.001) and increased risk of death (HR = 3.309, 95%CI: 2.395-4.572, P < 0.001) compared to the other kidney after SOT subgroups[87]. Lonze *et al*[90] looked at outcomes in KAH or KALu transplant recipients reported to UNOS and found that 5-year graft survival however was lower than for primary KT recipients (61% KAH *vs* 73.8% primary kidney, P < 0.001; 62.6% KALu *vs* 82.9% primary kidney, P < 0.001). Notably, death-censored graft survival (DCGS) was comparable to primary kidney transplant (84.9% KAH *vs* 88.2% primary kidney, P = 0.1; 87.6% KALu *vs* 91.8% primary kidney, P = 0.6). Moreover, renal transplantation incurred a survival benefit compared to dialysis after heart transplantation (HR = 0.57, 95%CI: 0.45-0.74, P < 0.001) and lung transplantation (HR = 0.46, 95%CI: 0.30-0.71, P < 0.001). Haugen *et al*[91] sought to answer if the survival benefit of kidney after non-kidney SOT extended to older recipients (≥ 65 years of age). In their analysis of the SRTR, they found that while DCGS was comparable to older kidney transplant recipients [adjusted HR (aHR) = 1.13, 95%CI: 0.93-1.37, P = 0.2], mortality was increased (aHR = 1.40, 95%CI: 1.28-1.54, P < 0.001). KT relative to no transplant lead to a survival benefit for NKSOT recipients (aHR = 0.47, 95%CI: 0.42-0.54, P < 0.001).

DISCUSSION

In this review, we abridged current literature describing kidney disease in NKSOT describing kidney disease in pancreas, heart, lung, liver, and IT recipients. We also discussed diagnosis, management and described the emerging RRT of kidney after NKSOT. Kidney disease after NKSOT is not one size fits all; although shared risk factors inherent to solid organ failure and the perioperative period exist, these are heterogeneous populations that experience AKI and CKD at varying degrees and rates. Chronic renal dysfunction after SOT is a nascent area of study due to prolonged survival after NKSOT being a relatively recent development in the field. More questions than answers persist on crucial management aspects: At what level of kidney impairment should we consider combined kidney-nonrenal SOT? What is the role of mGFR? Kidney biopsy? Cystatin C? Should the degree of kidney impairment influence maintenance immunosuppression *i.e.*, CNI use? What is the best way to manage proteinuria in this

population? Are their roles for novel biomarkers for predicting AKI recovery or CKD progression? Ought sodium-glucose cotransporter-2 inhibitors be used in this population?

The allocation dilemma weighs heavier in the broader context of the entire waitlist. Decisions regarding kidney after solid organ transplantation or even combined kidney-SOT with the knowledge that maximization of a limited resource, based on years of survival gained from KT, is not in this population presents serious ethical challenges in terms of justice, defying a utilitarian approach. Clinicians and researchers alike spanning multiple disciplines including physician-scientists, primary care providers, general nephrologists, transplant surgeons, non-kidney transplant specialists, as well as transplant nephrologists are tasked and capable of ushering in a new era of kidney disease prevention, diagnosis, management, preservation of kidney function, and when possible subsequent KT. With these efforts promoting robust, well-designed, multi-center prospective randomized controlled trials, hope exists towards deciphering the ever-present ambiguities surrounding kidney disease in non-renal organ transplantation and improving future patient, kidney, and allograft outcomes.

CONCLUSION

Kidney disease after SOT is an incipient condition demanding further inquiry. While some truths have been revealed about this chronic disease, as we have aimed to describe in this review, continued multidisciplinary efforts are needed more than ever to combat this threat to patient and allograft survival.

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Country/Territory of origin: United States

ORCID number: Kurtis J Swanson 0000-0001-5952-9054.

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ORIGINAL ARTICLE

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Emergency department visits and hospital admissions in kidney transplant recipients during the COVID-19 pandemic: A hospital-based study

Wachira Wongtanasarasin, Phichayut Phinyo

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Wachira Wongtanasarasin, Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Wachira Wongtanasarasin, Department of Emergency Medicine, UC Davis School of Medicine, Sacramento, CA 95817, United States

Phichayut Phinyo, Department of Family Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Phichayut Phinyo, Center for Clinical Epidemiology and Clinical Statistics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

Corresponding author: Wachira Wongtanasarasin, MD, Attending Doctor, Department of Emergency Medicine, Faculty of Medicine, Chiang Mai University, 110 Intavarorot Street, Sriphum, Chiang Mai 50200, Thailand. wachir_w@hotmail.com

Abstract

BACKGROUND

Several studies have demonstrated that the coronavirus disease 2019 (COVID-19) has affected daily living and the healthcare system. No previous study has described the consequences of COVID-19 on emergency department (ED) visits and hospital admission among kidney transplant (KT) recipients.

AIM

To investigate the impact of the COVID-19 pandemic on ED visits and hospital admissions within 1 year in patients who underwent KT in Thailand.

METHODS

We conducted a retrospective study at a university hospital in Thailand. We reviewed the hospital records of KT patients who visited the ED during the outbreak of COVID-19 (from January 2020 to December 2021). We used the previous 2 years as the control period in the analysis. We obtained baseline demographics and ED visit characteristics for each KT patient. The outcomes of interest were ED visits and ED visits leading to hospital admission within the 1st year following a KT. The rate of ED visits and ED visits leading to hospital admissions between the two periods were compared using the stratified Cox

proportional hazards model.

RESULTS

A total of 263 patients were included in this study: 112 during the COVID-19 period and 151 during the control period. There were 34 and 41 ED visits after KT in the COVID-19 and control periods, respectively. The rate of first ED visit at 1 year was not significantly different in the COVID-19 period, compared with the control period [hazard ratio (HR) = 1.02, 95% confidence interval (CI): 0.54-1.92; *P* = 0.96]. The hospital admission rate was similar between periods (HR = 0.92, 95%CI: 0.50-1.69; *P* = 0.78).

CONCLUSION

ED visits and hospital admissions within the 1st year in KT recipients were not affected by the COVID-19 pandemic. Despite these findings, we believe that communication between post-KT patients and healthcare providers is essential to highlight the importance of prompt ED visits for acute health conditions, particularly in post-KT patients.

Key Words: Emergency department visit; Hospital admission; Kidney transplant; COVID-19; Acute health conditions

Core Tip: Coronavirus disease 2019 (COVID-19) affects kidney transplant (KT) recipients in terms of hospital admission rates. This study showed that despite emergency department (ED) visits remaining unchanged during the COVID-19 pandemic, hospital admission rates increased. Although we could not establish the cause-effect relationship of these changes, we encourage healthcare providers to provide post-KT patients recommendations to visit ED promptly for acute health conditions.

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INTRODUCTION

In the United States, there were approximately 143 million total visits to an emergency department (ED) in 2018[1]. Over the last two decades, the rate of ED visits has increased, exceeding what could be accounted for by population growth[1]. Multiple factors, including extremes of age, women, public insurance, minority race/ethnicity, and country region, are associated with higher rates of ED visits in the general population[2]. Recently, there has been a significant increase in acute care delivery following hospitalization[3,4]. Acute care after hospital treatment is considered an indication of poor quality of care in some contexts, including kidney transplant (KT) patients[4,5]. Patients with end-stage renal disease (ESRD) account for 7.1% of total Medicare expenditures in the United States despite accounting for only 0.9% of Medicare treatments[6,7]. Patients with ESRD have visited the ED at a 6-fold higher rate than the general population; however, most previous studies excluded KT patients, who account for a growing proportion (around 22.8%) of prevalent ESRD patients[7]. The long-term advantages of KT are well documented and include improved survival and quality of life compared to dialysis[8,9]. On the other hand, the management of patients after KT is complex and resource-intensive, necessitating extensive care coordination, frequent laboratory monitoring, and ongoing patient engagement[9,10]. Furthermore, KT recipients frequently have multiple comorbidities, which complicates their care[11,12].

In recent years, coronavirus disease 2019 (COVID-19) has become the most critical disease and influenced human health across the globe[13]. This pandemic affects not only physical health but also mental health and well-being[14]. Transplant recipients, including KT patients, who are receiving immunosuppressive therapy are at the highest risk of severe illness, and as a result, are at a higher risk of an adverse outcome from COVID-19[15]. One of the unique aspects of the transplant recipient's life is that, in the post-operative phase, the patient should live in an isolated space, pay special attention to their living environment, and prefer a limited social life because of the immunosuppressive treatment involves immunosuppression in the patient[14]. A previous study demonstrated that the COVID-19 pandemic is associated with a significant reduction in average daily ED visits; however, the admission rates were increased[16]. This research investigated the effect of COVID-19 and the consequences on ED visits and admission rates among KT recipients within 1 year. In addition, this study assessed the

differences in the diagnoses of KT patients who visited an ED between COVID-19 and regular periods.

MATERIALS AND METHODS

Protocol

We conducted a single-center retrospective observational study at a university tertiary hospital between January 2018 and December 2021. The study protocol was approved by the institutional review board (IRB) of the Faculty of Medicine, Chiang Mai University (EXEMPTION-8745/65; Chiang Mai, Thailand). The IRB waived informed consent due to its retrospective design. Patient confidentiality was preserved by using anonymous health records. All methods employed in this study were performed following relevant guidelines and regulations.

Setting and study population

Maharaj Nakorn Chiang Mai Hospital (MNCMH) is a university hospital with 1500 beds, 151 intensive care units (ICUs) and sub-ICU beds, 28 operating rooms, and doctors from all subspecialties on duty. According to the Canadian Triage and Acuity Scale, the triage categorization is based on a five-level scale, ranging from blue (level 1, resuscitation) to white (level 5, non-urgency). Our ED provides a 24-h service with emergency physicians and skilled nurses. We categorized seven types of dispositions in the current study: ICU admission, general ward admission, observational unit admission, referral to another hospital, discharge, discharge against doctor's recommendation, and death.

We included all adult patients (age ≥ 18 years) who underwent KT at MNCMH between January 2017 and December 2020. Patients who died in the hospital after KT before hospital discharge were excluded. We collected data only from KT patients who visited the ED of MNCMH within 1 year after the date of transplantation (between January 2018 and December 2021). Extreme outliers and high-volume ED visitors (KT patients using the ED more than ten times per year) were excluded from the study population and were not included in the study analysis.

Data collection

Data were collected through the electronic medical records and chart review. To assess risk factors for ED visits and admissions following KT, age, sex, donor types, insurance, and Charlson comorbidity index were collected. Specifically, for KT recipients who visited the ED within 1 year after transplantation, we collected the following data: (1) Time to first and any ED visit since transplantation; (2) Triage level; (3) Total ED time; (4) Type of disposition; and (5) Invasive procedures during ED stay, which were intubation and cardiopulmonary resuscitation. The diagnosis for each ED visit is also collected using the International Classification of Diseases code.

Outcomes and data analysis

The primary outcome of interest was ED visits in the 1st year following KT. All recipients were followed until death or out of the study period. In-hospital deaths were retrieved from hospital medical records. Patients who did not visit ED at the end of the study period were considered censors. For patients with recurrent ED visits, the time to ED visit was defined as the time from the index date of transplantation to the date of the recurrent ED visit. The risk interval was, therefore, set as marginal since we assumed that the patients were at risk of any ED visit from the date of their transplantation.

Secondary outcomes included ED visits leading to hospital admissions following KT's 1st year. The number of ED visits and hospital admissions for any reason was calculated and compared between January 2018 and December 2019 and between January 2020 and December 2021. All responsible diagnoses from January 2018 to December 2019 were compared to all diagnoses from January 2020 to December 2021. We described continuous data using the mean ± SD for normally distributed variables. For skewed data, median and interquartile range were calculated. Categorical data were summarized using frequency and percentage. The independent *t*-test was used to compare continuous variables. For categorical variables, Fisher's exact probability test was performed. All tests were two-sided, with significance for all tests being determined as $P < 0.05$. All analyses were performed using STATA 16 (StataCorp, College Station, TX, United States).

For the primary analysis, the rate of ED visits within 1 year after KT was compared using the stratified Cox proportional hazards model. We presented two analytic approaches for each survival outcome, the rate of first ED visits and any ED visit after transplantation. For the rate of the first ED visit, we restricted the analysis to only the first ED visit, whereas all ED visits during the 1st year period were considered in the analysis of the rate of any ED visits. We employed the modeling method for recurrent events described by Kelly and Lim[17]. The risk interval was defined as the total time (marginal). We used a restricted risk set and assumed event-specific baseline hazards. To quantify the effect of the COVID-19 pandemic period on the control period, hazard ratios (HRs) were estimated from the stratified Cox's regression model. They were reported with 95% confidence intervals (CI) and *P* values. Kaplan-Meier curves were demonstrated, and a comparison of differences was made by the log-

rank test.

RESULTS

Patient characteristics

A total of 263 KT recipients were enrolled in this study, 112 in the COVID-19 period (underwent KT between January 2019 and December 2020) and 151 in the control period (underwent KT between January 2017 and December 2018). No recipient died during the follow-up period. Figure 1 illustrates the flow diagram of this study population. The mean ages were 45.5 ± 10.4 years and 43.7 ± 13.4 years for COVID-19 and control groups, respectively. Most of the participants received deceased donors. There were no significant differences in baseline demographics between the two periods (Table 1). Baseline demographics of KT patients who visited an ED during the study periods are summarized in Table 1.

ED visits

A total of 17.1% of KT recipients visited ED within 1 year after transplantation (15.3% in the COVID-19 period and 18.5% in the control period), accounting for 75 ED visits. The mean times to first ED visit since transplantations were 130.8 ± 106.2 and 120.6 ± 105.3 d for the COVID-19 and control periods, respectively. On the other hand, the rates of invasive procedures were similar among both periods. Table 2 summarizes the clinical variables of KT patients who presented to the ED within 1 year after transplantation. The rate of first ED visit at 1 year was not different in the COVID-19 period, compared with the control period when adjusting for confounding variables (HR = 1.02, 95%CI: 0.54-1.92; P = 0.96, Figure 2). Similarly, the rate of any ED visit in the following year was also not different between the two periods (HR = 1.24, 95%CI: 0.73-2.10; P = 0.43, Table 3). The five most responsible diagnoses are demonstrated in Table 4. Fever and abdominal pain were ranked first during the control period, while abdominal pain was the top diagnosis during COVID-19.

Hospital admissions

The admission rate in the COVID-19 period significantly decreased during the study period, compared with the control period (38.2% *vs* 65.9%; P = 0.02). In addition, the rate of any ED visit leading to hospital admission in the following year was also not different (HR = 0.92, 95%CI: 0.50-1.69; P = 0.78, Table 3).

DISCUSSION

In this retrospective study of KT patients, about one-sixth of KT recipients had at least 1 ED visit in the 1st year following transplantation. However, the rates of ED visits and hospital admissions were not affected by the impact of the COVID-19 pandemic. We also found that abdominal pain was responsible for most diagnoses across the COVID-19 and control periods. The impact of COVID-19 on ED visits and hospital admissions is demonstrated in several previous studies[15-17]. To the best of our knowledge, this is the first study investigating the effect of the COVID-19 pandemic on ED visits and admission rates among KT patients. KT recipients are usually advised to isolate themselves from the community because of the greater risk of being infected. Consequently, they might not visit the ED promptly. Our previous study showed that an average daily ED visit was significantly reduced during the COVID-19 pandemic, probably due to the fear of reaching COVID-19 in the hospital[15]. However, the present findings showed the difference. Despite the fear of contacting COVID-19, we found that ED visits by post-KT patients were not disturbed. A previous study demonstrated that KT recipients had a higher chance of a more severe course of COVID-19 infection than hemodialysis patients[18]; however, another finding showed that the severity and adverse outcomes were not different between KT recipients and those without for the COVID-19 infection[19].

Recently, telemedicine has become one of the most powerful strategies used to follow-up KT recipients[18,19]. Results from Yadav and Singh's study found that application of telemedicine in the transplant population enhances medication compliance, reduces hospitalization rates, and makes living donor evaluation convenient[19]. Telemedicine could be recommended as an alternative method, especially in the pandemic era, to avoid and reduce the rate of transmission in the hospital in KT population.

Although ED visits are not different between the two groups in our study, hospital admissions were higher for the COVID-19 group. This may reflect the natural consequence of inappropriate and untimely ED visits, resulting in a higher severity of diseases. We proposed that the reasons for these findings could be multifactorial. First, KT patients have a higher baseline chance of visiting ED than other patients. Previous studies have shown that acute care utilization in the following year after KT is relatively high[4,7,9]. In one retrospective study conducted in the United States, nearly half of KT

Table 1 Baseline demographics of kidney transplantation patients during the study period

Characteristics	COVID-19, *n* = 112	Control, *n* = 151	*P* value
Male sex, *n* (%)	70 (62.5)	93 (61.6)	0.92
Age at transplant, mean ± SD	45.5 ± 10.4	43.7 ± 13.4	0.23
Age at transplant, *n* (%)			0.20
< 40	35 (31.3)	55 (36.4)	
40-59	68 (6.7)	77 (51.0)	
≥ 60	9 (8.0)	19 (12.6)	
Donor type, *n* (%)			0.65
Living donor	41 (36.6)	59 (39.1)	
Deceased donor	71 (63.4)	92 (60.9)	
Insurance, *n* (%)			0.66
Universal coverage	24 (21.4)	56 (37.1)	
Social security scheme	33 (29.5)	40 (26.5)	
Government officer	55 (49.1)	55 (36.4)	
Charlson comorbidity index, mean ± SD	1.7 ± 1.5	1.8 ± 1.5	0.59

COVID-19: Coronavirus disease 2019.

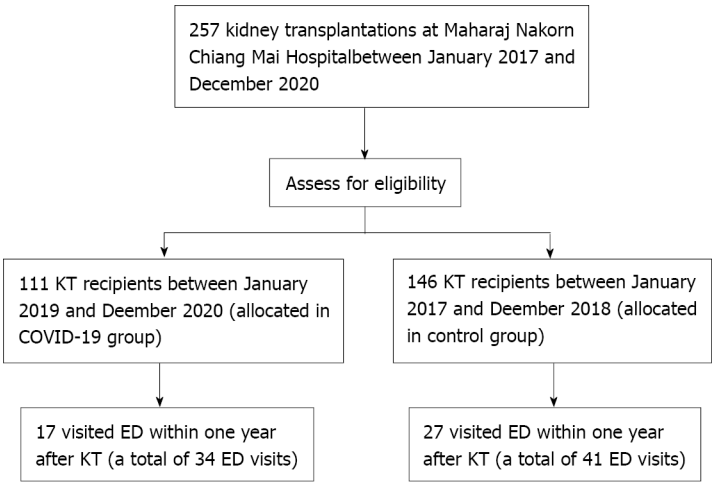

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Figure 1 Study flow. COVID-19: Coronavirus disease 2019; ED: Emergency department; KT: Kidney transplantation.

patients visited the ED within 1 year after KT[7]. Second, post-KT recipients are prescribed immunosuppressive agents. Usually, they are informed to seek medical evaluation even they have minor symptoms, such as low-grade fever or abdominal pain. Furthermore, fever and other unspecified symptoms could be one of the clinical features of COVID-19[20]. KT recipients might intend to visit ED as they considered themselves suspected of having this COVID-19 infection. Interestingly, our study found that hospital admissions were markedly increased in the COVID-19 group. Consistent with previous evidence, hospital admission during this disastrous period is likely higher than usual, mainly because of untimely and delayed ED visits[15].

Our findings regarding ED visits and admission rates during the COVID-19 pandemic may serve as a body of literature regarding the impact of COVID-19 in the various spectrum, including KT recipients. Not only the number of ED visits among post-KT patients were not less than the regular period, but also the admission rates were significantly high. Our data also suggest that clinicians and healthcare professionals should encourage KT recipients to visit EDs on time to reduce unfavorable outcomes.

Table 2 Clinical variables of kidney transplantation patients who presented to the emergency department within 1 year during the study period

Variables	COVID-19 (January 2020-December 2021), *n* = 34	Control (January 2018-December 2019), *n* = 41	*P* value
Time to first ED visit since transplantation in day, mean ± SD	130.8 ± 106.2	120.6 ± 105.3	0.88
Triage level, *n* (%)			0.71
Resuscitation	2 (5.9)	1 (2.4)	
Emergency	13 (38.2)	13 (31.7)	
Urgency	12 (35.3)	20 (48.8)	
Less urgency	5 (14.7)	6 (14.6)	
Non-urgency	2 (5.9)	1 (2.4)	
Total ED times in min, mean ± SD	275.8 ± 263.5	232.7 (120.6)	0.35
Total ED times in min, median (IQR)	210.5 (130-330)	222 (138-300)	0.35
Admission, *n* (%)	13 (38.2)	27 (65.9)	0.02
Type of disposition, *n* (%)			0.10
ICU admission	1 (2.9)	1 (2.4)	
General ward admission	12 (35.3)	25 (61.0)	
OU admission	0 (0)	1 (2.4)	
Referred	0 (0)	0 (0)	
Discharge	21 (61.8)	14 (34.2)	
Against advice	0 (0)	0 (0)	
Death at ED	0 (0)	0 (0)	
Intubation, *n* (%)	0 (0)	1 (2.4)	0.36
CPR, *n* (%)	0 (0)	0 (0)	N/A

COVID-19: Coronavirus disease 2019; CPR: Cardiopulmonary resuscitation; ED: Emergency department; ICU: Intensive care unit; IQR: Interquartile range; N/A: Not applicable; OU: Observational unit.

Table 3 Multivariable hazard ratios of emergency department visit and hospital admission by risk characteristics

Outcomes	Multivariable HR[1]	95%CI	*P* value
First ED visit	1.02	0.54-1.92	0.96
Any ED visit	1.24	0.73-2.10	0.43
ED visit leading to hospital admission	0.92	0.50-1.69	0.78

[1]Adjusted for sex, age, donor, insurance, Charlson comorbidity index.
CI: Confidence interval; ED: Emergency department; HR: Hazard ratio.

Limitations

This study had some limitations to be considered. This method could not account for underlying trends in hospital admission and ED attendance despite comparing two time periods. Differences in hospital admission patterns may be associated with the epidemic or the limits by chance. This problem might be solved with additional time series analysis or regression modeling over a longer time. We only conducted the investigation at a single university hospital. As a result, the design may be valid and generalizable to the situation with the same degree of care. Furthermore, some baseline data were not recorded, including causes of ESRD and hospital length of stay during index transplantation. Moreover, another perspective that this study did not address was the quality of life of post-KT patients who visited ED in the first following year. Further research should evaluate this aspect of the patients.

Table 4 Top five emergency department diagnoses recorded during the study period

No	ICD-10	Diagnoses	%
January 2018-December 2019			
1	R509	Fever, unspecified	12.8
2	R104	Other and unspecified abdominal pain	12.8
3	N185	Chronic kidney disease, stage 5	10.3
4	A099	Gastroenteritis and colitis of unspecified origin	10.3
5	A419	Septicemia, unspecified	10.3
January 2020-December 2021			
1	R104	Other and unspecified abdominal pain	23.7
2	N390	Urinary tract infection, site not specified	10.5
3	A419	Septicemia, unspecified	7.9
4	A099	Gastroenteritis and colitis of unspecified origin	5.3
5	R074	Chest pain, unspecified	5.3

ICD: International Classification of Diseases.

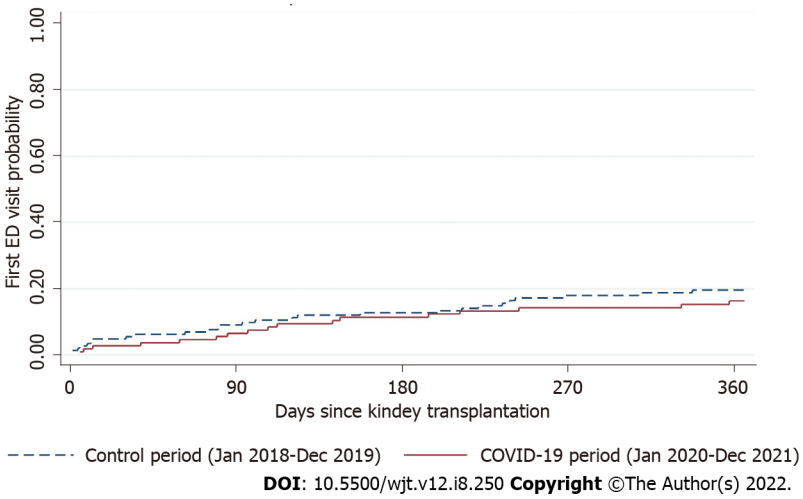

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Figure 2 Kaplan-Meier estimates of first emergency department visits in kidney transplantation patients who visited emergency department during coronavirus disease 2019 period (solid line) and control period (dot line). COVID-19: Coronavirus disease 2019; ED: Emergency department.

CONCLUSION

In conclusion, COVID-19 also affects KT recipients in terms of hospital admission rates. The present study points out that despite ED visits not being changed during the COVID-19 pandemic, hospital admission rates were increased. Although we could not determine the exact cause of this change, we believe that communication between post-KT patients and healthcare providers is necessary to emphasize the importance of timely ED visits for acute health conditions, especially in immunocompromised hosts like post-KT patients.

ARTICLE HIGHLIGHTS

Research background

Several investigations have shown that the coronavirus disease 2019 (COVID-19) has an impact on daily life and the healthcare system.

Research motivation

There has been no previous research on the effects of COVID-19 on emergency department (ED) visits and hospitalizations among kidney transplant (KT) patients. We conducted this study to explore the effects of COVID-19 on ED visits among post-KT recipients.

Research objectives

The aim of this study was to investigate the impact of the COVID-19 pandemic on the ED visits and hospital admissions within 1 year in patients who underwent KT in Thailand.

Research methods

We conducted a retrospective study. We reviewed hospital records of KT patients who visited ED during the outbreak of COVID-19. We used the previous 2 years as the control period in the analysis. We obtained baseline demographics and ED visit characteristics of each KT patient. The outcomes of interest were ED visits and ED visits leading to hospital admission within the 1st year following a KT.

Research results

We included a total of 263 patients: 112 during the COVID-19 period and 151 during the control period. There were 34 and 41 ED visits after KT in the COVID-19 and control periods, respectively. The rate of first ED visit at 1 year was not significantly different in the COVID-19 period, compared with the control period. The hospital admission rate was also similar between periods.

Research conclusions

The COVID-19 pandemic had no effect on KT recipients' ED visits or hospital admissions in the 1st year after transplantations.

Research perspectives

Despite these findings, we suggest that communication between post-KT patients and healthcare professionals is crucial in emphasizing the significance of timely ED visits for acute health issues, especially in post-KT patients.

FOOTNOTES

Author contributions: Wongtanasarasin W and Phinyo P designed the protocol, contributed to data collection, and data analyses; Wongtanasarasin W contributed to the formal analysis and wrote the first draft of the manuscript; and all authors read and critically reviewed the final version of the manuscript.

Institutional review board statement: The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chiang Mai University (EXEMPTION-8745/65).

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Country/Territory of origin: Thailand

ORCID number: Wachira Wongtanasarasin 0000-0002-1418-0036; Phichayut Phinyo 0000-0002-8543-6254.

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ORIGINAL ARTICLE

Retrospective Study

Trends and outcomes of liver transplantation among older recipients in the United States

Kenji Okumura, Joon Sub Lee, Abhay Dhand, Hiroshi Sogawa, Gregory Veillette, Devon John, Ryosuke Misawa, Roxana Bodin, David C Wolf, Thomas Diflo, Seigo Nishida

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Kenji Okumura, Joon Sub Lee, Abhay Dhand, Hiroshi Sogawa, Gregory Veillette, Devon John, Ryosuke Misawa, Roxana Bodin, David C Wolf, Thomas Diflo, Seigo Nishida, Department of Surgery, Westchester Medical Center/New York Medical College, Valhalla, NY 10595, United States

Corresponding author: Kenji Okumura, MD, Department of Surgery, Westchester Medical Center/New York Medical College, 100 Woods Road, Valhalla, NY 10595, United States. kenji.okumura@wmchealth.org

Abstract

BACKGROUND

The average age of recipients and donors of liver transplantation (LT) is increasing. Although there has been a change in the indications for LT over the years, data regarding the trends and outcomes of LT in the older population is limited.

AIM

To assess the clinical characteristics, age-related trends, and outcomes of LT among the older population in the United States.

METHODS

We analyzed data from the United Network for Organ Sharing database between 1987-2019. The sample was split into younger group (18-64 years old) and older group (≥ 65 years old).

RESULTS

Between 1987-2019, 155758 LT were performed in the United States. During this period there was a rise in median age of the recipients and percentage of LT recipients who were older than 65 years increased ($P < 0.05$) with the highest incidence of LT among older population seen in 2019 (1920, 23%). Common primary etiologies of liver disease leading to LT in older patients when compared to the younger group, were non-alcoholic steatohepatitis (16.4% *vs* 5.9%), hepatocellular carcinoma (14.9% *vs* 6.9%), acute liver failure (2.5% *vs* 5.2%), hepatitis C cirrhosis (HCV) (19.2 % *vs* 25.6%) and acute alcoholic hepatitis (0.13% *vs* 0.35%). In older recipient group female sex and Asian race were higher, while model for end-stage liver disease (MELD) score and rates of preoperative mechanical

ventilation were lower ($P < 0.01$). Median age of donor, female sex, body mass index (BMI), donor HCV positive status, and donor risk index (DRI) were significantly higher in older group ($P < 0.01$). In univariable analysis, there was no difference in post-transplant length of hospitalization, one-year, three-year and five-year graft survivals between the two groups. In multivariable Cox-Hazard regression analysis, older group had an increased risk of graft failure during the five-year post-transplant period (hazard ratio: 1.27, $P < 0.001$). Other risk factors for graft failure among recipients were male sex, African American race, re-transplantation, presence of diabetes, mechanical ventilation at the time of LT, higher MELD score, presence of portal vein thrombosis, HCV positive status, and higher DRI.

CONCLUSION
While there is a higher risk of graft failure in older recipient population, age alone should not be a contraindication for LT. Careful selection of donors and recipients along with optimal management of risk factors during the postoperative period are necessary to maximize the transplant outcomes in this population.

Key Words: Liver transplant; Elderly; Outcomes; Hepatocellular carcinoma; Nonalcohol steatohepatitis

Core Tip: Liver transplantation (LT) among older patients is becoming more acceptable in the United States. The overall outcomes of LT for patients ≥ 65 years are comparable to younger recipients. While there is a higher risk of graft failure in older recipient population, age alone should not be a contraindication for LT. Careful selection of donors and recipients along with optimal management of risk factors during the postoperative period are necessary to maximize the transplant outcomes in this population.

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INTRODUCTION

Liver disease is one of the most frequent causes of death in the United States[1,2]. Liver transplantation (LT) is the most effective life-saving treatment for patients with end-stage liver disease and liver failure. Over the past few decades, the number of LT in the United States has increased and outcomes of these transplants have significantly improved[3,4]. According to the United Network for Organ Sharing (UNOS) database, in 1987 there were 1713 LT performed in the United States. Since then, there has been a more than five-fold increase in the number of LTs, with 8906 cases performed in 2020. As the general population becomes older, the average ages of LT recipients and donors have increased as well[5]. Over the past three decades, the characteristic of donors and recipients of LT for end-stage liver disease has changed considerably[3,6-8]. Our goal was to assess trends in the etiology of underlying liver disease, and outcomes of LT among older population in the United States.

MATERIALS AND METHODS

Patients and selection criteria

We evaluated all patients 18 years or older who underwent LT in the United States from January 1, 1987 to December 31, 2019 in the UNOS database. Patients without a documented primary diagnosis were excluded from the analyses. This study was approved by our Institutional Review Board.

Patient characteristics and outcome variables

All data were collected from the UNOS registry. Demographic information, such as listing diagnosis, age, gender and race, along with time on waiting list prior to transplant were included in the analyses. Additional variables, such as model for end-stage liver disease (MELD) score at listing on the waitlist and at the time of transplant, body mass index (BMI), pre-transplant diabetes mellitus (DM), hepatitis C

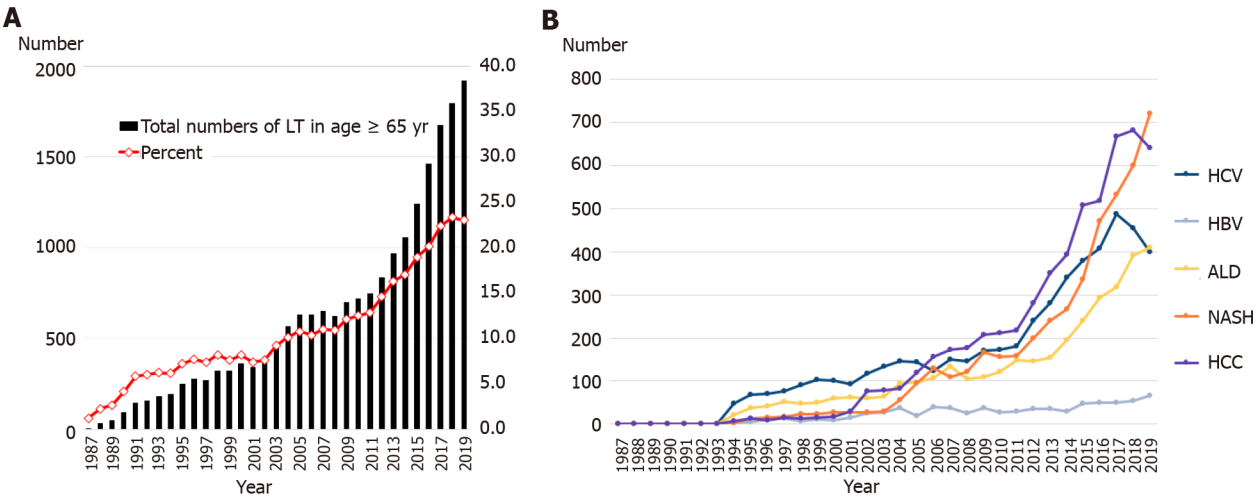

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Figure 1 Trend of liver transplant and indications for liver transplant in older group (age ≥ 65 years). A: Trend of liver transplant in older group (age ≥ 65 years); B: Trend of indications for liver transplant in older group (age ≥ 65 years). LT: Liver transplantation; HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALD: Alcohol related liver disease; NASH: Non-alcoholic steatohepatitis; HCC: Hepatocellular carcinoma.

virus (HCV) status, dialysis prior to transplant, previous abdominal surgery, spontaneous bacterial peritonitis, trans-jugular intrahepatic portosystemic shunt, portal vein thrombosis, mechanical ventilation status and donor risk index (DRI)[9], were included as well. The study groups were defined as older (≥ 65 years old) and younger (18-64 years old).

Statistics

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, United States). Non-parametric analyses were used to compare continuous variables (Mann-Whitney *U* test) and categorical variables (Chi-square test or Fisher's exact test). The overall survival and graft survival were calculated from the date of transplant to the date of the event using the Kaplan-Meier method. Survival curves were compared by using the log-rank test. Cox-Hazard regression analyses were applied to assess the association between multiple covariate factors and survival rates between two groups. Results were presented as hazard ratios and reported with 95% confidence intervals with *P* values. $P < 0.01$ was taken as statistically significant.

RESULTS

Recipient characteristics

Of the 155758 individuals who received a LT during the study period, 20000 were in older group (≥ 65 years old) and 135758 patients were in younger group (18-64 years old). The trends of LT in older patients are shown in Figure 1A. The overall number and percentage of LT in older group increased over the years, and the percentage of older recipients became > 20% after 2016. The trends of indications for LT in the older population is shown in Figure 1B. HCV cirrhosis was the most common indication for LT from 1994 to 2005. The number of patients requiring LT due to hepatocellular carcinoma (HCC) and non-alcoholic steatohepatitis (NASH) also gradually increased during the study period. HCC became the most common indication for LT in older group from 2006 to 2018. In 2019, NASH became the most common indication for LT in older group.

Table 1 presents the characteristics of recipients who underwent LT during the study period. The median age of recipients was 52 years in the younger group and 67 years in the older group. Recipients in older group were more likely to be female, White, and Asian compared to those in younger group ($P < 0.001$). Recipients in younger group were more likely to be HCV positive and have portal vein thrombosis, while recipients in older group were more likely to have pre-transplant DM. For primary etiology of liver disease, younger group was more likely to have alcohol-related liver disease (ALD), HCV cirrhosis and acute liver failure, while older group was more likely to have NASH and HCC. Additionally, the younger group was more likely to be on mechanical ventilation at the time of LT and have a prior history of LT.

Donor characteristics

The median donor age was higher in the older group (43 years *vs* 38 years, $P < 0.001$) (Table 2). The donors of older recipients were more likely to be female, have a higher BMI, and have a higher DRI.

Table 1 Baseline characteristics of the study population comparing age young group (age 18-64) *vs* older group (age ≥ 65 years)

	Young group, age 18-64 (*n* = 135758)	Older group, age ≥ 65 (*n* = 20000)	*P* value
Age (IQR)	52 (45-58)	67 (66-69)	< 0.001
Female, *n* (%)	47934 (35.3)	7612 (38.1)	< 0.001
Race, %			< 0.001
White	73.5	75.5	
Black	8.9	6.0	
Hispanic/Latino	12.5	12.1	
Asian	3.8	5.4	
Others	1.3	0.9	
BMI (IQR)	27.4 (24.0-31.7)	27.7 (24.5-31.5)	0.571
HCV, %	44876 (33.1)	5236 (26.2)	< 0.001
Diabetes, *n* (%)	226584 (22.3)	6784 (35.7)	< 0.001
L[1]-MELD	18 (12-26)	15 (10-22)	< 0.001
R[2]-MELD	21 (14-30)	18 (12-26)	< 0.001
Primary disease, %			
Alcohol cirrhosis	22.3	15.3	< 0.001
HCV cirrhosis	25.2	19.0	< 0.001
NASH	5.9	16.4	< 0.001
HCC	6.9	14.9	< 0.001
Acute liver failure	5.2	2.5	< 0.001
Acute alcoholic hepatitis	0.35	0.13	< 0.001
Previous surgery, *n* (%)	48407 (35.7)	8899 (44.5)	< 0.001
SBP, *n* (%)	9147 (6.7)	1084 (5.4)	< 0.001
TIPSS, *n* (%)	7231 (5.3)	1187 (5.9)	0.001
Portal vein thrombosis, *n* (%)	4875 (3.6)	1162 (5.8)	< 0.001
Mechanical ventilation, *n* (%)	10464 (7.6)	888 (4.3)	< 0.001
Dialysis, *n* (%)	14284 (10.5)	2059 (10.3)	0.167
Wait days, d (IQR)	82 (16-263)	118 (27-310)	< 0.001
Re-transplant, *n* (%)	10125 (7.5)	727 (3.6)	< 0.001

[1]Listing.
[2]Most recent.
IQR: Interquartile; BMI: Body mass index; HCV: Hepatitis C virus; NASH: Non-alcohol steatohepatitis; HCC: Hepatocellular carcinoma; SBP: Spontaneous bacterial peritonitis; TIPSS: Trans-jugular intrahepatic portosystemic shunt; MELD: Model for end-stage liver disease.

Outcomes

Kaplan-Meier survival analysis showed no significant differences in the 1, 3, and 5-year graft survival between the two groups, but overall survival was lower in the older group (Table 2). Multivariable Cox-Hazard regression analyses were performed to identify the factors associated with five-year graft failure (Table 3). Factors associated with five-year graft failure were recipient age ≥ 65 years, pre-LT DM, re-LT, male gender, African American race, ventilation at the time of LT, high MELD score (per 10), recipient portal vein thrombosis at time of LT, recipient HCV positive status, and high DRI. Transplants performed during the latter part of the study had a protective effect on five-year graft survival. In a subgroup analysis of older recipients, male gender, pre-LT DM, previous LT, ventilation at the time of LT, higher MELD score (per 10), portal vein thrombosis, HCV positive status, and higher DRI were associated with worse five-year graft survival (Table 4 and Figure 2).

Table 2 Donor characteristics and post-transplant outcomes

	Young, age 18-64 (*n* = 135758)	Older, age ≥ 65 (*n* = 20000)	*P* value
Donor age (IQR)	38 (24-52)	43 (28-56)	< 0.001
Donor female, *n* (%)	53967 (39.8)	8434 (42.2)	< 0.001
Donor race, %			< 0.001
White	70.3	68.2	
Black	14.6	15.5	
Hispanic/Latino	11.6	12.4	
Asian	2.1	2.4	
Others	1.4	1.6	
Donor BMI (IQR)	25.6 (22.5-29.5)	26.2 (23.0-30.3)	< 0.001
Donor HCV, *n* (%)	4912 (3.6)	907 (4.5)	< 0.001
Cold ischemia time, h (IQR)	6.9 (5.0-9.0)	6.1 (4.8-8.0)	< 0.001
Donor risk index (IQR)	1.53 (1.35-1.81)	1.61 (1.38-1.94)	< 0.001
Outcomes			
LOS, d (IQR)	11 (7-20)	10 (7-19)	0.261
Graft survival rate, (%)			
1 yr	84.0	84.1	0.416
3 yr	77.0	77.1	0.206
5 yr	72.6	72.9	0.010
Overall survival rate			
1 yr	88.6	86.5	< 0.001
3 yr	82.5	79.5	< 0.001
5 yr	78.3	75.1	< 0.001

IQR: Interquartile range; BMI: Body mass index; LOS: Post-transplant length of hospital stay; HCV: Hepatitis C virus.

DISCUSSION

This study utilized the UNOS database to analyze the trends and outcomes of LT in older patients. The results show an overall increase in total number of LT in older population over time, as well as significant changes in the trends of the primary etiology of LT. In older recipients, univariable analysis showed comparable graft survival, while multivariable analysis showed a lower graft and overall survival. But, these inferior results in older population may otherwise be considered acceptable.

The improvements in surgical techniques and perioperative care have allowed for a gradual increase LT for older recipients[4,5]. The presence of chronic liver diseases like HCV, NASH, and associated HCC in the older patients may have led to an increase in end-stage liver disease, requiring LT[10]. The recent improvements in HCV treatment has likely played a significant role in the change in primary indication for LT. Overall, the most current common indication for LT is ALD across all ages, however, our study shows that NASH and HCC are the leading causes of LT, with no increase in ALD in the older population. Durand *et al*[4] have shown that in LT, older recipients have a lower chance of liver allograft rejection. Additionally, they reported that patients with non-autoimmune conditions, such as NASH and alcoholic cirrhosis, do not require higher maintenance immunosuppression compared to other LT recipients[4]. Historically a subset of patients with positive HCV serostatus had a recurrence of HCV after LT[11]. HCV recurrence post-LT and subsequent chronic HCV infection would lead to drastic consequences, as chronic inflammation, fibrosis, and ultimately graft failure[12]. However, with the development of Direct-Acting Antivirals (DAA), there has been a major shift in the primary etiology of LT with the overall decrease in need of LT for chronic HCV infection[6]. Our analyses further showed that recipient HCV status was one of the risk factors for graft failure. This was likely before the availability of DAA, which has now become the therapy of choice for effectively curing HCV infection [13]. The recent studies show that DAA achieves high sustained virologic response in LT recipients and the elimination of HCV will prevent chronic inflammation, thereby avoiding the risk of compromising

Table 3 Multivariable cox regression for five-year graft survival

Variables	*B* (SE)	Hazard ratio (95%CI)	*P* value
Year of transplant	-0.04 (0.002)	0.958 (0.955-0.961)	< 0.001
Age ≥ 65	0.24 (0.02)	1.27 (1.22-1.32)	< 0.001
Male	0.10 (0.02)	1.11 (1.08-1.14)	< 0.001
BMI (per10)	-0.05 (0.01)	0.95 (0.93-0.98)	0.001
Race			0.001
Caucasian	Ref	1.0 (Ref)	
African American	0.23 (0.02)	1.26 (1.21-1.31)	< 0.001
Hispanic	-0.11 (0.02)	0.90 (0.86-0.94)	< 0.001
Asian	-0.21 (0.04)	0.81 (0.75-0.87)	< 0.001
Pre-LT diabetes	0.20 (0.02)	1.22 (1.18-1.26)	< 0.001
Ventilation	0.51 (0.03)	1.67 (1.59-1.76)	< 0.001
Pre-LT dialysis	0.20 (0.02)	1.23 (1.17-1.28)	< 0.001
Retransplant	0.44 (0.03)	1.55 (1.47-1.63)	< 0.001
PVT	0.21 (0.03)	1.23 (1.16-1.31)	< 0.001
R[1]-MELD (per 10)	0.04 (0.01)	1.05 (1.03-1.06)	< 0.001
HCV recipient	0.28 (0.01)	1.33 (1.29-1.36)	< 0.001
Donor race			< 0.001
Caucasian	Ref	1.0 (Ref)	
African American	0.06 (0.02)	1.06 (1.02-1.10)	0.001
Hispanic	0.10 (0.02)	1.11 (1.06-1.16)	< 0.001
Asian	0.19 (0.04)	1.21 (1.11-1.31)	< 0.001
Donor risk index	0.34 (0.03)	1.41 (1.34-1.48)	< 0.001
Cold ischemia time	0.014(0.002)	1.014 (1.010-1.019)	< 0.001

[1]Most recent.

BMI: Body mass index; LT: Liver transplantation; PVT: Portal vein thrombosis; CI: Confidence interval; HCV: Hepatitis C virus; MELD: Model for end-stage liver disease.

the graft[14,15].

As in our study, pre-transplant DM has previously been shown to be associated with worse outcomes in LT[16]. Diabetes is a metabolic disease and is associated with increased morbidity after LT[17,18]. The prevalence of NASH in patients with type 2 diabetes is more than 2-fold higher compared to the general population[19]. Poorly controlled diabetes is also strongly associated with NASH and accelerates the progression of liver disease. NASH and diabetes also increase cardiovascular risks[20]. These cumulative risk factors should be carefully evaluated for the post-transplant management of older patients.

In patients with cirrhosis, the requirement of mechanical ventilation at time of transplant is associated with an increased risk of post-operative mortality[21]. In our study, older patients were less likely to be intubated at the time of transplant, this would be related to cautious recipient selection. The patients' requirements for dialysis and comorbidities of kidney dysfunction also had a significant impact on the outcomes of LT[22], which is further correlated with a higher MELD score. In our study, older patients had a lower MELD score and need for dialysis at the time of transplant, which might reflect the individual transplant center selection criteria for older recipients.

There were several limitations to this study. First, primary diagnosis at the time of listing for LT was used, but this diagnosis may not be accurate. If an alternative diagnosis is found post-transplant, these changes may not be recorded in the UNOS database. Secondly, we have evaluated only the patients who received LT, which means that older patients with comorbidities and/or severe clinical conditions who were not considered to be a candidate for LT, added to the selection bias in this study. Finally, long-term data regarding the graft and overall survival among older recipients is limited.

Table 4 Multivariable cox regression for five-year graft survival in older group

Variables	*B* (SE)	Hazard ratio (95%CI)	*P* value
Year of transplant	-0.05 (0.004)	0.954 (0.947-0.961)	< 0.001
Male	0.19 (0.04)	1.21 (1.12-1.30)	< 0.001
Re-transplant	0.41 (0.08)	1.50 (1.28-1.76)	< 0.001
Pre-LT diabetes	0.17 (0.04)	1.18 (1.10-1.27)	< 0.001
Ventilation	0.42 (0.08)	1.52 (1.30-1.76)	< 0.001
Portal vein thrombosis	0.18 (0.07)	1.20 (1.05-1.36)	0.006
MELD (per 10)	0.13 (0.02)	1.14 (1.10-1.18)	< 0.001
HCV Recipient	0.21 (0.04)	1.23 (1.15-1.33)	< 0.001
Donor age (per 10)	0.03 (0.01)	1.03 (1.002-1.054)	0.032
Donor risk index	0.25 (0.06)	1.29 (1.15-1.44)	< 0.001
Cold ischemia time	0.017 (0.006)	1.02 (1.01-1.03)	0.003

LT: Liver transplantation; MELD: Model for end-stage liver disease; HCV: Hepatitis C virus; CI: Confidence interval.

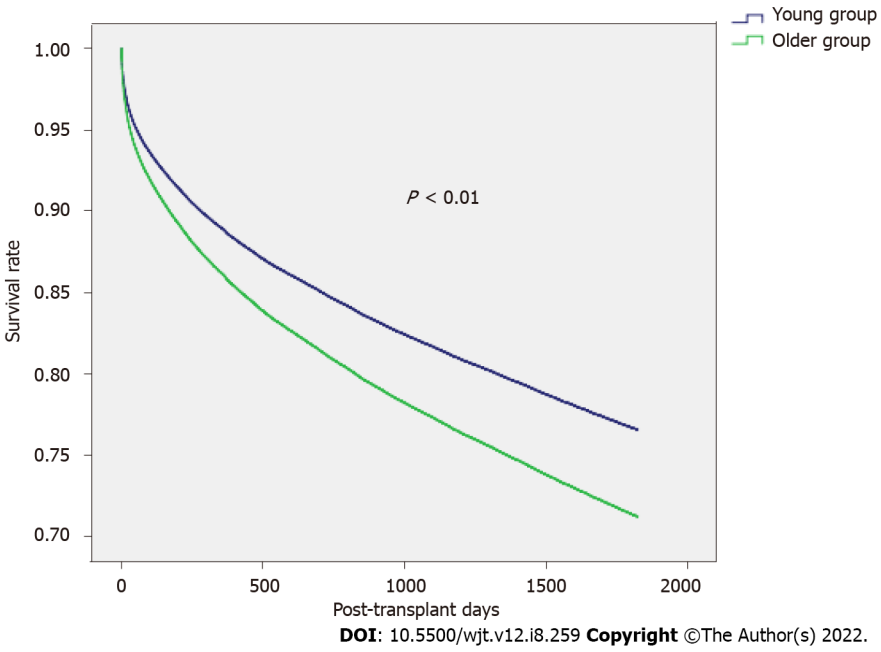

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Figure 2 Comparison of graft survival in older group (age ≥ 65 years) *vs* young group (age 18-64).

CONCLUSION

The number of LT in older recipients has significantly increased over time along with the change in indication of LT. Older age alone should not be a contraindication for LT, however, careful evaluation processes and postoperative care are necessary to improve the transplant outcomes.

ARTICLE HIGHLIGHTS

Research background

The average age of liver transplant and the number of liver transplant in the older recipients is increasing.

Research motivation

We wanted to investigate the outcomes of expansion of criteria of liver transplantation (LT) with increasing inclusion of older recipients and donors. We also wanted to identify any potentially modifiable risk factors that may be associated lower with graft or patient survival.

Research objectives

We compared one, three- and five-year graft and patient survival between two groups of liver transplant recipients: Younger group (18-64 years old) and older group (≥ 65 years old) between the period of 1987-2019 in the United States.

Research methods

We analyzed data from the United Network for Organ Sharing database between 1987-2019. The sample was split into younger group (18-64 years old) and older group (≥ 65 years old).

Research results

The number of LT for older patients was highest in 2019 (1920). In the older group, the percentage of non-alcoholic steatohepatitis and hepatocellular carcinoma as the primary etiology for LT was higher than younger group compared to the older group (16.4 % *vs* 5.9%; 14.9% *vs* 6.9%). On univariable analysis, there was no difference in post-transplant length of hospitalization, one-year and five-year overall survivals between the two groups. On multivariable Cox-Hazard regression analysis for graft survival, older group (hazard ratio: 1.27, $P < 0.001$) had higher risk of graft failure which was associated with male gender, pre-transplant diabetes, previous history of LT, ventilation at the time of LT, high model for end-stage liver disease score, recipient portal vein thrombosis, hepatitis C virus positive status, and higher donor risk index.

Research conclusions

Older age alone should not be considered to be a contraindication for LT.

Research perspectives

Careful evaluation process and postoperative care are necessary to improve transplant outcomes.

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FOOTNOTES

Author contributions: Okumura K, Nishida S contributed to the study design, data analysis, data interpretation, and writing manuscript; Lee JS, Dhand A, Sogawa H, Veillette G, John D, Misawa R, Bodin R, Wolf DC, and Diflo T revised manuscript and critical revisions; and all authors approved the final version of the manuscript.

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ORCID number: Kenji Okumura 0000-0002-7751-2624; Joon Sub Lee 0000-0003-1151-1343; Abhay Dhand 0000-0003-3527-1938; Hiroshi Sogawa 0000-0003-3724-9005; Gregory Veillette 0000-0001-8635-0578; Devon John 0000-0002-2192-4929; Ryosuke Misawa 0000-0001-8429-3135; Roxana Bodin 0000-0002-8679-239X; David C Wolf 0000-0001-6819-9675; Thomas Diflo 0000-0002-4059-2309; Seigo Nishida 0000-0002-1504-3551.

Corresponding Author's Membership in Professional Societies: American Association for the Study of Liver Diseases.

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SYSTEMATIC REVIEWS

Gastrointestinal manifestations, risk factors, and management in patients with post-transplant lymphoproliferative disorder: A systematic review

William Reiche, Abubakar Tauseef, Ahmed Sabri, Mohsin Mirza, David Cantu, Peter Silberstein, Saurabh Chandan

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William Reiche, Abubakar Tauseef, Mohsin Mirza, Department of Medicine, CHI Creighton University Medical Center, Omaha, NE 68124, United States

Ahmed Sabri, David Cantu, Department of Pathology, CHI Creighton University Medical Center, Omaha, NE 68124, United States

Peter Silberstein, Division of Hematology and Oncology, Department of Medicine, CHI Creighton University Medical Center, Omaha, NE 68124, United States

Saurabh Chandan, Division of Gastroenterology and Hepatology, Department of Medicine, CHI Creighton University Medical Center, Omaha, NE 68124, United States

Corresponding author: William Reiche, DO, Doctor, Department of Medicine, CHI Creighton University Medical Center, 7500 Mercy Road, Omaha, NE 68124, United States.
reichewilliam@gmail.com

Abstract

BACKGROUND
Patients with a history of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) are at an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). The gastrointestinal (GI) tract is commonly affected as it has an abundance of B and T cells.

AIM
To determine typical GI-manifestations, risk factors for developing PTLD, and management.

METHODS
Major databases were searched until November 2021.

RESULTS
Non-case report studies that described GI manifestations of PTLD, risk factors for developing PTLD, and management of PTLD were included. Nine articles written within the last 20 years were included in the review. All articles found that patients with a history of SOT, regardless of transplanted organ, have a propensity to develop GI-PTLD.

