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AIMS AND SCOPE

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

WJV mainly publishes articles reporting research results obtained in the field of virology and covering a wide range of topics including arbovirus infections, viral bronchiolitis, central nervous system viral diseases, coinfection, DNA virus infections, viral encephalitis, viral eye infections, chronic fatigue syndrome, animal viral hepatitis, human viral hepatitis, viral meningitis, opportunistic infections, viral pneumonia, RNA virus infections, sexually transmitted diseases, viral skin diseases, slow virus diseases, tumor virus infections, viremia, and zoonoses.

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EDITORIAL

Intensive care unit adaptations in the COVID-19 pandemic: Lessons learned

Anwar Khedr, David Rokser, Jeanine Borge, Hannah Rushing, Greta Zoesch, Wade Johnson, Han-Yin Wang, April Lanz, Brian N Bartlett, Jessica Poehler, Salim Surani, Syed A Khan

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Abstract

The coronavirus disease 2019 pandemic had deleterious effects on the healthcare systems around the world. To increase intensive care units (ICUs) bed capacities, multiple adaptations had to be made to increase surge capacity. In this editorial, we demonstrate the changes made by an ICU of a midwest community hospital in the United States. These changes included moving patients that used to be managed in the ICU to progressive care units, such as patients requiring non-invasive ventilation and high flow nasal cannula, ST-elevation myocardial infarction patients, and post-neurosurgery patients. Additionally, newer tactics were applied to the processes of assessing oxygen supply and demand, patient care rounds, and post-ICU monitoring.

Key Words: COVID-19; Pandemics; Oxygen; Intensive care units; ST elevation myo-

cardial infarction; Nasal cannula

Core Tip: In this editorial, we demonstrate how the coronavirus disease 2019 pandemic changed our lives in the intensive care unit (ICU), especially in the management of surge capacity and allocation of resources in a 10-bed ICU of a United States suburban midwest community hospital. These strategies included managing complex patients in our progressive care unit, assessing oxygen supply and demand, performing patient care rounds, and post-ICU monitoring.

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INTRODUCTION

"Calamity tempestuous, oracle of destruction, ravishing through nations, ordained to devastation, negator of humanity, the annihilation of grace" is how our colleague depicted the coronavirus disease 2019 (COVID-19) pandemic in a recently authored poem[1]. The COVID-19 pandemic has wreaked havoc on healthcare systems all around the world[2,3]. To increase bed capacities and resources, elective surgeries were postponed[4]. Innovative approaches were implemented to perform virtual visits and perform patient care rounds[5,6]. Some hospitals have implemented structural modifications and changed strategies of resource allocation to face the intensive care unit (ICU) surge capacity and the sudden increased demand for invasive mechanical ventilation[7,8].

To meet the need for increasing demand for ICU beds, our staff at Mayo Clinic Health System (MCHS) in Mankato worked tirelessly to maximize our ICU capacity while maintaining high-quality patient care. MCHS Mankato is a 161-bed community hospital with a 15-bed multispecialty ICU staffed 24/7 by intensivists fellowship trained in critical care, a part of the Mayo Clinic enterprise in Southern Minnesota. A 19- bed progressive care unit (PCU) staffed by our hospitalist team manages patients with less acuity. Admission guidelines for both units are as per the Society of Critical Care Medicine admission criteria.

Over 80000 COVID-19 cases were diagnosed in Minnesota by September 2020[9]. Additionally, due to nationwide bed and staff shortages[2], we had to maximize our capacity to have an ICU literally without walls. Our multidisciplinary team determined that mitigation was required to overcome limited capacity[2,10,11]. Alterations to our daily routine had to be made with shared decision-making and increased communication across specialties[7]. In this editorial, we are providing a brief overview of these efforts and outcomes between November 2020 and December 2021.

PCU for do not resuscitate/do not intubate patients requiring noninvasive ventilation

Patients utilizing noninvasive ventilation (NIV) with do not resuscitate (DNR)/do not intubate (DNI) status were managed in the ICU prior to the pandemic. A collaboration between the critical care team, respiratory therapy, nursing, and hospitalist team was established to manage patients requiring NIV in the PCU. The Critical Care team managed the NIV, and the hospitalist group provided additional medical management. The challenges of this placement included a greater need for communication between very busy teams, and a potential urgent need for critical care beds if hemodynamic instability developed. Prior to November 2020, only 13 DNR/DNI patients were ever managed with NIV in the PCU. A total of 22 patients requiring NIV were managed during the last two months of 2020 (> 69.2% increase), with 79 total NIV patients being admitted to the PCU in 2021 (> 125.7% increase). This approach was found to be especially helpful for patients with prolonged respiratory failure, such as was seen with COVID-19[12,13].

ST-elevation myocardial infarction patients to the PCU

Prior to COVID-19, ST-elevation myocardial infarction (STEMI) patients were admitted to the ICU. Due to the need for more ICU beds, Critical Care, Cardiology, hospitalists, and nursing staff collaborated to manage hemodynamically stable STEMI patients in the PCU. A previous study showed that although > 80% of stable patients with STEMI are treated in the ICU after primary percutaneous coronary intervention, the risk for developing a complication requiring ICU care is 16%, which confirmed that

ICU was overutilized by stable STEMI patients[14]. Challenges to this approach included the necessity for enhanced cardiac education provided to the PCU nurses, increased requirement for more multidisciplinary coordination, and the urgent need for an ICU bed if hemodynamic instability occurs. After our adaptations, STEMI ICU admissions decreased from 107 (156 total STEMI cases) in 2020 to 51 (141 total STEMI cases) in 2021, a total reduction of 32.4%. There were no adverse events reported with this strategy.

Evaluating placement of post-operative neurosurgery patients

Before COVID-19, neurosurgical patients who underwent complex procedures were frequently managed post-operatively in the ICU regardless of hemodynamic stability. The neurosurgical and critical care teams implemented a collaborative process to assess each case for ICU appropriateness[15-17]. Those who did not need active ICU intervention (*e.g.*, pressors, intracranial monitoring, advanced oxygen therapy) were admitted to the PCU for management. Limitations of this approach included nurse training, the need for increased multidisciplinary collaboration, and the need for an emergent bed within the ICU if decompensation occurred. Prior to November, 28 of 61 post-operative neurosurgical patients were admitted to the ICU in 2020. From November 2020 through December 2020, 9 of 14 patients were managed in PCU. Sixty-two out of 109 post-operative neurosurgical cases were admitted to ICU in 2021.

High flow nasal cannula in PCU

Patients requiring greater than 0.60 FiO_2 using high flow nasal cannula (HFNC) were transferred to the ICU prior to November 2020. It was determined that all HFNC patients, regardless of code status or FiO_2 requirement, would be managed in the PCU unless the additional need for ICU admission occurred[18-20]. Nursing, respiratory therapy, and provider comfort were initial challenges. Before November 2020, 71 patients were managed in the PCU with HFNC requiring less than 0.6 FiO_2. From November 2020 until the end of 2021, a total of 187 patients were treated in PCU with HFNC, an increase of 116%. Many COVID-19 cases required prolonged HFNC without additional adjunctive critical care management, which opened ICU beds for patients requiring more complex support such as invasive mechanical ventilation[19,21].

Oxygen supply/demand assessment

Due to fixed medical gas availability, daily meetings between the respiratory therapy and critical care teams were conducted to evaluate oxygen consumption and demand. A report created in the electronic medical record delivered real-time data regarding oxygen devices in use. Medical gas pressure alarm values alerted the team to wean oxygen or change the patient to an alternative oxygen-conserving device if the gas supply reached a critical level. During times when the hospital oxygen supply reached a critically low level, ICU physicians and respiratory therapists assessed all HFNC patients for judicious use. In appropriate cases, NIV was utilized temporarily to decrease oxygen consumption while working on alternative approaches to minimize use. Additional attention was given to shutting off oxygen devices when not in use. Other tools and criteria were developed to assess oxygen resources and distribution[22,23].

Collaborate team care rounds with social distancing and visitor restrictions

A multidisciplinary approach is necessary to manage critically ill patients, and daily team rounds are an essential component of the ICU routine. Many critically ill patients cannot make medical decisions and rely on family members for assistance. During the COVID-19 pandemic, this was complicated by visitor restrictions resulting in family members calling 24/7 to receive updates and to advocate for patients. Calls were often accompanied by emotions such as anger, guilt, fear, frustration, and sadness related to the inability to be at the bedside. For the patients being alone posed a higher risk of ICU delirium. A telemedicine approach was adopted to involve the patient's family and maintain social distancing between the interdisciplinary team members, including the physician, advanced practice provider, respiratory team, nurses, pharmacist, dietician, and therapists[6,24]. During rounds *via* conference call, each team member would give a progress update and present their plan of care for the day. The physician or advanced practice provider would then summarize the plan of care and answer any questions the family had. The family was encouraged to participate throughout the rounding process actively and stay on the line for the entire process, typically about 10 min per patient[6]. Prior to the pandemic, both patients and families participated in the ICU interdisciplinary team rounds which were always conducted at the bedside. Due to the risk of exposure, the need to conserve full personal protective equipment, and the restricted visitor policy this approach was adopted. We wanted the families to receive real-time updates and assessments from the entire interdisciplinary team. Our rounds were a small gesture to lessen the emotional burden and were valued by family members. The ICU team also arranged virtual zoom or other video calls with patients and their families daily to reduce the risk of ICU delirium.

Post-ICU monitoring

Prior to the COVID-19 pandemic, ICU patients were typically monitored for 24 h in the ICU after receiving substantial life support (*e.g.*, mechanical ventilation, vasopressors, continuous renal replacement therapy). In response to increased demand for critical care beds across midwest America, ICU patients were moved to lower acuity beds at the earliest appropriate opportunity. To prevent ICU readmissions, rapid response nurses and virtual ICU providers (Mayo Clinic Enhanced Critical Care) followed every critical care discharge for 48 h regardless of hospital location. This practice has been used in different ways and has proved to decrease ICU mortality and hospital length of stay[25,26]. With this intervention, the ICU readmission rate remained low at 2% much lower than national data. Additionally, this provided extra support to hospitalists and nurses unfamiliar with managing patients immediately following ICU-level care.

CONCLUSION

Despite the significant increase in acuity within the ICU, the multidisciplinary team maintained a total ICU mortality rate index of 0.92 and a COVID-19 mortality rate index of 0.37. The length of stay index for the total ICU population was 0.95 and 1.39 for patients diagnosed with COVID-19. These numbers are impressive as they were achieved despite ICU acuity increasing as more stable patients, such as hemodynamically intact STEMI and post-operative neurosurgical patients, were transitioned to PCU care. Each member of the multidisciplinary team was crucial to our success. By maximizing our ICU resources and capacity, these interventions allowed us to better serve our community. The COVID-19 pandemic is not the last crisis that the world will face. This is the time for the call to action for the institutions to have alternative innovative strategies and learn the lesson from their shortcomings during the COVID-19 pandemic. This narrative is a prelude to our efforts and may be beneficial to other hospitals in case of another crisis.

FOOTNOTES

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Dipeptidyl peptidase 4 inhibitors in COVID-19: Beyond glycemic control

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Abstract

Coronavirus disease 2019 (COVID-19) is associated with a high risk of mortality and complications in patients with diabetes mellitus. Achieving good glycemic control is very important in diabetic patients to reduce complications and mortality due to COVID-19. Recent studies have shown the mortality benefit and anti-inflammatory effects of Dipeptidyl-peptidase-4 inhibitors (DPP-4i) in diabetic patients with COVID-19. DPP-4i may have a beneficial role in halting the severity of infection primarily by three routes, namely viral entry inhibition, anti-inflammatory and anti-fibrotic effects and glycemic control. This has raised the promising hypothesis that DPP-4i might be an optimal strategy for treating COVID-19 in patients with diabetes. This review aims to summarise the possible therapeutic non-glycemic effects of DPP-4i in diabetic patients diagnosed with COVID-19 in the light of available evidence.

Key Words: Dipeptidyl-peptidase-4; Diabetes mellitus; COVID-19; Mortality

Core Tip: Patients with pre-existing comorbidities, particularly diabetes mellitus (DM), are at increased risk of complications from coronavirus disease 2019 (COVID-19). Beyond their glycemic effects, Dipeptidyl-peptidase-4 inhibitors (DPP-4i) have proven effective in COVID-19 individuals with DM. Available observational studies and trials have shown a significant mortality reduction in COVID-19 patients with DM when DPP-4i were continued during the course of illness. As a result, COVID-19 individuals with DM may choose DPP-4i as the preferred anti-diabetic medication if it is not contraindicated.

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INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic is caused by a novel beta coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is similar to SARS-CoV-1 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[1]. Since late 2019, the disease has spread rapidly worldwide, posing a significant threat to public health. To date more than 539 million patients have been infected across the globe leading to over 6.32 million deaths[2]. The overall mortality rate for COVID-19 ranges from 0.7% to 10.8%[3]. Nearly two-thirds of severely affected individuals have comorbidities, most commonly cardiometabolic disorders, with diabetes mellitus (DM) accounting for 17% of cases[4].

Although DM is not associated with an increased risk of COVID-19, it confers a high risk of rapid progression in the severity of the infection and hence a poor prognosis. Specifically, people with DM are more prone to invasive mechanical ventilation, intensive care unit (ICU) admission, and the development of organ dysfunction, as compared with patients without diabetes[5,6]. A recent meta-analysis of 83 eligible studies with 78874 COVID-19 hospitalized patients found that people with pre-existing DM had a doubling of the risk for severe or critical COVID-19 illness (odds ratio [OR] 2.10, 95% confidence interval [95%CI] 1.71-2.57) and a tripling of the risk for in-hospital mortality (OR 2.68, 95%CI 2.09-3.44)[7]. Putative pathogenic processes linking COVID-19 and DM include hyperglycemia-mediated immune dysregulation, inflammation, and activation of the renin-angiotensin-aldosterone pathway[8].

The increasing spread of the SAR-CoV-2 infection and the high morbidity necessitates rapid identification of an effective therapy. While developing novel therapies (such as antivirals and vaccines) is a priority, repurposing "old" medications or reconsidering previously well-characterized targets with an emerging function in COVID-19 is the need of the hour. Dipeptidyl-peptidase-4 (DPP-4), also known as cluster of differentiation 26 (CD26), has recently been suggested as a potential target receptor for SAR-CoV-2[8,9]. MERS-CoV, a beta coronavirus similar to SARS-CoV-2, uses DPP-4 as an entrance receptor. Due to its similarity with the MERS-CoV, it has also been proposed that DPP-4 may aid SARS-CoV-2 entry into the target cells[10]. In this context, DPP-4i have gained increasing interest as a therapeutic target in patients with COVID-19.

DPP-4 is a 110 kDa glycoprotein, a membrane-bound endopeptidase that cleaves many peptide hormones such as cytokines, growth factors, and incretin hormones like glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP)[11]. Also, DPP-4 interacts with cellular proteins such as adenosine deaminase and caveolin-1 to regulate immune responses[12]. DPP-4 exists in two forms in the body, a membrane-bound form or as a soluble form (sDPP-4)[13]. The extracellular portion of DPP-4 is cleaved from cell membranes to form the 727 amino acid soluble moiety sDPP-4, which circulates in the plasma with retained enzyme activity. The DPP-4 receptor is found on the surface of nearly every cell and plays a role in immune regulation, signaling, and cell apoptosis. It is widely expressed in many tissues such as the kidney, gastrointestinal tract, and lungs. The primary role of DPP-4 is to regulate glucose and insulin metabolism by degradation of incretin hormones such as GLP-1 and GIP. Visceral adipose tissue has greater expression of DPP-4 and it has been linked to adipocyte inflammation and insulin resistance. DPP-4 promotes inflammation in subjects with type 2 diabetes through both catalytic and noncatalytic pathways. DPP-4 directly regulates the immune system by activating T cells and upregulating CD86 expression and the nuclear factor kappa B (NF-kB) pathway[14].

DIPEPTIDYL- PEPTIDASE-4 INHIBITORS

DPP-4i are oral anti-diabetic drugs that affect glucose homeostasis by inhibiting the enzyme DPP-4. DPP-4i prolong the half-life of incretins by deactivating DPP-4, which cleaves and inactivates them. Incretin hormones, GLP-1 and GIP are responsible for the regulation of postprandial insulin[15]. DPP-4i have been suggested to have cardiovascular benefits. Hence, these medications are commonly used in diabetic patients with a history of cardiovascular or chronic renal disease[16]. They achieve reasonable glycemic control with no significant effect on body weight, no risk of hypoglycemic events, and a safe cardiovascular profile. They have also shown a favorable effect on surrogate vascular markers, such as lipid profile, blood pressure, and endothelial function[13].

PROPOSED MECHANISMS OF DPP-4I IN COVID-19

DPP-4i can effectively control blood glucose levels with a favorable safety profile. Good glycemic control can improve the prognosis and outcome of COVID-19[17]. Hence, DPP-4i can influence the clinical outcome in COVID-19 patients through their glycemic effects. The mechanisms by which DPP-4i influence the clinical outcomes in COVID-19 patients with DM beyond their glycemic effect are still under speculation and are detailed below (Figures 1 and 2).

DPP-4 AND SARS-COV-2 INTERACTION

Role as an alternate co-receptor

SARS-CoV-2 binds to specific host receptors on the target cell to facilitate entry into the host cell. The SARS-CoV-2 enters the cell *via* binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE-2) receptor on the surface of the host cell membrane. The binding of the S-protein causes a conformational change in the receptor, which is essential for its activation. This critical step known as priming comprises the cleaving of the spike protein by cellular serine proteases. This step enables viral fusion with the cellular membrane and promotes viral entry into the target cell[18]. Studies have shown a wide distribution of ACE-2 across human tissues, including the lung, gastrointestinal tract, and kidney. However, the expression of ACE-2 on alveolar type 2 cells, which is supposed to be the primary target cell of SARS-CoV-2, is markedly low. This has created interest in a possible role for other co-receptors for viral entry[19].

In-silico modelling of the SARS-CoV-2 spike protein, predicted a potential interaction with the DPP-4 in addition to ACE-2[20]. These models suggest that DPP-4 may be a co-receptor for SARS-CoV-2 viral entry. As DPP-4 is widely expressed in cells and tissues other than the respiratory tract, it may facilitate the spread of SARS-CoV-2 infection to a wider range of tissues[10]. DPP-4 is the receptor for the MERS-CoV spike protein, which mediates viral entrance into host cells[21]. Due to the high homology between SARS-CoV-2 and MERS-CoV, DPP-4 may also be an accessory entry receptor for SARS-CoV-2[22]. The presumed role of DPP-4 as a co-receptor for SARS-CoV-2 is still under study[14].

Cross-talk between DPP-4 and ACE-2 receptor

DPP-4 interacts with several essential proteins for viral processing, including ACE-2, implying a possible cross-talk between the two proteins[23]. *In vivo* studies have shown that the DPP-4i sitagliptin inhibits ACE activity and reduces angiotensin II levels in rats[24]. This cross-talk could interfere with viral surface binding and fusion, thereby affecting spread of the infection.

Role of soluble DPP-4

The fact that DPP-4 exists in two forms, a soluble form (sDPP-4) and membrane-bound form, adds to the intricacy of the role of DPP-4i in COVID-19. Previous research has shown that sDPP-4 acts as a decoy receptor for MERS-CoV, preventing viral replication[12]. The same may be applicable to SARS-CoV-2. sDPP-4 may bind SARS-CoV-2, preventing the virus from attaching to membrane-bound DPP-4 in the host cell, thereby hindering viral spread. A German study showed a reduced circulating level of sDPP-4 in patients with severe COVID-19[25]. A similar scenario was reported in MERS-CoV infected patients [26]. Previous studies have shown that sDPP-4 was significantly lower in older individuals than younger individuals[27]. Serum levels of sDPP-4 are also altered in various clinical diseases, such as DM, obesity, and metabolic syndrome, and are linked to insulin resistance[27,28]. This may contribute to the severe presentation of SARS-CoV-2 infection in diabetic, obese, and elderly individuals. In this regard, a recent study has shown a 50%-100% rise in the levels of sDPP-4 in mice after exposure to DPP-4i[29]. Hence, DPP-4i, in addition to interfering with viral entrance, may enhance viral particle sequestration in the circulation by increasing sDPP-4 levels, limiting viral growth in humans.

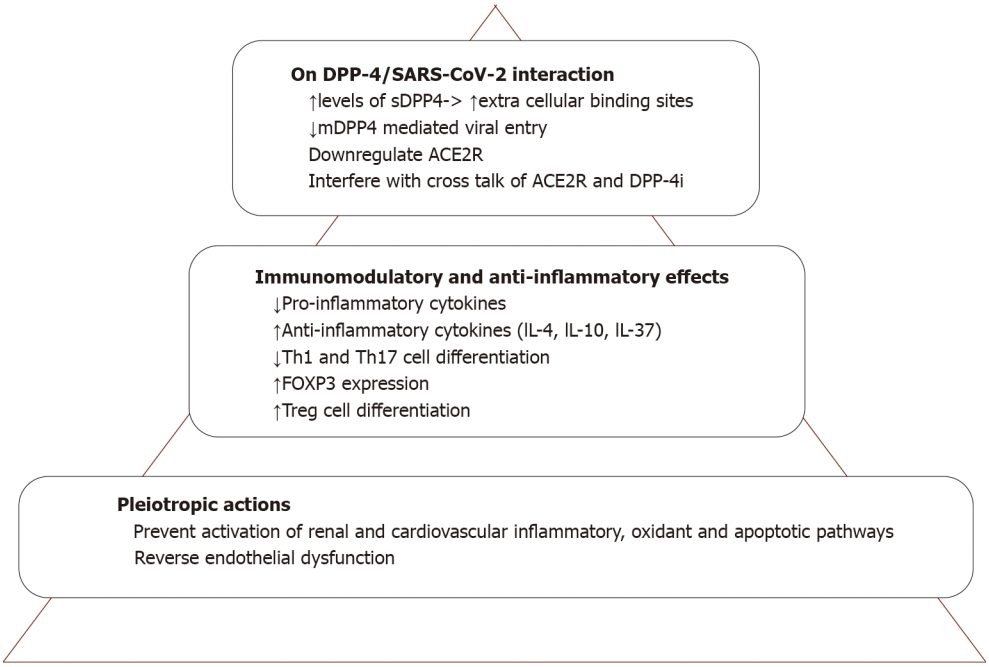

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Figure 1 Proposed mechanisms of dipeptidyl peptidase-4 inhibitors in coronavirus disease 2019 infection. ACE2R: Angiotensin converting enzyme 2 receptor; COVID-19: Coronavirus disease 2019; DPP-4: Dipeptidyl peptidase-4; FOXP3: Forkhead box P3; IL: Interleukin; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4; TGF-β: Transforming growth factor beta.

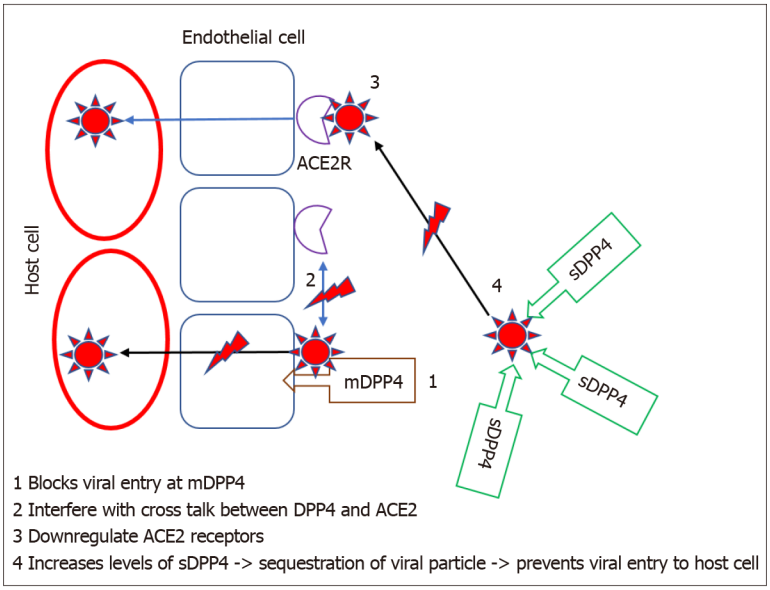

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Figure 2 Hypothetical interactions between dipeptidyl peptidase-4 and severe acute respiratory syndrome coronavirus 2 virus. ACE-2: Angiotensin-converting enzyme 2; ACE2R: Angiotensin converting enzyme 2 receptor; DPP-4: Dipeptidyl peptidase-4; mDPP4: Membrane bound DPP4; sDPP4: Soluble DPP4.

Immunomodulatory role of DPP-4i

Dysregulated inflammation accounts for the severity of COVID-19. The severe presentation is linked to a hyperinflammatory state, characterized by an abnormal increase in circulating levels of pro-inflammatory cytokines such as Interleukin (IL)-1, IL-2, IL-6, Interferon-γ and tumor necrosis factor (TNF), leading to acute respiratory distress syndrome, disseminated intravascular coagulation, multi-organ failure, and death. There is significant activation of CD4+ and CD8+ T cells in COVID-19 patients and a skewing of T-cells toward the T-helper 17 functional phenotype[30]. DPP-4 is found in various cell lines involved in immune control, such as Th17 T helper cells, natural killer cells, activated B cells, macrophages, and myeloid cells[31]. DPP-4 promotes T cell proliferation, NF-kB activation, CD86

expression, and excessive production of inflammatory cytokines, all of which contribute to inflammation. Additionally, GLP-1, which DPP-4 degrades, also possesses anti-inflammatory properties[32].

DPP-4i reduce pro-inflammatory cytokines and mediators such as IL-1, IL-6, C-reactive protein (CRP), and TNF-alpha and thereby mitigate the severity of COVID-19. Many studies have shown that sitagliptin has anti-inflammatory effects in diabetic patients, which leads to an increase in the anti-inflammatory cytokine IL-10 and a decrease in several pro-inflammatory cytokines, such as TNF-alpha [13]. Therefore, the immunomodulatory effects of DPP-4i may prevent dysregulated inflammation and cytokine storms in COVID-19 patients, thereby reducing the severity of the disease.

Pleiotropic effects of DPP-4i

DPP-4i confer multiple vasculoprotective effects, which reduce the risk of comorbidities associated with DM, including hypertension, cardiovascular disease (CVD), and kidney disease. Insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, and immune dysfunction may all contribute to endothelial dysfunction and arterial stiffness in DM. Beyond glycemic control, DPP-4i regulate these pathogenic mechanisms through GLP-1-dependent and independent pathways for CVD protection[33]. DPP-4i have been proven in numerous trials to prevent atherosclerosis, improve endothelial function, and promote wound healing possibly by modulating monocyte/macrophage-mediated responses, reducing oxidative stress, and decreasing neutrophil recruitment and activity[33]. As a result, Du *et al* [34] recently proposed DPP-4i as a potential therapy for preventing or treating CVD produced either directly or indirectly by the COVID-19-induced cytokine storm. Through their immune-modulatory action, DPP-4i have also been useful in obesity-related inflammation, hepatic fibrosis, myocarditis, diabetic nephropathy, and chemotherapy-induced kidney injury in animal research trials[31].

DPP-4 inhibition directly reduces lipopolysaccharide-induced lung damage in mice and human lung epithelial cells[35]. Soare *et al*[36] recently discovered that DPP-4 enhances fibroblast activation by increasing transforming growth factor β, a harbinger of tissue fibrosis. Hence, the inactivation of DPP-4 has significant anti-fibrotic effects, validated in numerous experimental models of pulmonary and skin fibrosis. Sadikot *et al*[37] have recently claimed that GLP-1 could be a new treatment for acute respiratory distress syndrome, demonstrating that human GLP-1 reduces NF-kB activation in cultured macrophages and a mouse model of acute lung damage. All these studies point to a possible anti-fibrotic role for DPP-4i.

OBSERVATIONAL STUDIES

With the above hypothesis, several observational studies have been performed to investigate the impact of DPP-4i on clinical outcomes in type 2 diabetes mellitus (T2DM) patients hospitalized for COVID-19 (Table 1).

In a cohort study conducted at the university hospital of Padova, amongst 403 patients hospitalized for COVID-19, 85 had DM, and nine were on DPP-4i. DPP-4i users and comparators had no significant difference in ICU admission or death rate[38]. In a retrospective observational study of 120 patients with diabetes, Chen *et al*[39] found that DPP-4i users and non-users had identical clinical outcomes. Users of DPP-4i had a non-significant higher rate of in-hospital death than non-users (OR 1.48, 95%CI 0.4-5.53). Similarly, after propensity score matching, Pérez-Belmonte *et al*[40] found that DPP-4i users were not at higher risk for adverse outcomes such as ICU admission, mechanical ventilation, multi-organ dysfunction, or long-term hospital admissions. In a few other observational studies there was no link between DPP-4i therapy and COVID-19-related mortality[41-46] and severity[44,47].

On the contrary, few observational studies have revealed that DPP-4i have favourable effects on COVID-19-related outcomes. In a case series encompassing 387 patients admitted to a research hospital in Lombardy (Northern Italy) with COVID-19, 90 patients were diabetic and 12.2% were on DPP-4i. After adjusting for confounders, DPP-4i use was associated with a decreased death risk [adjusted hazard ratio (HR) 0.13; 95%CI 0.02–0.92]. Furthermore, DPP-4i users required less non-invasive mechanical ventilation, implying that their pneumonia was less severe[48].

In a multicentric retrospective observational study conducted in Northern Italy, 169 age and gender-matched subjects treated with sitagliptin plus insulin were compared with a similar number of subjects treated with insulin therapy. Primary outcomes assessed were hospital discharge and death, and secondary outcomes analyzed were ICU admission, the need for mechanical ventilation, and extracorporeal membrane oxygenation. The sitagliptin users had significantly lower mortality (18% *vs* 37%, $P < 0.001$) even after adjusting for confounders like age, gender, comorbidities, and ongoing treatment (HR 0.44; 95%CI 0.29-0.66). On day 30, a larger number of patients treated with sitagliptin were discharged from the hospital than those on conventional therapy (71% *vs* 59%, $P < 0.01$). Compared to usual treatment, sitagliptin was associated with a lower probability of needing mechanical ventilation and ICU admission. At follow-up, patients treated with sitagliptin had significantly lower inflammatory markers such as procalcitonin and CRP and lower mean blood glucose levels during hospitalization[49].

Similarly, a Korean database-based retrospective study found that DPP-4i treatment was significantly associated with better clinical outcomes even after adjusting for age, gender, comorbidities, and

Table 1 Observation studies assessing coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy

Sl no	Ref.	Design, location	Population	Findings
Studies with neutral outcomes with the use of DPP-4i				
1	Fadini *et al* [38], 2020	RO, Italy	Registry based DM patients with and without COVID-19. Subgroup analysis of proportion of DPP-4i users	Diabetic COVID-19 patients who were on DPP-4i had a similar disease outcome as those who were not
2	Chen *et al* [39], 2020	RO, China	Single centre hospitalised COVID-19 patients with DM; DPP-4i users (n = 20) compared with nonusers (n = 100)	Mortality OR 1.48, 95%CI 0.4-5.53, P = 0. 56
3	Pérez-Belmonte *et al*[40], 2020	RO, Spain	Registry based COVID-19 patients with DM. DPP-4i users (n = 105) compared with nonusers (n = 105)	Composite outcome of ICU admission, mechanical ventilation, or in-hospital death: OR 1.12, 95%CI 0.65-1.95, P = 0.675
4	Silverii *et al* [41], 2021	RO, Italy	Registry based all deaths due to COVID-19 infection; Subgroup analysis of DPP-4i users (n = 13) *vs* nonusers (n = 146) in DM patients	Mortality risk in COVID-19 infection. HR 1.0, 95%CI 0.5-2.1, P = 0.56
5	Kim *et al* [42], 2020	RO, Korea	Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (n = 85) and others (n = 235)	Mortality OR 1.47, 95%CI 0.45-4.78, P = 0.52; Severe disease OR 1.05, 95%CI 0.44-2.49, P = 0.92
6	Noh *et al* [43], 2021	PO, South Korea	Registry based COVID-19 patients with DM; Mortality in DPP-4i users (n = 453) compared with nonusers (n = 133)	All-cause mortality: HR 0.74, 95%CI 0.43-1.26; Severe disease HR 0.83, 95%CI 0.45-1.53
7	Zhou *et al* [44], 2020	RO, China	Multi-centre, hospitalised COVID-19 patients with DM; Subgroup analysis of DPP-4i users (n = 142) *vs* nonusers (n = 1257)	28-d mortality: aHR = 0.44, 95%CI: 0.09-2.11, P = 0.31); Secondary outcomes such as septic shock, acute respiratory distress syndrome, organ (kidney, liver, and cardiac) injuries, were also comparable between the two groups
8	Yan *et al*[47], 2020	RO, China	Hospitalised COVID-19 patients; Subgroup analysis of DPP-4i use in patients with severe illness	No significant association between use of DPP-4i and COVID-19 severity after adjustment for age, sex, and BMI (OR 0.32, 95%CI 0.02-2.18, P = 0.31)
9	Izzi-Engbeaya *et al*[45], 2021	RO, United Kingdom	Registry based COVID-19 patients with DM admitted to 3 hospitals (n = 337); DPP-4i users (n = 93)	Admission to ICU or death OR 1.27 (0.79-2.05)
10	Israelsen *et al* [46], 2021	RO, Denmark	Registry based COVID-19 patients with DM; DPP-4i users (n = 284) compared with SGLT2i users (n = 342)	DPP-4i users- 30-d mortality aRR 2.42 (95%CI 0.99-5.89) when compared with SGLT-2i users. DPP-4i use was not associated with decreased risk of hospital admission
Studies with positive outcomes with the use of DPP-4i				
1	Mirani *et al* [48], 2020	RO, Italy	Single centre hospitalised COVID-19 patients with DM; DPP-4i users (n =11) compared with nonusers (n=79)	DPP-4i users had lower risk of mortality (aHR 0.13, 95%CI 0.02-0.92; P = 0.042)
2	Solerte *et al* [49], 2020	RO case control, Italy	Hospitalised COVID-19 patients with DM; Case sitagliptin + Standard care (n = 169) Controls – age sex matched patients with Standard care (n = 338)	Mortality: HR 0.44, 95%CI 0.29–0.66, P = 0.0001); Admission to ICU: HR: 0.51, 95%CI 0.27-0.95, P = 0.03; Mechanical ventilation HR: 0.27, 95% CI 0.11-0.62, P = 0.03; Hospital discharges 120 *vs* 89, P < 0.01
3	Rhee *et al* [50], 2021	RO, South Korea	Registry based COVID-19 patients with DM; DPP-4i users (n = 263) *vs* non users (n = 832); Assessed for severity of disease	OR for severe disease was 0.303 (95%CI 0.135-0.682) among DPP-4i users
4	Nafakhi *et al* [51], 2020	RO, Iraq	Newly diagnosed COVID-19 pneumonia; Subgroup analysis to assess predictors for adverse outcomes	DPP-4i users had decreased length of ICU stay. (OR 0.3, 95%CI 0.2-3, P = 0.04)
5	Wargny *et al* [52], 2021	PO, France	Registry based COVID-19 patients with DM. Subgroup analysis of DPP-4i use in patients succumbing to death within 28 d	The need for mechanical ventilation and death within seven days were similar in DPP-4i users compared to nonusers. (OR 0.83, 95%CI 0.65-1.05, P = 0.12). Discharge at day 28: OR 1.22, 95%CI 1.02-1.47, P = 0.03)

6	Wong *et al* [53], 2021	RO, China	Registry based COVID-19 patients with DM (n = 1214); DPP-4i users (n = 107) compared with others (n = 1107)	DPP4i users were associated with lower odds of clinical deterioration (OR 0.71, 95%CI 0.54-0.93, P = 0.013), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69, P < 0.001), invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42, P < 0.001), reduced length of hospitalization (-4.82 days, 95%CI -6.80 to -2.84, P < 0.001). No difference seen in mortality
Studies with negative outcomes with the use of DPP-4i				
1	Dalan *et al* [54], 2021	RO, Singapore	Single centre hospitalised COVID-19 patients with and without DM; Subgroup analysis of DM patients using DPP-4i (n = 27) and others (n = 49)	DPP-4i were at higher risk of ICU admission (aRR 4.07, 95%CI 1.42-11.66) and mechanical ventilation (aRR 2.54, 95%CI 0.43-14.99)
2	Khunti *et al* [55], 2021	RO, United Kingdom	Registry based Nationwide cohort data; HR of COVID-19-related mortality assessed in patients with diabetes on DPP-4i	HR 1.07 (1.01-1.13)

COVID-19: Coronavirus disease 2019; DPP-4i: Dipeptidyl peptidase-4 inhibitors; CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; n: Number of patients on DPP-4i; N: Number of patients with diabetes; OR: Odds ratio; PO: Prospective observational; RO: Retrospective observational; RR: Relative risk;

medications (adjusted OR 0.362, 95%CI 0.135-0.971). The study included 832 subjects with DM, of whom 263 were on DPP-4i[50]. Similarly, DPP-4i usage was related to a shorter ICU stay in 67 patients with DM admitted with COVID-19 pneumonia in a single centre in Iraq (OR 0.3, 95%CI 0.2-3)[51].

