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The impact of exercise on cardiovascular system: Molecular signaling pathway and cardiac adaptations

> See page 4 and 11

Can chest computed tomography be useful to emergency residents in the diagnosis of COVID-19 pneumonia?

> See page 45 and 49

Incidence and functional outcome of inter-carpal ligament injuries associated with fractures of distal radius

> See page 55 and 59

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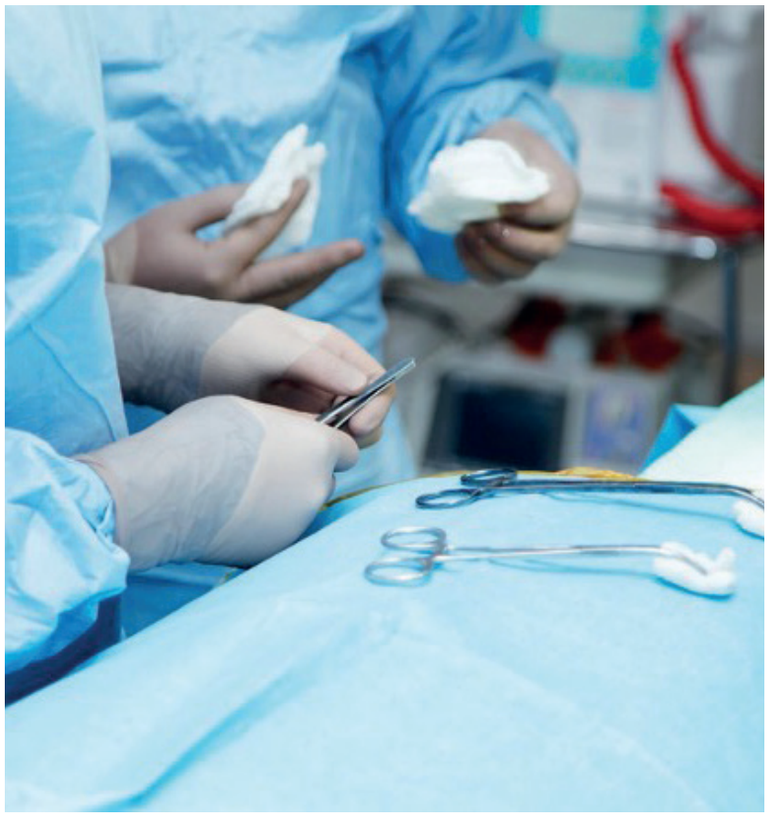

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The impact of exercise on cardiovascular system: Molecular signaling pathway and cardiac adaptations

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Abstract

The purpose of this review is to describe the impact of endurance and strength physical training on the cardiovascular system by reviewing the molecular signaling pathways, which plays a key role in different muscle adaptations, and the cardiac changes in terms of metabolic and cardiac remodeling, and hemodynamics. In response to endurance-exercise, multiple signaling pathways, including Ca^{2+}-dependent pathways, reactive oxygen species (ROS), AMP-dependent protein kinase (AMPK), and mitogen activated protein kinases (p38 MAPK), are involved in the regulation of peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α), which controls the mitochondrial biogenesis. Strength training increases the insulin-like growth factor (IGF-1) which initiates the phosphatidylinositol 3-kinase (PI3-k)-(AKT)-(mTOR) signaling cascade, resulting in the synthesis of proteins and the muscle hypertrophy. In addition to the well-documented changes in skeletal muscle, a critical component of the response to exercise training is the dynamic cardiac remodeling, which is classified as either pathological or physiological depending on triggers.

Keywords: sports cardiology, exercise physiology, sports medicine

Introduction

There is proof that exercise can improve muscular endurance, strength, and body composition, both in the general public and athletes [1]. While, physical activity lowers the risk of cardiovascular illnesses in the general population [2], it aims to result in better performance in sport activities in athletes. However, sport activities can be very different, ranging from long distance runners to heavy weightlifters. Clearly, training in athletes should be tailored according to the type of sport, aiming to increase predominantly either muscle resistance or strength. Thus, exercise can be classified into two major categories, endurance and strength, that trigger different responses on the cardiovascular system.

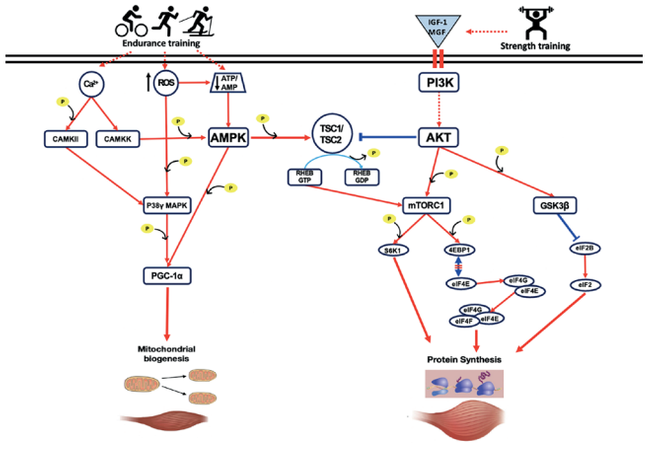
Endurance training is usually performed against a little load sustained for a prolonged time frame while strength training involves movement of the musculature of the body against an opposing force, known as resistance, for a short duration [3]. Thus, strength training is also known as resistance training [4]. Pure strength and endurance training, however, are uncommon and elite sports rarely consist of only one type of exercise. For example, rowing consists of applied strength training but has endurance training elements too. Although most activities combine endurance and strength training (concurrent exercise), this review will focus on the phenotypic shift in muscle induced by endurance and strength exercises and their influence on physiology and hemodynamics.

Exercise-induced muscle signaling pathways

Muscle adaptation happens through a complicated network of various biochemical pathways that are uniquely activated during functional training [5]. When subjected to physiological triggers, such as during exercise training, skeletal muscle responds by remodeling in order to meet the additional demands that are imposed by the stimulus. This modification is performed by extracellular stimuli that enter the cells, engage with receptors on the cell membrane, and activate intracellular signaling pathways. These pathways affect gene transcription and protein synthesis, which triggers muscle remodeling [6].

Although some pathways can be activated irrespective of the kind of exercise, different types of exercises result in different muscle signaling pathways [7] with endurance training and strength training predominantly affecting the capacity for substrate consumption and muscle growth, respectively [8,9]. In particular, endurance training causes improved capillarization, energy metabolism, mitochondrial biosynthesis, and the conversion of fast-to-slow fibre type, while strength training causes the biosynthesis of contractile and structural proteins, which results in muscle hypertrophy and improved contraction force generation [10,11]. Prior to, during, and following endurance- and resistance-based exercise, endogenous and exogenous substrate availability can modify the transcriptional activity of a subset of metabolic and myogenic genes as well as the control of signaling pathways that stimulate mitochondrial and myofibrillar protein synthesis [12]. Many researchers examined the requirements behind "endurance-based" or "strength-based" activity and provided interesting data on the unique adaptations in accordance with the specific training (Figure 1).

Figure 1 - Simplified molecular signalling pathways involved in endurance and strength exercise training



4EBP1 – Eukaryotic translation initiation factor 4E-binding protein 1; AKT – Protein kinase B; AMP – Adenosine monophosphate; AMPK - 5' AMP-activated protein kinase; ATP – Adenosine triphosphate; CAMKII - Ca2+/calmodulin-dependent protein kinase II; CAMKK - Ca2+/calmodulin-dependent protein kinase kinase; eIF2 – Eukaryotic initiation factor 2; eIF2B – Eukaryotic translation initiation factor 2B; eIF4E – Eukaryotic translation initiation factor 4E; eIF4G – Eukaryotic translation initiation factor 4G; eIF4F – Eukaryotic initiation factor 4F; IGF-1 – Insulin-like growth factor; GSK3β – Glycogen synthase kinase-3β; MGF – Mechano growth factor; mTORC1 - Mammalian target of rapamycin complex 1; p38γ MAPK – p38 Mitogen Activated Protein Kinase; PGC-1α – Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K - Phosphoinositide 3-kinases; RHEB GDP - Ras homolog enriched in brain in its Guanosine Diphosphate-bound form; RHEB GTP - Ras homolog enriched in brain in its Guanosine Triphosphate-bound form; ROS - Reactive oxygen species; S6K1 - Ribosomal protein S6 kinase beta-1; TSC1 - Tuberous sclerosis complex 1; TSC2 - Tuberous sclerosis complex 2.

Endurance training

AMP-dependent protein kinase (AMPK) and mitogen activated protein kinase (MAPK), as well as Ca^{2+}-dependent pathways and reactive oxygen species (ROS), play a part in controlling skeletal muscle mitochondrial biogenesis, angiogenesis, production of cell contractile proteins, and other adaptations [13]. The final receptor involved in the activation of mitochondrial biogenesis and angiogenesis is peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α) and current findings indicate a crucial role for p38 MAPK in PGC-1α regulation [14]. However, the signaling network is much more complex, with multiple regulatory events and several cross-interactions.

Reactive oxygen species (ROS)

Muscles produce ROS in different ways (e.g., NADPH oxidases, xanthine oxidases, mitochondria), which modulate several signaling pathways, including AMPK and MAPK, as a result of physical exercise, which affects several physiological changes. Increasing glucose uptake, mitochondriogenesis, and hypertrophy are outcomes of these pathways in skeletal muscle after physical exercise [15]. A change in the redox relationship in working muscles is caused by increased levels of ROS [16]. During eccentric contractions or highly intensive exercise, ROS can act as intracellular messengers by activating redox-sensitive transcription factors and signaling cascades.

There is evidence that the PGC-1 expression and metabolic adaptation brought on by endurance exercise in skeletal muscle are significantly influenced by ROS [17]. Most studies point toward hydrogen peroxide (H_2O_2), a non-radical ROS, considered a crucial signaling molecule for metabolic changes in skeletal muscle, and it has been shown that PGC-1 overexpression requires the H_2O_2 generated by contracting skeletal muscle cells [18]. Furthermore, the observation that H_2O_2 administration decreased cellular ATP levels, activated AMPK, and elevated PGC-1 mRNA suggested that H_2O_2 can stimulate PGC-1 production via AMPK [19]. In contrast, exercise-induced elevation of PGC-1 has been suppressed along with decreased phosphorylation of p38 MAPK by pharmacological suppression of xanthine oxidase using allopurinol [20], supporting the hypothesis that in vivo contraction-induced activation of p38 MAPK and consequent modulation of PGC-1 expression are mediated by ROS.

Signaling modulated by Ca^{2+} and calmodulin

Contractions of skeletal muscles cause the Ca^{2+}/calmodulin-dependent protein kinases to become active (CAMK). In particular, CAMKII, the main CAMK isoform, is phosphorylated (activated) by endurance training, while CAMKK is in control of muscle tissue contraction-induced activation of AMPK [21,22]. Because exercise regulates p38 MAPK and AMPK activation, respectively (see below), CAMKII and CAMKK may operate as upstream kinases in the control of PGC-1.

AMP-dependent protein kinase (AMPK)

A crucial regulator of the metabolism of skeletal muscle, AMPK serves as an intracellular sensor of ATP utilization. Active AMPK includes three subunits: α, β, and γ. There are several isoforms of each AMPK subunit. The majority of AMPK activation brought on by vigorous exercise is accounted for by the subtypes α2/β2/γ3 [23]. The interaction of these subunits with the nucleotides (AMP, ADP and ATP) provides AMPK with the capacity to determine the condition of cellular energy. Repeated muscular contractions and exercise greatly activate AMPK in skeletal muscle due to its function as a cellular energy sensor.

During energy stress, the concentration of intracellular AMP increases (i.e., ATP/AMP ratio lowers) as a sign of decreased energy and 5'-AMP binds to two domains of the γ subunits which activates AMPK. Hence, when the AMP level in the muscle rises during contraction, the activating effect progresses. As a result, ATP-producing catabolic activities are promoted, while ATP-consuming anabolic processes are inhibited [24]. Eventually, as a metabolic sensor, AMPK controls PGC-1 expression and stimulates mitochondrial biogenesis in skeletal muscle [25].

Mitogene activated protein kinases (p38 MAPK)

The protein kinases are activated by different forms of exercise. Among these kinases, p38 MAPK is most likely involved in the control of PGC-1 through transcription factors that bind to the PGC-1 promoter [26] and is essentially required for the regulation of PGC-1 brought on by endurance exercise. In this context, it has been shown that PGC-1 gene expression and skeletal muscle adaptability are facilitated by contractile activity-induced activation of the p38 MAPK pathway [27]. Of note, while the p38γ MAPK/PGC-1α regulatory axis is necessary for the exercise-induced angiogenesis and mitochondrial biogenesis, it has no role on fiber type transformation [15].

Peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α)

Increased mitochondrial content and functional exercise capacity are two features of endurance training adaptation that are recapitulated by overexpressing PGC-1α in skeletal muscle. As a result, PGC-1α is considered the "master regulator of mitochondrial biogenesis" and is a crucial element of the adaptations brought on by exercising with endurance training [28]. In reaction to metabolic stress, both p38 MAPK and AMPK are activated, investigations in cell culture and in vitro have shown that they may directly phosphorylate and activate PGC-1 [15]. PGC-1α is a transcriptional coactivator and a fundamental regulator of mitochondrial biogenesis in muscle and It has been defined that acute endurance exercise led to a 54% increase in nuclear PGC-1α protein [24,28].

Strength training

Strength training causes neuromuscular adaptations that improve muscle strength and power, increase in muscle cross sectional area, and changes in connective tissue stiffness. Mechanotransduction involves converting a mechanical signal into a biochemical event and can activate this pathway, which is crucial to the hypertrophic process because it coordinates the molecular foundation for both protein production and degradation [29].

In order to control rates of protein synthesis and/or breakdown and, over a lengthy period of time (weeks to months), muscular hypertrophy, strength exercise increases the activity of the phosphatidylinositol 3-kinase (PI3-k)-(AKT)-(mTOR) signaling cascade [12] resulting in the synthesis of proteins and the development of muscle [9]. A sequential activation cascade is initiated by a rise in insulin-like growth factor (IGF-1) or its splice variant mechano growth factor (MGF). Following this rise, AKT (Protein kinase B) activates two distinct pathways:

- mammalian target of rapamycin (mTOR);
- glycogen synthase kinase-3β (GSK3β),

both of which are essential for skeletal muscle growth [5,6].

Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin complex 1 (mTORC1) is a kinase that when activated causes cell growth and proliferation through phosphorylation cascades [30]. Two physically and functionally different complexes known as the mammalian target of rapamycin complex 1 (mTORC1) and the mammalian target of rapamycin complex 2 (mTORC2) are formed by the mTOR protein.

When hypophosphorylated, the eIF4E-binding protein 1 (4EBP1) attaches to eIF4E (Eukaryotic translation initiation factor 4E) to block it from interacting with eIF4G (Eukaryotic translation initiation factor 4G), which would otherwise assist in enhancing ribosome recruitment to mRNAs. Hence, it has the ability to inhibit the initiation of mRNA translation. When mTORC1 is activated by AKT, protein synthesis is promoted by direct phosphorylation of 4E-BP1 and Ribosomal protein S6 kinase beta-1 (S6K1) [31]. By phosphorylating 4E-BP1 at multiple sites, mTORC1 promotes its dissociation from eIF4E allowing the formation of the eIF4F (Eukaryotic initiation factor 4F) complex and the initiation of cap-dependent translation [32].