CONCLUSION
GI tract manifestations may be nonspecific; therefore, consideration of risk factors is crucial for identifying GI-PTLD. Like other lymphoma variants, PTLD is very aggressive making early diagnosis key to prognosis. Initial treatment is reduction of immunosuppression which is effective in more than 50% of cases; however, additional therapy including rituximab, chemotherapy, and surgery may also be required.

Key Words: Post-transplant lymphoproliferative disorder; Gastrointestinal manifestations; Reduction of immunosuppression; Risk factors; Epstein-Barr virus

Core Tip: Patients with a history of solid-organ or hematopoietic stem cell transplantation are at an increased risk of developing post-transplant lymphoproliferative disorder (PTLD). The gastrointestinal (GI) tract is commonly affected as it has an abundance of B and T-cells. GI tract manifestations may be nonspecific; therefore, consideration of risk factors is crucial for identifying GI-PTLD. Like other lymphoma variants, PTLD is very aggressive making early diagnosis key to prognosis. Initial treatment is reduction of immunosuppression which is effective in more than 50% of cases; however, additional therapy including surgery and chemotherapy may also be required. We performed a systematic review of GI-PTLD to better describe GI manifestations, risk factors for disease, and management of GI-PTLD.

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INTRODUCTION

While primary and secondary lymphoid neoplasms only constitute 1%-4% of all gastrointestinal (GI) malignancies[1,2]; post-transplant lymphoproliferative disorder (PTLD) is one of the most common post-transplant malignancies within the GI tract. PTLD is a lymphoma variant which can manifest in patients having solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). Patients with a history of SOT are at increased risk of developing PTLD which may be more prone to develop in the GI tract. Review of the typical GI symptoms and timing of symptom development will be invaluable to the clinician caring for patients with a transplantation history, especially as this patient population continues to grow. Risk factors for developing PTLD are important to identify as PTLD can present in a myriad of ways and clinical suspicion greatly aids in timely evaluation and treatment for PTLD. We performed a review of the GI manifestations of PTLD. We described risk factors associated with the development of PTLD. Additionally, we reviewed the management of patients diagnosed with PTLD and associated complications.

MATERIALS AND METHODS

Protocol

This review has been in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA)[5].

Eligibility criteria, literature search, and search strategy

An expert librarian conducted a systematic literature search using a priori protocol to identify studies reporting on GI-PTLD manifestations, risk factors for the development of GI-PTLD, and management of GI-PTLD. The search strategies included "gastrointestinal manifestations", "risk factors", "management", "reduction of immunosuppression", "post-transplant", "lymphoproliferative disorder", "EBV", and "PTLD". The search was run in November 2021 across multiple databases, including Medline, and Scopus. The search was restricted to articles in English and identified searches were exported to a reference manager (EndNote). We cross-checked reference lists of identified sources for additional relevant studies. We also cited high-quality articles in *Reference Citation Analysis* (https://www.refere

ncecitationanalysis.com).

Study selection

This systematic review included studies that evaluated GI manifestations of PTLD. Studies were included irrespective of primary organ transplantation. Information was gathered from nine of the most relevant articles pertaining to GI-PTLD. Additional studies were incorporated to provide background on PTLD manifestations, risk factors, imaging, treatment, and outcomes. Studies reporting performance in pediatric age groups (< 18 years), conference abstracts, and non-English studies were excluded. Studies were restricted to full text. Two authors decided on the final selection (Reiche W, Tauseef A). Details presented in PRISMA flow diagram (Supplementary Figure 1).

RESULTS

PTLD can manifest as nodal or more commonly as extranodal disease occurring in solid organ tissue outside of lymph nodes[6]. The most involved extranodal sites are the GI tract (23%-30%), lungs (4%-23%), bone marrow (15%-17%), central nervous system (5%-15%), liver (5%-13%), and the allograft itself (15%-19%)[7-9] in Figure 1. The GI tract is one of the most affected organs due to the preponderance of B and T lymphocytes which are prone to develop malignant change[10]. Patients with GI-PTLD usually present with nonspecific constitutional symptoms including fatigue, fever, night sweats, lymphadenopathy, and weight loss[11,12]. Not uncommonly, patients may also have nausea, vomiting, abdominal pain, abdominal fullness, diarrhea or increased ostomy output, and occult or evident bleeding. PTLD may present as a small bowel obstruction, GI bleeding, gastric or intestinal perforation, or obstruction [13].

One study evaluating the location of PTLD found the stomach was one of the most common sites of involvement. Out of a total of 472 patients, 56 patients (11.9%) had gastric PTLD while 415 patients (88.1%) had PTLD in other locations[13] (Table 1). The small bowel is another common area of involvement, PTLD of the small bowel was diagnosed in 50% of patients having PTLD after small bowel transplantation (SBT)[14]. In patients requiring surgery for GI-PTLD complications, organ involvement varied: Small bowel (50%), proximal right colon (31.2%), and stomach, duodenum, and transverse colon (6.2%)[15].

SOT or HSCT are known risk factors for developing lymphoma or other lymphoproliferative disorders[11]. While studies have shown GI-PTLD can develop after most types of transplant, the incidence of PTLD after intestinal transplantation was determined to be higher than other types of SOT [16]. The mean time to PTLD varies and is dependent on host factors and transplant type. One study found the mean time for development of PTLD is 1 year for patients having HSCT, while the time to PTLD presentation may be up to 7 years after SOT[11,16-18]. The mean interval from transplantation to PTLD diagnosis after SBT was 2.7 years[14]. After liver transplantation, the average time from transplantation to diagnosis of PTLD was 7.2 years[15].

Induction and maintenance regimens are selected based on the risk of acute organ rejection associated with the transplant. T-cell depleting therapy (recombinant anti-thymocyte globulin), interleukin-2 receptor subunit alpha (IL2RA), or no immunosuppression may be used for induction therapy. For instance, for adult heart transplants, T-cell depleting therapy is most commonly used for induction; however half of transplant patients do not receive induction[19]. In lung transplants, induction therapy is used nearly 80% of the time and most commonly IL2RA are used[20,21]. For kidney transplants, induction therapy is provided 90% of the time and is usually T-cell depleting therapy[22,23]. Most commonly, induction is not used after liver transplant[24,25]. For pancreas transplant induction, T-cell depleting therapy is most commonly used (90%)[26]. Lastly, intestinal transplant induction is usually comprised of T-cell depleting agents (63.9%) or no induction (27.8%)[27]. Current trends in maintenance immunosuppression therapy for pancreas, heart, lung, kidney, liver, intestinal transplants are as follows: Pancreas transplants most often use tacrolimus, mycophenolate mofetil (MMF) and nearly 70% of patients are on corticosteroids[26]. Heart transplant maintenance therapy most often includes tacrolimus and MMF and corticosteroids are used nearly 50% of the time[19]. Lung transplants typically are treated with tacrolimus, MMF, and corticosteroids (80%)[21]. Kidney transplants are either treated with tacrolimus, MMF, and corticosteroids (54.1%) or tacrolimus and MMF (36.8%)[22,23]. Liver transplants are typically treated with tacrolimus, MMF, and steroids in 65% of patients[24,25]. Intestinal transplants are treated with tacrolimus (73%) and corticosteroids may be used (37.4%)[28].

Imaging findings of GI-PTLD are variable and can appear as wall thickening, dilatation, an eccentric or exophytic mass, luminal ulceration, short segment intussusception, and soft tissue nodules in the peritoneum (Figure 2)[12]. Solid organ involvement is usually in the form of infiltrating lesions appearing as a solitary or a multi-nodular mass[17]. Additional risk factors for developing GI-PTLD include induction immunosuppression, prolonged duration of immunosuppression, younger age, fewer human leukocyte antigen matches, use of anti-lymphocyte antibodies, prior splenectomy, cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis C, and human herpesvirus 8 (HHV-8)[10,12,15,17,29,30] (Table 2). EBV is the most common risk factor for developing PTLD, risk is higher in recipients who

Table 1 Study details

Ref.	Localization of PTLD	Time from transplant to PTLD (yr)	Classification	
			Monomorphic	Polymorphic
Wozniak *et al*[17]	Small bowel: 9/19 Colorectal: 3/19 Liver: 2/19	7.4	9/19	10/19
Koo *et al*[14]	Small bowel: 11/12 Colorectal: 1/12	2.7	1/12	8/12
Khedmat *et al*[13]	Stomach + small bowel: 13/45 Stomach + pancreas: 3/45 Stomach + liver: 7/45 Stomach: 56/472	4.1	23/39	13/39
Khedmat *et al*[16]	Colorectal + liver: 10/73 Colorectal + small bowel: 22/73 Colorectal + stomach: 2/73 Colorectal: 81/563	4.1	36/57	18/57
Cruz Jr *et al*[15]	Colorectal: 6/17 Small bowel: 11/17	7.2	13/17	3/17
Ganne *et al*[18]	Small bowel: 1/8 Stomach: 1/8	4.8	0/2	2/2

PTLD: Post-transplant lymphoproliferative disorder.

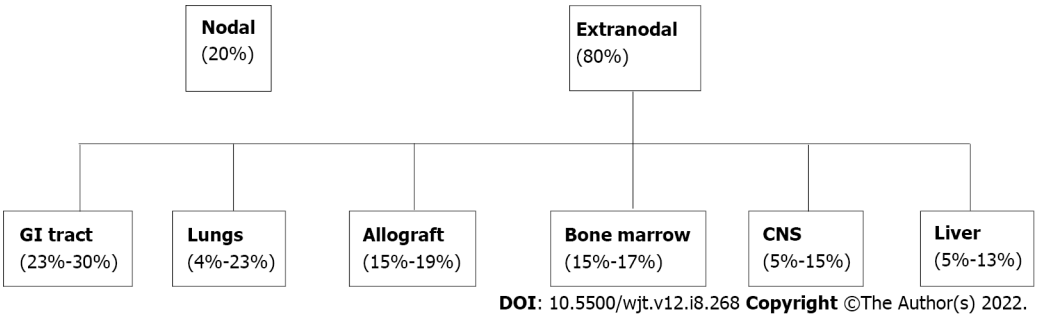

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Figure 1 Distribution of post-transplant lymphoproliferative disorder by organ involvement. GI: Gastrointestinal.

are initially seronegative but develop positivity after transplantation[15,31,32]. EBV can be transmitted *via* the graft; however, non-leukoreduced blood products also have the potential to transmit EBV[31]. EBV is present in 60%-70% of patients diagnosed with PTLD[30]. CMV can increase the likelihood of developing PTLD by seven times[33,34]. Hepatitis C and HHV-8 are also risk factors for developing PTLD especially when patients have EBV seropositivity[33]. If more than one risk factor is present, there appears to be cumulative risk[35].

According to the revised 2017 World Health Organization classification of tumors of hematopoietic and lymphoid tissues, PTLD is categorized into four major groups based on morphologic pattern: Non-destructive PTLD, monomorphic PTLD, polymorphic PTLD, and classic Hodgkin lymphoma PTLD. Apart from the polymorphic group, all other groups are further sub-categorized. Non-destructive PTLD are usually EBV-positive and are characterized by architectural preservation of the involved tissue without features suggestive of malignant lymphoma. The subcategories for non-destructive PTLD include plasmacytic hyperplasia, florid follicular hyperplasia, and infectious mononucleosis PTLD. Monomorphic or polymorphic PTLD may follow non-destructive PTLD lesions; however, most non-destructive PTLD have polyclonal B-cells. Polymorphic-PTLD are characterized by a heterogenous population that includes immunoblasts, plasma cells, and small to moderate sized lymphoid cells that

Table 2 Study details regarding gastrointestinal post-transplant lymphoproliferative disorder

Ref.	Noted findings regarding GI-PTLD
Plummer *et al*[11]	PTLD presentation is non-specific. Prognosis is variable dependent on burden of disease, age at the time of diagnosis, and morphological subtype
Small *et al*[7]	EBV infection is crucial in the pathophysiology of PTLD. EBV+ patients are more likely to respond to RIS. Chemotherapy can be utilized after RIS if RIS appears unsuccessful
Dako *et al*[12]	Imaging of PTLD involving GI tract is variable. Imaging of PTLD may appear as a large mass, luminal ulceration, intussusception, or soft tissue nodules
Wozniak *et al*[17]	Risk of acute cellular rejection increased when treatment for PTLD occurred. Notable risk factors for PTLD include chronic immunosuppression, viral infection, and increased time from transplantation
Koo *et al*[14]	Incidence rate of PTLD after small bowel transplantation was up to 50%
Khedmat *et al*[13]	Clinical presentation of PTLD is nonspecific. Early treatment with RIS, rituximab, chemotherapy, or surgical therapy, if indicated, can decrease mortality rates
Khedmat *et al*[16]	Patients with PTLD and colorectal symptoms were noted to have a higher risk of metastatic disease. Colorectal PTLD may occur more frequently and may be more aggressive in men compared to women. Multi-organ failure may be more common in men compared to women if there is colorectal PTLD
Cruz Jr *et al*[15]	Surgical intervention uncommonly required for PTLD. Most common surgical need is for intestinal obstruction
Ganne *et al*[18]	PTLD was found to respond to rituximab irrespective of EBV status. Patients with higher EBV titers usually benefited from combination RIS, rituximab, and CHOP therapy. EBV-specific donor cytotoxic lymphocyte infusions may be effective but may lead to graft rejection. GI bleeding may be a presenting feature of disease

PTLD: Post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; RIS: Immunosuppression; GI: Gastrointestinal.

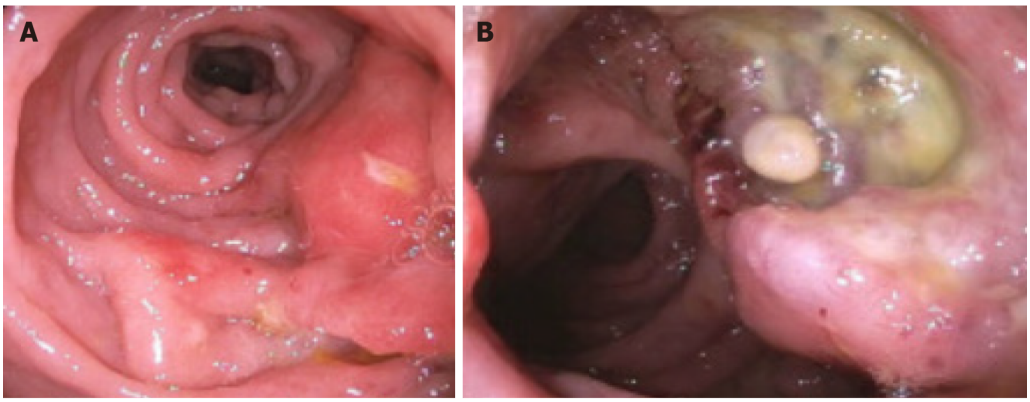

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Figure 2 Endoscopic appearance of post-transplant lymphoproliferative disorder. A: Nodular and ulcerated mucosa noted in the sigmoid colon; B: Ulcerated rectal mass.

efface the architecture of lymph nodes or may form destructive lesions but do not fulfill the criteria for lymphoma. Most cases of polymorphic-PTLD are EBV-positive. Monomorphic PTLD comprise 60%-80% of all PTLD and fulfill criteria for B-cell or T/natural killer-cell neoplasms (Figures 3-6). The least common form of PTLD are the classic Hodgkin lymphoma PTLD which are almost always EBV-positive [36].

Distinction is often made between early PTLD and late PTLD. The former more often associated with EBV positivity and graft involvement while less commonly associated with monomorphic morphology and less often presenting as extranodal disease[8]. Treatment has not been found to differ based on this categorization[29,37,38]. Studies comparing early *vs* late PTLD have not shown a significant difference in survival[39,40]. Determination of EBV status is a crucial first step after the diagnosis of GI-PTLD has been made. EBV-specific cytotoxic T-cell immunity or donor lymphocyte infusions have been used as second line therapies if reduction of immunosuppression (RIS) or rituximab is not working, patients with EBV may be more responsive to RIS than patients without EBV[7,18]. However, there is no approved treatment in the United States or Europe. Several studies have failed to show improvement with antivirals alone in instances when patients have EBV and PTLD[29,31,,40,,41,].

Once GI-PTLD diagnosis has been confirmed with endoscopic biopsy, patients can be managed with RIS, chemotherapy, and surgical intervention for complications[11]. The most important first step in

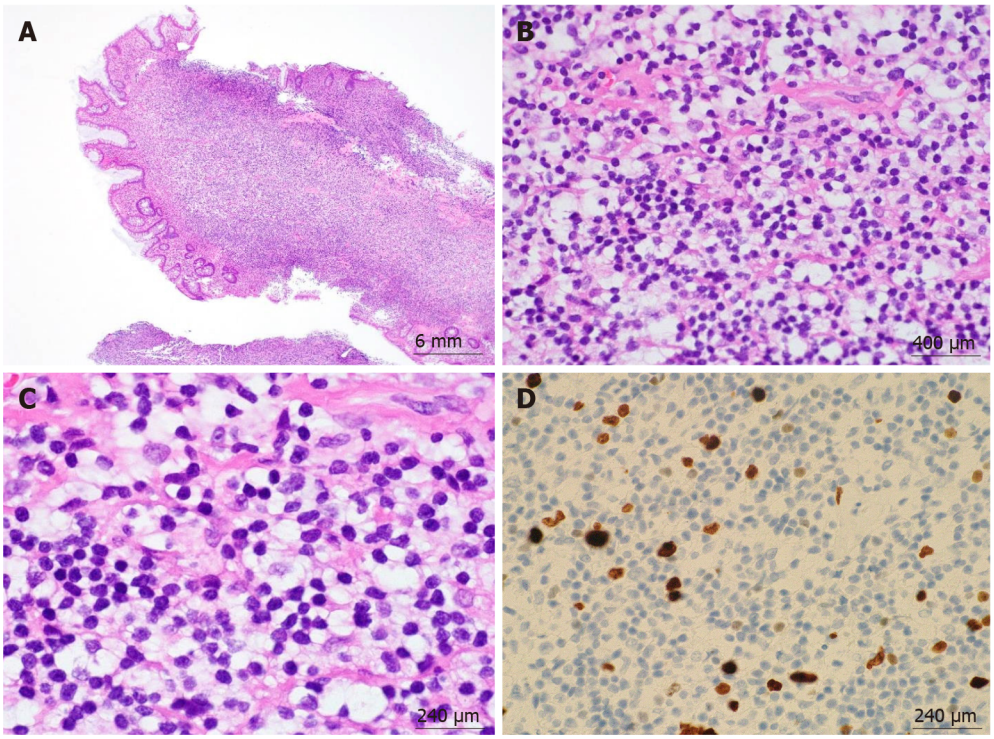

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Figure 3 Post-transplant lymphoproliferative disorder, monomorphic type (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue) arising in a sigmoid colon polyp. A: 4 ×/6 mm; B: 60 ×/400 μm; C: 100 ×/240 μm; D: 100 ×/240 μm. Hematoxylin & eosin stain showed a dense lymphoid infiltrate in the lamina propria composed of monotonous small-sized lymphoid cells with mature chromatin and abundant clear cytoplasm. Ki-67 showed low proliferation index.

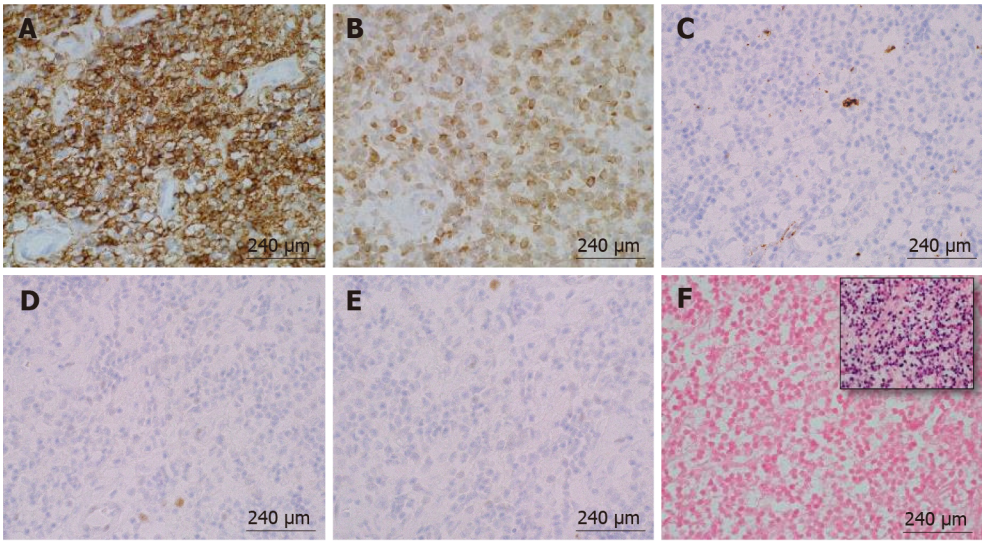

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Figure 4 Immunohistochemical and *in-situ* hybridization staining of post-transplant lymphoproliferative disorder, monomorphic type (extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue) arising in a sigmoid colon polyp. A: CD20, 100 ×/240 μm; B: B-cell lymphoma (BCL)-2, 100 ×/240 μm; C: CD10, 100 ×/240 μm; D: BCL-6, 100 ×/240 μm; E: CD5, 100 ×/240 μm; F: EBER-ISH (inset: Positive control), 100 ×/240 μm. The monotonous small-size lymphocytes stained positive for CD20 and B-cell lymphoma-2 and were negative for the rest of the stains.

treatment is RIS[11,15]. Immunosuppressant therapy is usually decreased to 50% for calcineurin-inhibitors (cyclosporine, tacrolimus) and MMF or azathioprine, if also prescribed, are discontinued[42]. In the largest study to date evaluating the efficacy of standard RIS, response was nearly 45%. Rates of up to 80% have been reported[31]. More than 70% of the time, RIS will be efficacious regardless of PTLD subtype, EBV status, and early *vs* late disease. RIS may not be sufficient in monomorphic PTLD[43]. RIS may not work if the disease is bulky, the cancer stage is severe, if multi-organ dysfunction is present, if

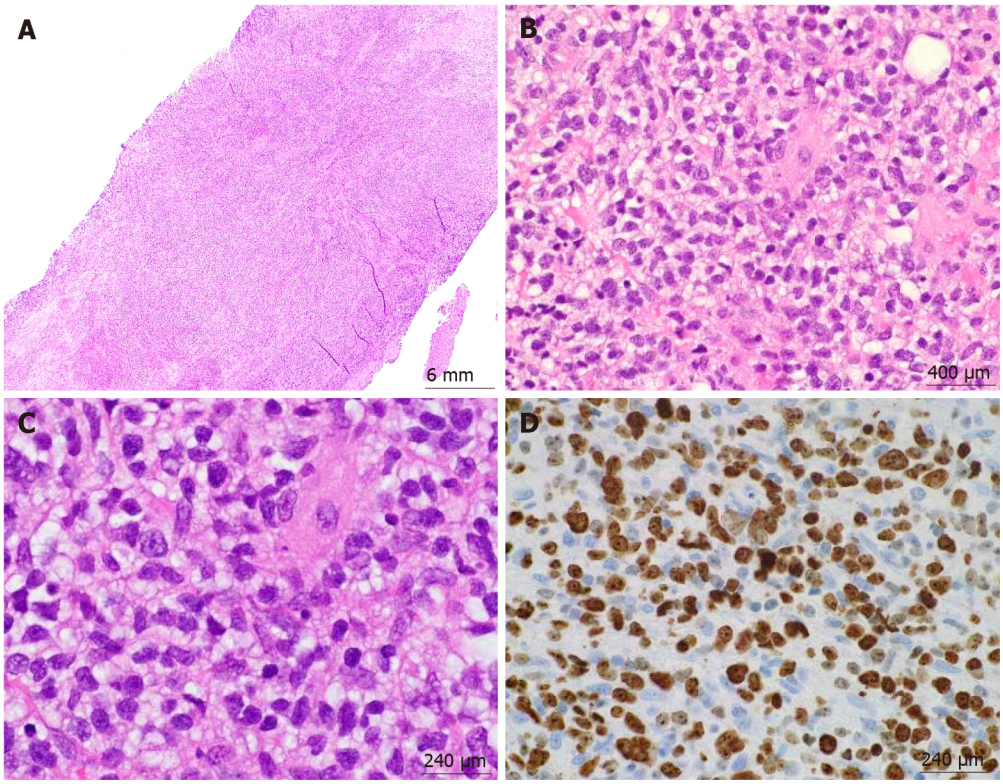

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Figure 5 Post-transplant lymphoproliferative disorder, monomorphic type (diffuse large B-cell lymphoma, non-germinal center type) arising from an ulcerated anal mass. A: 4 ×/6 mm; B: 60 ×/400 μm; C: 100 ×/240 μm; D: 100 ×/240 μm. Hematoxylin & eosin stain showed a diffuse lymphoid infiltrate composed of large pleomorphic cells with clear to eosinophilic cytoplasm, irregular nuclear contours, and prominent nucleoli in a background of fibroadipose tissue. Ki-67 showed high proliferation index.

quick treatment is needed, or for older adults[33,44]. Although beneficial as the first step in management, RIS can be associated with acute cellular rejection with the highest risk in the first year after transplantation[36].

If RIS is not sufficient, patients should be considered for antiviral therapy, rituximab, and chemotherapy[7]. Treatment is dependent on the PTLD subtype. Classical Hodgkin lymphoma PTLD is treated with standard adriamycin, bleomycin, vinblastine, and dacarbazine. Patients with PTLD diffuse large B-cell lymphoma type are treated according to the PTLD-1 trial with rituximab induction (weekly rituximab for four weeks) followed by stratification based on response. Patients in clinical remission may be treated with maintenance rituximab weekly for 4 wk. Patients with a suboptimal response may be treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (Figure 7)[45].

Rituximab has been found to be an effective therapy for PTLD. In one study including 8 patients with PTLD after SOT, complete resolution of PTLD was observed in 7 cases. Rituximab was administered at a dose of 375 mg/m^2 once a week for four consecutive weeks. Additionally, this study found patients with PTLD usually respond to anti-CD20 monoclonal antibodies irrespective of EBV status[18]. Radiotherapy has been found to have a favorable effect in stage 1 plasmacytoma-like PTLD; however, it is infrequently used for solitary PTLD. Radiotherapy is most often utilized in treatment for central nervous system PTLD[45].

Surgery should be considered in patients who develop GI complications including perforation, hemorrhage, and most commonly intestinal obstruction. Surgical resection is rarely considered in patients as PTLD tends to be multi-focal. A retrospective review of 5677 patients after isolated liver transplantation found only 16 patients developed post-transplantation GI complications associated with PTLD requiring surgical intervention. Overall mortality in this cohort was 69% and most patients died within the first year of explorative laparotomy. This same study found initial mortality higher in patients receiving surgery; however, long-term outcomes do not appear to be affected[15]. Prognosis is dependent on burden of disease, location of PTLD, morphological subtype, and other patient-related factors[11]. Once present, PTLD progression is aggressive; however, early appropriate treatment can decrease mortality rates. In one study comparing gastric PTLD and non-gastric PTLD, patients developing GI-PTLD had survival rates of 71% and 54% at one and five years, respectively[13].

Mortality rates in patients requiring surgery compared to rituximab and chemotherapy found no significant difference between treatment type. Mortality associated with surgical treatment was 16%, like that observed in patients who received rituximab. While mortality rates in patients treated with

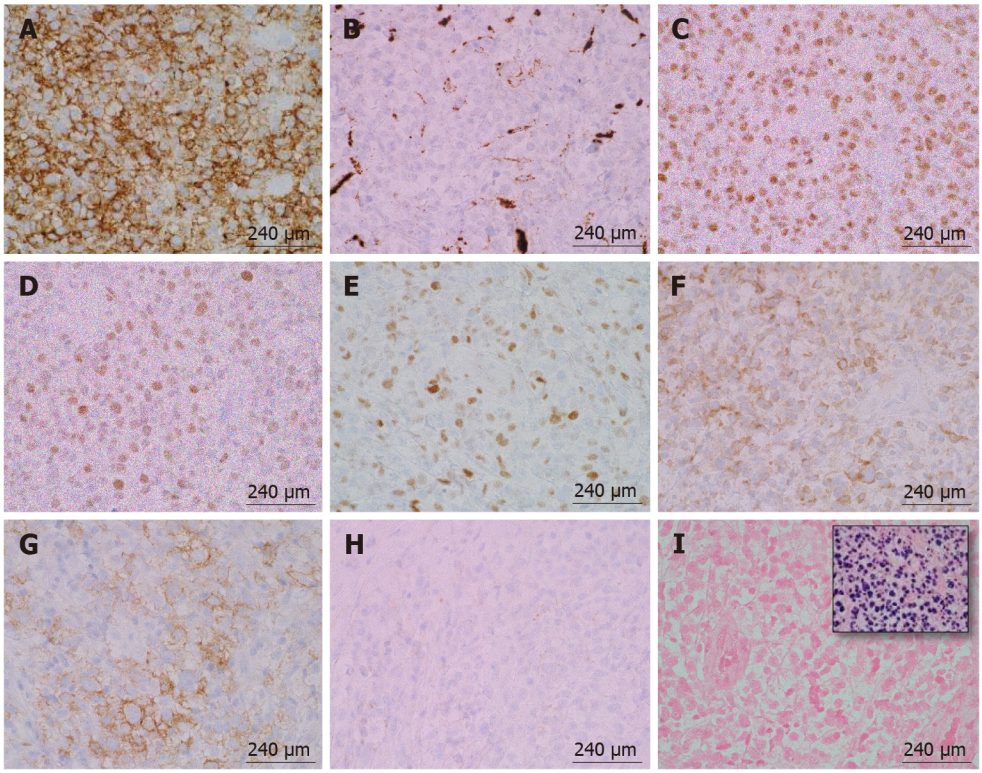

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Figure 6 Immunohistochemical and *in-situ* hybridization staining of post-transplant lymphoproliferative disorder, monomorphic type (diffuse large B-cell lymphoma, non-germinal center type) arising from an ulcerated anal mass. A: CD20, 100 ×/240 μm; B: CD10, 100 ×/240 μm; C: B-cell lymphoma (BCL)-6, 100 ×/240 μm; D: MUM-1, 100 ×/240 μm; E: c-MYC, 100 ×/240 μm; F: BCL-2, 100 ×/240 μm; G: CD30, 100 ×/240 μm; H: CD21, 100 ×/240 μm; I: EBER-ISH (inset: Positive control), 100 ×/240 μm. The large pleomorphic lymphocytes stained positive for CD20, B-cell lymphoma (BCL)-6, MUM-1, and BCL-2. These cells had a borderline staining for c-MYC (30%-40%), but FISH studies were negative for c-MYC rearrangements. CD30 was positive only in a subset of cells. EBER-ISH was negative.CD21 was negative and showed loss of follicular dendritic meshwork.

chemotherapy and radiotherapy with interferon alfa were 42.6% and 33%, respectively[13]. A favorable response to treatment has been noted in EBV-positive patients as they were more responsive to RIS compared to EBV-negative patients[29]. Similarly, a favorable outcome was also noted in patients who had localization to the stomach[13].

Conversely, colorectal involvement has been associated with a more severe disease presentation than PTLD involving non-colorectal sites. In one study, 75% of patients who developed colorectal symptoms had multi-organ involvement, significantly higher than the control group[16]. This same study found colorectal involvement was more likely in men. Male transplant patients developed colorectal PTLD more often than women 19.3% to 8.5%, respectively. Similarly, male transplant patients had a significantly shorter time from transplantation to diagnosis of the disease.

DISCUSSION

PTLD should be considered in patients with a history of SOT or HSCT as the large resident lymphocyte population in the GI tract has increased potential to develop malignancy. PTLD should be suspected to occur sooner after HSCT, within 1 year, and on average 4 to 5 years after SOT. However, there are multiple factors which appear to have a role in the time to development such as level of immunosuppression and presence of concomitant disease. Transplant type also appears to impact time to development as induction, maintenance, and the extent of inherent lymphoid tissue in the graft all contribute to the relative risk of developing PTLD. For instance, PTLD occurred sooner on average after small bowel transplant and later for liver transplant; in the studies reviewed, there was an approximate 4.5-year difference in time to onset of PTLD. Induction therapy, associated with increased risk of PTLD, is less frequently used after liver transplant while it is commonly used after intestinal transplants. The small bowel also has a greater supply of lymphoid tissue compared to the liver.

Diagnosis of PTLD can be problematic as the clinical spectrum and diagnostic testing are nonspecific. The illness script of PTLD is highly variable ranging from nonspecific abdominal symptoms to overt hemorrhage, perforation, or obstruction. The stomach and small intestine are the most frequently involved organs in the GI tract making clinical questioning and inquiry of symptoms which may

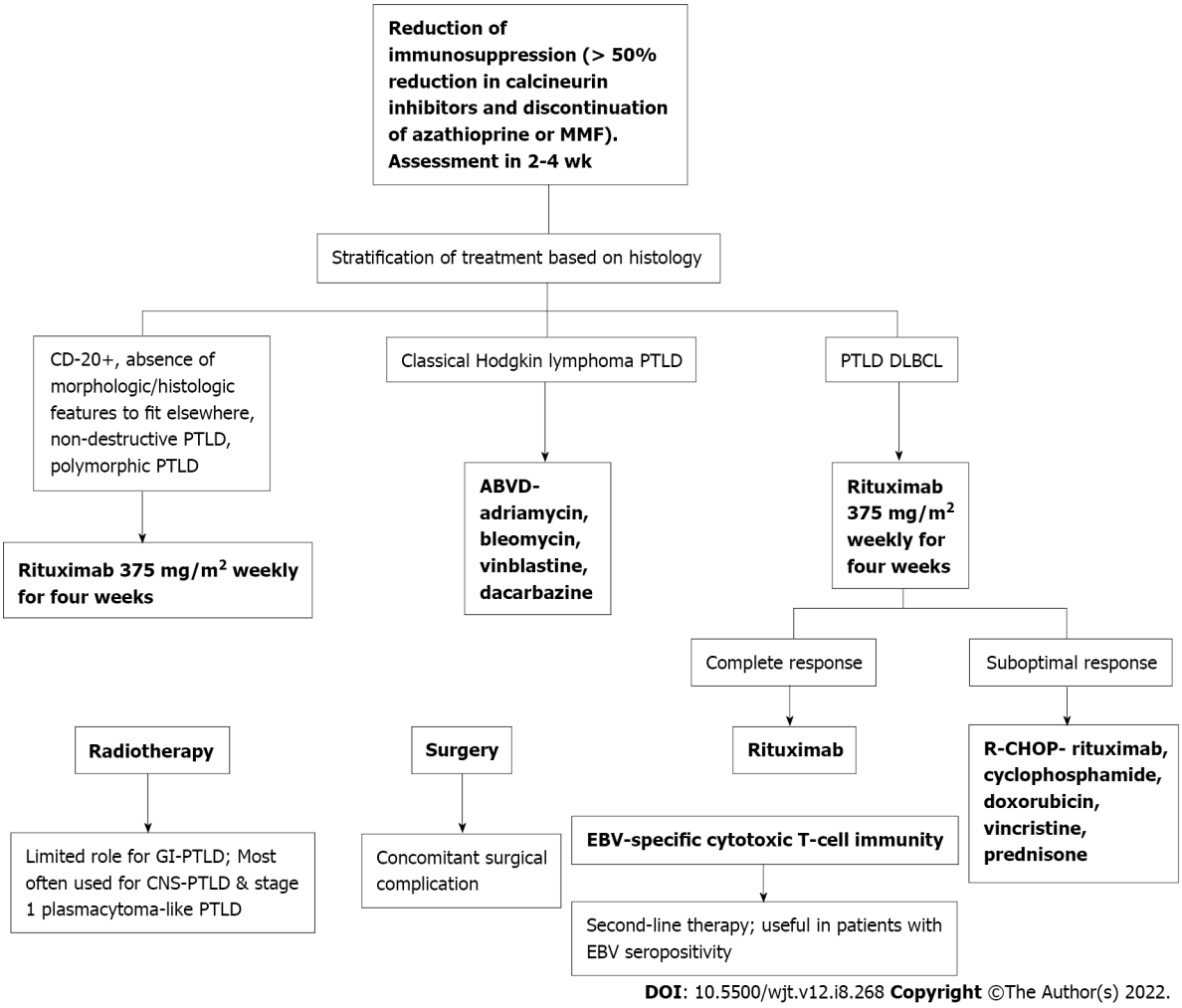

Figure 7 Workflow of the treatment for post-transplant lymphoproliferative disorder. PTLD: Post-transplant lymphoproliferative disorder; EBV: Epstein-Barr virus; GI: Gastrointestinal; MMF: Mycophenolate mofetil; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; DLBCL: Diffuse large B-cell lymphomas.

represent pathology in these organs important. Imaging findings of PTLD in the GI tract may range from focal intraluminal disease to perforation or metastatic disease. The various clinical presentations and wide-ranging imaging findings make it difficult to specifically identify PTLD by clinical presentation or imaging alone.

Consideration of PTLD should increase in patients with risk factors. Most importantly determination of EBV-status and risk factors for EBV infection need to be determined. EBV infection has been noted to increase the risk of PTLD by 6-76 times[46]. As mentioned previously, elucidation of details surrounding the transplant including transplant type, determination of RIS regimen including whether induction therapy was utilized are important. As transplantation continues to increase, so will the number of patients at risk for development of PTLD[14,19,22,23,25].

Like other lymphomas, PTLD is aggressive and mortality rates improve with early treatment. Prognosis and treatment are dependent on time of disease presentation, morphological subtype of PTLD, and concomitant systemic disease. The most important step in management is RIS; which is usually efficacious. Subsequently, rituximab and chemotherapy based on morphologic subtype have been found to be effective[18]. Differences in outcomes between surgery and treatment with rituximab are not well elucidated, nor is the role of endoscopy in management of PTLD. Broadly, treatment must consider both the risk of acute graft rejection and worsening lymphoproliferative disorder.

CONCLUSION

This study is a systematic review elucidating GI manifestations, associations, and management of GI-PTLD. Key points after review of the included studies are the presentation, imaging, and direct appearance of GI-PTLD is highly variable making clinical suspicion essential for timely diagnosis. Patients with nonspecific GI symptoms, and history of organ transplantation, should be evaluated for

GI-PTLD. Early detection is key for prognosis. Lastly, treatment is dependent on several factors and may include RIS, rituximab, chemotherapy, surgery, or a combination of these interventions. Initial treatment is intuitive and technically easy; however, RIS can be associated with acute graft rejections.

ARTICLE HIGHLIGHTS

Research background

Post-transplant lymphoproliferative disorder (PTLD) is one of the most common post-transplant malignancies within the gastrointestinal (GI) tract. PTLD is a lymphoma variant which can manifest in patients having solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT).

Research motivation

The current understanding of GI manifestations of PTLD including timing to development, risk factors for development, and treatment is limited by small sample size. Previous studies have noted a propensity for the GI tract to develop PTLD; therefore, more information regarding when it may develop, how it manifests, and treatments are needed especially as transplantation becomes more prevalent.

Research objectives

To identify the timing and clinical presentation of GI-PTLD, risk factors for its development, and treatment.

Research methods

We performed a systematic review after an extensive literature search.

Research results

The timing of GI-PTLD is variable but on average develops 4-5 years following SOT and may occur within 1 year after HSCT. Presentation may be insidious including nonspecific abdominal discomfort to fulminant hemorrhage, perforation, or obstruction. GI-PTLD is most likely to develop in the small intestine and stomach. Transplant type, level of induction and maintenance immunosuppression, Epstein-Barr virus-status among other risk factors increase the likelihood one may develop PTLD. PTLD is aggressive and mortality improves with early treatment which is dependent on extent of disease, and morphological subtype. The most important step of therapy is reduction of immunosuppression (RIS) which usually is effective.

Research conclusions

The presentation, imaging, and direct appearance of GI-PTLD is highly variable making clinical suspicion key for diagnosis. Early detection is key for prognosis; therefore, consideration of risk factors is essential. Treatment is dependent on several factors and may include RIS, rituximab, chemotherapy, surgery, or a combination of these interventions. Initial treatment is intuitive and technically easy; however, RIS can be associated with acute graft rejections.

Research perspectives

This study suggests ascertainment of risk factors is crucial for increasing clinical suspicion when assessing patients who may have GI-PTLD. The clinical and radiological presentation of GI-PTLD is highly variable; therefore, a high index of suspicion for GI-PTLD must be maintained so that early endoscopic diagnosis may allow for targeted treatment. Future prospective studies are needed to better elucidate incidence rates of GI-PTLD and the role of endoscopy in treatment.

FOOTNOTES

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ORCID number: William Reiche 0000-0001-8797-5764; Abubakar Tauseef 0000-0002-4317-1868; Ahmed Sabri 0000-0002-9220-4187; Mohsin Mirza 0000-0001-5454-3439; David Cantu 0000-0001-9993-1312; Peter Silberstein 0000-0003-1300-0846; Saurabh Chandan 0000-0002-2661-6693.

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Editorial Board Member of *World Journal of Transplantation*, Ahmed M Zidan, MD, MSc, PhD, Associate Professor, Surgeon, Consultant of General, HBP and Transplant Surgery, Assiut University Hospital, Assiut 7111, Egypt. ahmed.zidan@med.au.edu.eg

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MINIREVIEWS

Growing challenge of post-liver transplantation non-alcoholic fatty liver disease

Maria Styliani Kalogirou, Olga Giouleme

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Maria Styliani Kalogirou, Olga Giouleme, Gastroenterology and Hepatology Division of the Second Propedeutic Department of Internal Medicine, Hippokration General Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Corresponding author: Maria Styliani Kalogirou, MD, MSc, Doctor, Research Fellow, Gastroenterology and Hepatology Division of the Second Propedeutic Department of Internal Medicine, Hippokration General Hospital, Medical School, Aristotle University of Thessaloniki, Konstantinoupoleos 49, Thessaloniki 54642, Greece. maria.kalogi32@gmail.com

Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide, with an estimated prevalence of 25%. Post-liver transplantation (LT) recurrent or *de novo* hepatic steatosis is a common complication in recipients, irrespective of transplantation indication. Risk factors for graft steatosis mainly include obesity, immunosuppression, donor steatosis, and genetic factors. Liver transplant recipients are at high risk of developing insulin resistance, new-onset diabetes, and post-transplantation metabolic syndrome that is highly associated with immunosuppressive treatment. Post-LT NAFLD is often underdiagnosed due to the poor sensitivity of most routine imaging methods. The gold standard for the diagnosis of hepatic steatosis is liver biopsy, which is, however, limited to more complex cases due to its invasive nature. There is no approved pharmacotherapy in NAFLD. Lifestyle modification remains the cornerstone in NAFLD treatment. Other treatment strategies in post-LT NAFLD include lifestyle modifications, pharmacotherapy, bariatric surgery, and tailored immunosuppression. However, these approaches originate from recommendations in the general population, as there is scarce data regarding the safety and efficacy of current management strategies for NAFLD in liver transplant patients. Future prospective studies are required to achieve tailored treatment for these patients.

Key Words: Non-alcoholic fatty liver disease; Steatohepatitis; Hepatic steatosis; Liver transplantation; Cirrhosis; Metabolic syndrome

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a common complication in liver transplant recipients. Despite the rising prevalence and potentially progressive nature of this entity, there are currently no recommendations regarding NAFLD diagnosis and management in the post-transplant setting. Future studies are urgently needed to fill this knowledge gap and define optimal diagnostic and treatment approaches in this patient population.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of steatosis in at least 5% of hepatocytes in the absence of any secondary causes, such as excessive alcohol consumption or other chronic liver diseases[1]. NAFLD encompasses a wide spectrum of histological findings, ranging from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH), the latter of which is additionally characterized by lobular inflammation and hepatocyte ballooning[2]. NAFL is generally considered a slowly progressive or non-progressive condition, while NASH is associated with an increased risk of disease progression to cirrhosis and hepatocellular carcinoma[3].

EPIDEMIOLOGY

NAFLD has become the leading cause of chronic liver disease worldwide, with an estimated prevalence of 25%, which is constantly rising in parallel to the worldwide obesity pandemic[4]. NAFLD is often considered the hepatic component of the metabolic syndrome and is associated with other metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and insulin resistance (IR)[5]. Due to the increasing prevalence and high risk of progression, NASH has become the second most common indication for liver transplantation (LT) in the United States, reporting a 170% increase from 2004 to 2013[6,7]. LT leads to the resolution of NASH-related complications; however, the underlying metabolic risk factors remain, and are even exacerbated following LT, resulting in a high rate of post-LT NAFLD recurrence[8]. In addition, many recipients are prone to develop a post-LT metabolic syndrome (PTMS), mainly due to the reversal of the cirrhosis-related catabolic state and immunosuppression side effects, leading to *de novo* NAFLD[9].

Recurrent NAFLD

Recurrence of steatosis and steatohepatitis in recipients with a pre-transplant diagnosis of NASH is more common compared to *de novo* NAFLD, with a prevalence ranging between 8% and 100% in a follow-up period of 1-10 years[10]. Yalamanchili *et al*[11] studied 257 patients transplanted for NASH or cryptogenic cirrhosis. Post-LT steatosis was reported in 31% of patients; however, bridging fibrosis or cirrhosis was only found in 5% and 10% of recipients after 5 years and 10 years, respectively[11]. In a recent retrospective study of 275 NASH recipients, the prevalence of NAFLD and NASH recurrence was 22% and 11%, respectively[12]. However, it should be underlined that most studies have important heterogeneity regarding NAFLD diagnosis and patient selection. Recipients with cryptogenic cirrhosis as an indication for LT were included in most of these studies, resulting in a possible NAFLD recurrence overdiagnosis[11,13,14].

De novo NAFLD

De novo NAFLD is defined as the presence of steatosis or steatohepatitis in patients who underwent LT for indications other than NASH[15]. Up to one-third of liver transplant recipients develop *de novo* NAFLD depending on a combination of host and graft factors[16,17]. Dumortier *et al*[16] studied 599 non-NASH liver transplant recipients and reported a prevalence of *de novo* NAFLD of 31%[16]. The authors demonstrated several independent risk factors for the occurrence of post-LT *de novo* steatosis, such as post-LT obesity, tacrolimus-based immunosuppression therapy, diabetes mellitus, and pre-transplant liver graft steatosis, demonstrating a dose-dependent relationship between the number of these risk factors and the risk of developing *de novo* NAFLD. In a recent meta-analysis by Losurdo *et al*[15] the pooled prevalence of *de novo* NAFLD and NASH was 26% and 2%, respectively, at a follow-up period of 6 mo to 10 years[15]. The highest prevalences were observed in patients transplanted for either alcoholic (37%) or cryptogenic cirrhosis (35%), or those receiving tacrolimus (26%). Data remain,

however, scarce regarding these entities, while the retrospective design and small sample size of most studies represent important limitations.

RISK FACTORS

Several risk factors have been associated with post-LT NAFLD occurrence (Table 1). As mentioned above, the pre-transplant metabolic risk factors persist following LT, despite the resolution of liver disease. In addition, the commonly used maintenance immunosuppressive regimens, namely corticosteroids, calcineurin inhibitors (CNIs), and mammalian targets of rapamycin (mTOR) inhibitors are directly linked to obesity, hypertension, dyslipidemia, and hyperglycemia, exacerbating the existing metabolic profile of transplanted patients or leading to a new-onset PTMS. Recipients are at high risk of developing PTMS, irrespective of LT indication, with an estimated prevalence ranging from 44%-58% at 6 mo following LT[17]. The presence of PTMS has been associated with both recurrent and *de novo* NAFLD[16,18,19]. Pre-transplant graft-steatosis, genetics, and other recipient-related risk factors appear to contribute to the development of both recurrent and *de novo* NAFLD in the transplanted population [20]. In a recent observational study of 108 recipients, it was concluded that recipient-related factors are more important than donor-related factors in the development of NAFLD, following LT[21].

Genetic factors

Several studies have attempted to reveal the role of genetic predisposition in the development of post-LT NAFLD. Both recipient and donor genetics have been associated with an increased risk of graft steatosis. The role of patatin-like phospholipase domain-containing protein 3 (PNPLA3) in the development of NAFLD is well established. Finkenstedt *et al*[22] showed that LT recipients who carry rs738409-GG in PNPLA3 are at increased risk of post-LT NAFLD[22]. In another study of 176 liver transplant patients, Trunečka *et al*[23] demonstrated that the expression of PNPLA3 p.148M variant in donors represents an independent risk factor for graft steatosis[23]. The donor transmembrane 6 superfamily member 2 c.499A allele was also associated with a higher risk of steatosis in recipients[24]. John *et al*[25] found that recipient, but not donor, adiponectin polymorphisms rs1501299 G/G and rs17300539 G/G were related to a higher prevalence of post-LT graft steatosis[25].

Immunosuppression

The maintenance immunosuppressive agents used after LT can exacerbate a preexisting metabolic syndrome in recipients, or lead to a new-onset PTMS, thereby contributing to the development of recurrent and *de novo* NAFLD[26]. Corticosteroids are widely used in the immediate post-operative period against allograft rejection. They increase the hepatic output of glucose and decrease insulin production and peripheral glucose uptake, inducing IR. Corticosteroid use has been associated with an increased risk of T2DM, dyslipidemia, hypertension, and rapid weight gain in recipients following LT [27]. CNI therapy (cyclosporine and tacrolimus) is also recognized as a risk factor for metabolic syndrome and consequent post-LT NAFLD. They are linked to hypertension, dyslipidemia, new-onset T2DM, and chronic renal disease, with tacrolimus having a more prominent diabetogenic effect compared to cyclosporine, which is mainly associated with post-transplant hypertension[26,28,29]. However, studies investigating the direct association between CNI therapy and post-LT NAFLD seem to provide conflicting results[16,30,31]. Another commonly used class of immunosuppressive drugs, mTOR inhibitors, appear to have metabolic adverse effects, being associated with significant dyslipidemia and IR[26]. Sirolimus increases adipose tissue lipase activity and decreases lipoprotein lipase activity, resulting in hypertriglyceridemia, especially with concomitant cyclosporine therapy[32,33]. In a retrospective study of 430 post-LT biopsies, Galvin *et al*[31] reported that sirolimus use was predictive of *de novo* NAFLD following LT[31].

Donor graft steatosis

Donor steatosis has also been suggested as a potential risk factor for post-LT *de novo* and recurrent NAFLD. While microvesicular steatosis does not affect graft function or survival, donor livers with severe macrovesicular steatosis have been associated with an increased risk of primary graft dysfunction, inferior graft survival, and requirement for retransplantation[34]. However, there is not enough evidence to support the predictive role of donor steatosis in the development of post-LT NAFLD. Three studies have indicated an association between pre-existing donor graft steatosis and post-LT NAFLD, whereas findings in a meta-analysis by Saeed *et al*[35] did not support this association [16,35-37].

Pre-transplant liver disease

Aside from NASH, specific other LT indications have been associated with an increased risk of *de novo* NAFLD. Recipients with a pre-transplant diagnosis of alcoholic liver disease (ALD) are at higher risk of developing *de novo* post-LT steatosis[16,30]. Hepatitis C virus infection was also reported as a risk factor for post-LT NAFLD[31,38]. In a meta-analysis by Losurdo *et al*[15], the authors reported the highest

Table 1 Risk factors associated with post-transplantation non-alcoholic fatty liver disease

Recipient factors	Donor factors
Obesity/post-LT weight gain	Macrovesicular graft steatosis
T2DM	Genetics
Dyslipidemia	
Genetics	
Immunosuppression	
LT indication: NASH, HCV, ALD	

ALD: Alcoholic liver disease; HCV: Hepatitis C virus; LT: Liver transplantation; NASH: Non-alcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.

prevalence of *de novo* NAFLD in patients that underwent an LT for ALD and cryptogenic cirrhosis (37% and 35%, respectively)[15].

PROGNOSIS

Despite the high prevalence of recurrent and *de novo* NAFLD following LT, progression to NASH and advanced fibrosis is less frequent in these patients. Dumortier *et al*[16] reported recurrent steatosis in 31% of recipients; however, NASH and advanced fibrosis/cirrhosis were only observed in 3.8% and 2.25% of patients[16]. Yalamanchili *et al*[11] confirmed these findings, reporting similarly low incidence rates of NASH and cirrhosis in patients with post-LT NAFLD (4% and 10%, respectively)[11]. However, in the meta-analysis by Saeed *et al*[35], the authors reported significantly higher rates of recurrent and *de novo* NASH (38% and 17%, respectively)[35]. Overall survival of patients transplanted for NASH-related cirrhosis is comparable to those with non-NASH indications in most studies[39-41]. In a recent retrospective analysis of 68950 patients that underwent LT for end-stage liver disease of various indications, Haldar *et al*[42] confirmed the aforementioned findings and demonstrated a patient survival at 1, 5, and 10 years post-LT of 84.1%, 73.4%, and 62.1%, respectively, for NASH patients that underwent LT[42]. Overall graft survival was also reported similar between NASH recipients *vs* those with non-NASH LT indications. Mortality in patients transplanted for NASH was mainly attributed to cardio/cerebrovascular disease and infection rather than liver-related complications. However, the true impact of recurrent or *de novo* NAFLD on overall and graft survival has not been largely investigated. Dureja *et al*[43] studied 88 liver transplant recipients and found no difference in post-LT survival between patients with NAFLD recurrence and those without in a follow-up period of 5 years[43]. More relevant studies with longer follow-up time are necessary to clarify whether post-LT NAFLD *per se* is associated with increased mortality in the post-transplant setting.

MANAGEMENT

There are scarce data regarding the treatment of NAFLD in liver transplant patients. Main treatment strategies include lifestyle modifications, pharmacotherapy, bariatric surgery, and alteration in immunosuppression therapy[44]. The first approach in the management of post-LT NAFLD is lifestyle modification including adequate physical activity, weight loss, and calorie restriction. No drugs have been approved for the treatment of NAFLD and none of the proposed pharmacotherapies has been studied in the post-transplant population. In the latest American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines, pioglitazone, and vitamin E, either as monotherapy or as combination therapy, have been proposed as a potential treatment approach in biopsy-proven NASH patients[45]. However, there are concerns about the safety of long-term use of vitamin E, as it has been associated with an increased risk of prostate cancer and hemorrhagic stroke[46,47]. Pioglitazone has been associated with weight gain and should be, therefore, cautiously recommended in transplanted patients, for fear of exacerbating post-LT obesity and PTMS [48]. Bariatric surgery is recommended in cases where obese patients cannot achieve weight reduction following LT; however, there are concerns regarding the potential malabsorption and altered pharmacokinetics of immunosuppressive drugs[49,50]. Optimization of immunosuppression is of vital importance to reduce drug-induced metabolic risks and subsequent NAFLD in the post-LT period. Early steroid withdrawal, minimization, and alterations of immunosuppressive regimens based on patient's metabolic complications are common approaches in the management of PTMS. More specifically, in cases where hypertension is the major metabolic complication, conversion from

cyclosporine to tacrolimus has been shown to have a beneficial effect on blood pressure[51]. Similarly, reducing tacrolimus dosage or switching to another immunosuppression regimen has been associated with better glycemic control in recipients with new-onset T2DM[52]. mTOR inhibitors, on the other hand, should be avoided in cases of severe uncontrolled dyslipidemia[32,33].