In the coronavirus disease and diabetes outcome (CORONADO) study, a multicentric prospective observational trial conducted in France, 2796 patients hospitalized for SARS-CoV-2 with DM were assessed. Around 21.6% of the participants were on DPP-4i. The primary outcome as assessed by the need for mechanical ventilation and/or death within seven days was similar in DPP-4i users compared to nonusers (OR 0.83; 95%CI 0.67-1.03)[52]. Wong *et al*[53] retrospectively analyzed 1214 T2DM patients with confirmed COVID-19 admitted to public hospitals in Hong Kong. They found a lower risk for clinical deterioration (OR = 0.71, 95%CI 0.54-0.93), hyperinflammatory syndrome (OR = 0.56, 95%CI 0.45-0.69) and invasive mechanical ventilation (OR = 0.30, 95%CI 0.21-0.42) in DPP-4i users. However, DPP-4i users had no significant in-hospital mortality reduction.

A retrospective review of 717 COVID-19 patients admitted to a health care centre in Singapore found contradictory results. Patients on DPP-4i (n = 27) showed greater odds of ICU admission than those on other glucose-lowering medicines (adjusted relative risk [RR] 5.14, 95%CI 1.5-17.7). Also, patients on DPP-4i were more likely to require mechanical ventilation; however, no data on mortality were provided[54]. Similarly, Khunti *et al*[55] in their nationwide observational cohort study in the UK analysed the HR of COVID-19-related mortality in people prescribed DPP-4i. DPP-4i users had a HR of 1.07 (95%CI 1.01-1.13) for COVID-19-related mortality.

The evidence available from observational studies on the link between DPP-4i and DM and COVID-19 outcomes suggests some heterogeneity. These outcomes were extensively evaluated in multiple meta-analyses[56-62]. Bonora *et al*[56] analyzed seven studies that reported data on mortality. There was no significant difference in death rate between patients treated with DPP-4i and other anti-diabetic medications (RR 0.74, 95%CI 0.47–1.16). Han *et al*[57] also showed similar results with a statistically non-significant lower mortality (OR 0.95, 95%CI 0.72-1.26) or poor composite outcomes (OR 1.27, 95%CI 0.91–1.77) in diabetic COVID-19 patients. Similarly, Pal *et al*[58] included nine observational studies of high quality consisting of 7008 COVID-19 patients with DM. A pooled analysis of unadjusted and adjusted data revealed no significant link between DPP-4i usage and mortality. However, subgroup analysis discovered that DPP-4i use in the hospital (rather than before admission) was related to lower mortality (adjusted OR 0.27, 95%CI 0.13-0.55). Contrary to the above studies, Nguyen *et al*[59] in their recent meta-analysis linked DPP-4i to a higher mortality risk (OR 1.23, 95%CI 1.07-1.42).

DPP-4i appear to have a neutral action in COVID-19, but the available studies are still insufficient to draw definitive conclusions. It is worth noting that all the data are from retrospective observational studies and that most of them were not specifically designed to study the effects of DPP-4i. The discrepancies reported for the connection between DPP-4i and COVID-19 outcomes could be explained by variations in methodology, baseline characteristics, and sample size.

RANDOMIZED CONTROLLED TRIALS

Two randomized controlled trials (RCTs) have evaluated DPP-4i in patients with diabetes and COVID-19 (Table 2).

Abuhasira *et al*[63] investigated 64 patients who were randomized to receive linagliptin 5 mg once daily or standard of care medication in an open-label, prospective, multicentre RCT (32 in each group).

Table 2 Randomized controlled trials assessing coronavirus disease 2019 outcomes and dipeptidyl peptidase-4 inhibitors therapy

Sl no	Ref.	Design, location	Comparators	Age (mean ± SD)	% male	Primary outcomes	Secondary outcomes	Results
1	Abuhasira *et al*[63]	Open-label, prospective, multi-centre trial, Germany	Linagliptin 5 mg + standard therapy (n = 32); Standard therapy (n = 32)	65.5 ± 16; 68.4 ± 11.5	65.6%; 53.1%	Time to clinical improvement	Proportion of patients with 2- point clinical improvement at 28 d, mortality at 28 d, length of hospitalization, ICU admissions, and MV	Time to clinical improvement (HR 1.22; 95%CI, 0.70-2.15; P = 0.49); In-hospital mortality; (OR 0.56; 95%CI, 0.16-1.93). No difference in secondary outcomes
2	Guardado-Mendoza *et al*[64]	Parallel double blind single centre trial, Mexico	LI group (n = 35) I group (n = 38)	57 ± 2; 60 ± 2	51%; 76%	Need for assisted MV and mortality	Glucose levels and insulin requirements, pulmonary parameters and clinical progression	Reduced risk of assisted MV; (HR 0.258, 95%CI 0.1-0.7, P = 0.009), improved blood glucose levels, lower insulin requirements in LI group

HR: Hazard risk, I: Insulin, LI: Linaglitin plus insulin, MV: Mechanical ventilation, OR: Odds ratio, RR: Relative risk, SD: Standard deviation.

The time to clinical improvement within 28 d of randomization was the primary outcome measured. Treatment with linagliptin in addition to standard therapy did not enhance time to resolution of symptoms (HR 1.22, 95%CI, 0.70-2.15) or death on day 28 (OR 0.56, 95%CI 0.16-1.93). Furthermore, no differences in any of the secondary outcomes, such as the proportion of patients admitted to an ICU, mechanical ventilation rates, length of hospitalization, or supplemental oxygen use, were observed between the study groups. However, due to containment of the COVID-19 epidemic in Israel, the experiment was prematurely terminated, leaving the study underpowered to identify possible differences in the primary results and mortality.

In a parallel, double-blind RCT, Guardado-Mendoza *et al*[64] evaluated the efficacy of the combination of linagliptin and insulin on metabolic control and prognosis in hospitalized patients with COVID-19 and DM. A total of 73 patients were randomly assigned to either 5 mg linagliptin plus insulin (LI group, n = 35) or insulin alone (I group, n = 38). The need for assisted mechanical ventilation and mortality were the two primary outcomes. Secondary outcomes were glucose levels and insulin requirements during the first 5-10 days in the hospital, pulmonary parameters, and clinical progression of COVID-19. Both groups had similar average hospital stays (12 ± 1 *vs* 10 ± 1 d, P = 0.343). Three patients in the LI group and twelve in the I group needed assisted mechanical ventilation (HR 0.258, 95%CI 0.092-0.719), and two patients in the LI group and six in the I group died after a 30-d follow-up period (P = 0.139). The inclusion of linagliptin reduced the relative risk of assisted mechanical ventilation by 74% and improved pre- and postprandial glucose levels, requiring less insulin and posing no increased risk of hypoglycemia.

CONCLUSION

Beyond their well-known glycemic role, DPP-4i have anti-inflammatory, immunomodulatory, and anti-fibrotic properties. They are among the non-insulin glucose-lowering medications that are safe and effective in treating T2DM, even in the presence of COVID-19, without increasing the risk of significant side effects such as hypoglycemia. As a result, practical recommendations for the management of diabetes in patients with COVID-19 do not propose stopping DPP-4i. Even though results from observational studies and a few RCTs have been inconsistent, the existing evidence suggests that DPP-4i are safe for patients with T2DM and COVID-19. Studies showed a trend towards reducing mortality in COVID-19 patients with DM, especially with continued in-hospital use of DPP-4i. As a result, it is appropriate to start or continue DPP-4i in COVID-19 individuals with DM unless contraindicated.

FOOTNOTES

Author contributions: Naik D conceptualized the work; Narayanan N wrote the first draft and provided critical inputs; Sahoo J, Naik D, and Kamalanathan S supervised the writing and critically revised the manuscript; Narayanan N edited the final draft; all authors have read and approved the final version of the manuscript

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic affects all countries and populations worldwide, significantly impacting people with autism with a high risk of morbidity and mortality due to COVID-19. Approximately 25% of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. In addition, they frequently have various comorbid conditions that increase the severity of COVID-19. In addition, severe COVID-19 during pregnancy may increase the risk of autism in the offspring. Furthermore, severe acute respiratory syndrome coronavirus 2 could target human nervous system tissues due to its neurotrophic effects. The COVID-19 pandemic intensely impacts many patients and families in the autism community, especially the complex management of autism-associated disorders during the complete lockdown. During the complete lockdown, children with autism had difficulties coping with the change in their routine, lack of access to special education services, limited physical space available, and problems related to food and sleep. Additionally, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community supports are no longer functioning to protect them. Early detection and vaccination of children with autism against COVID-19 are highly indicated. They should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. In this review, we discuss the various effects of COVID-19 on children with autism, the difficulties they face, the increased risk of infection during pregnancy, how to alleviate the impact of COVID-19, and how to correct the inequalities in children with autism.

Key Words: Autism; ASD; Autism Spectrum Disorder; Children; COVID-19; Testing; Vaccination; Neurotropism; SARS-CoV-2

Core Tip: The pandemic of coronavirus disease 2019 (COVID-19) has dramatically impacted children with special needs. Besides the COVID-19-related high morbidity and mortality, other changes associated with the pandemic negatively impacted the educational and health-related issues of children with autism. The lockdown adversely affected sensory-motor development, cognitive abilities, sleep, morale, behavior, and social interactions in a large proportion that may reach 50% of children with special needs. Children with autism should be prioritized for testing and proper management of COVID-19 and other infectious diseases.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic affected worldwide countries and populations. It is caused by a strain of coronaviruses called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)[1]. It has cast great shadows and impacts on children with special needs. It deprived them of many opportunities to improve their condition, especially with the massive interruption of medical follow-up and rehabilitation during the lockdown and the difficulty in physical communication that a child with special needs requires to develop and upgrade his mental and physical abilities, as we follow the policy of physical distancing[2]. The lockdown significantly impacted the sensory-motor development, cognitive skills, sleep, morale, behavior, and social interactions in about 50% of children with special needs. There is also plenty of evidence suggesting the adverse effects of SARS-CoV-2 and the measures we take to limit its spread to children with disabilities and their families[3]. In addition, some primary health conditions in children with disabilities and special needs may expose them to a higher risk of contracting the virus and suffering from complications to a higher degree. These children, particularly those who suffer from sensory processing and integration such as tactile, vestibular, proprioceptive, and difficulties in hearing, vision, and cognitive performance, also face problems taking necessary preventive measures during epidemic periods such as wearing masks, keeping a physical distance, washing hands, and using sanitizer[4]. Autism is a spectrum disorder (ASD) with a wide variation in clinical manifestations. In this manuscript, we will use the term autism rather than ASD.

Autism itself poses a significant burden on the family with a child affected by it. It puts a severe financial and psychological burden on the family. This effect has multiplied several times with the COVID-19 pandemic[5]. This review aims to highlight the various impacts of COVID-19 on children with autism, the difficulties they encounter, including vaccination and testing, the infection-induced risk during pregnancy, and the different suggestions to alleviate the effects of COVID-19 and correct the inequalities in children with autism.

IMMUNE STATUS OF CHILDREN WITH AUTISM

Approximately one-quarter of children with autism have an asymptomatic or symptomatic immune deficiency or dysfunction. Many of these children may have asymptomatic immune dysregulation, so it is imperative to rule it out, particularly in children with gastrointestinal disorders[6]. Rose *et al*[7] found that children with autism have more oxidative stress and less glutathione-mediated redox/antioxidant ability than typically developed children. This oxidative stress and impaired glutathione redox homeostasis have a significant role in immune dysregulation observed in children with autism. Gastrointestinal dysbiosis is frequently encountered in children with autism and causes impaired mucosal barrier, gastrointestinal dysfunction, and immune system and nervous system dysregulation. The gastrointestinal dysfunction and the increased oxidative stress induce mitochondrial dysfunction, affecting both the mental function and immune status of children with autism[8]. Thus, during long-term exposure of children with autism to toxic stress and environmental deprivation during the COVID-19 pandemic, they suffer regressions in sensory-motor, physical, and mental health development[9].

Despite children with autism having low serotonin concentrations in the brain, they have an elevated blood count of mast cells with high blood and urine serotonin levels. These elevated serotonin concentrations in tissues out of the blood-brain barrier are related to mast cell activation with increased mast cell cytokines/chemokines; another significant contributor to the immune and neuroinflammatory dysregulation observed in children with autism[10,11]. Natural killer cells may be crucial in developing neurodevelopmental disorders, including autism. Enstrom *et al*[12] found abnormal gene expression and altered natural killer cell function in children with autism with increased production of interferon-gamma (IFNgamma), granzyme B, and perforin under resting conditions and decreased production under stressful conditions. In addition, Manzardo *et al*[13] found that three cytokines involved in hematopoiesis and five cytokines involved in the attraction of T-cells, monocytes, and natural killer cells are lower in children with autism than in typically developed siblings.

Heuer *et al*[14] found significantly decreased plasma IgG and IgM levels in children with autism than in children with developmental delay or typical development. They also found that the degree of IgG and IgM levels reduction was significantly correlated with the Aberrant Behavior Checklist score; the more the drop is, the more the aberrant behavior. In addition, IgA deficiency is associated with an increase in the autism rate. Wasilewska *et al*[15] found that insidious changes in serum immunoglobulins with low-normal IgA and increased B cell activation marked by the rise in CD19/CD23-positive cells occur in children aged 3-6 years with regressive autism. These immune and neuroinflammatory dysregulations are major pathogenic components in autism, as evidenced by the high pro-inflammatory cytokines in postmortem biopsies obtained from the brain of children with autism. These immunological changes can serve as a marker for the development of autism.

Furthermore, individuals with autism have an increased prevalence of a positive family history of autoimmune disorders (such as rheumatoid arthritis and autoimmune thyroiditis), specific major histocompatibility complex haplotypes, and abnormal immunological marker levels[16]. Consequently, autism is strongly linked to abnormal immune responses, which may be an area for targeted intervention to prevent or treat children with autism. Unfortunately, COVID-19 effects on the immune system make children with autism more vulnerable to other diseases and further regression[17].

NEUROTROPIC EFFECTS OF SARS-COV-2

Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the central nervous system (CNS) or the peripheral nervous system (PNS) or as a part of the virus's systemic effect. Recent studies using human brain organoids showed that SARS-CoV-2 could target human nervous system tissues[18]. Although neurological disorders are relatively uncommon with coronavirus infections, two strains can enter and persist in the brain cells, including SARS-CoV and SARS-CoV-2[19]. COVID-19 showed moderately severe neurological problems (Figure 1), ranging from mild symptoms such as headache, dizziness, and smell and taste impairment to severe manifestations including Guillain–Barre syndrome, encephalitis, neuropsychiatric disorders, neurocognitive impairment, psychosis, vision impairment, dementia, and cerebrovascular defects as ischemic strokes, or intracerebral hemorrhages[20-22].

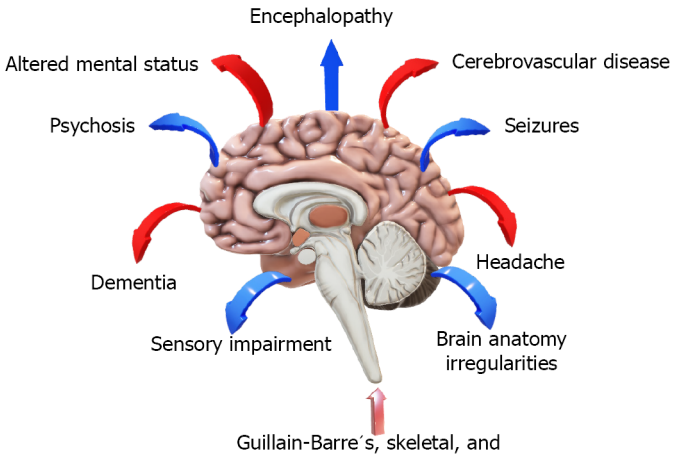

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Figure 1 The various neurological symptoms observed in patients with coronavirus disease 2019.

The structural brain damage detected by magnetic resonance imaging and the presence of viral RNA in cerebrospinal fluid (CSF) and autopsy brain samples from patients with COVID-19 and neurological manifestations proves SARS-CoV-2-induced neurological effects. These neurological sequelae of SARS-CoV-2 are either due to the direct CNS toxic effect of the virus (as many brain cells express angiotensin-converting enzyme-2 (ACE2) receptors, the primary SARS-CoV-2 receptor, and other linked proteins and receptors such as Neuropilin-1 (NRP-1) and CD147) or as a result of a virus-mediated CNS inflammation and immune dysregulation due to the aggressive cytokine storm or the abnormal immune response[23-25].

COVID-19 AND MORTALITY RATES IN CHILDREN WITH AUTISM

COVID-19 is a systemic disease that could affect any organ or system. Many risk factors increase the rate and severity of infection with SARS-CoV-2, including male gender, older age, and medical comorbidities such as obesity, immune deficiency, autoimmune diseases, diabetes mellitus, or hypertension. Children with autism have many physical and behavioral risk factors that expose them to higher infection, morbidity, and mortality rates related to COVID-19[26]. Children with autism may require more exposure to outside caregivers and other children with a higher chance of encountering carriers of SARS-CoV-2. They frequently have persistent oral sensory-seeking behavior, which exposes them to an increased risk of contracting the virus[27]. Pica is approximately seven times more common in children with autism than in the general population, which exposes them to more infection risk. They also have challenges applying the pandemic's social distance and hygiene-related guidelines[28]. They are not able or scared to wear a mask and maintain physical distance, exposing themselves and others to a higher risk of spreading or catching COVID-19. They do not understand what COVID-19 is and cannot tolerate the sensory inputs related to preventive measures they require to protect themselves[29].

Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. Immune deficiency is commonly reported in children with autism, increasing the risk and severity of infections, including COVID-19[30]. IgA deficiency is a significant risk factor for both autism and infection with SARS-CoV-2. Serum IgA levels positively correlate with total lymphocyte counts and negatively correlate with C-reactive protein levels. Consequently, IgA deficiency, low lymphocyte count, and high C-reactive protein levels are significant risk factors for severe COVID-19[31]. Patients with autism have cytokine dysregulation with increased inflammatory cytokines production and impaired immune response at different levels[32]. Autism is four times more common in males than in females. Males are more prone to infection, particularly with SARS-CoV-2[33, 34]. Gut dysbiosis is frequently found in children with autism and is linked to many gastrointestinal and neurobehavioural symptoms[35]. There is a bidirectional relation between infection with SARS-CoV-2 and the gut microbiota. Infection with SARS-CoV-2 causes respiratory and gastrointestinal microbiota dysbiosis, which negatively impacts gastrointestinal and respiratory health. Dysbiosis of the gut microbiota produces an appropriate environment for replication of SARS-CoV-2 and subsequent pathogenic effects. Gut dysbiosis can induce pulmonary dysbiosis through the gut-lung axis, which determines the course and severity of COVID-19. On the other hand, gut microbiota diversity and the predominance of beneficial bacteria can improve the course of COVID-19 and alleviate the severity of the disease[36,37].

Schott *et al*[38] showed an increased risk of SARS-CoV-2 infection in patients with autism, especially in those who live in a residential facility, those who receive home services from outside caregivers, who need a lengthy hospitalization, and those with comorbidities. Krieger *et al*[39] showed an increased rate of infection and hospitalization in persons with autism, especially men between 40 to 60 years. Karpur *et al*[40] showed that persons with autism are nine times more likely to be hospitalized and six times more likely to have extended hospital stays than those without autism.

When hospitalized, children with autism have difficulties in social communication, the ability to express their symptoms, and understanding and following the safety guidelines. Many children with autism also have various challenging behaviors (*e.g.*, spreading and spitting saliva, pica and licking staff, and spreading stool that helps spread the virus. They strongly resist the change in the hospital environment and have aggravated stereotyped behavior patterns. Wearing protective equipment by the healthcare provider is another challenge and increases stress among children with autism[41]. In addition, people with autism may suffer some discrimination in the priority of receiving medical care depending on their counties' Intensive Care Unit (ICU) Triage Protocols and Policies. For example, the triage system in Spain used "severe baseline cognitive impairment" as an exclusion criterion for ICU admission in their triage guidance for COVID-19 ICU admission, according to the "Working Group of Bioethics of the Spanish Society of Intensive, Critical Medicine and Coronary Units." These features increase the risk of morbidity and mortality when hospitalized[41,42]. A systematic review and meta-analysis by Catalá-López *et al*[43] showed a higher mortality rate in persons with autism or attention-deficit/hyperactivity disorder than in the general population (relative risk of 2.37 and 1.97, respectively).

COULD COVID-19 DURING PREGNANCY INDUCE AUTISM?

Febrile maternal infection during pregnancy doubles the risk of autism in their offspring[44]. Currently, there is no evidence for the vertical transmission of SARS-CoV-2 from the mother to the fetus, which could be related to the preventive effect of lactoferrin at the placental interface. However, the virus could be transmitted postnatally through the mother's respiratory droplets or breastmilk[45]. In addition, severe COVID-19 during pregnancy induces the release of the inflammatory cytokine storm, which may cause fetal damage if not controlled. The brain is one of the target organs affected by inflammatory damage that could present later with autism manifestations[46]. The etiology of autism is multifactorial, with interacting genetic and environmental factors. Maternal immune activation is a significant risk factor for the offspring's neurodevelopmental diseases such as schizophrenia and autism [47]. Children with autism are more liable to many mental health disorders such as depression, sleep disorders, addiction, attention deficit, and hyperactivity behaviors since the COVID-19 pandemic started[48] (Panda).

Moreover, children with autism are among the most vulnerable populations affected by extended hours of online learning, flat-screen media, and mental health consequences during and after the COVID-19 pandemic[9,49]. Prenatal brain inflammation causes neurodegenerative changes and " short-circuiting the electrical system" in the amygdala, crucial for emotional feeling ability and fear regulation. Children with autism have exaggerated fear responses compared to their peers in neutral events. The Hypothalamic-Pituitary-Adrenal (HPA) axis system is hyper-responsive due to unpleasant sensory stimuli and/or benign social situations[50].

Insulin-like growth factor-1 (IGF-1) is a central component in perinatal oligodendrocytes-mediated neo-neuronal myelination, as it is essential for the survival of Purkinje cells in the cerebellum. IGF-1 deficiency is implicated in the pathogenesis of autism[51]. It is formed together with the growth hormone by the placenta. Maternal COVID-19 infection induces maternal immunologic activation with a marked increase in the production of pro-inflammatory cytokines, which inhibit placental IGF-1 synthesis. Reduced IGF-1 production downregulates perinatal myelination of the developing nervous system and brain dysconnectivity. If this downregulation is not corrected, a permanent neurologic deficit will occur or worsen[52,53].

In addition, SARS-CoV-2 can activate mast cells which in turn cause microglial activation. These changes release excess inflammatory molecules, stop synapses "pruning," impairing neuronal connectivity, and reduce the fear threshold, disrupting the emotional expression observed in children with autism[54]. The effects of impaired neuronal connectivity and reduction in the fear threshold worsen the problem as children with autism already have an overall sluggish HPA axis in responding to physiological or physical manipulation. These children have shown hypo-responsiveness to stressors that involve social evaluative threats[50].

The infection-induced inflammatory antenatal immune milieu is the chief trigger causing impaired fetal brain development, with long-term cognitive impairments. It is advisable to delay future pregnancy until the pandemic ends, immunization before preplanned pregnancies, follow safety guidelines with frequent hand washing, and regular testing in pregnant ladies to discover asymptomatic infection early[55]. A study in the New York metropolitan area showed that about 15% of pregnant women who presented for delivery were COVID-19 positive and mostly asymptomatic[56].

This percentage can indicate how many pregnant ladies carry the SARS-CoV-2 without symptoms worldwide, especially in areas without proper testing facilities. The effects of asymptomatic COVID-19 on the offspring are still unknown and need further research. To minimize the impact of COVID-19 infection during pregnancy, the mother is advised to have a high choline and luteolin supplement in addition to vitamin D, n-3 polyunsaturated fatty acids, and folic acid, which have beneficial effects on brain function development in infants of mothers who encountered viral infections in early pregnancy [57]. Luteolin is a potent natural flavonoid inhibitor of mast cells and microglia activation and blocks SARS-CoV-2 binding to its ACE2 receptor[54].

IMPACT OF COVID-19 ON AUTISM MANAGEMENT

To minimize the risk of COVID-19 spread, most governments imposed a near complete lockdown with extreme measures such as home confinement and shutting of special education systems. Most children with autism stopped receiving the required education and clinical therapies during the lockdown. In addition, children with autism usually resist changes in their routines. Consequently, most of them suffered during the lockdown with the closure of their kindergartens, schools, and other services they usually attend daily. At the same time, the family showed changes in its structure with the availability of a parent who is frequently absent from home, more time spent with a sibling, or separation from their grandparents who were usually present. The uncertainty about COVID-19 and the rapid and constant flow of information could devastate people with autism and increase their distress[58,59]. In addition, children with autism or intellectual disabilities are more liable to be abused by others during the pandemic when the standard community-protecting supports are no longer functioning[60]. In addition, the extended homestay increases inattentive-hyperactive behavior, screen and games addiction, and sleep disorders that lead to comorbid mental health disorders in children with autism. Depriving children with autism of their therapeutic intervention induces environmental deprivation of specific sensory tools, equipment, and inputs that help to accelerate developmental shifting and progress rates. This change is critical since online education and home training on their own cannot overcome clinical symptoms in children with autism[61].

These changes impose additional stress upon them and their families, with interrupted language development, exacerbated anxiety, more frustration, and short temper related to the fear of regression of the gained skills and sadness due to cessation of general care and support by dedicated clinical therapists and teachers. Children with autism had a significant increase in stimming, self-injury, nervousness, violence, impulsiveness, and binge eating behaviors during the pandemic[62]. Tokatly *et al* [63] showed a link between the absence of speech therapy and the increased rate of repetitive behaviors. In addition to the increased COVID-19-related infection, morbidity, and mortality rate observed in children with special needs, the pandemic deepens the gap in the healthcare inequalities provided for people with autism, adding excess risk for morbidity and mortality.

The COVID-19 pandemic poses various challenges to individuals with autism, their families, and caregivers. In recent Simons Powering Autism Research for Knowledge (SPARK) surveys, most adults with autism and caregivers of children with autism reported adverse effects in almost every field of their lives. While many are handling it well and even have encouraging experiences to share, 82% of families included in the survey reported mental health adverse effects on their children with autism. In comparison, 95% of parents and 93% of adults with autism reported adverse effects on their mental health[64]. In addition, several parents of children with autism committed suicide due to the severe psychological pressure and stress during the care of their children[65].

Mutluer *et al*[28] showed that individuals with autism had difficulties understanding what COVID-19 is and the actions it needs with challenges in applying hygiene-related and social distance regulations of the pandemic. Furthermore, the classic online learning programs do not have supportive accommodations that help children with autism learn while modulating the audio-visual sensory stimuli overload. Consequently, most of them are less likely to follow the proposed behavioral and hygienic habits such as routine hand washing that aim to prevent or reduce the risk of infection or the constant wearing of face masks due to their age, maturity, and limited developmental capacities and disabilities. The majority of the studied individuals stopped getting the required special education during the studied period of the pandemic. They also showed some features related to post-traumatic stress disorders, such as behavioral problems (including increased stereotypies and aggression), hypersensitivity, reduced and impaired sleep, and appetite alterations. They also had significant differences in all Aberrant Behavior Checklist subclasses (ABC) before and after the pandemic conditions. Their caregivers showed an increased anxiety level related to their behavior with a high ABC total score; specifically, the lethargy/social withdrawal subscale score predicted the parents' anxiety score.

Being parents of a child with autism is a real challenge, especially during the COVID-19 pandemic. During the lockdown, shutting down special education and rehabilitation facilities made the parents primarily the only full-time caregivers. Consequently, they depend on their skills to cope with their kids, with the loss of support and guidance from specialists and experts. In many cases, the caregivers of these children are not educated or trained enough to care for their children and manage them like their

typical peers. They may be unable to provide adequate care for their children's clinical symptoms such as seizures, tics, bulimic behavior, or sensory cravings and avoidances. Thus, the developmental rate drops dramatically without adequate clinical and professional special education services for children with autism[66].

Tokatly *et al*[63] showed that the most common problem encountered by the parents of children with autism is coping with the change in their routine, lack of access to special education services, limited physical space available, and food and sleep-related problems. Despite that, some children suffered worsening in their behavioral, developmental, or social domains; others succeeded in overcoming the challenges they encountered and even benefited from them. The researchers emphasized that the best way to help children with autism catch up with these severe modifications in their routine lifestyle is to provide a robust support system to their parents. Many parents lost their jobs or at least had a decrease in their income during the pandemic, with reduced affordability for the cost of special education and rehabilitation services for their children and increased anxiety levels[67]. The long-term effects of the pandemic and infection with SARS-CoV-2 on children with autism need more time to be evaluated.

In contrast, some individuals with autism and their families may manage autism more efficiently during COVID-19-related circumstances. For example, lockdown allowed the parents to spend more time with their children, allowing more sharing of activities, more co-watching, more adherence to rules and routine and limited socialization and physical contact in individuals with autism which could decrease the social-related stress and less physical contact with infected people. The lockdown also reduced the sensory overload for some children with autism and helped them enroll in online schooling that they could not attend in person due to their atypical behaviors in the classroom[68]. Asbury *et al*[68] found that a few children with autism and their families reported some positive effects of lockdown, such as decreased stress related to facing the daily routine challenges such as going to school and other public places or worrying about socializing with others. Some children could change their routines, accept new routines or make their routines. Some of them started to eat foods that they were not familiar with. Increased free time permitted for repetitive trials helped improve their abilities and skills. The availability of family time to spend together enhances the child's communication skills and allows the parent to identify these abilities[63]. The key factors that determine the successful coping of parents during the lockdown are their abilities to satisfy the child's needs, positive attitude in general, their creativity, and attending inventive problem-solving training by healthcare professionals and an occupational therapist specialized in Ayres Sensory Integration® (ASI) for sensory environmental adaptations, functional abilities, and independence in activities of daily living[69] (Dubois-Comtois).

In addition, Sergi *et al*[70] showed that children with autism involved in an Applied Behavior Analysis (ABA) based intervention during the lockdown period showed improvements in their communication, socialization, and personal autonomy. They also showed the significant effect of parents' training in avoiding delays in the generalization of socially significant behaviors following the radical treatment interruption in this group of children. Perhaps the best thing related to the COVID-19 pandemic is our awareness of how good our pre-COVID-19 lives were. Research has shown that consistent telehealth and home-based in-person occupational, physical, and speech therapies were beneficial in helping children with autism maintain their developmental rates and progress to the next level. However, parents and caregivers reported less satisfaction with telehealth services than with in-person therapy sessions. Furthermore, parents who reported higher emotional dysregulation in their children were less satisfied with ABA services[71].

INDIRECT IMPACT OF COVID-19

An indirect effect of COVID-19 was the significant reduction of the national income in most countries, which led to a lack of spending on health services related to the management of autism and giving priority to patients with COVID-19. At the same time, numerous community-based services provided by non-profit organizations and the private sector stopped due to acute financial instability. These financial crises caused a delay in the available diagnostic services and, consequently, a delay in the required therapy with a waiting list that could extend to more than a year[72]. Another significant indirect effect is the accuracy of the conducted studies during the pandemic. For example, there were difficulties in performing autism research due to social distancing and the need for the participants to wear masks. These behavioral and environmental changes increase stress conditions, making interpreting the behavior of individuals with autism difficult and affecting the research results. In addition, there is a high risk of missing scientific accuracy during moments of crisis[17].