Glycogen synthase kinase-3 beta (GSK3β)

AKT is associated with an alternative pathway, running concurrently with mTOR, that induces hypertrophy via phosphorylating GSK-3β [33]. When GSK3β is phosphorylated, eIF2B (Eukaryotic translation initiation factor 2B) activity is reduced, facilitating the translation initiation process [34]. In particular, studies have demonstrated that strength training enhances GSK-3β phosphorylation, which blocks eIF2B, both immediately and three hours after, confirming the notion that this pathway is involved in the stimulation of protein synthesis brought on by strength training [5,6,35].

Link between endurance and strength exercise

The cross-talk between the two signaling pathways (endurance and strength training) is based on the tuberous sclerosis complex (TSC) signaling and in particular on two TSC proteins (TSC1 and TSC2) that form a functional complex and inhibit phosphorylation of S6K1 and 4EBP1. In particular, TSC2 is a GTPase-activating protein (GAP) toward Ras homolog enriched in the brain (RHEB). The GTP-bound form of RHEB stimulates cell growth and proliferation within the cell because it functions as an activator for mTORC1.TSC2 enhances the intrinsic GTPase activity of the GTP-binding protein RHEB, facilitating RHEB's conversion to its GDP-bound inactive state [36,37]. Thus, TSC2 would operate as a RHEB GAP to inhibit RHEB GTP from activating mTORC1.

TSC2 is also influenced by AMPK which phosphorylates TSC2 at two locations, which is the proposed mechanism by which it inhibits TOR and, consequently, protein synthesis and muscle hypertrophy [38,39]. This is supposed to increase the GAP activity, transforming the GTP-bound form into the GDP-bound form that no longer activates mTOR [39]. Furthermore, AKT phosphorylates TSC2 in response to mitogen stimulation, which lowers RHEB GAP activity and increases RHEB-GTP levels and, as a result, mTOR kinase activity [40].

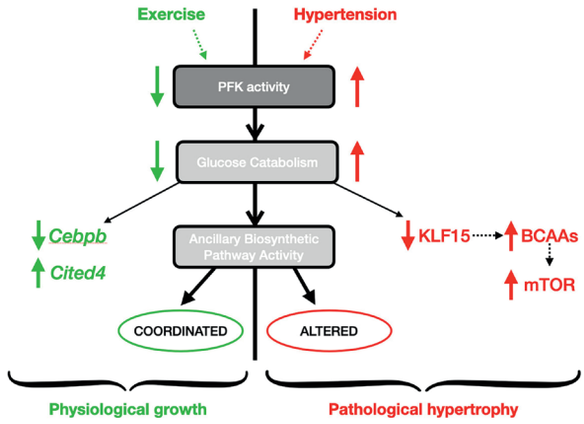
While strength training triggers the activation of AKT, which specifically reduces the inhibitory effects of the TSC on mTOR, thus activating mTOR in response to growth stimuli [37], on the other hand aerobic exercise AMPK decreases protein synthesis via lowering mTORC1 activity [5,7].

The impact of exercise on cardiac adaptations

Metabolic remodeling (Figure 2)

In addition to the alterations in skeletal muscle that are well-documented, an essential part of the response to exercise training is the dynamic cardiac remodeling needed to match peripheral demand with an adequate cardiac output. During exercise and the first few hours following exercise, the heart's ability to use glucose through glycolysis is diminished. Genes that are important for metabolic remodeling, transcription, cell division, differentiation, proliferation, and contraction

Figure 2 - Cardiac remodelling from a metabocentric perspective



BCAAs (Branched-chain amino acids); C/EBPB (CCAAT/enhancer-binding protein beta) is a transcription factor, participating in cell proliferation, differentiation and development; Cited4 (CBP/p300-Interacting transactivator with E (glutamic acid)/D (aspartic acid)-rich-carboxyl terminal domain); KLF15 (Krüppel-like factor 15) is a critical transcriptional regulator of BCAA metabolism; it inhibits mTOR(mammalian target of rapamycin) activity; PFK – Phosphofructokinase.

appear to be regulated by changes in metabolism brought on by phosphofructokinase (PFK). To activate transcriptional pathways directing heart development and hypertrophy, exercise-induced alterations in PFK activity are required. PFK activity in the myocardium is controlled by exercise, and the consequent changes in metabolism are sufficient to trigger a transcriptional pathway that affects exercise-induced cardiac development [41].

Declines in PFK activity appear to be particularly critical for directing the exercise gene program by upregulating Cited4 levels and downregulating Cebpb expression, as well as for coordinating glucose-derived carbon for anabolic activities. Additionally, the metabolic periodicity brought on by exercise may affect mitochondrial dynamics and support the maintenance of healthy mitochondrial pools. Lower intensity exercise appears to promote myocardial glucose catabolism, but relatively high intensity, sustained exercise may decrease myocardial glucose catabolism, start mitochondrial fission, and improve mitochondrial function [42].

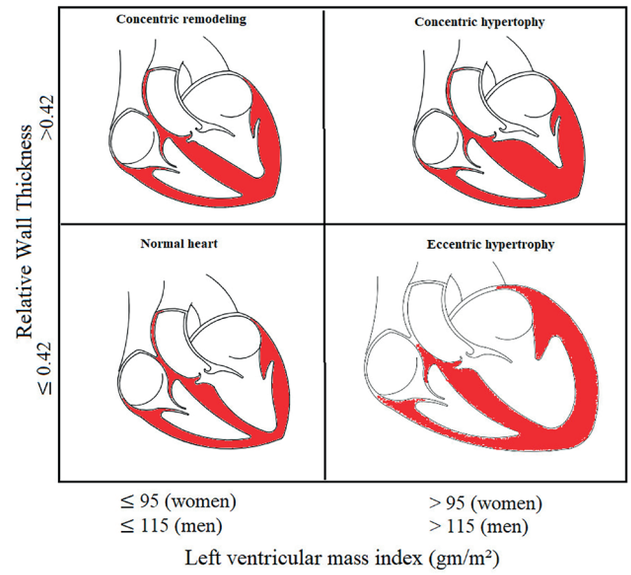
Cardiac remodeling (Figure 3)

The geometrical pattern of the left ventricle is categorised based on LV mass and relative wall thickness (RWT = (2 x posterior wall thickness) / (LV internal diameter at end-diastole). Individuals with normal LV mass may have either normal geometry (RWT <0.42) or concentric remodeling (RWT >0.42). An increased LV mass identifies subjects with left ventricular hypertrophy (LVH) and according to the RWT they can be divided into concentric (RWT >0.42) or eccentric (RWT <0.42) LVH [43,44].

Left ventricular morphology can change during life time due to changes in myocardial wall thickness and/or left ventricular dimensions. Eventually, LVH (i.e., increased myocardial mass) may develop. According to the triggers, this process can be classified as either physiological or pathological [42].

Mechanical stress and neurohumoral stimulation are the two main factors that cause cardiac hypertrophy. These factors influence a number of cellular processes, involving sarcomere construction, protein synthesis, gene expression, and cell metabolism, which eventually trigger and sustain the hypertrophic process [45-47].

Figure 3 - Left ventricular geometrical patterns of cardiac remodelling



Left ventricular mass index = LVM (left ventricular mass)/body surface area; Relative wall thickness = 2 x posterior wall thickness / LV internal diameter at end-diastole

Physiological cardiac remodeling

Physiological LVH is characterized by normal cardiac anatomical structure and architecture, with normal or increased contractility [48]. Exercise triggers a growth program without inducing the fetal-gene program, which is different from pathological remodeling. It also causes an increase in energy metabolic capacity that can meet the higher energy needs induced by continuous activity. The latter regimen keeps the heart function within normal limits [49].

In sports with high-dynamic and low-static demand (for instance, tennis) LVH is mostly eccentric, while high-static demand sports, like weightlifting, induce mostly concentric LVH. In activities like cycling that require both high-dynamic and high-static demands, the hypertrophy is balanced and mixed [50,51]. These morphological changes could be reversed after a detraining period from one to three weeks [52] but the return to a full “normal” heart dimension is still unclear [53].

In some cases, the morphology of an athlete's heart may resemble the one in people with hypertrophic cardiomyopathy. Given that hypertrophic cardiomyopathy is a frequent reason for sudden mortality in athletes, differentiating this condition from the normal athlete’s heart is of paramount importance, however there are significant challenges, in particular in subjects with LV wall thickness of 13-15 mm, who represent a grey zone. In this subset, several features can be considered to support the diagnosis of an athlete’s heart, including LV cavity >55 mm, normal LV filling pattern, decrease wall thickness with deconditioning, max VO2 >45 ml/Kg/min [54].

Pathological cardiac remodeling

The pathological hypertrophic remodeling differs from the physiological LVH in its transcriptional markers [55]. The expression of genes involved in fuel metabolism and bioenergetics is reprogrammed in a recognized way during the development of pathological cardiac hypertrophy and in the failing heart. Expression of nuclear and mitochondrial genes implicated in several mitochondrial energy transduction and respiratory pathways is downregulated, and the capacity to burn the major fuel (fatty acids) is decreased [56]. The cardiomyocyte starts a growth program as a reaction to hypertension or pressure

overload that is defined by the activation of a "fetal" gene program that includes altered sarcomere isoform gene expression and enhanced natriuretic peptide production [49]. The coordination between the growth of the cardiomyocytes and angiogenesis in the heart is dysregulated during the progression of heart failure from adaptive cardiac hypertrophy, and angiogenesis is necessary for the anatomical and functional development of the heart [48,57].

Several forms of overloads to the left ventricle may be brought on by cardiovascular disorders. Whereas volume overload is frequent in individuals with mitral regurgitation, aortic regurgitation, dilated cardiomyopathy, and chronic coronary artery disease, pressure overload is typical in cases of arterial hypertension and aortic stenosis. Typically, cardiac conditions such myocardial infarction and dilated cardiomyopathy coexist with ventricular dilatation and an increase in cardiomyocyte length which leads to the development of pathological eccentric hypertrophy [48]. In contrast, pathological concentric hypertrophy typically arises in conditions like hypertension or aortic stenosis where cardiomyocytes ordinarily thicken more than they lengthen [48,58].

Changes in hemodynamics

Every type of exercise has a different hemodynamic impact, which triggers separate cardiac adaptation (Table 1).

Table 1 Hemodynamic response to different types of training

	Endurance exercise	Strength exercise	Comments
VO2 max	increase	increase/stable	Endurance exercise increases the body's ability to absorb oxygen (VO2), in contrast VO2 rarely rises during a strength training session.
Resting heart rate	decrease	stable	As long as cardiac output at rest doesn't change, the rise in stroke volume is followed by a commensurate decline in heart rate.
Stroke volume	increase	stable	The LV end-diastolic volume is increased with endurance training, which results in an increase of the stroke volume.
Maximal cardiac output	increase	stable	With a maximum exercise effort, the rise in SV causes a considerable increase in cardiac output.
Systolic BP (rest)	Decrease or stable	stable	Systolic and diastolic BP increases during resistance exercise, but not endurance. Blood pressure of people with arterial hypertension drops toward normal as they exercise more, regardless of type of the exercise. This is brought on by a decrease in the artery's overall peripheral resistance as well as an improvement in flexibility of smooth muscles of blood vessels.
Diastolic BP (rest)	Decrease or stable	stable	
LV hypertrophy	Asymmetric	Symmetric	Strength training mostly causes concentric LVH, whereas endurance training primarily causes eccentric LVH. Balanced and mixed hypertrophy is seen in concurrent exercise demands.
Overload state	Volume > pressure	Pressure > volume	Endurance exercise induces volume overload on the heart, while strength exercise induces pressure overload and volume overload

Endurance exercises

The body responds to aerobic exercise by increasing oxygen uptake (VO2), heart rate, cardiac output, and stroke volume, which peaks initially before plateauing. At rest, skilled endurance athletes' cardiac output can range between 5 and 6 liters per minute and up to 40 liters per minute during maximal exertion [59]. Along with an increase in cardiac output, blood pressure also rises, but not as much as it would during strength training. As a result, the heart of an endurance athlete must adjust to both volume and pressure overload. Because volume load plays a major role in endurance training, the heart grows eccentrically after exercise [60], with new sarcomeres sequentially added to those that already exist. As a result, the inner diameter of the left ventricle increases and the wall thickness increases as well [61].

Endurance exercise also reduces blood pressure at rest with a more pronounced effect on hypertensive compared with normotensive individuals [62]. Wide pulse pressure (rising systolic blood pressure, coupled with a decline in diastolic blood pressure) and a little rise in mean pressure are the results of decreasing peripheral vascular resistance [63].

Strength exercises

Compared to athletes with endurance training, strength athletes have different cardiovascular adaptations. Elite level resistance exercise is linked to abrupt and strong pressure reactions which translates into a markedly elevated systolic and diastolic blood pressure, with little effect on the stroke volume and only a slight increase in heart rate [64]. During a strength exercise VO2 barely increases; however, with a higher workload the increases in the intrathoracic pressure due to the Valsalva manoeuvre results in lower venous return and low cardiac output. To sustain cardiac output and blood pressure, a reflex increase in heart rate and vasoconstriction, respectively, occurs [63].

In weightlifting athletes, due to the elevated afterload, high intraventricular pressure is required to open the aortic valve, which may cause an abrupt elevation in blood pressure [65]. High afterload and intraventricular pressure during the ejection phase enhance myocardial wall stress, which is the principal trigger of cardiac hypertrophy in the pressure-overloaded heart [66]. The concentric LVH that occurs in the heart of a resistance-trained athlete in response to a rapid, intense pressure overload may occasionally be accompanied by an enlargement of the left ventricular diameter [67].

Ageing heart and the effects of exercise

It is well known that physical activity prevents or delays chronic diseases [68]. Compared to other recognized components of cardiovascular disease risk, capacity for exercise is a more accurate predictor of death in males [69]. Furthermore, in patients with postinfarction heart failure, exercise intensity was a key determinant in reversing LV remodeling and enhancing quality of life, endothelial function, and aerobic capacity [70]. In individuals with heart failure who are clinically stable, aerobic exercise training, particularly long-term (6 months) length, reverses left ventricular remodeling which was evaluated using the ejection fraction (EF), end-diastolic volume (EDV), and end-

systolic volume (ESV). Strength training in contrast did not alter or exacerbate ventricular remodeling, whether it was done alone or in conjunction with aerobic exercise [71].

Conclusion

In this article we have reviewed the effects of different forms of exercise on the cardiovascular system by evaluating the molecular signaling pathways, which are crucial for muscle adaptations. Adaptation to endurance exercises mainly occurs through PGC-1α, which regulates mitochondrial biogenesis, and is regulated by biochemical processes such as Ca^{2+}-dependent pathways, reactive oxygen species (ROS), AMP-dependent protein kinase (AMPK), and mitogen activated protein kinases (p38 MAPK). Strength training, on the other hand, raises levels of insulin-like growth factor (IGF-1), which starts the PI3-k-(AKT)-(mTOR) signaling cascade.