CONCLUSION

Post-LT NAFLD remains a great challenge for hepatologists and transplant surgeons. Early detection of modifiable risk factors plays a crucial role in preventing disease occurrence. There is an unmet need for specific recommendations regarding both NAFLD screening and management in the post-transplant setting. Post-LT diagnosis tends to be underdiagnosed due to poor sensitivity of routine imaging modalities, whereas liver biopsy is not routinely used for NAFLD diagnosis, due to its invasive nature and possible complications. Regarding disease management, while numerous studies have investigated potential treatment approaches for NAFLD in non-transplant patients, there are scarce data on liver-transplant recipients, with most treatment strategies being extrapolated from recommendations in the general population. However, certain limitations in transplanted patients, such as reduced physical activity, immunosuppressive therapy, and drug-drug interactions with NAFLD treatment regimens, as well as treatment dilemmas regarding minimization or alteration of immunosuppression therapy in the setting of PTMS remain major problems for hepatologists. Prospective, longitudinal studies in liver transplant recipients are necessary to optimize screening, disease monitoring, and treatment in this special patient population.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Maria Styliani Kalogirou 0000-0001-9985-4038; Olga Giouleme 0000-0003-0176-3598.

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MINIREVIEWS

Liver transplantation during COVID-19: Adaptive measures with future significance

Argyrios Gyftopoulos, Ioannis A Ziogas, Martin I Montenovo

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Argyrios Gyftopoulos, School of Medicine, National Kapodistrian University of Athens, Athens 14564, Greece

Ioannis A Ziogas, Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, United States

Martin I Montenovo, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, United States

Corresponding author: Martin I Montenovo, FACS, MD, Associate Professor, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Vanderbilt University Medical Center, 1313 21st Ave S, Nashville, TN 37232, United States.
martin.montenovo@vumc.org

Abstract

Following the outbreak of coronavirus disease 2019 (COVID-19), a disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the field of liver transplantation, along with many other aspects of healthcare, underwent drastic changes. Despite an initial increase in waitlist mortality and a decrease in both living and deceased donor liver transplantation rates, through the implementation of a series of new measures, the transplant community was able to recover by the summer of 2020. Changes in waitlist prioritization, the gradual implementation of telehealth, and immunosuppressive regimen alte-rations amidst concerns regarding more severe disease in immunocompromised patients, were among the changes implemented in an attempt by the transplant community to adapt to the pandemic. More recently, with the advent of the Pfizer BNT162b2 vaccine, a powerful new preventative tool against in-fection, the pandemic is slowly beginning to subside. The pandemic has cert-ainly brought transplant centers around the world to their limits. Despite the unspeakable tragedy, COVID-19 constitutes a valuable lesson for health systems to be more prepared for potential future health crises and for life-saving tran-splantation not to fall behind.

Key Words: Liver transplantation; COVID-19; SARS-CoV-2; Vaccine; Immunosuppression; Telehealth

Core Tip: Several articles in the bibliography report on the state of liver transplantation during coronavirus disease 2019 (COVID-19). To our knowledge, this is the first review to retrospectively investigate the various changes that occurred throughout the pandemic, but also recognize which interventions, and to what extent, are possibly going to help the transplant community improve beyond the end of COVID-19; in the event of a major health crisis in the future, transplant programs should be able to adapt even faster to the rapidly changing landscape, in order for life-saving transplantation not to fall behind.

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INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has changed the landscape for transplant programs across the United States[1]. Although helpful, the experience gained from previous outbreaks, like the middle eastern respiratory syndrome coronavirus, could not quite compare to the full-scale pandemic of the last two years. Therefore, transplant programs were largely unprepared for the challenges of the current pandemic, as evidenced by the complex moral decision of temporarily holding life-saving transplantation for fear of COVID-19 transmission amongst immunocompromised patients, the healthcare personnel, and the community[2]. Despite primarily being a respiratory pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacts liver biochemistry and many other organs[3,4]. The S protein on the surface of SARS-CoV-2 binds the angiotensin-converting enzyme 2 receptor on the surface of hepatocytes, injecting its viral genome inside liver cells [5]. Aside from its direct cytotoxic effect, SARS-CoV-2 may adversely affect the liver through its systemic inflammatory response and, indirectly, through many potentially hepatotoxic medications employed to combat COVID-19[6]. At the same time, the effect of COVID-19 on cirrhotic patients can be especially severe due to their baseline immunosuppression in the setting of chronic liver disease[7]. However, it is not uncommon for SARS-CoV-2 to cause only mild elevations in hepatic enzymes, with patients otherwise remaining asymptomatic, either due to the virus' minor hepatotoxicity or through COVID-19-related inflammation of the muscles, with little direct injury to the liver[8].

Because of the significant health risks the new coronavirus poses to patients with chronic liver disease and liver transplant recipients, the transplant community had to adapt to the pandemic. In the spring of 2020, and in the states most severely affected by COVID-19, new listings were 11% lower than anticipated, there were 59% more deaths in patients waiting for a transplant than expected, and 34% fewer deceased donor liver transplantations. Fear of transmission amongst patients and healthcare workers has led to a series of new measures, such as regular testing, mandatory protective equipment against the virus, and telehealth to replace in-person visits during the pandemic[9]. At the same time, the race to develop new vaccines against SARS-CoV-2 has given hope that the end of the pandemic is slowly approaching. COVID-19 accelerated the implementation of measures already in motion in the transplant community, albeit at a slower pace.

This review aims to retrospectively evaluate the status of liver transplantation during the pandemic, the effectiveness of multiple vaccine doses in liver transplant recipients, the recent change in the waitlist prioritization policy, potential alterations in immunosuppressive regimens for COVID-19 positive recipients, and explore the benefits and drawbacks of telehealth during and after the pandemic.

LIVER TRANSPLANTATION IN THE COVID-19 ERA

As the pandemic is slowly getting better controlled, the scientific community has a chance to evaluate how COVID-19 has affected liver transplantation programs during this unforeseen worldwide health crisis by tracing changes regarding vaccination protocols, waitlist prioritization, immunosuppression regimens, and the implementation of telehealth. These adaptive mechanisms may prove to be an invaluable lesson in the face of future health threats so that the rate of liver transplants will not descend again.

A query of the United Network for Organ Sharing database showed that, throughout the pandemic, whenever the number of new coronavirus cases peaked, primarily during the winter months, the number of transplants showed a concurrent decrease (Figure 1). In early 2020, from mid-March to mid-April, in states most severely affected by COVID-19, there were 11% fewer new listings, 49% fewer living donor transplantations, 9% fewer deceased donor liver transplantations, and 59% more deaths while waiting for a transplant than anticipated[10]. Despite every successive COVID-19 wave inherently

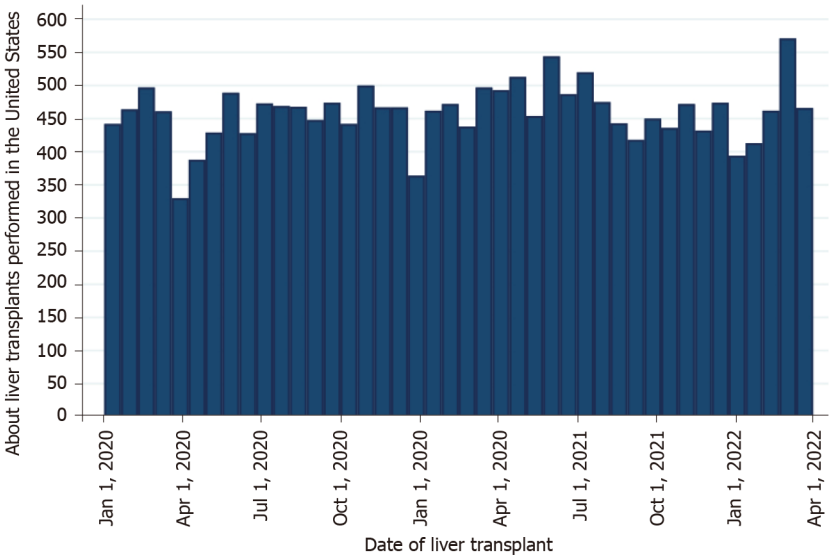

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Figure 1 Number of adult liver transplants performed in the United States between January 1, 2020, and April 1, 2022 (data from the United Network for Organ Sharing database). The number of liver transplants performed during the course of the coronavirus disease 2019 pandemic. An initial decrease in the Spring of 2020 was countered with a series of measures, that restored the number of transplants by the Summer of 2020. With each consecutive wave, primarily during the winter months, there were fewer adult liver transplants.

carrying different epidemiologic outcomes than those of the first wave, transplant programs seemed to adapt to the changing landscape, as by August of the same year, except for deceased donor liver transplants, rates were within the expected range[11]. The increased waitlist mortality, particularly during the first few months of 2020, can be explained by a multitude of factors, including deaths from end-stage liver disease while waiting for transplantation, the inability to admit patients facing complications of chronic liver disease, and the particularly severe impact of SARS-CoV-2 on obese patients with concurrent non-alcoholic steatohepatitis listed for transplantation[12]. While SARS-CoV-2 has a direct toxic effect on the liver, the extent to which it can affect patients with chronic liver disease has not been definitively established; only mild elevations in liver enzymes are known to occur, with patients remaining otherwise asymptomatic[13,14].

Observing how the transplant community managed to adapt relatively quickly by the summer of 2020, following a brief period of increased waitlist mortality and decreased living and deceased liver transplantation rates during the spring of 2020, it would be of great interest to investigate how the new liver transplant allocation policy change influenced that result. In December 2018, United Network for Organ Sharing approved a new allocation policy called the "acuity circle policy", eventually implemented on February 4, 2020, coinciding with the beginning of the COVID-19 pandemic in late 2019 [15]. The new model would replace the "donation service area" distribution system, whereby one area was served by only one specific organ procurement organization. Under the new policy, the distance between donor and recipient was the primary determinant of organ allocation. Inevitably, states with lower COVID-19 incidence, where transplant centers were still active, received a larger volume of transplant patients from other, more heavily infested areas.

However, it is difficult to know the degree to which the changes that occurred after the acuity circle allocation policy resulted from the implementation of the new model or the concurrent outbreak of the coronavirus pandemic shifting the landscape for liver transplant allocation across the United States. By some preliminary estimates, under the new allocation system, adult patients with lower model for end-stage liver disease (MELD) scores have received fewer transplants, while at high MELDs, transplantation rates were actually increased[10]. According to Radhakrishnan and Goldberg, the new allocation policy has led to delays in procurement times due to the logistics involving procurement team travel, the challenges in working with new centers, and the increased number of possible local recipients [16]. On the other hand, pediatric liver transplant recipients, median MELD/pediatric end-stage liver disease scores decreased under the new system, indicating that they were now receiving transplants earlier, thus avoiding the life-threatening risk of being diagnosed with late-stage disease by the time of transplantation[17]. As the acuity circle allocation policy is relatively new, future studies may retrospectively prove its value during the outbreak of COVID-19 and may even display its usefulness after accounting for the drastic changes brought on by the pandemic. Regardless, seeing how the transplant community was able to adapt during the current pandemic, the acuity circle policy may prove to be a valuable tool, guiding efforts to improve waitlist mortality and deceased and living donor transplantation rates in the face of potential health crises in the future[9,13].

IMMUNOSUPPRESSION AND COVID-19 IN LIVER TRANSPLANT RECIPIENTS

At the beginning of the pandemic, it was postulated that the use of immunosuppressive regimens in liver transplant recipients would predispose them to a higher risk for severe disease following COVID-19 infection. In a study of 39 solid organ transplant recipients, reported mortality following COVID-19 was 37.5% in the liver group[18]. Despite the limited number of patients, mortality was significantly higher in immunosuppressed patients than in other studies. In a nationwide Korean study by Baek *et al* [19] that included a total of 6435, both immune-competent and immunocompromised subjects, mortality in the immunocompromised group was 9.6% - including patients who had undergone transplantation in the last three years, were taking steroids or other immunosuppressants, were diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome or had a known malignancy[19]. The potential risk of post-transplant immunosuppression regimens contributing to a more severe clinical course in SARS-CoV-2 infected patients had to be balanced against the inevitable risk of rejection following reduction of the treatment. An individualized approach to immunosuppressive regimen alteration in the setting of COVID-19 was stressed by Giannis *et al*[20], whereby not all transplant recipients, and certainly not all COVID-19 positive patients, are the same; in other words, COVID-19 complicated the already individualized approach to transplant regimen selection and therapeutic-range dose regulation even further[20]. An Iranian study recruiting 265 liver transplant recipients with a median time since transplantation of 68 mo identified 25 patients who contracted COVID-19, four of whom eventually died. For fear of organ rejection, the patients' immunosuppressive regimens were only slightly modified, with mycophenolate mofetil (MMF) dose being reduced to limit liver enzyme level elevation. While previous studies have argued in favor of lowering immunosuppression during COVID-19, Sheikhalipour *et al*[21], among others, have shown that despite minimal alterations in the patients' immunosuppressive regimen, most participants fully recovered from COVID-19[22]. Ethical considerations regarding the risk of acute rejection following a significant reduction in the immunosuppressive regimen make randomized control trials investigating the role of immunosuppression discontinuation or decrease in the setting of COVID-19 inherently challenging.

The choice of immunosuppression has proven to variably affect postoperative mortality for coronavirus-positive liver transplant recipients. Tovikkai *et al*[23] conducted a large retrospective study including 3837 liver transplant recipients from the United Kingdom. They showed cardiovascular disease and non-hepatic malignancy amongst transplant recipients were the primary determinants of mortality within 10 years after transplantation[23]. Interestingly, in a study by Becchetti *et al*[24], coronavirus-positive liver transplant recipients did not necessarily have worse outcomes than other solid transplant recipients, while only active extra-hepatic cancer was associated with increased mortality from SARS-CoV-2 infection, but cardiovascular disease did not predispose to a worse outcome. Immunosuppression was reduced in 39% of patients and discontinued in 7% - primarily in patients taking MMF[24]. Importantly, patients who did not require hospitalization due to COVID-19-related complications had no change in their immunosuppressive regimen, arguing that maintaining the immunosuppressant dose stable may not negatively impact outcomes in liver transplant recipients infected with SARS-CoV-2[20]. Colmenero *et al*[25] conducted a cohort study including 111 liver transplant recipients who tested positive for COVID-19, whom they followed for 23 d. Out of the 96 patients requiring admission, there was an 18% mortality rate, which was actually lower than that of the general population (28% and 42% in patients requiring high-dependency unity and intensive care unit admission, respectively), pointing towards a potential anti-viral effect of immunosuppressive therapy, with the exception of MMF[26]. Although immunosuppressive regimen modification is a complex decision, one to be made by the transplant center regarding each individual patient, MMF has been associated with increased rates of severe COVID-19 at doses greater than 1000 mg per day, perhaps explained by the peripheral $CD4^+$ depleting effect of MMF acting in synergy with the cytotoxic T-cell effect of SARS-CoV-2[25]. On the contrary, mammalian target of rapamycin inhibitors have memory T-cell boosting effects, while calcineurin inhibitors are postulated by *in vitro* studies to tone down the cytokine storm responsible for acute respiratory distress syndrome in patients with COVID-19[27,28].

COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS

With the advent of the BNT162b2 vaccine, a safe and effective preventive strategy against COVID-19 was made available to transplant recipients. In a study by Hardgrave *et al*[29], amongst 103 unvaccinated liver transplant recipients, before vaccination had been made widely available, 90-d mortality was 10%, with age > 60, use of belatacept and cyclosporin being associated with an increased risk, and tacrolimus acting as a protective factor. Interestingly, comorbidities (hypertension, diabetes, obesity) were not significantly associated with high mortality rates amongst unvaccinated individuals[29]. Prior studies have demonstrated the safety and efficacy of inactivated and subunit vaccines against various pathogens in solid transplant recipients[30]. It is not unlikely, however, for immunocompromised patients to be unable to mount an adequate immune response following vaccination. Interestingly, liver transplant recipients have shown better immune response rates to SARS-CoV-2 vaccination than other

solid organ recipients. Out of the 43 liver transplant recipients who received the second dose of the BNT162b2 vaccine, 79% developed antibodies, compared to 100% of immunocompetent individuals, but their response was reportedly superior to that of other solid organ recipients in the bibliography[31]. According to the recent Global Hepatology Society Statement and the European Association for the Study of the Liver, liver transplant recipients are strongly encouraged to get vaccinated with any approved COVID-19 vaccine, as the benefits outweigh the risks of SARS-CoV-2 infection[32-34].

The BNT162b2 vaccine is an mRNA vaccine that has proven to be safe, albeit with low immunogenicity, particularly following its second dose, in specific categories of liver transplant patients[35]. In a group of 107 patients, just 76% achieved immunity six months following their second vaccine. However, after receiving their third dose, 91% of patients had sufficient antibody titers against SARS-CoV-2[36]. Various factors have been reported to affect the degree of immunogenicity following vaccination in liver transplant patients (Figure 2). Combined immunosuppression with a calcineurin inhibitor and another agent, either MMF, steroids, or mammalian target of rapamycin inhibitors (double or triple regimen), were risk factors for a reduced immune response after the second dose of the BNT162b2 vaccine[37,38]. Renal impairment was also associated with lower vaccine responses following the second dose, with a mean estimated glomerular filtration rate of 56 mL/min amongst patients who were unable to mount an adequate immune response *vs* 75 mL/min amongst patients who had a positive immunoglobulin G spike[35]. Interestingly, renal toxicity is one of the key side effects of calcineurin inhibitors - the predominant immune suppressive agents used post-transplantation, which have even been shown to harbor a protective effect against severe COVID-19 disease[39]. Older age is another significant risk factor for lower immunogenicity, with one study showing a mean age of 63 years in liver transplant recipients with a negative immune response, compared to 58 years in positive vaccine responders[35]. Furthermore, in a group of 365 patients, a higher body mass index (mean 27.7 in seronegative recipients *vs* 26.7 in positive vaccine responders, $P = 0.031$) and a shorter time since liver transplantation (11.9 years in seronegative recipients *vs* 14.7 years in seropositive transplant patients, $P = 0.031$) were also significant risk factors for attenuated vaccine response, according to Guarino *et al*[40]. Mazzola *et al*[41] identified diabetes as an additional risk factor for a negative response after the second dose of the SARS-CoV-2 BNT162b2 vaccine in a study that included 133 liver transplant recipients, with 46 out of 55 diabetic patients in the study group not mounting an adequate immune response following the second dose.

The variable effectiveness following each dose of the COVID-19 vaccine may reflect a different effect on T and B cell populations after every booster, with each cell type playing a different role in the immune system's defense against SARS-CoV-2. Despite the importance of humoral immunity in preventing infection following vaccination, the role of T-cell-mediated immunity has not been established[42]. Although T cells (CD4, CD8) are theoretically implicated in the defense against SARS-CoV-2, a recent study by Ruether *et al*[43] showed decreased rates of cellular immunity in liver transplant recipients following the second BNT162b2 vaccine dose[38]. On the contrary, in 74 patients treated with rituximab, only 39% of patients seroconverted, indicating that $CD19^+$ B cells seem primarily responsible for the immune response generated following the second vaccine dose. Interestingly, according to Davidov *et al*[44], after receiving the third dose, 98% of patients seroconverted, compared to only 56% following the second dose. At the same time, T-cell counts increased significantly in all 12 liver transplant recipients who were evaluated[44]. A similar T-cell amplifying effect was demonstrated by Schrezenmeier *et al*[45] in a study of 25 kidney transplant recipients who had been unable to mount an adequate humoral response after their second dose. Thirty-six percent of those patients eventually generated humoral immunity, with $CD4^+$ T-cell levels significantly increased in the same patients[45]. In recipients with lower humoral titers following vaccination, a T-cell response may instead protect against the virus. Fernández-Ruiz *et al*[46] demonstrated that 22% of liver transplant recipients had an adequate T-cell spike response following their third vaccine dose. The role of T-cell mediated cellular immunity against SARS-CoV-2 as a complementary or second-line defense mechanism against the virus is yet to be investigated by future studies.

TELEHEALTH IN LIVER TRANSPLANTATION

SARS-CoV-2 has had a profound effect on nearly all aspects of medicine. Liver transplant centers, among others, have had to adjust their practices to the new landscape[47]. High-volume centers were notably affected the most; the number of transplants performed had decreased initially, and the time spent on the waitlist had shortened. With approximately 15% of organs originating from coronavirus-positive donors, protocols and treatment regimens had to change. Notably, telemedicine emerged as a solution to the consecutive lockdowns and the unavoidable halt to in-person patient visits[25]. While it is not without its downsides, there is a clear consensus on the benefits telehealth can have in liver transplant programs during the pandemic. As new protocols are implemented, telehealth is proving to be an effective alternative to in-person visits even after the end of the pandemic.

Proper follow-up, along with improvements in perioperative care, surgical technique, and immunosuppression, is largely responsible for the improved outcomes in liver transplant recipients

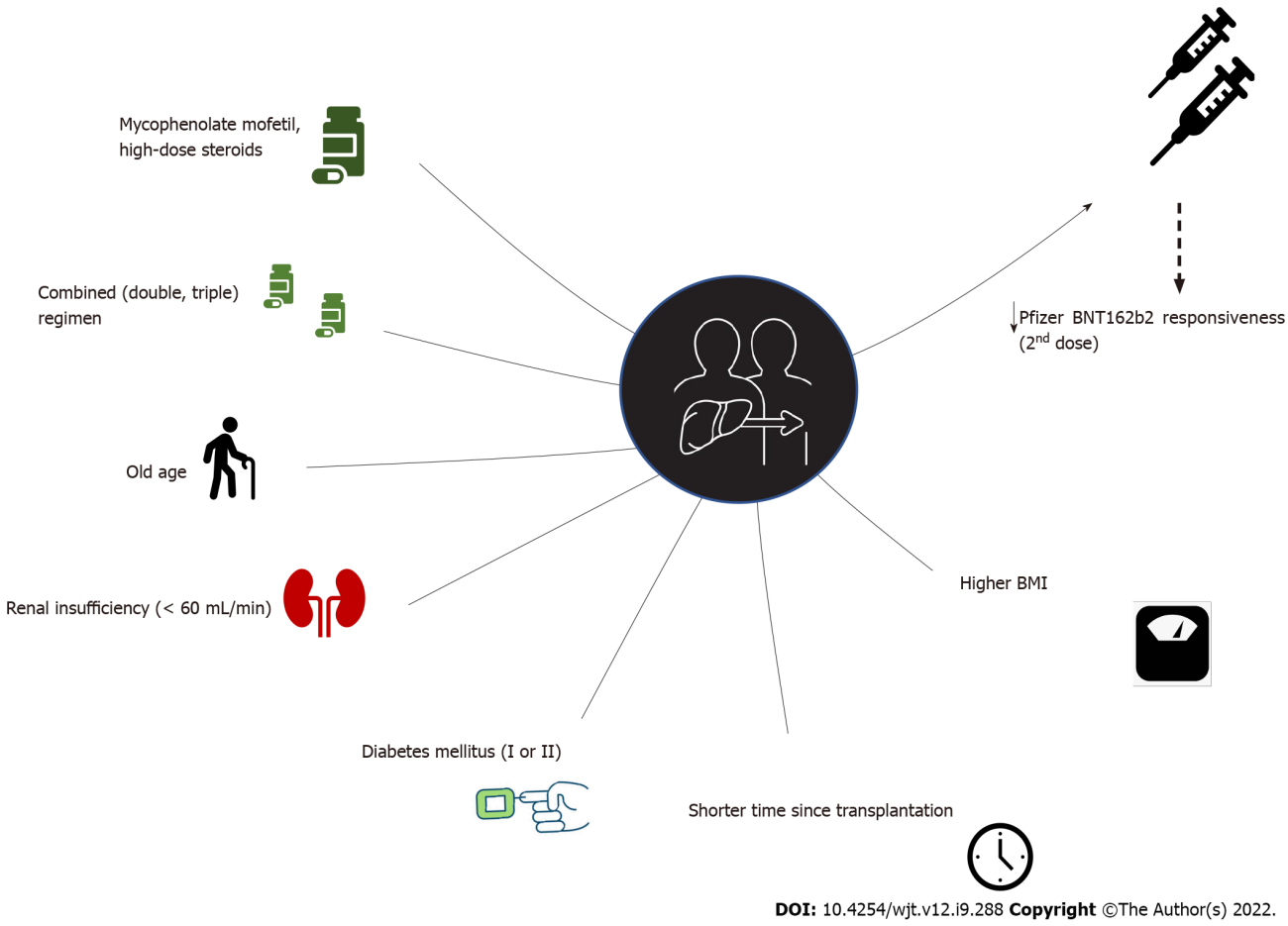

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Figure 2 Factors contributing to decreased response rate following the second dose of the BNT162b2 vaccine in liver transplant recipients. BMI: Body mass index.

over the last decades[48]. Survival after transplantation is slowly approaching that of the general population, but at the same time, there is an increasing number of patients requiring postoperative follow-up. In the first five years following transplantation, major causes of mortality include cardiovascular disease and infection, while death after that time is usually attributed to malignancy, renal failure, and cardiovascular disease[49]. Therefore, the importance of regular follow-up to ensure compliance with treatment, proper imaging, and biochemical studies cannot be understated. While cooperation between primary care providers, transplantation centers, and liver clinics is crucial, especially for patients living further away from the transplant hospital, telehealth may offer another option[50].

Prior studies have demonstrated the usefulness of telehealth in heart failure and diabetic glucose regulation, exhibiting similar results to telephone follow-up and in-patient visits[51]. With regards to liver transplantation, one study showed that long-term follow-up *via* telehealth had comparable outcomes to in-person follow-up, with the only drawback of requiring stricter control over tacrolimus levels[52]. Importantly, 75% of physically stable transplant patients expressed interest in telemonitoring, with distance from the hospital being a major contributing factor. A different study by Le *et al*[53] involving a small number of matched patients followed *via* telehealth underlined the increased satisfaction from shorter wait times and complete absence of travel, with 90% of patients stating they would opt for telemedicine again. In an interesting approach toward new technologies, Levine *et al*[54] had 108 patients assigned to regular in-person follow-up, app-assisted follow-up in the form of tacrolimus level monitoring, and app-plus-smartwatch groups (mean ages 53, 52, and 50, respectively), demonstrating no significant difference in tacrolimus levels overall. Moreover, telehealth can impact multiple constituents of post-transplant patient care, from immunosuppression to lifestyle modification, as demonstrated by Barnett *et al*[55] in a group of 19 liver transplant recipients, in whom telemedicine effectively promoted adherence to dietary and exercise recommendations.

Despite all the benefits telemedicine has to offer, especially amidst a pandemic, there are undeniable downsides to its use (Table 1). One study involving 98 young adults (*i.e.*, individuals acquainted with new technologies), who had undergone liver transplantation in childhood, showed that during the COVID-19 pandemic, of the 12 patients who were followed up *via* video calls, nine had experienced rejection episodes and were using telehealth as an adjunct to in-person visits[56]. Delman *et al*[57] also

Table 1 Telehealth in liver transplantation - benefits and possible drawbacks/areas of improvement

Benefits	Drawbacks
Ease of follow-up (lack of travel)	Lack of a physical exam
Fewer costs	
Saves time	
Preferred by patients living in remote areas	
As effective as in-person follow-up (stricter drug level control may be required)	Few studies demonstrated increased readmissions associated with telehealth follow-ups[56]
Ease of access (smartphone, smartwatch apps)	Lack of access to technology (hardware)
	Institution-level
	Patient-level
Multiple aspects of postop patient care (immunosuppression, diet, exercise, *etc.*)	Communities/homes with limited internet access (software)
	Technical problems (hardware)
	Lack of a private setting in shared living environments
	Limited English proficiency, need for an interpreter
	Auditory/visual impairment, additional need for aids
	Concerns regarding adherence of younger patients

pointed out a rather concerning drawback regarding increased readmissions following telemonitoring. Despite not being statistically significant (41.9% *vs* 61.5% 30-d readmission rate in patients followed by telehealth), the exhibited difference could be partly explained by the lack of a physical exam; still, hospital length-of-stay was significantly shorter in the telemedicine group. Another possible drawback of new technologies is the relative lack of access, as not all centers and not all patients can afford newer computer systems. At the same time, the learning curve may also prove to be a challenge for healthcare professionals and patients alike, who are not acquainted with the new technologies[57]. Despite being more adept at embracing emerging technologies, young people may actually be the ones more challenged regarding adherence, therefore constantly being at risk of rejection[58]. Lower socioeconomic status may further contribute to inequalities in the use of new technologies; namely, internet access is not always available; many patients may lack an appropriately private setting for the physician-patient encounter to take place; they may have limited English proficiency, or limiting visual or hearing impairment that may hinder proper physician-patient communication[59]. Furthermore, technical problems often arise, as demonstrated by a recent randomized control trial recruiting 54 patients; only 17% of patients could attend all appointments without technical issues. Regardless, patients agreed that video appointments saved them time and money, were easier to attend, and limited the exposure of immunocompromised individuals to COVID-19 during the peak of the pandemic[60]. All in all, the ideal use of new technologies may entail their co-implementation with the classic processes (*i.e.*, outpatient visits), especially as pandemic-related restrictions are slowly being lifted, contrary to telehealth replacing in-person appointments entirely. An interesting point could be made regarding the need for general physicians ''closer to home'' to be more deeply involved in the care of transplant recipients, complementing the role of telehealth and perhaps aiding the transplant community to overcome certain limitations associated with its use (*i.e.*, lack of a physical exam, software and hardware-related issues, accessibility difficulties)[61].

CONCLUSION

Overall, during the last two-and-a-half years, the COVID-19 pandemic has significantly changed liver transplant programs worldwide. It is fair to say that certain changes, such as updated vaccination protocols or immunosuppressive regimen modifications, would never have happened had it not been to ameliorate the effect of COVID-19 on transplant recipients. Other changes, however, such as the reformed waitlist prioritization policy and the implementation of telehealth, were accelerated by the pandemic. It is up to the scientific community to assess the outcome of these measures now that the pandemic is slowly subsiding; what was initially viewed as a "necessary evil" by many physicians could be a unique opportunity to overcome limitations and address pitfalls in the current system. In addition to the already existing problems, such as liver donor shortage, future health crises are now becoming a pressing concern, threatening to make the work of transplant centers even more challenging

than it already is. The COVID-19 pandemic could be an invaluable lesson as, despite its terrible implications, perhaps it catalyzed significant changes in the transplant community that will help surgeons adapt in the face of significant health crises in the future.

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FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Argyrios Gyftopoulos 0000-0002-6545-0884; Ioannis A Ziogas 0000-0002-6742-6909; Martin I Montenovo 0000-0001-8645-7797.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Vitamin D deficiency may predispose patients to increased risk of kidney transplant rejection

Semih Buyukdemirci, Ebru Gok Oguz, Sanem Guler Cimen, Hatice Sahin, Sertac Cimen, Mehmet Deniz Ayli

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Semih Buyukdemirci, Department of Internal Medicine, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Ebru Gok Oguz, Hatice Sahin, Mehmet Deniz Ayli, Department of Nephrology, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Sanem Guler Cimen, Department of General Surgery, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Sertac Cimen, Department of Urology, Sağlık Bilimleri Universitesi, Ankara 65000, Altındağ, Turkey

Corresponding author: Sanem Guler Cimen, Doctor, FEBS, Adjunct Associate Professor, Department of General Surgery, Sağlık Bilimleri Universitesi, Güvenlik Caddesi No 87/6, Ankara 65000, Altındağ, Turkey. sanem.cimen@sbu.edu.tr

Abstract

BACKGROUND

Vitamin D deficiency occurs in more than 80% of kidney transplant recipients. Its immunomodulatory effects can predispose transplant recipients to rejection and chronic allograft nephropathy (CAN). This study determined the association between serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

AIM

To determine the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

METHODS

Adult renal transplant recipients followed at the clinic between January 2013 and 2018 were included. Recipients requiring graft biopsy due to declined function, hematuria, and proteinuria were reviewed. The two groups were compared regarding collected data, including the biopsy results, immunologic parameters, vitamin D, parathyroid hormone (PTH), phosphorus, albumin levels, and graft function tests.

RESULTS

Fifty-two recipients who underwent graft biopsy met the inclusion criteria. In all,

14 recipients had a vitamin D level > 15 ng/mL (group 1) *vs* ≤ 15 ng/mL (group 2) in 38. In total, 27 patients had biopsy-proven rejection, and 19 had CAN. There was only 1 recipient with biopsy-proven rejection in group 1, whereas there were 24 patients with rejection in group 2. The rejection rate was significantly higher in group 2 than in group 1 ($P < 0.001$). Four patients were diagnosed with CAN in group 1 *vs* fifteen in group 2. There was no significant difference in the CAN rate between the two groups. PTH was higher at the time of graft biopsy ($P = 0.009$, $P = 0.022$) in group 1 with a mean of 268 pg/mL. Donor-specific antibodies were detected in 14 (56.0%) of the recipients with rejection. Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant ($P = 0.003$). The albumin levels were significantly lower in patients with rejection than in those without rejection ($P = 0.001$). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have an impact ($P = 0.027$, $P = 0.007$, $P = 0.023$, $P = 0.008$). In multivariate regression analysis, the same factors did not affect rejection.

CONCLUSION

The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to determine the effect of serum vitamin D levels on allograft rejection.

Key Words: Kidney transplantation; Rejection; 25 (OH) vitamin D; Vitamin D; Chronic allograft nephropathy

Core Tip: This study analyzed the results of 130 kidney transplant recipients. Of the 52 recipients who underwent graft biopsy and met the study inclusion criteria, 14 had a vitamin D level > 15 ng/mL *vs* ≤ 15 ng/mL in 38. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to clearly discern the effects of serum vitamin D level on the renal allograft rejection rate.

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INTRODUCTION

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves quality of life. In addition, following kidney transplantation, 75% of recipients return to work, and approximately 1 in 50 females can get pregnant[1]. For recipients to experience these benefits, close follow-up and optimization of modifiable risk factors are crucial. One of the modifiable risk factors is the serum vitamin D level[2].

It is known that 25 (OH) vitamin D plays a significant role in calcium and phosphate balance. Furthermore, a low vitamin D level can have deleterious effects on renal allografts[3,4]. A large prospective clinical study on kidney transplant recipients reported that a low 25 (OH) vitamin D level was associated with a reduced glomerular filtration rate (GFR) at 9 mo post-transplantation[5]. Moreover, vitamin D has a wide range of effects on the immune, renal, and cardiovascular systems[6]. The vitamin D receptor (VDR) is found in almost every immune cell including macrophages, CD4+/CD8+ T lymphocytes, and dendritic cells. VDR induces allograft tolerance by directing naive T lymphocytes to transform into T helper type 2 cells phenotypically; this process is defined as vitamin D-influenced immunomodulation[7].

The immunomodulatory features of vitamin D have been observed in autoimmune diseases such as psoriasis and rheumatoid arthritis and in experimental transplant models showing that vitamin D analogs amplified cyclosporin A's inhibitory effects on acute and chronic allograft rejection[8,9]. Likewise, vitamin D analogs inhibit adventitial inflammation and intimal hyperplasia in rat aortic allografts [10]; however, the effect of the vitamin D level on the allograft rejection and chronic allograft nephropathy (CAN) rates have not been studied in detail in kidney transplant recipients. Therefore, this study

determined the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

MATERIALS AND METHODS

Study design and population

This single-center retrospective cohort study was performed at the Health Sciences University of Turkey, Diskapi Research and Training Hospital, Department of Nephrology and Transplantation, Ankara, Turkey. All adult renal transplant recipients followed at the transplant clinic between January 2013, and July 2018 were reviewed. Among these patients, recipients requiring allograft biopsy due to progressive graft function decline, new-onset hematuria, and proteinuria were included in the study.

Allograft biopsies were performed as per Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines[11]. Banff 97 criteria were used to evaluate biopsy specimens[12]. Biopsy specimens were considered adequate if they had ≥ 10 glomeruli and two arteries; patients with inadequate biopsy specimens were excluded from the study. Additionally, patients with post-transplant follow-up < 1 year were excluded from the study to establish a homogeneous cohort. The serum vitamin D level was measured every 3 mo, as per the KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder. All recipients received vitamin D replacement therapy considering their serum vitamin D levels, as per KDIGO guidelines[13].

Demographic characteristics, medical history, prior type and duration of dialysis, donor type, human leukocyte antigen (HLA) mismatches, maintenance immunosuppression, biopsy results, and serum vitamin D level at the time of graft biopsy were obtained from hospital records by a research nurse. In addition, as this study determined the relationship between serum vitamin D level and allograft biopsy results, other biochemical parameters associated with rejection and CAN, such as the GFR, and serum creatinine, albumin, calcium, phosphate, and parathyroid hormone (PTH) levels at the time of graft biopsy, were also recorded. The study protocol was approved by the hospital's ethical review committee (06.08.2018-no. 53/20) and was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul. All patients provided written informed consent.

Immunosuppression

Recipients of live donor kidneys were induced with interleukin 2 receptor blockers and steroids, whereas recipients of deceased donor kidneys were induced with anti-thymocyte globulin and steroids. Maintenance immunosuppression was based on mycophenolate mofetil (MMF), prednisone, and calcineurin, or mammalian target of rapamycin inhibitors.

Vitamin D status

The serum vitamin D level was measured using the chemiluminescence method (Kit No: A98856; Beckman Coulter Inc., Sykesville, MD, United States). A serum vitamin D level > 30 ng/mL (*i.e.*, > 75 nmol/L) was considered adequate. Concentrations between 15 and 30 ng/mL (40-75 nmol/L) were considered vitamin D insufficiency, whereas < 15 ng/ mL (< 37.5 nmol/L) was considered vitamin D deficiency according to KDIGO guidelines[13].

Biochemistry

The serum PTH concentration was measured *via* immunochemiluminescent assay (Kit No: A16972; Beckman Coulter). Total calcium, phosphate, glucose, blood cell count, albumin, uric acid, total cholesterol, triglyceride, C-reactive protein (CRP), and creatinine levels were measured using standard methods (Kit Nos: OSR61117, OSR6222, OSR 6221, DW20180105, OSR6202, OSR 6298, OSR 6116, OSR6199, and OSR6178, respectively; Beckman Coulter). The GFR was calculated using the modification of diet in renal disease formula.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, United States). The distribution of data was analyzed using the Kolmogorov-Smirnov test. Mean ± SD was used for descriptive analysis of parametric quantitative data, whereas number and percentage were used to analyze the qualitative data. The student's *t*-test was used for parametric data analysis, and the Mann-Whitney *U* test was used for non-parametric data analysis. Pearson's chi-square test was used to analyze qualitative data. The level of statistical significance was set at $P < 0.05$. Binary logistic regression analysis was used to determine the independent factors related to rejection. After excluding multicollinear variables, clinically relevant variables and parameters presenting statistical significance were subject to the binary logistic regression analysis. The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to show the factors affecting the outcomes.

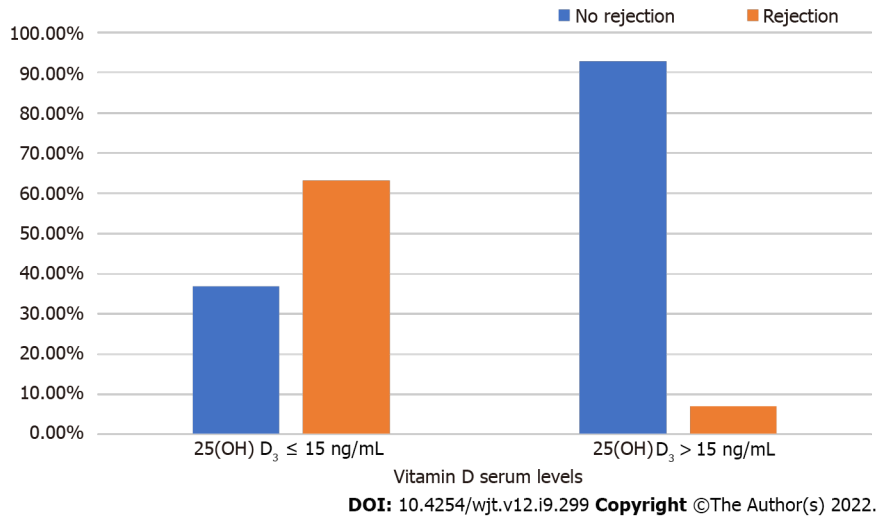

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Figure 1 Baseline vitamin D levels at the time of biopsy, and the rejection rate in the low and high vitamin D level groups ($P < 0.001$).

RESULTS

Among 130 kidney transplant recipients, 52 met the study inclusion criteria. The mean age of the recipients was 41 ± 11.9 years, of which 38 (73.1%) were male and 14 (26.9%) were female. During the post-transplantation period, 25 (48.1%) patients had hypertension and 15 (28.8%) had diabetes mellitus. Pre-transplantation duration of dialysis was 5.8 ± 4.71 years, and hemodialysis was the most common therapy (82.7%). The majority (65.4%) of the study population received live donor kidney transplants, of which 3 (5.8%) were transplanted preemptively. Of the 34 live donors, 20 were spousal donations, 10 were first-degree relatives, and 4 were second-degree relatives.

The average age of the donors was 49.6 ± 9.7 years, and the majority of them were 29 (55.8%) male. The mean post-transplant duration of follow-up was 5.91 ± 1.83 years. The mean number of HLA mismatches was 3 ± 1. Delayed graft function developed in 9 (17.6%) patients. Fourteen (27.5%) patients were donor-specific antibody (DSA)-positive at the time of renal biopsy. Kidney failure had occurred due to hypertension in 25 (48.1%), diabetes mellitus in 15 (28.8%), glomerulonephritis in 7 (13.5%), post-renal kidney disease in 3 (5.8), and unknown reasons in 2 (3.8%) of the recipients (Table 1).

Maintenance immunosuppressive regimens at the time of graft biopsy were as follows: 38 (73.4%) patients were on a combination of MMF, tacrolimus, and prednisone, whereas 11 (20.9%) were receiving a combination of MMF, cyclosporine, and prednisone. Only 3 (5.7%) of the recipients used mechanistic target of rapamycin inhibitor-based regimens. At the time of allograft biopsy, the average serum trough calcineurin level was 4.8 ± 0.8, cyclosporine serum level ng/mL was 545 ± 89, and the mean daily intake of MMF was 1.7 ± 0.3 gr/d. Within the study cohort 20 patients were receiving vitamin D treatments according to the KDIGO guidelines. Among the 52 allograft biopsies, 25 (48%) showed rejection. Acute T cell-mediated rejection, acute antibody-mediated rejection (ABMR), and chronic active ABMR were observed in 6 (11.5%), 10 (19.2%), and 9 (17.3%) of the recipients, respectively. CAN was noted in 19 (36.5%) of the recipients. Calcineurin toxicity was observed in 3 (5.8%) patients, whereas BK virus nephropathy and recurrent nephritis were noted in 4 (7.7%) and 1 (1.9%), respectively.

The study population was divided into two groups based on the serum vitamin D level (Table 2). Patients with a vitamin D level > 15 ng/mL constituted group 1, and those with a level ≤ 15 ng/mL constituted group 2. The two groups were compared concerning graft function, HLA mismatches, biochemical parameters, GFR, and rejection status. Group 1 included 14 (27%) patients, and group 2 included 38 (73%). There were no significant differences concerning age, comorbidities, or HLA mismatches between the groups ($P > 0.05$). Males were predominant in group 2 ($P = 0.035$). Four (28.6%) recipients in group 1 and 15 (39.5%) recipients in group 2 were diagnosed with CAN. There was no significant difference in the CAN rate between the two groups ($P > 0.05$). Only 1 (7.1%) recipient was diagnosed with rejection in group 1 and 24 (63.2%) recipients in group 2. The biopsy-proven rejection rate was significantly higher in group 2 compared to group 1 ($P < 0.001$) (Figure 1).

The estimated GFR (eGFR) was 38 ± 18.3 in group 1 and 41 ± 19.7 in group 2. There was no significant difference between these groups regarding eGFR ($P > 0.05$). In addition, hemoglobin, serum glucose, albumin, CRP, calcium, phosphate, uric acid, total cholesterol, triglyceride, blood urea nitrogen, and creatinine did not significantly differ between the two groups ($P > 0.05$). The mean PTH level was 205 pg/mL in group 1 and 268 pg/mL in group 2. PTH level was higher in group 2 than in group 1 ($P = 0.007$).

Table 1 Demographic characteristics of the kidney recipients at the time of graft biopsy

Parameter	Patients, *n* = 52
Mean age, yr	41 ± 11.9
Male, *n* (%)/female, *n* (%)	38 (73.1)/14 (26.9)
DM, *n* (%)/HT, *n* (%)	15 (28.8)/25 (48.1)
Hemodialysis, *n* (%)/peritoneal dialysis, *n* (%)	43 (82.7)/6 (11.5)
Mean dialysis duration, yr	5.8 ± 4.71
Pre-emptive, *n* (%)	3 (5.8)
Donor type: Living, *n* (%)/Cadaver, *n* (%)	34 (65.4)/18 (34.6)
Donor sex: Male/female	29 (55.8)/23 (44.2)
Donor age in yr	49.6 ± 9.7
Time since transplantation, yr	5.91 ± 1.83
Number of HLA mismatches	3 ± 1
DGF, *n* (%)	9 (17.6)
DSA, *n* (%)	14 (27.5)
Cyclosporine/tacrolimus serum levels, ng/mL	545 ± 89/4.8 ± 0.8
MMF, gr/d	1.7 ± 0.3
Pre-transplant kidney failure etiology	
DM, *n* (%)	15 (28.8)
HT, *n* (%)	25 (48.1)
Glomerulonephritis, *n* (%)	7 (13.5)
Post-renal kidney failure, *n* (%)	3 (5.8)
Unknown, *n* (%)	2 (3.8)

CSA: Cyclosporine A; DM: Diabetes mellitus; DGF: Delayed graft function; DSA: Donor-specific antibody; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; TAC: Tacrolimus.

The study cohort was also divided into two groups based on the presence or absence of biopsy-proven rejection (Table 3). The mean age was 39 ± 12.9 in the rejection group and 42 ± 10.9 in the no-rejection group. In the rejection group females were predominant [22 (88%) *vs* 16 (59.3%); $P = 0.020$]. The comorbid status, previous dialysis vintage, and donor characteristics did not differ between these two groups ($P > 0.05$). Hemoglobin, glucose, CRP, calcium, uric acid, lipid profile, and the number of HLA mismatches did not differ between groups ($P > 0.05$). Nevertheless, there were significant differences in the serum albumin, phosphorus, PTH, vitamin D, and DSA levels. The albumin was 4.0 ± 0.5 g/dL in the no-rejection group *vs* 3.5 ± 0.6 g/dL in the rejection group ($P = 0.001$). Phosphorus, PTH, and vitamin D levels in the no-rejection group were 3.9 ± 1.52 mg/dL, 197 pg/mL, and 17.4 ± 7.2 ng/mL, respectively. The results of these parameters in the rejection group were 5.3 ± 1.96 mg/dL for phosphorus, 310 pg/mL for PTH, and 9.7 ± 3.4 ng/dL for vitamin D serum levels. The *P* values of these comparisons showed a statistically significant difference between the two groups ($P = 0.009$, $P = 0.022$, and $P = 0.003$, respectively). DSA positivity was present in 14 (56%) of those with rejection (56%), whereas no patients in the non-rejection group had DSA positivity ($P < 0.001$). There was no significant difference between the two groups regarding serum cutaneous neurogenic inflammation levels and daily MMF dose ($P > 0.05$). Kidney failure with a GFR < 15 mL/min was observed in 5 (18.5%) patients in the non-rejection group and 12 (48%) in the rejection group. The kidney failure rate was significantly higher in the rejection group ($P = 0.024$); patients in the rejection group had lower GFRs and higher serum creatinine levels ($P = 0.012$ and $P = 0.016$, respectively). The serum vitamin D level was significantly lower, and the PTH level was significantly higher in the rejection group than in the non-rejection group ($P = 0.003$ and $P = 0.022$). A regression analysis was performed using rejection risk factors (Table 4). In univariate regression analysis, female sex, serum vitamin D level, phosphorus, and albumin were found to be effective in the development of rejection ($P = 0.027$, $P = 0.007$, $P = 0.023$, $P = 0.008$). However, these risk factors did not demonstrate a significant effect ($P > 0.05$).

Table 2 Comparison of demographic characteristics and laboratory findings in the low and high vitamin D level groups at the time of graft biopsy

Vitamin D level	Group 1 (> 15 ng/mL), *n* = 14	Group 2 (≤ 15 ng/mL), *n* = 38	*P* value
Age, yr	40 ± 11.9	41 ± 12.0	0.856
Male, *n* (%)	7 (50)	31 (81.6)	0.035
DM/HT, n (%)	2 (14.3)/6 (42.9)	13 (34.2)/19 (50)	0.300/0.759
Hemodialysis/peritoneal dialysis	12 (92.3)/1 (7.7)	31 (86.1)/5 (13.9)	1.00
Mean dialysis duration, yr	5.9 ± 4.5	5.6 ± 3.7	0.839
Preemptive, *n* (%)	1 (7.1)	2 (5.3)	1.00
Rejection, *n* (%)	1 (7.1)	24 (63.2)	< 0.001
CAN, *n* (%)	4 (28.6)	15 (39.5)	0.534
Number of HLA mismatches	3 ± 1	3 ± 1	1.00
ESRD actual, *n* (%)	7 (58.3)	10 (27)	0.80
Hemoglobin, g/dL	11.5 ± 2.0	10.7 ± 2.4	0.266
Glucose, mg/dL	106 ± 60.7	98 ± 33.9	0.433
Albumin, g/dL	4.0 ± 0.4	3.7 ± 0.6	0.063
Uric acid, mg/dL	7.1 ± 1.8	7.7 ± 1.5	0.276
Urea, mg/dL	68 ± 35.3	77 ± 38.6	0.416
Creatinine, mg/dL	2.08 ± 0.61	2.21 ± 1.22	0.702
eGFR, mL/min/1.73 m^2	38 ± 18.3	41 ± 19.7	0.609
Proteinuria, g/d	1.0 ± 0.9	2.5 ± 3.1	0.261
Cholesterol, mg/dL	186 ± 36.9	177 ± 46.2	0.515
Triglyceride, mg/dL	178 ± 82.9	191 ± 110.1	0.877
Calcium, mg/dL	8.9 ± 0.99	8.7 ± 0.80	0.400
Phosphorus, mg/dL	4.8 ± 1.84	4.5 ± 1.86	0.657
PTH, pg/mL (range)	205 (78-927)	268 (59-955)	0.007
CRP, mg/dL	24 ± 48.2	21 ± 29.9	0.483

CAN: Chronic allograft nephropathy; CRP: C-reactive protein; DM: Diabetes mellitus; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; PTH: Parathyroid hormone.

DISCUSSION

Vitamin D deficiency is associated with a broad spectrum of diseases, including autoimmune conditions such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes. In addition, vitamin D deficiency is associated with a severe decrease in the GFR and shorter life expectancy in patients with chronic kidney diseases[14-16].

Epidemiological studies conducted with kidney transplant recipients reported that the prevalence of vitamin D deficiency is as high as 90%, possibly due to the side effects of immunosuppressive regimens and a reduction in sun exposure related to the recommendation that these patients avoid sunlight[2,3,17,18]. Falkiewicz *et al*[19] reported severe 1.25-dihydroxyvitamin D deficiency in 83% of kidney transplant recipients and that these patients had a high graft failure rate, which is in agreement with the present finding that the mean serum vitamin D level was 12.3 ± 6.2 ng/mL, indicating severe vitamin D deficiency. Findings regarding the relationship between vitamin D and organ rejection are inconsistent. For example, Zimmerman *et al*[5] reported no relationship between the vitamin D level and acute allograft rejection. By contrast, Kim *et al*[20] who conducted a prospective clinical trial that considered 25 nmol/L as the threshold for vitamin D deficiency, observed a correlation between a low vitamin D level and the acute rejection rate. Similarly, Lee *et al*[21] reported that kidney transplant recipients with a vitamin D level < 50 nmol/L within 30 d of transplantation had a higher risk of acute rejection during the 1st year post-transplant. Additionally, Bienaimé *et al*[22] showed that vitamin D deficiency led to interstitial fibrosis and tubular atrophy within the kidney parenchyma in kidney transplant recipients.

Table 3 Demographic characteristics and laboratory findings according to rejection status at the time of graft biopsy

Rejection	No	Yes	*P* value
Patients, *n*	27	25	
Mean age, yr	42 ± 10.9	39 ± 12.9	0.316
Female, *n* (%)	16 (59.3)	22 (88.0)	0.020
DM, *n* (%)/HT, *n* (%)	7 (25.9)/13 (48)	8 (32.0)/12 (48)	0.629/0.991
Donor type Cadaver, *n* (%)	7 (25.9)	11 (44.0)	0.171
Donor age, yr	47.7 ± 9.6	51.8 ± 9.6	0.133
Time since transplantation, yr	4.4 ± 1.4	5.3 ± 3.1	0.236
Number of HLA mismatches	2.2 ± 1.2	2.6 ± 1.2	0.263
DSA, *n* (%)	0	14 (56.0)	< 0.001
Cyclosporine/tacrolimus serum levels, ng/mL	576 ± 98/4.7 ± 0.9	490 ± 29/4.9 ± 0.7	0.063/0.352
MMF, gr/d	1.7 ± 0.3	1.7 ± 0.3	0.601
ESRD actual, *n* (%)	5 (18.5)	12 (48)	0.024
Hemoglobin, g/dL	11.5 ± 2.2	10.4 ± 2.3	0.095
Glucose, mg/dL	95 ± 37.7	107 ± 46.7	0.399
Albumin, g/dL	4.0 ± 0.5	3.5 ± 0.6	0.001
Uric acid, mg/dL	7.3 ± 1.6	7.7 ± 1.6	0.364
Creatinine, mg/dL	1.78 ± 0.44	2.59 ± 1.40	0.016
eGFR, mL/min/1.73 m^2	45 ± 19.3	36 ± 18.3	0.012
Cholesterol, mg/dL	177 ± 37.2	181 ± 49.8	0.810
Triglyceride, mg/dL	180 ± 103.4	196 ± 104.1	0.379
Calcium, mg/dL	8.8 ± 0.79	8.7 ± 0.92	0.562
Phosphorus, mg/dL	3.9 ± 1.51	5.3 ± 1.96	0.009
PTH, pg/mL (range)	197 (59-440)	310 (106-955)	0.022
Vitamin D, ng/mL	14.7 ± 7.2	9.7 ± 3.4	0.003
CRP, mg/mL	20 ± 24.9	23 ± 43.2	0.05

CRP: C-reactive protein; DM: Diabetes mellitus; DSA: Donor-specific antibody; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; PTH: Parathyroid hormone.