With social distancing becoming an essential method of COVID-19 prevention, telemedicine and telehealth possibly become the ideal communication methods between caregivers and patients[73]. There has been a flood of videoconferences, "live presentations" in social networks, online training classes on online learning platforms, telepractice concerning different fields such as psychiatry, psychology, occupational therapy, speech therapy, and other remote activities that offer support, guidance, and treatment when applicable. Telemedicine requires an effective internet service, which may not be available in less developed countries or areas, which deepens the inequalities in the health

services provided to children with autism[74]. Even with strong internet, most children with autism may have difficulties following the screen during online teaching. One of the vital factors is the shortage of the sensory, motor, and cognitive accommodations needed to support the mind, brain, and body functions during the learning process. Furthermore, governments are not sufficiently drawing and applying the contributions of healthcare professionals to the academic learning process. Thus, children with autism are generally more prone to gaps in their developmental and learning processes that can be successfully implemented and reflected in the nations' economies[75].

On the other hand, there is a silver lining to the pandemic; scientists hurry to find alternative ways to continue their research and invent reasonable solutions to assist remote diagnosis, proper assessment, and manageable treatment accessible for all and increase participation in their clinical research[76]. Simultaneously, the COVID-19 pandemic represents a perfect opportunity to study the epidemiology of autism and the effects of the pandemic on environmental, genetic, and psychosocial factors on autism mechanisms over a long period worldwide[77]. We may have an unprecedented chance to study how the environment, stress, mental health comorbidities, and autism interact. The pandemic is also an excellent chance to test the efficacy of social robots for education and medical care for individuals with autism. Social robots work in a highly predictable and lawful system and provide children with autism with a highly organized learning environment that helps them focus on essential stimuli. Robots can provide these services during epidemics without the risk of transmitting infection. In addition, children with autism communicate more engagingly and have better social behaviors with robots than with human trainees[78,79].

TESTING CHILDREN WITH AUTISM FOR COVID-19

Individuals with autism should have a high priority for COVID-19 testing and other similar pandemic situations because they have an increased incidence of medical comorbidities (such as cardiovascular or respiratory diseases, hypertension, autoimmune conditions, obesity, and diabetes), high incidence of living in residential care, and difficulties in adherence to strict personal hygiene and physical distancing practices. However, most countries do not consider people with autism as a high-priority group[80]. Individuals with autism have high sensory sensitivities. Consequently, nasal and throat swabs or aspirations become a real challenge for the patient, the family, and the performing healthcare personnel. Children with autism may even need sedation to carry out testing, which may not be available in many situations. Hence, it is better to have more flexible testing procedures, such as saliva testing. People with autism may also encounter the challenge of waiting for a long time and presenting in unfamiliar places for testing. They also may have a problem using the necessary personal protective equipment[59]. Symptoms of COVID-19 may be atypical in people with autism who may indicate the need for a high index of suspicion and the need for equitable access to proactive testing and screening, especially for those with medical comorbidities or who live in high-risk settings such as those who live in supported accommodation or residential care[59].

To alleviate the testing-related anxiety, the parents can create a social narrative that tells the individual with autism what will go on and what they will do during testing. This preparation is better in enumerated steps so the parents can mark done with each completed step[81].

Figure 2 is an example of a visual demonstration of the nasopharyngeal swabbing steps. The narrative should match the person's abilities to understand with fewer words. It is better to put every step on a separate page, and to read the social narrative many times on the day before testing in order for the person to get used to the steps. The caregiver can distract the person's attention during nasal swabbing by using any distracting activities such as coloring a picture or watching a video or alleviate their anxiety by using a relaxing activity such as rubbing their hands or squeezing a squeeze ball if they are used to this[81]. The visual demonstration can also be available in the special care kits to be used by the healthcare provider when encountering persons with special needs to alleviate their tension. Light sedation or analgesia can be given before the test if the person is too anxious and cannot be calmed down[82,83]. An occupational therapist specializing in ASI in the testing and vaccination units helps children with autism have successful testing and vaccination by calibrating the sensory stimuli towards the child's brain and body using standardized and modified measurable evidence-based methods[84].

COVID-19 VACCINES IN AUTISM WHY? AND HOW?

As COVID-19 has a significant negative impact on people with autism, they need to be rapidly vaccinated. Many people with autism have a delay in COVID-19 vaccination as many families are concerned about the vaccine's effects on their children or the country's policy that shows hesitation against vaccinating children with mental and developmental disabilities[85]. A study by Choi *et al*[86] showed that only 35% of the parents of children with autism are willing to vaccinate their children with anti-COVID-19 vaccines. The vaccination rate increases with proper education and evidence-based recommendations. This delay in immunizing children with autism poses an increased risk of severe

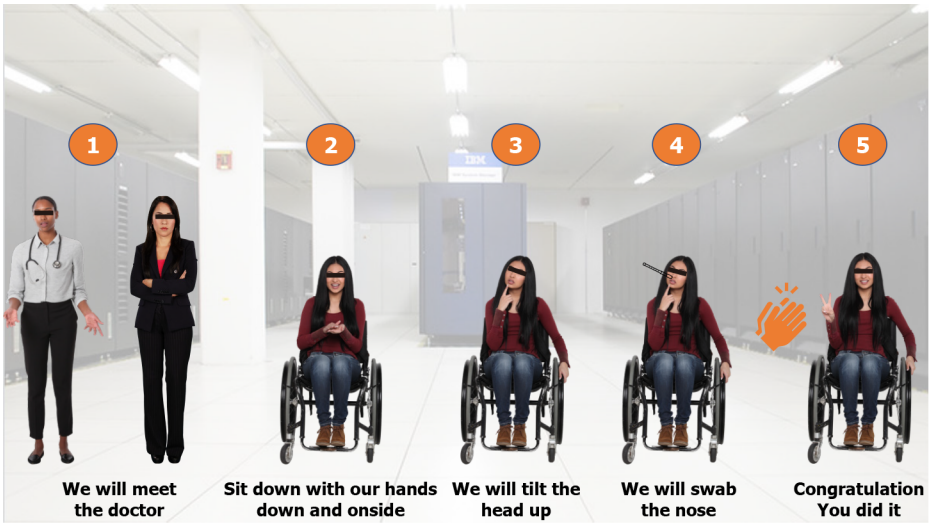

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Figure 2 Visual demonstration of nasopharyngeal swab testing steps.

COVID-19, especially with continuous viral mutations. With the high mortality rate of COVID-19, individuals with autism, especially with intellectual disabilities and other health problems, should be vaccinated as soon as possible, as the vaccines can prevent their death. Individuals with autism and their family members and caregivers should have the vaccine to decrease the risk of COVID-19. These individuals are less likely to adhere to the proper hygiene protocol, cannot wear masks for a long time, and cannot express their symptoms, such as sore throat. Thus, vaccination of their close contacts is also indicated. Vaccination of the parents and caregivers will decrease the chance of getting sick and reduce the possibility of leaving the child without proper care. Interestingly, Weinstein *et al*[87] found a higher rate of COVID-19 vaccination among individuals with autism aged 16-40 years across both sexes than in the controls, but not below the age of 16.

There are different types of COVID-19 vaccinations: COVID-19 Inactivated Vaccines (*e.g.*, Sinovac, Sinopharm), COVID-19 Viral Vector / Adenovirus Vaccines (*e.g.*, Oxford/AstraZeneca, the Johnson and Johnson, CanSino, and Sputnik V vaccines), genetic/mRNA vaccines (*e.g.*, Moderna and Pfizer/BioNTech COVID-19 vaccines), and live attenuated vaccines (Codagenix vaccine: under trials)[88]. Currently, the "Center for Disease Control and Prevention" (CDC) recommends two doses of Pfizer-BioNTech COVID-19 vaccine for five through 11 years of age separated by at least three weeks and an additional primary dose at least four weeks after the initial 2-dose primary series with a total of three doses. According to the CDC, Moderna, and Pfizer/BioNTech, COVID-19 vaccines are at least 90% effective in preventing symptomatic infection by SARS-CoV-2 after two weeks from the second dose [89]. The vaccines are equally effective and safe for individuals with autism as they are for others. People with various disabilities, including autism, were included in most vaccine clinical trials, which showed that the vaccines were safe and effective for everyone. To date, there is no link between COVID-19 vaccination and autism. In addition, maternal COVID-19 infection during pregnancy doubles the risk of autism, emphasizing the importance of immunization[90].

As mentioned earlier, similar to COVID-19 testing, vaccination is also a real challenge for the individual with autism, the family, and the health care provider responsible for the vaccination. Getting a vaccination poses an added challenge, especially since the shots are often not given in a typical doctor's office without a supportive occupational therapist ASI certified. This change in the routine disrupts their usual way of therapeutic care and education, which can be very upsetting. Every parent knows their child best. Therefore, they need to introduce the idea that they need to go driving somewhere, be exposed to somebody, wear protective equipment, and is going to give the vaccine. The parents should explain this many times for a week or day before the vaccination, using a narrative teaching story, video modeling, or visual social demonstration, giving the child enough time to process, understand and accept this new information and routine before the expected appointment. The parents should also help them feel better if they experience vaccine side effects. The CDC and The Autism Society of America prepared various tools, resources, and visual explainers that the parents and caregivers could use to explain the vaccine and the possible adverse effects after receiving the vaccine [91,92].

Table 1 Recommendations to minimize the effects of pandemics on people with autism

Intensive education:	Mandatory education of people with autism, their families, and caregivers about the symptoms and signs of COVID-19 and similar infections and the behavioral procedures to decrease the infection spread[28].
	Emphasize the importance of good sleep hygiene and nutrition during the pandemic[63].
	Educating, supporting, and strengthening the parents' ability to adjust could be particularly valuable in times of extreme life difficulties and during ordinary times that may not be expected[93].
	Training children with autism about how to use personal protective equipment (PPE) by their caregivers will prepare them for the social adaptations during pandemics[94].
	Launching regular mandatory education and updating all the healthcare providers about the management guidelines created for people with autism, supported by specialist providers such as psychiatrists, psychologists, occupational therapists, speech therapists, behavioral therapists, and other specialties as indicated[95].
Prioritization:	For testing and vaccination for people with autism, their families, and caregivers[86].
	For hospitalization and ICU admission in triage protocols[41,42].
	Regular or on-demand access to psychological services regardless of the enrolment[96].
During quarantine:	Allow for one-on-one home visits[97].
	Allow meeting the healthcare provider (*e.g.*, physiotherapist, behavioral therapist) in a previously disinfected open area[97].
	Allow for small classes, and preadmission testing, allowing people with COVID-19 negative testing results to enter the class[98].
	Give permitted exceptions for people with autism, granting them to leave their homes more than once daily[98].
	Providing a sensory-friendly sanitized space for children with autism to release their extra energy, or at least providing tools to help them remove their excess energy, such as a physioball or bringing a swing or trampoline at home to prevent behavioral regression. Encourage physical activity to preserve general well-being[99].
	Provide formal and informal care with psychological and financial support for the well-being and proficiency of parents of children with autism[100].
	Provide weekly or "hotline" consultations for the parents of children with autism to help manage rising general and specific COVID-19-related issues[63].
	Allowing a caregiver or support person to attend to the individual with autism in the hospital, following all required infection control protocols[97].
	During and after the pandemic, preventive measures: to implement an intensive preventive intervention program for children with autism to reduce and prevent relapse and future physical and mental health regressions in future pandemics and/or similar situations [101].

CONCLUSION

The COVID-19 pandemic affects all countries and populations worldwide, including people with autism. Besides respiratory illness, COVID-19 causes unexpected neurological complications, possibly due to direct viral effects on the nervous system. Children with autism frequently have various comorbid conditions that increase the severity of COVID-19 when encountered. There is an increased risk of SARS-CoV-2 infection in patients with autism with high morbidity and mortality rates. Children with autism should be prioritized for testing, vaccination, and proper management of COVID-19 and other infectious diseases. We must correct the inequalities children with autism face in receiving education and healthcare services by collaborating with governmental, non-profit organizations, and individuals to reach this goal.

With the hope that the COVID-19 pandemic will be in the gasping stage, we learned many lessons to be implemented to prevent its adverse effects on people with autism when similar situations occur in the future. We should regularly re-evaluate the mental and physical conditions and development of children with autism and find alternative treatment methods. The medical and rehabilitation teams are critically required to support children with autism and their families and ensure the continuity of physical and mental healthcare during and after the pandemic. Some suggested recommendations to minimize the impact of such pandemics on children with autism are shown in Table 1.

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MINIREVIEWS

Monkeypox: An emerging zoonotic pathogen

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Abstract

Monkeypox virus (MPXV), which belongs to the orthopoxvirus genus, causes zoonotic viral disease. This review discusses the biology, epidemiology, and evolution of MPXV infection, particularly cellular, human, and viral factors, virus transmission dynamics, infection, and persistence in nature. This review also describes the role of recombination, gene loss, and gene gain in MPXV evolvement and the role of signal transduction in MPXV infection and provides an overview of the current access to therapeutic options for the treatment and prevention of MPXV. Finally, this review highlighted gaps in knowledge and proposed future research endeavors to address the unresolved questions.

Key Words: Poxviridae; Orthopoxviruses; Monkeypox viruses; Epidemiology

Core Tip: Since May 13, 2022, cases of monkeypox have been reported to the World Health Organization (WHO) from 12 Member States that are not endemic to the monkeypox virus across three WHO regions. This emergent pathogen is a significant concern worldwide after severe acute respiratory syndrome coronavirus 2 and requires epidemiological and other data on the virus. The objective of this review is to report comprehensive data on this virus.

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INTRODUCTION

Monkeypox virus (MPXV) is one of the human orthopox viruses (OPVs), which consist of variola virus (VARV), cowpox virus (CPXV), and vaccinia virus (VACV)[1]. Monkeypox has similar clinical manifestations to smallpox, but has a milder rash and a lower fatality rate[2]. The aims of this review are to describe the current data on MPXV evolution, epidemiology, and infection-control mechanisms.

History of monkeypox virus

When two smallpox-like illnesses appeared in monkey colonies housed for scientific study, the first cases of monkeypox were discovered in 1958[3]; therefore, the name monkeypox and the first human case of the virus were registered in 1970 in the Democratic Republic of the Congo[4]. Attempts to destroy the MPXV have since been documented in humans in other Central and West African countries [5].

Morphology, genome organization, and morphogenesis

The morphology of MPXV virions has been shown to include brick- or ovoid-shaped particles[6]. Membrane links, a tightly packed core containing enzymes, transcription factors, a double-stranded DNA genome, and an outer membrane protecting the whole structure have been observed[7,8]. Although its whole life cycle occurs in the cytoplasm of infected cells, its genome contains linear double-stranded DNA (197 kb). The genome encodes all the proteins necessary for viral DNA replication, transcription, and virion assembly[6,9]. Cells infected with the poxvirus generate the intracellular mature virus and extracellular enveloped virus, two contagious viruses[10,11] (Figure 1).

INFECTION BIOLOGY, DIAGNOSIS, AND TREATMENT

Animal models

An animal model for studying ethnic illness uses a channel of contamination that matches the herbal transmission of the virus or displays development, morbidity, and death similar to those seen during ethnic infection[12,13]. The animal model also has to mirror human instances in at least one or more methods of transmission[14]. Additionally, the red patches on all MPXV-examined animals at the vaccination site showed a decrease in size compared to nearby animals, and beginning around 14 d after the challenge, a continual rise in body size across fully breathing animals in the vaccinated group[15, 16]. In a study that examined the sensitivity of 38 inbred strains of mice (32 classical inbreed stresses and six wild strains), only three of the wild-derived strains (CAST/EiJ, PERA/EiJ, and MOLF/EiJ) were highly sensitive to MPXV, whereas all other inbred lines were strong after intranasal MPXV infection[2, 17].

Transmission

Human-to-human and animal-to-human transmission are two potential MPXV transmission pathways [18]. Human-to-human transmission stability is correlated with droplet infection and interactions with body fluids, patient factors, and skin lesions in a contaminated individual[6,18]. The Congo Basin group is more virulent than the West African group and contributes more to interpersonal transport[19]. Direct contact and ingestion of the herbal viral host's food are the two routes by which transmission occurs from animals to humans[20,21]. Furthermore, zoonotic transmission can occur *via* direct touch, including blood, body fluids, and mucocutaneous lesions on a contaminated animal[22].

Sexual transmission of MPXV: MPXV outbreaks are not typical, as many patients are unrelated to travel to Central or West Africa and episodes of the virus in endemic areas. The MPXV is currently observed among men who have sex with men (MSM) in the United Kingdom. In the studies conducted, a high proportion of simultaneous sexually transmitted diseases and frequent anogenital symptoms were found, which indicates the possibility of transmission during close skin-to-skin or mucous contact during sexual activity[1,23,24].

Transmission by MPXV-contaminated surfaces: Although co-transmission between people and animals was identified as the primary method of infection dissemination in several investigations, transmission in patient care staff *via* surfaces contaminated with MPXV was seldom recorded. The

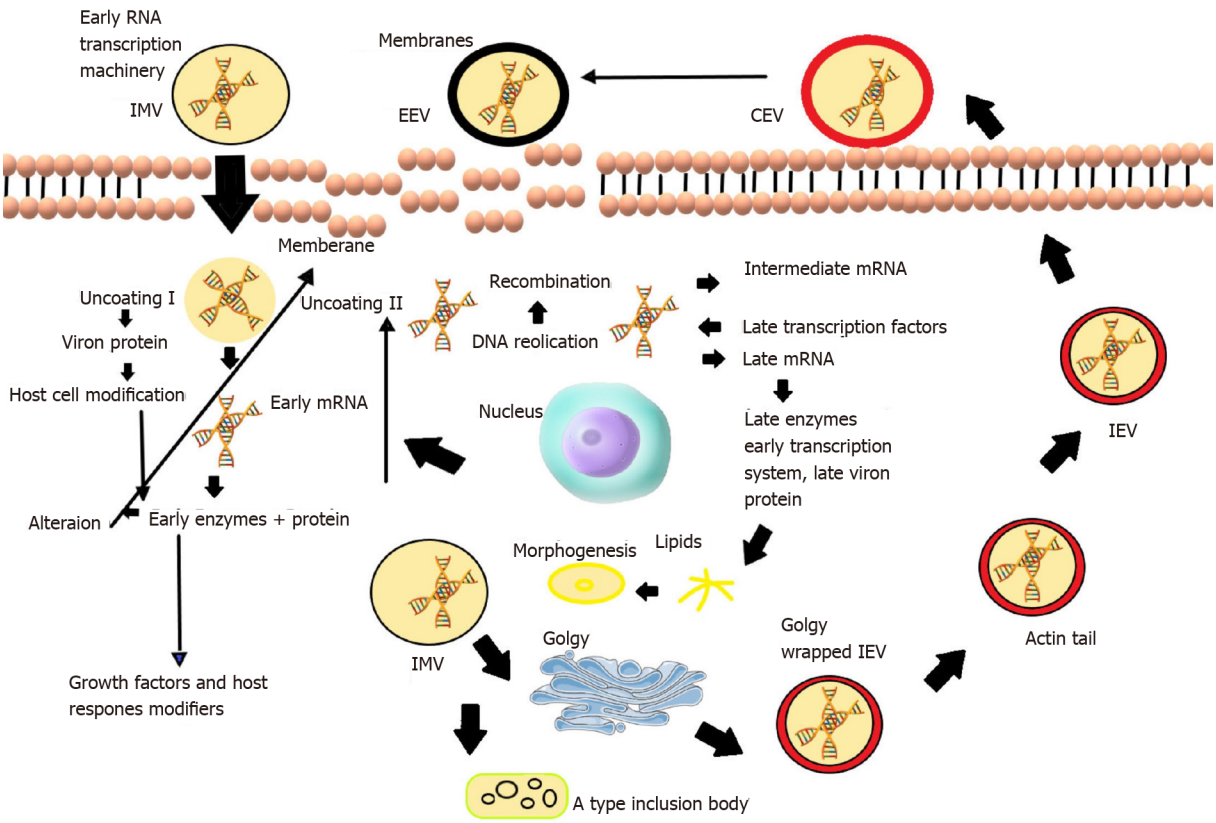

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Figure 1 Cycle of monkeypox virus. When the virion binds and fuses with the host cell membrane, the viral core is released in the cytoplasm. Enzymes, and then factors, initiate transcription. Most virions remain in the cytoplasm. Virus- and host-encoded proteins concerning cell surface-associated enveloped virions and cell surface-associated enveloped virions guard them to complement activation. IMV: Intracellular reduced virion; EEV: Extracellular enveloped virion; CEV: Cell surface-associated enveloped virion; IEV: Intracellular enveloped virion.

MPXV may also spread indirectly *via* contaminated objects. However, the environmental contamination of surfaces with MPXV is not well understood[25].

Diagnostic methods

Phenotypic approaches: Phenotypic methods: According to the clinical diagnosis, in MPXV infection, a prodromal sickness usually accompanies it with a variety of symptoms over 3-5 d, including fever > 38.3°C, back pain, myalgia, headache, acute asthenia, pharyngitis, drenching sweats, malaise, and notably lymphadenopathy[6,26-28]. Vesiculopustular rashes begin on the face during 1-10 d of development, affecting 95% of patients[29], followed by the palms and soles (75%), oral mucosa (70%), genitalia (30%), and conjunctiva (20%). These skin lesions evolve from macules to papules, vesicles, pustules, and finally, scabs or crusts that fall[28]. Lesions in MPXV patients appear monomorphic, pea-sized, and complex, similar to smallpox[30]. The presence of lymphadenopathy in MPXV infection is one of the clinical markers that set it apart from smallpox, along with lesion appearance and limited centrifugal spread[31]. These skin manifestations compromise the skin eruption period of the disease, in which patients are contagious. Before that, patients are not able to transmit the virus. The natural history in patients without complications regularly lasts 2-4 wk[28]. Possible detection of MPXV based on clinical signs is essential to identify suspicious cases during surveillance. Nevertheless, the clinical case definition for MPXV based on unconfirmed studies has high sensitivity (93% to 98%) and low specificity (9% to 26%)[31,32]. Virus transmission occurs by direct bodily contact with pores and skin then skin lesions, along with sexual contact; or contact with contaminated materials, such as clothing, bedding and dishes, within 21 d before signs appear. Laboratory research does not validate the clinical definition, but an epidemiological link, including contact with a proven case does[28].

Genetic methods: It is recommended that genetic techniques, including polymerase chain reaction (PCR) or real-time PCR (RT-PCR), be performed in a biosafety level 3 facility[33].

Routine detection of MPXV DNA in clinical and veterinary specimens and cell cultures infected with MPXV is performed by RT-PCR targeting conserved regions of the outer coat protein (*B6R*) gene, l DNA polymerase E, the DNA-dependent RNA polymerase subunit 18 (rpo18), and the *F3L* genes[33,34]. Restriction fragment length polymorphism (RFLP) of genes or PCR-amplified gene fragments is also

used to detect MPXV DNA, but RFLP is time-consuming and requires viral culture[35]. Additionally, as RFLP of PCR products requires enzymatic digestion after gel electrophoresis, it may not be an appropriate method in a clinical setting where speed, sensitivity, and specificity are essential. Whole genome sequencing (NGS) is valuable in detecting MPXV and OPVs, but this technique is expensive, and downstream sequencing records processing requires extensive computing[36-38]. Therefore, NGS may not be a siutable detection method in resource-poor locations in sub-Saharan Africa. Although RT-PCR remains the optimal method for the identification of MPXV, this must be complemented by genome sequencing technology to provide information on the genome, which is essential for evidence-based epidemiology (Figure 2)[32].

Immunological methods: These methods include enzyme-linked immunosorbent (ELISA) and immunohistochemical assays to determine IgG and IgM antibodies and detect viral antigens[39]. Immunochemical analysis can distinguish poxvirus from herpes virus infection using polyclonal or monoclonal antibodies to all OPVs[11]. It has been shown that antibodies to the virus also have cellular responses and enhancements at the time of disease onset. Approximately 5 d and 8 d or more after the onset of the rash, IgM and IgG are formed in the serum, respectively[40]. Detection of IgM and IgG antibodies in unvaccinated individuals with a history of inflammation and severe illness may increase indirect MPXV discrimination. Despite this, these methods are not specific for MPXV detection and can detect other types of OPVs[32,41]. On the other hand, IgM can assess MPXV infection in people with a history of smallpox vaccination[42]. A positive IgM capture ELISA test indicates recent exposure to OPV (possibly MPXV in endemic areas) in vaccinated individuals.

Conversely, a positive IgG capture ELISA test indicates that a person has been exposed to OPV through vaccination or natural infection. Therefore, IgM and IgG in a sample are strong evidence of recent exposure to an OPV in previously vaccinated or naturally infected individuals. Thus, IgM in individuals vaccinated against smallpox in MPXV-endemic regions reflects recent exposure to MPXV [43,44].

Electron microscopy: MPXV under an electron microscope appears intracytoplasmic brick-shaped with lateral bodies and a central core measuring about 200–300 nm. Although this method is not a definitive diagnostic technique as OPV species cannot be differentiated morphologically, it provides a clue that the virus belongs to the Poxviridae family [45].

Virus-host interaction

Host and tissue tropism: Members of the OPV family are thought to exhibit diverse spectra of host tropisms[46]. Although the reservoir host for MPXV has not been definitively identified, many mammalian species are naturally infected with MPXV[47]. Thus, it is believed that MPXV has a wide host range. Previously, after the challenge with Congo Basin MPXV, large amounts of viral DNA and viable virions died in a variety of animal tissues, suggesting broad tissue tropism. The immunohistochemical and histopathological tests by Falendysz *et al*[48] found that the MPXV antigen was identified in ovarian, brain, heart, kidney, liver, pancreatic, and lung tissues, and ovarian tissues were susceptible to MPXV[49].

Host responses to the virus: PXVs develop many strategies to escape the host's immune response to infection. Natural killer (NK) cells kill virus-infected cells by secreting cytokines that stimulate the activity of other cell types, such as T cells and dendritic cells[50]. MPXV infection can change lymphocyte numbers, NK cell changes in non-human primates (NHPs), lymphadenopathy, and lymphocyte consumption in MPXV-infected NHPs. Gavin *et al*[51] using prairie pooches showed a noteworthy increment in the number of all NK subsets (CD16- CD56-, CD16+, CD56+, and CD16+ CD56+) on the seventh day after vaccination. Moreover, the expression of chemokine receptors (CXCR3, CCR5, CCR6, and CCR7) on each NK cell subset suggest that, following the MPXV challenge, receptor expression was delayed or reduced[11,52]. Hammarlund *et al*[53] anticipated that MPXV has a safe avoidance component such as CPXV. The avoidance process utilized by MPXV ensures the viral store is resistant by repressing the activation of CD4+ and CD8+ T cells after interaction with MPXV-infected cells. Acknowledgment of MPXV-infected monocytes by antiviral CD4+ and CD8+ shows that MPXV does not activate the generation of cytokines (IFN-γ or TNF-α) by virus-specific T cells[52]. Antiviral T-cell responses are substantially increased following contamination with VARV alone. However, T-cell cytokine responses decreased by 95% after co-infection, including MPXV and VARV, and by 80% when low-dose MPXV was added (VARV: MPXV ratio was 10:1)[54].

Treatment

Vaccination: The smallpox vaccine protects humans against smallpox. The smallpox vaccine incorporates a live vaccinia virus, and not a killed virus[55]. Vaccinated people must take precautions, as the vaccine can result in side effects[56]. Most humans have mild reactions such as flank pain, fever, and body aches[51]. However, some people may react differently, and some side effects can be life-threatening[57]. Although smallpox vaccination can shield humans from smallpox for approximately 3-5 years, its potential to protect humans then decreases, and for long-term protection, additional vaccinations may be needed[58]. Several reviews suggest that smallpox vaccination provides cross-protection

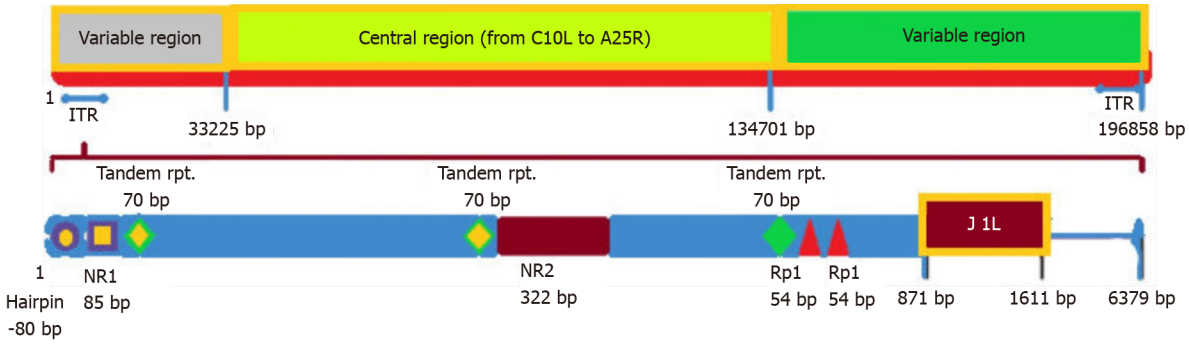

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Figure 2 Genomic structure of monkeypox virus. The entire genome consists of over 196858 bp along the central genomic vicinity of 101476 bp. Both extreme variables (right is longer than left) include a 6379 bp inverted terminal repeat. ITR: Inverted terminal repeat.

against common OPV species and MPXV. Of humans vaccinated against smallpox, 85% did not develop MPXV infection[59]. The smallpox vaccine (ACAM2000™) was advocated by the Centers for Disease Control and Prevention (CDC)[60].

The attenuated vaccine, IMVAMUNE, is no longer available in MPXV areas[61]. A third-generation modified Ankara vaccine has been selected with the aid of the Food and Drug Administration (FDA) and the European Medicines Agency to prevent varicella or monkeypox in adults (age 18 years) with a high risk of VARV and MPXV infection[61,62]. Unlike the ACAM2000 vaccine, IMVAMUNE is no longer used in humans with immunodeficiency, such as immune disorders and atopic dermatitis. Neither ACAM2000 nor IMVAMUNE is used in specific populations[61,62]. Vaccination is also recommended for sexually high-risk individuals, including MSM, and those with a history of sexually transmitted diseases such as human immunodeficiency virus (HIV), syphilis, and gonorrhea. However, there are no statistics on immunization, including smallpox vaccines JYNNEOS®/IMVANEX® that may confer protection against sexually transmitted MPXV[51,63].

Antivirals: There is no approved, safe remedy for MPXV infection. A 4-trifluoromethylphenol derivative and tecovirimat (ST-246 or TPOXX®), supported by the FDA, have been examined using animal models[64]. These agents have been shown to be beneficial in infected animals. According to a CDC report, clinical trials, including on tecoirimate, show that although the treatment is well tolerated and safe, there are inadequate statistics on its usefulness in treating monkeypox in humans[61,65,66]. Similarly, *in vitro* studies with cidofovir or brincidofovir (CMX001 or hexadecyloxypropyl-cidofovir) reduced viral DNA polymerase, and is an acyclic nucleoside phosphate conjugate of cidofovir[61,66,67]. However, brincidofovir has increased cytotoxicity and higher antiviral activity than cidofovir towards VARV, MPXV, VACV, and CPXV *in vitro*.

Brincidofovir has a high selectivity index and is 25-fold greater than cidofovir. Cidofovir is a nucleotide monophosphate analog. Another dynamic agent against poxviruses is NIOCH-14, a precursor of tecovirimat[66-68]. Although the activity of NIOCH-14 towards VARV, MPXV, and ECTV is similar to that of tecovirimat in *in vitro* studies, its production is less complicated than tecovirimat, and has been recognized as an essential antiviral in the future. Ribavirin and tiazofurin inhibited the activity of every OPV tested including VARV and MPXV[59,61,68,69]. Saquinavir, ritonavir, and nelfinavir are protease inhibitors, and efavirenz, stavudine, and zidovudine are reverse transcriptase inhibitors and have been used against OPVs. In addition, two adenosine analogs (C-ca3-Ado and C3-Npc A) have been shown to have protective activity against OPVs in viral replication assays, and these analogs are also inhibitors of S-adenosylhomocysteine hydrolase (SAH)[59,61,67,68]. These SAH hydrolase inhibitors have broad antiviral activity but had no detectable effect on CPXV *in vitro*. Using specific mechanisms, cidofovir and N-(2-hydroxypropyl) methacrylamide inhibited viral duplication in PXVs. However, adefovir and dipivoxil showed no sizeable activity against poxviruses.

Furthermore, adenosine oxide N1 had a considerable effect on OPV by inhibiting CPXV viral reproduction *in vitro* by blocking viral mRNA translation[52,68,70]. Although there is no optimal therapy, MPXV is managed only by supportive than evidential treatment, and is only suitable for symptomatic individuals[66,68]. Thus, environmentally friendly MPXV vaccination and antiviral agents are required to prevent transmission from asymptomatic people.

Biocidal agents and disinfectants: On June 5, 2022, a study was conducted to assess the published data regarding the antiviral effect of biocides and disinfectants against MPXV and orthopoxviruses. Vaccinia viruses must be rendered inactive by at least four log10 using 70% ethanol (70%, 1 min), peracetic acid (0.2%, 10 min), and probiotic cleanser (1%-10%, one h) on contaminated surfaces. These tests also demonstrated the efficacy of glutaraldehyde (2%; 10 min), orthophthalaldehyde (0.55%, 5 min), iodine (0.04%-1%) and sodium hypochlorite (0.25%-2.5%; 1 min). Vaccinia virus was not affected by copper

levels (99.9%) but MPXV was at 3 min[71].

CONCLUSION

As of May 2022, instances of MPXV have been recorded in nations where the infection is not endemic and are still being reported in several endemic nations. As a result, MPXV is no longer restricted to areas where it is endemic as, in recent years, visitors from Africa have brought MPXV to the United States, the United Kingdom, Israel, and Singapore. MPXV is a dangerous reemerging pathogen. MSM males in the United Kingdom have contracted MPXV *via* community transmission without directly interacting with travelers from endemic nations. In addition, a study reported admission to the Hospital for Infectious and Tropical Diseases in Romania of a 26-year-old HIV-positive male with high fever (up to 39 ℃), chills, rectal pain, vesiculo-pustular rash, dysphagia, and skin lesions primarily in the anogenital area who had developed a mild form of the disease. This was the first MPXV case officially verified in Romania with suspicious epidemiological and clinical symptoms. Excellent knowledge on how to prevent and control MPXV infection, and improve contact tracing is required. This is particularly true in populations with high-risk characteristics. Public health officials and medical professionals should rule out MPXV in all patients who exhibit the typical rash and risky sexual behavior, especially those who have recently had sex with partners who visited countries where MPXV cases have been reported or partners who exhibit the same clinical symptoms even if they do not travel abroad[72]. As a result, it is essential to focus more on national and international research efforts for laboratory diagnosis, infection control, and treatment strategies. These strategies should also support sexual health and other specialized services in managing this condition. For MPXV outbreaks around the world, the Surveillance Outbreak Response Management Analysis System must be established and implemented.