Furthermore, we described the changes in the metabolism, geometric pattern, and cardiac hemodynamics induced by different types of physical training. Endurance training via volume overload combined with pressure load induces eccentric LVH, in contrast to the strength exercise that mainly induces pressure load on the heart causing concentric LVH. There is still a "grey area" in differentiating between hypertrophic cardiomyopathy and athlete's heart which could be solved by thorough investigation of LV cavity, LV filling pattern and wall thickness after deconditioning.

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Mapping the terrain: A comprehensive exploration of health literacy among youth

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Abstract

Health literacy is identified as a crucial public health concept that demands the attention of policymakers due to its profound impact on population health. This comprehensive review explores the landscape of health literacy among youth, examining current circumstances, relevant policies, available resources, tools, and effective strategies. We aimed to comprehensively map and synthesize the existing literature on the current state of health literacy among young individuals. Employing a data-centric methodology, the review meticulously analyzes existing literature and research in the domain of youth health literacy. We displayed the results of the analysis, distributing them into appropriate blocks. The review emphasizes the need for deeper research to assess health literacy gaps among youth and select appropriate assessment tools. It also highlights the imperative to enhance the health literacy of young individuals, which presents a significant global challenge. Developed nations' governments show considerable interest in this issue, with potential legislative measures to foster competencies from early personal development. The review notes that multiple factors such as socioeconomic status, health risk behaviors, health status, gender, and age interplay with health literacy, requiring attention to disparities among at-risk populations. Despite numerous tools available for assessing general health literacy, the lack of a standardized international tool remains a concern for public health professionals. Addressing health literacy necessitates a multifaceted approach that considers diverse influences on health education, communication, and behavior, especially among youth. Tailored interventions designed for specific populations can bridge literacy gaps and enhance overall well-being.

Keywords: health literacy, young population, health promotion

Introduction

Over the past decades, health literacy (HL) has gained significant attention from researchers, activists, and health policymakers, reflecting its evolving importance in healthcare understanding and outcomes [1]. Sorensen et al defined health literacy as individual skills and institutional frameworks, along with the available resources and dedication, collectively empower individuals to attain, comprehend, evaluate, and apply information and services effectively, maintaining and promoting their well-being [2]. In a simplified approach, health literacy describes an individual's ability to manage their health and navigate the healthcare system. In this context, health literacy is not static, it develops throughout a person's life (for example, through schooling), and is influenced by individual, situational and social factors. As a result, it can be regarded as a dynamic and situation-dependent concept at the individual level [3].

Health literacy, however, is something more than just being able to read brochures and successfully schedule an appointment with a doctor. Health literacy is critical for population empowerment because it improves people's access to health information and their capacity to use it effectively [4]. The concept of health literacy goes beyond the idea of personal resource. A higher level of health literacy benefits whole society, for example, by mobilizing communities to influence various factors that affect health. This understanding justifies growing calls for the perception of health as the joint responsibility of both individuals and public policy-makers and health

systems [5]. In this sense, health literacy extends beyond the narrow concept of health education and communication centered on individual behavior to include environmental, political, and societal issues that influence health.

Children and adolescents are the key target population for scientific research on health literacy since basic cognitive, physical, and emotional development, as well as the creation of health-related behaviors and abilities, take place during childhood and adolescence [6]. However, there is a lack of expertise and scientific consensus on what abilities and knowledge children and adolescents require to make informed medical decisions. Health literacy of children and adolescents is described in the literature as a collection of interconnected abilities, skills, obligations, and knowledge that allow access to medical information and make informed and effective decisions to enhance health [7].

The European Consortium on HL put forth the subsequent HL definition for the broader populace: “HL involves literacy and includes individuals' comprehension, drive, and ability to access, grasp, evaluate, and apply medical information for decisions about healthcare, disease prevention, and well-being, with the goal of maintaining or improving quality of life throughout life's stages” [8]. Nevertheless, in no single country can there be an explicit application of the concept of HL in childhood and adolescence [9].

The aim of our scoping review is to comprehensively map and synthesize the existing literature on the current state of HL among young individuals. This review seeks to explore and analyze the prevailing situation, key issues, relevant policies, available tools, and effective interventions pertaining to HL among the youth (Figure 1). By conducting this scoping review, our objective is to provide a comprehensive overview of the landscape of HL among young people, identify gaps in research and practice, and offer insights that can inform future research directions, policy formulation, and the development of targeted interventions to enhance HL in this critical demographic group.

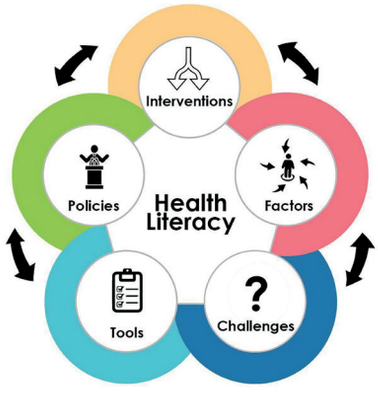

Figure 1 - Mapping the Health Literacy terrain

Material and methods

The authors analyzed publications in the field of HL among young people, the development of the subject, research trends, and displayed the results of the analysis, intuitively distributing them into appropriate blocks. A search of open access publications yielded a total of 5159 articles retrieved from the core Pubmed, Web of Science, Scopus databases using the keywords "health literacy and students", "health literacy and youth", and "health literacy and children". The authors of this review analyzed the abstracts and main conclusions of these publications for compliance with the stated aim, with the subsequent inclusion of relevant publications in the review.

Based on the results of a literature search, the authors included in this review 114 researches and disclosed the following aspects of youth HL:

- Existing problems in the field of HL among young people and their dimensions.
- Legislation and regulation of the problem of HL among the young population
- Factors that affect HL levels in the young population
- HL Assessment Tools
- Available interventions to improve HL levels.

Health literacy levels overview

Health literacy of general population

It was shown that low HL was associated with various negative consequences at the individual and society levels, such as deterioration in health indicators and a lower level of use of medical services [10].

Studies among general population revealed various levels of HL. Thus, according to a European HL survey conducted among eight European countries at least one in every ten (12%) respondents had insufficient HL, and nearly one in every two (47%) had insufficient or problematic levels. Nevertheless, the distribution of these levels exhibited significant variations across different countries (29–62%). Higher percentages of people with low HL were discovered in demographic subgroups defined by economic disadvantage, low social status, lack of education, old age, implying the existence of a social gradient [11].

In a comprehensive nationwide cross-sectional study encompassing 15,728 Danish individuals aged ≥25 years, almost four in ten respondents’ encountered challenges when it came to accessing, comprehending, assessing, and applying health-related information. Remarkably, 8.18% displayed inadequate HL, while 30.94% exhibited problematic HL. It's worth noting that insufficient HL closely correlates with lower socio-economic status, compromised health, sedentary lifestyle, and overweight conditions. However, its connection to positive health behaviors, such as abstaining from smoking and excessive alcohol consumption, is comparatively weaker [12].

The study's findings on HL in Portugal suggest that 7 out of 10 people in Portugal (mainland) have high HL levels. Additionally, the findings imply that "navigation in the health system" tasks are the hardest in terms of particular health literacies [13].

Scientific research on HL has also been conducted in Kazakhstan. Thus, in 2013-2014, as part of a population-based cross-sectional study with the participation of six countries of the Asian region (including Kazakhstan), the study of HL was conducted using a comprehensive tool - the HLS-EU-Q47 questionnaire developed for the European HL Survey. This questionnaire is focused on the measurement of GVH not only in clinical settings, but also among the general population. The study validated the HCS-EU 47 questionnaire, translated into seven languages, in several Asian countries [14].

Aringazina et al. studied the distribution of HL levels among the population of five cities of Kazakhstan by the ability to search, understand, evaluate, and use information for health promotion. The study showed that the majority of respondents freely handle information in the field of health, regardless of gender, and the ability to manipulate information is expressed almost equally in each category of the assessment tool [15].

Health literacy of students and youth

Rababah et al. discovered that the field of study, health-related vs. others, had a substantial impact on all HLQ scales. On all scales, students in health-related faculties scored much higher

than students in other faculties. Other characteristics influencing students' HL included age, gender, smoking status, and year of study, with field of study having the greatest impact on the degree of HL among college students [16].

The research carried out by Vozikis and colleagues revealed that the HL of the college students in the study demonstrated a moderate to elevated range with their well-being being notably favorable at the same time. Furthermore, various elements including economic and demographic aspects like household earnings, sex, and health-related habits such as alcohol consumption, smoking, and physical activity were found to correlate with the participants' HL level and overall health condition [17].

In the study conducted by Patil et al, which explored HL and digital HL among college students in the US, more than half of the sample (51%, N=130) reported low HL. Students with low HL were, on average, 2.3 years older than those with adequate HL ($p<0.001$). Students who identified as female or gender variant were roughly twice as likely to have adequate HL as students identifying as male ($p<0.001$). No significant differences between HL levels were found across ethnic or racial groups. There was no significant association between HL level and political affiliation [18].

Younger individuals demonstrate lower levels of HL. About 25.5% of the research subjects in a cross-sectional survey of junior middle school pupils (ages 12 to 15) were found to have poor HL. Higher HL among students was connected with better quality of life (QOL) ($P<0.01$) [19].

Legislation and regulation of the problem of health literacy among the young population

Attention is being paid to HL at the legislative level. Thus, there is an established HL Council in the District of Columbia, US, that shall advise the Mayor and the Council on promoting HL for residents of the District and helping residents develop a working knowledge of mental health [20].

In order to improve HL, particularly among young people, the National Academy of Sciences, Engineering, and Medicine in Washington, US, regularly hosts round tables on the topic. These gatherings bring together leaders from academia, business, government, foundations, and associations, as well as advocates for patients' and consumers' interests. The Roundtable's mission is to educate, motivate, and engage a wide range of stakeholders in order to encourage the development, implementation, dissemination of evidence-based HL practices and policies with the aim to enhance everyone's health and wellbeing [21].

The National Action Plan initiated by the U.S. Department of Health and Human Services strives to engage a diverse range of stakeholders in a cohesive, cross-sector initiative aimed at enhancing health literacy. Seven goals that will increase HL are included in the action plan, along with methods for attaining them [22].

In addition, International HL organizations have been established in other countries: namely, the Asian HL Association, the Health Literacy Center of the Canadian Public Health Association, the Global Literacy Working Group in New Zealand; Health Literacy in the United Kingdom; Health Literacy in the United Kingdom; the Irish National Adult Literacy Agency; Shanghai Declaration on Health Promotion [23].

Our country is no exception. Chapter 12 of the Constitution of the Republic of Kazakhstan enshrines the constitutional rights and obligations of citizens of our country in the field of healthcare. According to Article 80 of the Constitution, citizens of the Republic of Kazakhstan, first of all, are obliged to take care of the preservation of their health, bear joint responsibility for the maintaining and enhancement of personal and public well-being. [24, 25].

The problem of forming a healthy lifestyle has received the priority status of state policy: in the Development Strategy of Kazakhstan until 2030, one of the most important long-term priorities is defined as "Health, education and well-being of citizens of Kazakhstan", which emphasizes the political, economic, socio–medical importance of a healthy lifestyle. In this regard, the comprehensive use by the healthcare system of a powerful social component, such as the participation of citizens in the preservation and strengthening of public health, in the formation of a healthy lifestyle, is of particular importance, especially for the younger generation, since it determines the future of the country, its scientific and economic potential. The observed deterioration in the health of adolescents on the threshold of entering working age and reproductive age makes it necessary to study social factors that ensure the preservation and improvement of their health [26].

In order to increase the HL of the population and strengthen the promotion of a healthy lifestyle in Kazakhstan, a Roadmap for 2023-2025 has been developed and is being implemented, the Ministry of Health of the Republic of Kazakhstan reports. As a result of the implementation of the Roadmap measures, it is expected to reduce the consumption of tobacco products, alcoholic beverages and surfactants; improve mental and reproductive health; reduce injuries. It is expected that one of the main objectives of the roadmap implementation will lead to an increase in the proportion of citizens of Kazakhstan leading a healthy lifestyle to 30% by 2025; Reduction in the prevalence of tobacco smoking among the population of Kazakhstan aged 15 years to 19% by 2025; Reduction in the incidence of obesity among children (0-14 years) to 90 per 100 thousand population by 2025 [27].

Factors that affect health literacy levels in the young population

Socio-demographic factors

Several studies have examined the relationship between HL and demographic factors, providing insights into how they can impact HL levels.

One study conducted in Greece assessed the functional HL among university students and found no significant association between age and HL [17]. The study by Vamos et al. (2016) investigated HL profiles of Texas university students and revealed that, in relation to "Appraisal of health information," younger students aged "15-24 years" exhibited lower HL levels compared to their colleagues aged "25 years or older" [28]. These findings suggest that age may not be a significant determinant of HL among young people.

However, other studies have shown that age can influence HL levels in specific populations of young people. For example, a study in Malaysia and Sri Lanka found that younger students had lower HL levels compared to older students [29]. Similarly, a study in Germany found that HL levels among adolescents declined with age [30]. These findings indicate that age can have an impact on HL levels in certain contexts.

Rababah's study uncovered that freshmen, sophomores, and juniors displayed diminished HL levels across measured dimensions, including "Feeling understood and supported by healthcare providers," "Appraisal of health information," and "Understanding health information." Additionally, the research identified associations between health literacy and gender. Rababah et al.'s investigation highlighted those female students demonstrated elevated HL levels compared to male counterparts in specific domains, such as "Social support for health,"

"Navigating the healthcare system," "Ability to find good health information," and "Understanding health information." [16].

The study by Vamos et al. (2016) uncovered a notable gender-related finding, indicating that women reported higher levels of HL in aspects such as " Adequate comprehension of health information to make informed decisions" and " Evaluation of health information" compared to men, emphasizing gender disparities in health information comprehension and decision-making [28].

The study investigated the connections between the study variables and HL domains. Notably, a correlation was established between gender and general HL, with females exhibiting notably higher HL scores across all health domains [31]. However, other studies have shown mixed results regarding gender differences in HL. When comparing Korean males and females, it was found that the latter were less likely to know how to read and fill out medical forms ($\chi2=6.594$, df=2, p=.037), to have trouble reading the directions on medicine bottles ($\chi2=7.515$, df=2, p=.023) and to understand written information from a doctor, nurse, or nurse practitioner ($\chi2=9.975$, df=2, p=.007) [32]. Some studies have found that women have higher HL levels, while others have not found significant gender differences [33-36].

Furthermore, the study conducted in China found notable geographic variation in HL levels, with the proportion of respondents with adequate HL varying across different regions. Similarly, another study in China found regional heterogeneities in HL levels among the Chinese population [37]. These findings suggest that HL levels can vary based on the geographic location within a country.

Additionally, the study conducted by Bánfai-Csonka et al. found that nationality was an influencing factor in HL among university health science students. The study reported a significant correlation between nationality and HL levels [38].

Lifestyle factors

Svendsen et. al. identified notable links between HL and physical activity, with sedentary behavior linked to higher odds of lower HL scores, while moderate exercise was associated with reduced odds of inadequate and problematic HL. Moreover, this group of authors found the significant relationships between HL and the long-term health risk indicator BMI, indicating that obesity (BMI>30) was linked to lower HL scores, while higher HL scores were associated with normal BMI and demonstrated associations with overweight (BMI>25). Furthermore, HL demonstrated associations with alcohol consumption, consistent drinking habits, and issues related to alcohol consumption [39].