Vitamin D deficiency is associated with glomerular disease in native and transplanted kidneys, and this finding has been attributed to endothelial cell dysfunction. Therefore, it was proposed that a low serum vitamin D level and an elevated fibroblast growth factor-23 level hinder endothelial cell function and lead to endothelial injury[23-25]. Although normal endothelium expresses major histocompatibility complex (MHC) class I antigens only, in endothelial injury and inflammation cases, MHC class II antigens are also expressed on the cell surface. These MHC class II antigens increase the recruitment and adhesion of CD4+ T cells and initiate allorecognition. Alloantigen recognition subsequently triggers the production of inflammatory mediators and activates the complement cascade[26-28]. The present study could not evaluate endothelial dysfunction or MHC class II antigen expression due to its retrospective design; however, a correlation between a low serum vitamin D level and the kidney rejection rate was observed ($P < 0.001$).

On the other hand, as graft rejection and CAN share some immunological pathways, we suggest that the serum vitamin D level might play a role in CAN risk[29]. To the best of our knowledge, the present study is the first to examine the relationship between vitamin D deficiency and CAN. In the present study, the CAN rate did not differ according to the vitamin D level ($P = 0.534$).

The present findings indicate that the long-term graft survival rate remains moderate, even with meticulous management of risk factors, including vitamin D replacement. In this study, patients with rejection had higher phosphorus and PTH measurements at the time of graft biopsy ($P = 0.009$, $P = 0.022$), and vitamin D and albumin levels were significantly lower in this group ($P = 0.003$, $P = 0.001$). Univariate regression analysis elucidated that female sex, serum vitamin D, phosphorus, and albumin

Table 4 Univariate and multivariate regression analyses for rejection

	Univariate regressions				Multivariate regression			
	B	OR	95%CI	*P* value	B	OR	95%CI	*P* value
Age	-0.02	0.97	0.93-1.02	0.381	-0.04	0.95	0.87-1.03	0.265
Sex, female	1.61	5.04	1.20-21.06	0.027	1.12	3.08	0.31-30.45	0.336
Donor type Cadaver, *n* (%)	0.46	1.58	0.50-5.00	0.434	1.52	4.60	0.71-29.77	0.109
Donor sex, female, *n* (%)	-0.33	0.71	0.23-2.15	0.555	0.40	1.50	0.26-8.38	0.643
Donor age, yr	0.03	1.04	0.98-1.10	0.192	0.40	1.04	0.95-1.13	0.340
DGF, *n* (%)	-0.22	0.80	0.18-3.40	0.763	-1.41	0.24	0.01-4.36	0.337
MMF, gr/d	0.78	2.19	0.69-6.97	0.183	0.84	2.32	0.33-16.37	0.397
Serum fosfor (mg/dL)	0.43	1.53	1.06-2.22	0.023	0.63	1.87	1.01-3.48	0.05
Vitamin D, ng/mL	-0.153	0.85	0.76-0.96	0.007	-0.12	0.88	0.72-1.06	0.196
PTH	0.01	1.00	1.00-1.01	0.052	0.01	1.00	0.99-1.00	0.516
Albumin (g/dL)	-1.49	0.22	0.07-0.68	0.008	-1.17	0.30	0.05-1.69	0.177
CSA serum level, ng/mL	-0.01	0.99	0.99-1.00	0.265	0.01	1.00	0.99-1.00	0.983
TAC serum level, ng/mL	0.167	1.18	0.92-1.51	0.189	0.02	1.01	0.54-1.89	0.955

CI: Confidence interval; CSA: Cyclosporine A; DGF: Delayed graft function; MMF: Mofetil mycophenolate; OR: Odds ratio; PTH: Parathyroid hormone; TAC: Tacrolimus.

were significant risk factors affecting rejection. However, in the multivariate regression analysis, these risk factors did not affect the rejection status ($P > 0.05$).

The present study had some limitations, including a retrospective single-center design; the retrospective design might have led to selection and recall biases, and its single-center nature precludes generalization of the findings. In addition, the study population was small and might have been insufficient for establishing the existence of cause and effect relations.

CONCLUSION

In conclusion, the serum 25 (OH) vitamin D level of kidney transplant recipients remained low despite vitamin D replacement recommended by KDIGO guidelines. However, the multivariate regression analysis did not find the same variables effective on rejection. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to more clearly discern the effects of the serum vitamin D level on the renal allograft rejection rate.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is commonly diagnosed in patients with kidney transplantation. Deficiency rate remains high despite replacement therapies as per the Kidney Disease Improving Global Outcomes guidelines.

Research motivation

Vitamin D has immunomodulatory effects and vitamin D receptors can be found in various types of cells including T cells and dendritic cells. Its deficiency may predispose transplant recipients to rejection and chronic allograft nephropathy (CAN).

Research objectives

This study determined the association between the serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

Research methods

Retrospective clinical study involving adult kidney transplant recipients requiring graft biopsy due to declined function, hematuria, and proteinuria.

Research results

Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant (P = 0.003). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have impact (P = 0.027, P = 0.007, P = 0.023, P = 0.008). In multivariate regression analysis, the same factors did not affect rejection.

Research conclusions

The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to appreciate the effect of serum vitamin D levels on allograft rejection.

Research perspectives

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves the quality of life. However, the long term success of kidney transplantation depends on preventing the chronic allograft dysfunction. Chronic allograft dysfunction is secondary to various immunological, infectious and drug related insults to the graft. Its prevention depends on close clinical follow-up and optimization of controllable variables, such as serum vitamin D levels.

FOOTNOTES

Author contributions: This study was conducted at Ankara Diskapi Research and Training Hospital, affiliated with the Health Sciences University of Turkey; the Departments of Internal Medicine, Nephrology, Urology, and General Surgery were involved in conducting the study; Oguz EG and Ayli MD designed the research; Buyukdemirci S and Cimen SG performed the research; Sahin H collected the data; Cimen S analyzed the data; Cimen SG wrote the paper.

Institutional review board statement: The study protocol was approved by the hospital's ethical review committee (06.08.2018-no. 53/20) and was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Informed consent statement: All the patients provided written informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: We opt not to share our data, however if required for research purposes contact to the corresponding author is recommended.

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Country/Territory of origin: Turkey

ORCID number: Semih Buyukdemirci 0000-0002-0384-3877; Ebru Gok Oguz 0000-0002-2606-3865; Sanem Guler Cimen 0000-0002-5266-9529; Hatice Sahin 0000-0002-7146-4828; Sertac Cimen 0000-0002-0252-8840; Mehmet Deniz Ayli 0000-0003-3145-1595.

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LETTER TO THE EDITOR

Simultaneous kidney transplantation and ipsilateral native nephrectomy in patients with autosomal dominant polycystic kidney disease

Rabea Ahmed Gadelkareem, Amr Mostafa Abdelgawad, Nasreldin Mohammed

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Rabea Ahmed Gadelkareem, Amr Mostafa Abdelgawad, Nasreldin Mohammed, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Assiut 71515, Egypt

Corresponding author: Rabea Ahmed Gadelkareem, MD, Assistant Professor, Department of Urology, Assiut Urology and Nephrology Hospital, Faculty of Medicine, Assiut University, Elgamaa Street, Assiut 71515, Egypt. dr.rabeagad@yahoo.com

Abstract

The simultaneous kidney transplantation and ipsilateral native nephrectomy for autosomal dominant polycystic kidney disease does not seem to be associated with increased rates of comorbidity and complications. This outcome can efficiently be achieved when the indication and surgical approach of native nephrectomy are properly justified.

Key Words: Autosomal dominant polycystic kidney disease; Kidney transplantation; Native nephrectomy; Retroperitoneal approach; Surgical complications

Core Tip: The current results showed that simultaneous kidney transplantation (KT) and ipsilateral native nephrectomy for autosomal dominant polycystic kidney disease is not associated with higher rates of comorbidity and complications. However, the indications should be justified to include forming a sufficient surgical space, such as with huge kidneys, alleviating symptoms, such as with infected cysts and accessing preemptive KT. On the other hand, the retroperitoneal surgical approach of the native nephrectomy should be employed, despite the anatomical challenges of approaching the native kidney from the same approach as the transplantation procedure.

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TO THE EDITOR

We read with interest the article by Darius *et al*[1], who studied the effect of the simultaneous ipsilateral native nephrectomy and kidney transplantation (KTIN) in a cohort of 154 patients with autosomal dominant polycystic kidney disease (ADPKD). This procedure was performed in 77 patients who were compared with another 77 patients who had KT alone. The authors addressed certain points in this issue such as the indications, preoperative and perioperative variables and complications. They concluded that KTIN is a safe strategy without a negative impact on the rates of surgical comorbidity, complications and graft survival.

We agree with the authors' conclusions that generally KTIN for ADPKD may not increase the rates of comorbidity and complications of KT. Also, we believe that this surgical strategy has very important practical implications on the field of KT, proving the surgical feasibility and safety of one-stage surgery, non-affection of graft survival and a high patient satisfaction. Despite the numerous studies that have reported these outcomes, there are many unresolved controversies that still warrant further studying due to the insufficient evidence-based proofs in the literature[2-5].

In light of the results of this study, relevant literature status and our own experience, we will address some practical points that are crucially relevant to this subject. These points may contribute to the verification of the advantageous implications of KTIN on the KT practice, especially the living donor KT. Although our routine policy is to perform KTIN for ADPKD patients, we have encountered a few serious comorbidities and complications in those patients. We present this brief experience in the purpose of strengthening the focus and attention to the unfavorable sequels of KTIN to avoid them, but not to argue against the results reported by the authors or the growing evidence of the advantages of this strategy in the literature[5].

The authors addressed the common indications of KTIN in the symptomatic patients and they were similar to those indications reviewed and mentioned in the literature without much controversy. They included creating a surgical space for the graft as a cardinal indication, intractable renal pain, significant hematuria, intra cyst infections and hemorrhage, gastrointestinal symptoms such as early satiety, recurrent kidney stones, risk of malignancy and preemptive KT strategy[1,2,5]. Similarly, the current results revealed that the rate of KTIN was higher in patients who had preemptive KT[1]. The latter KT strategy is now an important issue in the literature representing a prominent indication of KTIN in patients with ADPKD, especially with the living donor KT. In regards to the asymptomatic patients who have a possibility of accessing preemptive KT, the number of surgeries can be reduced and the residual kidney functions and diuresis can be preserved until the time of KT surgery[4].

As the authors stated in their methods, the retroperitoneal surgical approach should be used to avoid the involvement of the peritoneal cavity and its contents. In the case of transperitoneal nephrectomy, lymphorrhea and hypoalbuminemia may represent serious complications, threatening the graft and patient survival. We had a serious experience with 2 cases of transperitoneal bilateral KTIN for ADPKD. The indications of the transperitoneal approach were the need of bilateral native nephrectomy and a history of previous surgery on the native kidneys. Prolonged lymphorrhea and hypoalbuminemia represented serious challenges in the management of one of our patients. Also, a very rare incident of pathology in the form of concomitant ADPKD and primary oxalosis was confirmed in the other patient. Both patients died with septicemia after a consecutive series of comorbidity and complications that were empowered by the transperitoneal approach. Hence, we may mention that the safety of KTIN is not absolute, especially when another major pathology coexists. In concordance, many drawbacks have been reported, including the prolongation of the time of surgery, increased need of blood transfusion and increased rates of early urinary tract infections[3]. On the other hand, bilateral native nephrectomy may have advantages when approached *via* the laparoscopic and robotic-assisted techniques in these cases, but the challenges and outcomes of these techniques are still controversial[6-8]. In any case, all of these unfavorable effects warrant proper surgical planning and prompt management of the medical and surgical sequels evolving during the perioperative period which may have a great effect on the whole of KT outcomes.

A recent systematic review by Xu *et al*[5] reached similar conclusions in regards to the vascular complications and safety of KTIN. This meta-analysis revealed that there was no evidence to support that the KTIN procedure increases the rates of the perioperative mortality and complications[5]. Finally, we believe that this study can be considered a step forward in providing cumulative strong evidence for the superiority of KTIN against the staged surgery. Accordingly, we should recommend a critical justification of the indications and timing of the native nephrectomy in patients with ADPKD

undergoing KT. Also, the retroperitoneal approach should be strictly used in these cases. Finally, efficient and meticulous hemostasis and ligation of the renal lymphatics should be performed.

FOOTNOTES

Author contributions: Gadelkareem RA searched and collected the data; Abdelgawad AM contributed in scientific review and revision of the letter; Gadelkareem RA, Abdelgawad AM and Mohammed N wrote and revised the letter; and all authors revised and approved the letter for submission.

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Country/Territory of origin: Egypt

ORCID number: Rabea Ahmed Gadelkareem 0000-0003-4403-2859; Amr Mostafa Abdelgawad 0000-0002-4336-1573; Nasreldin Mohammed 0000-0002-0232-9497.

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Editorial Board Member of *World Journal of Transplantation*, Behjat Seifi, PhD, Professor, Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran 1416753955, Iran. b-seifi@tums.ac.ir

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ORIGINAL ARTICLE

Prospective Study

Effect of panel reactive antibodies on T cell immunity reinstatement following renal transplantation

Lampros Vagiotas, Maria Stangou, Efstratios Kasimatis, Aliki Xochelli, Grigorios Myserlis, Georgios Lioulios, Vasiliki Nikolaidou, Manolis Panteli, Konstantinos Ouranos, Nikolaos Antoniadis, Daoudaki Maria, Aikaterini Papagianni, Georgios Tsoulfas, Asimina Fylaktou

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Lampros Vagiotas, Grigorios Myserlis, Nikolaos Antoniadis, Georgios Tsoulfas, Department of Transplant Surgery, School of Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Maria Stangou, Efstratios Kasimatis, Georgios Lioulios, Manolis Panteli, Konstantinos Ouranos, Aikaterini Papagianni, Department of Nephrology, School of Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Aliki Xochelli, Vasiliki Nikolaidou, Asimina Fylaktou, Department of Immunology, National Peripheral Histocompatibility Center, Hippokration General Hospital, Thessaloniki 54642, Greece

Daoudaki Maria, Medical School Aristotle University of Thessaloniki, Biochemistry Laboratory, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Corresponding author: Maria Stangou, PhD, Assistant Professor, Department of Nephrology, School of Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, 49 Konstantinoupoleos Street, Thessaloniki 54642, Greece. mstangou@auth.gr

Abstract

BACKGROUND

Chronic kidney disease is associated with immunological disorders, presented as phenotypic alterations of T lymphocytes. These changes are expected to be restored after a successful renal transplantation; however, additional parameters may contribute to this process.

AIM

To evaluate the impact of positive panel reactive antibodies (PRAs) on the restoration of T cell phenotype, after renal transplantation.

METHODS

CD4CD28null, CD8CD28null, natural killer cells (NKs), and regulatory T cells (Tregs) were estimated by flow cytometry at T0, T3, and T6 which were the time of transplantation, and 3- and 6-mo follow-up, respectively. Changes were estimated regarding the presence or absence of PRAs.

RESULTS
Patients were classified in two groups: PRA(-) (n = 43) and PRA(+) (n = 28) groups. Lymphocyte and their subtypes were similar between the two groups at T0, whereas their percentage was increased at T3 in PRA(-) compared to PRA(+) [23 (10.9-47.9) *vs* 16.4 (7.5-36.8 μ/L, respectively; P = 0.03]. Lymphocyte changes in PRA(-) patients included a significant increase in CD4 cells (P < 0.0001), CD8 cells (P < 0.0001), and Tregs (P < 0.0001), and a reduction of NKs (P < 0.0001). PRA(+) patients showed an increase in CD4 (P = 0.008) and CD8 (P = 0.0001), and a reduction in NKs (P = 0.07). CD4CD28null and CD8CD28null cells, although initially reduced in both groups, were stabilized thereafter.

CONCLUSION
Our study described important differences in the immune response between PRA(+) and PRA(-) patients with changes in lymphocytes and lymphocyte subpopulations. PRA(+) patients seemed to have a worse immune profile after 6 mo follow-up, regardless of renal function.

Key Words: Chronic kidney disease; Panel reactive antibodies; Lymphocyte subpopulation; CD4CD28null cells; CD8CD28null cells

Core Tip: Chronic kidney disease is associated with phenotypic and functional changes in the immune system. This study evaluated the impact of positive panel reactive antibodies (PRAs) on restoration of the T cell phenotype after renal transplantation. Our study described important differences in the immune response between PRA(+) and PRA(-) patients with changes in lymphocytes and lymphocyte subpopulations. PRA(+) patients seemed to have a worse immune profile after 6 mo follow-up, regardless of renal function.

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INTRODUCTION

Chronic kidney disease (CKD) is associated with phenotypic and functional changes in the immune system, including both innate and adaptive immunity, causing detrimental clinical consequences. Total lymphopenia is one of the major concerns in CKD, whereas changes in T lymphocytes include both elimination of their population and alterations of their subtypes. Some of these phenotypic and functional changes have been described by investigators[1,2]. We previously showed that CKD, even at the pre-dialysis stage, results in reduced levels of CD4, CD8, and regulatory T cells (Tregs). Furthermore, it affects the expression of CD28 molecule on T lymphocytes, leading to an increased proportion of CD4CD28null and CD8CD28null cells[1,2].

The CD28 molecule constitutes a primary co-stimulatory receptor, which is essential for successful T cell activation, proliferation, and survival. It is mainly expressed on naive T cells in humans, but its expression on memory T cells depends on their differentiation status. Expansion of circulating T lymphocytes lacking the CD28 molecule represents an adaptive mechanism following repeated antigenic stimulation, and has been considered an age-associated immunological alteration[3-7].

Initiation of hemodialysis (HD) cannot restore these structural changes of lymphocytes. Even more, the HD itself, as an extracorporeal circulation, use of dialyzers, may have an additive deleterious effect [1]. Conversely, successful renal transplantation allows patients to stop dialysis and reinstates kidney function. Accordingly, as part of returning to normality, it is also expected to restore patients' immune profile[8,9].

However, despite the indisputable beneficial effect of renal transplantation on immune status, there may be parameters that affect the outcome of graft function and potentially influence the reestablishment of immunological disorders. Most of these parameters are closely associated with the patient's immune status at the time of transplantation. Immune status of the CKD patient is determined by phenotypic and functional alterations of lymphocytes due to CKD, and even more interesting for those patients undergoing renal transplantation, by the presence of human leukocyte antigen (HLA) sensit-

ization. HLA sensitization refers to the presence of antibodies in the potential recipient against HLA molecules of the selected donor. While on the waiting list, CKD patients may develop antibodies against HLA antigens as a result of blood transfusions, previous transplantations, or pregnancies[10,11], generally described as panel reactive antibodies (PRAs)[12]. The risk of sensitization increases as there is exposure to more than one sensitizing factor[9,13]. PRA screening is routinely performed in CKD patients before renal transplantation to assess recipients' exposure and sensitization. PRA titers before kidney transplantation may be used to predict acute rejection and guide the immunosuppressive treatment, including induction treatment. The presence of PRAs is not uncommon, as patients have to wait long for a kidney transplant, and meanwhile, are exposed to blood transfusions or get pregnant [12]. The purpose of this study was to evaluate the effect of positive PRA on restoration of the immunological T cell phenotype following successful renal transplantation.

MATERIALS AND METHODS

Study population

The study was conducted between January 2020 and October 2021 at the Department of Renal Transplantation, Hippokration General Hospital (Thessaloniki, Greece). Seventy-eight kidney transplantations were performed, from which seventy-one fulfilled the criteria and were included in the study. Three of the recipients were adolescents, aged 13, 16, and 17 years; the rest were adults. All participants provided informed consent before their enrollment in the study. The trial was approved by the local ethics committee and followed the general principles of the Declaration of Helsinki (2008 Amendment).

Inclusion criteria: Patients eligible for the study were 13-70-years-old, and had undergone a living or deceased donor kidney transplantation. Regarding the deceased donors, we included only Donation after Brain Death and not Donation after Cardiac Death transplants. All transplantations were ABO-compatible with a negative complement-dependent crossmatch. The patients were followed for 6 mo in the outpatient clinic, and all were treated with the same treatment protocol.

Exclusion criteria: Patients were excluded from the study in case of recent (less than 3 mo) cytomegalovirus (CMV) or bacterial infection; recent malignancy (less than 5 years); or active autoimmune, inflammatory disease, or hematological disorder. Also, patients who had been on immunosuppressive treatment during the last 12 mo prior to kidney transplantation were excluded, as were patients not compliant with the treatment instructions.

Schedule of the study

Each patient receiving a kidney transplantation was assessed for eligibility to be included in the study. For patients who fulfilled the inclusion criteria, as described above, the day of enrollment in the study was the day of transplantation. Blood samples were taken in the morning, before the administration of any immunosuppressive treatment, and used for laboratory and immunological assessments. During the posttransplant period, renal function, medication, and possible side effects were recorded. Following discharge from the hospital, after renal transplantation, all patients were regularly followed up at the outpatient clinic on a monthly basis. Their immune profile was recorded on the day of transplantation (T0), and at the 3- and 6-mo follow-up (T3 and T6, respectively). At the same time intervals, the function of the renal graft was evaluated and the results were correlated with the immunophenotype.

Demographic, clinical data from donors and recipients, HLA mismatches, and cold ischemia time were recorded at T0, and delayed graft function (DGF), acute rejection episodes, infections, and hospitalization time were recorded and analyzed at T3 and T6, 3 and 6 mo after transplantation. All patients received the same immunosuppressive regimen, according to the Immunosuppressive Protocol, including basiliximab or antithymocyte globulin (ATG), steroids, tacrolimus, and multimode fiber. Eleven patients (15.5%) received ATG, reasons to receive ATG were as follows: 4/11 because of retransplant and 7/11 because of the presence of PRA(+). Seven patients had DGF during the first 7 d following transplantation. Basiliximab was used as induction immunosuppression in 84.5% of the patients.

Laboratory measurements

Flow cytometry: T cell subsets were identified using multicolor flow cytometry with standard techniques on the Navios EX flow cytometer (Beckman Coulter, Sykesville, MD, United States). Whole blood samples were drawn from patients at the scheduled time points (T0, T3, and T6), collected in EDTA tubes, and processed for the evaluation of lymphocyte count and their subpopulations. T lymphocyte subsets determined were CD3+CD4+, CD3+CD8+, CD3-CD16+CD56+, CD3+CD4+CD28-, and CD3+CD8+CD28-, using the following monoclonal antibodies: CD3-FITC (clone: UCHT1; Beckman Coulter), CD16 (clone: 3G8; Beckman Coulter), CD56 clone: N901(NKH-1)-PE; Beckman Coulter), CD4-APC (clone: 13B8.2; Beckman Coulter), CD8 PC5.5 (clone: B9.11l Beckman Coulter), CD28-ECD (clone:

CD28.2; Beckman Coulter), and CD45-PC7 (clone: J33; Beckman Coulter). Peripheral blood mononuclear cells were obtained by Ficoll density gradient centrifugation. Immunophenotyping of Tregs was performed with the combination of the following monoclonal antibodies: CD45-PC7 (clone: J33; Beckman Coulter), CD4-FITC (clone: 13B8.2; Beckman Coulter), CD25-PC5 (clone: B1.49.9; Beckman Coulter), and FOXP3-PE (clone: 259D; Beckman Coulter).

Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows, version 27.0 (SPSS Inc., Chicago, IL, United States). The Shapiro-Wilk or Kolmogorov-Smirnov test was applied to examine the normality of distribution for continuous variables. For all comparisons, $P < 0.05$ was considered statistically significant. Mean ± SD and medians and interquartile range were used to describe data from normally distributed and non-parametric variables, respectively. Similarly, the student's *t*-test for non-paired and paired variables, and Mann-Whitney *U* test and Wilcoxon signed-rank test were respectively performed to compare differences between groups. To investigate the change in subpopulations among T0, T3, and T6, repeated measures analysis of variance (ANOVA) for parametric variables or Friedman's ANOVA for non-parametric variables was used.

RESULTS

Seventy-one recipients of a kidney transplant were included in the study. Characteristics of patients are depicted in Table 1.

Differences between PRA(-) and PRA(+) patients

Differences in clinical and laboratory findings: Of the study population, 43 patients had negative PRA, and were classified as PRA(-), whereas 28 had positive PRA, and were classified as PRA(+). There were no differences between the two groups in terms of age, sex, and time on HD, [defined as HD vintage (HDV)]. Also, no differences were found between the two groups in the proportion of patients who underwent preemptive transplantation, had an episode of acute rejection or were administered ATG, as well as in those who had DGF (Table 2).

No significant differences in lymphocyte numbers and T lymphocyte subpopulations were noticed between PRA(-) and PRA(+) patients at the time of transplantation. An increase in percentage of CD4CD28null and CD8CD28null cell within PRA(+) patients did not reach statistical difference (Table 3).

Correlations of immunological parameters at time point T0

In the whole cohort of patients, age was significantly correlated with the percentage of CD4CD28null ($r = 0.3$, $P = 0.03$), percentage and number of CD8CD28null (r = 0.4, $P < 0.001$ and $r = 0.3$, $P = 0.03$, respectively) and percentage of NK cells ($r = 0.3$, $P = 0.02$). HDV had a negative correlation with total lymphocyte number ($r = -0.3$, $P = 0.04$), CD4+ lymphocytes ($r = -0.3$, $P = 0.01$), and Tregs ($r = -0.4$, $P = 0.006$). Patients who underwent preemptive kidney transplantation had a better immune profile than patients already enrolled in HD or continuous ambulatory peritoneal dialysis. In these patients, a significantly increased percentage and number of lymphocytes was observed, 27.9 (14%-37.7%) *vs* 18 (6.4%-40%) $P = 0.03$, and 1705 (100-2800) *vs* 1200 (700-2700) cells/μL, $P = 0.03$, respectively. Reduction in the percentage of CD4CD28null, 1.7 (0.4%-2.9%) *vs* 6.7 (0%-33.7%), $P = 0.04$ and CD8CD28null, [14.9 (6.1%-22.1%) *vs* 39.7 (114%-91%), $P = 0.002$, 207 (85-266) *vs* 477 (105-1131), $P = 0.002$] were also noticed as well as a significant increase in Tregs, affecting both percentage, 5.6 (1.7%-8.3%) *vs* 3.9 (0.1%-11.5%) $P = 0.05$, and total number of Tregs, 32.1 (24-47) cells/μL *vs* 18.9 (0.5-74) cells/μL, $P = 0.006$.

Differences in the outcome of subpopulations depending on the existence of PRA

Changes in lymphocytes and their subpopulations following renal transplantation are depicted in Tables 4 and 5, for PRA(-) and PRA(+) patients, respectively. In both groups, PRA(-) and PRA(+), the percentage and total number of lymphocytes were increased. However, the response of lymphocyte changes was earlier and stronger in PRA(-) patients, as their percentage raised from T0 to T3, mean rank 15.35 to 20.98, $P = 0.002$, compared to 10.2 and 13.9, P = NS in PRA(+). This prompt response resulted in a significant increase in the number of total lymphocytes, in PRA(-), during the period T0 to T3, mean rank 10.57 to 20.41, $P < 0.0001$.

Although at time point T0, there was no significant difference in the percentage or total number of lymphocytes between the two groups of patients, at T3, PRA(-) had significantly increased percentage of lymphocytes, compared to PRA(+), 23 (10.9-47.9) *vs* 16.4 (7.5-36.8) μ/L, respectively, $P = 0.03$. At time T6, although there was still a superiority in PRA(-) patients the difference did not reach statistical significance, $P = 0.06$.

Table 1 Clinical and demographic characteristics of kidney transplant recipients

Characteristics	
Age, yr, median (range)	46 (13-70)
Male/female	49/22
Living kidney donor	22.5%
Deceased kidney donor	77.5%
Previous kidney transplant	7.0%
Preemptive transplantation	4.2%
PRA(-)	60.5%
Early rejection, within first 6 mo after KT	4.2%
Induction therapy	
Basiliximab	84.5%
ATG	15.5%
Maintenance immune suppression	
Tacrolimus/mycophenolate/prednisone	100.0%
Other	0.0%
Distribution of underlying kidney disease	
Polycystic kidney disease	22.5%
Primary glomerulopathies	21.1%
Reflux nephropathy	12.6%
Diabetes mellitus	4.2%
Nephrosclerosis/hypertension	4.2%
Urinary tract infections/ stones	3.7%
Other	16.2%
Unknown	15.5%

ATG: Antithymocyte globulin; KT: Kidney transplant; PRA: Panel reactive antibody.

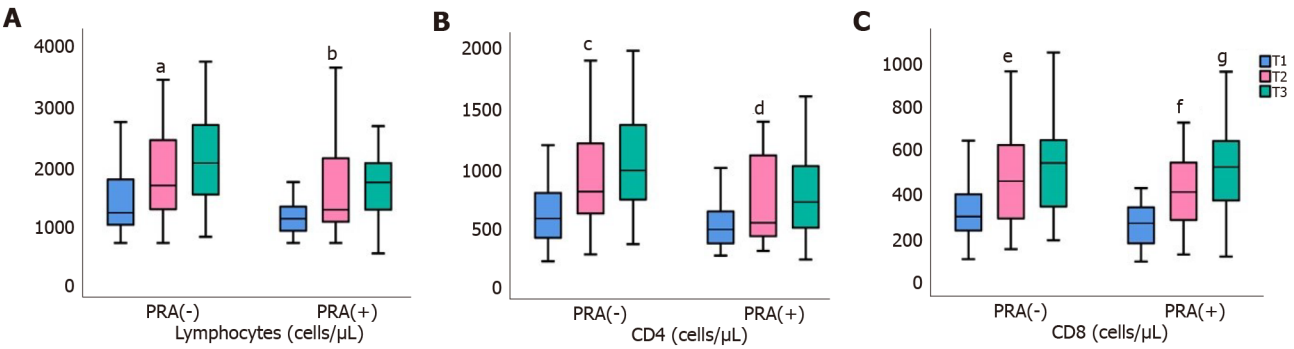

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Figure 1 Sequential changes. A: Total lymphocyte populations; B: CD4 cells; C: CD8 cells. Differences between panel reactive antibody (PRA)(-) and PRA(+) patients. [a]*P* < 0.001 *vs* T0; [b]*P* = 0.003 *vs* T0; [c]*P* < 0.001 *vs* T0; [d]*P* = 0.006 *vs* T0; [e]*P* < 0.001 *vs* T0; [f]*P* = 0.003 *vs* T0; [g]*P* = 0.03 *vs* T0.

Changes in CD4(+) and CD8(+) cells and CD4CD28null and CD8CD28null subtypes

Both CD4 and CD8 cells were significantly increased in the two groups of patients, from T0 to T3. Figure 1 depicts changes of total lymphocytes, and also, in CD4 and CD8 cells after transplantation in PRA(-) and PRA(+) patients. There was a definite increase and gradual increase of total lymphocytes, together with CD4 and CD8 cells, from T0 towards T6 in both groups of patients, with changes in all

Table 2 Differences between panel reactive antibodies (-) and (+) patients

Parameter	T0 (at renal transplantation)		
	PRA(-)	PRA(+)	*P* value
Age, yr	45 (13-65)	47 (14-70)	NS
HDV, mo	82.5 (0-251)	112 (0-165)	NS
Time of cold ischemia, h	18 (0-30)	16.5 (0-30.5)	NS
Pre-emptive RT, %	6 (13.6)	1 (3.6)	NS
Acute rejection episode, %	2 (4.5)	1 (3.6)	NS
ATG administration, %	5 (11.4)	7 (25)	NS
DGF, %	7 (15.9)	4 (14.3)	NS

ATG: Antithymocyte globulin; DGF: Delayed graft function; HDV: Hemodialysis vintage; PRA: Panel reactive antibody; RT: Renal transplantation.

Table 3 Lymphocyte numbers and subpopulations in panel reactive antibodies (-) and (+) patients at time of transplantation (T0)

Parameter	T0, at renal transplantation		
	All patients	PRA(-)	PRA(+)
n	71	43	28
Lymphocyte, %	18.1 (6.4-40)	18.8 (6.4-38.4)	17.8 (11.2-40)
Lymphocyte, cells/μL	1200 (700-2800)	1200 (700-2800)	1100 (700-2600)
CD4+, %	42.0 (20.6-68.6)	44.4 (20.6-68.6)	41.5 (25.3-59.5)
CD4+, cells/μL	515 (206-1453.2)	557 (206-1453.2)	435 (253-1362.4)
CD8+, %	24.55 (10.5-53.1)	25.1 (12,2-37.7)	23.4 (10.5-53.1)
CD8+, cells/μL	301.5 (91.7-665.6)	301.5 (102.9-641.7)	294.9 (91.7-665.6)
CD4+/CD8+	1.7 (0.6-5.6)	1.5 (0.9-5.6)	2 (0.6-5)
CD4+CD28-, %	5.4 (0.0-33.7)	4.8 (0.2-33.7)	7.2 (0-32.1)
CD4+CD28-, cells/μL	26.9 (0.0-206)	26.7 (0-160)	27.3 (0-206)
CD8+CD28-, %	38.6 (6.1-91.5)	38.3 (6.1-68.2)	48.4 (15.1-91.5)
CD8+CD28-, cells/μL	121.5 (13-583)	113.6 (17-315)	122 (13-583)
CD16/56, %	18 (3.6-50.6)	17.7 (3.6-50.6)	18.4 (4.4-34.2)
CD16/56, cells/μL	198.1 (50.4-750.5)	210 (50.4-750.5)	190.4 (94.8-393.6)
Tregs, %, on CD4	4 (0.1-11.5)	3.9 (0.1-11.5)	4.2 (1.5-7.3)
Tregs, cells/μL	20 (0.52-74.38)	20.2 (0.5-74.3)	18.9 (5.8-73.5)

PRA: Panel reactive antibody; Tregs: Regulatory T cells.

three cell types being statistically significant even during the first 3 mo following transplantation.

Regarding CD4CD28null cells, although there was a significant reduction in the percentage of CD4CD28null subtypes from T0 to T3, in both PRA(-) and PRA(+) patients, $P = 0.04$ and 0.01, respectively, population of cells and their percentage were stabilized thereafter, until T6, leading to no significant changes in these cell types during follow up, regardless of the presence of PRA. The results are descried in Tables 3 and 4 and depicted at Figure 2. On the other hand, there was a marked reduction in CD8CD28null cells, both percentage and numbers only in PRA(-) patients, from T0 to T3, $P = 0.03$, and from T3 to T6, $P = 0.02$. Such changes were not evident in PRA(+) patients, in contrast there was a significant increase in these cells during the first 3 mo (from T0 to T3).

Changes in NK cells and Tregs

In PRA(-) there was a significant reduction in the percentage of NKs after renal transplantation, from T0 to T3 and from T3 to T6, $P < 0.0001$ and $P = 0.006$, respectively, and this was accompanied by significant

Table 4 Changes in T lymphocyte subpopulations at T0, T3, and T6 time points in patients with panel reactive antibodies (-)

Parameter	T0	T3	T6	*P* value
Lymphocyte, %	18.8 (6.4-38.4)	23 (10.9-47.9)	25.4 (8.4-52)	0.001
Lymphocyte, cells/μL	1200 (700-2800)	1650 (700-4100)	1900 (800-3700)	< 0.0001
CD4+, %	44.4 (20.6-68.6)	49.8 (22.7-77.1)	49.1 (16.2-71.4)	0.004
CD4+, cells/μL	557 (206-1453.2)	782 (261.8-1951.6)	872 (330-2001.6)	< 0.0001
CD8+, %	25.1 (12.2-37.7)	26.9 (12.4-50.1)	27.4 (13.3-49)	NS
CD8+, cells/μL	301.5 (102.9-641.7)	456.3 (148.6-1402.8)	514.5 (189.2-1397.8)	< 0.0001
CD4CD28null, %	4.8 (0.2-33.7)	2.8 (0-21.1)	2.7 (0.1-36.4)	NS
CD4CD28null, cells/μL	26.7 (0.9-149)	27.5 (0-160)	26.5 (09-241)	NS
CD8CD28null, %	38.3 (6.1-68.2)	28.4 (8.3-80.5)	32.8 (6.7-90.7)	NS
CD8CD28null, cells/μL	113.6 (17-315)	112.6 (28-1129)	158 (18-1267)	NS
CD16/56, %	17.7 (3.6-50.6)	6.6 (1.9-24.2)	9.3 (2.9-28.6)	< 0.0001
CD16/56, cells/μL	210 (50.4-750.5)	121.6 (33-622.2)	151.2 (44-774.4)	< 0.0001
Tregs, %, on CD4	3.9 (0.1-11.5)	3.3 (0.9-6.8)	4.1 (1.4-8.8)	NS
Tregs, cells/μL	20.2 (0.5-74.3)	29.4 (7.5-122.9)	38.4 (8-104)	< 0.0001

Tregs: Regulatory T cells.

Table 5 Changes in T lymphocyte subpopulations at T0, T3, and T6 time points in patients with panel reactive antibodies (+)

Parameter	T0	T3	T6	*P* value
Lymphocyte, %	17.8 (11.2-40)	16.4 (7.5-36.8)	20.9 (12.2-36.4)	0.07
Lymphocyte, cells/μL	1100 (700-2600)	1300 (700-3600)	1700 (525-3200)	0.009
CD4+, %	41.5 (25.3-59.5)	42.3 (29.2-65.3)	46.5 (27.4-62)	NS
CD4+, cells/μL	435 (253-1362.4)	548.9 (292-1371.3)	744 (220-1888)	0.008
CD8+, %	23.4 (10.5-53.1)	27.4 (10.3-53.6)	29.9 (11.6-56.2)	0.005
CD8+, cells/μL	294.9 (91.7-665.6)	408 (123.6-1234.8)	504.9 (114.4-955.4)	< 0.0001
CD4CD28null, %	7.2 (0-32.1)	5.3 (0.2-24.8)	4 (0.1-28.6)	NS
CD4CD28null, cells/μL	27.3 (0-206)	22.8 (1.5-234)	24.2 (1.3-244)	NS
CD8CD28null, %	48.4 (15.1-91.5)	47.1 (10.7-82.1)	36.5 (7.7-82)	NS
CD8CD28null, cells/μL	122.2 (13-583)	200 (19-547)	160 (22-726)	NS
CD16/56, %	18.4 (4.4-34.2)	11.4 (2.9-26)	7.9 (3-24.6)	< 0.0001
CD16/56, cells/μL	190.4 (94.8-393.6)	157.5 (34.8-450)	135.7 (23.76-385.7)	0.07
Tregs, %, on CD4	4.2 (1.5-7.3)	3.3 (1.2-6.8)	4.4 (1.4-8.6)	NS
Tregs, cells/μL	18.9 (5.8-73.5)	20.9 (7.4-65.8)	26.7 (8.5-103.8)	NS

Tregs: Regulatory T cells.

elimination in the number of NK cells, (P = 0.002 and P = 0.005, respectively) in Figure 2. In contrast, within PRA(+) patients, the only significant changes were reported in the percentage of NK cells, during the time period, from T0 to T3, P = 0.001.

Similar differences were noticed between the two groups of patients regarding Tregs. The percentage of Tregs was increased only in PRA(-) patients, and this alteration was restricted only in the time period 3 to 6 mo, from T3 to T6, P = 0.02. Regulatory T cell population, however, was increased significantly in the same group, from T0 to T3, P = 0.01 and from T3 to T6, P = 0.003, while these cells showed no difference in PRA(+) patients from T0 to T3, and only mild restoration fromT3 to T6 (Figure 3).

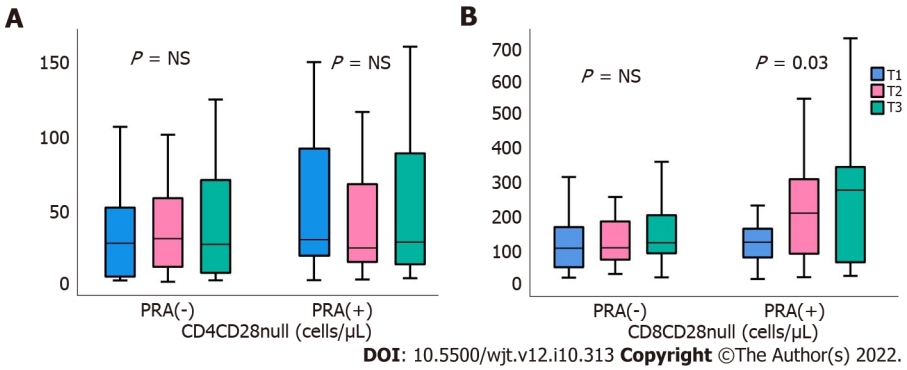

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Figure 2 Changes in the number of CD4CD28null and CD8CD28null cells during follow up in panel reactive antibody patients. A: CD4CD28null cells; B: CD8CD28null cells.

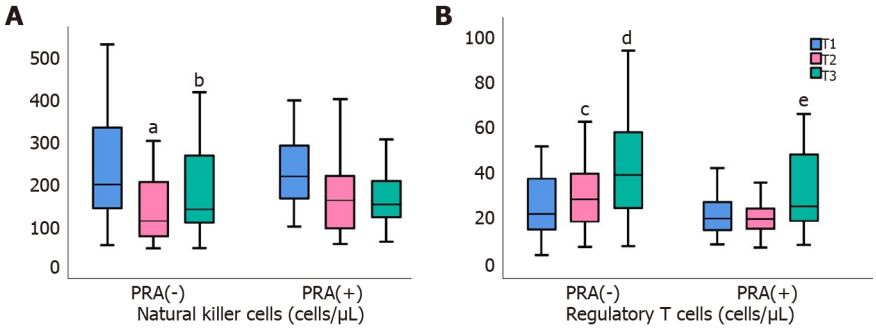

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Figure 3 Changes in natural killer cells and regulatory T cells during follow-up in panel reactive antibody (-) and panel reactive antibody (+) patients. A: Natural killer cells; B: Regulatory T cells. [a]*P* = 0.002 *vs* T0; [b]*P* = 0.005 *vs* T3; [c]*P* = 0.01 *vs* T0; [d]*P* = 0.003 *vs* T3; [e]*P* = 0.04 *vs* T3. PRA: Panel reactive antibody.

DISCUSSION

The presence of high PRA levels, as a consequence of previous exposure to foreign HLAs[13], represents an increased possibility of preformed DSA occurrence, which is associated with the highest likelihood of graft loss[9,14]. Sensitization leads to the production of antibodies against HLA class I and HLA class II antigens, and activates different cell subpopulations, inducing immune response and possible rejection. The presence of HLA antibodies in the early term of transplantation may be more harmful to allografts, as they are associated with a higher incidence of acute rejection compared to patients who may develop antibodies later[12].

In this study, we evaluated the effect of PRA on the alterations of total lymphocytes and their subpopulations, following successful renal transplantation. For this reason, patients undergoing renal transplantation were divided in two groups, PRA(+) and PRA(-), according to the presence or absence of PRA at time of transplantation. All patients were followed prospectively for 6 mo at the Renal Transplant Outpatient clinic, and their renal function, medication, and clinical and laboratory parameters were assessed every month. Likewise, total lymphocytes, CD4, CD8, their subsets, CD4CD28null and CD 8CD28null, natural killer (NK) cells and Tregs were estimated by flow cytometry at the time of transplantation, and the 3- and 6-mo follow-up.

Although lymphocyte number was significantly and rapidly increased very early during follow-up, there were important differences in the immune response between PRA(-) and PRA(+) patients. The percentage and total number of lymphocytes were significantly improved during the first 3 mo in PRA(-) patients after transplantation. By contrast, the former showed a delayed and weak response in PRA(+) patients. Also, changes in lymphocyte subpopulations showed differences between the two groups. PRA(+) patients were characterized by a shift towards the CD8+ cell population, while in PRA(-) patients, CD4+ cells predominated during follow-up. As the presence of PRA was not associated with sex, age, time on HD, or impaired renal function, we anticipated that differences in T lymphocytes between PRA(-) and PRA(+) patients could not be attributed to other parameters such as HDV or renal function impairment, but rather were directly connected to the effect of PRA.

Interestingly, the expression of CD28 antigen on both CD4 and CD8 cells was not substantially affected by transplantation. CD28 loss is related to normal aging, but is also a consequence of chronic

autoimmune and inflammatory diseases[15-19], while recently, CD28 elimination has been described in patients with CKD. The reduction of this receptor in CKD patients has been attributed to uremia, chronic inflammation, oxidative stress, CMV infection, and chronic dialysis[1,17-20].

We found that the percentage of CD4CD28null cells showed a reduction in both groups during the first 3 mo, yet they were subsequently stabilized until the end of follow-up. Regarding CD8CD28null cells, the beneficial effect was proven only in PRA(-) and not in PRA(+) patients, in whom there was a significant increase after the 3rd mo posttransplantation. This is in accordance with previous studies, which showed that CD28 antigen was significantly eliminated in both CD4 and CD8 cells after renal transplantation[21]. In a recent study, lymphocytes from renal transplant patients, who were followed for up to 5 years posttransplant, showed a tendency towards senescent phenotype, including a gradual increase in CD4CD28null and CD8CD28null cells. These findings indicate that despite restoring renal function with a successful renal transplantation, immune phenotype cannot be completely retained. Apparently, immunosuppression and steroid administration have a crucial role in this phenomenon, and this has been proved by the alterations in T cell phenotypes, after the withdrawal of steroids[22].

CD4+CD28null T cells are differentiated from classic T helper cells and share many features of cytotoxic CD8+ T cells and NK cells. They express a cytotoxic profile by producing proinflammatory cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor alpha, and cytotoxic molecules[18,23,24]. CD28null T cells are considered terminally differentiated senescent cells, with shortened telomeres and great ability of cytotoxicity[19]. Thus, any alloreactivity of these cells may be detrimental for the transplant[20]. The gradual disappearance of CD28 following transplantation is controversial, with some investigators showing that loss of CD28 on CD4 T cells promotes immunosuppression resistance and allograft rejection[25,26], while others showing that loss of CD28 on T cells is related to immunosuppressive activity[17], leading to allograft tolerance and stabilization and is also associated with a lower frequency of late rejection and graft loss[27-29]. The role of PRA in CD28 expression seems crucial; however, there is a shortage of related information in the literature. The presence of anti-HLA antibodies may simply reflect the activation of adaptive immunity; however, they can induce endothelial damage, leading to *de novo* expression of endothelial neoantigens and vascular remodeling, as well as immune activation and chronic inflammation[30]. Therefore, the indirect effects of PRAs on the persistence of lymphocytes with cytotoxic activity may explain the increased levels of CD28null cells, but also their correlation with NK cells and regulatory T cells.

Changes in NK cells after transplant were more prominent. In both groups of patients, the percentage of NK cells was rapidly reduced during the first 3 mo, but only in PRA(-) patients was a reduction in the percentage of cells followed by the elimination of NK cell absolute numbers. NK cells play a crucial role in antibody-mediated rejection as occurs by the presence of HLA-DSAs[31-33]. NK cells are a source of IFN-γ production and they stimulate the T helper type 1 immune response. A direct interaction of NK cells with CD4+ T lymphocytes[34] increases their reactivity, which may motivate the mechanisms of acute rejection[33].

Most investigators support a mutual antagonism between NK and Treg cells[35]. Tregs seem to play major role in the long-term outcome of renal transplantation, as their population in the 6th and 12th mo posttransplantation was found to maintain immune tolerance in transplantation and is associated with better long-term graft survival[28,36-38], and some investigators have proven a time-dependent reduction of Tregs after kidney transplantation as a result of immunosuppressive treatment[28]. In our study, Tregs were almost spontaneously increased in PRA(-) patients during the first 3 mo of follow up, and continued to improve thereafter until the end of follow-up; by contrast, they showed only a delayed increase in PRA(+) patients.

CONCLUSION

In conclusion, this study demonstrated that T cell reinstatement following renal transplantation was closely affected by the presence of PRAs. Although lymphocyte population increased early after transplant, this beneficial effect did not involve all subpopulations. NK cells were reduced in both groups, Tregs were increased, but only in PRA(-) patients, whereas CD28null cells were not significantly restored regardless of the presence of PRAs.

ARTICLE HIGHLIGHTS

Research background

It is essential to try to both understand and evaluate the effect of panel reactive antibodies (PRAs) on T cell immunity reinstatement, which follows renal transplantation. The potential association between subset changes and posttransplant graft function should be studied further.

Research motivation

This study demonstrated that T cell reinstatement following renal transplantation was closely affected by the presence of PRAs. Although the lymphocyte population increased early after kidney transplantation, this beneficial effect did not involve all subpopulations. Natural killer (NK) cells are reduced in both groups, regulatory T cells (Tregs) were increased, but only in PRA(-) patients, whereas CD28null cells were not significantly restored regardless of the presence of PRAs.

Research objectives

Patients were classified into two groups: PRA(-) (n = 43) and PRA(+) (n = 28). Patients who underwent preemptive kidney transplantation had a better immune profile than those already enrolled in hemodialysis or continuous ambulatory peritoneal dialysis.

Research methods

Flow cytometry analysis was performed in 71 recipients of kidney transplantation at the time of transplantation, and at 3 and 6 mo after transplantation to estimate CD4CD28null, CD8CD28null, NK, and Treg cells.

Research results

The impact of positive PRA on the restoration of T cell phenotype after renal transplantation was evaluated.

Research conclusions

Given the fact that PRA screening is a widely used test performed routinely in patients with chronic kidney disease (CKD) before renal transplantation to assess recipients' exposure and sensitization, we believe it is essential to try to both understand and carefully evaluate the effect of PRA on T cell immunity reinstatement, which follows renal transplantation.

Research perspectives

CKD is associated with phenotypic and functional changes in the immune system, including both innate and adaptive immunity, with detrimental clinical consequences. A successful renal transplantation will allow patients to stop dialysis and reinstates kidney function. Accordingly, as part of returning to normality, it is also expected to restore patients' immune profile.

FOOTNOTES

Author contributions: Fylaktou A, Papagianni A, and Tsoulfas G designed the research study; Xochelli A, Nikolaidou V, Panteli M, and Ouranos K contributed new reagents and analytic tools; Vagiotas L, Kasimatis E, and Lioulios G performed the study; Antoniadis N, Miserlis G, and Vagiotas L provided the patients; Vagiotas L, Stangou M, and Daoudaki M analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

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Country/Territory of origin: Greece

ORCID number: Lampros Vagiotas 0000-0002-5176-6781; Maria Stangou 0000-0003-2496-9863; Grigorios Myserlis 0000-0003-1985-9336; Konstantinos Ouranos 0000-0001-9034-5026; Nikolaos Antoniadis 0000-0001-6939-3373; Aikaterini Papagianni 0000-0003-0437-5208; Georgios Tsoulfas 0000-0001-5043-7962.

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CASE REPORT

COVID-19 in a pregnant kidney transplant recipient - what we need to know: A case report

Roberta Angelico, Maria Luisa Framarino-dei-Malatesta, Giuseppe Iaria

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Roberta Angelico, Department of Surgical Sciences, HPB and Transplant Unit, University of Rome Tor Vergata, Rome 00100, Italy

Maria Luisa Framarino-dei-Malatesta, Department of Gynecologic-Obstetrical and Urologic Sciences, Policlinico Umbero I, Sapienza University of Rome, Rome 00100, Italy

Giuseppe Iaria, Kidney Transplant Unit, San Camillo Forlanini, Rome 00100, Italy

Corresponding author: Roberta Angelico, FEBS, MD, PhD, Assistant Professor, Department of Surgical Sciences, HPB and Transplant Unit, University of Rome Tor Vergata, Viale Oxford 31, Rome 00100, Italy. roberta.angelico@gmail.com

Abstract

BACKGROUND

In the era of the coronavirus disease 2019 (COVID-19) pandemic, kidney transplant recipients are more susceptible to severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection, developing severe morbidity and graft impairment. Pregnant women are also more likely to develop severe COVID-19 disease, causing pregnancy complications such as preterm births and acute kidney injury.

CASE SUMMARY

Herein, we report the case of a pregnant woman with a third kidney transplantation who developed COVID-19 disease. The reduction of immunosuppressive drugs and strict monitoring of trough blood levels were needed to avoid severe SARS-CoV-2-related complications, and permitted to continue a healthy pregnancy and maintain good graft function. In such a complex scenario, the concomitance of COVID-19-related morbidity, the risk of acute rejection in the hyperimmune recipient, graft dysfunction and pregnancy complications make the management of immunosuppression a very difficult task and clinicians must be aware.

CONCLUSION

Tailoring the immunosuppressive regimen is a key factor affecting both the graft outcome and pregnancy safety.

Key Words: Kidney transplantation; Pregnancy; SARS-CoV-2 infection; COVID-19 disease; Immunosuppression; Complications; Case report

Core Tip: Kidney transplant (KT) recipients are susceptible to coronavirus disease 2019 (COVID-19). Pregnant women are more likely to develop severe COVID-19, causing pregnancy complications such as preterm births and acute kidney injury. The management of immunosuppression in pregnant KT recipients with severe acute respiratory syndrome coronavirus infection is crucial for the avoidance of severe morbidity to the patient and the fetus, and to escape renal graft dysfunction.

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INTRODUCTION

Kidney transplant (KT) recipients are susceptible to coronavirus disease 2019 (COVID-19), with an associated 18%-39% intensive care admission rate and 13%-39% mortality[1]. Pregnant women are more likely to develop severe COVID-19, causing pregnancy complications such as preterm births and acute kidney injury[2,3].

CASE PRESENTATION

Chief complaints

In October 2020, a 37-year-old woman at 20 wk of gestation, who had received a third KT 2 years ago, presented with fever, cough, and anosmia.