FOOTNOTES

Author contributions: Beig M, Mohammadi M, Nafe Monfared F, and Nasereslami S were the study's principal investigators; Beig M and Mohammadi M were involved in the concept and design of the study; Mohammadi M and Nasereslami S revised the manuscript and critically evaluated the intellectual content; All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically assessed the academic ranges; All authors have read and approved the manuscript's content and confirmed the accuracy or integrity of any part of the work.

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Wachira Wongtanasarasin

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Abstract

The 2019 coronavirus disease (COVID-19), resulting from the severe acute respiratory syndrome 2 virus, has transformed our globe and provided a new perspective on respiratory tract infections. However, COVID-19 would not be recognized as a condition restricted to only pneumonia. This narrative review was conducted by searching manuscripts in several databases, including PubMed/MEDLINE, Web of Science, and Reference Citation Analysis, from December 2019 to July 2022. Many studies have revealed a broad spectrum of potential systemic symptoms, including biliary complications. Although biliary injury has been observed in a very low proportion of COVID-19 patients, it is associated with increased mortalities and long-term morbidities. We identify a cholangiopathy condition in individuals during infection and after recovering from severe COVID-19, defined by a significant increase in serum alkaline phosphatase and signs of bile duct injury. Understanding the pathogeneses behind this condition would help us develop new techniques to prevent these complications. This review thoroughly discusses and summarizes the current information regarding COVID-19-associated cholangiopathy. In addition, the possible explanations for COVID-19-associated cholangiopathy are presented. Since the exact pathogenesis may not be concluded, this review could provide relevant information to encourage additional investigations shortly.

Key Words: COVID-19; Cholestatic injury; Cholangiopathy; Alkaline phosphatase

Core Tip: The 2019 coronavirus disease (COVID-19) is not only regarded as a respiratory tract disease but also demonstrates a wide range of systemic consequences, including the biliary tract. A significant increase in serum alkaline phosphatase and signs of biliary injury on imaging and/or pathology are the hallmarks of COVID-19-associated cholangiopathy. Direct viral invasion, ischemic injury related to microvascular coagulopathy, drug-induced cholestatic liver injury, alteration of gut microbiota, and cytokine release syndrome are proposed as potential explanations for cholangiopathy associated with severe COVID-19 infection.

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INTRODUCTION

Since December 2019, the recent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), later confirmed as the source of the 2019 coronavirus disease (COVID-19), has turned into a global threat to public health[1]. With a rapidly increasing number of overall cases, the World Health Organization announced the disease pandemic in March 2020. Currently, COVID-19 has caused about 577 million cases and over 6 million deaths worldwide[2].

SARS-CoV-2 is greatly transmitted by droplet transmission[3], with respiratory symptoms (*i.e.*, sore throat, cough, dyspnea) being the most prevalent manifestation as a result of host seeding *via* angiotensin-converting enzyme 2 (ACE-2) receptors present primarily in type II alveolar cells of the lungs[4,5]. Although respiratory and non-specific symptoms such as fever, myalgia, and fatigue represented the most common presentations in patients with COVID-19 infection, gastrointestinal and hepatic symptoms have also been observed[6,7]. Infected individuals reported nausea, vomiting, and abdominal discomfort[6,8,9]. Current evidence has proposed pneumonia as a severe COVID-19 feature [10]. However, complications are notably distinguishable, and the virus has impacted different organ systems[11]. At initial presentation and in hospitalized patients, the incidence of abnormal serum liver function tests (LFTs) varies from 22% to 67%, with levels of elevation ranging from minor to severe[12-14]. Autopsy findings from the case series also demonstrated mild microvesicular steatosis and lobular with portal inflammation[15].

To date, the findings have concentrated on evidence of hepatocellular injury, serum aspartate aminotransferase (AST), and alanine aminotransferase (ALT) elevations[16-18]. Several studies also observed that abnormal LFTs during hospitalization had been linked with disease severity[19-22]. One article that included over 2000 patients in the United States investigated ALT increases and their associations with disease severity, also emphasizing the rarity of cholestasis[20]. Despite a myriad of research on the severe COVID-19 progression, we noticed a small number of reported reports on the consequences. Previously, Faruqui *et al*[11] described a condition characterized by increases in LFTs, particularly markedly elevated serum alkaline phosphatase (ALP), and radiographic findings indicating biliary tract inflammation, primarily bile duct stricture, similar to those seen in critically ill patients with secondary sclerosing cholangitis (SSC)[23]. Still, this condition named COVID-19-associated cholangiopathy is not antecedently reviewed and discussed. This review comprehensively summarizes up-to-date reports from studies highlighting this condition and its perspective. Moreover, possible explanations for COVID-19-associated cholangiopathy are provided and discussed. We anticipate that this review could underline the importance of this condition since it appears to have significantly negative effects on patients' recovery and may potentially result in long-term morbidities.

SEARCH STRATEGY

This narrative review was performed considering articles published from December 2019 to July 2022. The manuscripts were searched electronically using several standard databases, including PubMed/MEDLINE, Web of Science, and Reference Citation Analysis. Various search terms and Medical Subject Headings (MeSH) were used to identify potential articles: "COVID-19", "cholestasis", "alkaline phosphatase", and "obstructive jaundice" (Supplementary Table 1). This mini-review may only serve as a hypothesis-generation of all relevant articles existing in the literature. The extensive details of this condition may have been reviewed elsewhere. The included articles were only those that were published in English.

COVID-19-ASSOCIATED CHOLANGIOPATHY

COVID-19-associated cholangiopathy (COVID-C) or COVID-19 cholestasis has been proposed to describe a condition that occurs in individuals during and after severe COVID-19 infection[11]. It is characterized by elevated liver enzymes, especially substantial increases in serum ALP, and imaging-based biliary tract inflammation[11]. This condition appears to have significant negative effects on patient recovery. After other indications of COVID-19 have recovered, it may cause delayed morbidity [17], the necessity for a liver transplant, and death[11].

Elevated serum ALP and serum gamma-glutamyl transferase levels

COVID-19 is frequently linked with aberrant LFTs, despite the absence of disease-specific lesions on radiographic imaging or biopsy. Liver damage has been discovered to be a common feature of the highly deadly coronavirus-associated illness in humans[24]. Previous studies, mainly from China, have identified abnormal LFTs in infected individuals from the early stages of the recent SARS-CoV-2 pandemic[25-27]. Several systematic reviews with meta-analysis found that any abnormal LFTs were reported in 25%-47%[12-14,26]. Most abnormalities were elevated serum AST and ALT, representing hepatocellular injury[12,13]. Recent literature showed that acute hepatocellular injury during COVID-19 positively correlates with more severe COVID-19 disease[20]. Furthermore, SARS-CoV-2 can enter the liver *via* the ACE-2 receptor proteins found on the bile duct epithelium, which theoretically results in "direct viral cholangiocyte injury". Supporting this concept, the findings from meta-analyses reported serum ALP elevations occurring in up to 4.0%-13.7% of patients[12-14]. In addition, recent studies identified serum ALP elevation as an independent predictor for unfavorable outcomes, including intensive care unit (ICU) admission and hospital mortality[13,28]. Furthermore, Da *et al*[17] documented that COVID-19 patients with increased ALP levels (> 3 times of normal upper limit) were correlated with a higher likelihood of prolonged mechanical ventilation and death. In the same way, a study conducted in Iraq reported that most SARS-CoV-2 patients had abnormal liver enzyme activities, which might be associated with viral replication in the liver[16].

Similarly, serum gamma-glutamyl transferase (GGT) activity represents a sign of hepatobiliary damage, particularly cholestasis and biliary impact[29]. Previous meta-analyses revealed that COVID-19 patients had higher GGT levels than those without, ranging from 15.0-22.5%[12,13]. Although the ACE-2 receptor is primarily expressed in the biliary tree, the evidence found that both abnormal serum ALP and GGT levels were lower than abnormal serum AST and ALT levels. We hypothesize that some abnormal hepatocellular enzymes may result from baseline chronic liver diseases. Furthermore, individuals with COVID-19 and concurrent advanced-stage liver disease may be more susceptible to severe liver damage than those without.

Abnormal biliary tract imaging associated with COVID-19 infection

Faruqui *et al*[11] reported that only 0.6% of patients with severe COVID-19 infection developed aberrant radiographic findings consistent with cholestatic liver damage. All had severe pneumonia with sepsis and required mechanical ventilation during admission. Extracorporeal membrane oxygenation was used on three of them. All patients underwent magnetic resonance cholangiopancreatography, which indicated aberrant findings such as beaded intrahepatic channels, peribiliary diffusion high signal, bile duct wall thickening and hyperenhancement, and common bile duct dilatation[11]. These cholangiopathies described in that study are comparable to SSC observed in patients following prolonged ICU stays[23]. This disease has been encountered in critically ill patients with infection, polytrauma, burns, or after major surgery[30,31]. SSC also has been described in a case report or small case series[11,30,31]. It has been defined as a cholangiopathy with radiographic characteristics similar to those observed in primary SSC and comparable to ischemic cholangiopathy reported following liver transplantation[31]. Endoscopic retrograde cholangiopancreatography or liver histology was used to diagnose several individuals who had SSC following a severe illness. Gelbmann *et al*[30] recorded endoscopic observations of biliary casts with the reduced biliary flow and eventual cholangitis, as well as verified cholangitis and hemorrhagic exudates in bile ducts from liver biopsy. All 26 patients in that research had respiratory failure and required mechanical ventilation[30]. The relationship between severe SSC patients and COVID-19 cholangiopathy highlights a potential connection between hypoxic liver damage or ischemic liver failure and cholestatic liver injury[11]. The portal vein and the hepatic arteries supply the liver parenchyma or hepatocytes. On the other hand, the intrahepatic biliary tree is nourished only by hepatic artery branches *via* the peribiliary vascular plexus. Given its dependence on only arterial supply, the biliary epithelium appears more sensitive to ischemia than hepatocytes, which get dual supply[32,33]. This is illustrated by instances of hepatic artery thrombosis, which occurs in 9% of adult liver transplant patients following arterial blood supply termination, commonly leading in biliary ischemia lesions such as necrosis with biliary leakage and ischemic strictures[34].

POSSIBLE EXPLANATIONS FOR COVID-19-ASSOCIATED CHOLANGIOPATHY

Direct viral invasion

Direct viral cholangiocyte injury is a hypothetically pathogenic mechanism of the virus leading to cholestatic liver injury since SARS-CoV-2 may enter the liver *via* the ACE-2 receptor protein found on the bile duct epithelium[35]. In liver tissues taken from 4 deceased donors of liver transplants, it is demonstrated that specific ACE-2 activity was expressed in 60% of cholangiocytes, compared with 3% of hepatocytes, suggesting that the virus might directly bind to specific ACE-2 receptors on cholangiocytes[36]. They discovered that ACE-2 expression in cholangiocytes is equivalent to ACE-2 expression in type II lung alveolar cells[36]. Also, subsequent reports have found that biliary epithelial cells exhibit a high level of ACE-2[35,37]. An *in vitro* investigation of human liver cells revealed that cholangiocytes might be more vulnerable to being infected with SARS-CoV-2 than other viruses[35]. Previous literature illustrated that viral particles in cholangiocytes had been found in ultrastructural and histological studies, highlighting the possibility that cholestatic damage may be caused by SARS-CoV-2 direct infection of biliary epithelial cells[11,38]. Furthermore, transmembrane protease serine 2 (TMPRSS2), the key host protease that allows several coronaviruses to enter the cells, including SARS-CoV-2, has been found to be associated with viral invasion mechanism since its activity was expressed in cholangiocytes[39]. Its actions lead to cell apoptosis, impaired transportation of bile acids, and epithelial barrier dysfunction[35]. On the other hand, another report documented that the proportion of cells expressing ACE-2 and TMPRSS2 was only 2.50% for cholangiocytes and 0.04% for hepatocytes, questioning the uncertain hypothesis of a direct viral effect on liver and bile duct cells[40].

Ischemic injury referred to the microvascular coagulopathy

The previously discussed cholestatic injury might result from ischemic damage caused by microvascular coagulopathy and/or hypotension during critical illness or sepsis[11,19,21]. Researchers have found that SARS-CoV-2 enters the host *via* the respiratory epithelial ACE-2 receptor[41]. ACE-2 is, nevertheless, widely expressed in endothelial cells of minor and major vessels across the body[37]. The expression of ACE-2 in vascular endothelium has been proposed as a key pathogenetic factor in the widespread coagulation that contributes considerably to COVID-19 morbidity and mortality[19,21]. A recent case series discovered many platelet-fibrin microthrombi in postmortem liver cells[36]. However, another case series of 40 COVID-19 cases found sinusoidal microthrombi in only 15%, whereas most reported macrovascular steatosis (75%) and mild lobular necroinflammation and portal inflammation (50%)[42]. These controversial issues, nonetheless, did not exclude the possibility of intravascular microthrombi and thrombosis theory. More research on this topic may be warranted.

Drug-induced cholestatic liver injury

Another possible explanation for COVID-C is drug-induced cholestatic liver injury. A wide range of medications has been investigated throughout this pandemic. Among these, remsidivir[43,44], lopinavir [45], ritonavir[45], and interleukin-6 antagonists (tocilizumab)[46] have been reported as a cause of increased ALT levels. However, the pattern of biliary injury from pathological examination strongly supports this hypothesis was insufficient[43,44,46]. Besides, no single medication was constantly delivered to all patients with COVID-19 infection, resulting in inconclusive confirmation of this issue.

Alteration of gut microbiota

Interestingly, changes in the gut microbiota may also lead to cholestatic damage[47]. When SARS-CoV-2 infected the enterocytes, it inhibited the absorption of intestinal tryptophan; therefore, resulting in the generation of antimicrobial peptides, mostly through the downregulation of ACE2 following viral entrance[48,49]. It has been proposed that disruption of the gut-liver axis may increase the likelihood of developing severe COVID-19 in patients with non-alcoholic fatty liver disease[50]. In addition, the gut microbiota has been used as a prospective target for adjuvant therapy during SARS-CoV-2 infection[51, 52].

Cytokine release syndrome

Moreover, cytokine release syndrome (CRS), which occurs in both SSC and COVID-19, is another sign that the pathophysiology of SSC-associated severe illnesses and COVID-C may be pathogenetically similar[32]. Documents indicating that CRS can produce severe cholestatic liver damage suggest that the biliary epithelium is partially sensitive to CRS-immune mediated damage[53]. Overall, we may assume that the inducers, such as SARS-CoV-2 epithelial infection, microthrombosis, or the magnitude of the COVID-19 CRS, aggravate the severity and frequency of COVID-19 infection[11].

CLINICAL IMPLICATION

This review provided some important and interesting points. Recently, many researchers raised the

question of when the COVID-19 pandemic will end. One statistical report showed that the COVID-19 pandemic could terminate in 2022, but COVID-19 could be one or two times more fatal than seasonal influenza by 2023[54]. Understanding the complications and consequences after COVID-19 infection would help clinicians prevent such conditions and improve the quality of care during the post-infection period. Knowledge and evidence regarding COVID-19-associated cholangiopathy are comparably low despite the growing literature on COVID-19 and other complications. This review could pave the way for a better comprehension of this condition. Future research to completely explain the behind mechanism would advance the treatment and management paradigm. Furthermore, this mini-review will emphasize that all healthcare professionals recognize this disease and its circumstances better.

CONCLUSION

SARS-CoV-2 infection has taken our world into a disastrous situation. Severe COVID-19 patients may encounter COVID-19-associated cholangiopathy, similar to those with SSC after critical illness. COVID-19 infection initially signifies the virus's contact with ACE-2 receptors (expressed in cholangiocytes and vascular endothelium). Based on current evidence, several theories were described in this review, including direct viral invasion, microvascular coagulopathy, alteration of gut microbiota, drug-induced liver injury, and cytokine release syndrome (Figure 1). The exact underlining pathogenesis might not be concluded at this moment, raising the importance of further investigations into this issue. COVID-C may be rarely found in patients with severe COVID-19 infection but is associated with increased mortality and impaired quality of life. We anticipate that the findings described in this review will advance more translational research, resulting in a better understanding and improved treatment of COVID-C in the near future.

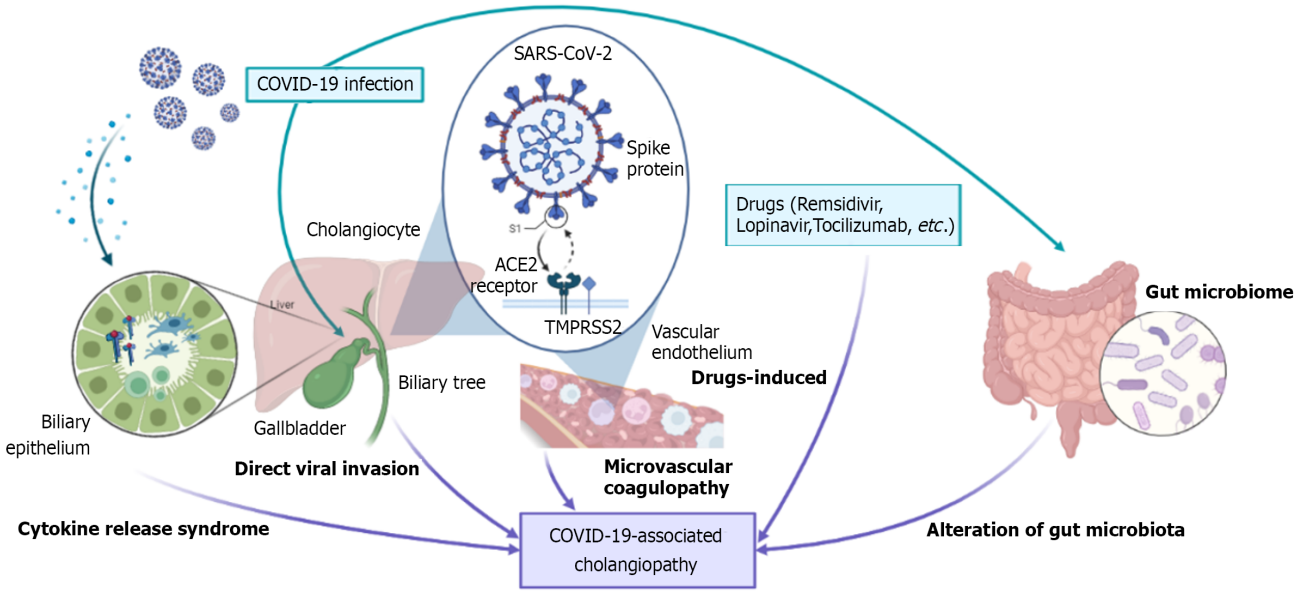

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Figure 1 Possible mechanism involved in the pathogenesis of COVID-19-associated cholangiopathy during and after COVID-19 infection. ACE-2: Angiotensin-converting enzyme 2; COVID-19: 2019 coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2: Transmembrane protease serine 2.

FOOTNOTES

Author contributions: Wongtanasarasin W designed the protocol, contributed to data collection, data evaluation, data visualization, wrote the first draft of the manuscript, and critically reviewed the final version of the manuscript.

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MINIREVIEWS

COVID-19-induced liver injury in adult patients: A brief overview

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Abstract

Coronavirus disease has spread worldwide since 2019, causing important pandemic issues and various social health problems to date. Little is known about the origin of this virus and the effects it has on extra-pulmonary organs. The different mechanisms of the virus and the influence it has on humans are still being studied, with hopes of finding a cure for the disease and the pathologies associated with the infection. Liver damage caused by coronavirus disease 2019 (COVID-19) is sometimes underestimated and has been of important clinical interest in the past few years. Hepatic dysfunctions can manifest in different forms which can sometimes be mild and without specific signs and symptoms or be severe with important clinical implications. There are several studies that have tried to explain the mechanism of entry (hepatotropism) of the virus into hepatocytes and the effects the virus has on this important organ. What clearly emerges from the current literature is that hepatic injury represents an important clinical aspect in the management of patients infected with COVID-19, especially in frail patients and those with comorbidities. The aim of our brief overview is to summarize the current literature regarding the forms of hepatic damage, complications, mechanisms of pathology, clinical features of liver injury, influence of comorbidities and clinical management in patients with COVID-19 infection.

Key Words: COVID-19; SARS-CoV-2; Hepatotropism; Hepatic injury; Cirrhosis; Cytokine storm; Angiotensin-converting enzyme 2

Core Tip: Liver damage can occur in patients infected by coronavirus disease 2019 (COVID-19). The organ damage can be due to various mechanisms such as direct infection, immune injury, drug-induced damage, hypoxia or inflammation response. It is of clinical importance to manage hepatic damage in COVID-19-positive patients. Patient outcomes, the success of therapy, prevention of life-threatening complications and management of existing comorbidities depend on proper organ functioning.

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INTRODUCTION

In December 2019, a new ribonucleic acid (RNA) virus in humans was reported in China, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This viral infection has spread quickly throughout the world ever since the first outbreak. The virus causes coronavirus disease 2019 (COVID-19) which has had a great global impact[1]. SARS-CoV-2 started as a zoonotic infection but currently also affect humans. The disease propagates quickly between humans *via* air droplets, sneezing and coughing, especially amongst people that are in close contact with each other. Studies have also shown the possibility of fecal-oral transmission[2]. The majority of SARS-CoV-2 infected patients can be asymptomatic or can present with mild symptoms which range from coughing, fever, headache, anosmia, *etc*. About 15% of cases, however, can show severe pulmonary disease leading to respiratory dysfunction, which can progress to multiorgan failure, coagulopathy and even death[3-5]. Common risk factors for severe disease progression include male sex, advanced age and coexisting comorbidities (*i.e.* heart disease, tumors, diabetes, hypertension, *etc*)[6,7].

Possible hepatic involvement has been shown in two recent types of pathogenic Coronaviruses, which include SARS-CoV-2 and middle east respiratory syndrome coronavirus. These two viruses show striking genetic similarities, thus hepatic involvement is not entirely unexpected[8]. COVID-19 patients showing injury of the liver can present with abnormal liver biochemical indicators, such as elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin, in addition to low levels of albumin[9,10]. The possible mechanisms involved in viral infections include: a direct effect of the virus on hepatocytes or biliary epithelium; liver injury related to accentuated immune response (cytokine storm) and immune-mediated damage; drug toxicity; and ischemic hepatitis. These complications can be favored in patients having multiorgan dysfunction and hemodynamic instability [11]. COVID-19 can give rise to a worsening of existing chronic liver disease (CLD) which can lead to higher mortality due to acute-on-chronic liver failure and/or hepatic decompensation.

Our overview provides a brief summary based on the various forms of hepatic damage, complications, mechanisms, clinical features of liver injury, influence of comorbidities and clinical management in patients with infection of SARS-CoV-2.

SEARCHING OF THE LITERATURE

We conducted a search of the literature published between January 1, 2011 to June 1, 2022, using PubMed (https://pubmed.ncbi.nlm.nih.gov) and Reference Citation Analysis (https://www.referencecitationanalysis.com). The database was first searched using the key words "SARS-CoV-2 AND hepatic injury, hepatic damage AND therapy". We considered only studies in English and those referring to humans and with abstract, thus reducing the count to 350 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. Only articles with abstracts were considered. Each study was independently assessed by at least two reviewers (Grando M and Balbi M), and rating decisions were based on the consensus of the reviewing authors. Our manuscript was based on the most relevant and pertinent studies which included 76 references listed in the paper.

Mechanism and hepatotropism of SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) is expressed in about 80% of pulmonary alveolar cells, but also in other organs. It seems to be a susceptible receptor for SARS-CoV-2. In vitro studies during the SARS epidemic showed that ACE2 acts as the host receptor for viral entry[12]. Moreover, furin gene and transmembrane serine protease 2 (TMPRSS2) have also shown to play an important role in infection. Cells expressing these specific receptors can be indicative of putative hepatic permissive cells[13].

Hepatic distribution of ACE2 is particular. Single-cell RNA sequencing analyzed from livers from normal patients have shown higher levels of gene expression in cholangiocytes, sinusoidal endothelial cells and hepatocytes[14,15]. The ACE2 expression levels in cholangiocytes are like those found in pulmonary type 2 alveolar cells of the lungs, thus indicating that the liver could be a potential target for SARS-CoV-2[16]. In addition, studies have reported that furin and TMPRSS2 have shown a broad gene expression profile in many types of liver cells[14]. In three single-cell RNA combined analysis from sequencing obtained from healthy liver tissue, relatively few hepatocytes co-expressed ACE2 and TMPRSS2[17]. Zhao *et al*[18] conducted studies on liver ductal organoids that expressed ACE2 and TMPRSS2. These were shown to recapitulate infection of SARS-CoV-2, which could be indicative that the epithelium of the bile duct may support entry of pseudo particles[18]. The exact reasons to explain these findings are not known. It may be possible, however, that the virus may show low levels of replication in cholangiocytes *in vivo* in the absence of cell death.

The effects of coexisting liver disease and injury on SARS-CoV-2 hepatotropism is still not known. Studies performed before COVID-19 have reported an increase in liver ACE2 expression in patients with cirrhosis due to hepatitis virus C when compared with normal patients[19]. Moreover, liver mRNA TMPRSS2 and ACE2 expression have shown to be upregulated in non-infected obese individuals and non-alcoholic steatohepatitis patients[20]. Studies based on liver injury in animal models using ligation of the bile ducts have shown elevated expression and activity of hepatic ACE2 and the presence of hypoxia markers[19,21]. Inflammation and injury of the liver may potentially enhance hepatotropism of SARS-CoV-2 by influencing the expression of viral receptors, with ACE2 shown as an interferon-inducible gene in the epithelia of the respiratory system in humans[22,23]. While the tissue specific factors involved in the infection of SARS-CoV-2 are not completely known, the importance of accessory receptors like the receptor B type 1 high-density lipoprotein scavenger (SR-B1) can help better understand *in vitro* facilitated coronavirus attachment[24].

Clinical presentation

Liver biochemistries abnormalities are frequent in COVID-19 patients which has been reported to be seen in 15-65% of individuals infected with SARS-CoV-2[13]. Liver biochemistry abnormalities are generally characterized by mild to moderate elevated ALT and AST levels, accompanied by a slight increase in bilirubin levels and gamma-glutamyl transferase (GGT)[25]. Hypoalbuminemia, a typical manifestation of a hepatic synthetic dysfunction, has been reported to be associated with a worsening in COVID-19 outcomes[26-28]. Despite the presence of ACE2 in cholangiocytes, patients have shown to have elevated levels of transaminases. Several studies, however, have reported the development of cholangiopathy after severe COVID-19, which was characterized by marked elevation in serum alkaline phosphatase (ALP) accompanied by bile duct injury shown in imaging scans. ALP peaks can be seen in patients with worse prognosis. AST elevations can also be seen as a result of myositis[29]. Studies have showed that levels of AST at hospital admission tended to correlate with ferritin[30]. However, further studies are needed to determine whether COVID-19 aggravates cholestasis in individuals with primary sclerosing cholangitis and primary biliary cholangitis[31,32]. The clinical manifestation[10,13,28,32] of the disease can include gastrointestinal alterations like nausea, anorexia, vomiting, diarrhea, *etc*. Patients can also complain of abdominal pain, especially in the right upper quadrant region.

Prognosis

The prognostic significance of elevated liver enzymes in COVID-19 patients is currently debatable. Unpublished data from Wuhan, China showed increased GGT levels in severe cases of COVID-19[8]. Several reports have demonstrated that high levels of AST and ALT can be associated with negative outcomes including mechanical ventilation and management in an intensive care unit (ICU)[33-36]. A recent review showed that the pooled frequency of elevations of ALT and AST was similar in all COVID-19 cases, however, the prevalence of AST elevations was more than ALT in patients with severe COVID-19 disease[37]. Increased liver enzymes are commonly seen in patients needing severe critical care. Studies have reported raised AST in 62% of patients in the ICU compared to 25% in a non-ICU setting[38]. The current literature in this field can potentially be prone to bias considering that infected individuals with severe health issues tend to undergo more laboratory testing than patients with mild symptoms.

The influence of liver enzymes on mortality is debatable. Several studies have stated that there are no apparent associations between mortality rates and elevations in levels of liver enzymes[33,39]. Other studies, however, have reported elevated levels of liver enzymes (*i.e.* AST and ALT elevations higher than five times the normal ranges) in patients with greater risk of mortality[27,40]. Some authors have suggested that indicators based on liver biochemical levels can be useful predictors of prognosis and severity in COVID-19 individuals, however, it is important to note that the prognostic significance could also be due to enhanced host response and active treatments that could be more aggressive in patients with important signs and symptoms[41].

Hepatic damage

The complex mechanisms of liver injury during SARS-CoV-2 infection are of important clinical

importance but are still not all completely known. Hepatic damage could be related to the direct cytopathic effect of the virus. Huang *et al*[42] found that liver injury as the first clinical manifestation in COVID-19 patients was very rare and that hepatic damage in COVID-19 patients appeared mostly due to secondary liver injury. Numerous studies have speculated that in addition to the virus itself causing initial liver injury, other factors involved could cause secondary liver injury. These mechanisms include: an uncontrolled immune reaction; systemic inflammatory response syndrome (SIRS); ischemia and reperfusion; cytokine storm injury; and liver injury induced by drugs[38,41,43].

Direct damage: Liver injury in patients with COVID-19 could be partially caused by direct SARS-CoV-2 viral invasion and hepatocyte destruction. Several studies have reported hepatic necrosis foci located near peri-portal areas and terminal hepatic veins, without signs of surrounding inflammatory cellular infiltration (consistent with acute liver injury patterns)[43,44]. Amongst hospitalized patients with COVID-19, elevations of serum AST levels have been shown to be positively correlated with levels of ALT, which have not been seen with markers of systemic inflammation like ferritin and C-reactive protein (CRP)[30]. Increased liver enzyme levels in COVID-19 patients could possibly be due to direct hepatic injury. Bile duct epithelium shows ACE2 expression which tends to be much greater than that seen in hepatocytes. Compensatory proliferation in parenchymal cells of the liver arising from cells of the bile duct may lead to the upregulation of ACE2 expression in the liver. This could be an important mechanism involved in SARS-CoV-2 induced liver injury.

The direct hepatic damage caused by the virus is still a hypothesis, especially considering the low number of autopsies performed in COVID-19 patients and the relatively low ACE2 expression in the liver. The direct toxic attack of SARS-CoV-2 on the liver is still questionable and remains debatable. Moreover, biomarkers for cholangiocyte injury, such as GGT and ALP have also been seen in some patients, which tends to be consistent with injury to biliary epithelial cells[39]. COVID-19 patients can show elevated total bilirubin levels. These results could be indicative that SARS-CoV-2 can directly bind to cholangiocytes expressing ACE2, thus giving rise to cholangiocyte injury. Further clinical and histopathological studies are needed to confirm these hypothetical mechanisms.

SIRS and cytokine storm: Like numerous other diseases, SARS-CoV-2 is associated with systemic inflammation, which could cause elevations in biochemistries in the liver due to the release of cytokine [45]. Individuals with relatively high serum ALT levels tend to show elevated levels of CRP, D-dimer, ferritin and IL6[46]. Studies have shown elevated serum levels of interleukin (IL) IL2 receptor and IL6 in COVID-19 individuals which tend to correlate with the severity of the disease[47]. Moreover, other cytokines such as tumor necrosis factor IL18, IL4 and IL 10 have shown to be increased, as do peripheral blood pro-inflammatory CCR4+, CCR6+ and Th17 cells[48]. After being infected, a large number of immune cells may be overactivated and induced to secret excessive cytokines and chemokines. This can lead to acute respiratory syndrome and SIRS which can give rise to cell damage and necrosis.

Ischemia and reperfusion injury: Individuals with COVID-19 tend to show different degrees of hypoxemia. Systemic hypoxia might also have a contributory role. Studies have shown raised AST levels with other viral pneumonias including influenza A (H1N1) infection[49]. With hypoxia and ischemia, glycogen consumption, lipid accumulation and adenosine triphosphate depletion of hepatocytes can inhibit cell survival signal transduction which can lead to hepatocyte death. It is important to note that hepatic ischemia-reperfusion injury (HIRI) is considered as a normal pathophysiological process. The mechanisms behind this injury are closely related to neutrophils, Kupffer cells, reactive oxygen species and calcium overload. HIRI can induce neutrophils, Kupffer cells and platelets which induce destructive cellular processes that can cause inflammation and injury to cells [11]. Ischemia and hypoxia could surely be involved in the mechanisms of liver damage in patients with severe and critical COVID-19 disease.

Histological studies have showed altered intrahepatic blood vessel derangement, coagulopathy, antiphospholipid antibodies and abnormal hepatic perfusion which could be indicative of micro thrombotic disease[50,51].

Antibody-dependent enhancement: Antibody-dependent enhancement (ADE) involves the interaction between the Fc receptor and/or complement receptor with the virus-specific antibody to enhance the virus' ability to enter granulocytes, macrophages and monocytes. Studies have shown that antibodies against the SARS-CoV-2 spike protein trigger ADE causing the virus to enter immune cells that do not express ACE2[52-54]. The liver has numerous immune-response cells. ADE could also mediate SARS-CoV-2 in immune cell infection by a pathway not dependent on ACE2 and be involved in injury to the liver.

Drug induced injury: Drug-induced liver injury may have been more common during the initial periods of the pandemic which could have been favored by the use of experimental therapies[53]. It is also important to note that the common symptom in COVID-19 patients tends to be fever which may lead to the abundant use of antipyretic agents that contain acetaminophen, which is known to cause liver damage when excessively used without prescription in certain patients.

Antiviral drugs that are currently available have not proven to be very effective in controlling the disease. During the outbreak, patients were given ritonavir, lopinavir, oseltamivir, *etc*. Raised hepatic enzyme levels have been reported in patients receiving lopinavir/ritonavir therapy (56.1% *vs* 25%)[54, 55]. Remdesivir is another antiviral drug that is used to inhibit the replication of SARS-CoV-2 virus and studies have shown increased levels of blood creatinine, acute kidney injury and higher levels of liver enzymes in patients using the drug[56]. A study published in 2019 showed that CYP3A4 may have an important role in hepatotoxicity mediated by ritonavir and that oxygen free radical can be produced by the CYP3A4 metabolic pathways[56]. Covalent binding could occur with substances found in the cells of the liver which can cause peroxidation of membrane lipid, damage the integrity and ca2+-ATPase pathway of the membrane, influence the homeostasis of external and internal cell levels of Ca2+ and impair the function of critical organelles within the liver cells. This can eventually lead to tissue damage and cell death. In addition, the overuse of ritonavir and lopinavir could activate the endoplasmic reticulum stress pathway, induce apoptosis, inhibit the replication of hepatocytes, induce inflammatory reactions and accelerate liver injury by aggravating oxidative stress[11]. Drug-induced damage needs to be included in the differential diagnosis. This requires a thorough and accurate medical history in addition to pertinent examinations and testing to exclude other forms of liver injury and diseases.