Evans et.al. found that students who rated their health as not satisfactory were twice as likely to have limited HL as those who rated their health as satisfactory [40].

Rababah's findings indicate that the smoking status of college students is a significant predictor of HL. Nonsmokers had higher scores of HL on seven of the nine HLQ scales compared to smokers [16].

In the study conducted among Danish students, it was defined that the health-related experiences of the students tended to influence their HL as well. In four of the nine domains, students who had prior contact with hospitals as inpatients or outpatients scored higher than those who had not [41].

Socio-economic factors

It is argued that the HL level is associated with the direction of education. For example, research suggests that high levels of HL are associated with education in medicine and health sciences, in particular, Public Health [16, 41-44]. At the same time, conflicting data are indicating that students of health professions have a low level of HL, and there are also difficulties in interacting with e-health [45-47].

Other important socio-economic determinants of HL that are positively correlated with it are the socio-economic status of families and parents' education. This is attributed to the fact that caregivers with a higher education and socioeconomic status contribute to a better orientation of their children in health knowledge and behavior. Such families have a higher income, allowing them to provide children with better access to information and services and the best schools [48-50]. Moreover, a low level of HL is found among those students who report insufficient financial situations and low social status compared to older classmates [51].

Marital status is also noted as one of the socio-economic factors of HL among students. For example, living alone is a predictor of lower HL [52, 53].

Health-related factors

Frequent access to health services was associated with higher HL. Frequent health check-ups, whether due to illness or as a preventive measure, lead to frequent contact with healthcare professionals, thus contributing to higher HL among university students. Also, higher levels of HL are observed among students with less anxiety about their health (Figure 2) [49, 54].

Figure 2 - Traits of a person with high Health Literacy level

Health literacy assessment tools

Given the importance of HL, it is prudent to develop comparable and reliable measurement tools to assess HL in the population. Based on the role of interested parties in improving HL we believe that research institutions should develop and improve tools for assessing HL. To date, there are various systems or scales for assessing and measuring HL based on different subjects, both general HL, a specific disease or condition, health care, and tools that target different age groups and nationalities.

A systematic review conducted by Mahmoud Tavousi et al. highlighted that the initial tools for assessing HL emerged in the early 1990s and continue to be relevant in contemporary research. Over the period between 1993 and 2021, a total of 39 tools aimed at measuring general HL were identified [55].

Among the historically prominent tools for general health assessment, the following instruments have been frequently employed:

1. Rapid Estimate of Adult Literacy in Medicine (REALM) (1993), designed to evaluate reading proficiency and pronunciation skills [56].

2. Test of Functional HL in Adults (TOFHLA) (1995), aimed at assessing reading comprehension and numeracy abilities [57].

3. Newest Vital Sign (NVS) (2005), a concise clinical screening tool targeting reading comprehension and numeracy proficiency [58].

Despite their wide usage, these tools have faced criticism for several reasons. Some critiques include their limited coverage of various facets of HL, their inappropriateness for use in intervention-based studies, or their failure to encompass a health promotion perspective. Moreover, it's worth noting that the majority of these measurement scales were initially developed and predominantly used in clinical settings [59].

The advancement of tools for studying medical literacy has led to the proliferation of various versions of existing instruments. These adaptations have been tailored to different languages and diverse population groups. Some notable instances include:

- Rapid Estimate of Adult Literacy in Medicine (REALM) and its 16 iterations.
- Test of Functional Health Literacy in Adults (TOFHLA), which has seen the development of 6 versions, including its abbreviated form S-TOFHLA with 13 versions.
- Newest Vital Sign (NVS) has undergone 15 variations.

During the last decade two well-constructed instruments have emerged as noteworthy additions:

1. The Health Literacy Questionnaire (HLQ) (2013): This instrument stands out for its departure from established theories in the initial development stages. Emphasis was placed on comprehensively grasping the insights and expertise of health practitioners, community members, and peers. The HLQ comprises nine scales, each capturing a unique facet of the multidimensional construct of HL. Robust psychometric properties are evident across all scales. A significant recommendation stemming from this study is the endorsement of the HLQ's usage to identify disparities between the perspectives of clinicians and patients.

2. The Health Literacy Survey Questionnaire (HLS-EU-Q) (2013): Alongside its subsequent iterations, this questionnaire has made a notable contribution to the field. The questionnaire encompasses a total of 47 items that evaluate 12 distinct subdomains of HL. These subdomains are constructed around four fundamental information-processing abilities possessed by individuals, namely accessing, comprehending, evaluating, and applying information. Additionally, these abilities are explored within the context of health promotion and disease prevention.

These refined tools signify a substantial stride in the evolution of medical literacy assessment methods, offering a more comprehensive understanding of individuals' HL experiences [60-62]. The HLS-EU-Q tool has also been used in studies in Asian countries, including Kazakhstan [63], the variety of language versions of this questionnaire makes it one of the most widely used in the world.

In a systematic review conducted by Soares V.L. et al. of 31 instruments, none of their psychometric properties were rated as "very good" according to the COSMIN Risk of Bias checklist. The authors noted that the use of reliable tools for the development and evaluation of interventions in families with diabetes is important for improving HL, namely critical literacy and the effectiveness of diabetes treatment [64].

Among infectious diseases, HIV is the leader in the development of HL research tools. During the coronavirus pandemic and after, tools for studying medical literacy in this area began to be actively developed. Knowledge about the symptoms and transmission of infection, worry about infection, and practices related to mask usage and hand hygiene were most frequently evaluated [65]. A diverse array of specific content measures gained prominence, encompassing various dimensions such as parental and maternal health, insurance literacy, occupational health, dietary preferences, personal weight perception and concerns, awareness of alternative medicine, interactions with healthcare providers, and various other aspects [55].

The increasing emphasis on cultivating HL among children and adolescents has led to the exclusive incorporation of HL promotion in early childhood within the policy brief of the World Health Organization's agenda for investing in HL within the European Region. Additionally, this focus has found its place in the recently published Shanghai declaration on health promotion [66].

A systematic review by Okan O et al. spanning the years 1990 to 2015 identified a total of 15 tools designed for measuring HL among children and adolescents. Scholars, in alignment with insights from developmental research, assert that the foundation for effective HL is laid during early childhood. Within the spectrum of identified tools, ten novel instruments were devised specifically for children and/or adolescents, encompassing the age group of 15 and older, which also extended to encompass adult age groups [67]. Among these, REALM-teen stands out as the pioneer HL tool for adolescents. This tool represents a teenage adaptation of the Rapid Assessment of Adolescent Literacy in the Field of Medicine (REALM-teen), an English word recognition test intended for use as a concise literacy assessment tool within medical institutions [68]. Additionally, a teenage version of the Adult Functional Medical Literacy Test (TOFHLAd) [69] and the Newest Vital Sign (NVS), employed for gauging children's literacy in health-related matters [70], have been presented. In Austria, a study utilized the HL tool HLS-EU-Q47, originally devised and validated for adults aged 15 and above, which was subsequently modified into a condensed version tailored for adolescents [11].

Improving health literacy: A multifaceted approach

Effective management of HL levels requires consideration of various aspects and approaches tailored to different types of HL and target populations. When addressing specific health conditions resulting from health choices, beliefs, or life circumstances such as immigration or natural disasters, a customized strategy for improving HL is essential. This spectrum of HL factors, if incorporated into the formulation of HL improvement policies from the outset, could have a transformative impact.

Despite the significance of HL, its distinct impact on health education and communication methodologies is not yet adequately reflected in many interventions. Progress in supporting national policies, implementing programs, and providing intervention tools for community practitioners has been slower than anticipated [71]. While numerous interventions have been reported in clinical settings, these primarily focus on functional HL in terms of task-oriented skills [72]. Nonetheless, interventions targeting HL have demonstrated the potential to enhance HL levels and subsequently induce changes in health behaviours. This presents a promising avenue to alleviate health inequalities among populations at the greatest risk [73]. In developing nations, healthcare systems face substantial challenges in addressing the needs of vulnerable communities. Factors such as lack of medication compliance, shortage of health educators, and barriers arising from language, socio-political, economic, and cultural factors hinder HL advancement. Research underscores that these challenges contribute to higher mortality and morbidity rates within vulnerable populations [74]. Effective HL requires a foundation of mutual understanding and communication between patients, families, and healthcare providers.

Promising interventions targeting HL embrace distinctive features that contribute to their effectiveness. Firstly, these interventions are tailored to the needs of participants with low

HL, addressing their specific requirements. Secondly, they emphasize interactive and critical skills rather than focusing solely on knowledge acquisition. Lastly, these interventions present information in an easily digestible manner, avoiding complexity and utilizing animated spoken text [75]. Such interventions have exhibited improvements in motivation, knowledge, empowerment, and self-confidence, indicating their potential for broader application [76]. In a study conducted in Turkey higher HL levels were observed among women who had prior exposure to information regarding Breast Self-Exams, Clinical Breast Exams, mammography, and mammary ultrasonography. Notably, improved HL in women corresponded to an enhanced interest in seeking out screening techniques crucial for the early identification of breast cancer [77].

A strategic initiative for enhancing citizens' HL is health education. Notably, China has established professional health organizations (PHOs) that offer comprehensive health education and promotion services [78]. In the United States, the "OPtimising HEalth LIterAcy and Access" (Ophelia) project comprises three key phases: assessment, intervention development, and continuous improvement. This multifaceted approach seeks to bolster HL by enhancing service delivery, refining processes, and evaluating outcomes [79].

Categorizing interventions into distinct categories reveals the diverse methodologies employed. These categories include traditional HL interventions, art-based approaches, active learning strategies, and technology-based interventions [80]. Traditional methods encompass lectures, passive lessons, and distribution of pamphlets, while art-based interventions engage creative approaches like drama and storytelling. Interactive learning interventions, such as group discussions, promote active participation, and technology-based interventions leverage digital platforms for knowledge dissemination [81]. Digital tools such as eHealth and mHealth technologies hold promise for direct-to-consumer HL interventions. Particularly, mHealth applications cater to smartphone users and can offer accessible solutions for HL improvement. However, concerns regarding privacy, security, and usability remain barriers to widespread adoption [82]. Evaluating the efficacy of these tools is essential, especially considering the potential impact of social media on HL and the dissemination of health-related information [83].

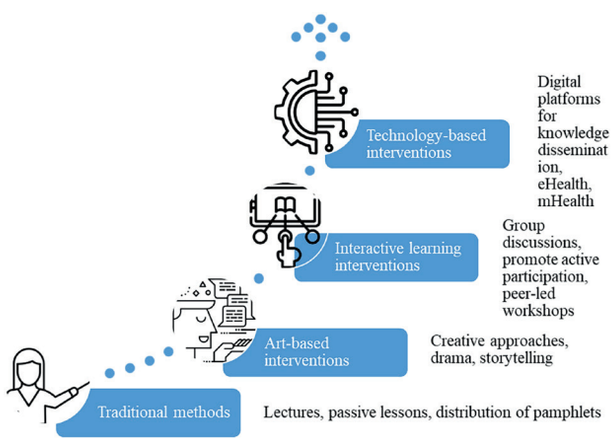

Figure 3 - Core Health Literacy interventions

In the realm of health professions education, the importance of HL is increasingly recognized. Effective communication and assessment skills, especially within real-world patient interactions, prove essential for health professionals to bridge the HL gap [84]. Current evidence highlights the need for more comprehensive training programs in evidence-based medicine and HL for both healthcare providers and patients [85].

Interventions designed to improve HL extend beyond clinical settings, encompassing diverse domains like nutrition, physical activity, and immigrant populations. In the realm of nutrition, interventions targeting individuals with low HL seek to simplify information and reduce reliance on medical jargon [86]. Similarly, interventions focusing on physical activity emphasize the importance of creating opportunities for public engagement, promoting active lifestyles, and improving road safety [87, 88]. The unique challenges faced by immigrant populations necessitate culturally sensitive interventions. Effective strategies include using native languages, involving participants in program development, and collaborating with community members who share similar experiences [89]. Nurses play a vital role in these interventions, bridging the gap between healthcare providers and culturally diverse populations [90].

Moreover, interventions have explored HL's connection with specific health domains such as calcium intake and mental health awareness [91]. Recognizing the pivotal role of healthcare practitioners, particularly registered dietitian nutritionists, in addressing HL gaps can lead to improved dietary choices and overall health outcomes [92]. Implementing evidence-based interventions and strategies to tailor care to individuals' needs and goals is crucial in achieving positive outcomes [93].

All of the interventions and measures mentioned above are applicable for young generation, the key point of these is the tailored approach based on research outcomes, not just general understanding or experts' opinions. It is essential for young people to make informed decisions about their health, such as choosing healthy foods, getting regular exercise, and avoiding risky behaviors. There are a number of interventions that have been shown to improve HL among young people. These interventions can be delivered in a variety of settings, including schools, community centers, and health clinics. We tried to delve into the array of measures and interventions geared towards improving HL among this population group, with insights drawn from a diverse selection of credible sources.

The role of families is pivotal in shaping health behaviors. Educational programs that engage parents and guardians in discussions about health topics and effective communication strategies create a supportive ecosystem for young people to make informed decisions [71, 94]. Collaborative efforts between educational institutions, healthcare providers, and community organizations facilitate HL improvement. Workshops, health fairs, and community-based events bring together various resources to disseminate accurate health information and provide opportunities for hands-on learning [95, 96].

Schools serve as crucial platforms for HL interventions [97, 98]. Typically, the basic literacy challenges that arise during the school years tend to endure into an individual's adolescence and beyond, and usually connected to broader health concerns [99]. Comprehensive health education programs that encompass topics such as nutrition, sexual health, mental well-being, and substance abuse prevention can equip young individuals with essential knowledge to navigate their health effectively [100-102]. It's important to emphasize the significance of teacher HL as a provider in the National Health Education Standards [103]. Incorporating interactive teaching methods, real-world scenarios, and peer-led initiatives enhances engagement and relevance. Achievements, quizzes, and challenges not only enhance knowledge retention but also motivate continuous learning. [104, 105]. Even medical students' have different issues regarding HL. For instance, in a study from the US more than 60% of students struggled to identify HL as an important determinant [106]. Embedding HL components within existing curricula, such as science or social studies, ensures that health-

related topics are not treated as standalone subjects but are seamlessly integrated into broader educational goals. This approach emphasizes the practical relevance of HL in daily life [107-109].

Gamification utilizes game elements to engage and educate users. Health-related mobile apps and online platforms can employ gamification techniques to deliver health information in an interactive and engaging manner [110,111]. Given the digital era's prevalence, digital HL is paramount. Online platforms, health-related apps, and social media channels can either empower or misinform young people [112,113]. Educational programs that teach critical evaluation of online health information, privacy protection, and reliable resource identification are essential to develop digital HL skills [114].

Peers exert considerable influence during adolescence and early adulthood. Peer-led workshops, discussion groups, and awareness campaigns enable relatable information sharing and discussions on health topics, e.g. vaccine hesitance and confidence. This approach fosters a comfortable environment for open dialogue, making health information more accessible and relatable.