History of present illness

The patient presented with fever, cough, and anosmia.

History of past illness

Her past medical history consisted of end-stage chronic kidney disease due to focal and segmental glomerulosclerosis, requiring three sequential KTs due to chronic rejections with a panel reactive antibody titer of 100%.

Personal and family history

The patient's personal and family histories were unremarkable.

Physical examination

At presentation, the severe acute respiratory syndrome coronavirus (SARS-CoV-2) polymerase chain reaction (PCR) test was positive.

Laboratory examinations

Biochemical tests showed 7.640/μL white blood cells, C-reactive protein of 10.1 mg/L and creatinine of 1.18 mg/dL (baseline at pregnancy: 1.1 mg/dL). The immunosuppression (IS) regimen consisted of steroids (5 mg/d), once-daily tacrolimus (extended-released Envarsus, target level: 7-8 μmol/L) and azathioprine (1 mg/kg/d), the latter started 1 year previously, replacing mycophenolate acid as she declared the intent to become pregnant.

Imaging examinations

Chest X-ray was negative for pneumonia.

FINAL DIAGNOSIS

SARS-CoV-2 infection in a KT pregnant lady.

TREATMENT

At diagnosis of SARS-CoV-2 infection, azathioprine was suspended, while steroids and tacrolimus were maintained at unchanged doses. During the infection, the patient developed moderate respiratory symptoms and close clinical monitoring was performed, showing persistent stable graft function, steady tacrolimus blood levels and regular fetal growth. One month later, the patient achieved a complete clinical recovery. The SARS-CoV-2 swab became negative after 40 d. At 39 wk of gestation, she had an uneventful delivery of a healthy male infant (weight: 3.2 kg; Apgar score: 9/10) by caesarean section.

OUTCOME AND FOLLOW-UP

At the time of delivery, the placenta and the newborn were not tested for SARS-CoV-2. The patient's renal graft function remained stable throughout the post-delivery period, and after 17 mo of follow-up the creatinine was 1.09 mg/dL (Table 1). During pregnancy, anti-human leukocyte antigen donor-specific antibody (DSA) screening was performed and these antibodies were not detected. In particular, no evidence of post-COVID-19 DSA was identified. Graft biopsy was not done. At the last follow-up, both the mother and the child were in good clinical condition.

DISCUSSION

The reduction of the immune response due to both IS drugs and pregnant status render pregnant KT recipients vulnerable to viral infections such as SARS-CoV-2[1,2]. In our case, this was further enhanced by her non-vaccinated status, since at that time the vaccine for SARS-CoV-2 was not available yet. Therefore, the concomitance of COVID-19-related morbidity, the risk of acute rejection in hyperimmune re-KT, graft dysfunction and pregnancy complications make the management of IS a very difficult task.

In KT recipients, recommendations suggest the modification of IS drugs according to the severity of COVID-19, ranging from no modification in asymptomatic patients, antimetabolite withdrawal in mild/moderate symptomatic disease, to complete drug discontinuation in severely ill patients requiring mechanical respiratory support[4,5]. In this case, we decided to withdraw azathioprine, which inhibits purine synthesis, aiming to avoid the depletion of T- and B-cells during the SARS-CoV-2 infection. Tacrolimus and steroids at low-doses remained the only IS drugs, without increasing their blood target-levels. The extended-released formula of tacrolimus Envarsus, which provides effective and stable blood concentration with less toxic levels compared to other Tacrolimus formulae[6], permitted the safe control of rejection risk and the avoidance of severe COVID-19. Thus, a recent report suggested that a mammalian target of rapamycin inhibitor may have potential antiviral benefits in SARS-CoV-2 infection [7].

In this case, strict monitoring of DSA was performed before and after COVID-19, since the IS regimen had been reduced. Despite the significant decrease of the IS and the high risk of rejection due to the hyperimmune status of third-KT recipients, our patient did not develop new DSA or rejection episodes. These data confirm a recent report investigating the alloreactive immune response during and after SARS-CoV-2 infection in KT recipients, which showed that the incidence of acute rejection is about 1.3% (all in hospitalized patients) and the occurrence of post-COVID-19 DSA is 4% overall, ranging from 0% to 8% in non-hospitalized and hospitalized patients, respectively[8]. Despite the immunosuppressed status of a third KT pregnant lady, our patient was very lucky because she was in this group of patients who do not develop severe COVID-19 disease. Since the stable kidney function and the pregnant status, we did not perform a graft biopsy in order to avoid possible biopsy-related complications. Additionally, venous thromboembolism prophylaxis was not administrated as no evidence was present, but its utility should be explored in pregnant COVID-19 KT recipients.

Pregnancy in KT recipients may be associated with a high-risk of maternal complications and decreased graft function, which could further deteriorate in the presence of COVID-19[9]. In fact, the occurrence of acute kidney injury in infected pregnant KT recipients could be due to the SARS-CoV-2 infection or to other pregnancy-related causes, which need to be differentiated[10]. In immunosuppressed transplant recipients as well as pregnant women, SARS-CoV-2 showed the potently to replicate into the kidney causing renal disfunction[11,12]. Lastly, despite the fact that the risk of acquiring SARS-CoV-2 infection during pregnancy seems to be similar to that of non-pregnant patients, severe maternal COVID-19 is associated with acute kidney injury and preterm birth.

The risk of congenital infection with SARS-CoV-2 to the newborn is still unknown[2,13]. In our case, the placenta and the baby were not tested for SARS-CoV-2 PCR, therefore unfortunately we do not have these interesting data. Moreover, despite KT pregnant recipients are more susceptible to chronic infection such as cytomegalovirus (CMV) infection, we didn't detect any CMV infection during pregnancy. This is the first report focusing on IS management in SARS-CoV-2-positive pregnant KT recipients.

Table 1 Patients' characteristics

Variables at presentation	Values
Demographics	
Age, yr	37
Sex	Female
Race	White
Number of KT	3
Primary nephropathy	Focal and segmental glomerulosclerosis
Causes of previous KT losses	Chronic rejection
Time from last KT	24 mo
Comorbidities	Arterial hypertension
Pregnancy	
Gestation age, wk	20
Fetal grow	Regular
Symptoms/signs	
Fever, T > 37.5 °C	Yes
Dyspnea	Yes
Anosmia	Yes
Myalgias	Yes
SARS-CoV-2 status	
SARS-CoV-2 swab test positive	Yes (positivity for 40 d)
SARS-CoV-2 vaccination	No
Biochemical tests	
At infection diagnosis	
Creatinine, mg/dL	1.18
WBC as × 10^3/mmc	7.640
Lymphocytes, cells/mmc	1.590
PTL as × 10^3/mmc	202
C-reactive protein, mg/L	10.1
Procalcitonin, ng/mL	0.52
Peak during infection	
Creatinine, mg/dL	1.3
WBC as × 10^3/mmc	12.700
Lymphocytes, cells/mmc	3.400
PTL as × 10^3/mmc	250
C-reactive protein, mg/L	20.2
Procalcitonin, ng/mL	2.01
Immunosuppression regimen	
Tacrolimus	Continued at unchanged doses (target levels: 7-8 μmol/L)
Azathioprine	Withdrawal
Steroids	Continued at unchanged doses (5 mg/d)
Outcomes	
Recovery from COVID-19 disease, mo	1

De novo DSA after SARS-CoV-2 infection	No
Rejection episode	No
Delivery	
Time of delivery, wk	39
Newborn status	Healthy, no complication
Time of follow-up after infection, mo	17
Renal function at last follow-up	
Creatinine, mg/dL	1.09

COVID-19: Coronavirus disease 2019; DSA: Donor-specific antibody; KT: Kidney transplant; PTL: Primary testicular lymphoma; SARS-CoV-2: Severe acute respiratory syndrome coronavirus; WBC: White blood cell.

CONCLUSION

We suggest that all efforts should be made to avoid severe maternal COVID-19 disease through tailored adjustment of the IS regimen and close monitoring of calcineurin inhibitor trough-blood levels, graft function and fetal parameters. Currently, mRNA vaccines against SARS-CoV-2 are recommended both in KT recipients and pregnant women, and may help in preventing severe COVID-19 disease[14,15]. However, KT patients have been shown to frequently be poor responders to the vaccines, thus remaining at high risk of developing severe COVID-19[16], especially in pregnancy. In fact, recent data suggest that only selected KT recipients seem to respond to the third booster dose of SARS-CoV-2 vaccine (assessed by anti-receptor binding domain immunoglobulin G titers and/or positive interferon-gamma-releasing assay)[17]. Moreover, in pregnancy, the boosting effect of a third vaccine dose is suggested to have a potential benefit only in those who completed the two-dose vaccine series in early pregnancy or prior to conception[16]. We feel that, although no data are yet available on the efficacy of the vaccine in preventing COVID-19 disease in pregnant KT recipients, a complete vaccine cycle against SARS-CoV-2 with three doses should preferably be performed before pregnancy. In addition, clinicians should be ready to tailor IS drugs when a member of this rare population is infected by SARS-CoV-2.

FOOTNOTES

Author contributions: Angelico R contributed to the study conception and design, writing; Framarino-dei-Malatesta ML was involved in the acquisition of clinical data, analysis, and interpretation; Iaria G contributed to the study conception; and all authors were involved in critical revision.

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Country/Territory of origin: Italy

ORCID number: Roberta Angelico 0000-0002-3439-7750; Maria Luisa Framarino-dei-Malatesta 0000-0001-7824-7511; Giuseppe Iaria 0000-0002-3429-6407.

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The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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REVIEW

Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation

Konstantinos Ouranos, Anthi Chatziioannou, Ioannis Goulis, Emmanouil Sinakos

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Konstantinos Ouranos, Anthi Chatziioannou, Ioannis Goulis, Emmanouil Sinakos, 4th Medical Department, Hippokratio Hospital, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Corresponding author: Konstantinos Ouranos, MD, 4th Medical Department, Hippokratio Hospital, Aristotle University of Thessaloniki, 49, Konstantinoupoleos Str, Thessaloniki 54642, Greece. kostassky@hotmail.com

Abstract

Hepatocellular carcinoma (HCC) is an aggressive primary liver neoplasm that, according to tumor stage, can be treated with resection, transplantation, locoregional treatment options, or systemic therapy. Although interventions only in early-stage disease can offer complete tumor regression, systemic therapy in advanced disease can significantly prolong overall survival, according to published clinical trials. The emergence of immunotherapy in the field of cancer therapy has had a positive impact on patients with HCC, resulting in atezolizumab–bevacizumab currently being the first-line option for treatment of advanced HCC. In light of this, application of immunotherapy in the preoperative process could increase the number of patients fulfilling the criteria for liver transplantation (LT). Implementation of this approach is faced with challenges regarding the safety of immunotherapy and the possibly increased risk of rejection in the perioperative period. Case reports and clinical trials assessing the safety profile and effectiveness of neoadjuvant immunotherapy, highlight important aspects regarding this newly evolving approach to HCC management. More studies need to be conducted in order to reach a consensus regarding the optimal way to administer immunotherapy prior to LT. In this review, we summarize the role, safety profile and future considerations regarding the use of neoadjuvant immunotherapy prior to LT in patients with HCC.

Key Words: Hepatocellular carcinoma; Immunotherapy; Tumor downsizing; Liver transplantation; Neoadjuvant; Rejection

Core tip: Immunotherapy has been used in the treatment of advanced hepatocellular carcinoma (HCC) with promising results. Extending its use in the preoperative period prior to liver transplantation (LT), either alone or in combination with other locoregional treatment modalities, could increase the pool of potential LT candidates. Data from case reports and ongoing clinical trials assessing neoadjuvant immunotherapy prior to LT could revolutionize the current consensus regarding HCC downsizing practices and improve survival of patients with this type of malignancy.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, constitutes the sixth most common cancer worldwide and the fourth most common cause of cancer-related mortality[1]. Incidence of HCC has been on the rise in some parts of the world, such as Europe and the USA, where the main risk factors for HCC development include HBV and HCV infection, alcohol consumption and nonalcoholic fatty liver disease (NAFLD)[2-4]. Due to the fact that HCC has been the fastest-rising cause of cancer-related mortality[2], and that most patients present at an advanced stage at the time of diagnosis, multiple treatment approaches have been thoroughly investigated by the scientific community in an effort not only to detect the cancer at an earlier stage, when more treatment modalities are applicable, but also ensure complete eradication of the tumor.

Optimal treatment options for HCC depend on tumor morphological characteristics, liver functionality and overall physical status of the patient, as suggested by the Barcelona Clinic Liver Cancer staging system (BCLC); one of the most used staging systems. According to BCLC, very early (0) and early (A) stages are potentially curative with radiofrequency ablation (RFA), surgical resection or liver transplantation (LT), with an overall survival (OS) > 60 mo. Patients with intermediate (B), advanced (C) and terminal (D) disease, however, who are not candidates for curative resection or transplantation, are best treated with transarterial chemoembolization (TACE), systemic therapy and supportive care, respectively, and face a grim prognosis with an OS of 20 mo for stages B and C and < 3 mo for stage D[5-7].

Patients with early-stage disease who are not candidates for surgical resection can undergo liver transplantation (LT) as a curative option, given that they fulfill the respected criteria, with a 4-year survival rate of 75%. These criteria, widely known as the Milan criteria (MC), screen patients for liver transplantation eligibility based on morphological characteristics of the tumor. However, strict application of the MC can exclude many patients from receiving the potentially curative treatment of LT, solely on the basis of tumor size and number[8,9]. In an effort to include more patients within the MC and further utilize the clinical benefits of LT, the concept of downstaging has been introduced in the treatment of HCC. Downstaging refers to a decrease in the tumor burden to the point where patients meet the MC and can receive LT. Downstaging options include, but are not limited to, TACE combined or not with doxorubicin eluting beads (TACE ± DEB), RFA, microwave ablation (MWA), transarterial radioembolization (TARE), irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), stereotactic body radiotherapy (SBRT), and systemic therapy[10]. Post-transplant survival rate in patients who had undergone LT after successful downstaging to MC have been shown to be comparable to that of patients undergoing LT and initially presenting within the MC[11].

In the modern era of cancer immunotherapy, alteration of signals that modulate the interaction between cancer cells and cells of the immune system, has led to many advances in the treatment of various cancer types, including HCC[12]. Although immunomodulating therapies are mainly used in advanced HCC, neoadjuvant immunotherapy is a promising approach as a means of downstaging the tumor prior to LT, yielding positive outcomes in the post-transplant period[13,14]. The aim of this review is to summarize the role of immunotherapy as a downstaging technique and also highlight future considerations regarding its safety and clinically beneficial endpoints in the perioperative period and beyond.

ORTHOTOPIC LT FOR HCC

The MC have been widely used as a tool for determining which patients are eligible for LT. According to these criteria, patients may undergo LT if the following requirements are met: (1) Single tumor with a diameter ≤ 5 cm; or (2) up to three tumors, each ≤ 3 cm in diameter and no extrahepatic spread or

vascular involvement. Although patients with HCC transplanted within the MC have a 4-year survival rate of 75% and a recurrence-free survival rate of 83%, there are studies suggesting that patients not fulfilling the MC may still benefit from LT[15,16]. Overdependence on the MC may mask the true number of patients that would benefit from a transplant. In light of this, several expanded criteria have been proposed in an effort to include patients in the transplant process. What makes these criteria stand out from MC, is that they take into account not only morphological characteristics of the tumor, but also integrate biological aspects of the disease and response to locoregional treatment (LRT) in their algorithm[17]. One of the most commonly used biological parameter is -fetoprotein (AFP). AFP serves as marker of HCC differentiation and can be used in the pretransplant period to identify patients at high risk for HCC recurrence after LT. AFP levels ≥ 1000 ng/mL are associated with poor outcomes following LT, although there are no established guidelines that indicate the optimal AFP threshold that accurately predicts post-LT outcomes[18,19]. Other well-studied biological parameters that can be taken into consideration include des--carboxyprothrombin (DCP) levels, neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index, aspartate aminotransferase-to-platelet ratio index, and aspartate aminotransferase-to-neutrophil ratio index[18]. Evaluation of tumor response to LRT is a newly evolving concept in optimal selection of patients for LT, that aims to downstage patients within the MC, promising comparable survival rates to patients with HCC receiving LT and already within the MC. Response to treatments that result in decreased tumor burden can be viewed as a complementary marker of the biological aggressiveness of the tumor and risk of HCC recurrence after LT[15]. All of the proposed expanded criteria that include the aforementioned parameters have 5-year survival rates that approximate that of MC, resulting in many institutions adopting them for the purpose of selecting patients with HCC for LT[18].

Application of the expanded criteria, however, requires an adequate reserve of available organs for transplantation, since more patients are included in the transplant process. And while this is not a problem for countries located in Asia, where living donor LT (LDLT) is the main organ source, western countries mainly depend on deceased donor LT (DDLT), which necessitates strict selection of eligible patients for LT[19]. Moreover, patients receiving DDLT typically have longer wait times when compared to patients receiving LDLT, raising concern for tumor progression in such circumstances. The above remarks highlight the importance of careful selection of patients for LT, in order to maximize the positive outcomes following LT. Downstaging therapy, ideally within the MC, is common practice nowadays and has a robust armamentarium of treatment approaches that serve to reduce tumor burden and make HCC amenable to transplantation. Also, bridging therapy aims to halt tumor progression and allow patients to receive curative treatment. Although there are no clear-cut indications for downstaging or bridging therapy, results from various studies suggest that patients presenting with tumor characteristics beyond the established criteria for LT, as well as patients with waiting times ≥ 6 mo until LT, should receive neoadjuvant therapy[20,21]. Outcomes following implementation of pretransplant treatment modalities have been mixed. A study from Yao *et al*[8] revealed post-transplant survival and recurrence-free probabilities of patients with HCC successfully downstaged within MC to be comparable to those observed in patients with HCC and already within the MC at the time of diagnosis[22]. Other studies conducted by Lao *et al*[23], Chapman *et al*[24], and Gordon-Weeks *et al*[25] have also reached to similar conclusions. However, several other studies examining the effect of LRT on post-LT outcomes found out that neoadjuvant therapy is not associated with improved outcomes and may even increase recurrence of HCC following downstaging protocol implementation[26-30]. The lack of consistent outcomes following LRT application prior to LT has generated an extensive discussion of whether conventional LRT should be modified or enriched with the aim of enhancing the downstaging and bridging options for HCC[31]. Immunotherapy has been on the spotlight of HCC in recent years and is mainly used for late-stage disease when curative treatment is unfeasible, resulting in improved OS and progression-free survival (PFS)[32]. Neoadjuvant immunotherapy as a form of LRT prior to LT is a promising new approach that aims to leave behind the flaws associated with conventional LRT and increase the number of patients receiving curative treatment.

IMMUNOTHERAPY FOR ADVANCED HCC

Tumor microenvironment in HCC

The liver is an immunogenically active organ. Under normal conditions, antigen-presenting cells (APCs) take up, process and present the antigens that enter the hepatic sinusoids on T cells, in an effort to elicit a robust immune response and prevent tissue damage. Kupffer cells, which are liver-specific macrophages, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs) constitute the most important APCs in the liver parenchyma and, apart from their antigen-presenting role, complement the immunological repertoire of the liver by other means as well[33]. Kupffer cells produce anti-inflammatory molecules, mainly interleukin (IL)-10 and transforming growth factor (TGF)-β, attracting regulatory T (Tregs) cells that possess immunosuppressive properties, whereas LSECs and HSCs express high levels of programmed cell death ligand (PDL)1, contributing to attenuation of the immune response[34]. As a result, the liver can fight off antigens that could cause tissue damage and

also maintain immune tolerance, thereby avoiding autoimmunity.

HCC development is governed by alterations in the normal liver environment that promote tumoral spread *via* upregulation of immunosuppressive molecules that hinder the immune response against cancer cells[35]. Maintenance of this immunosuppressive tumor microenvironment (TME) is achieved not only by liver-residing immune cells, but also from migrating populations of lymphocytes, collectively referred to as tumor-infiltrating cells (TICs)[36]. According to the subpopulation being studied, TICs can elicit an antitumoral immune response or result in upregulation of immune evasion by cancer cells. Figure 1 depicts the dynamic and complex interactions of the components of the TME and their effect on tumor spread[35-38] (Figure 1).

Mechanisms of immune evasion are of special concern, since many cancer treatment modalities depend on them. Immune checkpoint molecules modulate T-cell activation and function, attenuate the immune response against cancer cells and allow for unchecked cellular proliferation[39,40]. More specifically, PDL1, expressed by cancer cells or cells of the TME, binds to PD1 on the surface of T cells, leading to T-cell exhaustion and inability to mount an effective immune response. Also, cytotoxic T-lymphocyte-associated protein (CTLA)-4 on T cells outcompetes CD28 for B7 on the surface of APCs, leading to loss of the co-stimulatory signal necessary for T-cell activation[41]. In order to halt tumorigenesis, alteration of the signals that promote immune evasion was made possible with the introduction of antibodies known as immune checkpoint inhibitors (ICIs). Such antibodies that mainly target PD1 (cepilimumab, nivolumab and pembrolizumab), PDL1 (atezolizumab, durvalumab and avelumab) and CTLA-4 (ipilimumab), have been used in the treatment of various cancers, including HCC, and have been shown to correlate with improved OS in major studies assessing their efficacy[42].

Role of immunotherapy in advanced HCC

Although systemic therapy targeting signal conduction pathways appeared in the treatment of HCC in 2007, immunotherapy lagged for about a decade before making a debut in 2017[43-45]. Nivolumab, a PD1 immune checkpoint inhibitor, was the first monoclonal antibody to be assessed in the treatment of advanced HCC. The CheckMate 040 was a noncomparative, dose escalation and expansion trial that included 262 patients (48 in the dose escalation and 214 in the dose expansion phase) and revealed that nivolumab had an objective response rate (ORR) of 15%–20% according to the mRECIST criteria and a median OS of 13.2–15 mo; findings that were comparable to the outcomes produced by sorafenib, the first-line treatment for HCC at that time. Due to the fact that no control arm was available in that trial, subsequent analyses comparing nivolumab to sorafenib were conducted. The CheckMate 459 phase III trial, assigning 743 patients with HCC to receive either nivolumab (intervention arm) or sorafenib (control arm), however, failed to show a statistically significant improvement in median OS [hazard ratio (HR) 0.85 (95% confidence interval (CI): 0.72–1.02); *P* value above the protocol-defined significance level] and PFS [HR 0.93 (95% CI: 0.79–1.1); *P* value above the protocol-defined significance level], but revealed a clinically significant median OS of 16.4 mo versus 14.7 mo in the intervention and control arms, respectively. Even more, grade 3/4 adverse effects were reported in 22% of patients treated with nivolumab compared with 49% of patients treated with sorafenib, justifying the use of this immunomodulating therapy in patients who are not candidates for sorafenib[32,46-48]. Pembrolizumab, another PD1 immune checkpoint inhibitor, was also assessed in the KEYNOTE 224 study, yielding an ORR of 17% and median OS of 12.9 mo[49]. Phase III trials assessing the comparative efficacy of pembrolizumab to best supportive care, failed to show significance in the primary endpoints of OS and PFS; albeit a clinically significant increase in OS[32,50,51]. Several other monoclonal antibodies have been thoroughly investigated as potential first-line treatment options for advanced HCC, including tislelizumab, durvalumab, avelumab, tremelimumab and atezolizumab. Results from these studies have revealed promising outcomes regarding the effect of these immunotherapies in OS and PFS when compared to currently established first-line options for HCC. Table 1 summarizes the major trials that harness immunotherapy, either alone or in combination with other modalities (*e.g.*, addition of a second ICI or systemic therapy), for the treatment of advanced HCC[32,33,39-42,46,47,49,52-54] (Table 1).

The IMbrave150 trial was a cornerstone in the management of advanced HCC. This global, open-label phase III randomized trial compared atezolizumab–bevacizumab with sorafenib in the treatment of advanced HCC. Atezolizumab is a PDL1 ICI and bevacizumab is a vascular endothelial growth factor inhibitor. 501 patients were randomly assigned in 2:1 ratio to receive either atezolizumab-bevacizumab or sorafenib until there was clinical benefit or emergence of unacceptable side effects. The primary endpoints were OS and PFS, whereas secondary endpoints included ORR, duration of response, deterioration of quality of life, physical functioning, and role functioning. According to the results, median OS was 19.2 mo (95% CI: 17.0–23.7) with atezolizumab–bevacizumab and 13.4 mo (95%CI: 11.4-16.9) with sorafenib [HR 0.66 (95% CI: 0.52–0.85), $P < 0.001$], whereas PFS was 6.9 mo (95% CI: 5.7–8.6) with atezolizumab–bevacizumab and 4.3 mo (95% CI: 4.0–5.6) with sorafenib [HR 0.65 (95% CI: 0.53–0.81), $P < 0.001$]. Results of secondary endpoints were also significant and favored the atezolizumab–bevacizumab arm. Grade 3/4 adverse effects occurred in 56.5% and 55.1% of patients in the intervention versus control arm, respectively, with the most frequent severe adverse effect in the atezolizumab–bevacizumab group being high-grade hypertension (15.2% of patients)[55]. The overall outcome of this study resulted in atezolizumab-bevacizumab being the current first-line treatment option for managing advanced HCC[56-59].

Table 1 Clinical trials assessing the effectiveness of immunotherapy in patients with advanced hepatocellular carcinoma

Trial name	Phase	Intervention	Status
Single-agent immunotherapy			
NCT02576509	III	Nivolumab *vs* sorafenib	Completed
NCT02702414	II	Pembrolizumab (single-arm study)	Completed
NCT02702401	III	Pembrolizumab *vs* BSC	Completed
NCT03062358	III	Pembrolizumab and BSC *vs* BSC and placebo	Not yet completed; estimated completion date: June 2023
NCT03412773	III	Tislelizumab *vs* sorafenib	Not yet completed; estimated completion date: May 2022
NCT02989922	II/III	Camrelizumab (single-arm study)	Not yet completed
NCT01008358	II	Tremelimumab (single-arm study)	Completed
Combination of immunotherapy with other treatment modalities[1]			
NCT02423343	I/II	Galunisertib and nivolumab (dose escalation and cohort expansion study)	Completed
NCT03893695	I/II	Ascrinvacumab and nivolumab (single-arm study)	Not yet completed; estimated completion date: June 2022
NCT03059147	I	PI3 kinase/BRD4 inhibitor small molecule and nivolumab (single-arm study)	Not yet completed; estimated completion date: October 2022
NCT03211416	I/II	Pembrolizumab and sorafenib	Not yet completed; estimated completion date: December 2022
NCT03713593	III	Lenvatinib and pembrolizumab *vs* Lenvatinib and placebo	Not yet completed; estimated completion date: December 2023
NCT03316872	II	Pembrolizumab and SBRT (single-arm study)	Not yet completed; estimated completion date: December 2023
NCT03099564	I	Pembrolizumab and Radioembolization (single-arm study)	Not yet completed; estimated completion date: June 2022
NCT03939975	II	Pembrolizumab or nivolumab or toripalimab with thermal ablation, RFA or MWA	Completed
NCT02715531	I	Atezolizumab with bevacizumab or other chemotherapy agents	Completed
NCT03434379	III	Atezolizumab and bevacizumab *vs* Sorafenib	Not yet completed; estimated completion date: June 2022
NCT03755791	III	Atezolizumab and cabozantinib *vs* sorafenib *vs* cabozantinib	Not yet completed; estimated completion date: December 2023
NCT04310709	II	Reforafenib and Nivolumab (single-arm study)	Not yet completed; estimated completion date: May 2023
NCT03869034	II	HAIC and sintilimab *vs* HAIC	Completed
NCT03794440	II/III	Anti-VEGF monoclonal antibody and sintilimab *vs* sorafenib	Not yet completed; estimated completion date: December 2022
NCT03764293	III	Apatinib and PD1 monoclonal antibody *vs* sorafenib	Not yet completed; estimated completion date: June 2022
NCT03755739	II/III	Pembrolizumab and/or ipilimumab administered *via* arterial infusion or intra-tumor fine needle injection *vs* pembrolizumab and/or ipilimumab administered *via* vein infusion	Not yet completed; estimated completion date: November 2033
NCT04273100	II	PD1 monoclonal antibody and TACE and lenvatinib (single-arm study)	Not yet completed
NCT03857815	II	PD1 monoclonal antibody and SBRT (single-arm study)	Not yet completed
NCT01853618	I/II	Tremelimumab and/or TACE and/or RFA (sequential assignment)	Completed
NCT04124991	I/II	Durvalumab and TARE (single-arm study)	Not yet completed
NCT03475953	I/II	Regorafenib and avelumab (sequential assignment)	Not yet completed; estimated

completion date: December 2022

[1]Combination therapy includes using two or more ICIs, an ICI plus systemic therapy and/or ICI plus LRT. BSC: Best supportive care; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; PI3 kinase: Phosphoinositide 3 kinase; BRD4 inhibitor: Bromodomain-containing protein 4 inhibitor; SBRT: Stereotactic body radiotherapy; RFA: Radiofrequency ablation; MWA: Microwave ablation; HAIC: Hepatic arterial infusion chemotherapy; VEGF: Vascular endothelial growth factor; PD1: Programmed cell death receptor; ICI: Immune checkpoint inhibitor; LRT: Locoregional therapy.

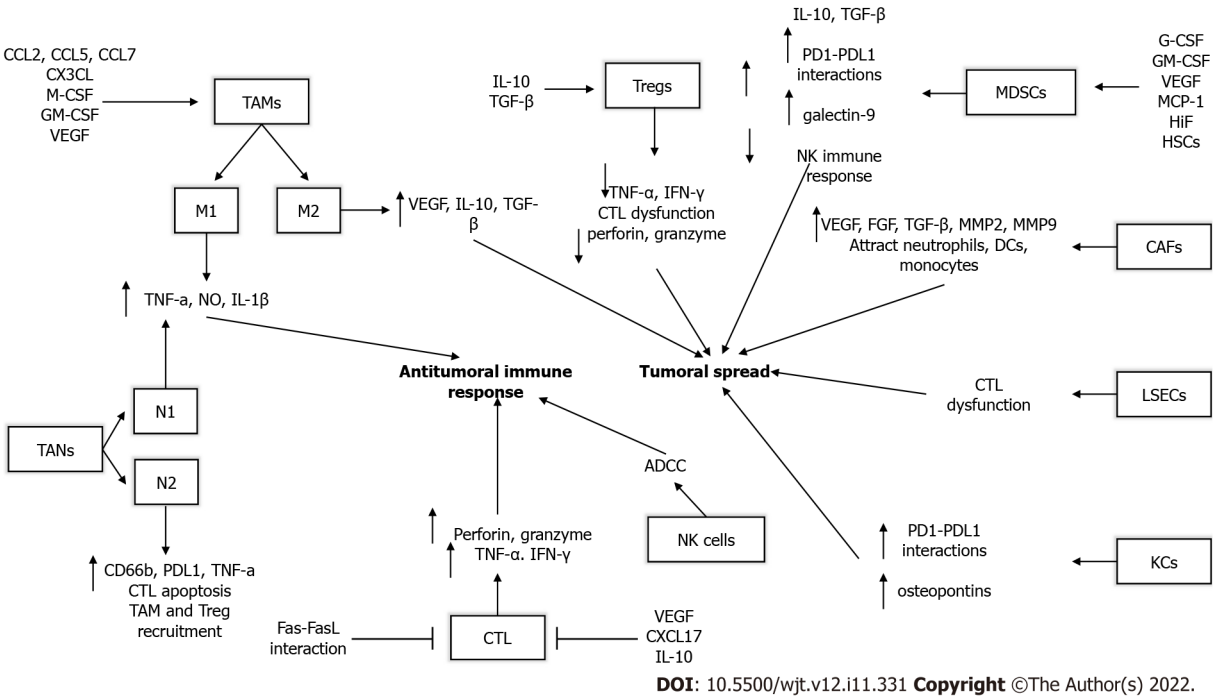

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Figure 1 Schematic representation of the major components of the tumor microenvironment in patients with hepatocellular carcinoma. The main elements of the TME can affect tumoral spread both positively and negatively. The migration of TAMs and TANs can enhance the antitumoral immune response (M1 and N1 subpopulations) through the production of inflammatory mediators, such as TNF-α, NO and IL-1β, whereas M2 and N2 subpopulations promote tumoral spread by producing immunosuppressive molecules and modulating T-cell function. The immune upregulating effects of NK cells and CTLs are typically blunted in patients with HCC due to the presence of factors secreted by components of the TME. MDSCs mute NK responses, increase levels of galectin-9, IL-10, TGF-β, and promote PD1-PDL1 interactions, favoring tumor spread. Treg cells, LSECs and KCs all promote HCC development by inducing CTL dysfunction, immune evasion, and expression of immune-downregulating factors. CCL2: Chemokine receptor type 2; CCL5: Chemokine receptor type 5; CCL7: Chemokine receptor type 7; CX3CL: Chemokine (C-X3-C motif) ligand 1; M-CSF: Macrophage colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; VEGF: Vascular endothelial growth factor; TAMs: Tumor associated macrophages; M1: Subpopulation 1 of TAMs; M2: subpopulation 2 of TAMs; IL-10: Interleukin 10; TGF-β : Transforming growth factor beta; TNF-a: Tumor necrosis factor alpha; NO: Nitric oxide; IL-1β: Interleukin 1 beta; TANs: tumor associated neutrophils; N1: Subpopulation 1 of tans; n2: subpopulation 2 of TANs; CD66b: Cluster of differentiation 66 type b; PDL1: Programmed cell death ligand 1; PD1: Programmed cell death receptor 1; CTL: Cytotoxic CD8+ T cells; Tregs: T regulatory cells; FasL: Fas ligand; IFN-γ: Interferon gamma; CXCL17: Chemokine (C-X-C motif) ligand 17; NK cells: Natural killer cells; MCP-1: Monocyte chemoattractant protein-1; HiF: Hypoxia inducible factor; HSCs: Hepatic stellate cells; MDSCs: Myeloid derived suppressor cells; CAFs: Cancer associated fibroblasts; FGF: Fibroblast growth factor; MMP2/9: Matrix metalloproteases 2 and 9; LSECs: Liver sinusoidal endothelial cells; KCs: Kupffer cells.

Recently, the HIMALAYA study assessed the efficacy of combination tremelimumab and durvalumab in advanced HCC. This phase III study involved 1234 patients that were randomly assigned to receive durvalumab and tremelimumab or sorafenib or durvalumab monotherapy. The ORR was 20.1% in the durvalumab–tremelimumab group compared with 5.1% and 17% in the sorafenib and durvalumab groups, respectively. The PFS and OS were 3.78 and 16.4 mo in the durvalumab and tremelimumab group, 4.07 and 13.8 mo in the sorafenib group, and 3.65 and 16.6 mo in the durvalumab group. Grade 3/4 adverse events occurred at a lower rate in the durvalumab–tremelimumab and durvalumab groups when compared with the sorafenib arm. Overall results of this breakthrough study open up new treatment options that could be integrated into the treatment algorithm of HCC management[60].

As suggested by the above remarks and Table 1, clinical trials assessing the combination of immunotherapy and systemic therapy or the use of two ICIs concurrently, have shown greater outcomes when compared to trials that use single-agent therapy (immunomodulating or systemic) in the intervention arm. An ambitious treatment approach is the combination of ICIs with LRT, the latter of which is traditionally used in early-stage disease or as a means of downstaging or bridging therapy prior to LT

[61]. The idea behind this approach is that LRT can alter the TME by inducing a robust antitumoral immune response and reduce the number of immunosuppressive molecules. Although these effects could theoretically justify LRT as a single therapy to control tumor progression, evidence suggests that such responses are weak and transient and cannot completely control the tumor. The addition of immunotherapy could amplify the antitumoral responses produced by LRT, thus creating a synergistic interaction between ICIs and LRT that could effectively control tumor spread[62,63]. There are a few trials assessing the combination of LRT with ICIs, since most of them take advantage of immunotherapy in the form of adoptive cell and vaccine therapy. However, results from these studies have demonstrated favorable outcomes in terms of OS and safety, thus encouraging the implementation of this combination in case other first-line treatment modalities fail[62].

Although combination immunotherapy is a superior approach than single-agent immunotherapy for the treatment of HCC, there are a few remarks that need to be pointed out. The need of combining various immunotherapeutic drugs in specific dosages may come as a challenge for smaller hospitals that are neither readily equipped, nor familiar with the specific combination regimens used to treat HCC. The lack of availability of highly efficacious drugs in resource-limited hospitals prevents the widespread application of immunotherapy, leaving healthcare providers with a restricted panel of drug options, mainly systemic chemotherapeutic agents, that, although effective, do not demonstrate the superiority of immunotherapy in treating HCC. Unfortunately, this hurdle inevitably affects pre-transplant ICI use for the same reasons mentioned above.

IMMUNOTHERAPY AS A DOWNSTAGING THERAPY PRIOR TO LT

It seems evident that immunotherapy has an integral role in the management of advanced HCC. The success of ICIs use in the long-term survival of patients with HCC has brought into question whether immunotherapy could also produce significant outcomes in early-stage disease and mainly as neoadjuvant treatment modality prior to LT. Although data on this topic are scarce, valuable information can be extracted regarding the future applications of ICIs in HCC management.

Goals of neoadjuvant immunotherapy

Delivery of immunotherapy prior to LT serves the same goals as application of conventional LRT, and, at the same time, establishes new perspectives in terms of prediction of post-LT outcomes and survival following transplantation. Bridging and downstaging ICI therapy is a novel approach to maintaining or even increasing the pool of transplant HCC candidates able to undergo curative LT. Beyond that, ICIs may have additional benefits post-LT, since they may be able to decrease disease recurrence by treating micrometastatic disease that was not detected prior to LT[14]. The basis behind the already mentioned promising benefits of neoadjuvant immunotherapy stems from the ability of ICIs to reconstitute the immune response towards an antitumoral microenvironment that halts disease progression. More specifically, histological analysis of a specimen from a subject enrolled in a study evaluating the perioperative use of ICIs in patients with HCC revealed an increase in the number of cytotoxic $CD8^+$ T cells and levels of interferon (IFN)-γ, which are both known to mitigate the immunosuppressive TME seen in HCC and at the same time mount an effective antitumoral, inflammatory response that controls tumor spread. Also, although the cluster of Treg cells, which are known to induce an immunosuppressive environment and promote cancer spread, was increased, there was an eventual complete pathologic response observed in the analyzed specimen. This could be due to the high $CD8^+$ T cell/Treg cell ratio, favoring the antitumoral immune response, or to the presence of a mixed population of regulatory T cells that serve to halt disease progression[64]. Other studies have also evaluated the mechanisms responsible for producing favoring outcomes following periprocedural ICI administration and have concluded that the overwhelming infiltration of tumor-specific CD8+ T-cells, the release of inflammatory cytokines, such as IFN-γ and tumor necrosis factor (TNF)-α, the elevated number of tumor neoantigens that attract T cells and the relative decrease in the number of immunosuppressive and Treg cells, all contribute to the positive immunomodulating outcomes of neoadjuvant ICI use[65-68]. Overall, neoadjuvant immunotherapy prior to LT in HCC serves three main goals: (1) Preventing patients from waitlist dropout, when the time interval to LT is substantial (bridging therapy); (2) increasing the number of patients eligible for transplantation by including them in established LT criteria (downstaging therapy); and (3) ensuring micrometastatic spread eradication after LT, thereby increasing the chances of prolonged survival after surgery.

Considerations regarding the safe use of neoadjuvant immunotherapy prior to LT in patients with HCC

When contemplating ICI administration prior to LT, one has to take into account the time interval between the last dose of ICI therapy and LT, factors that predict response to ICI therapy, in order to prevent graft rejection, and the possible adverse events associated with ICI and how they could be effectively managed.

Post-LT ICI administration has been linked to donor allograft rejection[69]. Indications for using immunotherapy after transplant include recurrence of malignancy or emergence of a new tumor that is responsive to ICI therapy. When a transplant process takes place, immunosuppression typically follows to prevent the host immune response against the transplanted allograft. ICI administration, by upregulating the T-cell response and dampening the signals that create a state of relative immunosuppression that is desirable post-LT, can result in T cells attacking the graft, resulting in dysfunction, subsequent rejection, and eventual graft and/or patient loss. Despite this feared outcome, studies evaluating graft function after ICI administration in patients undergoing LT have been mixed, and no consensus has been reached regarding the safety profile of immunotherapy in the perioperative period[70]. A case series study evaluating 13 HCC patients who received ICI post-LT revealed that four patients (31%) developed graft rejection[71]. Another study identified a cohort of 14 patients who received ICIs post-LT, with four of them (29%) experiencing graft rejection[72]. Moving to the downstaging setting, it is important to consider a washout period between the last dose of immunotherapy and LT in order to downregulate the immune response that was accentuated during ICI therapy, thus allowing the allograft to be successfully transplanted. The ideal time interval until LT has not been decided, mainly due to the limited number of studies harnessing ICIs as a downstaging tool, but there are some important aspects to consider regarding this topic. The half-life of the immunomodulating agent could be used as an adjunctive parameter to calculate the time of immunotherapy discontinuation to LT. However, further understanding of the mechanism of action of ICIs may prove the above remark unreliable. Indeed, occupancy of drug-specific targets by these medications can be prolonged, resulting in a duration of effect that extends beyond the period one would calculate based on the half-life of the ICI[73]. For example, although the half-life of nivolumab is ~25 d, it has been observed that its effects may last for up to 2 mo following a single infusion of the drug, due to sustained occupancy of PD1 on the surface of T cells. Although a short washout period would theoretically correlate with increased risk of graft rejection, there are notable examples that prove this point wrong. A study by Tabrizian *et al*[13] assessed the outcome of nine HCC patients who were transplanted in a single center between 2017 and 2020 after receiving nivolumab 240 mg every 2 wk as downstaging therapy. Washout period did not exceed 30 d for any patient after discontinuation of treatment and, notably, two patients discontinued nivolumab 1 and 2 d prior to LT. Following transplantation, no severe graft rejection, tumor recurrence or death occurred, with one patient developing mild rejection that was appropriately managed with an increase in the dose of tacrolimus. Intraoperative blood transfusion was administered in the two patients who received LT within 2 d of nivolumab discontinuation, which could have accelerated the rate of drug washout[13]. In another study by Chen *et al*[74], a patient who underwent LT and discontinued preoperative toripalimab 93 d before the procedure, suffered ICI-induced acute hepatic necrosis. Results of these studies could indicate that half-life of a drug could not by itself predict the optimal time to LT after downstaging therapy implementation. Other potential parameters or markers should be investigated in order to attain a more precise estimate of the washout period.

Predicting if a liver graft is suitable for transplantation after ICI administration is a promising feat that could smooth out the perioperative process. PDL1 molecule expression on the transplanted graft could act as surrogate biomarker of the safety of ICIs in terms of inducing or not graft rejection. The idea behind this approach is that PDL1-negative grafts will have fewer rejections when compared to positive ones, since ICIs will not be able to mount an inflammatory immune response in the absence of drug-binding molecules on the cells of the transplanted parenchyma, thus maintaining the immunosuppressive environment required for LT. A study by Shi *et al*[75] was conducted to compare the graft rejection rate in five cancer patients who received PDL1-negative allografts when compared to controls with an unknown PDL1 status in their transplanted liver, after receiving the immunomodulating agent toripalimab. Results showed that none of the five patients who received PDL1-negative grafts experienced rejection, whereas another patient treated off-record who received PDL1-positive graft, experienced rejection after ICI administration. In another study conducted by Friend *et al*[76], graft rejection was detected in two HCC patients who received nivolumab after being transplanted with PDL1-postive allografts. DeLeon *et al*[77]. conducted a retrospective evaluation of seven cancer patients undergoing LT to assess the safety of post-transplant ICI use. Five out of seven patients in the study were assessed for PDL1 expression and two of them were positive. One of the two patients who received PDL1-poisitive grafts also demonstrated high levels of tumor-infiltrating lymphocytes in the transplanted liver. The results of the final study indicate that apart from PDL1 status, other potential biomarkers should be assessed to predict the outcomes of ICI use in the operative period. Although no major studies have been conducted up to date that could reliably emphasize the role of miscellaneous biomarkers that predict the safety of ICI use during LT, immunohistochemical analysis of the transplanted allograft could be used as a surrogate parameter that aims to better delineate the outcome of LT following ICI administration.

Although rejection is an undesirable outcome of ICI therapy, other adverse events can also occur, collectively known as immune-related adverse effects (iRAEs). Such adversities can prolong or even terminate the transplant process, not only because iRAEs may make the patient ineligible for LT, but also because effective management of such outcomes may prolong the time interval to LT, resulting in progression of the malignancy and dropout from the transplantation criteria. Most iRAEs present within the first 2 wk of treatment initiation, although they can occur at any time. Every organ can be involved,

and severity can range from mild to life-threatening[78,79]. Results from major clinical trials have found that grade 3/4 adverse events occur at an acceptable rate that would justify their use in HCC treatment. In the IMBrave150 trial, grade 3/4 adverse effects occurred in 56.53% of patients who were treated with atezolizumab–bevacizumab when compared with 55.13% of patients in the control group who were treated with sorafenib. The percentage of high-grade adverse effects in the intervention group was not attributed solely on atezolizumab, since hypertension, the most common high-grade adverse event observed in the study, was most likely attributable to bevacizumab[47,58]. In the KEYNOTE 240 trial, grade 3/4 adverse effects occurred in 52% of patients treated with pembrolizumab compared with 46.27% in the control arm[47].

It is not yet clear which class of ICIs is safer. While CTLA4 plays an important role in the induction of graft tolerance, PD1/PDL1 interactions result in both induction and maintenance of graft tolerance. Theoretically, this could imply that immunotherapy targeting PD1 and/or PDL1 molecules is more likely to cause organ rejection than agents that target CTLA4[80]. However, there are still no published studies that assess the comparative safety profiles of various classes of immunotherapy, so no definite conclusions can be drawn[71]. Regardless of which class will be chosen, treatment of iRAEs is the same, with glucocorticoids being the most common immunosuppressant agent that can effectively ameliorate negative outcomes of ICIs[78]. Patients undergoing LT for HCC usually have compromised liver function. Nonetheless, ICI use is safe in this patient population, since these drugs are not metabolized in the liver.

As already mentioned before, the paucity of available donors for LT substantially limits this treatment approach for the management of HCC. Although currently not employed in the armamentarium of HCC management, autologous LT is a theoretically promising approach that could increase the number of patients receiving curative treatment. Data regarding autologous LT following immunotherapy are not yet available, but a hypothetical explanation of the mechanism behind this approach could ignite future discussions around this topic. Liver regeneration capabilities are well studied in the literature. The effects of immunotherapy in the TME have been extensively discussed above and generally promote an antitumoral immune response that aims to halt tumor progression and decrease tumor burden. As such, more liver parenchyma can be restored to its physiologic architecture. Such an occurrence can aid in the autologous LT process by increasing the available tissue for extraction and reimplantation following diseased liver removal. As ideal as this approach may sound, challenges along the way, such as remaining unidentified tumor burden, metastatic disease and recurrence of malignancy are all topics of concern that need further investigation. For the time being, autologous LT following immunotherapy requires more research in order to delineate the exact mechanisms that could result in positive outcomes.

Clinical trials and case reports assessing the use immunotherapy as a downstaging technique prior to LT in patients with HCC

Case reports: According to literature review, 20 cases involving patients with HCC receiving ICIs prior to LT have been published[13,73,74,81-83] (Table 2). The majority of the patients were male (85%) and the mean age was 58.4 years. The most common underlying liver disease was HBV-induced liver disease, while HCV infection, alcoholic liver disease and NAFLD were also observed. One patient had no underlying liver disease. The most commonly used ICI prior to LT was the PD1 inhibitor nivolumab (55% of cases). Other immunomodulating agents used were toripalimab, durvalumab, camrelizumab and pembrolizumab. The time interval between the last dose of ICI and LT varied significantly among the cases, with one patient receiving the last ICI dose 1 d prior to LT and another one almost 29 mo prior to the operation. No recurrence of the tumor occurred in patients that had a successful LT after ICI use. Nonfatal perioperative complications, excluding rejection, occurred in only one patient, who developed bile leak that was appropriately managed without further consequences. Out of the 20 cases described, two patients had fatal rejection and two others experienced mild rejection that was adequately treated. The first patient with fatal graft rejection, described by Chen *et al*[74], had chronic HBV infection. He underwent DDLT due to recurrent HCC that was previously treated with resection, RFA, TACE, MWA, sorafenib, lenvantinib and toripalimab. The last cycle of ICI therapy was administered 93 d prior to LT. Following the procedure, the patient's liver function status deteriorated rapidly, and a liver biopsy performed on the second postoperative day revealed massive liver tissue necrosis that was attributed to toripalimab. The patient expired 3 d after the procedure[73]. The second patient with fatal graft rejection, described by Nordness *et al*[81], had chronic HCV infection. He underwent DDLT due to recurrent HCC previously treated with resection, sorafenib, RAE, TACE and nivolumab. The last dose of nivolumab was administered 8 d prior to LT. On postoperative day 5, rapid elevation of liver enzymes was noted, and the patient deteriorated clinically to the point where he was transferred to the intensive care unit. A biopsy that was performed on the next day revealed acute hepatic necrosis with a dense lymphocytic infiltration, findings that point towards a diagnosis of ICI-induced graft rejection. Reversible graft rejection that was observed in two patients was due to low levels of immunosuppressive medications and was appropriately treated with dose escalation, without inflicting any major damage to the graft recipients.

Table 2 Summary of case reports assessing immune checkpoint inhibitors as a downstaging and/or bridging therapy prior to liver transplantation in patients with hepatocellular carcinoma

Sex	Age, yr	Underlying liver disease	ICI	Cycles (d)	Washout period	Post-LT outcome
M	66	ALD	Nivolumab	34	105	No rejection
M	65	HCV	Nivolumab	44	8	Fatal rejection
M	39	HBV	Toripalimab	10	93	Fatal rejection
M	69	None	Nivolumab	21	18	No rejection
F	56	HCV	Nivolumab	8	22	No rejection
M	58	HBV	Nivolumab	32	1	No rejection
M	63	HCV	Nivolumab	4	2	No rejection
M	30	HBV	Nivolumab	25	22	Mild rejection[1]
M	63	HBV	Nivolumab	4	13	No rejection
M	66	HBV	Nivolumab	9	253	No rejection
F	55	HBV	Nivolumab	12	7	No rejection
F	53	NASH	Nivolumab	2	30	No rejection
M	61	HBV	Durvalumab	NA	> 90	No rejection
M	53 ± 12.1	NA	Camrelizumab and/or Pembrolizumab	3 ± 2	870 on average	1 rejection in the cohort[1]

[1]The rejection was appropriately treated and the patient suffered no major adverse outcomes. ICI: Immune checkpoint inhibitor; HCC: Hepatocellular carcinoma; M: Male; F: Female; LT: Liver transplantation; ALD: Alcoholic liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; NA: Not available.

Clinical trials: Currently, there is a limited number of clinical trials assessing the use of ICIs prior to LT in patients with HCC. However, there are multiple studies evaluating neoadjuvant administration of immunotherapy prior to liver resection in patients with HCC[39] (Table 3). These are mainly phase I/II studies with no control arm that assess safety, efficacy, and tolerability of the immunomodulating agent, either alone or in combination with other therapies. Nivolumab is the most used ICI in these studies[84-88]. Other ICIs used include tislelizumab, cemiplimab, toripalimab and camrelizumab[89-92]. Most of these trials are ongoing, with most of them not having any published results. Analysis of completed studies, however, reveals satisfactory objective response rates and an acceptable rate of adverse events, setting the stage for the recommencement of phase III, randomized studies that will provide us with valuable information regarding the benefits of neoadjuvant immunotherapy before resection or LT.

To date, there are two clinical trials of neoadjuvant immunotherapy prior to LT in patients with HCC. The first trial (NCT04425226) is a randomized study that will assess the neoadjuvant use of pembrolizumab and lenvatinib as a downstaging and/or bridging therapy prior to LT in 192 patients with HCC. Participants will receive pembrolizumab 200 mg intravenously on day 1 of each 21-d cycle. Treatment will continue until unacceptable toxicity develops or until there are at least 42 d remaining to LT. Concurrently, study subjects will receive lenvatinib 8–12 mg orally at least 38 d every 6 wk and until there are at least 7 d prior to LT. The primary endpoint will be RFS, whereas secondary endpoints include the disease control rate, the percentage of patients who will experience adverse outcomes and who will discontinue study treatment due to an adverse event, and the ORR. Results of the study are expected in December 2024[93]. The second trial (NCT04035876) is a phase 1/II, single-arm study that evaluated the use of camrelizumab and apatinib as downstaging and/or bridging therapy prior to LT in 120 patients with HCC. Participants received camrelizumab 200 mg intravenously every 2 wk and apatinib 250 mg orally every day. Camrelizumab was discontinued 5 wk before and apatinib 1 wk before LT. Primary endpoints included objective remission rate and RFS, whereas secondary endpoints included OS, time to progress and rate of adverse events. Results of this study are not yet available[94].