Other mechanisms: There are several other potential contributors that can help provide a better understanding of abnormal liver biochemistries in COVID-19. Current literature has also described COVID-19 as a vascular disease, in which endothelial cells can be infected and cause endothelitis. Subsequent microvascular dysfunction can lead to hypercoagulability, tissue edema and organ ischemia [57,58]. Moreover, some studies have shown that AST levels can exceed ALT during the disease which is not typical in classic hepatocellular patterns of liver injury. This is commonly seen in alcohol-related liver disease and cirrhosis. These alternative factors that may play a role in hepatic damage in COVID-19 patients remain unknown and require future clinical and histological studies. The mechanisms may include mitochondrial dysfunction related to COVID-19 and hepatic steatosis induced by SARS-CoV-2 [59].

Aggravation or recurrence of existing liver disease

Patients with pre-existing CLD can get COVID-19. Whether or not CLD patients tend to be more susceptible to infection of SARS-CoV-2 is still not known. Data from large case series based on health records do not suggest that these patients are over-represented[60]. CLD patients tend to have immune disfunction due to the disease and/or to long-term immunosuppressants treatments (as in immune hepatitis). These chronic patients have been reported to have worse clinical outcomes when compared to patients without underlying liver diseases. Preliminary studies have reported a potentially higher mortality rate and a more severe disease course in these patients, however, further studies with large cohorts are needed[61-63].

Cirrhosis: Acute hepatic decompensation (AHD) is typical in individuals with COVID-19 and cirrhosis. Studies have reported that about 50% of patients with cirrhosis and COVID-19[62] show AHD which typically manifests as worsening ascites and encephalopathy. Amongst COVID-19 infected patients with cirrhosis, studies have shown an increase in mortality and morbidity with increasing disease severity based on the Child-Pugh class. The number of hospitalized individuals reported in COVID-Hep the SECURE-Cirrhosis registries have showed no significant differences amongst patients with CLD and CP classes A, B and C[63]. Studies however, have reported an increase in: ICU admissions; patients needing renal replacement therapy; individuals using mechanical ventilation; and mortality rates.

SARS-CoV-2 infection does not seem to cause the progression of liver disease beyond the natural clinical course of cirrhosis. The composition of the gut microbiota may play an important role in regulating disease severity and host immune responses. Considering that cirrhosis can induce changes in the function and composition of the gut microbiota, in addition to influencing the intestinal permeability, gut-liver axis alterations may play a role in the clinical severity in COVID-19 patients[13].

Non-alcoholic fatty liver disease: The influence of non-alcoholic fatty liver disease (NAFLD) on COVID-19 infected individuals is debatable. Studies have reported that it may be difficult to identify the effects of NAFLD from other metabolic conditions and viral-induced steatosis. A retrospective series based on about 200 SARS-CoV-2 patients showed NAFLD to be a risk factor in: COVID-19 infection severity; elevated levels of liver enzyme; and longer shedding times of the virus[13].

Immune hepatitis, viral chronic hepatitis: Studies have reported that individuals with autoimmune hepatitis tend to show COVID-19-related mortality rates similar to normal matched-individuals of the population[64]. Immunosuppression use does not seem to be an independent mortality risk factor. With regards to chronic hepatitis B individuals in the phase of immune tolerance, studies still need to be performed to show if these individuals have persistent liver injury after infection. Studied based on guidelines from the Chinese Medical Association reported that for hepatitis-B individuals using antiviral drugs, discontinuation of anti-HBV therapy could favor replication and reactivation of HBV after high-dose hormone therapy (*i.e.* estrogens, estradiol, progesterone, ethisterone, medroxyprogesterone, norethindrone, cyproterone, norgestrel, clomiphene, *etc*) during SARS-CoV-2 infection[65].

Clinicians that deal with autoimmune liver disease know that an unspecific infection may induce a flare of these diseases. It could be possible that SARS-Cov2 favors the onset of several types of autoimmune disease and/or induces an autoimmune phenomena.

Liver transplant: It is not yet clear if liver transplant (LT) recipients are more susceptible to COVID-19. A prospective study based on more than 100 individuals showed that patients that underwent liver transplantation had an increased risk of SARS-CoV-2 infection which could probably be due to the chronic immunosuppression therapy[66]. Moreover, data from the United Kingdom and Spain have shown that SARS-CoV-2 diagnoses tend to be greater in LT patients when compared to normal individuals. Biases in the data could be present, however, considering the increased testing and intense management in LT patients[67,68]. Studies have reported that LT recipients tended to be more likely to present gastrointestinal symptoms when compared to non-LT patients[69]. Clinical data incorporating adjustments for concurrent comorbidity suggest that LT individuals do not seem to be at greater risk of COVID-19 severity or mortality when compared to normal individuals[67,68].

Treatment

In the presence of acute liver injury, clinicians should first assess the probable causes of injury before taking on applicable measures. Although liver injury is a normal complication of COVID-19 infection, most infected individuals show mild abnormalities in liver function that are not permanent and tend to resolve without therapy[38]. COVID-19 individuals showing liver damage can be treated with anti-jaundice, hepatoprotective or anti-inflammatory drugs (*i.e.* glycyrrhizic acid, polyene phosphatidylcholine, adenosylmethionine and ursodeoxycholic acid)[70]. Hepatoprotective drugs should be administered prudently. It is preferable to avoid administering more than 2 types of these drugs at the same time. For individuals with critical and severe COVID-19 disease with liver injury, the clinician should consider carefully managing the respiratory and circulatory support systems. Xu *et al*[71] showed that an artificial liver blood purification system may be beneficial in severe patients. This could be due to the rapid removal of inflammatory mediators, thus limiting cytokine storms, and enhancing the balance of water-electrolytes. In COVID-19 individuals with suspected liver damage caused by drugs, clinicians should consider dose reduction or suspension. Acetaminophen (paracetamol) can be useful in patients with COVID-19, however, dosing (preferably not exceeding 2000 mg in a 24 h period) must be carefully monitored[72]. Future studies in large cohorts having long-follow-ups are needed in determining the long-term effects of COVID-19 induced liver injury.

CONCLUSION

Liver damage caused by COVID-19 is very common, especially in individuals with severe or critical disease. This aspect is also more relevant in patients with pre-existing CLD. The damage can be caused by various mechanisms such as direct infection, immune injury, drug induced, hypoxia or inflammation response. Further studies, however, are needed to understand the pathogenic mechanisms that lead to this damage and the hepatotropic mechanism of the virus. It is of utmost importance to monitor and manage abnormal liver function in COVID-19 positive patients, considering that the success of therapy, prevention of life-threatening complications and worsening of comorbidities also depends on proper hepatic functioning in the global management of these patients.

FOOTNOTES

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MINIREVIEWS

Hepatic manifestations of coronavirus disease 2019 infection: Clinical and laboratory perspective

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Abstract

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has become a global challenge of unprecedented nature since December 2019. Although most patients with COVID-19 exhibit mild clinical manifestations and upper respiratory tract involvement, in approximately 5%-10% of patients, the disease is severe and involves multiple organs, leading to multi-organ dysfunction and failure. The liver and gastrointestinal tract are also frequently involved in COVID-19. In the context of liver involvement in patients with COVID-19, many key aspects need to be addressed in both native and transplanted organs. This review focuses on the clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19 with no prior liver disease, patients with pre-existing liver diseases and liver transplant recipients. A brief overview of the history of COVID-19 and etiopathogenesis of the liver injury will also be described as a prelude to better understanding the above aspects.

Key Words: COVID-19; Liver injury; SARS-CoV-2; Clinical manifestations; Liver function tests; Cirrhosis

Core Tip: The novel coronavirus disease 2019 (COVID-19) has affected the entire globe with devastating consequences on the health and economy of all countries. Primarily a disease of the upper respiratory tract, it may involve multiple organs in severe cases, which are fortunately rare. The liver and gastrointestinal tract are also frequently involved in COVID-19. Involvement of the liver is multifaceted and may be asymptomatic or may lead to acute liver failure. This review article focused on various clinical presentations and laboratory abnormalities of liver function tests in patients with COVID-19. This will help in creating awareness among the general physicians, gastroenterologists, hepatologists and infectious disease consultants regarding this important complication.

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INTRODUCTION

During the past 20 years, three major outbreaks by coronaviruses have occurred. These include severe acute respiratory distress syndrome (SARS), Middle East respiratory syndrome and coronavirus disease 2019 (COVID-19)[1]. Among these, COVID-19, caused by SARS coronavirus 2 (SARS-CoV-2) was reported for the first time in Wuhan, China in December 2019, which later spread in pandemic form throughout the world[2]. In patients with COVID-19 infection, upper and lower respiratory tract involvement, *e.g.*, common cold, bronchiolitis, and pneumonia, are the dominant manifestations. Primary clinical symptoms of COVID-19 patients are fever, dry cough, fatigue and myalgia. However, in many cases, SARS-CoV-2 affects other organs such as the heart, gastrointestinal tract, liver and kidneys with organ-specific symptoms (Table 1). Many patients with severe disease may die from multiorgan failure. In this review, we described liver involvement in COVID-19, which can be studied from many aspects. The focus of this review, however, was on clinical and laboratory manifestations of liver disease in COVID-19 patients, in the native healthy liver, native diseased liver and in the transplanted liver.

For this narrative review, we searched the electronic databases of Web of Science, Scopus, Embase, PubMed and Google Scholar. The search terms used were: COVID-19, combined with the following terms; acute liver injury (ALI), acute-on-chronic liver failure (ACLF), chronic liver disease (CLD), cirrhosis of liver, hepatitis, deranged liver function tests (LFTs), liver failure, SARS-CoV-2, angiotensin-converting enzyme 2, hepatocellular carcinoma (HCC), liver transplantation, autoimmune liver disease, alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV). The search was carried out within the time frame of January 1, 2020 to May 2022. We found 4758 records and used 85 (mainly original articles or guidelines) for extracting information to be presented in this review.

PATHOGENESIS OF LIVER INJURY

COVID-19 causes liver damage that is mostly hepatocellular in nature as demonstrated by increased transaminase levels. It is often asymptomatic and manifests with derangement in liver functions on laboratory testing. COVID-19-induced liver injury is due to a multitude of reasons, which possibly differ from case to case according to various clinical scenarios[1]. Various mechanisms have been proposed including the direct cytopathic effect of the virus itself, immune dysfunction, systemic inflammatory response syndrome, cytokine storm, sepsis, vascular thrombosis, hypoxia and ischemia-reperfusion injury, as shown in Figure 1. Additionally, drug-induced liver injury has also been implicated as a possible secondary mechanism of liver impairment in patients with COVID-19[3].

The entry of SARS-CoV-2 into human host cells with resultant injury is primarily mediated *via* a metalloproteinase enzyme, called angiotensin-converting enzyme 2 (ACE2) receptor, located in various tissues, including the lungs, liver and gastrointestinal tract[4]. The previous RNA-seq data in the Human Protein Atlas database (www.proteinatlas.org) has demonstrated relatively low expression of ACE2 in the liver that, in all respects, could be considered a potential target. In particular, ACE2 expression is limited to the cholangiocytes of normal hepatic tissue and, to a minimal extent, in the hepatocytes[4]. A low throughput study of ACE2 protein expression in selected cell types of multiple organs showed a low frequency of ACE2 occurrence in cholangiocytes but not in hepatocytes, Kupffer cells and endothelial cells[5]. However, the antibody detection might be subjected to nonspecificity and sensitivity issues. Neither data sources could provide a definitive conclusion of cell type specific expression of the *ACE2* gene in the liver.

Table 1 Major clinical manifestations and laboratory abnormalities in coronavirus disease 2019

Signs/symptoms
Systemic and respiratory system manifestations
Fever, cough, malaise, dyspnea, fatigue, sputum
Cardiovascular system manifestations
Heart failure, arrhythmia, shock, tight chest, acute myocarditis
Gastrointestinal manifestations
Anorexia, diarrhea, loss of appetite, loss of taste, gastrointestinal bleeding, nausea and vomiting, abdominal pain, mild pancreatitis, mild colitis
Hepatobiliary manifestations
Abnormal liver function tests, jaundice, hypoalbuminemia, new-onset decompensation, acute-on-chronic liver failure, cholangiopathy, acalculous cholecystitis
Kidney manifestations
Acute kidney injury, proteinuria, hematuria
Neurological manifestations
Dizziness, headache, skeletal muscle injury, acute cerebrovascular disease, seizures

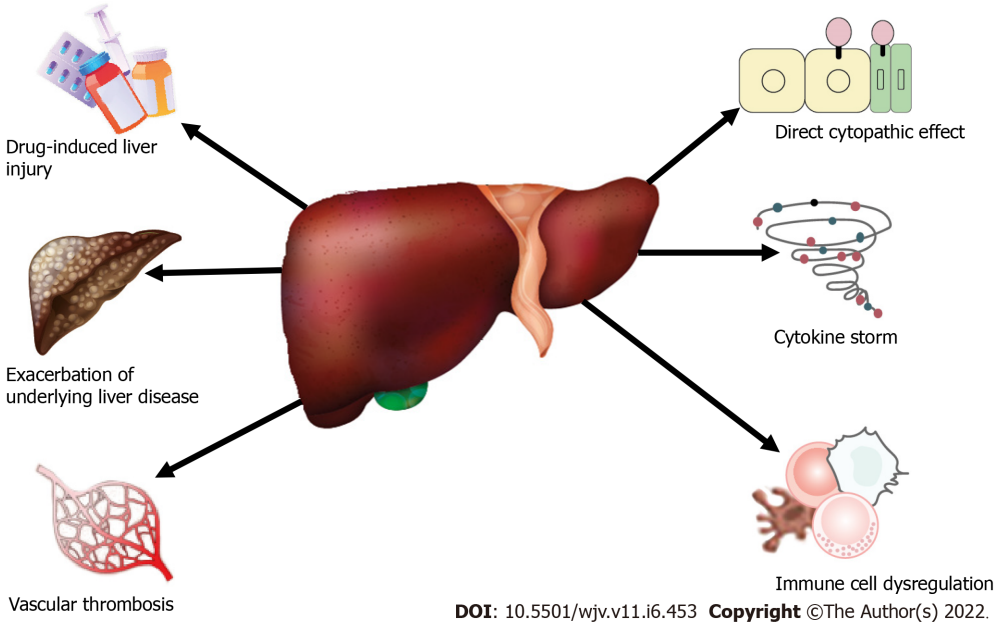

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Figure 1 Schematic illustration of possible mechanisms of liver injury in coronavirus disease 2019. Other mechanisms (not shown) may be involved.

Recent advances of single cell technologies allow unbiased profiling of all cell types in given tissues at an unparalleled scale. Chai *et al*[5] performed an unbiased evaluation of cell type specific expression of ACE2 in healthy hepatic tissues employing scRNA-seq data of two independent cohorts. This study revealed significant enrichment of ACE2 expression in cholangiocyte clusters (59.7% of cells) compared to hepatocytes (2.6% of cells) suggesting that SARS-CoV-2 might directly bind to ACE2-positive cholangiocytes, and the liver abnormalities of COVID-19 patients may not be due to a direct hepatocyte damage but, probably, to cholangiocyte dysfunction. It is well established that cholangiocytes play an essential role in liver regeneration and immune response; hence, their dysfunction may contribute to liver damage (Figure 2). Overexpression of the ACE2 receptor on hepatocytes has been observed in patients with liver fibrosis/cirrhosis and in cases of hypoxia. This might explain the high probability of liver injury in these populations[6]. Since liver biopsies of COVID-19 patients show focal hepatic necrosis without significant surrounding inflammatory infiltration, this points toward direct viral injury. However, considering high receptor levels in cholangiocytes rather than hepatocytes and as most of the COVID-19 patients manifest with elevated transaminases, the possibility of direct viral attack is less likely[7]. Other possible pathways of virus entry in hepatocytes have also been suggested to play a

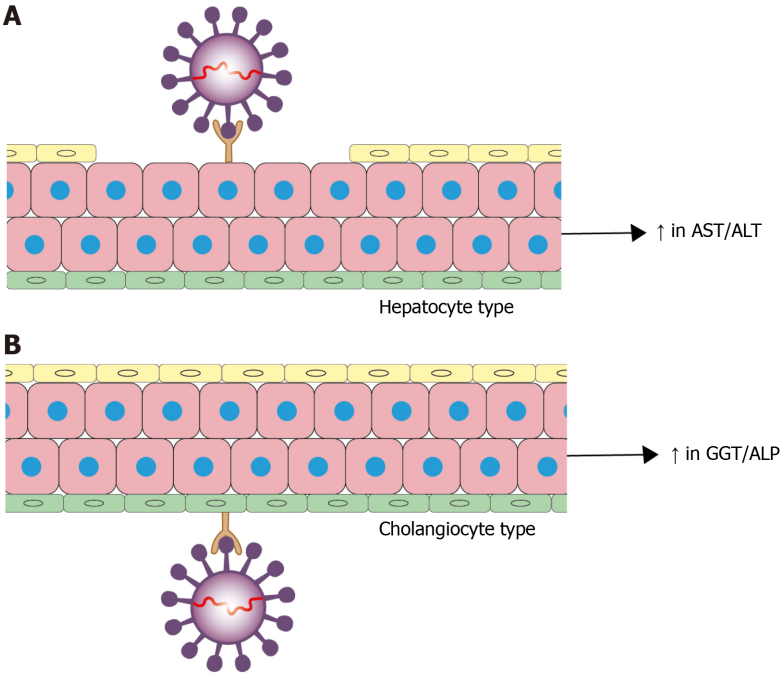

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Figure 2 Two principal types of severe acute respiratory syndrome coronavirus 2 infection of the liver parenchyma. A: Direct severe acute respiratory syndrome coronavirus 2 infection targeted to hepatocytes is designated as hepatocellular type; B: Direct viral entry into biliary epithelial cells is known as the cholangiocyte type. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-Glutamyltransferase; ALP: Alkaline phosphatase.

role in liver involvement in COVID-19 (Figure 3).

Another mechanism potentially associated with hepatic injury is the cytokine storm generated by the coronavirus infection. Excess inflammatory burden and potential immune-mediated damage lead to increased vascular permeability, multiorgan failure and death[1,3]. Similarly, studies have documented a correlation between high levels of interleukins, a group of cytokines, and severity of COVID-19[8].

In addition, COVID-19-related vascular thrombotic complications with consequent hypoxia and shock can lead to liver injury mediated by the ischemia-reperfusion injury mechanism. Ischemia-reperfusion injury involves a biphasic process of ischemia-induced cell injury and reperfusion-induced inflammatory response. Thus, an activated proinflammatory immune cascade due to the aforementioned processes can be a possible mechanism of liver injury in COVID-19 patients[3,6,9].

Finally, studies have also reported variable degrees of hepatotoxicity with medications used in the treatment of COVID-19[10,11]. Hundt *et al*[12] reported the use of medications needed to treat COVID-19 virus (remdesivir, hydroxychloroquine, lopinavir/ritonavir and tocilizumab) as a significant predictor of raised transaminases [> 5 × upper limit of normal (ULN)] during hospitalization for COVID-19. Cai *et al*[13] described lopinavir/ritonavir as a risk factor for liver injury in COVID-19 patients [odds ratio (OR): 4.44; 95% confidence interval: 1.50-13.17]. However, these authors did not report significant risk with the use of antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, herbal medications and interferon.

Muhović *et al*[14] reported severe drug-induced liver injury with tocilizumab in patients previously treated with chloroquine and lopinavir/ritonavir. As interleukin-6 is known to be associated with liver regeneration and metabolism, it is postulated that inhibition of interleukin-6 by tocilizumab may be the potential cause of liver enzyme derangement[11,15]. Hepatotoxicity can be expected in COVID-19 patients as the liver metabolizes nearly all medications used in COVID-19. Several mechanisms, like upregulation of ACE2 receptors and downregulation of cytochrome p450, sensitize the hepatocytes to the SARS-CoV-2 virus or therapeutic agents. While on the other hand, the pharmacological features of medications may increase susceptibility to liver injury[11].

In summary, the progression of COVID-19 from a mild to severe form is associated with a dysregulated immune response, which leads to uncontrolled viral replication and cellular damage, thus further exacerbating the immune-mediated damage, which includes liver damage[16].

CLINICAL MANIFESTATIONS

The SARS-CoV-2 genomic sequence has shown similarity with the SARS coronavirus and Middle East respiratory syndrome coronavirus. Like these viruses, respiratory symptoms along with gastrointestinal

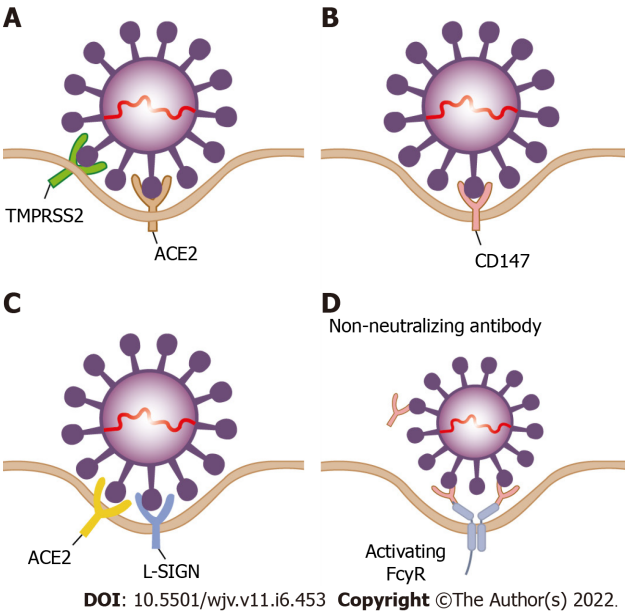

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Figure 3 Possible pathways of virus entry in hepatocytes. A: The angiotensin converting enzyme-2 in conjunction with transmembrane protease serine protease 2 is considered the predominant receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into cells; B: CD147 is another possible receptor for SARS-CoV-2 entry into hepatocytes. CD147 is highly expressed in tumor tissues, inflamed tissues and pathogen-infected cells including hepatocytes; C: L-SIGN (CD209L) may serve as a liver-specific cell receptor for SARS-CoV-2 infection of hepatocytes; D: Antibody-dependent enhancement may also facilitate SARS-CoV-2 infection of hepatocytes. During antibody-dependent enhancement of infection, suboptimal non-neutralizing antibodies cannot completely neutralize the virus; instead, they bind with the Fc receptors expressed on hepatocytes, leading to virus entry and infection. ACE2: Angiotensin-converting enzyme 2.

and liver involvement have been reported in SARS-CoV-2[17]. Clinical manifestations in COVID-19 infected patients with no previous liver comorbidities may range from asymptomatic liver function abnormalities to liver failure, as shown in Table 1[1,18].

ABNORMAL LIVER FUNCTIONS

The reported prevalence of liver injury in COVID-19 varies widely from 10.5% to 58.0% depending on many factors[4,19]. Various studies have reported a slight derangement of total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin levels[19,20]. The reported figures of complications in COVID-19 are slightly lower as compared to SARS-CoV and Middle East respiratory syndrome-CoV infections, as shown in Table 2. A systemic review reported a 15.0% elevation of AST and ALT, while a 16.7% elevation of bilirubin was reported[21]. Similarly, a meta-analysis pooled 13251 COVID-19 patients and reported a mild decrease in albumin in 39.8% cases, with a mild increase in AST in 22.8% and ALT levels in 20.6%[19]. Parohan *et al*[22] reported older age, male sex, obesity and underlying liver disease as commonly associated risk factors for deranged LFTs.

Furthermore, the extent of liver enzyme derangement has been associated with the severity of COVID-19 infection and its prognosis. Marjot *et al*[23] and Wang *et al*[24] reported higher levels of AST in intensive care unit (ICU) admitted COVID-19 patients. Similarly, Guan *et al*[25] reported 18.2% liver enzyme derangement in non-severe disease as compared to 39.4% with severe disease in 1099 Chinese patients affected by COVID-19 infection. The authors also described higher bilirubin, ALT and AST levels in COVID-19 patients that had either passed away or required ICU admission and/or the need for mechanical ventilation as compared to those patients who did not[25].

Different studies have reported different prognoses of deranged LFTs in COVID-19 patients. Moreover, different studies have used different definitions of liver injury. Ding *et al*[26] labeled liver injury as a 3 × ULN increase in ALT or AST or 2 × ULN increase in total bilirubin, direct bilirubin or alkaline phosphatase. The authors documented ALI in 0.5% of the COVID-19 patients without underlying liver disease. In addition, all patients had concomitant debilitating conditions like acute respiratory distress syndrome, septic shock, kidney injury, *etc*. Hajifathalian *et al*[27] defined ALI as elevation of any parameter of a liver biochemistry panel and demonstrated a higher risk of ICU admission and death in patients with ALI. Phipps *et al*[28] retrospectively studied a large cohort of in-hospital patients based on raised ALT levels, graded liver injury into no/mild (< 2 × ULN), moderate (2-5 × ULN) or severe (> 5 × ULN) forms. Although only 6.4% of the study population developed severe injury, it was significantly associated with severe clinical outcomes including death. The authors also proposed that severe liver injury can be used as a prognostic factor in hospitalized patients. Considering

Table 2 Rates of hepatic complications in different clinically significant human coronavirus infectious diseases

Hepatic complications	SARS-CoV-2, %	SARS-CoV, %	MERS-CoV, %
Increase in ALT	13.3-28.0	52.5-8.07	11.0-56.3
Increase in AST	22.0-58.0	37.1-86.9	15.0-86.8
Increase in TB	10.5-18.0	30.0	NA
Decrease in serum albumin	36.8	40.4-72.0	NA
Co-morbidity with liver disease	HBV-positive patients were more prone to develop severe disease (32.9%) *vs* HBV-negative patients (15.3%)	HBV infection was not associated with worse clinical outcomes	NA

ALT: Alanine transaminase; AST: Aspartate transaminase; HBV: Hepatitis B virus; MERS: Middle east respiratory syndrome; NA: Not applicable; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SARS-CoV: Severe acute respiratory distress syndrome; TB: Total bilirubin.

the association of deranged LFTs with disease severity and prognosis, Tian and Ye[17] suggested that changes in LFTs should be vigilantly monitored for early identification and management.

Although, the majority of studies have reported higher levels of liver enzymes with the severity of COVID-19, a few case reports also documented liver failure in patients without underlying liver disease. Gurala *et al*[18] and Weber *et al*[29] documented acute liver failure in patients without comorbidities and presenting with worsening pulmonary symptoms. However, Orandi *et al*[30] reported acute liver failure documented by replicating SARS-COV-2 RNA in hepatocytes in a young female with COVID-19 presenting with non-respiratory symptoms. Moreover, Busani *et al*[31] reported two fatal cases of acute liver failure in patients with COVID-19 secondary to herpes simplex virus 1 infection. Both patients were treated with tocilizumab.

The resolution of liver injury post-COVID-19 hospitalization is not well studied. A large retrospective study demonstrated persistent deranged LFTs post-discharge in 31.7% of the study population. Thus, it was suggested that recovery from liver injury after resolution of COVID-19 symptoms could be delayed [26]. Hence, the European Association for the Study of the Liver (EASL) position paper recommends monitoring LFTs not only during hospitalization but also post-discharge in COVID-19 patients with persistent deranged laboratory parameters[32].

CHRONIC LIVER DISEASE

CLD, an immunocompromised state, makes the patient susceptible to various diseases including COVID-19 virus[4]. The reported prevalence of CLD amongst COVID-19 patients ranges between 2%-11%[23]. Studies have reported contradictory outcomes for CLD patients with COVID-19. Some have documented higher mortality rates while others negated these findings.

An international registry study between March 2020 and July 2020 documented 745 CLD patients from 29 countries infected with COVID-19 virus. Of the total study population, 386 (51.8%) had cirrhosis, 345 were hospitalized, 108 required ICU admission, and 71 required mechanical ventilation. Among these, 123 (32%) cirrhotic patients died mainly due to pulmonary complications (64%). Moreover, in comparison with non-cirrhotic CLD patients, multivariate analysis documented age, higher Child-Turcotte-Pugh (CTP) score and ALD as significant prognostic factors. Additionally, increased morbidity and mortality were observed with an incremental increase in CTP score[33]. Similarly, a preliminary report of 152 CLD patients documented 39.8% mortality in patients with cirrhosis with CTP B and CTP C scores serving as significant predictors of mortality (P = 0.03 and < 0.001, respectively)[34].

A large National COVID Cohort Collaborative dataset study reported 220727 COVID-19 patients with CLD. Among which, 8941 were patients with cirrhosis, out of which, 8.8% required mechanical ventilation, while 8.9% of patients died at 30 d. In contrast, amongst 29446 non-cirrhotic patients, 2.0% required mechanical ventilation while 30 d mortality was documented in 1.7% of patients. The multivariate analysis documented higher odds of mortality among patients with cirrhosis compared to patients without cirrhosis with COVID-19 (adjusted hazard ratio: 3.31)[35]. However, a pooled analysis of six studies documented no significant association between the severity of COVID-19 and death in patients with CLD[36].

Similarly, in a nationwide Swedish cohort, a nonsignificant association was documented between mortality and COVID-19 in CLD patients. In addition, the presence or absence of cirrhosis did not have an impact on this association. However, the authors did document a slightly higher risk of hospitalization and development of severe COVID-19 in CLD patients as compared to matched controls (adjusted hazard ratio: 1.08 and 1.23, respectively)[37].

ALI at the admission of COVID-19-affected patients was documented in 14 (32.6%) patients, while (39.5%) developed ALI during the hospital stay. Acute decompensation was reported in 9.1%, while 11.6% developed acute-on-chronic liver failure. Further analysis documented higher mortality and complications (liver-related and overall) in decompensated cirrhotic patients with COVID-19. In non-cirrhotic patients with liver injury there was a higher propensity of ICU admission, but the recovery, hospital stay and mortality were comparable to those without liver injury[38]. In another study of 179 patients with cirrhosis with acute decompensation, 50% developed acute-on-chronic liver failure, and this complication was associated with a higher rate of mortality ($P < 0.001$)[33]. Thus, it may be concluded that not only the underlying liver disease but also the existing liver reserve may predict a patient's outcomes with COVID-19 infection. Hence, active and dynamic management of these patients should be done considering their high associated risk of morbidity and mortality.

Recognizing high-risk groups and those predisposed to the severe clinical courses are of utmost importance to plan preventive strategies and management. A limited number of studies have documented the variable impact of etiology on the severity of COVID-19 infection[37].

In a nationwide cohort of 42320 CLD patients, underlying etiology was not associated with a significant risk of hospitalization or development of severe COVID-19. In this study, 32.7% had viral hepatitis, 15.0% had NAFLD, 2.1% had ALD, and 44.0% had other etiologies. However, an international registry of 745 CLD patients with COVID-19 documented ALD as a predictor of mortality ($P = 0.04$). However, no significant association was documented with NAFLD, hepatitis B and C[33]. Similarly, a United States multicenter study also documented ALD along with decompensated cirrhosis and HCC as a liver-specific predictor of mortality in COVID-19 patients[39]. The authors suggested that the added cytokine storm of the SARS-CoV-2 virus to the already heightened inflammatory state in alcoholics could be the cause of the detrimental outcomes. Moreover, increased use of alcohol due to economic and social burdens during the COVID-19 era could be a contributing factor[39,40]. Wang *et al*[41], in a large case-control study, documented that patients with CLD secondary to alcohol-related liver damage and alcoholic liver cirrhosis have odds of 7.05 and 7.00, respectively, of developing COVID-19.

Viral hepatitides, mainly hepatitis B and C, have infected millions of people worldwide. A case-control study of electronic health records documented that adjusted odds of developing COVID-19 were 8.93 and 4.37 with chronic hepatitis C and chronic hepatitis B, respectively[41].

A higher prevalence of hepatitis B has been reported in COVID-19 patients in Asian studies, ranging from 0.8%-6.3%, while a lower prevalence rate of 0.1% has been reported in a United States-based study [41-43]. Although, the pathogenesis is unclear, studies have documented the variable associations of HBV on clinical outcomes of patients with COVID-19. In 105 COVID-19 and HBV co-infected patients, Zhang *et al*[44] reported 23 cases of HBV-related CLD patients with COVID-19. Among which, two patients with cirrhosis (8.7%) became critically ill. Yet, no mortality was reported.

Chen *et al*[45] retrospectively analyzed 20 HBV-positive patients amongst 326 COVID-19 patients. Authors reported three deaths in hepatitis B surface antigen-negative patients, while no patients in the hepatitis B surface antigen-positive group died. Moreover, no statistically significant difference was noted in LFTs, hospital stay and disease severity[45]. In another retrospective analysis of 5639 chronic hepatitis B patients with COVID-19, the authors concluded that current or past hepatitis B infection is not associated with increased mortality[46]. However, another Chinese study documented higher COVID-19 severity and mortality in HBV-infected patients[47]. Zou *et al*[48] observed liver injury as a significant cause of disease severity and mortality in chronic hepatitis B patients with COVID-19.

A chronic immunosuppressed state potentiates the risk of HBV reactivation in patients with chronic or resolved hepatitis B. Moreover, HBV reactivation is associated with high morbidity and mortality [49]. Few case reports have documented HBV reactivation in patients with COVID-19. Aldhaleei *et al*[50] reported a case of HBV reactivation in a patient with COVID-19 presenting with an altered level of consciousness and deranged LFTs. However, high HBV DNA levels were interpreted as reactivation without prior DNA levels.

It is postulated that the immunosuppressive therapy used in COVID-19 can attenuate the host immunity against HBV, thus leading to increased HBV replication. Moreover, with the later withdrawal of immunosuppressants, the reconstituted immune system might mount a heightened immune response against HBV antigen-laden hepatocytes, thus leading to liver injury[51]. Sagnelli *et al*[52] reported HBV reactivation in a patient with COVID-19 pneumonia 7 d after stopping corticosteroid therapy. Wu *et al* [53] also documented HBV reactivation in a COVID-19 patient on entecavir treated with recombinant interferon-alpha-2b, lopinavir/ritonavir and subsequently with methylprednisolone. However, Yip *et al* [46] did not document HBV reactivation in 10 patients on no treatment treated with corticosteroids for severe COVID-19. Nevertheless, the detrimental risk of hepatitis B reactivation persists with COVID-19 treatment. Thus, the Asian Pacific Association for the Study of the Liver (APASL) COVID-19 Taskforce recommends screening all COVID-19 patients for hepatitis B surface antigen. Moreover, antiviral treatment should be prescribed to hepatitis B-positive patients especially treated with interleukin-6 monoclonal antibodies or other immunosuppressive therapy[3].