So, addressing HL demands a comprehensive, multifaceted approach that considers the diverse aspects influencing health education, communication, and behavior, especially when managing it among young people. Targeted interventions, tailored to the unique needs of specific populations, have the potential to bridge HL gaps and enhance overall well-being. HL initiatives can encompass a wide range of domains, from traditional interventions to technology-driven approaches, and are essential for promoting better health outcomes and reducing health disparities (Figure 2).

Conclusion

This review delves into the analysis of prevailing HL among youth, examining issues, policies, tools, and interventions. The study highlights the significance of HL in shaping habits and attitudes among children and youth. Bridging gaps in HL, particularly among at-risk populations, is imperative due to its ties to demographics, socioeconomic status, and health behaviors. Further research is needed to measure HL accurately. Governments show a growing interest in legislating HL promotion. A standardized international tool for assessment is desired. A comprehensive approach is crucial, including tailored interventions and technology-driven initiatives, to enhance well-being and reduce disparities.

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CDKN2B-AS1 gene rs4977574 polymorphism in the severity of coronary artery disease in the Kazakh population

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Abstract

Coronary artery disease (CAD) is one of the leading diseases contributing to mortality. Although it has a hereditary nature, its genetic etiology remains unclear. Recently, many studies showed genetic risk factors using genome-wide association studies, and gene variant association with CAD. Despite the recent breakthroughs on various single nucleotide polymorphisms (SNP) linked to CAD, encompassing genes affecting metabolic disorders, influencing endothelial and smooth muscle dysfunctions, leading to plaque formation and myocardial infarction, most of those SNPs` functions remain to be pinpointed. Many studies showed significant associations between rs4977574 polymorphism of cyclin-dependent protein kinase inhibitors antisense RNA 1 (CDKN2B-AS1) gene on CAD in various ethnic groups. This review discusses the potential link between the CDKN2B-AS1 gene rs4977574 polymorphism and CAD in the Kazakh population.

Keywords: coronary artery disease, CDKN2B-AS1, rs4977574

Introduction

Genetic and environmental factors are the primary causes of pathological alterations in coronary artery endothelial tissue and vascular smooth muscle cells [1]. Advancements in coronary artery injury lead to Atherosclerotic plaque formation [2]. Despite the thorough studies on the potential causes of CAD, there is still a huge gap to fill [3]. Based on the existing scientific evidence, environmental factors such as smoking, obesity, high blood pressure, etc., and genetic factors such as single nucleotide polymorphisms are considered to explain CAD origin [4].

The hereditary influence on the development of coronary artery disease has been investigated since the mid-20th century, which was facilitated by the study of the history of cardiovascular disease within families. Remarkably hereditary effects were most pronounced in young adults [5].

Among all loci, the region of chromosome 9p21 has been studied especially well and makes up about 15-35% of carriers with an increased risk of coronary artery disease [6]. Although the exact mechanism of this locus is currently unknown, it is hypothesized that variants of this locus affect the expression of antisense non-coding RNA at the INK4 locus (inhibitors of cyclin-dependent kinase 4). The latter affect changes in the activity of CDKN2A and CDKN2B, which play an important role in the regulation of the cell cycle and proliferation of endothelial cells [7].

Previous studies have substantiated the potential protective role of CDKN2A/2B in VSMC proliferation and atherosclerotic changes. CDKN2A/2B belongs to the CDK inhibitor gene family and is considered to be a significant tumor suppressor gene [8]. The CDKN2A/2B gene comprises four exons, namely, 1α, 1β, 2, and 3, coding for two distinct proteins: P16INK4a (P16) and p14ARF (P14) and located at 9p21.3 [9]. The p21.3 band on the short arm of human chromosome 9 is broadly studied and many potential polymorphisms on this locus were linked to CAD. Specifically, human CDKN2B-AS1 gene polymorphism rs4977574 is linked to CAD onset [10]. Although this gene is located at the intron of the CDKN2A/2B gene, it has been proposed to have

a direct effect on the expression level of the CDKN2A/2B gene [11]. Although reported studies demonstrated the high prevalence of CDKN2B-AS1 gene rs4977574 polymorphism on CAD onset, there is still no commonly accepted consensus. Studies in Turkish [12] and Chinese [13] populations explored the significantly higher frequency of the G allele of the CDKN2B-AS1 gene rs4977574 polymorphism in myocardial infarction patients compared to controls, whereas the WTCCC study involving the British population showed lower G allele frequency [14]. We hypothesize this may be the result of ethnic background and, consequently any lifestyle differences of each population. Taizhanova D. et al showed a significant association of rs4977574 polymorphism in the Kazakh population (p-0.02). In this study, authors showed a significant association of four polymorphisms rs762551 (p=0.019), rs12976411 (p=0.011), rs2242480 (p=0.017), and rs4977574 (p=0.02) with CAD compared control groups [15]. However, the Bonferroni correction for multiple comparisons did not show any significant correlations in this study [15]. Although there is a lack of studies investigating on SNPs of 9p21.3 locus in the Kazakh population, other SNPs on other locus were studied. Karabayeva et al. showed a significant association of rs2407103, rs11775334, and rs2071518 polymorphisms on the 8th chromosome to myocardial and coronary artery remodeling [16]. Hua et al. showed significant relevance of the G allele of rs4977574 and the C allele of rs1333045 to CAD in the Chinese population, including Kazakh ethnic groups. The study included in total of 855 patients, where 598 patients with CAD and 297 were controls. In this study, high serum levels of apolipoprotein A (ApoA) were correlated with the AG + AA genotype of rs4977574 compared to those with the GG genotype (P=0.028) [13].

Role of CDKN2B antisense RNA 1 in CAD

The CDKN2A/2B gene is located approximately 100 kb apart from the chromosome 9p21 risk gene [17]. The p16 protein (p16INK4a), a member of the INK4 family, and p14arf are two proteins encoded from this region. The influence of p16 protein on CDK4 and CDK6 halts the transition of cells from the G1 phase to the S phase (Figure 1). Whereas the p14arf protein has a role in the activation of the p53 tumor suppressor [18]. Both proteins display widespread expression across various tissues and cell types and their somatic mutations are observed in cancer cells [19]. Suppression of cell proliferation and regulation of the cell cycle of VSMCs is one of the main mechanisms in atherosclerotic plaque formation leading to CAD. CDKN2B-AS1 gene rs4977574 polymorphism interacts with polycomb repressive complexes 1 and 2. Later leads to a decline in CDKN2A/2B expression [8,20]. Increased expression of the CDKN2B-AS1 gene upregulated in peripheral blood mononuclear macrophages carrying the G allele of the rs4977574 polymorphism has been shown [21]. Such increased expression may indicate increased cell proliferation, respectively, an increase in adhesiveness, and the appearance of atherosclerotic plaques. Another study showed that patients with CAD had reduced levels of CDKN2A and CDKN2B, again highlighting the association between this locus and CAD [17].

Other studies have shown statistically significant correlations between the level of transcription of CDKN2B-AS1 and the severity of coronary artery disease, this was justified by the fact that CDKN2B-AS1 affects the remodeling of the extracellular matrix and the modification of the vascular structure [22]. Qiao et al. showed a reliable correlation between the rs4977574 polymorphism and biomarkers, revealing a significantly increased risk of elevated HbA1c levels in individuals with the GG + GA genotype [23]. These data may indicate that rs4977574 may affect the function of pancreatic cells, and eventually lead to diabetes mellitus. Diabetes mellitus 2 increases the risk of coronary artery disease. Violation of glucose metabolism leads to the early development of coronary artery disease. It has been shown that transcription products of the CDKN2B-AS1 gene under the influence of risky SNP loci can regulate the expression of genes that are responsible for the metabolism of glucose and lipids in the blood, such as ADIPOR1, VAMP3, and C11ORF10 [24].

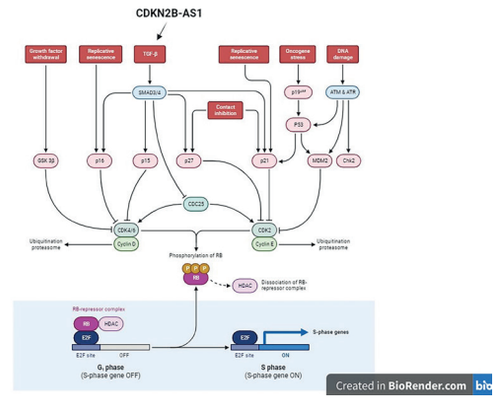

Figure 1 - Schematic representation of TGF-β signaling pathways regulated by CDKN2B-AS1 in EC and SMC. EC - endothelial cells; SMC- smooth muscle cells. Created in BioRender.com.

Huang et al. conducted a meta-analysis of the rs4977574 polymorphism in the CDKN2B-AS1 gene and its involvement in the severity of CAD. Since their case-control study deviated from the Hardy-Weinberg equilibrium (HWE), the results of the involvement of the rs4977574 polymorphism in the progression of CAD were questionable [25]. Another study showed similar results in an Asian population and confirmed the results of Huang et al., where the G allele was shown to contribute to an increased risk of CAD [26].

There were many studies conducted which are departed from HWE, although all of them showed a great association between rs4977574 polymorphism and CAD [25]. In the current understanding, rs4977574 polymorphism and CAD association should be analyzed categorizing participants into subgroups by ethnicity.

Conclusion

Despite all the existing evidence showing a significant association of rs4977574 polymorphism to CAD severity, further studies are needed to elaborate concrete mechanisms and discrepancies in different populations. Environmental factors differ in different ethnic groups, further studies are suggested to take this into account. Studies conducted among the Asian population certainly validate the potential relevance of rs4977574 polymorphism to CAD risk. However, there are very few studies published pertaining Kazakh ethnical group, therefore further studies are needed to elaborate on the significance of rs4977574 polymorphism to CAD in the Kazakh population.

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Pre-consultation history taking systems and their impact on modern practices: Advantages and limitations

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Abstract

The practice of gathering a patient's medical history has been a cornerstone of healthcare for centuries, providing the foundation for accurate diagnoses and effective treatment plans. However, traditional face-to-face consultations have limitations, including incomplete histories due to time constraints and potential communication barriers. To address these challenges, pre-consultation history taking systems emerged as a transformative solution, leveraging technology to optimize data collection and patient engagement. This review article explores the evolution, benefits, limitations, and impact of pre-consultation history taking systems on modern healthcare practices. These systems enable patients to respond to questionnaires or surveys before their scheduled appointments, empowering them to provide comprehensive medical histories at their own pace. Consequently, healthcare providers gain deeper insights into patients' health status, previous medical conditions, family history, lifestyle choices, and medication history. The significance of pre-consultation history taking lies in its potential to improve the quality of healthcare services. By obtaining more detailed and accurate medical histories before appointments, healthcare providers can optimize consultation time, enabling them to focus on addressing specific concerns and making informed decisions. Furthermore, patient engagement is enhanced, fostering a sense of collaboration between patients and healthcare professionals. Despite the advantages, the article addresses certain limitations, such as the digital divide and data accuracy concerns. Ensuring accessibility for all patient populations and maintaining robust data security measures are essential considerations. However, as technology continues to advance, pre-consultation history taking holds the promise of transforming the healthcare landscape and improving patient outcomes.

Keywords: pre-consultation history taking, telemedicine, telehealth, electronic consultation taking

Introduction

The acquisition of a patient's medical history has perennially stood as a pivotal element in healthcare, serving as the cornerstone for diagnostic processes and the formulation of treatment strategies. Traditionally, in face-to-face consultations with healthcare providers, patients would provide their medical history, but this method exhibited inherent limitations, including patients forgetting critical details, time constraints leading to incomplete histories, and potential communication barriers that could impact accuracy [1]. Furthermore, the improper sequencing of medical history and the introduction of fear or embarrassment during face-to-face interviews could contribute to distorted clinical assessments [1].

In recent years, technological advancements have revolutionized the process of gathering medical information, leading to the development of pre-consultation history taking systems. These systems offer patients the opportunity to respond to questionnaires or surveys before their scheduled appointments, allowing them to carefully consider and provide comprehensive details about their medical history [2]. The data collected through these platforms serves as a valuable resource for healthcare providers, furnishing them with profound insights into the patient's health status, previous medical conditions, family history, lifestyle choices, and medication history [3].

The significance of pre-consultation history taking systems lies in their potential to improve the quality of healthcare services. A study conducted in Japan evaluated the efficacy of a tablet-based pre-consultation history-taking system in optimizing appointment times for diabetic patients [4]. The results showed that the median pre-clinical time without a patient in a group of tablet-based questionnaire was 2 minutes and 45 seconds, while in a group of paper-based questionnaire, it was 5 minutes and 39 seconds (p=0.003). By obtaining a more detailed and accurate medical history prior to the patient's visit, healthcare providers can optimize the time spent during consultations. The same study demonstrated that the clinical time with a patient in a tablet-based group was 19 minutes and 37 seconds, while in paper-based group, it was 11 minutes 25 seconds (p=0.026) [4]. This efficiency empowers clinicians to concentrate on specific concerns, make well-informed decisions, and tailor personalized treatment plans. Additionally, these systems can facilitate a more patient-centered approach, empowering individuals to actively participate in their care and fostering a sense of collaboration between patients and healthcare professionals [4, 5].

The purpose of this article is to provide a comprehensive review of pre-consultation history taking systems and their impact on modern healthcare practices (Table 1). It seeks to delve into the advantages, challenges, and prospects of implementing such systems in clinical settings.

Table 1 Impact of pre-consultation history taking on healthcare.

Aspect	Key Points
Impact on Time Efficiency	• Tablet-based systems significantly reduce pre-clinical time before patient encounters. • Clinical time allocation is optimized for focused patient, leading to more in-depth consultations. • Studies show a notable reduction in consultation time with the adoption of tablet-based history-taking systems.
Evolution of History Taking	• Transition from face-to-face interviews to computerized history-taking systems. • Improved data collection through structured questionnaires or surveys completed by patients. • The history-taking process has evolved from manual entry to streamlined digital interactions.
Technological Advancements	• Integration of AI and NLP for efficient data analysis and interpretation. • Virtual triage assisting users in determining appropriate care levels, with a significant percentage finding it helpful. • The use of NLP applications in healthcare to interpret patient-reported data more effectively.

Evolution of history taking in healthcare

History taking during medical consultation mostly relies on direct, face-to-face interactions between patients and healthcare providers. Physicians typically conducted comprehensive interviews, employing open-ended questions to elicit information about symptoms, medical history, familial predispositions, lifestyle practices, and previous treatments [3]. This conventional approach was heavily dependent on the physician's expertise, communication skills, and ability to extract pertinent information from patients. However, inherent challenges such as patients forgetting crucial information, struggling to articulate complex medical details, or withholding sensitive information due to embarrassment or fear of judgment were prevalent [6-8]. The incompleteness of medical history information can lead to delays in clinical treatments as it plays a crucial role in the diagnostic and therapeutic decision-making process, thereby significantly impacting the quality of the diagnostic process [9, 10].