CONCLUSION

LT is a curative treatment approach for HCC. With respect to the current transplant criteria, conventional LRT has been widely used as downstaging and/or bridging therapy to increase the pool of

Table 3 Clinical trials assessing immune checkpoint inhibitor use in the neoadjuvant setting prior to liver resection in patients with hepatocellular carcinoma

Trial name	Phase	Intervention	Status
NCT03510871	II	Nivolumab and ipilimumab (single-arm study)	Not yet completed; estimated completion date: December 2022
NCT03682276	I/II	Nivolumab and ipilimumab (single-arm study)	Not yet completed; estimated completion date: September 2022
NCT03299946	I	Nivolumab and cabozantinib (single-arm study)	Completed
NCT04615143	II	Tislelizumab or tislelizumab and Lenvatinib (sequential assignment)	Not yet completed; estimated completion date: December 2025
NCT03916627	II	Cemiplimab (parallel assignment)	Not yet completed; estimated completion date: September 2029
NCT03867370	I/II	Toripalimab or toripalimab and Lenvatinib (sequential assignment)	Not yet completed; estimated completion date: October 2022
NCT03630640	II	Nivolumab (single-arm study)	Not yet completed; estimated completion date: November 2023
NCT04123379	II	Nivolumab *vs* nivolumab and CCR2/5 inhibitor *vs* nivolumab and anti-IL-8 antibody (parallel assignment)	Not yet completed; estimated completion date: October 2024
NCT04297202	II	SHR-1210 (anti-PD1 inhibitor) and apatinib (single-arm study)	Completed

CCR2/5: Chemokine receptors type 2 and 5; IL-8: Interleukin-8; PD1: Programmed cell death receptor 1; NA: Not applicable.

potential LT candidates. Nevertheless, the benefits of immunotherapy in patients with advanced HCC have generated an extensive discussion whether ICIs could be used safely and effectively in the pretransplant process in order to yield favorable outcomes. When contemplating neoadjuvant immunotherapy, the risk of graft rejection after LT is a matter of concern. Results from a limited number of case reports, however, showed that the risk may not be as high, with fatal rejection presenting in only two out of 20 cases of LT after ICI administration. More studies need to be conducted to delineate the factors that could reliably predict outcomes after LT in patients receiving neoadjuvant immunotherapy. Determination of surface molecule expression, such as PD/PDL1, obtained *via* liver biopsy, is a tempting marker that could predict response to outcome, but, utilized alone, does not seem to accurately include all patients that would benefit from ICIs. More markers need to be taken into consideration, either alone or in conjunction with other aspects of disease treatment that focus on the pharmacokinetics of immunotherapy. Drug half-life could theoretically play an important role in determining the ideal time interval spanning from ICI discontinuation to LT. In practice, however, no fatal rejection was observed in patients with cessation of drug therapy even 1 d before surgery, emphasizing the fact that individualization of treatment regimen is a superior approach than strict adherence to the properties of the drug in order to allocate patients to the appropriate drug scheme. Patient comorbidities, availability of other neoadjuvant treatment options, and the ability to timely treat emerging ICI-related adverse effects are all remarks that should be explored prior to initiating immunotherapy. Clinical trials that assess neoadjuvant ICI therapy, either before liver resection or transplantation, show promising results, both in treatment safety and efficacy, with primary and secondary study endpoints being met successfully. Insights from future studies, which are currently underway, are necessary to better understand the impact of neoadjuvant immunotherapy in the perioperative period and beyond.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Konstantinos Ouranos 0000-0001-9034-5026; Anthi Chatziioannou 0000-0002-8931-6786; Ioannis Goulis 0000-0002-2765-4157; Emmanouil Sinakos 0000-0003-0923-050X.

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MINIREVIEWS

Challenges in liver transplantation in the context of a major pandemic

Eleni Theocharidou, Danielle Adebayo

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Eleni Theocharidou, 2nd Department of Internal Medicine, Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642, Thessaloniki, Greece

Danielle Adebayo, Department of Gastroenterology and Hepatology, Royal Berkshire NHS Foundation Trust, London Road, Reading, RG1 5AN, United Kingdom

Corresponding author: Eleni Theocharidou, PhD, 2nd Department of Internal Medicine, Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642, Thessaloniki, Greece.
elenit@auth.gr

Abstract

Coronavirus disease-2019 (COVID-19) has led to a temporary suspension of liver transplant activity across the world and the remodeling of care for patients on the waiting list and transplant recipients with the increasing use of remote consultations. Emerging evidence shows that patients with more advanced liver disease are at increased risk of severe COVID-19 and death, whereas transplant recipients have similar risk with the general population which is mainly driven by age and metabolic comorbidities. Tacrolimus immunosuppression might have a protective role in the post-transplant population. Vaccines that have become rapidly available seem to be safe in liver patients, but the antibody response in transplant patients is likely suboptimal. Most transplant centers were gradually able to resume activity soon after the onset of the pandemic and after modifying their pathways to optimize safety for patients and workforce. Preliminary evidence regarding utilizing grafts from positive donors and/or transplanting recently recovered or infected recipients under certain circumstances is encouraging and may allow offering life-saving transplant to patients at the greatest need. This review summarizes the currently available data on liver transplantation in the context of a major pandemic and discusses areas of uncertainty and future challenges. Lessons learnt from the COVID-19 pandemic might provide invaluable guidance for future pandemics.

Key Words: COVID-19; Pandemic; Liver transplantation; Chronic liver disease; Immunosuppression; Vaccines

Core Tip: Coronavirus disease-2019 pandemic posed unprecedented challenges in terms of managing patients with advanced liver disease remotely, offering transplant for highly selected patients, managing immunosuppression, treating infected patients with chronic liver disease, transplanting infected patients, and utilizing grafts from infected donors. The transplant community responded rapidly to these challenges and many centers were able to resume activity soon after the first wave of the pandemic. Emerging data help shed light on areas of uncertainty and provide guidance for future challenges.

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INTRODUCTION

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the severe disease precipitated by the coronavirus disease 2019 (COVID-19) has had a profound impact on healthcare systems worldwide. The challenges posed on liver transplantation (LT) programs were unprecedented, and can be summarized in the following: (1) Pre-transplant aspects (management of patients on the LT waiting list, impact of COVID-19 on patients with advanced liver disease); (2) peri-transplant aspects (temporary suspension of LT programs, testing of donors/recipients, LT after recovery from COVID-19, utilization of grafts from positive donors); and (3) post-transplant aspects (COVID-19 in LT recipients, management of immunosuppression, safety of vaccination against SARS-CoV-2). The aim of this review is to provide an outline of the unforeseen challenges that the COVID-19 pandemic posed on LT programs worldwide.

MANAGEMENT OF PATIENTS ON THE WAITING LIST

The declaration of COVID-19 pandemic by the World Health Organization in March 2020 precipitated significant changes in the delivery of healthcare in an effort to minimize patient and staff exposure to SARS-CoV-2. The traditional face-to-face consultations, which have been the basis of patient-doctor communication, ceased suddenly, and gave place to new virtual models of communication[1]. Patients were encouraged to have blood tests or other essential investigations performed locally (usually with help of their general practitioner) to avoid travelling. Telephone- and/or video-assisted consultations rapidly became the norm during the pandemic. Sending prescriptions and medications *via* post was another approach utilized to reduce risk of transmission/acquisition.

Patients with chronic liver disease (CLD) and particularly with decompensated cirrhosis (including those on the waiting list for LT) were classified as having high risk for severe COVID-19, and were, therefore, instructed to strictly self-isolate for prolonged periods of time. Their assessment and management were completed remotely to a significant extent, while maintaining very limited face-to-face consultations for highly selected patients who were considered at risk for CLD complications[2]. Procedures such as ultrasonography for hepatocellular carcinoma (HCC) surveillance or endoscopy for variceal surveillance, were deferred unless the patient was considered at high risk of HCC or variceal bleeding, respectively, and following individual risk-benefit assessment. The international hepatology associations [European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL)] released promptly guidance for the management of patients with CLD, patients on the waiting lists and LT recipients[3-6]. The guidance included strict preventive measures (*i.e.*, vaccination against *Streptococcus pneumoniae* and influenza, prophylaxis against spontaneous bacterial peritonitis) to avoid hospital attendance and/or admission. The common denominator was avoidance of commuting and face-to-face contact unless it was considered essential. The caveats of no direct patient contact, in particular for patients on the waiting list, were acknowledged by clinicians, but it was felt that the risks of severe COVID-19 and death outweighed the risks associated with remote or virtual assessments[7]. An Austrian study that included patients with CLD admitted to hospital just before and after the outbreak of the pandemic, demonstrated the impact of the restrictions on patient satisfaction with regards to the quality of liver care[8]. The same study showed that CLD patients who were hospitalized during the pandemic were sicker indicating a higher threshold for hospital attendance and admission, and liver-related mortality was higher.

EVALUATION AND SELECTION OF CANDIDATES FOR LIVER TRANSPLANTATION

The same restrictions were applied to the evaluation and selection process of LT candidates. Many LT centers developed local policies for selecting patients and for prioritizing those who were already on the waiting list. Patients who were prioritized included those with acute liver failure, higher model for end-stage liver disease (MELD) score and those at risk for decompensation or HCC progression[4]. The evaluation process had to be remodeled taking into consideration travelling restrictions, distancing measures and minimization of exposure to SARS-CoV-2. LT assessments, *i.e.* patients and family education, social work and dietitian consultations, had to be performed either *via* video or telephone consultations. In several LT centers, the group education sessions were replaced by internet-based sessions with multiple participants.

The impact of COVID-19 on the waiting list for solid organ transplantation (SOT) was investigated in a study that used the Scientific Registry of Transplant Recipients (SRTR) data[9]. In March 2020 coinciding with the onset of the pandemic and in winter 2020/2021 coinciding with the second surge, there was a rapid decline in the length of the waiting list for SOT likely due to a reduced number of new listings, and a decline in the number of removals from the waiting lists due to reduced number of transplants performed. With regards to removals due to death, waiting list mortality remained constant for liver, but increased for kidney. The results of this study reflect the reduction in the activity (decreased transplant assessments/listings, decreased transplant activity) in many transplant centers not only in the US, but also worldwide.

TRANSPLANTATION ACTIVITY

The COVID-19 pandemic had a profound impact on SOT that was primarily driven by safety concerns regarding transmission (in the first phase when access to SARS-CoV-2 testing was very limited) and by limited resources (mainly intensive care beds). A web-based survey between September 7, 2020 and December 31, 2020 organized by three international societies (European Association for the Study of the Liver, European Society of Organ Transplantation- European Liver and Intestine Transplant Association, and International Liver Transplantation Society) compared transplant activity in the first six months of 2020 versus 2019[10]. Most transplant centers ceased activity for up to a month with the exception of patients with acute liver failure, high MELD score or acute-on-chronic liver failure, in which cases the decisions were made on a case-by-case basis. Out of 128 centers that responded to the survey, 30%-50% performed transplantations on patients with previous COVID-19. The majority reported lower transplant activity, fewer candidates being listed and higher waiting list mortality in 2020 compared to 2019. These differences were more profound in 'hit' countries (COVID-19 case fatality > 3.4%) than in 'non-hit' countries[10].

The analysis of the Global Observatory for Organ Donation and Transplantation data for 2019 and 2020 showed a global decrease in LT by 11.3%[11]. Almost all geographic regions were affected, but developed countries were able to subsequently recover transplant activity, whereas developing counties lagged. In the United States, 32 594 transplants were expected in 2020, and only 30 566 were performed (observed/expected (O/E) 0.94, confidence interval (CI): 0.88–0.99)[12]. A total of 58 152 waiting list registrations were expected and 50 241 transplants were performed (O/E 0.86, CI: 0.80–0.94). The observed/expected ratio for LT was 0.96 (0.89–1.04). There was a similar reduction in organ donation. The months with the lowest activity were April, May and December 2020. In Europe, there was a similar reduction in LT activity with areas with the highest incidence of COVID-19 showing the greatest reduction in activity.

The reduction in LT activity ranged from 25% (United States and France) to 80% (United Kingdom and India)[13]. Some countries/areas managed to maintain their LT activity (South Korea, some centers in Italy even in medium or high-incidence areas) by means of a rapid response to the pandemic and re-modeling of their pathways[13]. In the US, significant variability in LT activity was observed within regions of similar COVID-19 incidence[14]. This was presumably attributed to differences in resources, SARS-CoV-2 transmission among members of staff and leadership philosophy. The wider availability of SARS-CoV-2 testing might have been associated with the restoration of LT activity later in 2020.

COVID-19 IN TRANSPLANT CANDIDATES

Abnormal liver function tests are common in patients with COVID-19, and can be attributed to direct viral cytopathic effect, immune-mediated liver injury, hypoxia or drug-induced liver injury. Liver cells express SARS-CoV-2 entry receptors, including angiotensin-converting enzyme-2 receptors, and SARS-CoV-2 infection has been associated with strong upregulation of interferon responses in the liver, similar to other hepatotropic viruses[15]. These findings support SARS-CoV-2 hepatic tropism. Liver involvement in COVID-19 has been associated with higher mortality[16]. In patients with pre-existing chronic liver disease, COVID-19 can lead to exacerbation of the underlying disease, which in patients

with cirrhosis can result in acute decompensation[17]. Studies consistently show increased risk of mortality in patients with cirrhosis and COVID-19[18]. A study that included 305 SARS-CoV-2 positive patients with cirrhosis and compared them with SARS-CoV-2 positive patients without cirrhosis, and SARS-CoV-2 negative patients with and without cirrhosis, demonstrated a 3.5-fold increased mortality among patients with cirrhosis, and 1.7-fold increased mortality among SARS-CoV-2 positive patients [19]. Predictors of mortality in SARS-CoV-2 positive patients with cirrhosis were advanced age, decompensation, and higher MELD score.

The risk of death with COVID-19 is higher in patients with cirrhosis compared to patients with CLD without cirrhosis, and the risk increases with more advanced stages of liver disease. One of the largest international studies (29 countries) included 386 SARS-CoV-2 positive patients with cirrhosis, 359 SARS-CoV-2 positive patients with CLD without cirrhosis and 620 SARS-CoV-2 positive patients without CLD [20]. Mortality in patients with cirrhosis was significantly higher than in those with CLD without cirrhosis (32% *vs* 8%, $P < 0.001$). Mortality in Child-Pugh A cirrhosis was 19%, B 35% and C 51%. The main cause of death among patients with cirrhosis was respiratory failure in 71%. Acute decompensation occurred in 46%. Age and severity of liver disease were predictors of mortality.

In view of this data, international societies recommend testing for SARS-CoV-2 in every patient presenting with acute decompensation, and early admission for all patients with cirrhosis developing COVID-19.

An increasing number of cases of secondary sclerosing cholangitis following severe COVID-19 is being reported[21]. These patients had extensive intensive care unit (ICU) admission and developed prolonged cholestasis. Some of these cases improved with conservative management, but a case of LT has been reported[22].

SCREENING OF DONORS AND RECIPIENTS

International societies (AASLD, EASL and APASL) released guidance recommending screening of donors and recipients for SARS-CoV-2 with reverse transcription-polymerase chain reaction (RT-PCR) of upper respiratory tract secretions[3-5]. A negative RT-PCR is required within 48 hours from graft retrieval or LT[23]. In view of the high rates of false negative RT-PCR results, AASLD and APASL also recommend screening donors for recent exposure, fever or symptoms suggestive of COVID-19 and utilizing imaging of the chest (chest radiograph or computed tomography). Computed tomography of the chest is being increasingly used in the evaluation of COVID-19 patients, and is able to demonstrate lung changes even before RT-PCR becomes positive[23]. Screening of the recipient is similar and includes molecular testing, history of recent exposure, symptoms/signs and findings on imaging studies.

COVID-19 IN TRANSPLANT RECIPIENTS

It was initially hypothesized that LT recipients with SARS-CoV-2 infection might be at increased risk of death due to age, immunosuppression and metabolic comorbidities. Cohort studies published after the outbreak of the pandemic showed a case-fatality rate of 12%-25% which was not increased compared to the general population[24-32]. Tacrolimus immunosuppression was not found to be associated with the risk of death in the context of SARS-CoV-2 infection, on the contrary, it seemed to be protective as shown in some studies[31]. Age and comorbidities were the main predictors of outcome in most studies, similar to the general population[30]. The main findings of these studies are summarized in Table 1.

An analysis of the ELITA-ELTR COVID-19 registry between March 1 and June 27, 2020 included 243 adult LT recipients with COVID-19 across Europe[31]. Of them, 84% required hospital admission and 19% admission to the ICU. Overall mortality was 20%. Among those requiring ICU admission, the mortality rate was 25%. Respiratory failure was the main cause of death. Age > 70 years, diabetes mellitus and chronic kidney disease were independently associated with the risk of death. Tacrolimus was associated with lower probability of death.

A Spanish cohort study (SETH cohort) reported the outcomes of 111 LT recipients diagnosed with COVID-19. The incidence of SARS-CoV-2 infection in this cohort was almost double compared to the general population. Of them, 86.5% required hospital admission and 10.8% admission to the ICU[24]. Overall mortality rate was 18% and was lower than in the matched general population. Mycophenolate-containing immunosuppression was associated with increased risk of death, but not tacrolimus or everolimus. Immunosuppression withdrawal had no effect on outcome.

Similar results were reported by an international cohort study (18 countries) with 151 LT recipients with COVID-19 against 627 non-transplant COVID-19 patients[29]. Similar to previous reports, 82% of LT recipients required hospital admission. LT recipients were more likely to require ICU admission (28% *vs* 8%). Mortality rate was lower among LT recipients (19% *vs* 27%, $P = 0.046$). When the groups were matched for age, sex and comorbidities, LT was not associated with increased risk of death. Risk factors for death among LT recipients were age, creatinine and non-liver cancer.

Table 1 Severe acute respiratory syndrome coronavirus 2 infection in liver transplant recipients

Ref.	Origin of study population	Number of patients	Hospital admission (%)	ICU admission (%)	Mortality (%)	Risk factors for mortality
Belli *et al*[31]	Europe	243	84	19	20	Age > 70, diabetes mellitus, CKD
Colmenero *et al* [24]	Spain	111	86.5	10.8	18	MMF
Webb *et al*[29]	International (18 countries)	151	82	28	19	Age, creatinine, non-liver cancer
Kates *et al*[25]	United States	482 SOT (73 liver)	78	31	20.5	Age > 65, heart and lung comorbidities, obesity
Rabiee *et al*[26]	United States	112	72.3	26.8	22.3	Liver injury
Ravanan *et al* [28]	United Kingdom	597 SOT			25.8	Age
Becchetti *et al* [32]	Europe	57	72		12	Cancer
Becchetti *et al* [33]	Systematic review	1076	65	23	12.5	Middle-aged men, metabolic comorbidities

ICU: Intensive care unit; CKD: Chronic kidney disease; MMF: Mycophenolate mofetil; SOT: Solid organ transplant.

One study reported on the incidence of acute liver injury (defined by ALT 2-5x ULN) in LT recipients when compared to non-transplant CLD patients with COVID-19[26]. The incidence was lower in LT recipients (47.5% *vs* 34.6%, P = 0.037), but the presence of liver injury in the context of COVID-19 significantly increased the risk of mortality and ICU admission.

A systematic review of 1076 published cases provided more robust evidence on the outcomes of SARS-CoV-2 infection in LT recipients[33]. Majority of patients were male (67%). With regards to established risk factors for COVID-19, 39% had diabetes mellitus type 2, 44% had arterial hypertension, and 16% were obese. Overall, 65% required hospital admission, and 23% of the hospitalized patients required ICU admission. Death was reported in 135 cases. Infection was more common in middle-aged men with metabolic comorbidities. The mortality rate and case-fatality rate were not higher than in the general population. This finding does not confirm the initial concerns regarding COVID-19 course and outcomes in this presumably vulnerable population.

In summary, although the incidence of SARS-CoV-2 infection might be higher in LT recipients, the risk of death or ICU admission does not seem to be higher than in the general population. Age, metabolic comorbidities and cancer, which are established risk factors for severe COVID-19 and mortality, also increase the probability of worse outcomes in LT recipients similarly to the general population.

MANAGEMENT OF IMMUNOSUPPRESSION IN LT RECIPIENTS

Calcineurin inhibitors (CNIs), in particular tacrolimus, are the cornerstone of immunosuppression in LT. They inhibit calcineurin, thereby impairing the transcription of interleukin-2 and several other cytokines in T lymphocytes. CNIs form a complex with intracellular cyclophilin, which inhibits nuclear factor of activated T-cells (NFAT) resulting in inhibition of cytokine transcription and T-cell activation[34]. Tacrolimus is associated with increased susceptibility to infections, and risk of nephrotoxicity, neurotoxicity, diabetes mellitus and hypertension. Diabetes and hypertension are established risk factors for severe COVID-19. Renal dysfunction is not uncommon among patients with COVID-19, hence tacrolimus immunosuppression could theoretically increase this risk.

The initial concerns regarding the risk of severe COVID-19 and death in the context of immunosuppression in LT recipients were not confirmed by subsequent published evidence. Despite concerns, complete withdrawal of immunosuppression was rarely adopted and only in extremely severe cases. The ELITA-ELTR COVID-19 registry study demonstrated that tacrolimus was associated with lower risk of mortality [hazard ratio (HR) 0.55, 95%CI: 0.31–0.99] raising the possibility of a protective effect against SARS-CoV-2[31]. Tacrolimus dose was maintained in majority of patients who did not require hospitalization, whereas those with more severe disease that required hospital admission, and even more so those who required ICU admission, were more likely to have the dose adjusted or temporarily interrupted. This effect of calcineurin inhibitors might be mediated by inhibition of CoV growth *via* the cyclophilin pathway, and modulation of T-cell activation[35,36]. This potential protective effect was also demonstrated in the SETH cohort and the smaller COVID-LT study[24,33]. A systematic review and

meta-analysis of 11 cohort studies (published in the form of Letter to the Editor) showed that tacrolimus in SOT recipients was not associated with higher risk of severe COVID-19 (odds ratio (OR) 1.31, 95%CI 0.47–3.69) or increased mortality (OR 1.11, 95%CI 0.63–1.92)[37].

An important aspect raised in a small cohort study is monitoring of tacrolimus levels during SARS-CoV-2 infection. The latter might be associated with CYP3A4 suppression due to increased cytokine circulation. Tacrolimus is metabolized by CYP3A4. Out of 14 post-LT patients on stable tacrolimus immunosuppression, 13 experienced a significant increase in tacrolimus levels (up to 2-fold) during hospitalization for COVID-19 requiring a reduction in dose by nearly 50%[38]. The findings of this study raise awareness with regards to close drug level monitoring and dose adjustments in the context of SARS-CoV-2 infection.

Mycophenolate mofetil (MMF) inhibits lymphocyte proliferation. SARS-CoV-2 has a direct cytotoxic effect on CD8+ lymphocytes. SARS-CoV-2 infection in the context of MMF immunosuppression could have a synergistic effect on lymphocyte inhibition[34]. Data regarding the effect of MMF indicate a potential negative impact on the course of COVID-19. In the SETH cohort, patients receiving MMF had a more severe course of the disease, and this was more evident for doses higher than 1000 mg/d[24]. MMF was an independent predictor of mortality. This observation could be interpreted by the cytostatic effect that MMF exerts on activated lymphocytes, which alongside the cytotoxic effect of SARS-CoV-2 on the same target, might result in worse outcomes[39,40]. On the other hand, complete withdrawal of MMF at diagnosis ameliorated the risk of severe COVID-19. The most up-to-date EASL guidance recommends dose reduction or temporary discontinuation of antimetabolites (*e.g.*, azathioprine or MMF)[6] in patients with SARS-CoV-2 infection.

Complete withdrawal of immunosuppression does not seem to be associated with improved prognosis, hence is not encouraged[41]. However, immunosuppression might be associated with prolonged viral shedding following SARS-CoV-2 infection[42]. The currently available data indicate that comorbidities, which are not uncommon among LT recipients, rather than immunosuppression per se, increase the risk of severe COVID-19 and death. Although data are not extensive, CNI immunosuppression might reduce the risk of severe disease and fatal outcomes presumably by suppressing the augmented immune response precipitated by SARS-CoV-2. MMF at high doses might be associated with disease severity. It should be taken into consideration that reduction in immunosuppression is associated with risk of acute cellular rejection and graft loss. In this context, most international societies recommend against modifications of CNI immunosuppression. MMF reduction or temporary withdrawal is justified in the context of moderate-severe disease. Tacrolimus has numerous drug-to-drug interactions, and vigilance is required with drugs used in the context of COVID-19, such as tocilizumab and ritonavir-boosted nirmatrelvir[43].

IMMUNITY AND VACCINATION IN LT RECIPIENTS

The rapid spread of SARS-CoV-2 has led to the exceptionally fast development of vaccines with proven short-term safety and efficacy. In LT recipients, immunosuppressive therapy might be associated with impaired immune response to vaccination and lower immunogenicity than in immunocompetent individuals. Live attenuated vaccines are usually avoided after LT unless the benefit of vaccination outweighs the associated risks. Vaccines are also avoided in the first 3-6 mo after LT, which corresponds to the period of maximal immunosuppression, because of concerns regarding attenuated immune responses to vaccination[44]. Another theoretical concern is that immune responses to vaccines might trigger immune-mediated rejection, although this has not been confirmed in a meta-analysis[45]. EASL recommends that vaccination should be completed prior to LT whenever possible. Vaccines against SARS-CoV-2 are either mRNA or nonreplicating viral vector vaccines, which are safe in the context of immunosuppression.

With regards to COVID-19 vaccines, clinical trials have not included transplant patients receiving immunosuppressive therapy. Long-term safety and duration of protection in this population remains unclear. The ORCHESTRA SOT recipients cohort assessed antibody response after the first and second dose of mRNA vaccine[46]. The analysis included 1062 SOT patients (liver, 17.4%) and 5045 health care workers. The antibody response was significantly lower in SOT recipients (52.3% *vs* 99.4%), and the antibody levels were significantly lower in the same group. Predictors or better response were interval ≥ 3 years, liver transplant and azathioprine. A study of 35 LT recipients demonstrated partial antibody response to inactivated vaccines[47]. Interkeukin-2 receptor induction therapy and a shorter time after LT were associated with lower antibody response. These findings raise the possibility that booster vaccines might be required in LT recipients. These results were confirmed in a subsequent meta-analysis of 4191 CLD patients and LT recipients that showed antibody response rate after two doses of vaccine of 95% and 66%, respectively[48].

The suboptimal response to vaccination is associated with increased risk of breakthrough infections. A study that included 77 fully or partially vaccinated and 220 unvaccinated SOT recipients with SARS-CoV-2 infection, showed similar disease severity and mortality rates in the two groups[49]. A larger study of 1668 SOT recipients showed a 73% reduction in SARS-CoV-2 infection rate and 76% reduction

in mortality among fully vaccinated patients[49]. Fully vaccinated patients who acquired SARS-CoV-2 infection were less likely to have severe/critical COVID-19 or die compared to not fully vaccinated (22% *vs* 37%, and 0% *vs* 6.7%, respectively). Completion of vaccinations is likely to be critical in this population.

A third SARS-CoV-2 vaccine dose may confer additional benefit in SOT recipients, although still suboptimal compared to the healthy population. In a small cohort of 47 SOT recipients, a third dose increased median total anti-spike IgG (1.6-fold) and neutralizing antibodies (1.4-fold against delta)[50]. It is noteworthy that 32% had no detectable neutralizing antibodies against delta after third vaccination compared to 100% controls. Presence of neutralizing antibodies correlated with anti-spike IgG > 4 Log10 (AU/mL). The same researchers explored the effect of a fourth dose in the same population, and found that it increases anti-spike IgG and neutralizing capacity against many variants of concerns, with the exception of omicron against which neutralization remained poor[51].

A large meta-analysis including 11 713 SOT recipients demonstrated that the response for anti-spike antibodies after mRNA vaccine was 10.4% for 1 dose, 44.9% for 2 doses, and 63.1% for 3 doses[52]. Factors associated with poor antibody response were older age, deceased donor status, antimetabolite use, recent rituximab exposure and recent antithymocyte globulin exposure. The role of MMF as a negative predictor for antibody response has been demonstrated in further studies[53,54].

In summary, vaccination against SARS-CoV-2 confers some protection in SOT recipients, which is lower compared to the healthy population. Booster doses can improve neutralizing capacity, however, this remains suboptimal[55]. In this context, additional protective measures beyond vaccination are necessary in SOT recipients. EASL recommends vaccination against SARS-CoV-2 after the first 3-6 mo following LT, because vaccination in the context of high immunosuppression might not be effective[44]. In this setting, vaccination of household members is highly recommended. In the first phases of the pandemic, priority for vaccination was given to healthcare professionals caring for transplant patients in an effort to protect this vulnerable population.

TRANSPLANT FROM SARS-COV-2 POSITIVE DONORS

The initial response of transplant societies to the challenges posed by COVID-19 pandemic was to recommend testing for SARS-CoV-2 RNA in donors/recipients before transplant, and to recommend against LT in cases of positivity. In the course of the pandemic, some centers started performing life-saving LT for high-risk patients utilizing grafts from SARS-CoV-2 positive donors to recipients with active or resolved infection[56]. A multicenter Italian study included 10 LTs from donors with active COVID-19[56]. Two recipients were SARS-CoV-2 RNA positive at the time of LT. None of the remaining 8 recipients developed SARS-CoV-2 RNA positivity. Eight recipients had IgG antibodies against SARS-CoV-2. SARS-CoV-2 RNA was not detected in donor liver tissue at the time of LT. This study introduced the concept that using grafts from SARS-CoV-2 positive donors might be a safe practice, particularly in patients who are the highest need for LT.

The safety of this practice was confirmed in smaller case series. A series from the US with 5 SOTs (2 livers, 1 simultaneous liver-kidney, 1 kidney and 1 simultaneous kidney-pancreas) from SARS-CoV-2 positive donors to negative recipients showed no risk of transmission to recipients[57]. SARS-CoV-2 RNA was not detected in allograft biopsies.

A systematic review of all SOT from past or active SARS-CoV-2 infected donors until December 2021, included 69 recipients who received 48 kidneys, 18 livers and 3 hearts from 57 donors, and 6 additional lung transplants[58]. Ten of 57 (17.5%) donors had active COVID-19 and 18 had detectable SARS-CoV-2 RNA. Viral transmission was not documented among non-lung SOT recipients. However, viral transmission occurred in three lung recipients, who developed COVID-19 symptoms, and one of them subsequently died. Strategies to mitigate the risk of donor/graft-recipient transmission potentially include SARS-CoV-2-directed monoclonal antibody therapy and/or pre-emptive remdesivir administration, although the efficacy of this approach needs to be confirmed[59].

Decision-making regarding SOT from SARS-CoV-2 positive donors should take into consideration the risk of transmission/acquisition and the sequelae of developing COVID-19, as well as the risk of disease progression and death associated with the underlying disease[60]. Patients with cirrhosis, and particularly those with decompensated disease, who develop COVID-19 are at high risk of death. On the other hand, patients on the waiting list are at risk of death unless they are offered life-shaving LT, and the suspension of LT activity has led to increased mortality on the waiting list. Utilizing non-lung grafts from carefully selected infected donors might benefit patients who are at the highest risk of death without immediate transplant. Although this practice seems to be safe based on limited currently available data, patients and their families should be informed and actively involved in shared decision-making.

TRANSPLANT OF SARS-COV-2 POSITIVE RECIPIENTS

LT following recovery from COVID-19 has been a challenge as the appropriate time interval is not well defined as yet. Several cases of recipients with previous or active SARS-CoV-2 infection have been reported[61-63]. The decision to proceed to LT was made on a case-by-case basis taking into consideration the risk of death without immediate LT. The largest case series included 14 patients who received LT following symptomatic SARS-CoV-2 infection, 4 of whom had detectable RNA at the time of LT[64]. One recipient who was negative at the time of LT became positive 9 days post-LT. None of the patients developed SARS-CoV-2-related complications. In another case series, 4 patients received LT 2 weeks after SARS-CoV-2 positivity and 2 patients 4 weeks after a positive test[65]. One recipient died secondary to sepsis. Despite the encouraging results, there have been two reports of portal vein thrombosis and hepatic artery thrombosis in SARS-CoV-2 positive recipients of LT[66,67].

SARS-CoV-2 RNA negativity has been proposed as a prerequisite for proceeding safely with LT, and a time interval of 2-4 wk between resolution of symptoms and LT has been also proposed[14]. However, prolonged SARS-CoV-2 RNA shedding can have an impact on decisions to proceed and delay life-saving LT. Therefore, the absence of severe COVID-19 symptoms, in particular respiratory complications, might be a more important parameter in decision-making than RNA negativity per se. More evidence is required to form more specific guidance in that direction.

CONCLUSION

Since March 2020, the transplant community has faced unprecedented challenges derived from very limited resources and risk of transmission among patients and healthcare workers. The immediate response was suspension of activities that required face-to-face contact, conversion to technology-assisted remote consultations and suspension of transplant activity for most LT centers. Published evidence demonstrated that patients with CLD, especially those with more advanced stages of the disease, were at higher risk for severe COVID-19 and death. In-person consultations and LT were reserved for selected patients when the risk associated with the underlying liver disease outweighed the risk associated with SARS-CoV-2 transmission/acquisition. In the course of the pandemic, SARS-CoV-2 testing, antiviral treatments and vaccines became available and changed outcomes and practices. Many LT centers resumed transplant activity, though at different paces. Increasing evidence did not show that LT recipients are at increased risk of severe COVID-19 or death, and immunosuppression not only does not increase the risk, but might be protective against the immune-mediated sequalae of the virus. Our understanding of utilizing grafts from SARS-CoV-2 positive donors or transplanting SARS-CoV-2 positive recipients has increased dramatically and allowed a life-saving procedure to be performed for patients who might otherwise have died due to their liver disease. Preliminary data confirm the short-term safety of vaccines, but also showed a partial antibody response in LT recipients. There is no doubt that we need more data to form evidence-based guidance in areas such as: (1) Optimal and appropriate use of novel telemedicine technologies; (2) Balancing the risk from the underlying CLD and the rapidly spreading virus; (3) Continuing transplant activity without compromising safety for patients and workforce; (4) Utilizing grafts from infected donors to address shortage of grafts; (5) Transplanting actively or recently infected recipients who might otherwise die; (6) Managing immunosuppression in patients who acquire the infection; (7) Safety of antiviral therapies in patients with CLD and transplant recipients; (8) Schedule for vaccination and the need for booster doses; and (9) Long-term safety of vaccines.

The COVID-19 pandemic has provided lessons with regards to rapid remodeling of care in the context of a pandemic with a view to reducing the risk for vulnerable patient groups such as transplant candidates and recipients.

FOOTNOTES

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Country/Territory of origin: Greece

ORCID number: Eleni Theocharidou 0000-0001-8136-3927.

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MINIREVIEWS

Surgical chest complications after liver transplantation

Apostolos C Agrafiotis, Konstantina-Eleni Karakasi, Mathilde Poras, Stavros Neiros, Stella Vasileiadou, Georgios Katsanos

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Apostolos C Agrafiotis, Department of Thoracic Surgery, Saint-Pierre University Hospital, Université Libre de Bruxelles, Bruxelles 1000, Belgium

Konstantina-Eleni Karakasi, Stavros Neiros, Stella Vasileiadou, Georgios Katsanos, Department of Transplantation, Medical School, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki 54642, Greece

Mathilde Poras, Department of Abdominal Surgery, Saint-Pierre University Hospital, Université Libre de Bruxelles, Bruxelles 1000, Belgium

Corresponding author: Konstantina-Eleni Karakasi, MD, Surgeon, Department of Transplantation, Medical School, Aristotle University of Thessaloniki, Hippokration General Hospital, Konstantinoupoleos 49, Thessaloniki 54642, Greece. kelenikarakasi@gmail.com

Abstract

Liver transplantation is a major abdominal operation and the intimate anatomic relation of the liver with the right hemidiaphragm predisposes the patient to various manifestations in the chest cavity. Furthermore, chronic liver disease affects pulmonary function before and after liver transplantation resulting in a considerable percentage of patients presenting with morbidity related to chest complications. This review aims to identify the potential chest complications of surgical interest during or after liver transplantation. Complications of surgical interest are defined as those conditions that necessitate an invasive procedure (such as thoracocentesis or a chest tube placement) in the chest or a surgical intervention performed by a thoracic surgeon. These complications will be classified as perioperative and postoperative; the latter will be categorized as early and late. Although thoracocentesis or a chest tube placement is usually sufficient when invasive measures are deemed necessary, in some patients, thoracic surgical interventions are warranted. A high index of suspicion is needed to recognize and treat these conditions promptly. A close collaboration between abdominal surgeons, intensive care unit physicians and thoracic surgeons is of paramount importance.

Key Words: Surgical chest complications; Liver transplantation; Chest related morbidity; Multidisciplinary treatment; Surgery

Core Tip: Chest complications during and after liver transplantation significantly affects the surgical and hospitalization outcomes. This minireview focuses on surgical chest complications for transplant patients and categorizes them by time of appearance. This paper may be a helpful guide and tool for medical students, members of the transplantation team and all the collaborative specialties to recognize early chest complications and plan the appropriate treatment.

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INTRODUCTION

The diaphragm is the boundary between the thoracic and abdominal cavities. Yet, it is common in everyday clinical practice to observe pathologies that originate in one cavity impacting the other[1]. Liver transplantation is a major abdominal operation and the proximity of the operating field with the right hemidiaphragm predisposes it to various manifestations in the chest cavity. Furthermore, chronic liver disease affects pulmonary function before and after liver transplantation resulting in a considerable percentage of patients presenting with morbidity related to chest complications. Age, model for end stage liver disease (MELD) score, preexisting lung disorders and perioperative events, particularly transfusion, contribute to these complications[2]. Indeed, pulmonary complications constitute a significant problem after liver transplantation[3-5]. In one retrospective study enrolling 135 patients, the first postoperative chest roentgenogram was within normal limits in less than half of the cases[6]. In another cohort of adult-to-adult living donor liver transplantation, chest complications were observed in 19.8% of recipients[7]. In the retrospective study by Panfili *et al*[8], pulmonary complications were frequently revealed on imaging during the first postoperative week.

This review aims to identify the potential chest complications of surgical interest during or after liver transplantation. Complications of surgical interest are defined as those conditions that necessitate an invasive procedure (such as thoracocentesis or a chest tube placement) in the chest or a surgical intervention performed by a thoracic surgeon. These complications will be classified as perioperative and postoperative; the latter will be categorized as early and late.

PERIOPERATIVE COMPLICATIONS

Intraoperative pneumothorax is a well described complication of surgery with liver transplantation not being an exception and should be promptly recognized and treated as it can result in life-threatening tension pneumothorax. Pneumothorax can occur because of a bleb rupture, a tracheobronchial trauma during orotracheal intubation, an accidental lung puncture during central venous catheter placement or diaphragm perforation during dissection and barotrauma. Bozbas *et al*[9] described another mechanism during liver transplantation. After the extraction of a voluminous native liver, the rapid expansion of the right lower lobe resulted in a massive air leak, probably due to the development of important shear forces that damaged the pulmonary parenchyma. The insertion of a chest tube is the first therapeutic measure, while persistent air leaks or tracheobronchial lacerations should be treated accordingly.

POSTOPERATIVE COMPLICATIONS

Early postoperative complications

The most typical early postoperative complication is pleural effusion with an estimated incidence of 32%-47%[9-11]. It occurs more frequently on the right side, with left-sided occurrence being rare. Its pathogenesis is multifactorial. Ritschl *et al*[12] identified the following mechanisms responsible for the occurrence of pleural effusion: (1) Low serum albumin levels and postoperative hypoproteinemia; (2) High rates of intraoperative blood and fluid transfusions; and (3) Local mechanisms at the right side of the diaphragm. More specifically, the diaphragmatic defects allow fluid migration towards the chest cavity. Moreover, right hemi diaphragmatic paralysis caused by perioperative right phrenic nerve injury results in the right lower lobe atelectasis, favoring the development of pleural effusion.

There is no consensus concerning indications for chest tube placement and the choice of treatment modality depends mostly on clinical experience and individual appreciation. Similarly, there is no recommendation concerning the type and size of the chest tube. Chest tube placement is necessary for

22%-52% of liver recipients. In a large retrospective study analyzing 597 liver recipients,12 patients with effusion were treated by a chest tube and had a higher MELD score. Other significant risk factors are recipient body mass index (BMI), hospitalization status before liver transplantation [home, hospital, intensive care unit (ICU)], number of intraoperative red blood cell transfusions and donor BMI[5]. There are emerging recommendations advocating for preventive right chest tube placement in the early postoperative period since a decrease in infectious pulmonary complications and ICU stay has been observed[12]. However, the potential complications of invasive percutaneous pleural procedures (thoracocentesis and chest tube placement) should also be considered. The more frequent complications are pneumothorax due to accidental lung puncture and hemothorax due to coagulopathy or technical pitfalls causing minor (pleural) or significant (vascular injury most of the time involving an intercostal artery) hemorrhage. In a large retrospective multicentric study, the incidence of hemothorax was 0.42%, and it was more frequent among patients who underwent thoracocentesis[13]. Nearly half of these patients underwent thoracic surgery (thoracotomy or thoracoscopy). This condition was associated with a high (50%) mortality rate. Postoperative hemothorax can also occur after central venous catheter introduction, especially in patients with coagulopathy[13]. Diaphragmatic lacerations or resection during liver transplantation can also result in postoperative hemothorax. The mispositioning of the chest tube (in the subcutaneous tissues or a subdiaphragmatic location) must also be cited. Another complication is re-expansion pulmonary edema, which occurs during the rapid evacuation of massive pleural effusions[14].

Bacterial pneumonia is a common postoperative complication in liver recipients. In the retrospective study of Ma *et al*[15], one-third of patients enrolled developed bacterial pneumonia[15]. This group of patients had an extended hospital stay and more frequent pleural effusions than patients without pneumonia. Without prompt treatment, a parapneumonic pleural effusion can evolve into a pleural empyema, a significant source of morbimortality[16].

Mid-term and chronic postoperative complications

Liver recipients are prone to opportunistic infections because of immunosuppression. Some conditions may affect the lung and cause lung necrosis and cavitation[17]. Consequently, air leaks may result in pneumothorax, pneumomediastinum and subcutaneous emphysema[18,19]. A common pathogen is *Pneumocystis jirovecii,* and treatment is no different than in the general population; watchful waiting, chest tube placement or exploratory thoracoscopy. Pneumocystis pneumonia is a relatively late complication after liver transplantation; however, it can occur at an earlier setting (within 1 to 3 wk postoperatively). Its incidence is very low (inferior to 1% during the 1st year) in patients receiving prophylaxis, while it is estimated to be between 3% and 11% in the absence of prevention[19,20].

Invasive aspergillosis is the second most common fungal infection after liver transplantation and is associated with high mortality rates[21,22]. A high clinical suspicion is warranted, especially in the early postoperative period. A computed tomography scan is beneficial in identifying the characteristic lesions caused by invasive aspergillosis. Antifungal drugs are the mainstay of treatment, but lung resection can be curative in selected cases as in the case reported by Abe *et al*[23].

The diaphragm itself can be injured during liver transplantation and result in substantial morbidity, as in the case reported by Rosat *et al*[24]. Their patient experienced a left diaphragmatic herniation 5 years after orthotopic liver transplantation. This complication is more common in pediatric patients but rare in adult patients. A traumatic dissection and the excessive use of cautery during liver transplantation are factors responsible for the devitalization of the diaphragmatic muscle. The immunosuppression hinders the healing process. The negative intrathoracic pressure combined with the positive intraabdominal pressure results in the defect's enlargement and the migration of the abdominal viscera into the thorax. The clinical spectrum may vary from totally asymptomatic patients or the presence of non-specific digestive symptomatology to life-threatening visceral strangulation. Once a diaphragmatic hernia is detected, elective repair is warranted, and the abdominal approach is privileged over the thoracic, although there is still debate concerning optimal surgical access.

Chronic pleural effusions constitute a significant source of morbidity among liver recipients. A thick visceral fibrous peel develops if a pleural effusion is untreated, resulting in a trapped lung and restrictive respiratory syndrome. Cuk *et al*[25] provides an overview of this entity. In their retrospective study, the incidence of the trapped lung in patients with persistent pleural effusion was 21.4%. These patients present increased mortality, extended hospital stay and more surgical interventions in the chest. In this cohort, nearly all pleural effusions were exudates, which support the hypothesis that a chronic inflammatory process occurs in the pleural cavity resulting in the migration of fibroblasts and the development of the pleural peel. Parapneumonic pleural effusions, especially pleural empyema, are a major cause of trapped lung occurrence. Intraabdominal sepsis is a predisposing factor for developing pleural empyema[1]. A frequent pitfall while treating these patients is the false diagnosis of pneumothorax after a thoracentesis for pleural effusion. It is instead a suboptimal lung expansion rather than a true pneumothorax. Sometimes the thickened visceral pleura is visualized in the chest roentgenogram and the correct diagnosis can be established, avoiding thus unnecessary additional pleural interventions such as chest tube placement and elevated suction levels that can result in a lung tear. Shirali *et al*[16] analyzed the outcomes of 33 liver recipients with pleural space complications who necessitated a thoracic surgical intervention due to chronic pleural effusion and empyema. The most common thoracic

Table 1 List of complications and prevention measures

Timing of complication	Type of complication	Prevention measures
Intraoperative	Pneumothorax	High level of suspicion
		Cautious OT intubation
		CVC placement under echography guidance
		Low airway pressures during mechanic ventilation
		Closure of diaphragmatic defects encountered during LTx
Early postoperative	Pleural effusion	Correction of hypoproteinemia
		Limited perioperative blood transfusions
		Proper surgical technique
		Preventive chest tube placement
	Pneumothorax	Echographic guidance for percutaneous pleural procedures
	Hemothorax	Correction of coagulopathy
		Echographic guidance for percutaneous pleural procedures
		Proper surgical technique during LTx
	Atelectasis	Pain management
		Chest physiotherapy
		Drainage of pleural effusions
	Chest tube misplacement	Proper surgical technique
	Re-expansion pulmonary edema	Staged evacuation of massive pleural effusions
	Bacterial pneumonia	Chest physiotherapy
		Early extubation and weaning from mechanical ventilation
		Prevention and treatment of atelectasis
	Pleural empyema	Drainage of parapneumonic pleural effusions
Mid-term and chronic	Opportunistic infections causing lung necrosis and cavitation	Proper prophylaxis
	Invasive aspergillosis	High clinical suspicion
		Prompt imaging (CT scan)
	Diaphragmatic herniation	Proper surgical technique during LTx
	Trapped lung	Prompt treatment of pleural effusion before chronicity
		Radical treatment of pleural empyema

CT: Computed tomography; CVC: Central venous catheter; LTx: Liver transplantation; OT: Orotracheal.

operations were decortication and empyema evacuation. The 30-d morbidity was 69.7%. The authors concluded that developing pleural space complications requiring surgery in orthotopic liver transplant recipients suggests a poor prognosis.

CONCLUSION

Surgical chest complications following liver transplantation are prevalent and constitute a significant source of morbidity and mortality (Table 1). Most of these complications in liver recipients do not differ from the formal population, whilst others are specific to the transplanted patients primarily because of the immunosuppression. A thoracocentesis or a chest tube placement is usually sufficient when invasive measures are deemed necessary. Nevertheless, in some patients, thoracic surgical interventions are warranted. A high index of suspicion is necessary to recognize and treat these conditions promptly. A close collaboration between abdominal surgeons, ICU physicians and thoracic surgeons is of paramount importance.

FOOTNOTES

Author contributions: Agrafiotis AC, Poras M and Katsanos G were involved in the conception and design; Karakasi KE and Neiros S were administrative support; Poras M, Karakasi KE and Neiros S contributed to the provision of the study material; Poras M, Karakasi KE and Neiros S were involved in the collection and assembly of data; Agrafiotis AC, Vasileiadou S and Katsanos G were involved in the data analysis and interpretation; and all authors wrote the manuscript and approved the final manuscript.

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ORCID number: Apostolos C Agrafiotis 0000-0002-7525-208; Konstantina-Eleni Karakasi 0000-0003-2448-556X; Mathilde Poras 0000-0003-2524-2930; Stavros Neiros 0000-0002-5110-1122; Stella Vasileiadou 0000-0001-9143-6085; Georgios Katsanos 0000-0002-5845-8175.

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ORIGINAL ARTICLE

Observational Study

Effects of an active lifestyle on the physical frailty of liver transplant candidates

Ilias Marios Oikonomou, Emmanouil Sinakos, Nikolaos Antoniadis, Ioannis Goulis, Olga Giouleme, Maria Anifanti, Georgios Katsanos, Konstantina-Eleni Karakasi, Georgios Tsoulfas, Evangelia Kouidi

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Ilias Marios Oikonomou, Nikolaos Antoniadis, Georgios Katsanos, Konstantina-Eleni Karakasi, Georgios Tsoulfas, Department of Transplant Surgery, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Emmanouil Sinakos, Ioannis Goulis, The Fourth Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Olga Giouleme, The Second Propaedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Maria Anifanti, Evangelia Kouidi, Laboratory of Sports Medicine, Aristotle University of Thessaloniki, Thessaloniki 57001, Greece

Corresponding author: Ilias Marios Oikonomou, MD, MPhil, Surgeon, Department of Transplant Surgery, Aristotle University of Thessaloniki, 49 Konstantinoupoleos Street, Thessaloniki 54642, Greece. i.m.oikonomou@gmail.com

Abstract

BACKGROUND

Liver transplantation is the most important therapeutic intervention for end-stage liver disease (ELD). The prioritization of these patients is based on the model for end-stage liver disease (MELD), which can successfully predict short-term mortality. However, despite its great validity and value, it cannot fully incorporate several comorbidities of liver disease, such as sarcopenia and physical frailty, variables that can sufficiently influence the survival of such patients. Subsequently, there is growing interest in the importance of physical frailty in regard to mortality in liver transplant candidates and recipients, as well as its role in improving their survival rates.

AIM

To evaluate the effects of an active lifestyle on physical frailty on liver transplant candidates.

METHODS

An observational study was performed within the facilities of the Department of Transplant Surgery of Aristotle University of Thessaloniki. Twenty liver transplant candidate patients from the waiting list of the department were included in

the study. Patients that were bedridden, had recent cardiovascular incidents, or had required inpatient treatment for more than 5 d in the last 6 mo were excluded from the study. The following variables were evaluated: Activity level *via* the International Physical Activity Questionnaire (IPAQ); functional capacity *via* the 6-min walking test (6MWT) and cardiopulmonary exercise testing; and physical frailty *via* the Liver Frailty Index (LFI).

RESULTS

According to their responses in the IPAQ, patients were divided into the following two groups based on their activity level: Active group (A, 10 patients); and sedentary group (S, 10 patients). Comparing mean values of the recorded variables showed the following results: MELD (A: 12.05 ± 5.63 *vs* S: 13.99 ± 3.60; $P > 0.05$); peak oxygen uptake (A: 29.78 ± 6.07 mL/kg/min *vs* S: 18.11 ± 3.39 mL/kg/min; $P < 0.001$); anaerobic threshold (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min; $P < 0.01$); 6MWT (A: 458.2 ± 57.5 m *vs* S: 324.7 ± 55.8 m; $P < 0.001$); and LFI (A: 3.75 ± 0.31 *vs* S: 4.42 ± 0.32; $P < 0.001$).

CONCLUSION

An active lifestyle can be associated with better musculoskeletal and functional capacity, while simultaneously preventing the evolution of physical frailty in liver transplant candidates. This effect appears to be independent of the liver disease severity.

Key Words: Liver transplantation; Frailty; Six-minute walk test; Cardiopulmonary exercise testing; Exercise therapy; Observational study

Core Tip: This study highlights the importance of regular physical activity and exercise of low and medium intensities in the routine of liver transplant candidates. As liver transplantation is a highly demanding procedure, imposing a significant amount of stress across every system, physical frailty is steadily proving to be a factor of great importance, not only due to its role in mortality prediction but also due to its potential improvement *via* preoperative interventions.

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INTRODUCTION

Liver transplantation is the greatest tool for the management and treatment of end-stage liver disease (ELD)[1]. Nevertheless, there is a worldwide gap between the demand for liver transplants and the availability of organ donations[2], increasing the need for optimization of candidate prioritization and organ distribution[3]. It is well established in the literature that the model for end-stage liver disease (MELD) score is a unique tool in this direction[4]. Nevertheless, there are further clinical parameters that may play a substantial role in the waiting list mortality, especially in patients with lower MELD scores [5].

Sarcopenia is related to waiting list mortality and survival after liver transplantation[6-9]. Furthermore, sarcopenic candidates require longer inpatient care, not only on the intensive care unit level but also in ward-based care[10,11]. Functional capacity has also been described as a useful predictive tool, as it is related to better postoperative survival rates and required length of stay[12,13]. It is worth noting that cardiopulmonary exercise testing (CPET) is used quite extensively in other transplant candidates; nevertheless, it is not equally popular in the prelisting assessment of a liver transplant candidate[14,15]. One of the main disadvantages of CPET is the need for expensive equipment within a laboratory setting with equally trained healthcare professionals. The 6-min walking test (6MWT) is mentioned as an alternative assessor of functional capacity in the literature[16], the lower values of which are associated with increased mortality both in the waiting list and after transplantation[17,18].

Furthermore, physical frailty has been gaining growing attention due to its correlation with mortality prediction in liver transplantation. Physical frailty is a clinical syndrome that is correlated with both sarcopenia and functional capacity and is characterized by reduced strength and stamina, as well as increased mortality risk and postoperative dependence[19-21]. The Liver Frailty Index™ (LFI™) is an

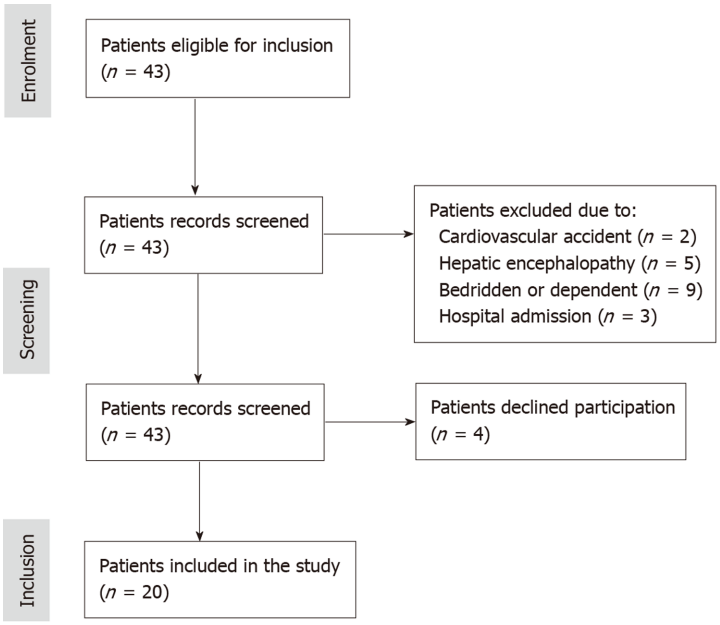

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Figure 1 Recruitment of patients for the observational study.

innovative tool, developed by Lai *et al*[22], which appears to significantly improve mortality prediction when combined with MELD, especially in patients with low MELD scores[22,23].

The course of liver disease is well correlated with a gradual diminishment of both functional capacity and musculoskeletal robustness. Taking the importance of the above clinical tools into consideration, not only on mortality prediction but also on patient prioritization, this observational study evaluated the effects of an active lifestyle on indices of physical functioning, in order to identify the effects of physical activity on physical frailty and cardiovascular capacity on liver transplant candidates.

MATERIALS AND METHODS

Study population

Liver transplant candidates from the Department of Transplant Surgery of the Aristotle University of Thessaloniki in the Hippokration General Hospital of Thessaloniki were recruited for the study. Patients enlisted in the liver transplantation waiting list registry, according to criteria of the Hellenic Transplantation Organization, were deemed eligible for enrollment. The observational study design excluded patients with other comorbidities hindering their activity level or the ones having received instructions from their physicians to limit it, due to a recent acute deterioration of their condition.