The prevalence of HCV in COVID-19 is not well reported. A case series from the United States of 5700 hospitalized patients with COVID-19 reported < 0.1% incidence of HCV infection[54]. However, a retrospective single-center study reported a higher incidence of 4.1%. In the latter study, the authors also reported HCV, age, D-dimers and serum ferritin as predictors of in-hospital mortality[55]. The

authors suggested that vascular endothelial dysfunction, elevated cytokine levels and the role of overexpressed transmembrane protease serine 2 could be the potential cause of morbidity and mortality of COVID-19 in HCV-infected patients.

Lensen *et al*[56] reported reactivation of HCV leading to patient mortality in an elderly patient following COVID-19 vaccination. However, the patient had multiple comorbidities along with HBV and HCV co-infection-related cirrhosis[56]. Although, a large veteran database study of HCV-positive patients documented a higher rate of hospitalization, the rates of ICU admission and mortality were similar to negative patients. Moreover, the rate of hospitalization increased with higher fibrosis[57]. The American Association for the Study of Liver Diseases recommends continuing therapy for HBV and HCV if patients are already on treatment when infected with COVID-19. In addition, HBV treatment should be considered in patients with a risk of HBV flare[58].

With the increasing prevalence of NAFLD, it is not surprising that a higher incidence of NAFLD is noted among COVID-19 patients. The prevalence varies from 30% to 55%. The range may be an overestimate, as most of the studies were concentrated on hospitalized patients[59]. NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease) is associated with factors like diabetes and obesity, which are known to aggravate COVID-19 severity[60]. An electronic health records-based study reported that CLD patients have an increased risk of acquiring COVID-19 with the highest odds in patients with NAFLD (adjusted OR: 13.11), nonalcoholic cirrhosis (adjusted OR: 11.5) and chronic hepatitis C (adjusted OR: 8.7)[41]. A systemic review and meta-analysis of 14 studies reported an increased risk of COVID-19 severity and ICU admission in patients with NAFLD. However, no difference in mortality was observed in comparison to non-NAFLD patients[61]. Similar findings have also been reported in other studies[60,62,63]. However, a single-center study from India reported a nonsignificant difference in hospital stay and mortality in COVID-19 patients with or without NAFLD [64]. Similarly, Madan *et al*[65] also documented no association of fatty liver with COVID-19 morbidity and mortality.

Thromboembolism risk is high in COVID-19 patients and is associated with high mortality[66]. A prospective cohort documented a statistically significant association of NAFLD with the development of pulmonary thrombosis in COVID-19 patients. Increased levels of proinflammatory proteins and cytokines may be the contributing factor in this debilitating disease process[59].

Like hepatitis B and C, the underlying liver fibrosis plays an important role in COVID-19 outcomes. Targher *et al*[67] determined the impact of non-invasive fibrosis scores, FIB-4 or NAFLD fibrosis score on COVID-19 severity. After adjustment for sex, obesity and diabetes, the authors documented a significant association of severe COVID-19 with high/intermediate FIB-4 or NAFLD fibrosis score[67].

Regarding autoimmune hepatitis (AIH), a database study of three large registries with 70 AIH patients documented no differences in rates of hospitalization, ICU admission and death between patients with and without AIH-related CLD. However, a higher risk of mortality was observed in the AIH cohort with CTP B and C. Interestingly, the use of immunosuppression was not associated with mortality[68]. Another case series reported uneventful clinical course of 10 AIH patients on immunosuppression[69].

Thus, liver disease etiology may play a role, but the underlying liver fibrosis is the cornerstone to determining susceptibility to COVID-19 and its outcomes. Furthermore, no studies have documented increased predisposition to COVID-19 infection or adverse outcomes in patients with CLD secondary to AIH, primary biliary cholangitis or primary sclerosing cholangitis[70].

HEPATOCELLULAR CARCINOMA

Studies amongst oncological patients have reported a higher risk of acquiring COVID-19 infection along with a greater risk of morbidity and mortality. Moreover, recent cancer treatment may also worsen the outcomes[71,72]. The reported mortality in cancer patients with COVID-19 ranges from 11% to 28%. Nevertheless, concomitant comorbidities, functional class and cancer activity status are associated with a poorer prognosis. Hence, the immunodeficient status of cancer patients determines clinical outcomes [72].

It is estimated that more than 70% of HCC patients have underlying CLD or cirrhosis[73]. It has been shown that the SARS-CoV-2 virus can aggravate liver damage in patients with underlying disease, thus making patients with HCC more susceptible to COVID-19-related morbid complications[74]. Yet, data on the outcomes of HCC with COVID-19 is scarce. A large United States-based multicenter study involving CLD patients infected with COVID-19 reported 52% mortality among patients with HCC (n = 22). Additionally, the authors concluded that decompensated cirrhosis, ALD and HCC were independent liver-related risk factors of mortality[75].

HCC is an aggressive tumor with a tumor volume doubling time of nearly 70 to 120 d[76]. A monthly ultrasound for 6 mo for HCC surveillance is thus recommended under normal circumstances. However, during the pandemic, the delay of 2-3 mo in surveillance has been considered acceptable[58,77]. Inchingolo *et al*[78] suggested prioritizing patients who are at high risk of incidence and/or recurrence of HCC and patients eligible for liver transplantation.

Since the majority of resources were diverted in managing and treating COVID-19 patients during the COVID-19 pandemic, various hepatological associations and societies drafted recommendations for the management of patients with HCC in these times[58,77,79].

Regarding the treatment of HCC, hepatology societies have recommended tailoring the treatment on a case-by-case basis. The American Association for the Study of Liver Diseases proposes that during the COVID-19 pandemic, HCC treatment with curative intent should not be delayed[58]. In addition, APASL recommends postponing surgical treatment and suspending vascular intervention if there is high risk of decompensation or comorbidities since it increases the risk of severe COVID-19. Moreover, ablation therapy could be considered an alternative therapy during this time[77]. Like APASL, EASL guidelines recommend postponing locoregional therapies as these are mostly for the purpose of cytoreduction[77,79]. Similarly, radiation therapy should only be considered in case of functional or life-threatening situations[77].

Although, APASL suggests a preference for oral tyrosine kinase inhibitors over intravenous therapy, EASL proposes dose reduction based on the individual patients[77,79]. Moreover, EASL recommends temporary withdrawal of immune-checkpoint inhibitor therapy in patients with HCC[79].

In general, in all patients with HCC, it is of utmost importance to screen patients for the SARS-CoV-2 virus prior to diagnosis or intervention. Assessment and/or treatment should be postponed until noninfective status is achieved in COVID-19-positive patients. Limited staff with protective gear along with hygienic measures should always be followed during each intervention to curtail the spread of the novel viruses[77].

SOLID ORGAN TRANSPLANTS

Globally, solid organ transplantation has been profoundly affected by the COVID-19 pandemic, resulting in decreased rates of organ procurement and transplantation[80,81]. Liver is the second most common solid organ transplanted in the world after kidney[82]. Although prolonged immunocompromised status and post-transplant associated comorbidities theoretically increase the susceptibility to COVID-19 severity, the data on liver transplant recipients is scarce. Contradictory to the initial reports, a recent multicenter and large database studies have reported similar outcomes in transplanted and non-transplanted COVID-19 populations[80,83,84]. The studies were performed on only hospitalized patients, so it could not be concluded that transplanted patients are prone to be hospitalized due to COVID-19[80]. Centers for Medicare and Medicaid Services has labelled transplant surgery in Tier 3b that is not to be postponed[85]. Owing to diverted and limited resources amidst the pandemic, hepatology societies have restricted liver transplants to urgent transplants only. Table 3 describes a summary of recommendations from various societies regarding liver transplantation activities during the COVID-19 pandemic.

LIMITATIONS

There are certain limitations to this study. We addressed the clinical presentation and laboratory abnormalities primarily, and pathogenesis and particularly pathology were not described. We also did not cover management and prognostic aspects of this infection in detail. New variants of COVID-19 virus were also not discussed nor the vaccination of patients with liver diseases.

FUTURE DIRECTIONS

There is a need for international collaboration for carrying out basic research for better understanding the pathogenesis of hepatobiliary injury in COVID-19 as it can pave the path for the development of targeted therapy and personalized medicine. The role of direct virus infection of the liver with consequent cytopathic effects *vs* indirect liver injury needs to be explored further. Expression profiles of various SARS-CoV-2 entry receptors vary across different *in vitro* and *in vivo* liver models; however, evidence of specific viral hepatotropism of SARS-CoV-2 is inadequate. Abnormal LFT values are common in patients with COVID-19; both the prognostic significance of these derangements and whether they are directly attributable to hepatic SARS-CoV-2 infection remain to be explored in future focused research.

CONCLUSION

In conclusion, liver involvement is common in patients with COVID-19 infection, particularly in those

Table 3 Summary of recommendations from various hepatology societies regarding liver transplantation during the coronavirus disease 2019 pandemic

Step	AASLD	EASL	APASL	Indian Transplant Society
Indications	Develop a hospital-specific policy for organ acceptance in consideration to community incidence of COVID-19 infection	Restrict transplant with poor short-term prognosis like ALF, ACLF, high MELD score and HCC at upper limit of Milan criteria	Can limit transplant to urgent cases (ALF, high MELD, high risk of HCC progression) according to resources and infection status of country	Until April 2020, elective transplants were withheld. However, in ALF and ACLF transplant could proceed
Pre- transplant evaluation	Test all recipients and donors for SARS-CoV-2 before transplantation. In case of COVID-19 infection in potential recipient, transplant can be considered after at least 14-21 d if symptoms are resolved and repeat SARS-CoV-2 test is negative. Vaccination of potential recipient is encouraged	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Reduction of hospital stay for transplant evaluation and consultation	All recipients and donors should be tested for SARS-CoV-2 before transplantation. Donor should also be evaluated for evidence of COVID-19 infection on chest CT	All recipients and donors should be tested for SARS-CoV-2 before transplantation
Post-transplant management without COVID-19	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage COVID-19 vaccination at least 6 wk post-transplant if partially vaccinated pretransplant than vaccination can be completed 1 mo after transplant	Dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in new transplant recipient. In cases of long-term transplant dose reduction/adjustment to current immunosuppression is not recommended. Stable patients could be followed through telemedicine. Encourage vaccination against *Streptococcus pneumoniae* and influenza	Standard immunosuppression protocols should be followed in post-transplant period
Post-transplant management with COVID-19	Consider lowering immunosuppression levels especially antimetabolite drugs (*e.g.*, azathioprine or MMF). Dose adjustment of immunosuppression should be based on severity of COVID-19. Monitor kidney function and calcineurin inhibitor levels	Dose adjustment of calcineurin- and/or mTOR- inhibitors may be required to avoid drug interactions with anti-viral therapy	Consider lowering immunosuppression levels in patients with moderate COVID-19 infection. Immunosuppression should be reduced in recipients with lymphopenia, fever or worsening pneumonia. Severe COVID-19 should be treated as per local protocol. Drug-to-drug interaction should be considered with anti-viral therapy	

AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on chronic liver failure; ALF: Acute liver failure; APASL: Asian Pacific Association for the Study of the Liver; COVID-19: Coronavirus disease 2019; CT: Computed tomography; EASL: European Association for the Study of the Liver; MELD: Model For End-Stage Liver Disease; HCC: Hepatocellular carcinoma; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

with moderate to severe disease. It is mostly asymptomatic or mild in nature. Conversely, patients with pre-existing liver disease are prone to serious COVID-19. Data on the impact of COVID-19 infection on patients with pre-existing diseases or liver transplants is either conflicting or scarce. Hence, large collaborative studies with prolonged follow-up are needed to fully comprehend the impact of this challenging infection on patients with liver diseases.

FOOTNOTES

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MINIREVIEWS

Potential risk of liver injury in epileptic patients during COVID-19 pandemic

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Abstract

Most of the antiseizure medications (ASMs) are metabolized in liver and many of them particularly first-generation ASMs have the potential to increase liver enzymes or induce liver injury. Hence, treatment of new onset seizures or epilepsy by ASMs during the course of coronavirus disease 2019 (COVID-19), which could potentially be complicated by hepatic dysfunction, is a challenging clinical issue. Intravenous form of levetiracetam which has no significant hepatic metabolism or drug-drug interaction is often a favorable option to control seizures in acute phase of COVID-19. Administration of enzyme inducer ASMs and valproate with the well-known hepatotoxicity and common drug interactions is not generally recommended. In patients with epilepsy who are under control with potentially hepatotoxic ASMs, close observation and cautious dose reduction or drug switch should be considered if any evidence of hepatic impairment exists. However, risks of possible breakthrough seizures should be weighed against benefits of lowering the hazard of liver injury. In patients with epilepsy who receive polytherapy with ASMs, transient dose modification with the tendency to increase the dose of ASMs with more favorable safety profile and less drug interaction and decrease the dose of drugs with main hepatic metabolism, high protein binding, potential to cause liver injury and known drug-drug reaction should be considered. Finally, decision making should be individualized based on patients' conditions and course of illness.

Key Words: COVID-19; Epilepsy; Seizure; Drug induced liver injury; Corona virus; Hepatic failure

Core Tip: Most of antiseizure medications (ASMs) are metabolized in liver and many of them particularly first-generation ASMs have the potential to increase liver enzymes or induce liver injury. Hence, treatment of new onset seizures or epilepsy by ASMs during the course of coronavirus disease 2019 (COVID-19), which could potentially be complicated by hepatic dysfunction, is a challenging clinical issue. In this review, we aimed to discuss the potential risks of liver injury in patients with COVID-19 who are under treatment for epilepsy or need to receive ASMs to subside acute symptomatic seizures.

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INTRODUCTION

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the globe, creating the coronavirus disease 2019 (COVID-19) pandemic[1]. Despite the advent of COVID-19 vaccines, the global pandemic continues[2,3]. Although, the lungs are the main target organs infected during COVID-19[4,5] and the initial reported symptoms of disease focused on the respiratory system[6]; this coronavirus can also invade multiple systems (immune and nervous systems) and target several organs and tissues (brain, liver, heart, lung, intestine, muscle, kidney, and gastrointestinal tract[3,7,8]). Liver is one of the most frequently impaired organs and elevation of serum aminotransferases has been recorded in some patients with COVID-19[9-11]. Most COVID-19 patients with liver dysfunction present elevations in one or more aminotransferases, with less than a three-fold increase from the normal values[12,13]. In most patients, liver injury seems to be self-limiting, neither requiring any specific intervention, nor is associated with acute liver failure[14,15]. Chen *et al*[4], in a retrospective study on 830 cases, reported 27.3% of the COVID-19 patients presented with mild abnormalities in the liver function and approximately 3.9% eventually developed liver insufficiency[4]. Yip *et al*[16], reported 23% elevation of liver enzymes and 2% acute liver injury in a cohort study of 1040 patients[16]. In another meta-analysis, approximately 25% of COVID-19 patients experienced elevation of liver enzymes which was directly correlated to the severity of COVID-19 disease[17]. Liver dysfunction could also increase the mortality rate in these patients[18].

Possible mechanisms of liver injury are complex and include direct viral attack, hypoxic/ischemic injury, COVID-19 hyperinflammatory response and potential hepatotoxicity from therapeutic drugs[19,20] (Figure 1).

With the advent of the COVID-19, another health burden involved around 50 million people with epilepsy worldwide[21]. Epilepsy does not make patients more vulnerable to COVID-19 or its severe manifestations[22]. But, management of COVID-19 in patients with epilepsy needs special considerations. Many antiseizure medications (ASMs) have interactions with drugs commonly used for treatment of COVID-19[23]. Many patients with autoimmune epilepsy are under treatment with corticosteroids and other immunosuppressive drugs which might affect the defense ability of immune system[24]. On the other hand, seizure and status epilepticus as neurological manifestations of COVID-19 have been reported in patients with and without epilepsy[25-29]. In certain types of epilepsy particularly Dravet syndrome, fever might trigger seizures. Meanwhile, usual antipyretic and antihistaminic medications might lower seizure threshold in patients with epilepsy[24].

Most of the ASMs have hepatic metabolism and many of them especially older ASMs have the potential to increase hepatic enzymes or cause severe liver injury[30]. Treatment with these ASMs in patients with COVID-19 who have a potential predisposition to hepatic dysfunction, should proceed cautiously considering certain characteristics of medications and disease course. In this review, we aimed to discuss the potential risks of liver injury in patients with COVID-19 who are under treatment for epilepsy or need to receive ASMs to subside acute symptomatic seizures.

ACUTE SYMPTOMATIC SEIZURE DURING THE COURSE OF COVID-19

Several mechanisms might be involved in occurrence of acute symptomatic seizures during COVID-19 infection. SARS-CoV-2 could directly invade central nervous system by targeting angiotensin-converting-enzyme-2 (ACE-2) receptor and consequent meningoencephalitis could be a potential etiology of seizure[31-34]. Also, three indirect mechanisms including down-regulation of ACE-2 expression, cytokine storm and hypoxia could precipitate seizures[31]. Metabolic derangement and organ failure are among the other possible causes of seizure in patients with COVID-19. Detection and management of etiology often need serum metabolic and electrolyte investigation, cerebrospinal fluid

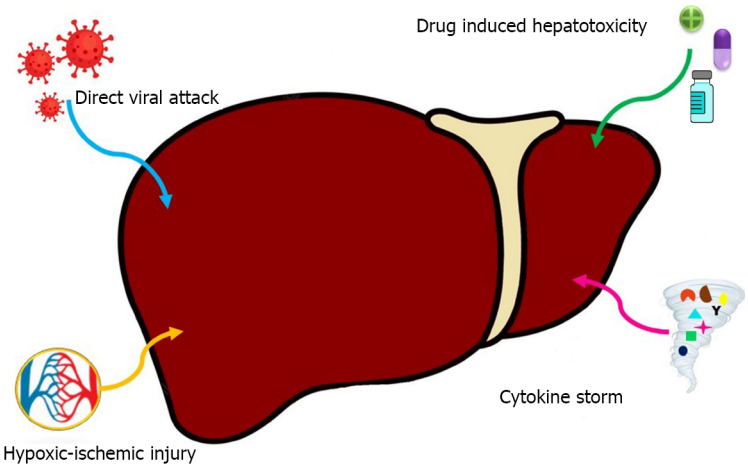

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Figure 1 Hepatic injury mechanism in coronavirus disease 2019.

analysis and brain imaging[28]. Short-term use of ASMs is often recommended to manage seizures in acute phase of COVID-19[35]. However, judicious selection of the ASMs is necessary to prevent exacerbation of organ failure, particularly liver dysfunction and also to decrease the possible drug interactions.

Moreover, new-onset refractory status epilepticus with a mortality rate of 10% to 20% has been reported secondary to COVID-19. Considering the undesirable response to ASMs, plasma exchange, intravenous immunoglobulin, steroids and immunosuppressives have been used for management of these patients with different success rates. There is no definite approach to manage these patients and the suggested treatment algorithm should be modified individually based on patient's conditions[29].

EPILEPSY AND COVID-19

The COVID-19 pandemic has had several negative impacts on patients with epilepsy, which are beyond the scope of this paper. In patients with epilepsy who experience COVID-19 infection, breakthrough seizures might occur for at least three reasons. Firstly, predisposing factors such as sepsis, sleep deprivation, metabolic derangement and electrolyte imbalance along with previously mentioned direct and indirect mechanisms of acute phase seizures, could precipitate breakthrough seizures in patients with epilepsy[31]. Secondly, fever can trigger seizures in certain types of epilepsy particularly Dravet syndrome[24]. Finally, common medications used for treatment of COVID-19 could induce seizure *via* lowering seizure threshold or decreasing the efficacy of ASMs through drug-drug interaction[36]. Thus, recognition and addressing all possible causes are necessary to control the seizures and prevent the consequent morbidity and mortality. This point is of the greatest importance in patients with drug-resistant epilepsy.

Furthermore, previously used ASMs in patients with epilepsy, might need modifications when COVID-19 complications such as cardiac, hepatic or renal dysfunction occur. Dose adjustment of ASMs should be considered in patients with hepatic or renal impairment. On the other hand, drug switch or dose reduction might be necessary if ASMs have the potential to aggravate organ failure. However, the possible risk of uncontrolled seizures induced by changes in type and dose of ASMs, should be weighed against the benefits of modifications and it might be injudicious for some ASMs with a high risk of withdrawal seizure and status epilepticus such as barbiturates.

ASMS WITH THE HIGH POTENTIAL OF LIVER INJURY

Valproic acid

Valproate is a broad-spectrum ASM with a high bioavailability (90%) and high protein binding (74%-93%). It has several mechanisms of action including increase in gamma amino butyric acid (GABA) activity and blockage of voltage-gated Na+, Ca2+ and K+ channels. Valproate extensively metabolized in the liver *via* glucuronidation, β-oxidation and oxidation by cytochrome P450[37]. Valproate inhibits CYP2C9, uridine glucoronate-glucuronsyl transferase (UGT), and epoxide hydrolase[22]. Protease inhibitors, such as lopinavir/ritonavir could increase metabolism of valproate by induction of valproate glucuronidation[37]. In contrast, valproate decreases the plasma concentrations of darunavir/cobicistat and increases the concentrations of lopinavir/ritonavir[36]. Valproate has no significant interaction with

the other anti-COVID-19 drugs. However, there is a red flag for using this ASM in patients with abnormal liver function. Hepatotoxicity is a well-known adverse event of valproate[38]. It might occur through different mechanisms such as formation of valproate reactive metabolites, inhibition of fatty acid β-oxidation and excessive oxidative stress[39,40]. Valproate-induced liver injury has different degrees. The most common type is asymptomatic increase in liver enzymes. More than 3 times increase in liver function tests makes drug discontinuation necessary. The known risk factors for valproate hepatotoxicity are young age, polytherapy, developmental delay, metabolic disorders, febrile illness and polymerase gamma 1 related disorders[38]. Furthermore, valproate can cause hyperammonemic encephalopathy which presents as progressive confusional state leading to coma[41,42]. This condition could easily be neglected in a critically ill patient with COVID-19.

In conclusion, despite the high efficacy in treatment of various type of seizures, factors including possible drug interaction, potential to cause liver injury, exacerbation of underlying liver dysfunction and induction of hyperammonemia, have limited the use of valproate as the first line treatment in patients with COVID-19 and new onset seizures. However, in patients with epilepsy and COVID-19 who were under control by valproate, decision making is more challenging. The clinician might choose not to switch the medication at the first step; but the possibility of interaction with mentioned anti-COVID drugs should be closely observed by therapeutic drug monitoring. In addition, in case of any evidence of liver dysfunction, there should be a low threshold to lower the dose or switch the drug.

Cytochrome p450 inducers

Phenytoin, carbamazepine, phenobarbital and primidone are among the first generation of ASMs. Their strong potential to induce various cytochrome p450 enzymes often causes several drug-drug interactions[43-46].

Phenytoin

Phenytoin is one of the oldest ASMs which plays its antiseizure role by enhancing rapid inactivation of voltage-gated sodium channels[47]. Phenytoin has a high protein binding (> 90%) and 70%-100% bioavailability. It is metabolized by CYP2C9 and CYP2C19 hepatic isoenzymes.

It induces CYP1A2, CYP2B, CYP2C, CYP3A4, and UGT[22]. Phenytoin significantly decreases the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine and has a potential to decrease serum level of lopinavir/ritonavir. Nitazoxanide partially increases and tocilizumab weakly decreases the serum concentration of phenytoin. Phosphenytoin, the water-soluble prodrug of phenytoin has the same drug-drug interactions[36].

Hepatotoxicity is a well-known adverse effect of phenytoin which probably occurs through increase in reactive oxygen species formation and cellular oxidized glutathione, decrease in intracellular reduced glutathione, enhancement of lipid peroxidation and mitochondrial damage[48,49]. Phenytoin-induced liver injury could have a broad spectrum from mild asymptomatic elevation in liver function tests to severe hepatotoxicity which is often associated with hypersensitivity reactions[37,48,50,51]. Although the cosmetic and systemic adverse events have limited its use in chronic epilepsy, phenytoin is commonly used to abort focal and generalized seizures and also status epilepticus in emergency department[52,53]. However, it is not a good option to control seizures in patients with COVID-19. Phenytoin might cause cardiorespiratory depression which is potentially harmful in critically ill patients, elderly and underlying cardiac disease[54]. The potential for hepatotoxicity and increase in free drug level in hepatic and renal impairment[55] also limited its use in COVID-19. Moreover, significant dug-drug reaction with anti-COVID-19 agents could be challenging.

Carbamazepine

Carbamazepine is an effective ASM with a high bioavailability (75%-85%) and high protein binding (70%-80%). Its mechanism of action is similar to phenytoin. Carbamazepine is metabolized in liver by CYP3A4 and CYP2C8 enzymes[37]. It induces CYP1A2, CYP2C, CYP3A4 and UGT[22] and so, has multiple drug-drug interactions with anti-COVID medications. It significantly decreases the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine. Co-administration of carbamazepine with lopinavir/ritonavir also might lead to decrease in serum level of anti-COVID agent. Atazanavir, darunavir/cobicistat and lopinavir/ritonavir could increase serum concentration of carbamazepine and cause toxicity. In addition, tocilizumab has the potential to decrease carbamazepine concentration[36].

In a report of ASM-induced liver injury by FDA, carbamazepine had the highest odds ratio (2.92) among the other ASMs of first generation[30] and hepatotoxicity is a well-known adverse effect of this potent ASM[56]. Metabolic activation and following immune responses are reported as possible mechanisms of carbamazepine-induced liver injury[57].

Carbamazepine has no parenteral formulation and needs about 3 to 5 wk to reach the steady state. So, it is not commonly used for treatment of seizures in acute phase. However, many of patients with epilepsy are under treatment with this ASM. When comorbidity with COVID-19 occurs in these patients, higher doses of antiviral agents might be needed to compensate the decrement of serum concentration caused by carbamazepine. On the other hand, patients should be closely observed for sign

and symptoms of carbamazepine toxicity in co-administration of atazanavir, darunavir/cobicistat and lopinavir/ritonavir. In critical patients with increased liver enzymes, reduction of carbamazepine dosage is generally recommended to prevent harmful increase in carbamazepine concentration and also further liver damage.

Phenobarbital and primidone

Phenobarbital, one of the first ASMs used to manage epilepsy, is of limited use currently. But it is still recommended as an alternative therapy in first and second line management of status epilepticus. Phenobarbital is also prescribed in some patients with epilepsy especially in countries with limited resources[58]. It plays its antiseizure role by affecting GABA-A receptors which leads to increase in chloride ions and consequently reduction of neuronal excitability. Phenobarbital has a high bioavailability (> 90%) and moderate protein binding (55%)[59].

Primidone is another old ASM which affects synaptic and extrasynaptic GABA receptors[42]. It is metabolized to phenobarbital and phenylethylmalonamide by CYP2C9, CYP2C19, and CYP2E1 enzymes[22]. Primidone is still prescribed for patients with epilepsy; but it has some other certain indications such as essential tremor as well[60]. It has a high bioavailability (> 90%) with a low plasma protein binding (10%)[59]. Phenobarbital and primidone induce CYP1A2, CYP2A6, CYP2B, CYP2C, CYP3A4, and UGT. Similar to other enzyme inducer ASMs, these two drugs considerably decrease the serum concentration of atazanavir, darunavir/cobicistat, remdesivir, chloroquine and hydroxychloroquine and could possibly decrease serum level of lopinavir/ritonavir. Darunavir/cobicistat significantly decreases the serum concentration of phenobarbital, but has no effect on primidone. Lopinavir/ritonavir might decrease primidone level[36].

Phenobarbital can cause large spectrum of hepatic adverse effects which could be various from asymptomatic increase in liver enzymes, to devastating hepatitis and acute liver failure. A possible mechanism of liver injury by phenobarbital is oxidative stress in hepatic mitochondria[38,61,62]. Due to availability of newer effective ASMs with more favorable safety profile in recent decade, phenobarbital has been less frequently administered in acute phase seizures. IV phenobarbital has the potential to cause cardiorespiratory depression[63] and elevation of liver enzymes[38] in critically ill patients with COVID-19 who are potentially in a compromised respiratory and hepatic state. Hence, phenobarbital is an inappropriate choice for treatment of seizures in COVID-19. In patients with epilepsy who are under treatment with phenobarbital and primidone, serious drug-drug interaction with anti-COVID-19 agents should be considered. Since, rapid taper and switch of these 2 drugs are impossible due to high risk of withdrawal seizure and status epilepticus, they should be continued cautiously with slight dose reduction in hepatic impairment and therapeutic drug monitoring. According dose modification of anti-COVID agents is also indispensable.

TREATMENT OF SEIZURES IN PATIENTS WITH LIVER INJURY

Several factors should be considered in treatment of seizures in acute phase of COVID-19. The selected ASM/ASMs should have the parenteral formulation to achieve a rapid appropriate serum level. The safety profile and low risk for systemic adverse effects are also very important; particularly if the disease course is already complicated with organ failure. Most of ASMs have hepatic metabolism and many of them could potentially cause hepatotoxicity which makes judicious selection and dose modification necessary. Moreover, several drug-drug interactions are expected between ASMs and anti-COVID drugs which could form a more complicated clinical scenario. The possible drug-drug interactions of common ASMs and anti-COVID-19 agents have been summarized in Table 1.

Levetiracetam, lorazepam, gabapentin, vigabatrin and pregabalin are ASMs which have no interaction with anti-COVID drugs[36]. Among these ASMs, only levetiracetam and lorazepam have the parenteral form. IV lorazepam is the first line treatment to abort generalized convulsive seizure[64]. Benzodiazepines predominantly have hepatic metabolism. Metabolism of lorazepam is not significantly affected by liver dysfunction and the possibility of liver injury is very low with its administration[65]. However, it might cause transient respiratory depression and exacerbation of hepatic encephalopathy [22]. So, cautious use of lorazepam is acceptable for first-line treatment of seizure; but it could not be used as maintenance therapy to prevent further seizures.

Levetiracetam is an efficient broad spectrum ASM which is commonly used in treatment of epilepsy, acute phase seizures and status epilepticus[66-69]. It has a high bioavailability (> 95%) and a very low protein binding (< 10%). Less than 2% of levetiracetam is metabolized in liver which makes it a safe drug with no significant pharmacokinetic interaction[22]. It is postulated that levetiracetam mainly presents its antiseizure effect by targeting the synaptic vesicle glycoprotein SV2A[70]. Levetiracetam is a safe ASM for patients with liver dysfunction. There are very rare reports of levetiracetam-induced liver injury and elevation of liver enzymes[30]. No significant difference in pharmacokinetic of levetiracetam is expected in patients with mild to moderate hepatic impairment. But 50% reduction in total dose is recommended due to decreased drug clearance in patients with severe hepatic failure (Child-Pugh Class C)[65]. Overall, IV formulation of levetiracetam is a safe and efficient choice for treatment of acute onset

Table 1 Drug-drug interaction between antiseizure medications and anti-coronavirus disease 2019 agents

	ATV	DRV/c	LPV/r	RDV	FAV	HCLQ/CLQ	TCZ	IFN-β-1α
Brivaracetam	Mi	-	Mi	-	-	Mo	-	-
Carbamazepine	S	S	Mo	S	-	S	Mi	Mo
Clobazam	Mo	Mo	Mo	-	-	-	-	-
Diazepam	Mo	Mo	Mo	-	-	-	-	-
Eslicarbazepine	Mo	Mo	Mo	Mo	-	Mo	-	-
Ethosuximide	Mo	Mo	Mo	-	-	-	-	-
Gabapentin	-	-	-	-	-	-	-	-
Lacosamide	Mi	Mo	Mi	-	-	-	-	-
Lamotrigine	-	Mo	Mo	-	-	-	-	-
Levetiracetam	-	-	-	-	-	-	-	-
Lorazepam	-	-	-	-	-	-	-	-
Oxcarbazepine	Mo	Mo	Mo	Mo	-	Mo	-	Mo
Perampanel	Mo	Mo	Mo	-	-	-	-	-
Phenytoin	S	S	Mo	S	-	S	Mi	Mo
Phenobarbital	S	S	Mo	S	-	S	Mi	Mo
Pregabalin	-	-	-	-	-	-	-	-
Primidone	S	S	Mo	S	-	S	Mi	-
Rufinamide	Mo	Mo	Mo	Mo	-	Mo	-	-
Topiramate	-	Mo	-	-	-	-	-	-
Valproic acid	-	Mo	Mo	-	-	-	-	Mo
Vigabatrin	-	-	-	-	-	-	-	-
Zonisamide	-	Mo	-	-	-	-	-	-

ATV: Atazanavir; DRV/c: Darunavir/cobicistat; LPV/r: Lopinavir/ritonavir; RDV: Remdesivir; FAV: Favipiravir; HCLQ/CLQ: Hydroxychloroquine/chloroquine; TCZ: Tocilizumab; IFN-β-1α: Interferon β-1α; S: Severe interaction, medications should not be co-administered; Mo: Moderate interaction, dose adjustment or close monitoring is required; Mi: Mild interaction, the need for dose adjustment or monitoring is unlikely.

seizures in COVID-19.

Eslicarbazepine acetate, oxcarbazepine, lacosamide, lamotrigine, clobazam, perampanel, rufinamide, tiagabine, topiramate, and zonisamide have mild to moderate interaction with anti-COVID drugs[22]. Among these ASMs, lacosamide is available in IV form and commonly has been used in treatment of seizure and status epilepticus[71,72]. Lacosamide has an almost complete bioavailability and a very low (< 15%) protein binding. It is metabolized to inactive O-desmethyl derivatives by CYP2C19 in liver[37]. Lacosamide enhances the slow inactivation of voltage-gated sodium channels[73]. In patients with mild to moderate hepatic impairment, reduction to 75% of maximum dose is recommended. But, lacosamide should not be administered in patients with severe hepatic dysfunction. Lacosamide-induced liver injury has not been reported in the literature[30]. So, IV lacosamide is an appropriate choice for aborting seizure in patients with epilepsy and COVID-19; but dose adjustment in hepatic dysfunction, interaction with darunavir/cobicistat and potential PR prolongation in coadministration with atazanavir and lopinavir/ritonavir should be cautiously considered[22].

Among previously mentioned ASMs with the higher probability of liver injury, IV formulations of valproate, phenytoin and phenobarbital are available. However, use of these ASMs should be limited to special conditions such as unavailability of new generation ASMs and refractoriness of seizures.