The traditional approach to history taking is time-consuming, imposing constraints on the number of patients a healthcare provider can effectively attend to within a given timeframe. The process of manually writing patient anamnesis into the medical practice system consumes a significant amount of consultation time for medical practitioners [3]. Furthermore, a report from ambulatory practice from USA reveals that approximately 53% of physicians' time is allocated to face-to-face interactions with patients in the examination room, leaving the remaining time for charting and desk work [11]. This highlights the substantial burden placed on the healthcare workforce due to non-examination tasks.

Emergence and development of pre-consultation systems

The emergence of digital technology prompted the healthcare industry to explore innovative approaches to enhance the history-taking process. Mayne and colleagues at the Mayo Clinic were pioneers in developing computerized history-taking programs, where patients were prompted to select their chief complaint from a predefined menu of complaints [12]. In a related study, Grossman et al. tested a similar clinical coverage program with a small group of in-patients, and the results demonstrated that computers recorded significantly more clinical information compared to physicians [13].

Subsequently, the system of history taking has evolved and improved significantly. Pre-consultation history taking systems empower patients to complete structured questionnaires or surveys before their scheduled appointments, enabling them to carefully consider their medical history and provide comprehensive responses [4]. This approach enables patients to furnish their medical histories at their own pace, thereby reducing the likelihood of overlooking crucial details.

The development of pre-consultation systems sought to enhance the accuracy and completeness of patient-provided information while optimizing the utilization of healthcare provider's time and reducing the burden of medical report documentation [14]. Healthcare providers could review the collected data before the consultation, enabling more informed and targeted discussions during the patient encounter. This approach served as a solution to address the challenges posed by limited physician time, concurrently maximizing the value of healthcare at a feasible cost [5].

Technological advancements and their role in shaping these systems

The evolution of pre-consultation history-taking systems has been significantly influenced by technological advancements, leading to the development of sophisticated and user-friendly platforms. Web-based questionnaires and mobile applications have become increasingly popular, catering to the convenience and preferences of patients in a digitally connected world [15, 16].

The integration of artificial intelligence (AI) and natural language processing (NLP) further streamlined these systems. AI algorithms can analyze patient responses, identify red flags, and prioritize critical information for healthcare providers, thereby facilitating efficient decision-making [17, 18]. AI is being applied in various medical tasks, including disease recognition, outcome prediction, and treatment. In the triage system, AI enhances decision-making and more accurately classifies patients based on symptoms, medical history, and other data. A multinational survey of patient utilization of triage system showed that in 75% of cases virtual triage assisted users in determining the appropriate care level [19]. Among 74.1% of participants, the recommended triage care differed from their initial healthcare intention, with 25.9% aligning their pre-triage intention with the virtual triage recommendation [19]. In addition, patient-facing NLP applications are under development in the healthcare domain. Natural language understanding (NLU) and natural language generating (NLG) chatbots are integral to these applications, with mobile phone applications and web platforms being the most commonly used means of interaction [20]. NLP capabilities empower systems to interpret patient-reported data, allowing for more contextually relevant follow-up questions and ensuring a personalized and time-efficient healthcare approach with improved predictive capabilities [21, 22].

The evolution of pre-consultation history-taking systems has been significantly influenced by technological advancements, leading to the development of sophisticated and user-friendly platforms. These innovative approaches have transformed the way medical information is collected, enhancing the quality of patient data, optimizing healthcare provider's time, and ultimately improving patient care and outcomes. Pre-consultation history taking systems have their own advantages and disadvantages (Figure 1).

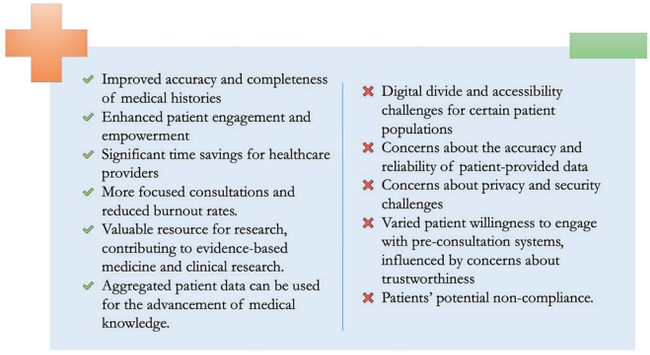

Figure 1 - Advantages and limitations of pre-consultation history taking systems.

Benefits and advantages

Improved accuracy and completeness of medical histories

Pre-consultation history taking systems play a crutial role in ensuring the accuracy and comprehensiveness of patients' medical histories. Incomplete information gathering during consultation can lead to diagnostic errors [23]. Clinicians are faced with the challenge of remembering numerous questions relevant to managing each medical condition and omitting crucial questions can significantly impact diagnosis and treatment outcomes. For instance, research reveals that approximately 50% of psychosocial and psychiatric problems go unnoticed [24], and a considerable portion of patient problems and concerns (54% and 45%, respectively) are not elicited by clinicians nor disclosed by patients [25].

The accuracy of diagnoses provided by physicians across various specialties ranges from 70% to 85% [26], while other research indicate that AI-based automated medical history-taking systems resulted in only 11% of diagnostic errors [27]. By providing patients with structured questionnaires, these systems guide individuals to provide relevant and detailed information about their health status, symptoms, and past medical conditions. This enhanced data collection results in a more precise and comprehensive medical history, reducing the likelihood of critical details being overlooked [2].

Zakim et al. (2021) conducted a study comparing the health records filled by physicians and computerized versions filled by the patients. The study was conducted in the emergency department and involved patients presenting with acute chest pain. The analysis revealed a lack of details in regard to the precise location of pain and its radiation in almost 50% of the records. In addition, the details in regard to alleviating factors and timing were different in those two types of records [28]. Although the data was collected from one hospital, the authors highlighted the advantages of standardized computerized historical records, not limited by human factors such as memory, expertise, and time devoted per case. The outcomes derived from the primary investigation assessing the impact of pre-consultation history-taking systems on healthcare administration, as employed in this manuscript, are delineated in Table 2.

Self-reported digital medical histories completed before visits can help foreigners with language barriers [32] or those with disabilities related to hearing or speech [33]. Furthermore, patients are more inclined to self-report sensitive information such as smoking or experiences of domestic violence [34]. This approach grants healthcare providers a more comprehensive understanding of the patient's health, ultimately enhancing diagnostic accuracy and facilitating more effective treatment decisions.

Enhanced patient engagement and empowerment

Active patient engagement is essential for improved health outcomes [29, 34]. The consensus is growing that patient engagement significantly enhances care quality and improves safety. When patients actively participate in their healthcare decisions and have a greater understanding of their conditions, treatment options, and preventive measures, it leads to better health outcomes and a safer healthcare experience [35]. Pre-consultation history taking systems empower patients empower patients to review and input their medical information at their convenience, fostering a sense of ownership and involvement in their care [36, 37]. This increased engagement often leads to higher patient satisfaction, better adherence to treatment plans, and a stronger patient-provider relationship.

Timesaving for healthcare providers

One of the most significant advantages of pre-consultation history taking systems is the time-saving aspect for healthcare providers. At the Congress of European Society of Cardiology, it was noted that doctors express concerns about spending increasing amounts of time dealing with computers and paperwork, which leaves them with less time for direct patient interaction and practicing medicine [38]. A Polish technology company, Infermedica, which develops a platform for digital medicine, reports that pre-visit interviews increase for 39% the

Table 2 Impact of Pre-Consultation History-Taking Systems on Healthcare Management

Study	Authors	Title	Year	Objective/ Purpose	Methodology	Key findings
1	Melms L, Schaefer JR, Jerrentrup A, Mueller T.	A pilot study of patient satisfaction with a self-completed tablet-based digital questionnaire for collecting the patient's medical history in an emergency department [1]	2021	The main objective of the study is to assess the effectiveness of a tablet-based questionnaire for non-urgent patients in the emergency department	The research employed a pilot study conducted in the waiting area of the central interdisciplinary emergency department of Marburg University Hospital. The participants were recruited through convenience sampling, approaching individuals randomly after the initial emergency triage and before their first contact with a physician. There were three questionnaires: 1 - demographic data, 2 - medical history, 3- user experience	86% of patients completed the questionnaires 91.9% had prior digital device experience. Computer skills varied, influencing completion time. High satisfaction and usability were reported Nearly all patients expressed confidence in using the digital questionnaire again. 91.7% trusted the data security. Positive impressions were reported by 93.0%, with 87.2% favoring digital questionnaires in the future.
2	Nishida A, Ogawa O.	The Effect of a Pre-consultation Tablet-Based Questionnaire on Changes in Consultation Time for First-Visit Patients With Diabetes: A Single-Case Design Preliminary Study [4]	2022	The study aims to assess the impact of pre-consultation tablet-based medical questionnaires completed by first-visit patients with diabetes in the waiting room on the consultation time with and without patients, exploring potential improvements in efficiency and time management in diabetes outpatient care.	The study employed a crossover design where paper- and tablet-based questionnaires were alternately used for diabetic patients visiting a physician at Kameda Medical Center. The medical questionnaire covered various aspects of diabetes history, lifestyle factors, and past medical information. Clinical time, pre-clinical time without a patient, post-clinical time without a patient, total clinical time, and total clinical time without a patient were measured using specific definitions, providing a comprehensive analysis of consultation times and efficiency.	20 patients participated in the study: 10 in the paper-questionnaire group, 10 in tablet-based questionnaire group Pre-clinical time without a patient was significantly shorter in tablet group (5:39 min vs 2:45 min, p = 0.003) Clinical time with a patient was significantly higher in tablet-based group (11:25 min vs 19:37 min, p = 0.026) Pre-consultation tablet-based questionnaires decreased the time spent on non-face-to-face medical care prior to consultations and increased the time spent face-to-face.
3	Harada Y, Shimizu T.	Impact of a commercial artificial intelligence–driven patient self-assessment solution on waiting times at general internal medicine outpatient departments: retrospective study [14]	2020	The main objective of the study is to assess whether the implementation of an AI-based automated medical history-taking device, AI Monshin, in lieu of handwritten self-administered questionnaires, can effectively reduce waiting times in a community hospital general internal medicine outpatient department.	The study employed a retrospective observational design, utilizing data from outpatients who visited the Department of General Internal Medicine at Nagano Chuo Hospital. Patients who visited the hospital between April 1, 2017, and April 16, 2020, were included in the study. The introduction of the AI Monshin tool, a tablet-based system for collecting patient data, was implemented on April 17, 2019. The primary outcome was the median waiting time per patient, and secondary outcomes included the median waiting time per month.	The study included data from 21,615 patient visits, with 15,000 visits before and 6,615 visits after the implementation of AI Monshin. The median waiting time was not significantly different between the two groups: 74.3 min before implementation, and 74.4 min after implementation In a supplemental analysis of data from 9054 of 21,615 visits (41.9%), the median examination time after AI Monshin implementation (6.0 minutes) was slightly but significantly longer than that before AI Monshin implementation (5.7 minutes) (p = 0.003). The implementation of an artificial intelligence–based, automated medical history–taking system did not reduce waiting time for patients visiting the general internal medicine outpatient department without an appointment, and there was a slight increase in the examination time after implementation

4	Gellert GA, Orzechowski PM, Price T, Kabat-Karabon A, Jaszczak J, Marcjasz N, et al.	A multinational survey of patient utilization of and value conveyed through virtual symptom triage and healthcare referral [19]	2023	To describe the use patterns, impact and derived patient-user value of a mobile web-based virtual triage/symptom checker.	Online survey of 2,113 web-based patient-users of a virtual triage/ symptom checker was completed over an 8-week period. Questions focused on triage and care objectives, pre- and post-triage care intent, frequency of use, value derived and satisfaction with virtual triage. Responses were analyzed and stratified to characterize patient-user pre-triage and post-triage intent relative to triage engine output.	During the study period, 93.9% of the 2,113 survey respondents using the virtual triage engine did so for themselves, with no incentives offered. The main motivations for using virtual triage were: to determine the need for a physician visit (44.2%), secure medical advice without visiting a physician's office (21.0%), or confirm/differ a diagnosis (14.2%). Virtual triage recommendations often differed from patients' pre-triage healthcare intentions; 74.1% had different recommendations, while 25.9% matched. The tool increased the likelihood of users changing their minds about the acuity level of care, with 51.2% changing to consulting a physician, 5.3% to an emergency department, and 20.7% to engaging in self-care. Virtual triage significantly increased the number of patients recommended for telemedicine or virtual consultations, from 16% pre-triage to 28% post-triage. Overall patient satisfaction with virtual triage was high, with 80.1% indicating they were likely or highly likely to use the application again.
5	Palermo TM, Valenzuela D, Stork PP.	A randomized trial of electronic versus paper pain diaries in children: impact on compliance, accuracy, and acceptability [25]	2004	The aim of this study was to compare two formats of a prospective daily diary (handheld computer=e-diary; paper diary=p-diary) on children's compliance, accuracy, and acceptability ratings.	Sixty children, ages 8–16 (M=12.3) with headaches or juvenile idiopathic arthritis, were randomized to receive either electronic diaries administered via home visits (n=30) or paper-based diaries (n=30) handed out during clinic visits for return by mail.	Children using electronic diaries (e-diaries) completed significantly more days of diary entries (M=6.6) compared to those using paper diaries (p-diaries) (M=3.8), indicating higher engagement with the e-diary format. Diaries returned by children in the p-diary group had significantly more errors and omissions compared to e-diaries, which had none, highlighting the greater accuracy of electronic diaries. Both diary formats were highly acceptable and easy to use according to children's ratings. A significant gender×diary format interaction was found for compliance, with boys demonstrating greater compliance with the e-diary format.
6	Kawamura R, Harada Y, Sugimoto S, Nagase Y, Katsukura S, Shimizu T.	Incidence of Diagnostic Errors Among Unexpectedly Hospitalized Patients Using an Automated Medical History–Taking System With a Differential Diagnosis Generator: Retrospective Observational Study [27]	2022	This study aimed to assess the incidence of diagnostic errors in an outpatient department, where an artificial intelligence (AI)–driven automated medical history–taking system that generates differential diagnosis lists was implemented in clinical practice.	The study employed a retrospective observational approach, using data from a community hospital in Japan. Patients aged 20 and older who utilized an AI-driven medical history–taking system were included, focusing on those with unplanned hospitalizations within 14 days of the index visit. The primary endpoint was the incidence of diagnostic errors, assessed by independent reviewers using the Revised Safer Dx Instrument. The study compared diagnostic error rates between cases where the AI system generated the final diagnosis and those where it did not, utilizing the Fisher exact test, and further explored contributing factors for confirmed errors through reviewer discussions.	Out of 150 cases using AI Monshin, 146 were analyzed. Most patients were elderly (median age 71 years). Among the cases, the final diagnosis was confirmed for 94.5% of patients. Diagnostic errors were confirmed in 11.0% of cases. The incidence was significantly higher in patients aged 65 and older (16% vs 2% in those under 65 years). Common contributing factors for diagnostic errors included problems ordering diagnostic tests, issues with data integration and interpretation, problems with the physical exam, and misinterpretation of performed tests. AI Monshin listed the final diagnosis in the differential diagnosis list in 7% of cases with diagnostic errors. Physicians made incorrect initial diagnoses in 6% of cases. Diagnostic errors resulted in harm in 88% of cases, with no deaths or permanent harm. Two cases (13%) required intervention, and 12 cases (75%) led to initial or prolonged hospitalization.