Therefore, patients were deemed ineligible if one of the following was true: Recent cardiovascular incident in the preceding 12 mo; grade 2 or higher hepatic encephalopathy; bedridden patients with complete dependence; and recent hospital admission requiring longer than 72 h of inpatient care due to condition deterioration.

A total of 43 patients had their records screened to be included in the observational study. Following the exclusion criteria described above, 19 patients were excluded. In particular, 2 patients were recovering from a recent cardiovascular incident, 5 were classified with hepatic encephalopathy of grade 2 or higher, 9 were completely bedridden and unable to self-accommodate everyday needs, and finally 3 required long inpatient care within the past 3 mo. The remaining 24 patients were contacted and informed about the study; four declined participation. The recruitment process diagram is presented in Figure 1. All patients participating in the study were informed about the purpose and methodology of the study and provided written informed consent. The study protocol was approved by the Department's Ethics Committee of Aristotle University of Thessaloniki (Protocol No. 65/2021). The study was performed from February 16 to June 21, 2021.

Activity level evaluation

The self-administered, short form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate the activity level of the participants. The IPAQ questionnaire was completed by the participants independently, without any guidance from the study investigators. It includes seven questions, collecting self-reported information for the number of days and time spent doing vigorous

Table 1 Study participants' age, sex, and primary cause of end-stage liver disease

No.	Age	Sex	Primary cause
1	32	Female	Primary biliary cholangitis
2	53	Female	Liver hemangioma
3	38	Female	Liver hemangioma
4	53	Male	Hepatitis B virus
5	38	Male	Autoimmune hepatitis
6	51	Female	Hepatocellular carcinoma
7	32	Male	Hepatocellular carcinoma
8	61	Female	Hepatitis B virus
9	63	Male	Non-alcoholic fatty liver disease
10	47	Female	Hepatic cystadenomas
11	62	Female	Primary biliary cholangitis
12	54	Male	Hepatitis C virus
13	52	Male	Alcohol-related liver disease
14	63	Male	Alcohol-related liver disease
15	49	Female	Hepatitis B virus
16	52	Male	Hepatitis B virus
17	50	Male	Hepatitis B virus
18	52	Female	Non-alcoholic fatty liver disease
19	50	Male	Non-alcoholic fatty liver disease
20	50	Female	Primary biliary cholangitis

activity, moderate physical activity, walking, and sitting each day during the course of 1 wk[24,25]. The participants completed the Greek version of the questionnaire[26]. Questions 1 and 2 were about the days and time spent on vigorous activities, questions 3 and 4 referred to activities of moderate intensity, questions 5 and 6 referred to walking, and question 7 asked about the time spent sitting. This tool classifies respondents into three categories of physical activity, namely low, moderate, and high, according to the following criteria[27]: (1) Category 1 - low, consisting of individuals failing to meet any of the criteria detailed below; (2) Category 2 - moderate, consisting of individuals that fulfill any of the following three criteria: At least 3 d of vigorous activity, lasting more than 20 min daily; at least 5 d of moderate activity or walking, lasting more than 30 min daily; and at least 5 d of exercise comprising of a combination of walking, moderate, and vigorous activities, equal to 600 metabolic equivalent of task (MET) minutes or more; and (3) Category 3 - high, consisting of individuals that fulfill either of the following: At least 3 d of vigorous activity, reaching at least 1500 MET minutes weekly; and daily exercise comprising of a combination of walking, moderate, and vigorous activities, reaching at least 3000 MET minutes weekly.

Functional capacity evaluation

Two different methods were used to evaluate the functional capacity of participants, namely CPET and the 6MWT. CPET was performed on the Trackmaster Treadmill (Full Vision Inc., Newton, KS, United States), using the Bruce protocol, whereas gas exchange was measured by the MedGraphics Breeze Suite CPX Ultima (Medical Graphics Corp., St. Paul, MN, United States). The test was performed under the supervision of trained personnel and a cardiologist, within the facilities of the Laboratory of Sports Medicine of the Aristotle University of Thessaloniki. Maximal effort was achieved by all participants, upon reaching a respiratory exchange ratio larger than 1.10. Peak oxygen uptake (VO_{2peak}) and anaerobic threshold (AT) were assessed to evaluate the functional capacity of the participants.

Furthermore, a 6MWT was performed indoors by all participants. The testing design included a 30-m long, flat, and circular track, which was clearly marked for every meter. Patients performed the test twice and the longest distance achieved was recorded as their result. They were also instructed to immediately abandon their attempt if they felt unwell or had uncontrollable fatigue. During the 6MWT, patients received verbal encouragement on the 2nd and 4th min of every attempt and a notification when 60 s were left. Pulse oximetry was used to measure the oxygen saturation and heart rate during the test,

Table 2 International Physical Activity Questionnaire responses

No.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Result
1	0 d	-	2 d	0 h 15 min	5 d	1 h 0 min	8 h 0 min	Moderate
2	2 d	0 h 15 min	4 d	30 min	5 d	1 h 0 min	4 h 30 min	Moderate
3	0 d	-	2 d	0 h 20 min	7 d	1 h 30 min	6 h 0 min	Moderate
4	0 d	-	0 d	-	3 d	0 h 30 min	8 h 0 min	Low
5	0 d	-	3 d	0 h 30 min	3 d	1 h 0 min	6 h 0 min	Moderate
6	0 d	-	2 d	0 h 20 min	4 d	0 h 45 min	6 h 30 min	Moderate
7	0 d	-	3 d	0 h 45 min	4 d	1 h 15 min	4 h 30 min	Moderate
8	0 d	-	2 d	0 h 15 min	2 d	0 h 30 min	7 h 30 min	Low
9	0 d	-	0 d	-	3 d	0 h 15 min	9 h 30 min	Low
10	0 d	-	3 d	0 h 30 min	3 d	0 h 45 min	6 h 15 min	Moderate
11	0 d	-	0 d	-	3 d	0 h 15 min	9 h 15 min	Low
12	0 d	-	2 d	0 h 20 min	3 d	0 h 30 min	6 h 45 min	Low
13	0 d	-	2 d	0 h 15 min	4 d	0 h 20 min	7 h 0 min	Low
14	0 d	-	0 d	-	5 d	0 h 15 min	8 h 0 min	Low
15	0 d	-	0 d	-	3 d	0 h 40 min	7 h 30 min	Low
16	0 d	-	2 d	0 h 20 min	3 d	0 h 30 min	6 h 0 min	Low
17	0 d	-	3 d	0 h 30 min	4 d	1 h 30 min	4 h 0 min	Moderate
18	0 d	-	3 d	0 h 20 min	4 d	1 h 0 min	6 h 0 min	Moderate
19	0 d	-	0 d	-	7 d	1 h 15 min	5 h 30 min	Moderate
20	0 d	-	0 d	-	3 d	0 h 30 min	8 h 0 min	Low

whereas the Borg scale Rating of Perceived Exertion was used to monitor exercise intensity.

Physical frailty evaluation

The LFI was used to evaluate the physical frailty of the study participants[28]. This clinical tool, developed by Lai *et al*[29], includes three tests that assess balance, neuromuscular coordination, and sarcopenia. The three tests are as follows: (1) Hand grip strength (using a dynamometer in the standard position, the participant squeezes the grip three times while the dynamometer rests on no surface); (2) Sit-to-stand test (from sitting position and keeping both arms folded in front of their chest, the participant is timed while standing up and sitting down five consecutive times); and (3) Balance test (the participant is timed standing up in three different balance positions, with feet side-by-side, semi tandem and tandem, while receiving no further support, for a maximum of 10 s).

Statistical analysis

IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. Continuous parameters were compared using the independent samples *t*-test. The values of the parameters of the sample were tested for normal distribution with the Shapiro-Wilk test. Point biserial correlation analysis was used to determine the relationship between activity level and the frailty and functional capacity variables. Difference between values was considered to be of statistical significance for *P* values less than 0.01. All data are presented as the mean ± standard deviation.

RESULTS

General characteristics of patients

Twenty patients were included in the study, all of whom are listed in the waiting list of the Department of Transplant Surgery in the Hippokration General Hospital of Thessaloniki. The majority of patients came from the city of Thessaloniki (n = 9, 45%), whereas the rest were distributed across the Greek mainland and islands. There were 10 male and 10 female patients included in the study, with a median age of 50.1 years. The primary causes of ELD of the participants were hepatitis B (n = 5, 25%), non-

Table 3 Peak oxygen uptake and anaerobic threshold results

No.	Group	VO_{2peak} in mL/kg/min	AT in mL/kg/min
1	Active	29.9	15.8
2	Active	40.8	21.1
3	Active	27.1	18.0
4	Sedentary	18.9	14.8
5	Active	25.7	14.1
6	Active	24.2	15.0
7	Active	39.6	18.8
8	Sedentary	18.4	14.2
9	Sedentary	13.8	12.8
10	Active	22.2	14.2
11	Sedentary	13.2	11.6
12	Sedentary	25.3	17.0
13	Sedentary	20.0	14.7
14	Sedentary	16.9	12.8
15	Sedentary	17.0	13.8
16	Sedentary	19.5	14.0
17	Active	30.0	16.9
18	Active	28.5	16.5
19	Active	29.8	16.7
20	Sedentary	18.1	13.9

AT: Anaerobic threshold; VO_{2peak}: Peak oxygen uptake.

alcoholic fatty liver disease (n = 3, 15%), primary biliary cholangitis (n = 3, 15%), alcohol-related liver disease (n = 2, 10%), liver hemangioma (n = 2, 10%), hepatocellular carcinoma (n = 2, 10%), hepatitis C (n = 1, 5%), autoimmune hepatitis (n = 1, 5%), and hepatic cystadenomas (n = 1, 5%). The mean MELD score for the patients in the study was 13.02 ± 4.71. Demographic details for each patient are listed in Table 1, including the primary cause of ELD per participant.

Activity level

All responses collected *via* the IPAQ can be seen in Table 2. Ten patients were classified as having a moderate physical activity level (category 2), whereas ten patients were found to be in the low physical activity level category (category 1). Using these responses, the sample was divided into two groups; patients with a moderate activity level were characterized as active (A), and patients with low activity level were allocated in the sedentary group (S). The active and sedentary groups were found to be similar regarding their MELD scores (A: 12.05 ± 5.63 *vs* S: 13.99 ± 3.60, respectively; $P > 0.05$).

Functional capacity

All participants successfully completed their CPET, successfully reaching a respiratory exchange ratio equal to 1.10 or higher. No patient had to abandon their examination due to excess fatigue or the presentation of adverse effects. No patient was instructed to terminate the exercise stress test due to changes to their electrocardiogram.

The mean VO_{2peak} achieved by active participants was higher compared to the mean value recorded by the sedentary group (A: 29.78 ± 6.07 mL/kg/min *vs* S: 18.11 ± 3.39 mL/kg/min, respectively; $P < 0.001$). Similarly, the AT in active subjects was higher than that in their sedentary counterparts (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min, respectively; $P < 0.01$). All results for VO_{2peak} and AT are presented in Table 3.

Regarding the 6MWT, all participants successfully completed two attempts, with the longest distance considered the test result. No complication was recorded, and no effort was abandoned due to fatigue or exhaustion. Detailed results per participant are presented in Table 4. The active group covered a larger mean distance on the test compared to the sedentary group (A: 324.7 ± 55.8 m *vs* S: 458.2 ± 57.5 m,

Table 4 Six-minute walking test results

No.	Group	6-min walking test in m
1	Active	396
2	Active	456
3	Active	595
4	Sedentary	250
5	Active	433
6	Active	397
7	Active	429
8	Sedentary	347
9	Sedentary	264
10	Active	502
11	Sedentary	259
12	Sedentary	360
13	Sedentary	431
14	Sedentary	362
15	Sedentary	320
16	Sedentary	330
17	Active	460
18	Active	456
19	Active	458
20	Sedentary	324

respectively; $P < 0.001$).

Physical frailty evaluation

The LFI was used to assess the robustness or frailty of the study participants. Patients successfully completed all exercises after first witnessing a demonstration. The sedentary group was more likely to score a greater LFI score and to be frail, whereas its mean value was above the limit for patient classification as frail compared to the active group, which was more likely to score smaller values (S: 4.42 ± 0.32 *vs* A: 3.75 ± 0.31, respectively; $P < 0.001$). The detailed performance per test is described in Table 5. Patients with a LFI greater than 4.4 were classified as frail[23,29]. No patient from the active group was classified as frail (LFI < 4.4, $n = 10$), whereas 6 patients were found to be frail according to the LFI in the sedentary group (LFI > 4.4, $n = 6$). Mean value comparisons are presented for all variables in Table 6.

Correlation analysis

Pearson correlation analysis was used to determine if disease severity was associated with worse functional capacity or higher frailty scores. Correlation was tested between MELD scores and LFI, VO_{2max}, AT, and 6MWT. No significant correlation was found between MELD and LFI ($r_p = 0.29$, $P > 0.05$), VO_{2max} ($r_p = -0.10$, $P > 0.05$), AT ($r_p = -0.25$, $P > 0.05$) or 6MWT ($r_p = -0.36$, $P > 0.05$).

Point-biserial correlation was run to determine the relationship between the activity level and functional capacity and physical frailty markers. MELD and activity level was not significantly correlated ($r_{pb} = -0.212$, $P > 0.05$), whereas there was significant correlation between activity level and LFI ($r_{pb} = -0.747$, $P < 0.001$), VO_{2peak} ($r_{pb} = 0.781$, $P < 0.001$), AT ($r_{pb} = 0.618$, $P < 0.01$), and 6MWT ($r_{pb} = 0.779$, $P < 0.001$). This relationship is presented in Table 7.

DISCUSSION

According to the results of this observational study, physical activity appears to prevent physical frailty and retain cardiovascular capacity in liver transplant candidates, independent of their MELD score. This can be potentially used as a tool for prehabilitation in listed patients for a liver transplant. Availability of liver transplants has always been well below demand, especially in Greece, with the coronavirus disease

Table 5 Liver Frailty Index test results

No.	Hand grip strength in kg			Sit-to-stand in s	Balance test in s			LFI
	Att. 1	Att. 2	Att. 3		Side-by-side	Semi-tandem	Tandem	
1	18	19	19	12.4	10.0	10.0	10.0	3.95
2	26	26	25	8.5	10.0	10.0	10.0	3.11
3	25	24	24	10.1	10.0	10.0	10.0	3.42
4	19	18	18	16.8	7.9	9.1	8.2	4.76
5	26	27	27	11.0	10.0	10.0	10.0	3.9
6	19	18	19	13.1	9.1	10.0	8.9	4.08
7	30	28	29	10.0	10.0	10.0	10.0	3.71
8	14	14	13	17.2	8.5	9.2	8.1	4.66
9	13	14	14	17.6	8.5	9.4	8.0	4.92
10	18	17	18	13.3	9.0	10.0	9.0	4.15
11	12	11	12	16.1	9.3	10.0	9.0	4.62
12	20	19	19	11.9	10.0	10.0	10.0	4.23
13	26	27	28	12.2	10.0	10.0	10.0	4.00
14	22	21	21	11.8	10.0	10.0	10.0	4.15
15	18	18	17	12.8	10.0	10.0	10.0	4.03
16	18	19	18	13.0	9.5	9.8	8.9	4.42
17	27	27	26	9.4	10.0	10.0	10.0	3.70
18	19	20	20	11.3	10.0	10.0	10.0	3.80
19	27	28	27	9.8	10.0	10.0	10.0	3.74
20	15	14	14	14.2	9.0	9.4	8.4	4.43

Att: Attempt; LFI: Liver Frailty Index.

Table 6 Mean values of peak oxygen uptake, anaerobic threshold, 6-min walking test and, Liver Frailty Index

Value	Active group	Sedentary group
VO_{2peak} in mL/kg/min	29.78 ± 6.07[a]	18.11 ± 3.39[a]
AT in mL/kg/min	16.71 ± 2.17[b]	13.96 ± 1.45[b]
6MWT in m	458.2 ± 57.5[a]	324.7 ± 55.8[a]
LFI	3.75 ± 0.31[a]	4.42 ± 0.32[a]

[a]$P < 0.001$.
[b]$P < 0.01$.
6MWT: 6-min walking test; AT: Anaerobic threshold; LFI: Liver Frailty Index; VO_{2peak}: Peak oxygen uptake.

2019 pandemic posing an even greater challenge. This study was driven by the need to identify possible important and potentially modifiable clinical parameters, which, when used in concordance with the MELD score, would be able to optimize the capacity of a medium-size transplant center[3,6].

According to the LFI, 30% (n = 6) of the study participants are classified as frail (LFI > 4.4)[23,29], a percentage that is concordant with the results of a previous review study[30]. Physical frailty has been associated with increased waiting list mortality, independently of the MELD score, presence of ascites or hepatic encephalopathy[31]. Furthermore, in the postoperative spectrum, frailty has been associated with increased 30-d mortality, extended inpatient and intensive unit care[32], increased rates of acute cellular rejection[33], increased dependency[34,35], and vertebrae fractures[36]. Constructed, the home-based exercise program appears to positively influence frailty indexes and partially restore musculo-skeletal robustness[37-40]. Our study compared each patient's physical activity level with their physical

Table 7 Correlation analysis between activity level and model for end-stage liver disease score peak oxygen uptake, anaerobic threshold, 6-min walking test, and Liver Frailty Index

Value	r_{pb}	*P* value
MELD	-0.212	> 0.05
VO_{2peak} in mL/kg/min	0.781	< 0.001
AT in mL/kg/min	0.618	< 0.01
6MWT in m	0.779	< 0.001
LFI	-0.747	< 0.001

6MWT: 6-min walking test; AT: Anaerobic threshold; LFI: Liver Frailty Index; MELD: Model for end-stage liver disease; r_{pb}: Point-biserial correlation coefficient; VO_{2peak}: Peak oxygen uptake.

frailty. Although patients were not under professional trainer guidance, frequent activity such as walking and gardening, appeared to have a preventive effect on the evolvement of physical frailty. This could potentially provide clinicians with an important tool in the preoperative treatment of candidates, while on the waiting list for a transplant, being a tool that could potentially improve transplantation outcomes.

Functional capacity has also been associated with postoperative dependency and mortality. Epstein *et al*[12] described an increased 100-d mortality in patients with lower peak oxygen uptake, whereas other studies have associated a smaller VO_{2peak} with extended intensive care unit stay and mechanical ventilation dependency[41]. Similarly, smaller distances in the preoperative 6MWT have been associated with increased mortality after liver transplantation[42,43]. In 2021, Henrique *et al*[18] identified a statistically significant increased risk of cirrhosis decompensation in patients with values smaller than 401.8 m in the 6MWT, whereas Bhanji *et al*[44] described a double risk of waiting list mortality in patients with values smaller than 250 m and its statistically significant reduction for every 100 m improvement. In our study, active participants were much more likely to record values above 401.8 m (80% *vs* 10%; $P < 0.01$), consistent with the findings of the effects of exercise in liver patients in other studies[45,46].

The inclusion of indexes of frailty and functional capacity in the clinical practice of liver transplantation appears to be a valuable aid in patient prioritization, especially in candidates with low MELD scores[47]. Furthermore, regular physical activity appears to be a valuable tool to improve these modifiable factors. Physical frailty has been reported as reduced in liver transplant candidates through the adoption of an active lifestyle in several studies[48,49], while functional capacity has been reported as similarly improved[45,50]. This can potentially lead to improved survival rates and reduced hospitalization length and readmission rates[51,52]. Our study shares similar results, further supporting the notion that physical activity can have a significant role in preoperative preparation for candidates, potentially achieving improved outcomes. Furthermore, our data suggests that home-based, patient-controlled exercise can have an adequate impact.

The active participants of our study, although not following an organized and formal exercise protocol, had substantially better musculoskeletal and functional status, appeared to be more robust, and could potentially have great tolerance to stressors. This suggests evidence that exercise interventions could have a positive impact on liver transplant candidates, without the need for formal and difficult exercise regimes that bear a higher risk of lower compliance. However, this study had limitations, namely the small sample size and no prospective results. Further data collection and follow-up could confirm the effects of this lifestyle on pretransplantation and posttransplantation survival, dependency, and complications.

CONCLUSION

In conclusion, an active lifestyle can potentially be a tool of preoperative preparation of liver transplant candidates to reduce mortality, hospitalization, and dependencies. Physical frailty and functional capacity can be improved with exercise training interventions. Clinical tools such as the 6MWT and the LFI could be used for better mortality prediction and patient prioritization, which is of significant importance in smaller and medium-sized transplant centers, where organ donation is unable to meet the existing high demand.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation forces a substantial stress on the human physiology, which is even more significant considered the deconditioning that accompanies end-stage liver disease (ELD). Physical frailty has emerged as an important factor both pre- and postoperatively, aiming to improve results and outcomes.

Research motivation

The limited amount of available organ donations in addition to the high demand in liver transplants, highlight the need for proper planning and prioritization, while at the same time working towards further outcome improvement.

Research objectives

The main objective was to identify if an active lifestyle can significantly improve physical frailty and functional capacity in patients with ELD.

Research methods

An International Physical Activity Questionnaire, a functional capacity assessment, and a physical frailty evaluation were utilized.

Research results

There was a statistically significant difference and statistically significant correlation between the activity level and the Liver Frailty Index, the peak oxygen uptake, the anaerobic threshold, and the 6-min walking distance.

Research conclusions

Physical activity can potentially improve functional capacity and frailty in liver transplant candidates.

Research perspectives

Future research should focus on the regimen of the exercise that would be more suitable, or better quantify the amount of physical exercise needed for these patients. Furthermore, the potential use of these markers in survival and outcomes should be evaluated.

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Country/Territory of origin: Greece

ORCID number: Ilias Marios Oikonomou 0000-0003-3620-4462; Emmanouil Sinakos 0000-0003-0923-050X; Nikolaos Antoniadis 0000-0001-6939-3373; Ioannis Goulis 0000-0002-2765-4157; Olga Giouleme 0000-0003-0176-3598; Maria Anifanti 0000-0003-0540-3581; Georgios Katsanos 0000-0002-5845-8175; Konstantina-Eleni Karakasi 0000-0003-2448-556X; Georgios Tsoulfas 0000-0001-5043-7962; Evangelia Kouidi 0000-0002-5023-2542.

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ORIGINAL ARTICLE

Observational Study

Parvovirus B19 status in liver, kidney and pancreas transplant candidates: A single center experience

Bojana Simunov, Anna Mrzljak, Zeljka Jurekovic, Snjezana Zidovec Lepej, Ana Bainrauch, Jadranka Pavicic Saric, Zeljka Hruskar, Leona Radmanic, Tatjana Vilibic-Cavlek

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Bojana Simunov, Zeljka Jurekovic, Department of Nephrology, Merkur University Hospital, Zagreb 10000, Croatia

Anna Mrzljak, Department of Gastroenterology and Hepatology, University Clinical Hospital Zagreb, Zagreb 10000, Croatia

Anna Mrzljak, Tatjana Vilibic-Cavlek, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Snjezana Zidovec Lepej, Leona Radmanic, Department of Immunological and Molecular Diagnostics, University Hospital for Infectious Diseases "Dr. Fran Mihaljevic", Zagreb 10000, Croatia

Ana Bainrauch, Department of Medicine, Merkur University Hospital, Zagreb 10000, Croatia

Jadranka Pavicic Saric, Department of Anesthesiology, Merkur University Hospital, Zagreb 10000, Croatia

Zeljka Hruskar, Tatjana Vilibic-Cavlek, Department of Virology, Croatian Institute of Public Health, Zagreb 10000, Croatia

Corresponding author: Anna Mrzljak, MD, PhD, Professor, Department of Gastroenterology and Hepatology, University Clinical Hospital Zagreb, 12 Kispaticeva, Zagreb 10000, Croatia. anna.mrzljak@gmail.com

Abstract

BACKGROUND

Parvovirus B19 (B19V) is associated with a wide range of clinical manifestations. The major presentation is erythema infectiosum. However, a persistent infection may cause pure red cell aplasia and chronic anemia in immunocompromized patients. The B19V seroprevalence varies with age and geographical location.

AIM

To determine the B19V serological status and DNAemia in kidney, liver, and pancreas transplant candidates.

METHODS

Patients who underwent kidney, liver, or simultaneous kidney and pancreas/liver

transplantation between January 2021 and May 2022 were included in the study. The serum samples were collected before transplantation. For detection of B19V DNA, a LightMix Kit B19V EC (TIB MOLBIOL, Berlin, Germany) was used. B19V IgM and IgG antibodies were detected using a commercial ELISA test (Euroimmun, Lübeck, Germany).

RESULTS

One hundred and thirty-one transplant candidates were included in the study, 71.0% male, with an average age of 53.27 years ± 12.71 years. There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas/kidney transplant (SPKT), and 0.8% simultaneous liver/kidney transplant recipients. No patients had detectable B19V DNA. B19V IgG seroprevalence was 77.1%. No acute or recent infections were detected (IgM antibodies). There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). Although seropositivity was lower in patients aged less than 30 years (66.6%) compared to the patients aged 30-59 years and > 60 years (80.4% and 78.1%, respectively), this difference was not significant. In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% and 78.9% (χ^2 = 0.104; P = 0.748). The seroprevalence did not differ among organ recipients, with 77.8%, 80.6%, and 50.0% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). No significant difference was found in the seroprevalence in kidney transplant patients according to dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; P = 0.372).

CONCLUSION

The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but there are still 22.9% of seronegative individuals who remain at risk for primary disease and severe manifestations. Further research should elucidate the necessity of B19V screening in peri-transplant management.

Key Words: Parvovirus B19; Seroprevalence; DNA; Kidney transplantation; Liver transplantation; Pancreas transplantation

Core Tip: Many liver, kidney, or pancreas transplant recipients are parvovirus B19 seronegative and at risk for primary disease and severe manifestations. Serological studies on pretransplant could simplify the diagnostic work-up of anemia after transplantation in these complex patients.

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INTRODUCTION

Parvovirus B19 (B19V) is a small non-enveloped single-stranded DNA virus of the family *Parvoviridae*, genus *Erythroparvovirus*[1]. It was first discovered in a healthy blood donor[2] and then linked to aplastic crises in children with sickle cell anemia[3]. Subsequently, the major presentation, erythema infectiosum (fifth disease), was described[4]. B19V mainly infects the human erythroid progenitor cells [5]. The cellular receptor is globoside (erythrocyte P antigen), found on erythroid cells, erythroid precursors and red cells of the placenta and fetal myocardium, fetal liver, and some megakaryocytes and endothelial cells[6]. Rarely, individuals may lack blood group P antigen, which confers resistance to B19V infection[7].

In healthy individuals, the disease is often asymptomatic or occurs as a two-phase illness: Fever and non-specific influenza-like symptoms during the early phase of viremia, followed by erythema, arthralgia, or both, at the time of appearance of specific antiviral antibodies[8,9]. The cutaneous manifestations of B19V infection vary. Four basic patterns have been reported: exanthema, gloves-and-socks, periflexural, and palpable purpura[10]. A robust humoral immune response is required to control B19V infection and clear DNAemia. Neutralizing antibodies to B19V structural proteins appear to confer life-long protective immunity[11]. Therefore, in immunocompromized patients unable to mount

sufficient antibody response, the infection may persist and cause pure red cell aplasia and chronic anemia[12,13]. More recently, other disease manifestations have been reported, ranging from hepatitis and myocarditis to meningoencephalitis[14-17].

In the transplant setting, B19V is long known to cause persistent anemia and pure red cell aplasia due to the inability of the immunosuppressed host to clear the virus[18-20]. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is unknown, with wide variances of rates reported in different studies, from 0% to 58%[21-24]. Some recent studies report a much lower rate, under 15%[23, 25]. It is noteworthy that the immune response mediates non-hematological manifestations of B19V infection; thus immune-mediated symptoms may be absent or blunted in transplant recipients. Therefore, a high level of suspicion should be present to diagnose the infection.

Serology may not reliably establish the diagnosis in the transplant population due to the inability to produce a sufficient antibody response, and polymerase chain reaction (PCR) should be used to detect viral DNA in this population[11]. High-level viremia is more likely associated with symptomatic disease [11]. Conversely, if detected at low levels, persistent DNAemia after infection may not be clinically significant[11]. Despite the lack of robust data, intravenous administration of immunoglobulins (IVIg) and decrease of immunosuppression levels are the mainstay of treatment of SOT recipients with symptomatic B19V infection[11,19]. Although IVIg's optimal dosage and duration are unknown, most patients respond well to treatment. Unfortunately, recurrence of anemia is common[26-28]. There are preliminary reports of foscarnet being used for treatment[29]. Cidofovir has shown *in vitro* efficacy, but further research is needed[30]. Also, the conversion from calcineurin inhibitor-based immunosuppression to everolimus has been described[31].

Currently, routine screening of donor and recipient serostatus for B19V is not recommended; there have been research efforts[24,32]. There is also a lack of epidemiologic data, including the seroprevalence in transplant candidates, depending on the region or organ type[11,33].

This study aimed to determine the B19V serological status and active viral replication by B19V DNA quantification in kidney, liver, and pancreas transplant candidates at a large national transplant center.

MATERIALS AND METHODS

Patients who were transplanted (kidney, liver, or simultaneous kidney and pancreas/liver) at Merkur University Hospital from January 2021 to May 2022 were included in the analysis. The hospital is a high-volume transplant center with approximately 110 liver and 50 kidney transplants performed yearly, representing over 90% of the liver transplantation program in the country and the only institution performing simultaneous transplantations. This was a single-center, prospective study.

The serum samples were collected before the transplantation. Data about the patients were collected prospectively using the hospital's electronic medical record.

Viral DNA was extracted from blood samples using a High Pure Viral Nucleic Acid Kit (Roche Applied Science, Penzberg, Germany). For quantification of B19V DNA in nucleic acid extracts, a LightMix Kit Parvovirus B19 EC (TIB MOLBIOL, Berlin, Germany) was used.

B19V IgG and IgM antibodies were detected using a commercial enzyme-linked immunosorbent assay (ELISA; Euroimmun, Lübeck, Germany). Results were interpreted according to the manufacturer's recommendations as follows: IgM ratio < 0.8 negative, 8.8-1.1 borderline, > 1.1 positive; IgG RU/mL < 4 negative, 4.0-5.5 borderline, > 5.5 positive.

Statistical analysis

Statistical analysis was performed using SPSS version 25 (Armonk, NY, United States, IBM Corp). A $P < 0.05$ was considered to be significant. The data are expressed as the median and interquartile range (IQR), or mean ± SD, as appropriate. Categorical variables are presented as frequency counts and percentages. The normality of the data distribution was tested using the Shapiro-Wilks test. The categorical values were compared using the χ^2 test. In cases with less than 5 outcomes, Fisher's exact test was used. For continuous variables, a parametric (Student's *t*-test, ANOVA) or nonparametric test (Mann-Whitney *U*, Wilcoxon, Kruskal-Wallis) was used, depending on the distribution.

RESULTS

A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. The median age was 57 years, IQR 43-63 years. The age distribution of patients is presented in Figure 1.

There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas-kidney transplant (SPKT) and 0.8% simultaneous liver-kidney transplant (SLKT) recipients (Table 1).

None of the tested patients had detectable B19V DNA. IgG seroprevalence was 77.1%. No recent infections (IgM antibodies) were detected.

Table 1 Study population characteristics (*n* = 131)

Item	Value
Age, yr (mean ± SD)	53.27 ± 12.71
Gender	
Male	93 (70.9%)
Female	38 (29.1%)
Transplant type	
Liver	90 (68.7%)
Kidney	36 (27.5%)
SPKT	4 (3.0%)
SLKT	1 (0.8%)
Virology results	
B19V DNA positive	0 (0%; one-sided 97.5% CI: 0-2.8)
B19V IgM positive	0 (0%; one-sided 97.5% CI: 0-2.8)
IgG B19V positive	101 (77.1%; 95% CI: 68.9-83.9)

SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; CI: Confidence interval.

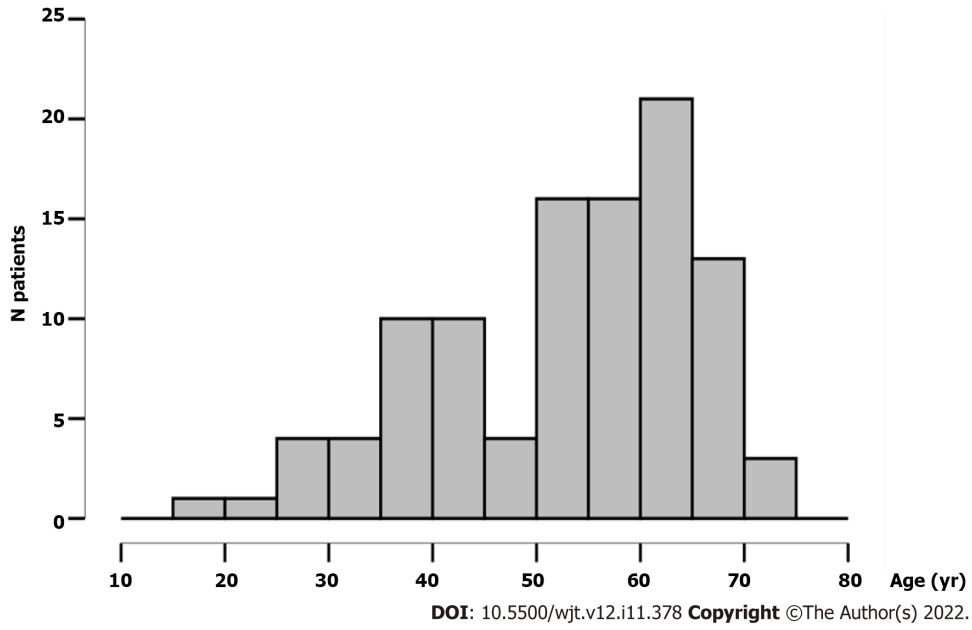

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Figure 1 Distribution of transplant candidates according to age.

There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% *vs* 78.9%, respectively (χ^2 = 0.104; P = 0.748). When divided into age groups, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30 to 59 years, and 78.1% in patients over 60 (χ^2 = 0.619; P = 0.734) (Table 2).

The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). There was only one SLKT recipient who was seronegative. The recipients of SPKT were significantly younger than kidney or liver recipients (36.0 years ± 6.8 years, 52.6 years ± 11.6 years and 54.8 years ± 12.9 years, respectively, P = 0.014).

There was no association between immunosuppression prior to transplantation and seropositivity. B19V seroprevalence was 81.3% in the subgroup which received immunosuppression prior to transplantation and 76.4% in the subgroup that did not (χ^2 = 0.176; P = 0.675).

Table 2 Parvovirus B19 IgG seroprevalence rates in transplant candidates

Characteristics	Tested, *n* (%)	IgG positive, *n* (%)	χ^2	*P* value
Gender			0.104	0.748
Male	93 (71.0)	71 (76.3)		
Female	38 (29.0)	30 (78.9)		
Age, yr			0.619	0.734
< 30	6 (5.8)	4 (66.6)		
30-59	56 (54.4)	45 (80.4)		
> 60	41 (39.8)	32 (78.1)		
Transplant type			5.297	0.151
Liver	90 (68.7)	70 (77.8)		
Kidney	36 (27.5)	29 (80.6)		
SPKT	4 (3.0)	2 (50.0)		
SLKT	1 (0.8)	0 (0)		
IS before transplantation			0.498	0.780
Yes	16 (18.2)	13 (81.3)		
No	72 (81.8)	55 (76.4)		
Dialysis modality				0.372[1]
HD	38 (95)	27 (71.1)		
PD	2 (5)	2 (100)		

[1]Fisher's exact test. SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; IS: Immunosuppression; HD: Hemodialysis; PD: Peritoneal dialysis.

No significant difference was found in the seroprevalence in kidney transplant candidates according to the dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; *P* = 0.372). In addition, there was no association with dialysis duration (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* = 0.775).

DISCUSSION

Our results show a high seroprevalence of B19V among transplant candidates. The seroprevalence of 77.1% was higher compared to a large previous study in the general Croatian population, where a seroprevalence of 64.1% was found[34]. Surprisingly, the seroprevalence did not differ with age, which is commonly reported. However, although not significantly, seropositivity was lower in patients aged less than 30 years (66.6%) compared to patients aged 30-59 and 60 years (80.4% and 78.1%, respectively). The transplant population tested in this study was skewed to slightly older recipients, as shown in the age distribution. This could partly explain the inability to detect the expected difference in seroprevalence with age. In the Croatian general population, seroprevalence in the matching age group 50-59 years was 69.1%[34], which is concordant to our findings. However, it is important to note that the seroprevalence in transplant patients younger than 30 years was higher (66.6%) compared to the same age group in the general population (53.2%)[34].

Additionally, it is important to emphasize that our study investigated transplant candidates, not recipients. The candidates, contrary to the recipients, have not yet received immunosuppression. The data on transplant candidates is even scarcer in literature than on SOT recipients[11]. A German study reported a similar seroprevalence rate of 82% in transplant candidates (kidney, liver, heart, and bone marrow)[35]. Moreover, no difference was found in seroprevalence between various organ recipients, but with a trend toward lower seroprevalence among simultaneous kidney and pancreas candidates. All kidney transplant candidates in our study were patients on dialysis. Few studies analyzed the B19V seroprevalence in hemodialysis or peritoneal dialysis patients. Prevalence rates of 67.5% and 54% were reported from Brazil and Iran, respectively[36,37], which is similar to our result of 71.1% in hemodialysis patients. In our study, we found no association of seroprevalence with the duration of hemodialysis (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* =

0.775). Due to better treatment of anemia today, most dialysis patients do not receive transfusions. Therefore, the duration of dialysis does not appear to be a risk factor. The lower prevalence in SPKT candidates was not statistically significant. The SPKT candidates were significantly younger than other transplant candidates, which could explain the trend. Moreover, although there is a paucity of data in the literature on B19V infection in SPKT recipients, the cases presented[38-40] imply a more severe course. We hypothesize that pancreas candidates may be at higher risk for infection given a larger proportion of seronegative recipients due to the immunosuppressive nature of diabetes[41] and the younger age of the recipients. The possible difference among various organ type recipients includes not only age as seen in SPKT recipients but also different numbers of blood transfusions due to bleeding events in cirrhotic patients. Interestingly there was no association between immunosuppression prior to transplantation (*e.g.*, for glomerulonephritis or autoimmune liver disease) and seropositivity.

Following acute infection in immunocompetent individuals, viral genomes may persist in various tissues for life. However, acute B19V infection can lead to severe complications in immunocompromized patients. In our study, no B19V DNA was found. In a German study, B19V DNA was detected in 4.0% of patients. Whereas DNAemia was found in 5.5%, 6.7%, and 5.7% of liver, heart, and bone marrow recipients, and viral genomes were found in only 1.4% of kidney recipients[35]. In a large recent Chinese study, a B19V DNA positive rate of 1.9% was reported in transplant candidates[25].

In addition, a large proportion of patients are still seronegative at the time of transplant and remain at risk for severe disease manifestations. Currently, there is no specific prevention of B19V disease. There is also no routine screening of donor and recipient serostatus for B19V. The true incidence of parvovirus infection in SOT recipients is unknown, with rates varying considerably across different studies[21-25]. There have been efforts in prospective routine monitoring of B19V in the first 6 mo after transplantation in seronegative SOT recipients. The findings showed low incidence rates (1.2% recipients per month) and even lower clinically significant events[24]. In another recent study, prospective monitoring revealed a higher incidence of B19V (10.17%), all infections occurred in seronegative recipients and were deemed clinically significant[42]. To conclude, large prospective data series on B19V disease in transplant recipients are lacking, but in our opinion, at the moment there is no rationale for routine B19V testing. However, pretransplant serostatus could be cost-efficient given the lower cost of a serological test than PCR testing and could potentially reveal patients at high risk. Post-transplant anemia is prevalent and often multifactorial. Serostatus could potentially hasten the diagnosis of B19V infection in selected patients and thus help avoid diagnostic delay and unnecessarily broad testing.

Moreover, B19V has also been implicated as a trigger for thrombotic microangiopathy[43,44], especially in the transplant setting[45-48]. These implications warrant additional research, but the information on serostatus could be beneficial during thrombotic microangiopathy workup, which is expensive and usually long-lasting. A large number of post-transplant thrombotic microangiopathies are regarded as secondary, either to immunosuppressive drugs or transplant itself; thus, B19V infection as a possible causative agent is probably underdiagnosed[49]. Identifying high-risk individuals pretransplant could be beneficial and help elucidate this pathophysiologically complex state[50].

Our study has limitations. Firstly, it is a single-center study with low numbers of rare transplantations, *e.g.*, SPKT and SLKT. Secondly, the incidence of clinical B19V infection was not reported in the post-transplant follow-up of these patients, reflecting the clinical significance of the serological status detected pretransplant. We plan to prospectively evaluate DNAemia and serostatus post-transplant as well as clinical manifestations to establish the clinical significance and epidemiology of B19V disease post-transplant. In addition, blood samples from control subjects were unavailable; therefore, it was not possible to compare the prevalence of B19V DNA in healthy individuals.

CONCLUSION

The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations. Further research should elucidate the utility of B19V screening in peri-transplant management.

ARTICLE HIGHLIGHTS

Research background

Parvovirus B19 (B19V) is an important pathogen in transplant settings. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is not well studied, and reported prevalence rates vary greatly.

Research motivation

Data on B19V infection in transplant settings are scarce.

Research objectives
To analyze the prevalence of B19V antibodies and DNA in SOT candidates (kidney, liver, or simultaneous kidney and pancreas/liver) at a large national transplant center.

Research methods
Serum samples collected before transplantation were tested for the presence of B19V IgM and IgG antibodies and B19V DNA. Patients' data were collected using the electronic medical record.

Research results
A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. None of the tested patients had detectable B19V DNA and IgM, while IgG seroprevalence was 77.1%. There was no difference in seropositivity between males and females (76.3% *vs* 78.9%). According to age, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30-59 years, and 78.1% in patients over 60. The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and simultaneous pancreas-kidney transplant, respectively. There was no association between immunosuppression prior to transplantation and B19V IgG seropositivity.

Research conclusions
The B19V seroprevalence is high in transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations.

Research perspectives
Further studies on large samples as well the B19V prevalence during the post-transplant period are needed to determine the clinical significance of B19V infection in transplant patients.

FOOTNOTES

Author contributions: Simunov B contributed to the concept of the study, collected and analyzed the data, and wrote the original draft; Jurekovic Z, Zidovec Lepej S, Bainaruch A, Pavicic Saric J, Hruskar Z, and Radmanic L analyzed the data; Mrzljak A and Vilibic-Cavlek T made contributions to the concept of the study, and revised the manuscript critically; all authors approved the final version of the manuscript.

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ORCID number: Bojana Simunov 0000-0002-1768-2277; Anna Mrzljak 0000-0001-6270-2305; Zeljka Jurekovic 0000-0003-0690-2577; Snjezana Zidovec Lepej 0000-0001-9852-5806; Ana Bainrauch 0000-0003-0219-1800; Jadranka Pavicic Saric 0000-0003-4124-8056; Zeljka Hruskar 0000-0002-9078-1773; Leona Radmanic 0000-0001-9362-7213; Tatjana Vilibic-Cavlek 0000-0002-1877-5547.

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EDITORIAL

Is the near coming xenotransplantation era relieving us from needing to look for more non-living organ donors?

Fernando M Gonzalez, Francisca del Rocío Gonzalez

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Fernando M Gonzalez, Department of Nephrology, Faculty of Medicine, Universidad de Chile, Santiago 7500922, Chile

Francisca del Rocío Gonzalez, Web Intelligence Centre, Faculty of Physics and Mathematical Sciences, Universidad de Chile, Santiago 8370397, Chile

Corresponding author: Fernando M Gonzalez, MD, Full Professor, Department of Nephrology, Faculty of Medicine, Universidad de Chile, Av. Salvador 486, Providencia, Santiago 7500922, Chile. fgonzalf@uc.cl

Abstract

Despite organ transplantation being the most successful treatment for end-stage organ dysfunction, the number of annual solid organ transplantations is much lower than that required to satisfy the demand of patients on waiting lists. The explanation for this phenomenon is the relative scarcity of non-living organ donors due to several factors, such as: (1) Late arrival of patients with a neurocritical condition to an emergency service; (2) lack of detection of those patients as possible organ donors by health professionals dedicated to procurement or by clinicians at emergency and intensive care units, for instance; (3) late transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support; (4) lack of confirmation of the physiological status of the possible donor; (5) late or incorrect positive diagnosis of the subject's death, either due to brain or cardiac death; (6) difficulty in obtaining legal authorization, either by direct relatives or by the authority, for the extraction of organs; and (7) deficient retrieval surgery of the organs actually donated. The recent reports of relatively successful xenotransplants from genetically modified pigs open the possibility to fix this mismatch between supply and demand, but some technical (organ rejection and opportunistic infections), and economic issues, still remain before accepting a progressive replacement of the organ sources for transplantation. An approximate economic cost analysis suggests that the hypothetical acquisition cost of any genetically modified pig derived organ is high and would not even satisfy the solid organ demand of the wealthiest countries.

Key Words: Organ donation; Xenotransplantation; Procurement; Kidney transplantation; Costs

Core Tip: The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: to maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

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INTRODUCTION

The recent promising xenotransplants derived from genetically modified pigs (heart and kidneys) will open a new discussion: To maintain and improve human non-living organ procurement or invest in the development of solid xenotransplant clinical services. Issues to be solved before reaching that point will be immunologic (preventing acute and chronic graft rejection), opportunistic infections from pigs (for example, porcine cytomegalovirus) and economic (how to finance and afford those technically complex organs for the population).

Solid organ transplantation has clearly improved medical performance in terms of the treatment of end-stage organ failure, as in the case of kidney, liver, or heart failure, among others. Consequently, it has improved the survival and quality of life of patients who suffer from those diseases[1]. Nevertheless, the main limitation in transplanting all patients in need is the availability of donors[2].

For many years it has been suggested that xenotransplantation might provide a solution to the imbalance between the demand and supply of organs for transplantation[3], but it has remained a theoretical option. The recent experiences of heart and kidney implants from genetically modified pigs, however, could mean that solving this imbalance may now be a real possibility and, therefore, it could mean that the activity of searching for and procuring organs, particularly from non-living donors, could decline[4-6].

However, this issue is still a subject of extensive technical considerations.

The prevalence of end-stage kidney, liver, or heart diseases increases as a country's population ages. Age-related chronic diseases appear along with this shift, and the medical treatments in use allow more patients to survive the acute phases of those diseases. As a consequence of this, as well as due to general improvement of road safety measures, potential organ donors no longer come from young subjects who die due to car accidents or trauma, but increasingly older adults and, often, with prevalent chronic diseases that reduce the functionality of the organs to be donated[7]. This could explain, in part, the asymmetries in organ donation rates in different countries, even when they are culturally similar, as occurs, for example, in those countries belonging to Latin America or those belonging to Western Europe[8].

If we analyze the figures of non-living donors in the world, we will see that there are marked differences between countries, ranging from 0.4 donors per million population (pmp) in the Dominican Republic or 4.4 pmp in Greece, to 38 pmp in the United States or Spain[8]. This implies that there are significant growth opportunities in the global procurement activity: Carrying out comparative studies of the realities of the procurement process between different countries and attempting to replicate the "best practices" of the leading countries could, as a conservative estimate, be enough to increase the global donation rate in America and Europe to 15-20 pmp, and could, thinking more ambitiously, be enough to even reach the leading countries[8].

The central question derived from the previous paragraph is why there are so many differences in countries' donation rates. In this regard, the procurement process (framed under a local legislation supportive towards organ donation) can be outlined as a series of stages that include: (1) Arrival of patients with a neurocritical condition (trauma or stroke, for example) to an emergency service; (2) Detection of that patient as a possible organ donor by health professionals dedicated to procurement (organ procurement organizations in the United States or procurement coordinators in Spain), or by clinicians at emergency and intensive care units, for instance; (3) Transfer of the patient to an intensive care unit to try to recover their health and to provide hemodynamic, ventilatory, and metabolic support (if there are critical beds available); (4) Confirmation of the physiological status of the possible donor and the organs to be donated — that is, the ruling out of pathological conditions that contraindicate the

subject as a potential donor (for example metastatic neoplastic disease, encephalitis due to transmissible viruses (rabies), and others); (5) Positive diagnosis of the subject's death, either due to brain or circulatory death; (6) Legal authorization, either by direct relatives or by the authority, for the retrieval of organs; and (7) Procurement surgery of the organs actually donated.

In any of these phases, effective donation is likely to be foiled. During the first year of the severe acute respiratory syndrome coronavirus 2 pandemic, in 2020, we witnessed a natural experiment in which it was possible to observe how the disease associated with the novel coronavirus disease 2019, reduced the arrival of patients with serious trauma or strokes to emergency services[9-11]; how hospitalizations in critical care units were reduced; and how the activity of local procurement units decreased, along with surgical retrieval activities and donation authorizations by family members[12]. These situations together explain why donation and transplant figures plummeted in several countries, including those in the United States and Spain[12,13].

If the failing stages of the process in each country could be improved, it would be feasible to increase their effective donation rates. For example, stage 1 could be improved with the implementation of rescue ambulance systems; stages 2 and 3 could be facilitated with the use of information technology [14]; stages 4 and 5 could benefit from the inclusion of trained professionals; and stage 6 could be improved by including experts in breaking bad news in the procurement team. These are general examples, but performing a careful benchmark analysis of the procurement stages in each country should provide even better improvement opportunities for each country, since the good initiatives observed in some countries could be adapted for other countries.

How much do the proposed improvements cost? Given that the main difficulty is setting up the procurement process and most of the countries have already carried out work to that end, the marginal cost should not be very high, since there would be no significant barriers to implementation of improvements from the economic point of view, and their cost could be easily apportioned by increasing organ implants and the savings that they imply for the health systems of each country.

On the other hand, we have the opportunity to use organs from animals with similarities to humans. Historically, at the beginning of the 20th century, xenotransplantation was conceived as the solution to replace failing organs[15]. However, all the experiences concluded that, although the surgical technique allowed the surgeons to successfully implant the organs, they irremediably did not function as a result of diffuse thrombosis in all the graft vessels. It was not until the second half of the same century when it was described that the cause of thrombosis was mediated by preformed antibodies in the recipients, against vascular antigens from the donor animal. This type of hyperacute rejection was impossible to overcome even with aggressive immunosuppression techniques in non-human models[16]. The second limitation was local thrombosis derived from immune aggression and an exaggerated activation of the complement system[17].

In fact, the cardiac graft implanted in January 2022 came from a transgenic pig with 10 genetic modifications: Three knock-outs of genes associated with cell membrane carbohydrates (galactose alpha-1,3-galactose, Sda blood group antigen and N-glycolylneuraminic acid), a knock-out for the growth hormone receptor, increased expression of CD-46 antigens and "decay accelerating factor" to mitigate the activation of the complement system, expression of thrombomodulin and protein C genes to reduce thrombogenicity, and finally, anti-inflammatory proteins CD-47 and heme-oxygenase-1[5]. The three kidneys implanted on similar dates somewhat later had similar genetic modifications, although in smaller numbers[4,6]. In all these cases, neither hyperacute rejection nor massive intraparenchymal thrombosis occurred, although elements of thrombotic microangiopathy were indeed observed. An additional element which requires cautious is the eventual transmission of infectious agents typical of pigs, such as the porcine-derived retrovirus, or the porcine cytomegalovirus, among others[4-6].

Despite these complications and the disastrous outcome of the recipient with the heart graft, these preliminary experiences are certainly auspicious and appropriate clinical studies will surely elucidate the real usefulness of xenotransplants from genetically modified pigs raised in highly controlled environments.

Assuming that this new xenotransplantation continues to develop favorably, one wonders how much each organ will cost and how many real patients it will benefit, with "real patients" being those who are not part of a clinical trial and who, therefore, must pay (themselves or their insurers) for the xenotransplantation and its associated pharmacological treatments.

One way to calculate the aforementioned cost could be using the economic benefit for society of transplantation with a traditional non-living donor as a reference, and based on these numbers, roughly estimate the value that each heart or kidney could have.

The cost per quality adjusted life year (QALY) of a heart transplant in someone who is on the waiting list receiving exclusive pharmacological therapy is close to US$97000, a figure that increases to US$226000 if the person waiting is connected to a left ventricular assist device[18]. If we consider that in the United States a figure of US$100000/QALY is considered acceptable for a heart transplant, this treatment would be economically viable only in the first group of patients and would therefore force transplant teams to enroll those who suffer from advanced heart failure early. For kidney transplantation, the cost per QALY is slightly less than US$50000[19,20].

Table 1 Organ procurement process and opportunities for improvement

Process	Improving opportunities
(1) Arrival of patients with a neurocritical condition to an emergency service	Implementation and improvement of rescue ambulance systems
(2) Identification as a possible organ donor by health professionals	Training health professionals, use of information technology
(3) Transfer to an intensive care unit to provide full support	Use of information technology, critical care bed selective dedication
(4) Confirmation of suitability to be a donor	Inclusion of trained health professionals
(5) Diagnosis of the subject's death, either due to brain or circulatory death	Availability of on-site neurologists and perfusionist specialists.
(6) Procurement surgery of the organs actually donated	Inclusion of experts in breaking bad news in the procurement team

The problem is, however, that the US$100000/QALY threshold is not necessarily valid for other countries. In fact, the willingness to pay of each country is correlated with its gross domestic product (GDP) per capita and, therefore, the cost-effectiveness analyses and the QALYs improved by a successful transplant should be adjusted for each country. By doing this, it becomes clear that the US$100000 for the United States does not compare fairly with the US$ < 10000 for Thailand or the US$20000-30000 for various South American and European countries which, in turn, also have lower GDP per capita[21].

The implications of the economic data presented are that the price to be paid for a desirable new good correlates with the expected benefit that good is estimated to provide. The price to be paid also correlates with the need for the return on investment demanded by the shareholders who own the companies that develop these improved goods. Finally, these two figures should be adjusted for the risk that such assets have to be successful in the market[22]. If we use the market price of onasemnogene abeparvovec-xioi for spinal muscular atrophy of €1.9 million as a reference, we may find that an independently calculated price would be close to €1.7 million[22]. The €200.000 (10% of €1.9 million) difference between both prices is, in the best of cases, an error in the calculation methodology or, in the worst scenario, an appropriation of "consumer surplus". The latter could imply that the price of an organ from a genetically modified pig would be close to the total QALY gained from the transplant (QALY/year multiplied by additional years of graft or host survival) plus a "consumer surplus" of 10%, which could be no less than US$500000 for a heart or US$250000 for a kidney (assuming that both grafts last only 5 years, which is a very conservative estimate) which, obviously, could be paid by very few people only from the wealthiest countries and certainly even the world strongest public health systems could not finance those transplants[21].