TREATMENT OF EPILEPSY IN PATIENTS WITH LIVER INJURY

Many patients with epilepsy need long-term treatment with ASMs and drug withdrawal or switch might lead to breakthrough seizures or status epilepticus for them. Since, anti-COVID drugs-which have the most interaction with ASMs-are generally administered for a short course, mild to moderate drug-

drug interactions could be cautiously managed by close observation, therapeutic drug monitoring and dose modifications. However, concurrent administration of drugs with severe interactions is not recommended. In these cases, the medical team should evaluate the risk and benefits of choosing a safer anti-COVID drug over switching the ASM.

In patients with controlled epilepsy who suffer from liver dysfunction during COVID-19 infection, appropriate dose adjustment of ASMs is the first step[22]. This approach could prevent serum concentration of drugs to reach the toxic level and also could protect liver from further injury. In this stage, there should be a low threshold to reduce the dose or switch ASMs with a high potential of hepatotoxicity. In patients with drug-resistant epilepsy or those who are on polytherapy with ASMs, transient dose reduction of hepatotoxic drugs and increase in dose of ASMs with more favorable profile might help the patients to pass the critical course without experiencing breakthrough seizures.

However, if severe liver injury occurs, some ASMs should be inevitably discontinued. Appropriate replacement of these drugs by safer ASMs such as levetiracetam could prevent seizure recurrence and subsequent complications.

CONCLUSION

COVID-19 pandemic has affected many people all over the world. Liver injury is a well-known complication of this infection and have an impact on management of patients with comorbidities. Particularly, management of seizure and epilepsy in patients with COVID-19 and liver injury could be challenging. Certain considerations should be taken in account in selection of ASMs for patients with new-onset seizures. Avoidance of ASMs with potential of hepatotoxicity, reasonable dose adjustment and monitoring of drug interactions with anti-COVID-19 drugs are necessary. Furthermore, in patients with epilepsy, cautious changes in dose and type of previously used ASMs are sometimes necessary. The possibility of drug-drug interactions along with the other comorbidities of patients should also be considered. Decision making by a medical team consists of different related specialties is often necessary to choose the best treatment method for the patients.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics of COVID-19 patients who underwent tracheostomy and its effect on outcome: A retrospective observational study

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Abstract

BACKGROUND

The exponential rise in Coronavirus disease 2019 (COVID-19) cases has resulted in an increased number of patients requiring prolonged ventilatory support and subsequent tracheostomy. With the limited availability of literature regarding the outcomes of COVID-19 patients with tracheostomy, we attempted to study the clinical characteristics and multiple parameters affecting the outcomes in these patients.

AIM

To determine all-cause mortality following tracheostomy and its association with various risk factors in COVID-19 patients.

METHODS

This retrospective study included 73 adult COVID-19 patients admitted to the ICU between 1 April, 2020 and 30 September, 2021 who underwent tracheostomy as a result of acute respiratory failure due to COVID-19. The data collected included demographics (age, sex), comorbidities, type of oxygen support at admission, severity of COVID-19, complications, and other parameters such as admission to tracheostomy, intubation to tracheostomy, ICU stay, hospital stay,

and outcome.

RESULTS

This study included 73 adult patients with an average age of 52 ± 16.67 years, of which 52% were men. The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. The mortality rate was 71.2% and 28.8% of patients were discharged alive. The mean duration of ICU and hospital stay was 25 ± 11 days and 28.21 ± 11.60 days, respectively. Greater age, severe COVID-19, mechanical ventilation, shock and acute kidney injury were associated with poor prognosis; however, early tracheostomy in intubated patients resulted in better outcomes.

CONCLUSION

Patients with severe COVID-19 requiring mechanical ventilation have a poor prognosis but patients with early tracheostomy may benefit with no added risk. We recommend that the timing of tracheostomy be decided on a case-by-case basis and a well-designed randomised controlled trial should be performed to elucidate the potential benefit of early tracheostomy in such patients.

Key Words: COVID-19; Intubation; Mechanical ventilation; ICU; Tracheostomy; Oxygen therapy

Core Tip: Tracheostomies are commonly performed in critically ill patients who require mechanical ventilation for a prolonged duration. Various recommendations and guidelines have been published regarding the safety of tracheostomy in Coronavirus disease 2019 (COVID-19) patients but literature with respect to indication, timing and outcome of tracheostomy in COVID-19 patients is still lacking. Therefore, in this study we aimed to describe the clinical characteristics of patients who underwent elective tracheostomies and multiple parameters affecting the outcomes in these patients. We found that patients with severe COVID-19 requiring mechanical ventilation had a poor prognosis but patients with early tracheostomy may benefit from this procedure.

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has resulted in extreme stress in healthcare establishments worldwide. Various studies have shown that 5%-15% of the patients with COVID-19 will develop severe disease requiring endotracheal intubation and mechanical ventilation[1,2]. Some patients may require prolonged ventilatory support. Tracheostomies are commonly performed in critically ill patients who require prolonged mechanical ventilation[3]. Compared with the orotracheal tube, the tracheostomy tube bypasses the mouth and pharynx resulting in better patient comfort and sedation requirement[4]. Other benefits of tracheostomy include a reduced incidence of ventilator-associated pneumonia, reduction in anatomical dead space leading to less work of breathing, easy airway suctioning and toileting, and facilitation of weaning from mechanical ventilation[5]. During the pandemic, tracheostomy will help in early transition of the patients from ICU care to ward care, thus helping to create a much-needed ICU bed that is always scarce in resource-limited countries with limited manpower. Tracheostomy will also help reduce the generation of highly infectious aerosols that are associated with the use of high flow oxygen devices or non-invasive ventilation[6].

Various guidelines have been published regarding the safety of tracheostomy in COVID-19 patients; however, literature regarding the indications, timing, and outcomes of tracheostomy in COVID-19 patients is lacking[7,8]. Some authors suggest that tracheostomy should be delayed for at least 14 days after endotracheal intubation to obtain better information regarding patient prognosis along with reduced viral load[9-13]. Early tracheostomy is advised so that patients can be weaned from the ventilator and transferred to ward care sparing the ICU bed[14]. However, these recommendations are based on expert opinions and a well-designed study is needed to provide a high level of evidence. In this study, we aimed to describe the clinical characteristics of patients who underwent elective tracheostomies and to study multiple parameters affecting the outcomes of these patients.

MATERIALS AND METHODS

Study overview

This study was conducted by the Department of Anaesthesiology, Pain Medicine, and Critical Care in a tertiary care centre. The retrospective data presented in this study is part of the project titled-Post discharge outcomes of COVID-19 patients following admission to the intensive care unit, which was approved by the institute ethics committee (IEC-291/17.04.2020). As the study is retrospective in nature, informed written consent from individual patients was waived. Major databases such as PubMed, Embase, Scopus, Web of Science and Google Scholar were searched to identify the latest literature. The search was strengthened using a new tool called Reference Citation Analysis (https://www.referencecitationanalysis.com/).

Inclusion criteria

The study included all confirmed COVID-19 adult patients admitted to the ICU who underwent tracheostomy between April 1, 2020 and September 30, 2021.

Exclusion criteria

All patients with missing data or polytrauma cases who were incidentally COVID-19 positive were excluded from the study.

Data collection

Data were retrospectively collected using medical records and a computerized patient record system. Data collected included demographics (age, sex), comorbidities, type of oxygen support at admission, the severity of COVID-19, complications, and tracheostomy-related parameters such as admission to tracheostomy, intubation to tracheostomy, ICU stay, hospital stay, and outcome. The timing of tracheostomy was classified as early (within 10 days of intubation) and late (more than 10 days of intubation).

Statistical analysis

The primary outcome of the study was to measure all-cause mortality following tracheostomy and its association with various risk factors. The secondary outcome included various tracheostomy-related parameters such as the timing of tracheostomy, admission to tracheostomy, intubation to tracheostomy, ICU stay, and hospital stay. Continuous variables were expressed as mean ± SD and categorical variables as number (percentage). Group comparison was performed using independent *t*-tests or Fisher's exact test. *P* values less than 0.05 were considered statistically significant.

RESULTS

During the study period, 113 mechanically ventilated patients with confirmed COVID-19 who underwent tracheostomy were screened for possible inclusion in the study. Seventy-three patients satisfied the inclusion criteria. They were further subdivided into survivors and non-survivors.

Table 1 shows the patient's demographics, comorbidities, COVID-19 severity, initial respiratory support, and tracheostomy-related parameters. The average age of the patients was 52 years (SD 16.67) and 52% were male. Hypertension was the most common comorbidity (35.6%) followed by chronic kidney disease with superimposed acute kidney injury (34.3%), diabetes (24.6%), cerebrovascular accident (15.1%), and coronary artery disease (5.44%). The most common oxygen therapy modality used at the time of ICU admission was mechanical ventilation (42.5%), followed by a non-rebreathing mask (19.2%), high flow nasal canula (10.9%), room air (12.3%), face mask (8.2%) and non-invasive ventilation (6.8%). Most of the patients who were admitted to the ICU were suffering from severe COVID-19 (50.6%) followed by moderate (30.2%) and mild (19.2%) disease. The mortality rate was 71.2% and 28.2% were discharged alive. The mean duration of ICU and hospital stay was 25 ± 11 days and 28.21 ± 11.60 days, respectively.

The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. In 35 (47.9%) patients, tracheostomies were performed early *i.e.*, within 10 days of intubation. Subgroup analysis among survivors and non-survivors showed that patients in the non-survivor group were older ($P = 0.02$), had severe COVID-19 ($P = 0.001$), and had a late tracheostomy ($P = 0.03$) as compared to survivors. However, the number of days from admission to tracheostomy, duration of ICU, and hospital stay were not significantly different between survivors and non-survivors (Table 2).

Table 1 Clinical-demographic parameters of COVID-19 patients who underwent tracheostomy

Characteristics	*n* = 73
Age (yr)	52 ± 16.67
Male	38 (52%)
Female	35 (48%)
Comorbities & COVID related complications *n* (%)	
HTN	26 (35.6%)
DM	18 (24.66%)
CAD	04 (5.44%)
CKD with AKI	25 (34.3%)
CVA	11 (15.1%)
TBI	02 (2.74%)
Stroke	05 (6.8%)
Pneumothorax	10 (13.7%)
Mucormycosis	06 (8.22%)
Shock	44 (60.2%)
COVID severity *n* (%)	
Mild	14 (19.2%)
Moderate	22 (30.2%)
Severe	37 (50.6%)
Initial respiratory support *n* (%)	
RA	9 (12.3%)
FM	6 (8.2%)
NRBM	14 (19.2%)
HFNC	8 (10.9%)
NIV	5 (6.8%)
MV	31 (42.5%)
Tracheostomy related events (mean ± SD)	
Admission to tracheostomy (d)	18.12 ± 12.98
Intubation to tracheostomy (d)	11.97 ± 9
ICU stay (d)	25 ± 11
Hospital stay (d)	28.21 ± 11.60
Death (*n*, %)	52 (71.2%)
Discharge (*n*, %)	21 (28.8%)

HTN: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; CKD with AKI: Chronic kidney disease with acute kidney injury; CVA: Cerebrovascular accident; TBI: Traumatic brain injury; RA: Room air; FM: Face mask; NRBM: Non-rebreathing mask; HFNC: High-flow nasal cannula; NIV: Non-invasive ventilation; MV: Mechanical ventilation.

DISCUSSION

This retrospective study describes the effect of tracheostomy in COVID-19 patients suffering from acute respiratory failure in a tertiary care centre in northern India. In our cohort of tracheotomized patients with COVID-19 pneumonia, we found that the average time from intubation to tracheostomy was 12 days; tracheostomy was performed in 6.4% of the patients admitted to the ICU. This rate is slightly lower than the French COVID-ICU study which reported a rate of 9%[15]. The patients in the non-survivor group were older and had severe COVID-19 and late tracheostomy.

Table 2 Comparison of tracheostomy-related events between survivors and non-survivors

Parameters		Survivors	Non-survivors	*P* value
Age (yr)		44.95 ± 4.19	54.84 ± 2.05	0.02
Gender male		12 (57.2%)	26 (50%)	0.38
Female		9 (42.8%)	26 (50%)	
Comorbidities	Present	06 (28.6%)	16 (30.77%)	0.54
	Absent	15 (71.4%)	36 (69.23%)	
COVID severity	Mild	10 (71.4%)	04 (28.6%)	0.001
	Moderate	03 (13.6%)	19 (86.4%)	
	Severe	08 (21.6%)	29 (78.4%)	
Admission to tracheostomy (d)		17.09 ± 2.54	18.53 ± 1.88	0.67
Intubation to tracheostomy (d)		9.19 ± 8.57	13.09 ± 9.02	0.01
Early tracheostomy (< 10 d)		14 (66.6%)	21 (40.3%)	
Late tracheostomy (> 10 d)		7 (33.4%)	31 (59.6%)	0.03
ICU stay (d)		26.19 ± 3.50	24.55 ± 1.41	0.6
Hospital stay (d)		30.85 ± 3.15	27.15 ± 1.41	0.21

The timing of tracheostomy in COVID-19 has been a matter of debate as published studies have presented heterogeneous results[8,16-19] and this debate is not going to be settled as most of the studies on tracheostomy are retrospective in nature. Various researchers have demonstrated that early tracheostomy has the advantage of rapid weaning from mechanical ventilation, decreased need for sedation, and shorter length of ICU stay[20]. Other proposed advantages include reduced risk of oropharyngeal and laryngeal damage as well as facilitation of oral feeding and oral care[21].

Before the COVID-19 pandemic, a systematic review by Adly *et al*[20] suggested that early tracheostomy *i.e.*, within 7 days, was associated with a reduced duration of mechanical ventilation, decreased mortality rate, and shorter length of ICU stay. A Cochrane review by Andriolo *et al*[22] found that early tracheostomy was associated with lower mortality rates and a higher probability of discharge from the ICU at day 28. However, a meta-analysis by Griffiths *et al*[23] and Siempos *et al*[24] demonstrated that there was no survival benefit following early tracheostomy as compared to late tracheostomy. The TracMan randomized controlled[25] trial comparing early (within 4 days) *vs* late tracheostomy (after 10 days), demonstrated that there were no differences in 30-day mortality and 1- and 2-year survival or length of ICU stay between them.

During the COVID-19 pandemic, various studies have described different timing of tracheostomy. Kwak *et al*[26], the Queen Elizabeth Hospital Birmingham COVID-19 airway team[27], Angel *et al*[28], Chao *et al*[10], Martin-Villares *et al*[18], Hernandez-Gracia *et al*[29] and Mario *et al*[30] have reported a mean time from intubation to tracheostomy of 12.2, 13.9, 10.6, 19.7, 12, 17 and 15 days, respectively. In our study, the mean intubation to open tracheostomy time was 11.97 days and in 47.9% (n = 35) of COVID-19 patients tracheotomies were performed within 10 days of intubation.

The subgroup analysis of tracheostomy among non-survivors and survivors showed that the mean age of non-survivors was higher than survivors. This poor outcome in older patients with tracheostomies is consistent with many studies published on COVID-19[1,18]. Similarly, non-survivors with tracheostomies were suffering from severe COVID-19, which was also consistent with previously published research. Furthermore, most of the non-survivors in our study had late tracheostomy demonstrating poor outcome in patients with late tracheostomy (beyond 10 days), which may be due to worsening of the disease at later stages. However, Tang *et al*[16] suggested better outcomes in tracheostomies done after 14 days whereas Aviles-Jurado *et al*[31] in their prospective study on the safety of tracheostomy reported that early tracheostomy (< 10 days) had no association with mortality. Other parameters such as the number of days from admission to tracheostomy, duration of ICU, and hospital stay were not significantly different between survivors and non-survivors. The overall mortality in our study was 71.2%, which was consistent with other studies reporting > 50% mortality in COVID-19 patients on mechanical ventilation[32,33].

Limitations

Our study had several limitations. First, it was a retrospective observational study with a relatively small sample size. Therefore, a well-designed multicentre randomized controlled trial with adequate sample size is needed to validate the findings in our study. Second, due to its retrospective nature, some

key statistical tests could not be performed. Thirdly, the various scores used in the ICU in predicting the outcome were not analysed. Lastly, we were unable to retrieve and calculate the incidence of complications associated with a tracheostomy. The present study may help other clinicians in designing a clinical trial for future research to identify the best time of tracheostomy in critically ill mechanically ventilated patients.

CONCLUSION

Our study describes the clinical characteristics and outcome of a cohort of patients who underwent tracheostomy after intubation due to COVID-19. The results showed that early tracheostomy (less than 10 days) was associated with reduced mortality. However, a well-designed randomized multicentre trial is needed to elucidate the potential benefit of early tracheostomy in mechanically ventilated COVID-19 patients. We also suggest that the timing of tracheostomy be decided on a case-by-case basis rather than following a strict rule.

ARTICLE HIGHLIGHTS

Research background

The rapid increase in Coronavirus disease 2019 (COVID-19) patients has resulted in an increased number of patients with severe disease requiring prolonged ventilatory support and subsequently tracheostomy. Details regarding the timing, and safety of tracheostomy in the management of COVID-19 patients continue to evolve.

Research motivation

With the limited availability of literature regarding the outcomes of COVID-19 patients with tracheostomy, we attempted to study the clinical characteristics and multiple parameters affecting the outcomes in these patients.

Research objectives

Our research objective was to determine the all-cause mortality after tracheostomy and its relation with various risk factors in COVID-19 patients.

Research methods

We conducted a retrospective observational study at a tertiary care hospital. The study included 73 adult COVID-19 patients admitted to the ICU between 1 April, 2020 and 30 September, 2021 who underwent tracheostomy as a result of acute respiratory failure due to COVID-19.

Research results

Seventy-three adult patients were included in the study with an average age of 52 ± 16.67 years, of which 52% were male. The average time for admission to tracheostomy was 18.12 ± 12.98 days while intubation to tracheostomy was 11.97 ± 9 days. The mortality rate was 71.2% and only 28.8% of patients were discharged alive. Greater age, severe COVID-19, mechanical ventilation, presence of shock and acute kidney injury were associated with a poor prognosis; however, early tracheostomy in intubated patients resulted in a better outcome.

Research conclusions

The study showed that early tracheostomy (less than 10 days) was associated with reduced mortality with no added risk to the patient. Furthermore, the timing of tracheostomy should be decided on a case-by-case basis rather than following a strict rule.

Research perspectives

A well designed randomised controlled trial should be performed to elucidate the potential benefit of early tracheostomy in COVID-19 patients.

FOOTNOTES

Author contributions: Singh A, Soni KD, Aggarwal R, Singh Y, Patel N, Kumar K, Chaudhary N, Perveen F, and Trikha A contributed to conception, study design, as well as data collection and evaluation; Singh A and Soni KD contributed to statistical analysis, and interpretation of data; Singh A, Singh Y, and Trikha A drafted the manuscript, which was revised by Soni KD; all authors have read and approved the final manuscript.

Institutional review board statement: The retrospective data presented in this study is the part of the project titled–Post discharge outcomes of COVID-19 patients following admission to the intensive care unit, which was approved by the institute ethics committee (Reference No. IEC-291/17.04.2020).

Informed consent statement: As the study was retrospective in nature, informed written consent from individual patients was waived.

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SYSTEMATIC REVIEWS

Musculoskeletal complications in long COVID-19: A systematic review

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) has crippled humanity since early 2020. Various sequelae of COVID-19 have been reported in different body systems. Musculoskeletal symptoms are widely reported during COVID-19 infection, but musculoskeletal complications in long COVID-19 are underreported. However, post-COVID-19 survivors have reported complaints of persisting or new-onset fatigue, myalgia, arthralgia, arthritis, muscle weakness, *etc* in clinical practice. The well-known detrimental effects of steroids on the musculoskeletal system coupled with their over-the-counter availability can also be anticipated since they were the cornerstone of life-saving management in this pandemic.

AIM

To determine the musculoskeletal complications in long COVID.

METHODS

We performed a systematic review of 'systematic reviews and meta-analyses'.

RESULTS

Of the 63 articles screened, 24 articles were included. Two articles specifically discussed children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation of musculoskeletal issues in long COVID-19 in particular. Fatigue was the most common musculoskeletal complication.

CONCLUSION

Fatigue is found to be very common along with myalgia and arthralgia. There were no studies on rehabilitation intervention in musculoskeletal complications specifically. Considering the lacuna in literature and the needs of the current situation, further studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed. Studies on functional impairment due to musculoskeletal involvement

are essential.

Key Words: Musculoskeletal complications; COVID-19; Long COVID-19; Post-COVID-19 syndrome; Rehabilitation; SARS-CoV-2

Core Tip: Though musculoskeletal involvement is reported in severe acute respiratory syndrome coronavirus 2 infection, the literature is limited for musculoskeletal symptoms in long coronavirus disease 2019 (COVID-19). Moreover, rehabilitation of each musculoskeletal complaint is not addressed in most reviews. We highlighted those keys areas through our review article. Fatigue is the most common musculoskeletal issue in long COVID-19. Considering the gaps in literature and current needs, future studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications.

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INTRODUCTION

Since 2020 the world has witnessed multiple waves of the coronavirus disease 2019 (COVID-19) pandemic caused by different variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at different times and places. As of September 1, 2022, 599 million confirmed cases and more than 6 million deaths have been reported[1]. The loss of lives, superimposed by the deterioration of the quality of life of a significant number of survivors, made this pandemic a huge hurdle for the whole world. A range of long-term effects or complications involving different body systems have been reported. The respiratory sequelae of COVID-19 have been widely investigated, but musculoskeletal complications are underreported. Here we performed a systematic review of systematic reviews and meta-analyses to find musculoskeletal complications caused by long COVID-19 conditions.

MATERIALS AND METHODS

Here a systematic review of systematic reviews and meta-analyses was conducted (Figure 1). We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Eligibility criteria

PICOS model: (1) Studies that considered patients with long-term COVID-19 symptoms at least > 4 wk of COVID-19 infections (population); (2) Studies where the primary aim was to evaluate long-term COVID-19 symptoms in mild, moderate, severe, and critical patients that have a follow-up of at least 14 d (interventions); (3) Studies with or without a control group (comparisons); (4) Studies that reported the long COVID-19 symptoms (outcomes); and (5) Systematic review and meta-analyses (study designs). From January 2020 to mid-July 2022, any relevant studies that followed the above mentioned PICOS model and that reported musculoskeletal complications in long COVID-19 were eligible for inclusion.

Search strategy

The search was carried out by two independent researchers in all electronic databases, mainly MEDLINE, EMBASE, Web of Science, and Google Scholar with this time period. We combined search terms and key words related to the population (*e.g.*, "COVID-19", "SARS-CoV-2", "long Covid-19", "long Covid", "long haulers") and outcomes (*e.g.*, "fatigue", "pain", "musculoskeletal", "myalgia", "myopathy", "arthralgia", "arthritis", "rheumatic", "joint"). We additionally filtered study designs "systemic review" and "meta-analyses" in humans.

Inclusion and exclusion

All the systematic reviews and meta-analyses on long COVID-19 following our above-mentioned PICOS model were included. After the preliminary search, we extracted the musculoskeletal complications that

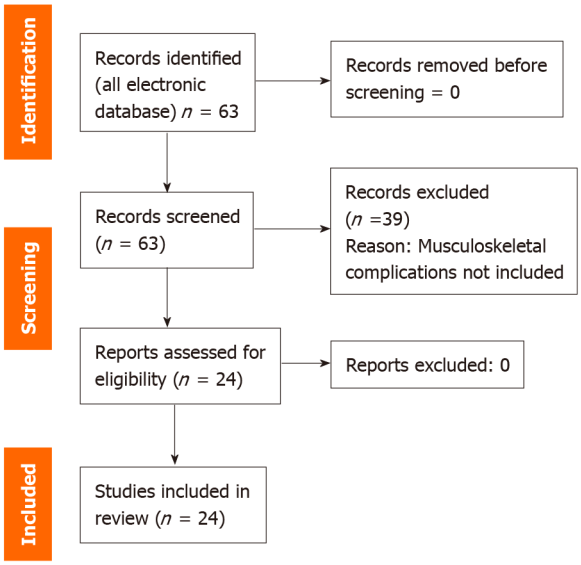

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Figure 1 Flow diagram of the study.

were reported in long COVID-19 studies or in post COVID-19 studies (at least 4 wk after COVID-19 active infection). We excluded any musculoskeletal issues that occurred after any neurological sequelae of long COVID-19 and excluded any myocarditis or issues related to smooth muscle dysfunction.

Study selection and data extraction

Titles and abstracts were screened for potentially eligible studies. Following an initial screening, full texts of potentially eligible studies were acquired for detailed evaluation eliminating all duplicates. Manual scanning of key articles and review papers was conducted to identify additional articles missed by the search strategy. Two reviewers assessed the articles independently and in case of any disagreements, the opinion of the third reviewer was consulted.

Analysis

We performed a descriptive analysis of the included reviews.

RESULTS

Of the 63 articles screened; 24 articles were included[2-25]. Two articles specifically discussed children and adolescents. One article discussed rehabilitation intervention. No article addressed rehabilitation on musculoskeletal issues in long COVID-19 in particular. Details of the selected articles are listed in Table 1.

DISCUSSION

According to the National Institute of Health and Care Excellence guidelines, post-acute COVID-19 and post-COVID-19 syndrome are included in long COVID. Post-acute-COVID-19 means ongoing symptomatic COVID-19 for people who still have symptoms 4 wk and 12 wk after acute COVID-19. On the other hand, post-COVID-19 syndrome means that patients are having persisting symptoms for > 12 wk after acute symptoms[26]. According to the World Health Organization, post-COVID-19 conditions generally occur 3 mo from the onset of COVID-19 with symptoms lasting for at least 2 mo and should be unexplained by any alternative diagnosis[27].

Another definition consists of "not recovering several weeks or months following the start of symptoms that were suggestive of COVID-19, regardless individuals were tested or not"[28]. Common symptoms reported are fatigue, shortness of breath, cognitive dysfunction/attention disorder, hair loss, and dyspnea[29,30]. Musculoskeletal symptoms of skeletal muscle, neurological, bone, and joint disorders have also been reported. The proinflammatory responses can impact nearly every organ system, including the musculoskeletal system. Myalgias, arthralgias, fatigue, exercise, and intolerance are some of the common musculoskeletal sequelae.

Table 1 Included systematic reviews and meta-analyses in this systematic review

Serial no.	Ref.	Reported musculoskeletal complications	Type of study	Types of patients	Rehabilitation intervention
1	Ludvigsson[2], 2021	Fatigue, muscle weakness	Systematic review	Children	No
2	Akbarialiabad *et al*[3], 2021	Fatigue (63%), muscle weakness	Systematic scoping review	All age groups	No
3	Michelen *et al*[4], 2021	Weakness (41%; 95%CI: 25%-59%), general malaise (33%; 95%CI: 15%-57%), fatigue (31%; 95%CI: 24%-39%)	Living systematic review	All age groups	No
4	Iqbal *et al*[5], 2021	48% fatigue in >12 wk	Systematic review and meta-analysis	All age groups	No
5	Vollbracht and Kraft[6], 2021	Vitamin C improved in post-COVID-19 fatigue; the IV vitamin C doses administered ranged from 3.5 g to > 75 g/d	A systematic review on intervention	All age groups	No
6	Jennings *et al*[7], 2021	Arthralgia 13% (6%-29%), myalgia 34% (2%-86%), fatigue 44% (10%-71%)	Systematic review	All age groups	No
7	Fernández-de-Las-Peñas *et al*[8], 2021	Fatigue (58%), headache (44%), joint pain (15%-20%)	Systematic review	All age groups	No
8	Malik *et al*[9], 2022	Fatigue (64, 54-73), arthralgia (24.3, 14.0-36.0), headache (21, 3-47)	Systematic review and meta-analysis	All age groups	No
9	Ceban *et al*[10], 2022	Fatigue in 30% of cases	Systematic review and meta-analysis	All age groups	No
10	Chen *et al*[11], 2022	Fatigue prevalence 0.23 (95%CI: 0.17-0.30)	Systematic review and meta-analysis	All age groups	No
11	van Kessel *et al*[12], 2022	Fatigue most common	Systematic review	All age groups	No
12	Alkodaymi *et al*[13], 2022	Fatigue 3-6 mo follow-up 32%, 36% 6-9 mo, 37% 9-12 mo, > 12 mo, 41%	Systematic review	All age groups	No
13	Fernández-de-Las-Peñas *et al*[14], 2022	Prevalence of post-COVID-19 myalgia, joint pain, and chest pain ranged from 5.65% to 18.15%, 4.6% to 12.1%, and 7.8% to 23.6%, respectively, at different follow-up periods during the 1st yr postinfection. Almost 10% of individuals infected by SARS-CoV-2 will suffer from musculoskeletal post-COVID-19 pain symptomatology at some time during the 1st yr after the infection	Systematic review	All age groups	No
14	Han *et al*[15], 2022	Fatigue/weakness (28%, 95%CI: 18%-39%), arthromyalgia (26%, 95%CI: 8%-44%)	Systematic review	All age groups	No
15	d'Ettorre *et al*[16], 2022	63% of fatigue reported	Systematic review	All age groups	No
16	Behnood *et al*[17], 2022	47% fatigue, 25% myalgia, 35% headache, females with higher pain symptoms	Systematic review	In children and young people	No
17	Nguyen *et al*[18], 2022	Fatigue (16%-64%), arthralgia (8%-55%), thoracic pain (5%-62%), myalgia (1%-22%), headache (9%-15%)	Systematic review	All age groups	No
18	Lopez-Leon *et al*[19], 2022	Fatigue (9.66%)	Systematic review	Children and adolescents	No
19	Abdel-Gawad *et al*[20], 2022	Fatigue (72.8%) and joint pain (31.4%)	Systematic review	All age groups	No
20	Almas *et al*[21], 2022	Fatigue (54.11%), arthralgia (16.35%), myalgia (5.78%), chest pain (10.37%)	Systematic review	All age groups	No
21	Maglietta *et al*[22], 2022	Fatigue and female sex association statistically significant, with OR = 1.54, 95%CI: 1.32-1.79	Systematic review	All age groups	No
22	Healey *et al*[23], 2022	fatigue (37%; 95%CI: 23%-55%), myalgia (12%; 95%CI: 5%-25%), headache (7%; 95%CI: 3%-16%), chest pain (3%; 95%CI: 1%-8%)	Systematic review	All age groups	No
23	de Oliveira Almeida *et al*[24], 2022	Fatigue. COVID-19 survivors can have a reduction in physical function, ability to perform activities of daily living and their health-related quality of life 1-6 mo post-infection	Systematic review	All age groups	No
24	Fugazzaro *et al*	Muscle strength, walking capacity, sit-to-stand performance	Systematic review	All age	Yes

[25], 2022	improvements		of rehabilitation interventions	groups

CI: Confidence interval; COVID-19: Coronavirus disease 2019; IV: Intravenous; OR: Odds ratio; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Why musculoskeletal system affected?

SARS-CoV-2 has three structural proteins (membrane protein, spike protein, and envelope protein). Spike glycoprotein through its subunits S1 and S2 helps in entering the host cells[31]. The angiotensin-converting enzyme 2 (ACE2) receptor acts as the entry receptor using the serine protease transmembrane protease, serine 2 (TMPRSS2) for spike protein priming[32]. Following the binding of the receptor, viral spike protein is broken down by TMPRSS2 proteolytically, which exposes a fusion peptide signal that helps in the fusion of viral and human membranes. It leads to the cytoplasmic release of viral RNA. Interestingly, ACE2 is found in the lung, heart, kidney, liver, gastrointestinal, and musculoskeletal systems.

In humans, endothelial cells, smooth muscle cells, pericytes, muscle stem cells, macrophages, B cells, T cells, natural killer cells, and myonuclei express TMPRSS2. Furthermore, several cells in the synovium including fibroblasts, monocytes, B cells, and T cells express ACE2 and TMPRSS2. However, only smooth muscle cells and pericytes express ACE2. Articular cartilage (proliferative, hypertrophic, and effector chondrocytes) express ACE2, and only homeostatic chondrocytes (which control circadian rhythm in cartilage) express TMPRSS2. In the meniscus, a few cartilage progenitors and regulatory fibrochondrocytes express ACE2 (no TMPRSS2 is detected). ACE2 is also found to be present in composite unenriched cortical and trabecular bone and osteoblast enriched tissues. TMPRSS2 was almost absent in composite bone tissue, and TMPRSS2 was detected in all osteoblast-enriched samples.

The presence of these receptors implies that skeletal muscle, synovium, and cortical bone may serve as potential areas of direct SARS-CoV-2 infection and its probable long-term sequelae[33]. The cytokines and signaling molecules are induced by the infection [C-X-C motif chemokine 10, interferon-gamma, interleukin (IL)-1β, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-α)]. They play a crucial role in the pathogenesis of clinical signs and symptoms and long-term sequelae of COVID-19. Interferon-gamma, IL-1β, IL-6, IL-17, and TNF-α show a negative impact on skeletal muscle (fiber proteolysis and decreasing protein synthesis). IL-1β and IL-6 may lead to fibrosis after inducing increased muscle fibroblast activity. IL-1β and TNF-α induce muscle fiber growth by inhibiting the differentiation and proliferation of satellite cells, the progenitor cells[34].

COVID-19 therapy sequelae in the musculoskeletal system

Corticosteroids, a lifesaving medication in the management of COVID-19, has been overused in many cases. Additionally, long-term corticosteroid use has been known to cause a variety of effects on the bone, including osteonecrosis, reduced bone mineral density (BMD), avascular necrosis of the hip joint, and osteoporosis with or without fracture. It implies that steroids might be an important cause of multiple musculoskeletal complications.

Skeletal muscle and fatigue

Many studies have reported fatigue myalgia and generalized weakness as some of the common persisting complaints in symptomatic infections of the disease[35]. In the previous epidemics of SARS, extensive myalgias and muscle dysfunction were also reported. Direct viral infection and/or the cytokine storm could lead to pathological changes in skeletal muscle tissue in addition to deconditioning due to prolonged disuse during the hospitalization or disease period.

Mayer *et al*[36] showed that a long intensive care unit stay is linked with a rapid and significant reduction in the volume of the rectus femoris muscle (average: 18.5%), until the 7th d of hospitalization. Carfì *et al*[37], in a study to follow up the post-COVID-19 patients in a hospital in Italy, found that in recovered patients, 87.4% responded with at least one persistent symptom, especially fatigue. Paneroni *et al*[38] evaluated the muscle strength of the quadriceps and biceps femoris of patients in post-discharge recovered COVID-19 cases. They found that 86% of cases had quadriceps weakness and 73% had biceps femoris weakness. These findings proved muscle dysfunction in individuals with long COVID-19. Jacobs *et al*[39] in their study to assess the persistence of symptoms and quality of life at 35 d after hospitalization of COVID-19 infection found fatigue as the most common persisting symptom.