7	Kneuertz PJ, Jagadesh N, Perkins A, Fitzgerald M, Moffatt-Bruce SD, Merritt RE, et al.	Improving patient engagement, adherence, and satisfaction in lung cancer surgery with implementation of a mobile device platform for patient reported outcomes [29]	2020	The objective for this study was to understand the utility of a mobile application (App) platform to engage patients whilst gathering data on patient compliance, perioperative experience and satisfaction. Patient satisfaction was further examined through measures such as the ability to reach a provider and their perspective on the usefulness of the App.	Patients with suspected lung cancer undergoing robotic resection between January–May 2019, were offered the SeamlessMD App, which was customized to meet requirements of the thoracic enhanced recovery pathway. The App guided patients through preoperative preparation, in-hospital recovery, and post-op discharge care with personalized reminders, task lists, education, progress tracking, and surveys.	Fifty patients participated in the study. Among the participants, 40% completed the preoperative compliance survey, and 62% completed the hospital satisfaction survey. Postoperative health-checks were completed by 54% of patients, with a median of 3 completed surveys per patient. Patients reported a significant decrease in maximum pain level (P=0.002) and anxiety scores (P<0.001) up to 30 days after surgery. The app-enabled health-checks improved confidence and decreased worries in over 80% of patients. About 40.9% reported that the health-checks helped avoid one or more calls, and 18.2% reported that the app helped avoid one or more visits to the hospital. Over 74% of patients reported the app as very or extremely useful in each of the preoperative, inpatient, and post-discharge settings.
8	Jamal F, Zouaghi O, Leroux PY, Staat P, Garrier O, Sanchez I, et al.	Can digital pre-consultation save medical time and improve outcome in cardiology? [30]	2019	The study aimed to analyze the patient's risk profile before the medical appointment, to estimate the average time saved for each consultation, and to test whether this data could modify the medical decisions.	A web-based interface allowed patients to report their data and calculate a risk score. Seventy five patients were included. The total list of questions was composed of 48 items. The referent cardiologist timed the duration of each questionnaire and reported if the early analysis of patient's information would change the healthcare path (identification of an emergency or a need for an additional test prior to consultation).	The study involved patients with an average age of 54 years, of which 63% were male. On average, patients completed 56% of the total questions, taking approximately 5 minutes and 10 seconds for each questionnaire. Digital pre-consultation significantly reduced the time required for each medical examination, potentially freeing up 160 hours of extra medical time per cardiologist per year for 1800 consultations. Early data analysis identified 27% of patients who would benefit from additional tests prior to consultation, potentially influencing the care path and prognosis. This included 5 patients with suspected coronary disease.
9	Montazeri M, Multmeier J, Novorol C, Upadhyay S, Wicks P, Gilbert S.	Optimization of patient flow in urgent care centers using a digital tool for recording patient symptoms and history: simulation study [31]	2021	The main objective of the study is to evaluate the potential impact of introducing a patient self-symptom and history-taking app in an urgent care center (UCC) through a system simulation approach, aiming to reduce waiting times, decrease crowding, and enhance overall system efficiency compared to the addition of staff.	A discrete-event approach was used to simulate patient flow in a UCC during a 4-hour time frame. The baseline scenario was a small UCC with 2 triage nurses, 2 doctors, 1 treatment/ examination nurse, and 1 discharge administrator in service. We simulated 33 scenarios with different staff numbers or different potential time savings through the app. We explored average queue length, waiting time, idle time, and staff utilization for each scenario.	Introducing an additional nurse reduced the queue length for triage nurses by around 60% but led to an approximately 75% increase in the queue length for doctors. Adding an extra doctor resulted in a 67% increase in the mean idle time of doctors. Adding one extra triage nurse led to a 336% increase in triage nurses' idle time and a 44% decrease in the doctor's idle time. The median triage nurses' utilization dropped from 96.9% in the baseline case to 40.5% with the addition of one extra triage nurse. The time-saving impact of the symptom and history-taking app was equivalent to adding one triage nurse, reducing patient queue length for triage by 25.73% with 2.5 minutes per patient time savings. Waiting time for a triage nurse dropped by 54.88% when maximum app time saving was modeled.

operational efficiency of medical centers by reducing the number of unnecessary visits, improving quality of consultations, and saving the time of doctors from bureaucratic tasks [39]. Another platform, Bright.MD, outlines that their telehealth solution can reduce the administrative burden of doctors up to 2 minutes per visit and save 13 minutes of consultation for physical assessment and clinical decision-making process [40].

By having patients complete questionnaires before their appointments, healthcare providers can focus on interpreting the collected data and addressing specific concerns during the consultation. This streamlined process eliminates the need for spending a considerable amount of time during the appointment solely on history-taking, allowing physicians to allocate more time to critical medical assessments and personalized patient care. The study of Jamal and colleagues revealed that patients spend approximately 5 minutes and 10 seconds on pre-consultation questionnaires, which save 160 hours of cardiologist's work in a year [30]. Regarding patient wait time, Montazeri et al. in 2021 found that saving 5 minutes per patient can decrease patient wait time by half [31]. Reduced patient wait time can also improve patient satisfaction, and consequently, their compliance and rapport [31]. Pre-consultation history taking systems reduce documentation burden and give doctors more time with patients, potentially reducing burnout rates among medical specialists [41, 42].

Supporting evidence-based medicine and research

The digitalization of healthcare has introduced new perspectives in medical research. Nowadays, electronic health records have emerged as an asset, empowering researchers to access a wide range of comprehensive and diverse information, enabling them to conduct in-depth analyses and gain insights into various healthcare phenomena [43, 44]. Similarly, the comprehensive data collected through pre-consultation history taking systems can serve as a valuable resource for evidence-based medicine and clinical research. By aggregating anonymized patient data from diverse populations, researchers can analyze trends, identify risk factors, and highlight disease patterns [45]. The wealth of information collected through these systems contributes to the advancement of medical knowledge and the development of more effective treatment protocols.

Limitations

While pre-consultation history taking systems offer numerous benefits, they are not without limitations. Understanding these constraints is crucial for healthcare institutions and providers looking to implement such systems effectively (Figure 1).

Digital divide and accessibility

Pre-consultation systems relying on digital technology may pose challenges for certain patient populations. The rapid adoption of digital health technologies may inadvertently leave certain populations behind, particularly those who do not regularly use the internet or mobile devices, such as older adults, individuals in low-income regions, and those in remote areas with limited internet connectivity [46, 47]. Limited access to smartphones, computers, or internet connectivity may hinder their ability to participate, potentially exacerbating health disparities [48]. As the healthcare industry advances technologically, it is essential to address these inequalities and ensure that pre-consultation history taking systems are accessible and inclusive for all segments of the population, regardless of their age, income, or geographic location.

Usability of the system by hospitals

Limitations of pre-consultation history taking systems include challenges related to their usability by doctors and their implementation in healthcare facilities. Despite the availability of patient-provided data, some doctors might still opt to repeat the same questions during the consultation, potentially raising doubts about the accuracy and reliability of the information, and the quality of the collected data [49]. Digital apps also cannot read body language and can ask irrelevant questions, decreasing their usability for both doctors and patients [50].

The meta-analysis evaluating studies reporting digital systems collecting medical history before the hospital visit indicated that the majority of studies lack information on the usability of systems in real life. Despite being implemented and used in clinical practice, several barriers hinder the widespread use of digital systems. For instance, integration of systems takes time and effort, and there is no common and united system for reporting the information collected for medical records. Additionally, given the absence of evidence demonstrating improved health outcomes, physicians may not be inclined to adopt these technologies [51]. These factors could contribute to doctors' hesitation in fully embracing and utilizing these systems in their clinical practice, highlighting a potential barrier to widespread adoption.

Data accuracy and reliability

The accuracy and reliability of patient-provided data depend on the patients' understanding of medical terminology and their ability to recall and report relevant medical information [3]. Alongside pre-consultation questionnaires, up to 60% of electronic records may contain inaccuracies or omissions, encompassing errors in patients' diagnoses, medical history, medications, allergies, test results, procedures, contact information, and appointment details [52]. The inaccuracies can pose significant challenges to healthcare providers, potentially leading to incorrect treatment decisions, compromised patient safety, and hindrances in delivering optimal care. Therefore, the outputs of pre-consultation history taking systems should be considered as a tool for preparing patients, serving not only as a guide for facilitating discussions with the doctor but also as a comprehensive overview of the patient's condition for the physician.

Privacy and security concerns

Collecting and storing sensitive patient information electronically raises privacy and security concerns. Healthcare institutions must ensure robust data protection measures to safeguard patient data from unauthorized access, breaches, or cyberattacks [53, 54]. The protection of patients' data requires expensive antivirus software [55]. This additional cost burden places financial strain on healthcare institutions and organizations involved in data collection, as they must allocate resources to ensure the security and confidentiality of patient information. As a result, healthcare costs may increase to maintain robust patient and data security measures, prioritizing the protection of sensitive health records and preserving patient trust in the healthcare system. Balancing the need for data security with cost-effective solutions remains a significant challenge for the healthcare industry as it strives to uphold the highest standards of patient privacy and cybersecurity [54].

Patient engagement and compliance

Not all patients may be willing or motivated to complete pre-consultation questionnaires, leading to incomplete data or limited engagement with the system. Patients frequently do not utilize digital health tools as mobile apps and pre-consultation history taking platforms [56]. The review of patients' perspectives on health apps and platforms identified four reasons for non-compliance: lack of trustworthiness, appropriateness, personalization, and accessibility [57]. Main concerns regarding such apps and platforms can be related to privacy and security. Some apps request sensitive information for optimal performance, and certain apps enable providers to share personal data and findings through the app. Patients express worries about app security, data visibility, and the possibility of data breaches [58, 59]. Accessibility of the digital health system can be another factor influencing compliance. Some research identified that patients faced challenges with app connectivity and encountered user interface issues. This frustration was particularly common among older adults and the elderly, who often have poor eyesight and lower digital literacy compared to other age groups [60-62]. Additionally, many elderly patients may have no interest in improving their digital skills for this purpose [63].

In the evolving landscape of healthcare, the integration of digital innovations, particularly pre-consultation history-taking systems, has shown substantial benefits. However, it is crucial to acknowledge and address the preferences of specific patient demographics, notably the elderly and individuals experiencing loneliness, who may prioritize direct human interaction in their healthcare experiences [64]. These patients may often need not only medical assistance but also social connection and may prefer visiting healthcare facilities for human-to-human communication. While pre-consultation systems significantly contribute to efficiency, diagnostic accuracy, and patient engagement, they may not fully cater to the social and emotional aspects of healthcare-seeking behavior, particularly in this demographic.

Conclusion

In conclusion, the evolution of pre-consultation history taking systems has brought numerous benefits and advancements to modern healthcare practices. By enabling patients to provide comprehensive medical histories before their appointments, these systems improve the accuracy and completeness of patient data, enhancing diagnostic accuracy and treatment decisions. Moreover, they foster patient engagement and empowerment, leading to better patient-provider collaboration and improved health outcomes. The timesaving aspect for healthcare providers allows for more focused consultations, reducing burnout rates among medical specialists.

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An examination of retinal findings with optical coherence tomography in hypothyroidism patients with vitamin D deficiency: A comparative study

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Abstract

Aim: This study aimed to examine the retinal layer before and after treatment in patients with hypothyroidism with vitamin D deficiency, since the vitamin also protects the retinal cells against inflammatory damage.

Material and methods: The free T3, free T4, and vitamin D levels of 104 patients with no ocular disease were first measured. Ophthalmological examinations of these patients, who were divided into three groups, were performed by specialist ophthalmologists, while retinal findings were examined using optical coherence tomography (OCT) and recorded. The first group was given vitamin D for three months, the second levothyroxine, and the third vitamin D + levothyroxine. After three months repeat OCT was performed, and the results were compared with the previous values.

Results: The thickness of the left inner nuclear cell layer of the patients in the vitamin D group increased significantly compared to pre-treatment. Post-treatment right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular, and left inner nuclear cell layer thicknesses were all significantly higher compared to pre-treatment in the patients in the levothyroxine + vitamin D group, while right outer retinal layer and left retinal nerve fiber thicknesses decreased ($p<0.05$).

Conclusion: A greater increase in cell layer thickness was observed in the group using vitamin D and levothyroxine together compared to those in which vitamin D and levothyroxine were employed alone. However, further studies on the effect of vitamin D on retinal cell development and protection against injury are now needed.

Keywords: Hashimoto's thyroiditis, hypothyroidism, optical coherence tomography, retina, vitamin D

Introduction

The most frequent cause of hypothyroidism, a disease caused by insufficient synthesis and/or release of thyroid hormones, is Hashimoto's thyroiditis (HT). This was first described in 1912 and is the most frequently encountered autoimmune thyroiditis in the general population. The disease emerges through the interaction of environmental (30%) and genetic (70%) factors [1]. Genetic factors include immune regulator genes, major histocompatibility genes (HLA), and thyroid-specific genes (Tg and TSHR) [2]. Environmental factors include smoking, alcohol use, iodine intake through diet, stress, selenium and Vitamin D deficiency, bacterial and viral infections, pregnancy, and medications [1,2]. Although HT is generally asymptomatic, some patients describe a sensation of heat, tightness, and pain in the neck [3]. Hypothyroidism is present in approximately 20% of patients at the time of diagnosis [4]. In contrast to other vitamins, Vitamin D is regarded as a hormone since it is synthetized in the body. It is known to affect bone

metabolism and Ca balance in the body. Studies have maintained that vitamin D can exhibit potentially protective effects in several human diseases, including various types of cancer, cardiovascular diseases, kidney and muscle diseases, hypertension, and type 2 diabetes mellitus [5-12]. Vitamin D exhibits neuroprotective and neuromodulatory effects, and is associated with several diseases that affect the central nervous system, such as Alzheimer's [13].The effects on the retina of vitamin D deficiency and hypothyroidism have been investigated separately in several studies [14,15]. However, we encountered no previous studies evaluating retinal findings with optic coherence tomography (OCT) in patients with hypothyroidism accompanying vitamin D deficiency and the relationship between these findings and vitamin D deficiency.

The purpose of this study was to investigate ophthalmological examination findings and retinal findings determined using optical coherence tomography, and the effect of the addition of vitamin D to hypothyroidism treatment on retinal cell layers in hypothyroid patients with vitamin D deficiency detected at the internal medicine clinic.

Material and methods

Setting and participants

One hundred four patients meeting the inclusion criteria between 01.06.2021 and 01.12.2021 were included in the study. Patients aged over 18 and meeting the inclusion criteria, with hypothyroidism and vitamin D deficiency, with no chronic disease, not receiving Vitamin D therapy, with no retinal disease, and with no corneal, lens, or vitreous opacity that might prevent OCT being performed were referred to the eye diseases clinic once their free T3, free T4, TSH, and vitamin D levels had been measured and recorded. The patients were divided into three groups, one receiving levothyroxine alone, one receiving vitamin D alone, and a third receiving combined levothyroxine and vitamin D. Routine ophthalmological examinations and visual acuity evaluations were performed by specialist ophthalmologists in the eye diseases clinic, and biomicroscopic examinations were also performed. Retinal images were than captured in a non-interventional manner using a Spectralis-OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) device in the eye diseases clinic. Ophthalmological findings and retinal layer thicknesses calculated from images obtained using an ACT device were recorded. The three groups were invited to attend check-ups after three months of treatment. Full participation was achieved, and no patient loss occurred. Retinal layer thicknesses were again recorded using OCT.