CONCLUSION

So, going back to our initial question: Is the near coming xenotransplantation era relieving us from having to look for more non-living organ donors? Our answer is "not at the moment"; even thinking that xenotransplants will have the same survival as allografts from human donors, their market prices will be prohibitive in many countries, forcing those countries to necessarily continue improving their actual procurement processes from non-living human donors (Table 1). Wealthy countries, however, are likely to be able to improve their transplant rates, at least in the short term, with organs from genetically modified pigs raised in highly controlled environments. Nevertheless, as the xenotransplantation technology and production processes improve, the prices will decrease allowing more consumers to afford a genetically modified xenograft. We did not include a discussion on allografts from living donors as besides the costs, it raises an ethical dilemma that was out of our scope.

FOOTNOTES

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Palak Patel, Department of Cardiology, West Roxbury VA Center, West Roxbury, MA 02132, United States

Nirav Patel, Department of Cardiology, University of Connecticut, Harford Hospital, Hartford, CT 06102, United States

Nirav Patel, Department of Cardiology, University of California, CA 90065, United States

Fahad Ahmed, Department of Internal Medicine, Hartford Hospital, Hartford, CT 06106, United States

Jason Gluck, Advanced Heart Failure, Hartford Hospital, Hartford, CT 06102, United States

Corresponding author: Jason Gluck, DO, FACC, Attending Doctor, Chief Physician, Advanced Heart Failure, Hartford Hospital, 85 Seymour Street, Hartford, CT 06102, United States. jason.gluck@hhchealth.org

Abstract

Significant scarcity of a donor pool exists for heart transplantation (HT) as the prevalence of patients with end-stage refractory heart failure is increasing exceptionally. With the discovery of effective direct-acting antiviral and favorable short-term outcomes following HT, the hearts from hepatitis C virus (HCV) patient are being utilized to increase the donor pool. Short-term outcomes with regards to graft function, coronary artery vasculopathy, and kidney and liver disease is comparable in HCV-negative recipients undergoing HT from HCV-positive donors compared to HCV-negative donors. A significant high incidence of donor-derived HCV transmission was observed with great success of achieving sustained viral response with the use of direct-acting antivirals. By accepting HCV-positive organs, the donor pool has expanded with younger donors, a shorter waitlist time, and a reduction in waitlist mortality. However, the long-term outcomes and impact of specific HCV genotypes remains to be seen. We reviewed the current literature on HT from HCV-positive donors.

Key Words: Heart transplant; Hepatitis C-positive donors; Direct-acting antiviral; Coronary allograft vasculopathy; Allograft rejection

Core Tip: Given the favorable preliminary data and ongoing opioid epidemic, the utilization of hepatitis C virus-positive hearts is on the rise, which is aiding in the closure of the gap between heart transplantation candidates and donors. Additionally, with future studies evaluating long-term outcomes and standardization of direct-acting antiviral therapy, more transplant centers will accept hepatitis C virus-positive organs.

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INTRODUCTION

Heart failure (HF) prevalence is increasing, with 6.2 million adults diagnosed from 2013 to 2016 compared to 5.7 million from 2009 to 2013. The prevalence is estimated to increase to more than 8 million by 2030[1,2]. In 10%-15% of patients, end-stage refractory HF will develop requiring advanced therapies including orthotopic heart transplantation (OHT) or durable mechanical support therapies[2,3]. There is a substantial mismatch between donors and recipients as there is an increasing prevalence of HF over the years with a constant rate of OHTs performed. During 2018, 268 patients died while waiting for OHT with 3883 patients being added to the transplant list and 3440 OHTs performed[4]. Expanding the donor pool with utilization of organs from hepatitis C virus (HCV)-positive individuals is an opportunity to close this gap.

Historically, HCV-positive donors were not considered due to high risk of HCV transmission, ineffective and unsafe HCV treatments, and overall inferior survival following heart transplantation (HT)[5,6]. With the discovery of direct-acting antivirals (DAAs), the donor pool has expanded with the addition of HCV-positive donors due to great success of treating HCV, limited interaction with immunosuppression, and optimal short-term outcomes following HT. Data of long-term outcomes are scarce, and there is a wide variation with the use of different DAA agents and optimal initiation among the studies. Therefore, we reviewed the current literature of HT from HCV-positive donors in HCV-negative recipients and discussed the epidemiology, outcomes of HT in the pre- and post-DAA era, complications, and potential barriers for more widespread utilization of HCV-positive donors.

MATERIALS AND METHODS

We searched the terms "heart transplant," "organ transplant," "transplant," and "hepatitis C" in various combinations in Medline through November 2021.

DONOR HCV STATUS CLASSIFICATION

HCV infection in donors can be classified using two serological markers: HCV antibodies (Ab), which typically present after 6-8 wk of exposure to HCV[7]; and nucleic acid testing (NAT), which is present during an active infection occurring after 3-4 d of exposure to HCV[8,9].

HCV Ab-positive NAT-negative

Donors that are HCV Ab-positive and NAT-negative have spontaneously cleared the virus or were treated with antiretrovirals. There is low to no risk of transmission of the virus to the HT recipient[10,11].

HCV Ab-positive NAT-positive

Donors that are HCV Ab-positive and NAT-positive have an ongoing infection or chronic active hepatitis. There is a high risk of HCV transmission to the HT recipient.

HCV Ab-negative NAT-positive

Donors that are HCV Ab-negative and NAT-positive have an acute HCV infection without adequate time for Ab production against HCV. There is a high risk of transmission in solid organ transplant recipients.

HCV Ab-negative NAT-negative

Donors that are HCV Ab-negative and NAT-negative are in the eclipse period (within a week) of acquisition of HCV when NAT is not detectable with negative HCV Ab. This serological classification typically includes high-risk donors and intravenous drug users (IVDU). The potential of such donors is 32.4 per 10000 in the United States[12].

EPIDEMIOLOGY AND HCV-POSITIVE DONOR POOL

HCV, a single-stranded RNA virus, is the most frequent blood-borne infection common among IVDUs [13,14]. The World Health Organization reports that the HCV worldwide prevalence is 71 million with an annual incidence of 50300 in 2018 in the United States and a 3-fold increase from 2009 to 2018 with a rate of 0.3 to 1.2 per 100000 population[15].

The prevalence of HCV infection among IVDUs increased from 28% in 2008 to 40% in 2015 in North America[14,16], and it is estimated to increase by 43% by 2030[17]. The pool of HCV-positive donors is increasing by 10-fold due to the current opioid epidemic in the United States and to the increase in deaths related to overdose since 2000, which is on the rise from 15.1% in 2010 to 26.1% in 2018[18]. In 2020, 81230 deaths due to opioid overdose increased by 38.4% over a 12-mo period from June 2019 to May 2020. These younger victims without significant comorbidities are a potential for prolonged organ survival following HT[19,20]. The United Network of Organ Sharing reported HT from HCV-positive donors is on the rise from 247 to 362 HT from HCV-positive donors from 2018 to 2019. A single center reported doubling their transplant volume by utilizing HCV-positive hearts from 130 to 260 from 2013 to 2018, with a reduced mean waiting period of 4 d[21]. Nationwide utilization of HCV-positive donors can increase the number of HTs resulting in reduction in the waiting period and closing the gap between donors and recipients.

HCV-POSITIVE TRANSPLANT IN THE PRE-DAA ERA

Limited data are available on HT from HCV-positive donors in the pre-DAA era (Table 1)[5,22-31]. Studies reported a high transmission rate of HCV with an inferior survival rate of 70% at 1 year compared to 89% in controls[5] and a 10-year survival rate of 25% in the HCV-positive group *vs* 53% in controls[31] due to a higher incidence of cardiac allograft rejections, cardiac allograft vasculopathy, progression to chronic HCV infection, and liver disease[5]. Haji *et al*[30] reported HCV seropositivity as an independent risk factor for overall mortality by 2.8-fold and increased incidence of cardiac allograft vasculopathy by 3-fold. Historically, interferon-based therapy was being utilized for HCV infection, which demonstrated poor tolerability and a risk of interaction with immunosuppressants[32]. Due to these complications and decreased overall survival, the use of HCV-positive donors diminished until recent years following the discovery of DAAs.

HCV-POSITIVE TRANSPLANT IN THE POST-DAA ERA

In 2011, DAAs were introduced demonstrating high efficacy in eradicating HCV and achieving remission[33]. In 2013, the combination of sofosbuvir and simeprevir achieved 92% sustained virologic response (SVR) at 12 wk after completion of the antiretroviral regimen without the addition of historical medications such as interferon and ribavirin[34]. In 2014, a four-drug combination was approved for acute HCV infection with ombitasvir, paritaprevir, ritonavir, and dasabuvir, which achieved 100% SVR [35]. These DAAs used in post-transplant recipients achieved comparable SVR to non-transplanted patients[11,33,36-38]. The overall survival in HCV-negative recipients receiving hearts from HCV-positive donors is comparable to HCV-negative donors (Table 2)[10,11,21,33,36,37,39-52].

POTENTIAL COMPLICATIONS OF HT IN HCV-NEGATIVE RECIPIENT FROM HCV-POSITIVE DONOR

HCV contraction

HCV contraction is 82% to 100% from HCV NAT-positive donors. Schlendorf *et al*[11] demonstrated 95.7% of donor-derived HCV from HCV NAT-positive donors, and the risk of acquiring HCV from HCV Ab-positive and NAT-negative donors is low. One study demonstrated no viremia up to 1 year in 10 HCV-negative recipients receiving hearts from NAT-negative donors[11]. The risk of developing HCV is variable across all the studies, but it appears to be reduced with the use of HCV NAT-negative

Table 1 Heart transplantation from hepatitis C virus-positive donors in the pre-direct-acting antivirals era

Ref.	Study type	Study group	Outcome
Pereira *et al*[22], 1991	Retrospective, observational	6 HCV-negative recipients underwent HT from HCV Ab-positive donors	50% of recipients acquired HCV infection and higher incidence of liver disease was noted
Hayashi *et al*[23], 1994	Case Report	46-yr-old male with end- stage cardiomyopathy receiving HT from HCV Ab-positive donor	Fulminant liver failure and patient died in less than 2 yr
Lim *et al*[24], 1994	Case Report	51-yr-old male undergoing HT from HCV Ab-positive donor	Fulminant hepatitis, which was treated successfully with interferon-based therapy; Died due to pulmonary aspergillosis
Zein *et al*[25], 1995	Observational	1 HCV-negative recipient underwent HT from HCV Ab-positive donors	Cholestatic liver disease and liver failure-related mortality
Pfau *et al*[26], 2000	Retrospective	5 recipients without HCV infection underwent HT with HCV Ab-positive donors	1 out of 5 recipients became HCV Ab-positive; Elevated liver enzymes were noted and normalized by 12 mo
Marelli *et al*[27], 2002	Retrospective	20 recipients (10 were status I and 10 were status II) without HCV infection underwent HT from HCV NAT-positive donors	Overall survival was 90% in status I and 80% in status II group; Higher incidence of rejection and CAV were noted
File *et al*[5], 2003	Retrospective	10 recipients without HCV infection underwent HT from HCV-positive and NAT-positive	All recipients became HCV NAT-positive, 6 out of 9 recipients developed hepatitis and severe liver injury occurring in 2 patients; Inferior survival of 70% was noted
Gudmundsson *et al*[28], 2003	Retrospective	7 recipients without HCV infection underwent HT from HCV Ab-positive donors	Overall 5-yr survival was 71.4%; 3 developed chronic active hepatitis, 1 died from liver failure
Wang *et al*[29], 2004	Retrospective	4 recipients without HCV infection underwent HT with HCV Ab-positive donors	1 recipient became HCV Ab-positive without clinical hepatitis
Haji *et al*[30], 2004	Retrospective	34 recipients without HCV infection underwent HT from HCV Ab-positive donors and evaluated overall mortality and CAV	75% of recipients became HCV seropositive; Higher mortality by 2.8-fold and accelerated CAV by 3.0-fold was noted compared to the control group
Gasink *et al*[31], 2006	Retrospective, registry-based, cohort	261 recipients without HCV infection underwent HT with HCV Ab-positive donor	Overall inferior 1-yr, 5-yr, and 10-yr survival compared to control; Higher incidence of liver disease and CAV were noted

Ab: Antibodies; CAV: Cardiac allograft vasculopathy; HT: Heart transplant; HCV: Hepatitis C Virus; NAT: Nucleic acid test.

donors compared to HCV NAT-positive donors. All patients with donor-derived HCV achieved SVR across all studies with DAA treatment.

Cardiac allograft rejection

Transplant allograft rejection, either cellular or antibody-mediated, is associated with poor allograft survival and increased mortality[53]. In the pre-DAA era, the studies demonstrated an increased rate of allograft rejection in HT recipients from HCV-positive donors, and the risk was directly associated with viremia post-HT[5,27,54]. Two potential pathways are linked with allograft rejection from HCV infection. The first is the activation of lymphocytes, predominately T cells, through direct and indirect pathways affecting the endothelium, and the second is direct allograft injury is mediated by upregulation of interferon-alpha and apoptotic and proliferative genes[55].

The incidence of allograft rejection was 58% in 12 HCV-negative recipients undergoing HT from HCV NAT-positive donors compared to 30% in 13 HCV NAT-negative donors with a mean follow-up of 147 d[56]. Another study demonstrated allograft rejection of 12% and 3% in HCV-negative recipients from HCV Ab-positive NAT-positive compared to HCV Ab-positive NAT-negative donors at 180 d follow-up, respectively. The time to first event of rejection was earlier in recipients with NAT-positive compared to NAT-negative donors demonstrating viremia directly played a role in acute allograft rejection[54]. Schlendorf *et al*[42] reported two events of acute cellular rejection requiring treatment in recipients who became viremic at a mean of 4 d, and the initiation of DAAs was delayed as they were introduced on an outpatient basis at a mean of 33 d. Therefore, early detection and aggressive implementation of DAAs are required to decrease the incidence of allograft rejection. Overall short-term survival in the current era is similar, but the long-term risk of allograft rejection remains to be seen.

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) is the major cause of morbidity and mortality following HT with an incidence of 8% at 1-year and 50% at 10-year[57], and the risk of CAV is increased by 3-fold in donor-derived HCV recipients[30]. The pathophysiology of CAV is not completely understood but presumed to be immune-mediated endothelial injuries observed with elevated intracellular adhesion molecule-1 in HCV-infected patients[58]. The risk was observed to be further increased with B cell cross-reactivity in

Table 2 Heart transplantation from hepatitis C virus-positive donors in the post-direct-acting antivirals era

Ref.	Study type	Study group	Outcome
Gottlieb *et al* [33], 2017	Case report	1 recipient without HCV infection underwent HT with HCV NAT-positive donor; treated with sofosbuvir/velpatasvir for 12 wk	A recipient acquired HCV infection on day 9, and it was cured at 12 wk
Jawad *et al* [39], 2018	Case report	1 recipient without HCV infection underwent HT with HCV-positive donor; in 2014, after approval of DAA, the patient was treated with sofosbuvir and daclatasvir for 8 mo	Patient acquired HCV infection in 2010 without any clinical sequelae and with treatment of DAA in 2014 it was eradicated; Progressive CAV was noted
Moayedi *et al* [40], 2018	Single center, single arm	2 recipients without HCV infection underwent HT with HCV NAT-positive donors	Low cost of HCV treatment compared to alternative treatment with mechanical cardiac support; Potential for 300-500 more HT annually noted
Moayedi *et al* [41], 2018	Retrospective, registry-based	From 2013 to 2017, 64 (5%) underwent HT from HCV-positive donors; Total of 1305 HCV-positive donors were recovered during this time period	Comparable survival was noted in recipients of HCV-positive donors to HCV-negative donors
Patel *et al*[10], 2018	Single center, single arm case series	14 HCV-negative recipients underwent HT in 2017 from HCV Ab-positive and NAT-negative donors	None developed HCV infection
Schlendorf *et al*[42], 2018	Single center, single arm prospective observational case series	13 HCV-negative (1 was treated) recipients underwent HT from HCV-positive donors and treated with DAA	69% of these recipients acquired HCV, and all of them achieved SVR following therapy with DAA except 1 who died due to pulmonary embolism
McLean *et al* [36], 2019	Single arm, single centered, prospective case series	10 HCV-negative recipients underwent HT with HCV NAT-positive donors, treated with elbasvir/grazoprevir after viral detection	Overall 9/10 recipients achieve SVR following DAA; 1 recipient died due to Ab cross-match leading to rejection, graft failure, and multiorgan failure
Woolley *et al* [43], 2019	Non-randomized, single center, prospective trial	8 HCV-negative recipients underwent HT from HCV NAT-positive donors; Treated with sofosbuvir-velpatasvir for 4 wk; Overall survival was compared to 12 recipients undergoing HT from HCV-negative donors	100% SVR was noted; Comparable survival rate at 12 mo in both groups
Frager *et al* [44], 2019	Single arm, single center, prospective trial	6 HCV-negative recipients underwent HT from HCV NAT-positive donors; multiple regimens of DAA were implemented	4 achieved SVR; 5 with 1R-2R rejection and 2 with stable chronic kidney disease; Decreased time on the waiting list noted
Schlendrof *et al*[11], 2019	Single arm, single center, prospective observational case series with a 1-year follow-up	80 HCV-negative recipients underwent HT from HCV Ab-positive and/or NAT-negative donors; Multiple DAA regimens utilized	95.7% of recipients acquired HCV infection from donors with HCV NAT-positive; DAA SVR was achieved in all recipients; No recipients acquired donor-derived HCV from NAT-negative recipients; Comparable 1-yr survival of 90.7% in both groups, and median wait time of 4 d was noted
Reyentovich *et al*[37], 2019	Non-randomized, single center, prospective observational case series	12 HCV-negative recipients underwent HT with HCV NAT-positive donors treated with glecaprevir/pibrentasvir for 8 wk compared to 13 controls undergoing HT from HCV-negative donors	Equivalent survival rate in both groups; Mean waiting period of 62 d noted
Aslam *et al* [45], 2019	Retrospective, single center, observational	21 HCV-negative recipients underwent HT with HCV Ab-positive and NAT-negative or positive donors	All recipients of NAT-positive donors acquired HCV infection; With DAA treatment 100% SVR was achieved; All recipients (2/2) were Ab-positive but NAT-negative and did not acquire HCV infection
Morris *et al* [46], 2019	Single center, retrospective	25 HCV-negative recipients underwent HT from HCV Ab-positive and NAT-positive (n = 23) or negative (n = 2) donors; DAA regimen was implemented, and outcomes were compared to 37 recipients undergoing HT from HCV- negative donors	22 of 23 recipients received hearts from HCV viremia acquired HCV infection; No difference in overall survival, rejection, hospitalization, and CAV between 2 groups; Delay in HCV treatment was due to insurance coverage
Lebeis *et al* [47], 2019	Single center, retrospective	23 HCV-negative recipients underwent HT with HCV-positive donors compared to control group receiving hearts from HCV donors	Recipients receiving preemptive treatment with DAA had preserved early allograft function receiving hearts from HCV-positive donors
Gaj *et al*[48], 2019	Single center, retrospective	Baseline characteristics were assessed in 111 HT; 23 of these organs came from HCV-positive donors	20% of recipients underwent HT from HCV-positive donors, and the donors were younger with a mean of 37 compared to 40 yr old; Short-term outcomes were similar in both groups
Kilic *et al*[21], 2020	Multicenter, retrospective, registry-based	Of 7889 HT, 343 HCV-negative recipients received hearts from HCV-positive donors	1-yr survival rate was indifferent between 2 groups; From 2016-2018, 28% of transplant centers utilized HCV-positive donors
Zhu *et al*[49], 2020	Single center, retrospective	10 HCV-negative recipients underwent HT from HCV-positive donors between 1997-2019	1-yr survival was 80%; 4 recipients acquired donor-derived HCV, and 3 of them demonstrated cure with DAA treatment

McMaster *et al* [50], 2020	Single center, retrospective	12 HCV-negative recipients underwent combined heart and kidney transplant from HCV Ab-positive and 10/12 were NAT-positive donors and were compared to 27 HCV-negative donors	A shorter median waitlist time for HCV-positive organs; Both groups had similar perioperative cardiac and renal function; Creatinine was higher in HCV-positive recipients at 3 mo compared to the control group, but at 1-yr it was similar in both groups; 80% of recipients acquired donor-derived HCV infection, and with DAA treatment 100% SVR was noted
Zalawadiya *et al*[51], 2020	Single center, retrospective	45 HCV-negative recipients underwent HT between 2016-2018 from HCV Ab-positive and NAT-positive donors; Renal function was assessed following transplantation	Data from 23 recipients were available at 12 wk and 18 recipients at 1 yr; No significant change in renal function up to 1-yr was noted
Reyentovich e *et al*[52], 2020	Single center prospective observational	22 HCV-negative recipients underwent HT between 2018-2019 from HCV NAT-positive donors; Data were compared to 28 HCV NAT-negative recipients	All recipients acquired donor-derived HCV; 20 recipients achieved 100% SVR following DAA therapy; Comparable outcomes with Ab-mediated rejection in both groups

Ab: Antibodies; CAV: Cardiac allograft vasculopathy; DAA: Direct acting antiretroviral; HT: Heart transplant; HCV: Hepatitis C Virus; NAT: Nucleic acid test; SVR: Systemic viral response.

HCV-positive heart recipients[30]. CAV has been associated with increased alloimmune response[59,60]. CAV directly affects the longevity of the graft, but treatment with DAAs rapidly clears viremia, and studies have demonstrated no statistically significant risk of CAV at 1 year following HT from HCV-positive donors[11,59]. Zalawadiya *et al*[61] reviewed intracoronary ultrasound of 54 HCV-negative recipients from HCV-positive hearts treated with ledipasvir and sofosbuvir for 12 or 24 wk following HT and up to 1-year follow-up. They found no significant difference in CAV compared to the control group. Schlendrof *et al*[11] also showed that 29 recipients receiving hearts from HCV-positive donors had no statistically significant incidence of CAV compared to HCV-negative donors. All current studies are single centered and small sample size with short-term follow-up of 1 year. However, compared to the pre-DAA era, the evidence shows that there is a decreased reduction in the incidence of CAV secondary to rapid and effective clearance of HCV with DAA-based therapy. Long-term risk of CAV and its impact on graft survival remains to be explored.

Liver disease

A higher incidence of liver disease was noted in the pre-DAA era attributing to increased mortality in HCV-positive recipients[31]. HCV is a known cause of progressive liver disease leading to liver cirrhosis and risk of hepatocellular carcinoma (HCC)[62]. Early eradication of HCV reverses the liver damage that is caused by inflammation from HCV and decreases the incidence of downstream effects. Untreated HCV in transplant patients resulted in fulminant liver failure, cholestatic liver disease, and chronic hepatitis[23-25].

Pre-DAA recipients receiving hearts from HCV-positive donors had higher liver-related mortality with a hazard ratio of 5.9[63]. In immunocompromised hosts, the progression to advanced liver disease and cirrhosis was accelerated by a median of 2 years to 10 years compared to 30 years in immunocompetent individuals[64], and the recipients receiving an anti-lymphocyte preparation peritransplant had a higher risk of liver disease[22].

HCV has 6 different genotypes, with 1 to 4 being the most the common worldwide[65,66]. Genotype 1b and 3b are associated with a higher rate of liver disease compared to other genotypes[67,68]. Genotype 2 carriers have an improved overall HCC survival, and other genotypes can lead to progressive liver disease and HCC[69]. Both antiviral therapies, including interferon and DAAs, reduce the risk of HCC following achievement of SVR[70], but DAAs are more tolerable and efficacious compared to interferon[71]. All HCV genotypes can be responsive with various combinations of DAA treatment. However, relapse of HCV has been observed after DAA treatment[72,73].

DAA in HT recipients

No data are available on the optimal initiation for DAA-therapies following HT. However, recent studies report an increased risk of rejection with delayed treatment[54]. Empirical initiation of DAAs have decreased the viral load and shown the rapid clearance of HCV in 10 d[74]. Hence, early initiation of DAAs post-transplant while in the hospital should be highly encouraged[11,75]. Fluctuating kidney function following HT limits the use of DAAs as some agents like sofosbuvir may adversely affect kidney function, but DAAs have been used successfully in renal transplant recipients with no impact on renal function[51].

DAAs are well tolerated with no major adverse effects, and recipients typically suffer from self-limiting constitutional symptoms like headaches, fatigue, or insomnia[75]. Overall cost of a 12-wk course of DAAs are expensive, ranging from $80000 to $100000, but recently the cost has been reduced to as low as $30000 in 2020[33,40,49]. This is far less compared to the cost of a mechanical cardiac support device with an average cost of hospitalization of $726000 and a yearly cost ranging from $30000 to $80000 for follow-up and maintenance[32,76]. The burden of caring for durable mechanical support

by the patient and their families should also be noted.

Overall survival

In the pre-DAA era, the overall mortality was increased by 2-fold in recipients receiving hearts from HCV-positive donors[5,6]. With the effective treatment against HCV with DAAs, the 1-year survival rate is 90.4% in HCV-positive recipients similar to HCV-negative recipients[37,48,61]. However, there is a scarcity of available data beyond 1 year. Larger studies are currently ongoing for evaluating long-term outcomes[11,37]. The average waiting period for HT is reduced and thereby decreasing waiting list mortality[11,37]. Data on multiorgan transplants are limited. McMaster *et al*[50] demonstrated equivalent survival rates in combined heart and kidney transplants with preservation of renal function[48-50].

Future of HCV-positive donor utilization

The studies have demonstrated comparable 1-year outcomes following HT from HCV-positive donors compared to HCV-negative donors with a potential for younger donors[47]. Generally, the recipients have an uncomplicated course following HT with rapid clearance of viremia with the use of DAAs with minimal interactions with immunosuppressants and few side effects[77,78]. One-year outcomes of HT recipients from HCV-positive donors are encouraging, but further studies are needed to evaluate the risk of allograft rejection, development of CAV, long-term sequela of liver disease and potential HCC risk, HCV genotype-specific effects, and recurrence of HCV and its impact on morbidity and mortality beyond the 1st year. In 2020, only 28% of the transplant centers were utilizing HCV-positive hearts[21], but with more experience and reassuring long-term outcomes, more transplant centers will begin accept HCV-positive organs.

CONCLUSION

As the IVDUs and opioid epidemic is on the rise in the United States, the donor pool, including HCV-positive hearts is going to increase in the coming years. With highly effective DAA therapy and comparable short-term outcomes following HT, it is reasonable to utilize these organs to meet the increasing prevalence of end-stage refractory HF patients. However, a multidisciplinary team approach and close monitoring of these recipients are needed with close observation for long-term sequelae.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Palak Patel 0000-0001-7136-7633; Nirav Patel 0000-0001-7797-7248; Jason Gluck 0000-0002-9123-830X.

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ORIGINAL ARTICLE

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Bakytbek Mankiev, Sanem Guler Cimen, Ismail Oskay Kaya, Sertac Cimen, Asir Eraslan

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Bakytbek Mankiev, Sanem Guler Cimen, Department of General Surgery, Sağlık Bilimleri Üniversitesi, Ankara 65100, Turkey

Ismail Oskay Kaya, Departments of Surgery, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara 65100, Turkey

Sertac Cimen, Department of Urology, Saglık Bilimleri Universitesi, Ankara 65100, Turkey

Asir Eraslan, Department of Urology, Somalia Turkish Training and Research Hospital, Mogadishu 23451, Somalia

Corresponding author: Sanem Guler Cimen, Doctor, FEBS, Adjunct Associate Professor, Department of General Surgery, Sağlık Bilimleri Üniversitesi, Altindag, Ankara 65100, Turkey. sanem.cimen@sbu.edu.tr

Abstract

BACKGROUND

Over the last few years, the deceased donor organ donation rate was declined or remained stable, whereas the live donor organ donation rate has increased to compensate for the demand. Minimally invasive techniques for live donor nephrectomy (LDN) have also improved the live donor kidney donation rates. This increase has led to an interest in the surgical procedures used for LDN.

AIM

To evaluate the LDN techniques performed in Turkey, the structure of surgical teams, and the training received. Additionally, the number of kidney transplantations at different centers, the surgeon experience level, differences in surgical approach during donor surgeries, and outcomes were assessed.

METHODS

A questionnaire was sent to the Turkish Ministry of Health-accredited transplant centers. It inquired of the number of LDN surgeries, surgical techniques, complications, optimization protocols, the experience of surgeons, and the training. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum), while categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann Whitney *U* test and the χ^2 test.

RESULTS

The questionnaire was sent to 72 transplant centers, all of which replied. Five centers that reported not performing LDN procedures were excluded. Responses from the remaining 67 centers were analyzed. In 2019, the median number of kidney transplants performed was 45, and the median number of kidney transplants from living donors was 28 (1-238). Eleven (16.5%) centers performed 5-10, while 34 (50.7%) centers performed more than 100 live donor kidney transplants in 2019. While 19 (28.4%) centers performed the LDN procedures using the open technique, 48 (71.6%) centers implemented minimally invasive techniques. Among the centers preferring minimally invasive techniques for LDN, eight (16.6%) used more than one surgical technique. The most and the least common surgical techniques were transperitoneal laparoscopic (43 centers, 89.6%) and single port laparoscopic LDN (1 center, 2.1%) techniques, respectively. A positive association was found between the performance of minimally invasive techniques and the case volume of a transplant center, both in the total number and live donor kidney transplants (15 *vs* 55, $P = 0.001$ and 9 *vs* 42, $P \leq 0001$ respectively). The most frequently reported complication was postoperative atelectasis ($n = 33$, 49.2%). There was no difference between the techniques concerning complications except for the chyle leak.

CONCLUSION

Turkish transplant centers performed LDN surgeries successfully through various techniques. Centers implementing minimally invasive techniques had a relatively higher number of live donor kidney transplants in 2019.

Key Words: Kidney donation; Live donor nephrectomy; Laparoscopic donor nephrectomy; Donor complications; Minimally invasive techniques; Donation rate

Core Tip: This study showed that centers using minimally invasive techniques had a relatively higher number of live donor kidney transplants in 2019. It also demonstrated that Turkish transplant teams performed live donor nephrectomy surgeries successfully through various techniques by considering that donor safety and center experience were the essential determinants when selecting the optimal approach for each donor.

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INTRODUCTION

Over the last few years, deceased donor organ donations have decreased[1]. In 2019, the overall organ donation rate was 46.5 per million population in Turkey[2]. This figure demonstrated a decline from the preceding years. However, this decline was less remarkable than in other European countries since live organ donation was promoted to compensate for demand. In line with this, countries like Turkey reported a rise in the number of living donor kidney transplantations during the pandemic. In 2019 according to the Turkish Ministry of Health data, 3963 kidney transplantations were performed in Turkey[2]. Among these patients, 3548 were transplanted from live donors. This increased living donor rate stimulated interest in Turkey's surgical techniques and live donor nephrectomy (LDN) practices.

The introduction of laparoscopic donor nephrectomy was by Ratner *et al*[3]. Various minimally invasive techniques have been described and performed for live kidney donation. These include hand-assisted laparoscopic, retroperitoneoscopic, single port, natural orifice, and robotic nephrectomy techniques[4]. Meanwhile, the open donor nephrectomy technique remained a gold standard for patients with variant anatomies and previous abdominal surgeries. Studies conducted in Europe and the United States showed that minimally invasive donor nephrectomy improved the live kidney donation rates[5,6]. Due to shorter recovery time, less post-surgical pain, and better cosmetic results, live kidney donors preferred minimally invasive techniques. Therefore, many transplant centers implemented these techniques with considerable success.

Despite the high number of live donor kidney transplantations in Turkey, the surgical techniques for LDN have not been widely studied. This study evaluates the LDN techniques performed in Turkey, the structure of surgical teams, and the training received. Additionally, the number of kidney transplant-

ations at different centers, the surgeon experience level, differences in surgical approach during donor surgeries, and outcomes were assessed.

MATERIALS AND METHODS

This study was conducted by the University of Health Sciences, Diskapi Training and Research Hospital, Department of Surgery after approval from the institutional ethical review committee (83/06). A previously used questionnaire to screen kidney transplant centers in Europe was modified for Turkish transplant centers and used for study purposes[7]. The questionnaire was prepared using online survey software (SurveyMonkey®, California, United States). It was sent *via* e-mail to the transplant surgeon, nephrologist, or urologist working in the transplant centers registered with the Turkish Ministry of Health. The e-mail addresses were retrieved from the Turkish Ministry of Health database and several national transplant society websites.

In May 2020, the first round of questionnaires was sent out, while the second round was sent in September 2020. Data collection was closed after the last questionnaire was received on December 2, 2020. The questionnaire consisted of questions regarding the number of living donor nephrectomies performed in 2019, surgical techniques used, the experience of primary surgeons, and the training they had received. Data regarding average blood loss, donor warm ischemia time (DWIT), surgical complications, preferred nephrectomy side, and kidney extraction site were also interrogated. All donors included in the study were live and related to the recipient.

Statistical analysis

Data analysis was performed using IBM SPSS (Statistical Package for Social Sciences) Statistics 17.0 (IBM Corporation, Armonk, NY, United States) software. The Shapiro-Wilk test was used to determine whether the distribution of discrete numerical variables was close to normal. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum); and categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in terms of discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann-Whitney *U* test. In the 2 × 2 cross-tabs, if the expected frequency was below 5 in at least one-quarter of the cells, the categorical data were evaluated by Fisher's exact probability test. The χ^2 test with continuity correction was used when the expected frequency was between 5-25. If no more than one-fifth of the cells had expected values equal to or less than 5, the categorical data were evaluated using the Fisher-Freeman Halton test. For $P < 0.05$, the results were considered statistically significant.

RESULTS

The questionnaire was sent to 72 kidney transplant centers, all of which replied. Five centers that reported not performing live donor kidney transplants were excluded. The responses from the remaining 67 centers were analyzed. In 2019, the median number of kidney transplants performed was 45 (1-484), and the median number of kidney transplants from living donors was 28 (1-238) (Table 1). Eleven centers (16.5%) reported performing 5-10, whereas 34 (50.7%) reported performing more than 100 live donor kidney transplants during 2019. Nineteen (28.4%) centers performed LDN using the open technique and 48 (71.6%) using minimally invasive techniques.

Composition and training of the surgical team

LDNs were carried out by a transplant surgeon in 27 centers (40.3%), by a general surgeon in 24 centers (35.8%), and by a urologist in 16 centers (23.9%) (Table 1). The surgical experience was 5 or more years in 42 centers (62.7%), whereas 12 centers (17.9%) were newly established with 1-3 years of experience in donor nephrectomies. In addition, the technique for LDN was adopted through fellowship training in 28 centers (41.8%), surgical residency training in 22 centers (32.8%), workshops and courses in 14 centers (20.9%), and other routes in 13 centers (19.4%). Fifty-seven centers (85.1%) reported having a second surgeon as a backup. Only 10 centers (14.9%) did not have a backup surgeon. The average blood loss ranged between 0-100 mL during LDN in 52 centers (77.6%). Ten centers (14.9%) reported an average of 100-200 mL blood loss. Sixty-one centers (91%) reported a DWIT of 1-5 min, while DWIT was 5-10 min in 4 centers (0.6%) and 10-15 min in 2 centers (0.3%). Forty-nine centers (73.1%) recorded surgeries for optimization. Technical troubleshooting protocol was in place in 61 centers (91%).

Minimally invasive techniques

Among the 48 centers preferring minimally invasive techniques for LDN, 8 (16.6%) implemented more than one surgical technique. The surgical techniques and number of centers using these methods are displayed in Figure 1. As can be seen in this figure, transperitoneal laparoscopic donor nephrectomy

Table 1 Transplant center characteristics, composition, and training of the surgical team

Characteristics	Values
Number of kidney transplants performed in 2019	45 (1-484)
Number of kidney transplants from living donors in 2019	28 (1-238)
Number of donor nephrectomies performed in 2019 percenter	
5-10	11 (16.5%)
11-25	6 (9.0%)
26-50	9 (13.4%)
51-100	7 (10.4%)
> 100	34 (50.7%)
Primary surgeon	
General surgeon	24 (35.8%)
Urologist	16 (23.9%)
Transplant surgeon	27 (40.3%)
Live donor nephrectomy technique	
Open donor nephrectomy	19 (28.4%)
Minimally invasive techniques	48 (71.6%)
Number of years using the preferred technique	
1-3 yr	12 (17.9%)
3-5 yr	13 (19.4%)
> 5 yr	42 (62.7%)
Type of training received by the surgeon	
Fellowship training	28 (41.8%)
Residency training	22 (32.8%)
Surgical courses	14 (20.9%)
Other	13 (19.4%)

was the most commonly performed technique, while single port laparoscopic donor nephrectomy was the least common technique.

The left donor nephrectomy was favored in 26 transplant centers (54.3%). The conversion rate was below 1% in 58 centers (86.5%). Eight centers (11.9%) reported a conversion rate between 1%-3%, and only 1 center (1.5%) reported a conversion rate of 3%-5%. The most frequent reason for conversion was venous bleeding (n = 10, 20.8%). Other reasons were abdominal adhesions (n = 8, 16.7%), technical problems related to gadgets and devices (n = 7, 14.6%), arterial bleeding (n = 5, 10.4%), adjacent organ injury (n = 1, 2.1%), and miscellaneous (n = 1, 2.1%).

Thirty-four surgeons (50.7%) stated having performed more than 100 donor nephrectomies as the primary surgeon with the accustomed technique in 2019 (Table 1). On the other hand, 11 surgeons (16.5%) reported performing 5-10 donor nephrectomies as the primary surgeon. There was a positive association between the performance of minimally invasive techniques and the case volume of a transplant center regarding both the total number of transplants and live donor kidney transplants (15 *vs* 55, P = 0.001 and 9 *vs* 42, $P \leq 0.001$ respectively) (Figure 2).

Variations in the minimally invasive techniques

Nine centers (18.8%) reported using hand assistance, whereas 39 centers (81.2%) did not. While 41 centers (85.4%) reported using vascular staplers for division of the renal pedicle, 6 centers (12.5%) used self-locking surgical clips, and 1 center (2.1%) titanium clips. Modification of the surgical technique due to anatomical variations or body mass index of the donor was not preferred in 56.7% and 68.7% of the centers, respectively. Pfannenstiel incision was the most preferred extraction site for the kidney (n = 30, 62.5%). It was followed by the paramedian (n = 9, 18.7%), midline (n = 7, 14.6%), and modified incisions (n = 2, 4.2%).

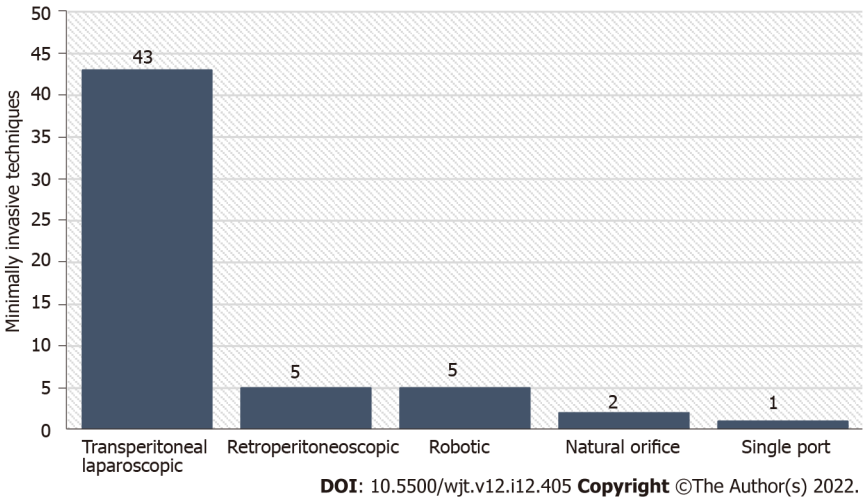

Figure 1 Distribution of minimally invasive techniques for donor nephrectomy.

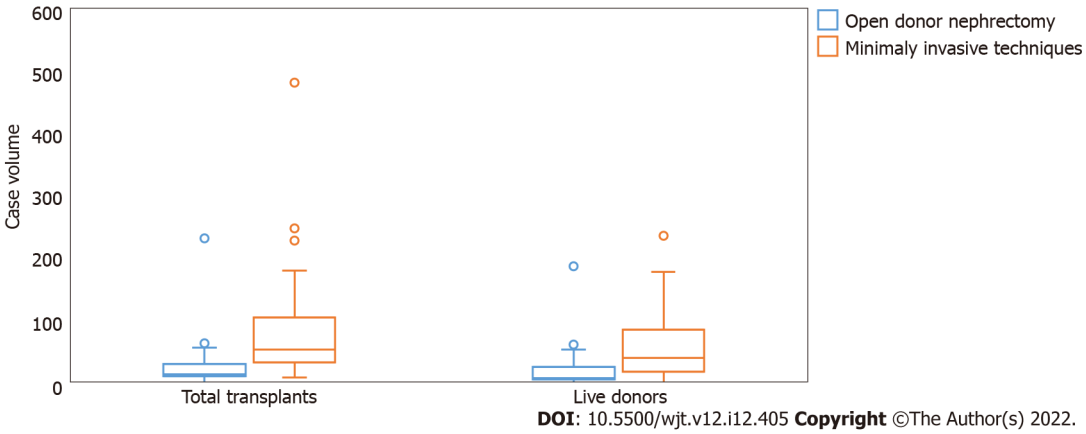

Figure 2 Association of minimally invasive technique usage and case volume.

Complications of donor nephrectomy surgeries

The most frequently reported complication was postoperative atelectasis (n = 33, 49.2%), while the second most frequent complication was bleeding requiring blood transfusion (n = 25, 37.3%) (Figure 3). Wound infection, hernia, and chyle leak were also reported (n = 22, 33.8%). Thirty-nine centers (81.2%) reported an incisional hernia rate of 1%-5%, while 6 centers (12.5%) reported a rate of 5%-10%, and 3 centers (6.3%) reported 10%-20%. Surgical site fluid collections, ileus, deep venous thrombosis, pneumonia, and urinary retention were also reported. Graft loss due to inadvertent intraoperative damage was encountered in two transplant centers (2.9%) (Figure 3). The rates of these declared complications did not differ among the centers using open and minimally invasive techniques except for the chyle leak (Table 2). Chyle leak was reported significantly more frequently by centers using the minimally invasive techniques (P = 0.006).

DISCUSSION

Persistent organ shortage has led to increased interest in live organ donation. As a result, the number of live kidney transplantations is increasing annually. It was previously reported that minimally invasive techniques for LDN might increase the number of donations. Nonetheless, the critical principle in live organ donation is the safety of the donor[8]. Therefore, donor safety should always be the greatest determinant when deciding on the LDN technique[9]. This study presented a cross-sectional view of the techniques of LDN, transplant team composition, training, and the list of the complications encountered at Turkish kidney transplant centers.

Our findings were similar to those of Klop *et al*[10]. They reported that 59 of the transplant centers in Europe performed minimally invasive techniques for LDN[10]. In their survey, 48 European transplant

Table 2 Rates of declared postoperative complications

	Centers performing open donor nephrectomy, *n* = 19%	Centers performing minimally invasive techniques, *n* = 48%	*P* value
Bleeding	7 (36.8%)	18 (37.5%)	> 0.999
Chyle leak	1 (5.3%)	21 (43.8%)	0.006
Surgical site fluid collection	5 (26.3%)	14 (29.2%)	> 0.999
Urinary retention	0 (0.0%)	2 (4.2%)	> 0.999
Atelectasis	11 (57.9%)	22 (45.8%)	0.536
Pneumonia	0 (0.0%)	2 (4.2%)	> 0.999
Deep vein thrombosis	3 (15.8%)	1 (2.1%)	0.066
Ileus	0 (0.0%)	6 (12.5%)	0.173
Hernia	5 (26.3%)	17 (35.4%)	0.670
Graft loss	1 (5.3%)	1 (2.1%)	0.490
Wound infection	7 (36.8%)	15 (31.3%)	0.880

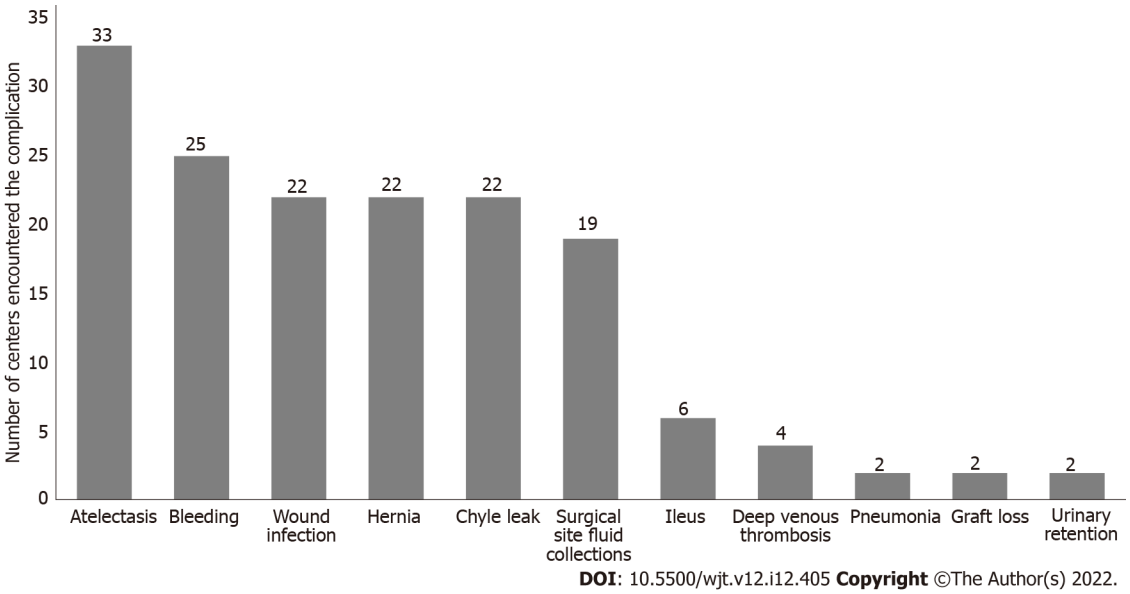

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Figure 3 Complications of donor nephrectomy surgeries.

centers used the laparoscopic approach, and 9 centers used the retroperitoneoscopic approach. In our study, 48 centers reported performing minimally invasive techniques. Among those, 43 used the laparoscopic approach, and 5 used retroperitoneoscopic methods. In line with the American and European centers, robotic surgery is also used for LDN in Turkey[11,12]. Five transplant centers in our study reported implementing robotic-assisted techniques. In 2009, only two centers in Europe used robotic-assisted techniques. However, this number increased gradually, with several case series being published in the literature[13-16].

In our survey, 19 centers reported using the open technique for donor nephrectomy. This result was in accordance with the findings of the European survey, which reported that 37 centers performed open donor nephrectomies[10]. This similarity indicates the international trend for minimally invasive techniques. As per the literature, the total number of kidney transplants and live donor kidney transplants is in line with the increased use of minimally invasive donor nephrectomy techniques in Turkish transplant centers[4,7,10].

A comparison of the centers regarding case volumes revealed a significant variation among centers in this regard. Thirty-four centers performed more than 100 live donor kidney transplants in 2019. These centers represented 50.7% of the transplant centers enrolled in our study. While these centers performed more than 3400 kidney transplants, the remaining 33 centers performed approximately 200 live donor kidney transplants in total. This disproportionate distribution can be explained by the higher number of

live donations in highly populous cities of Turkey, such as Istanbul and Ankara. On the other hand, in Europe, as of 2009, only four centers were performing more than 100 live donor kidney transplants per year, while 30 centers were performing fewer than 100 live donor kidney transplants[10].

The spectrum of postoperative complications did not differ between the centers performing minimally invasive donor nephrectomy and those performing open donor nephrectomy. Among all complications, only chyle leak was more frequently encountered in the centers using minimally invasive techniques. Two centers reported graft loss due to intraoperative damage of the graft: One from a center using open donor nephrectomy and the other from a minimally invasive center. In our study, the relationship between the caseload of the transplant center and the complication of graft loss could not be analyzed due to the small numbers.

The team setup and staff training in Turkish transplant centers demonstrate similar results with the other transplant centers in the United States and Europe, where 41.8% of the staff have received fellowship training for organ transplantation[17,18]. Our findings revealed that most (*i.e.*, 40.3) of the LDN procedures were performed by transplant surgeons in Turkish transplant centers. A scientific committee that consists of experienced transplant surgeons, nephrologists, transplant coordinators, and hepatologists evaluates the surgical trainee in terms of scientific and surgical qualifications for transplant proficiency. If the requirements are satisfied, then a certificate is given to the surgeon as a transplant surgeon. This certificate grants the surgeon to lead a transplant surgical team and perform transplants in his/her hospital.

The average blood loss ranged between 0-100 mL in 77.6% of the transplant centers in Turkey. The amount of blood loss and DWIT were compatible with the literature[19-22]. Technical troubleshooting protocol was in place and intraoperative video recording was routinely performed in the majority of the transplant centers in Turkey.

Eight centers in our study reported using more than one surgical technique. As a matter of course, performing LDN with more than one surgical technique provides advantages. These advantages are selecting the best technique for the donor and the ability to adapt the preferred technique to the donor anatomy, body mass index, surgical history, and abdominal adhesions. As an additional advantage, it can reduce the risk of conversion to open surgery. For example, in cases of venous bleeding, which was reported as the most common cause of conversion in our study, the surgeon can complete the surgery with a hand-assisted technique by placing an additional hand port.

To our knowledge, this is the first study evaluating donor nephrectomy techniques in Turkey. All transplant centers performing LDN responded to the survey and were included in our analysis. However, this study has some limitations which need to be considered while evaluating its findings. First, it is a survey study, and the reliability of the data depends on the accuracy of the answers and the honesty of the responders. Second, our findings could have been affected by a recall bias. However, this study provides an overview of the centers performing LDN in Turkey despite these limitations. The results of this study and future similar studies may act as instruments revealing any weaknesses that may need improvement.

CONCLUSION

Turkey is one of the leading countries for live organ donation. In this article we explored the transplant climate in Turkey *via* a detailed survey sent to transplant program directors. The questionnaire was sent to 72 kidney transplant centers, all of which replied. In 2019, the median number of kidney transplants performed was 45 (1-484), and the median number of kidney transplants from living donors was 28 (1-23). Among the 48 centers preferring minimally invasive techniques for LDN, 8 (16.6%) implemented more than one surgical technique. Transperitoneal laparoscopic donor nephrectomy was the most commonly performed technique, while single port laparoscopic donor nephrectomy was the least common technique. There was a positive association between the performance of minimally invasive techniques and the case volume of a transplant center regarding both the total number of transplants and live donor kidney transplants. To our knowledge, this is the first study evaluating donor nephrectomy techniques in Turkey. Therefore, this study represents the national transplant environment in Turkey.

ARTICLE HIGHLIGHTS

Research background

Minimally invasive surgical techniques for live donor nephrectomy (LDN) are varied. These techniques include hand-assisted laparoscopic, retroperitoneoscopic, single port, natural orifice, and robotic nephrectomy techniques. Turkey has a high number of live kidney donors. The reports regarding LDN in Turkey are missing. In this study, we demonstrated the center volume, preferred techniques for LDN, complications, team setup, and training of transplant teams.

Research motivation
In 2019 according to the Turkish Ministry of Health data, 3963 kidney transplantations were performed in Turkey. Among these patients, 3548 were transplanted from live donors. This increased living donor rate stimulated interest in various surgical techniques applied in Turkey and LDN practice.

Research objectives
To gain insight into the practices of LDNs in Turkish transplant centers.

Research methods
A questionnaire was sent to the Turkish Ministry of Health-accredited transplant centers. It inquired of the number of LDN surgeries, surgical techniques, complications, optimization protocols, the experience of surgeons, and the training. Descriptive statistics were outlined as follows: Discrete numeric variables were expressed as medians (minimum-maximum), while categorical variables were shown as numbers and percentages. As a result of the goodness-of-fit tests, if the significance of the differences between the groups in discrete numerical variables for which the parametric test statistical assumptions were not met, data were analyzed with the Mann Whitney U test and the χ^2 test.

Research results
The questionnaire was sent to registered transplant centers in Turkey. All 72 centers replied. In 2019, the median number of kidney transplants performed was 45 per center, and the median number of kidney transplants from living donors was 28. There was a wide range between the centers in terms of transplant numbers (1-238 transplant per year). The open technique was preferred by 19 centers (28.4%). The minimally invasive LDN was performed by 48 centers (71.6%). Among the centers, 8 (16.6%) used more than one surgical technique. A positive correlation between the performance of minimally invasive LDN and the case volume of a transplant center, both in the total number of transplants and live donor kidney transplants, existed (15 *vs* 55, $P = 0.001$ and 9 *vs* 42, $P \leq 0.001$ respectively). The most frequently reported complication was postoperative atelectasis ($n = 33$, 49.2%).

Research conclusions
The analysis of the questionnaire answers revealed that Turkish transplant centers successfully performed LDN operations using various techniques. A relatively higher numbers of living donor kidney transplants were performed in 2019 at centers using minimally invasive techniques.

Research perspectives
The data regarding the annual kidney transplant numbers, complication rates, and center successes should be released by the Ministry of Health in Turkey. This would allow the control and improvement of the transplant centers when necessary. Despite this, the current status of Turkish transplant centers, as observed in the results of this study, is comparable to transplant centers in Europe and the United States.

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FOOTNOTES

Author contributions: Mankiev B and Cimen SG designed the research; Cimen S and Kaya IO performed the research; Eraslan A collected data; Cimen S analyzed data; Cimen SG wrote the paper.

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Informed consent statement: The participants were informed about the questionnaire *via* e-mail, and after an online consent process the Survey Monkey questionnaire link was shared.

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Country/Territory of origin: Turkey

ORCID number: Bakytbek Mankiev 0000-0002-4995-1128; Sanem Guler Cimen 0000-0002-5266-9529; Ismail Oskay Kaya 0000-0002-1864-896X; Sertac Cimen 0000-0002-0252-8840; Asir Eraslan 0000-0002-2204-1327.

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