Fatigue was found to be the most common symptom followed by shortness of breath (31%), loss of smell (22%), and muscle ache (21%) by the Office for the National Statistics, census 2021, in the estimates of the prevalence of self-reported long COVID-19 and associated activity limitation using United Kingdom Coronavirus (COVID-19) Infection Survey data[40]. Compared with age-matched healthy controls, approximately 2-3 mo after discharge, moderate to severe cases had a 32% reduction in grip strength and a 13% reduction in the distance walked in 6 min[41].

Aiyegbusi *et al*[42] did a review on symptoms, complications, and management of long COVID-19 and found that 47% reporting fatigue as the most common, myalgia (muscle pain) in 25%, and joint pain in 20%. Varghese *et al*[43] found that 54% of the patients reported fatigue as one of the persisting symptoms. Huang *et al*[44] did a follow-up study from June 16, 2020 to September 3, 2020 to assess 6 mo consequences of COVID-19 in patients discharged from the hospital, and they reported fatigue (63%) and sleep difficulties (26%) as the most common symptoms. Miyazato *et al*[45] also reported fatigue as one of the prolonged and late-onset symptoms conducted in patients admitted for COVID-19 to the Disease Control and Prevention Center and National Center for Global Health and Medicine from February to June 2020. Daher *et al*[46] conducted a follow-up study on 33 confirmed COVID-19 positive patients 6 wk post-discharge to assess the pulmonary and extrapulmonary disease sequelae and found a significant tendency among the patients to suffer from fatigue symptoms with significant limitations of their mobility, which was reflected by reduced 6-min walking test distance among the extrapulmonary sequelae. In their study, characterizing long COVID-19 in an international cohort over 7 mo of symptoms and their impact, Davis *et al*[47] also reported the patients who have had or were suspicious of COVID-19 reported fatigue as the most common persisting symptom even after 6 mo.

Multiple etiologies of fatigue (physical, mental, emotional) could be present. Therefore, fatigue should be researched according to the accompanying symptoms or more specific features[48]. Another sequelae is intolerance to physical activities associated with a chronic fatigue condition and difficulty in returning to normal daily life[49]. Eighteen people living with long COVID-19 in the United Kingdom were interviewed with a semi-structured questionnaire in a qualitative study by Humphrey *et al*[50] showing people faced reduced physical function, compounded by the cognitive and psychological effects of long COVID-19.

Arthralgia and myalgia

Arthralgia is pain localized to the joints, while myalgia is pain localized to muscle. They are typically present in the early course of the disease and in patients experiencing long-term effects of COVID-19 or a prolonged disease course. Studies have described how SARS-CoV-2 infection induces systemic elevations of cytokines and signaling molecules. This 'cytokine storm' is thought to be implicated in musculoskeletal manifestations, among many others. Myalgia and arthralgia are reported as one of the most common persistent symptoms in patients with post-acute sequelae of COVID-19 and are more notable in patients who were prone to being positioned during intensive care unit admission[51].

In a study of 294 patients hospitalized with COVID-19, Hoong *et al*[52] observed that 30% of patients reported musculoskeletal complaints; 37.5% had myalgia, 5.7% had arthralgia, 6.8% had new-onset backache, and 50% had generalized body aches. Elhiny *et al*[53] reported that physical decline was the most common symptom reported in musculoskeletal complications. Patients who also had mild to moderate forms of the infection can experience exacerbated muscle and joint pain. Petersen *et al*[54] in their study of long COVID-19 in a longitudinal study in the Faroe Islands found out arthralgia is one of the most persistent symptoms following fatigue and loss of smell and taste.

Follow-up of adults with non-critical COVID-19 after symptom onset in a study by Carvalho-Schneider *et al*[55] found that 13% of the patients who never had arthralgia at the onset of the disease reported arthralgia 30 d after discharge and 21% after 60 d. The study by Chopra *et al*[56] on clinical predictors of long COVID-19 symptoms in patients with mild COVID-19 at 30 d post-discharge (long COVID-19) found myalgia as one of the most common persistent symptoms following fatigue and cough. Stavem *et al*[57] also reported myalgia as one of the most common persisting symptoms 1.5-6.0 mo after infection in non-hospitalized patients. Ghosn *et al*[58] in a large prospective cohort study in France among the post-discharge patients at 3 mo and 6 mo observed mostly fatigue, dyspnea, joint pain, and myalgia. COVID-19 has also been found to cause reactive arthritis and new-onset inflammatory arthritis typically occurring within a month after its diagnosis[59].

There were reported cases of reactive arthritis post discharge from COVID-19[60]. Derksen *et al*[61] in a Dutch study of 5 patients who presented with inflammatory arthritis 6.6 wk post COVID-19 infection, found that 2 patients had strongly positive and another patient had weakly positive anti-CCP antibodies, suggesting post-COVID-19 rheumatoid arthritis development.

BMD

C-X-C motif chemokine 10, IL-17, and TNF-α induce osteoclastogenesis and inhibit osteoblast proliferation and differentiation causing increased bone fragility[34]. Berktaş *et al*[62] assessed the BMD of hospitalized COVID-19 patients at diagnosis and follow-up visits using chest computed tomography. BMD was retrospectively measured by quantitative computed tomography. BMD decreased by a mean of 8.6% (± 10.5%) from diagnosis to follow-up. The osteoporosis ratio increased two-fold after hospitalization for COVID-19 because of this substantial bone loss.

An animal experimental study characterized the effects of SARS-CoV-2 infections on bone metabolism in an established golden Syrian hamster model for COVID-19. SARS-CoV-2 caused significant multifocal loss of bone trabeculae in the long bones and lumbar vertebrae of all infected hamsters implicating the same could happen in humans post-COVID-19. A multicenter study by Kottlor *et al*[63] showed that COVID-19 patients requiring intensive care had significantly lower BMD than those who were managed in non-intensive care settings.

Researchers at Indiana University School of Medicine discovered that the mouse models infected with the novel coronavirus lost nearly 25% of their bone mass within 2 wk of infection. They also found mouse models with a 63% increase in osteoclasts, the cells that cause the bone to break down.

Neuromuscular

Musculoskeletal manifestations can be a result of underlying neurological disturbances. The central and peripheral nervous systems control our movements *via* the spinal motor neurons, which act as the final common pathway to the muscles[64]. Many studies have reported peripheral neuropathy, most commonly Guillain-Barre and related symptoms. Guillain-Barre syndrome and critical illness-induced polyneuropathy/myopathy are two important peripheral neuropathies seen in COVID-19[65].

A follow-up study conducted for 8 mo in Denmark performed electromyography and conventional nerve conduction study of 20 patients with persistent fatigue. They found that all patients with myopathic electromyography reported physical fatigue; 8 patients reported about myalgia while 3 patients without myopathic changes complained about physical fatigue. Long-term COVID-19 does not cause large fiber neuropathy, but myopathic changes were seen[66]. Acute myopathies are reported in acute COVID-19 infection[67], which may have a detrimental effect in the muscle in the post infective stages.

Rehabilitation perspectives

COVID-19 has multisystem effects including physical as well as psychological effects. The wholesome evaluation and rehabilitation of such patients require a multifaceted and interdisciplinary approach to cover all aspects properly. Identification of the pre-existing disabling conditions contributing to the cumulative effect of long COVID-19 is also an important aspect. Reinfection, post-viral bacterial and fungal infections, baseline routine investigations along with C-reactive protein, fibrinogen, D-dimer, troponin, and ferritin can also be considered if clinically indicated. Cardiac function tests (echocardiography) should be done to check cardiopulmonary status before framing the exercise program.

Rehabilitation should be addressed holistically following the domains of the International Classification of Functioning, Disability, and Health. Studies have shown that early mobilization helps in the reduction of the harmful effects of the disease, especially on muscle and cardiopulmonary function, mobility, and function[68], implying rehabilitation of long COVID-19 should start from the beginning. Physical exercise should be individualized specifying intensity, frequency, duration, and type of exercise. Exercise should be gradually increased according to one's capacity. The patient should be educated with an emphasis on self-management. The patient should respect the pain and their own capabilities. Energy conservation techniques such as simplifying tasks, pacing the activities over time, and taking breaks should be followed. Repeated practice of functional activities and a set of specific actions according to the patient's priorities, needs, and goals may improve the functional aspects. All such activities need to be evaluated regularly to determine whether they should be continued, changed, or stopped[69].

However, no studies on rehabilitation intervention have been investigated in long COVID-19 for musculoskeletal complications in particular[70]. In our systematic reviews, we did only descriptive analysis. We did not address the individual cases or case series study or any cohort or trials, which may miss the characteristics of the individual cases in particular. However, performing a systematic review of all systematic reviews and meta-analyses provided a stronger evidence-based study.

CONCLUSION

Musculoskeletal involvement is common during active SARS-CoV-2 infection. Fatigue is very common during this phase. Here we have highlighted the musculoskeletal complications in long COVID-19 syndrome. Again, fatigue is found to be very common along with myalgia and arthralgia. There is a lack of studies on these aspects. Moreover, all the studies are heterogeneous, especially in terms of the duration of post-COVID and the definition of long COVID. There are no studies for rehabilitation intervention in musculoskeletal complications specifically. This study reinforced the gravity of the current situation. Considering the lacuna in literature and the needs of the current situation, further studies are warranted to standardize effective rehabilitation interventions in musculoskeletal complications. More homogenous studies are needed using proper case definition and duration of long COVID. Studies on functional impairment due to musculoskeletal involvement are needed.

ARTICLE HIGHLIGHTS

Research background

Research is lacking in musculoskeletal complications in long coronavirus disease 2019 (COVID-19).

Research motivation
Currently, many long COVID-19 patients are coming to outpatient departments of rehabilitation for musculoskeletal issues.

Research objectives
To find musculoskeletal complications in long COVID-19 and relevant rehabilitation interventions.

Research methods
A systematic review of systematic reviews and meta-analyses was done.

Research results
Among many musculoskeletal issues, fatigue was found to be the most common complication. Rehab intervention is severely lacking in literature.

Research conclusions
Rehabilitation need identification is of the utmost importance in musculoskeletal aspects of long COVID. Fatigue was found to be the most common complication.

Research perspectives
Identification of rehabilitation needed following identification of musculoskeletal complications is crucial in long COVID-19 cases.

FOOTNOTES

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LETTER TO THE EDITOR

Global challenge with the SARS-CoV-2 omicron BA.2 (B.1.1.529.2) subvariant: Should we be concerned?

Jalil Roohani, Masoud Keikha

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Abstract

BA.2 is a novel omicron offshoot of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has gone viral. There is limited knowledge regarding this variant of concern. Current evidence suggests that this variant is more contagious but less severe than previous SARS-CoV-2 variants. However, there is concern regarding the virus mutations that could influence pathogenicity, transmissibility, and immune evasion.

Key Words: SARS-CoV-2; Omicron; BA.2; B.1.1.529.2; Subvariant

Core Tip: BA.2 is novel omicron offshoot that goes viral. There is limit knowledge regarding this variant of concern. Current evidence suggested this variant is more contagious but less severe than previous severe acute respiratory syndrome coronavirus 2 previous variants. However, there is concern regarding the virus mutations that could be influenced pathogenicity, transmissibility as well as immune evasion.

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TO THE EDITOR

The proliferation of omicron (B.1.1.529) and its global dissemination

On November 25, 2021, 22 patients in Gauteng province, South Africa, were diagnosed with atypical pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Afterward, the Technical Advisory Group of the World Health Organization (WHO) designated the novel SARS-CoV-2 variant as B.1.1.529[1]. Omicron has been identified as the fifth variant of concern (VOCs); the B.1.1.529 genome contains over 50 mutations that increase transmissibility, infectivity, immune system evasion, and vaccine inefficacy[2].

In late November 2021, the South African National Institute of Communicable Diseases reported a 22.4% increase in infections with this variant in a single day[1]. Based on a retrospective study conducted in South Africa, the VOC omicron significantly increased the risk of reinfection (× 2.39) compared to the beta and delta variants, indicating that this variant has a higher potential to evade the immune system[3]. Belgium, Hong Kong, Israel, Germany, the Netherlands, and the United Kingdom reported the detection of the omicron variant shortly after.

On November 27, 2021 due to the omicron variant's spread to more than 50 countries, the United States and Australia banned all transportation to those countries. However, on November 29, 2021 the first omicron case in Australia was identified in a traveler who traveled to Johannesburg, South Africa (https://www.abc.net.au/news/2021-11-29/nt-covid-outbreakkatherine-traveller-positive-for-omicron/100657690). Subsequently, the VOC omicron was identified in populations that were unvaccinated, partially or fully vaccinated, and immune to previous natural infection.

The birth of omicron BA.2 (B.1.1.59.2)

According to the WHO classification, the omicron variant has three to four subvariants, namely BA.1, BA.1.1, BA.2, and BA.3; nucleotide sequencing analysis revealed that BA.1, BA.1.1, BA.2, and BA.3 subvariants possess 39, 40, 31, and 34 mutations, respectively. All three subvariants evolved simultaneously in South Africa[4] (Figure 1). According to the hypothesis of Gao *et al*[5], omicron subvariants have emerged in the unvaccinated African population with compromised immune systems. Immunocompromised individuals are unable to fight SARS-CoV-2 infection effectively, and they have the best opportunity for multiplication, mutagenesis, and the emergence of new surge variants. Furthermore, animals can act as reservoirs for the evolution of novel variants. Nonetheless, there has been an increase in cases of BA.2 in recent days, to the point where the BA.2 variant is now the most common SARS-CoV-2 variant in most European countries.

BA.2 is also known as the "stealth variant" because it lacks a deletion signature at positions 69-70 that was not detected by the spike (S) gene target failure assay; therefore, BA.2 was underestimated with the current reverse transcription polymerase chain reaction setup, and its detection is only possible *via* whole genome sequencing[6,7]. According to viral genome sequences uploaded to the global GISAID database, the United Kingdom, the United States, Denmark, Germany, and Canada are the five countries with the highest prevalence of BA.2 (https://www.gisaid.org/). By February 18, 2022, BA.2 was reported in 153 countries (https://www.gisaid.org).

The VOC BA.2 is a highly contagious subvariant

Beginning in 2022, BA.2 has been on the rise in European countries. On January 1, 2022, the prevalence of BA.2 in the United Kingdom was approximately 5%, and it has been steadily rising[8]. According to preliminary studies conducted in Denmark, the first reports of BA.1 and BA.2 occurred on November 25, 2021 and December 5, 2021, respectively. During the 52nd wk of 2021, BA.2 prevalence in Denmark was 20%, while more than 45% of circulating SARS-CoV-2 strains in Denmark during the 2nd wk of 2022 were the BA.2 subvariant[9]. To this end, BA.2 is spreading at an alarming rate across the globe (Figure 2).

Lyngse *et al*[9] demonstrated that the BA.2 subvariant was able to infect unvaccinated individuals (odds ratio = 2.19; 95% confidence interval: 1.58-3.14) and individuals vaccinated with a third booster (odds ratio = 2.99; 95% confidence interval: 2.11-4.20). According to the Danish Staten's Serum Institute, BA.2 is approximately 1.5 and 4.2 times more contagious than BA.1 and the delta variant[9,10]. Yu *et al* [11] observed that the neutralizing antibody titer against BA.1 and BA.2 is 23-fold and 27-fold lower than that of WA1/2020. According to their research, the mean neutralizing antibody titers after the third booster of the BNT162b2 mRNA vaccine were approximately 1.4-fold lower than BA.1, indicating the capacity of BA.2 to confer neutralizing antibodies and evade humoral immunity[11].

Chen and Wei[10] hypothesized that BA.2 mutations caused the ability of the immune evasion to be approximately 30% and 17-fold greater than that of BA.1 and the delta variants, respectively, and resistant to most monoclonal antibodies except for sotrovimab. Evidently, BA.2 will quickly become the next dominant global variant. In addition, the United Kingdom Health Security Agency (UKHSA) cautioned that contact tracing data from the United Kingdom estimates that BA.2 is more likely to infect household contacts than BA.1 (10.3%). UKHSA estimated that the increase in the number of BA.2 patients after a third booster dose vaccination was more significant than that of BA.1-infected population (63% for BA.1 *vs* 70% for BA.2)[12]. According to Covglobe data, the incidence of BA.2

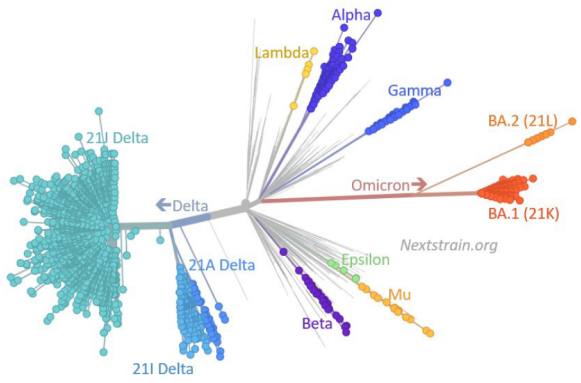

Figure 1 Severe acute respiratory syndrome coronavirus 2 genetic family tree diagram comprising omicron subvariants. Available from: https://www.npr.org/sections/goatsandsoda/2022/02/09/1047616658/take-a-look-at-sars-cov-2s-family-tree-its-full-of-surprises.

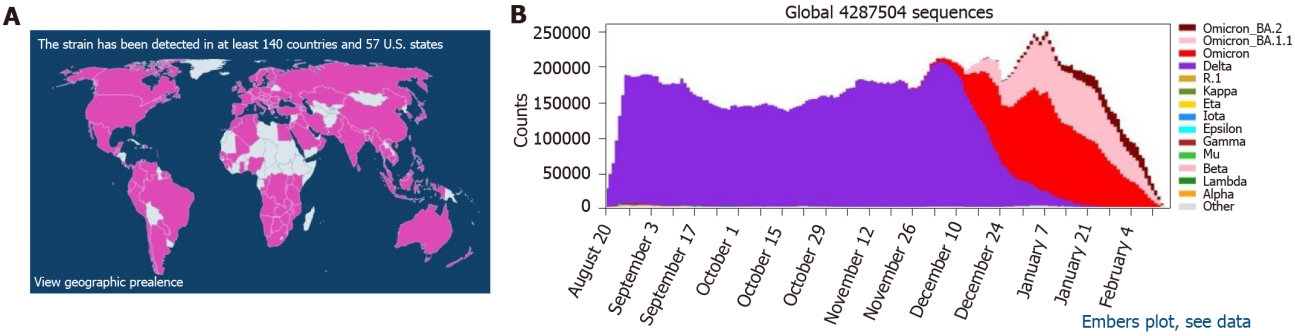

Figure 2 Global distribution of the BA.2 omicron subvariant in various countries/territories. Available from: https://gisaid.org/hcov19-variants/. A: According to GISAID databases, BA.2 is reported in more than 150 countries; B: The recent trend of BA.2 nucleotide sequence submission.

infections has been on the rise since October 2021 and has recently supplanted the VOC B.1.1.529; according to existing databases, BA.2 typically affects younger age groups (Figure 3).

BA.2 variant genome analysis

According to Nextstrain online server data, the omicron variant comprises three distinct branches: 21K (or Pangolin lineage12 BA.1), 21L (or BA.2), and BA.3 of the 21M omicron clade[4] (Figure 4). The BA.2 genome contains 20 shared and 6 unique mutations in the S protein compared to B.1.1.529 (archetypical) variant. BA.2 has significantly more mutations than BA1; most of these mutations are non-synonymous. By analyzing and comparing the genomes of BA.1 and BA.2, Wiegand *et al*[13] observed that BA.2 possesses the most genetic variation in the S protein (24-35 mutations, mean = 30.7) and that the effect of these mutations on virulence, viral transmission, and immune evasion has been identified in previous research. After the S protein, the nucleoprotein has the most genetic changes, but the majority of these changes are non-synonymous, affecting the sensitivity and specificity of diagnostic methods[13]. According to the CoronaTrend online server, the S, nsp6, and M proteins exhibited the most BA.2 mutations (Figure 5).

Kumar *et al*[4] demonstrated in a recent study that multiple alignments of four omicron subvariants revealed that BA.1 comprised 39 mutations, BA.1.1 comprised 40 mutations, BA.2 comprised 31 mutations, and BA.3 comprised 34 mutations. BA.1.1 has a single unique mutation of R346K, and BA.2 has eight mutations. Only one unique mutation exists in T19I, L24del (deletion), P25del, P26del, A27S, V213G, T376A, R408S, and BA.3 (R216del). Meanwhile, all subvariants comprise eleven shared mutations in their second receptor binding domain, including G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, and N501Y. By increasing the positive electrostatic surface, these mutations improve the interaction between the receptor binding domain motif and human angiotensin-converting enzyme 2[4]. They also observed that R400, R490, and R495 mutations in BA.2 formed new salt bridges and hydrogen, resulting in higher viral transmission than the BA.1 and BA.1.1 subvariants [4].

Desingu and Nagarajan[14] deduced that the BA.2 subvariant consisted of five distinct phylogenetically based original geographic regions, namely Sweden/Denmark, Philippines, Hong Kong, India, and China. They demonstrated that each of these clades exhibited unique mutations, such as the H78Y mutation in Denmark, the substitutions of ORF1a: A2909V and ORF3a: L140F in isolates from the

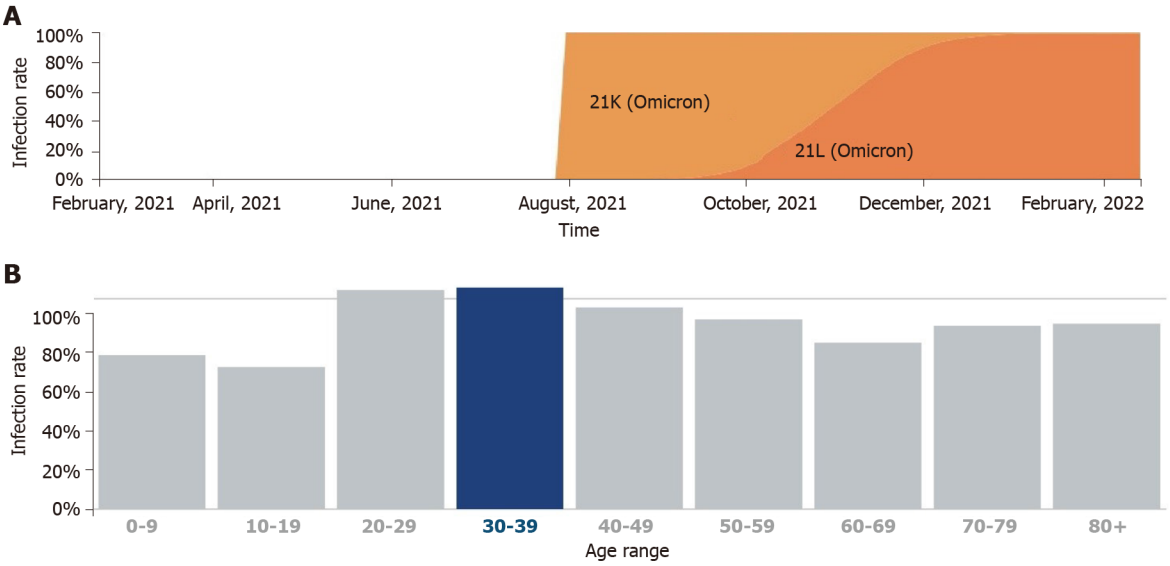

Figure 3 Global outbreak statistics for the BA.2 omicron subvariant. Available from: https://cov-spectrum.org/explore (https://covglobe.org). A: Rising trend of BA.2, available from: https://covglobe.org; B: Age distribution of individuals infected with BA.2, available from: https://cov-spectrum.org/explore.

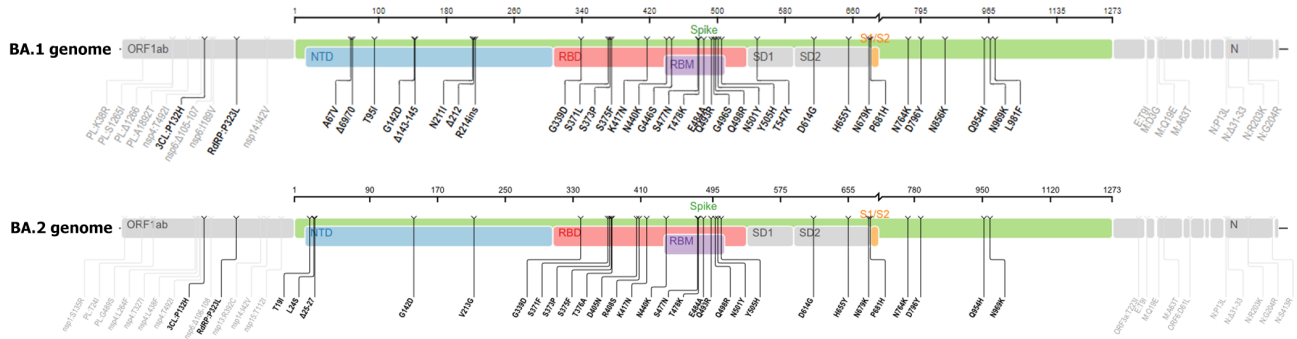

Figure 4 Comparison between the BA.1 and BA.2 omicron subvariant genomes. Available from: https://covdb.stanford.edu/page/mutation-viewer/#omicron.

Philippines and Hong Kong, and ORF1a: -3677L, ORF1b: S959P, and ORF7b: H42Y in the Indian subgroup. Each distinct mutation in the subpopulations modified the characteristics of BA.2 in terms of viral transmission, infectivity, disease severity, vaccine efficacy, and clinical outcomes in different geographic regions[14,15]. Recent studies suggest that mutations of P681H, H655Y, and N679K at the furin cleavage site increase the replication of omicron variants and as a result the transmissibility of omicron subvariants[4].

Vaccination against the BA.2 omicron subvariant

The 21L/BA.2 omicron variant has become predominant even after the third dose of the Pfizer-BioNTech vaccine, according to reports from Denmark (www.news-medical.net/news/20220214/First-survey-on-Omicron-BA2-in-France.aspx). Moreover, on January 26, 2022, Tyra Grove Krause stated, "*There is some evidence that it is more contagious, particularly among the unvaccinated, but it can also infect vaccinated individuals to a greater extent*" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus).

Lyngse *et al*[9] showed that the viral load of unvaccinated individuals is significantly greater than that of fully immunized populations. Thus, non-immunized individuals can more effectively release BA.2. Initial UKHSA surveys indicated that the effectiveness of the BA.2 vaccine against symptomatic BA.2 infection was greater than that of the BA.1 vaccine (13% for BA.2 *vs* 9% for BA.1); additionally, a third booster dose may increase the effectiveness of the BA.2 vaccine (70% for BA.2 *vs* 63% for BA.1)[12,16]. However, Peiris *et al*[17] evaluated the effect of the third dose of BNT162b2 or CoronaVac vaccines against BA.2; they concluded that three doses with BNT162b2 or vaccination with two doses of CoronaVac and a third booster dose with BNT162b2 increased plaque reduction neutralization antibody titer above the threshold for protection against symptomatic BA.2 infection.

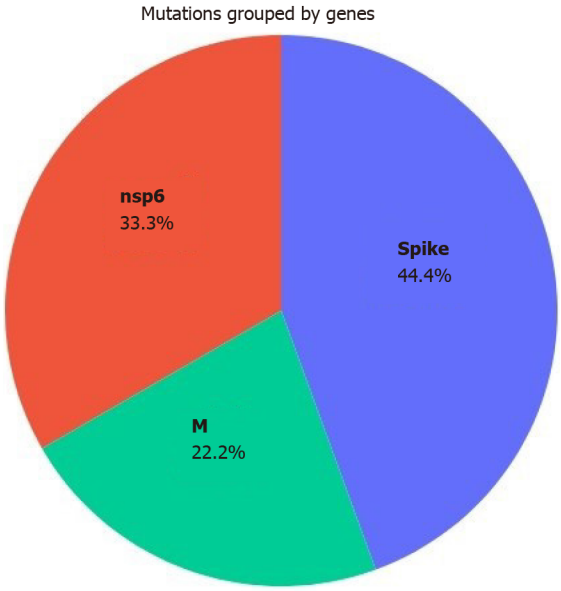

Figure 5 Significant mutation registrations of the BA.2 omicron subvariant. Available from: https://coronatrend.live/.

Although BA.2 mutations confer resistance to neutralizing antibodies, recent research shows that a third booster causes antibodies to cross-react with the omicron variant[18]. In addition, Lippi *et al*[19] revealed that the third booster vaccination increases neutralizing antibodies against the omicron variant and is a safe strategy until a new, more effective vaccine is introduced.

Further perspective

Despite the recent increase in BA.2 cases, the WHO has not yet given BA.2 a special designation. However, on January 21, 2022 the UKHSA designated BA.2 as a "variant under investigation" (https://www.gavi.org/vaccineswork/stealth-omicron-everything-you-need-know-about-new-ba2-subvariant-coronavirus). The WHO official Dr. Maria Van Kerkhove stated that BA.2 is significantly more contagious than BA.1 (https://www.cnbc.com/2022/02/08/who-says-omicron-bapoint2-subvariant-will-rise-globally.html); nonetheless, preliminary studies indicate that there is no difference between BA.2 and BA.1 in terms of hospitalization risk.

The remarkable increase in BA.2 infection cases and the rapidity with which it has spread in a short period of time is perplexing. In addition, intensive care unit admissions and mortality rates are rising, causing worldwide concern in healthcare facilities. According to the Infectious Diseases Society of America, the most effective treatments for SARS-CoV-2 B1.1.529 are monoclonal antibodies such as sotrovimab, evusheld, convalescent sera, and Oxford-AstraZeneca and Pfizer-BioNTech vaccines (https://www.idsociety.org/covid-19-real-time-learning-network/emerging-variants/emerging-covid-19-variants/#). Hand hygiene, physical distance, mask use, and mass vaccination, particularly a third booster dose, are recommended countermeasures to control the global spread of the BA.2 variant, as is the consideration of nationwide lockdowns.

FOOTNOTES

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LETTER TO THE EDITOR

Effect of the pandemic on rehabilitation healthcare services in India: Breaking barriers

Raktim Swarnakar, Shiv Lal Yadav

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Abstract

We would like to highlight the rehabilitation medicine perspective from India. Difficulties are impacted by the pandemic during this time, especially for people with disabilities. Awareness building among the public regarding the need for rehabilitation along with improvement in infrastructure is the key unmet need.

Key Words: COVID-19; India; Physical medicine and rehabilitation; Rehabilitation; Healthcare service; Disability

Core Tip: Rehabilitation is a vital component of Universal Health Coverage. The coronavirus disease 2019 pandemic impacted negatively on health care delivery and rehabilitation services have been hindered severely as well. Proper awareness and health care infrastructure building are essential aspects that need to be addressed soon.

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TO THE EDITOR

We read with interest the review article by Nimavat *et al*[1] where they have shown healthcare difficulties impacted by the pandemic in India. We would like to emphasize the awareness, accessibilities and barriers of rehabilitation healthcare services in India and how coronavirus disease 2019 (COVID-19) pandemic has influenced it. Globally, 1

in 3 people is living with a health condition that would benefit from rehabilitation[2]. India, despite facing many odds, has played a distinguished role during the pandemic in terms of health care. Being the second largest populated country, it pioneered the country-wide COVID-19 vaccination drive[3]. On the other hand, though World Health Organization stated that rehabilitation should be incorporated into Universal Health Coverage as essential and indispensable health care[2], unfortunately, rehabilitation aspects are often neglected mainly due to the lack of awareness and partly due to misconception.

Physiatrists (expert doctors in rehabilitation medicine) are mainly responsible for patient care regarding rehabilitation. It is catering its service *via* the physical medicine and rehabilitation (PMR) department in Indian hospitals. The three most common misconceptions about rehabilitation are: (1) 'Rehabilitation' is often wrongly equated with 'exercise'; exercises are part of rehabilitation but not the sole part of it. Rehabilitation is far broader, from medical management to surgical rehabilitation. Such thought confinement to 'exercise'/'physiotherapy' leads to losing the scope of overall possibilities of holistic rehabilitation; (2) 'Rehabilitation'/'Rehab' is wrongly equated with 'only drug addiction/mental illness rehab'. It results in losing opportunities for rehabilitation; and (3) It is considered wrongly as only 'tertiary prevention' of the disease spectrum, forgetting its immense role in an acute rehabilitation setting. Proper rehabilitation can reduce the duration of acute illness and also prevent disability.

In India, 2.21% (26.8 million) of the population has one or another kind of disability[4]. And in cases of disability, rehabilitation plays a vital role, even PMR departments in India are involved in disability certifications in India. The COVID-19 pandemic has caused disruption of routine rehabilitation services all over the world and India was no exception. People with disabilities like spinal cord injury/paraplegia faced multiple issues like barriers in obtaining rehab services from hospitals and visiting hospitals for health complications[5]. But telemedicine facilities and telerehabilitation launched during the pandemic and opened a new arena for catering the health care service across India. Moreover, comorbidities and disabilities are risks for severe COVID-19 which led to home confinement and health service deprivation. Furthermore, stigma is another factor which causes concealment and which in turn results in avoidance of utilization of health services[6].

In this context, urgent needs are: (1) To increase the doctor population ratio; (2) To increase rehabilitation service centers at block and primary hospital levels; (3) Awareness regarding rehabilitation and its perceived benefit should be emphasized among the general population; and (4) Considering the increasing population of non-communicable diseases caused by long COVID, rehabilitation services and infrastructure should be strengthened[7]. Keeping pace with other developed countries, where much awareness of rehabilitation exists[8]; in India, developing such awareness is a key unmet need. Furthermore, there is an increasing trend or demand for the utilization of rehabilitation health services among the pediatric differently-abled population, any chronic disabling conditions like osteoarthritis, rheumatoid arthritis, stroke, traumatic brain injury, spinal cord injury/disorder *etc*, increasing geriatric population, people with cancers, amputations and many more. It is imperative that for a better post-COVID world coordinated action should be taken by all stakeholders to strengthen the health system to provide quality and timely rehabilitation (rehabilitation initiative 2030)[2].

FOOTNOTES

Author contributions: Swarnakar R designed and analyzed the manuscript; Swarnakar R and Yadav SL performed the research and wrote the letter.

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