Statistical analysis

The research data were analyzed on SPSS (Statistical Package for the Social Sciences) version 23.0 software. In addition to descriptive methods such as number and percentage calculations and arithmetic mean, the Kolmogorov-Smirnov test was applied to evaluate normality of distribution. The paired t test and One-Way ANOVA (Tukey's test for post hoc) were used to compare normally distributed variables between the groups. The results were expressed at a 95% confidence interval, with p values <0.05 being regarded as statistically significant.

Results

The participants' descriptive characteristics

The mean age of the patients in the study was 48.46±11.57 years (min 22, max 73), 68.3% were women, 33.7% had a chronic disease, and 34.6% used levothyroxine + vitamin D therapy. Fifty percent of patients had severely low vitamin D levels (Table 1).

Table 1 The participants' descriptive characteristics (n=104)

Characteristic	n	%
Sex		
Female	71	68.3
Male	33	31.7
Chronic disease		
Yes	35	33.7
No	69	66.3
Vitamin D level		
Severely low	52	50.0
Moderately low	52	50.2
Group		
Levothyroxine	33	31.7
Vitamin D	35	33.7
Levothyroxine+Vitamin D	36	34.6
Age (Mean±SD)	48.46±11.57 (min. 22, max. 73)	

Retinal cell layer values before and after treatment in the study groups

No statistically significant associations were observed between retinal cell layer measurements and T3 levels among the different treatment groups (p>0.005). However, T3 levels differed significantly depending on the type of treatment (p<0.001). Advanced analysis performed to identify the group in which this difference appeared revealed significantly higher T3 levels in the levothyroxine group than in the other two groups. Examination of TSH levels in terms of type of treatment revealed significantly higher values in the levothyroxine + vitamin D group compared to the levothyroxine only group.

Right outer retinal cell layer thicknesses in the levothyroxine group decreased significantly compare to pre-treatment.

In the vitamin D group, left inner plexiform layer and left retinal nerve fiber thicknesses decreased compared to pre-treatment, while a significant increase was determined in left inner nuclear cell layer thickness compared to pre-treatment.

Significant increases were determined post-treatment in terms of right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular thickness, and left inner nuclear cell layer thickness compared to pre-treatment values in patients in the levothyroxine +vitamin D group, while right outer retinal layer and left retinal nerve fiber thicknesses decreased (p<0.005) (Table 2).

A comparison of the patients' pre- and post-treatment Vitamin D levels

Significant differences were determined between the levothyroxine, Vitamin D, and levothyroxine+ Vitamin D groups' pre-treatment Vitamin D levels (p<0.001) (Table 3).

A comparison of the patients' pre- and post-treatment Vitamin D levels in the study groups

Post-hoc analysis applied to identify the group from which the difference derived showed that pre-treatment Vitamin D levels were significantly higher in the levothyroxine group than in the other two study groups. However, no significant variation in post-treatment Vitamin D levels was observed among the groups.

Vitamin D levels increased significantly after treatment compared to pre-treatment levels in the levothyroxine, Vitamin D, and levothyroxine+ Vitamin D groups (p<0.001) (Table 4).

Table 2 Retinal cell layer values before and after treatment in the study groups

	Levothyroxine groupa Mean±SD	Vitamin D groupb Mean±SD	Levothyroxine+ vitamin D groupc Mean±SD	p*
Right central macular thickness (Before) Right central macular thickness (After) p**	271.51±31.02 273.45±25.84 0,319	266.14±25.91 268.28±22.95 0.106	266.70±26.00 269.03±23.09 0.012	0.382 0.374
Right nerve fiber layers (Before) Right nerve fiber layers (After) p**	11.54±3.44 12.18±2.05 0.321	11.80±3.35 12.42±2.67 0.104	11.47±2.76 12.55±2.48 0.029	0.903 0.799
Right ganglion cell layer (Before) Right ganglion cell layer (After) p**	14.72±8.04 13.66±3.75 0.497	15.22±9.17 14.37±6.44 0.491	13.33±4.54 13.19±2.61 0.858	0.555 0.552
Right inner plexiform cell layer (Before) Right inner plexiform cell layer (After) p**	19.06±6.48 19.12±3.22 0.958	19.85±6.47 20.00±4.70 0.882	17.86±3.97 19.38±3.04 0.071	0.340 0.609
Right inner nuclear cell layer (Before) Right inner nuclear cell layer (After) p**	19.66±8.05 19.87±3.45 0.878	19.40±7.47 18.74±4.03 0.586	17.52±5.34 18.44±3.78 0.362	0.383 0.259
Right outer plexiform cell layer (Before) Right outer plexiform cell layer (After) p**	26.76±9.24 25.78±3.58 0.546	26.94±6.66 27.42±5.62 0.697	26.19±7.99 26.05±5.20 0.919	0.919 0.333
Right outer nuclear cell layer (Before) Right outer nuclear cell layer (After) p**	87.87±11.71 93.06±8.03 0.019	86.74±13.71 89.28±9.90 0.205	87.16±13.53 91.61±8.72 0.040	0.937 0.217
Right pigment epithelial layer (Before) Right pigment epithelial layer (After) p**	16.60±4.28 16.66±1.45 0.941	15.54±2.63 16.31±1.45 0.086	15.27±1.56 16.22±1.74 0.011	0.161 0.466
Right inner retinal layer (Before) Right inner retinal layer (After) p**	182.72±33.92 181.36±13.91 0.830	179.42±29.02 178.31±19.30 0.794	175.25±21.19 181.19±14.22 0.100	0.549 0.673
Right outer retinal layer (Before) Right outer retinal layer (After) p**	87.72±4.77 85.30±4.23 0.041	85.94±4.69 85.40±3.92 0.592	86.69±3.83 85.05±4.30 0.042	0.257 0.937
Right retinal nerve fiber thickness (Before) Right retinal nerve fiber thickness (After) p**	99.06±11.56 100.96±10.61 0.261	101.54±7.64 99.40±6.48 0.061	98.94±9.17 97.44±8.52 0.248	0.442 0.243
Left central macular thickness (Before) Left central macular thickness (After) p**	269.87±28.45 273.60±10.70 0.463	263.65±19.83 269.71±16.14 0.052	261.58±17.13 269.72±12.80 0.020	0.279 0.394
Left nerve fiber layer (Before) Left nerve fiber layer (After) p**	13.15±7.83 12.09±1.89 0.469	11.68±2.17 11.77±2.17 0.812	12.16±2.22 11.50±2.14 0.319	0.406 0.501
Left ganglion cell layer (Before) Left ganglion cell layer (After) p**	13.66±4.78 12.63±1.98 0.249	12.91±3.39 13.08±2.79 0.726	13.18±3.75 12.55±3.29 0.499	0.721 0.688
Left inner plexiform layer (Before) Left inner plexiform layer (After) p**	19.60±6.87 17.48±2.20 0.106	18.80±3.23 17.82±2.99 0.040	18.00±3.65 17.36±2.88 0.363	0.386 0.759
Left inner nuclear cell layer (Before) Left inner nuclear cell layer (After) p**	19.78±7.18 21.24±4.23 0.305	17.40±4.62 20.34±4.53 0.001	18.33±5.67 21.61±4.53 0.009	0.249 0.470
Left outer plexiform cell layer (Before) Left outer plexiform cell layer (After) p**	27.51±8.41 27.12±3.58 0.801	26.14±6.24 27.20±3.76 0.275	26.77±6.69 26.16±4.74 0.679	0.732 0.497
Left outer nuclear cell layer (Before) Left outer nuclear cell layer (After) p**	89.00±12.30 92.87±10.91 0.136	91.20±11.07 92.28±11.26 0.646	85.72±11.39 93.02±11.52 0.001	0.139 0.958
Left pigment epithelial layer (Before) Left pigment epithelial layer (After) p**	16.96±6.89 15.30±2.44 0.218	16.34±5.15 15.48±2.20 0.337	15.52±1.64 15.41±2.23 0.818	0.487 0.947
Left inner retinal layer (Before) Left inner retinal layer (After) p**	181.45±27.46 182.42±15.67 0.842	176.91±20.14 180.68±15.67 0.233	174.11±17.49 179.63±13.77 0.081	0.380 0.703
Left outer retinal layer (Before) Left outer retinal layer (After) p**	86.51±7.50 84.63±4.32 0.247	86.31±4.95 85.31±5.20 0.364	85.83±3.68 85.63±4.03 0.817	0.870 0.651
Left retinal nerve fiber thickness (Before) Left retinal nerve fiber thickness (After) p**	96.12±14.08 95.15±9.41 0.647	100.14±8.02 96.31±7.05 0.007	97.02±10.87 93.63±9.12 0.025	0.299 0.423
T3	3.86±0.87	3.12±0.55	3.16±0.77	<0.001 a>b, a>c
T4	10.75±3.16	9.85±1.84	9.57±2.00	0.112
TSH	7.86±3.89	10.97±5.94	11.58±6.39	0.015 c>a

* One-way ANOVA, ** paired t test

Table 3 A comparison of the patients' pre- and post-treatment Vitamin D levels

Vitamin D	Mean±SD	p
Pre-treatment	13.92±5.84 (min.0, max.24)	<0.001
Post-treatment (3-months)	29.89±8.79 (min.13, max.88	

Table 4 A comparison of the patients' pre- and post-treatment Vitamin D levels in the study groups

	Levothyroxine groupa	Vitamin D groupb	Levothyroxine+ Vitamin D groupc	p
Pre-treatment	20.27±2.62	11.25±4.88	10.71±3.90	<0.001* a>b, a>c
Post-treatment	30.08±5.42	28.94±11.80	30.65±7.98	0.713*
P	<0.001**	<0.001**	<0.001**	

* One-way ANOVA, ** paired t test

Discussion

One of the environmental factors involved in the etiology of hypothyroidism is vitamin D deficiency [2]. Vitamin D has been shown to suppress the inflammatory cascade in the region between the retinal pigment epithelium and the choroid and to protect the retinal cells against inflammatory injury [16]. Decreased central retinal thickness measured using OCT in individuals with no disease has been found in subjects with vitamin D deficiency. In addition, an association has been found between vitamin D deficiency and decreased vision [17]. The findings of the present study suggest that vitamin D deficiency can give rise to thinning in specific retinal cell layers in hypothyroid patients. However, a significant increase was observed after treatment, particularly in the group receiving combined levothyroxine and vitamin D.

All members of the patient group in this study were hypothyroid, and thinning was determined in specific layers at initial examination. TSH levels were higher in the group using levothyroxine+vitamin. Ulas et al. compared the blood values and OCT findings of patients with chorioretinitis and a control group and determined high TSH values and a thinner choroid and retinal cell layer at OCT in the group with chorioretinitis. They therefore concluded that that thinning occurs in the cell layer in individuals with hypothyroidism [18].

Right outer retinal layer thicknesses in this study decreased significantly in the patients in the levothyroxine group compared to pre-treatment. Ozturk et al. examined the OCT findings of patients with primary hypothyroidism at one, three, and six months and reported no significant change in the thickness of the retinal nerve fiber layer after treatment compared to pre-treatment [19]. Yu et al. compared patients with thyroid-related ophthalmopathy and healthy volunteers and determined a thinner retinal nerve fiber layer in the ophthalmopathy group [20].

The thicknesses of the left inner plexiform layer and left retinal nerve fibers in this study decreased in the vitamin D group compared to pre-treatment, while left inner nuclear cell layer thickness increased significantly compared to pre-treatment. Fjeldstad et al. also determined no association between decreased retinal nerve fiber layer thickness or macular volume and Vitamin D deficiency in multiple sclerosis patients with no findings of optic neuritis [21]. These findings may be due to sampling differences.

Epidemiological studies recently showed an association between low 25-hydroxyvitamin D (25-OH-D) concentrations and impairment of visual acuity [22]. A positive association has also been reported between Vitamin D deficiency and age-related macular dysfunction [23-26].

Ozturk and Cankaya (2020) compared a group with vitamin D deficiency and a group with normal vitamin D levels and observed that deficiency produced adverse effects on contrast sensitivity function and also a difference in thickness in some segments of the retinal layers [27].

Statistically significant post-treatment increases in right central macular thickness, right nerve fiber layer, right outer nuclear cell layer, right pigment epithelial layer, left central macular, and left inner nuclear cell thicknesses compared to pre-treatment were observed in the group receiving levothyroxine + vitamin D. However, no significant increase was observed in the cell layers in the group receiving levothyroxine only. Link et al. examined the OCT retinal findings and visual acuity of a patient with vitamin D, vitamin A, and vitamin B6 deficiency before and after treatment and determined severe pre-treatment thinning in the inner plexiform layer and the ganglion cell layer, and vision impairment. However, an improvement in vision and increased thickness in the cell layers were determined after treatment [28].

Left inner nuclear cell layer thickness increased significantly in the present study in the group receiving vitamin D only. Another study involving a quantitative evaluation of retinal structure parameters in children with vitamin D deficiency compared retinal nerve fiber layer, central macula, retinal layer, and choroid thicknesses and structural retinal parameters including the central retinal artery and central retinal vein between the vitamin D deficiency group and healthy volunteers. The findings revealed choroidal thinning, a decreased central retinal artery diameter, and an increased central retinal vein diameter in the vitamin D deficiency group [29].

Robredo et al. investigated the effect of vitamin D against oxidative stress and inflammation in retinal pigment epithelium and retinal endothelial cell series and determined a decrease in proinflammatory cytokine and interleukin levels with the addition of vitamin D to treatment. This also suggests that Vitamin D exhibits anti-inflammatory effects [30]. In another study, Ekinci et al. showed that vitamin D3 [1.25 (OH) 2] exhibited an ameliorating effect against oxidative damage in retinal cell layers. At the same time, those authors reported that vitamin D represented an effective therapeutic alternative in the prevention of age-related macular degeneration [31].

Conclusion

The findings of this study suggest that changes occur in the retinal cell layers of hypothyroid patients. This research investigated the development of hypothyroidism, a condition mostly of autoimmune origin, as a result of vitamin D deficiency deriving from environmental factors and the relationship between vitamin D deficiency and retinal cell damage. The increase in the thickness in some retinal cell layers in the group receiving vitamin D therapy only was found to be statistically significant. However, an increase in thickness was observed in more cell layers in the group using vitamin D and levothyroxine in combination. This suggests that vitamin D levels should be measured in hypothyroid patients, and that appropriate doses and lengths of treatment should be administered in cases in which these levels are low. The number of studies on this subject is limited. However, we think that more significant results can be obtained with longer follow-up and treatment and larger sample numbers in the future.

Research limitations: One particular limitation of the study is that it was conducted in a single center.

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Evaluation of thoracic paravertebral block for pain relief in rib fractures

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Abstract

Introduction: Fracture of ribs causes severe pain which in turn activates the cascade of respiratory compromise. Pain management with regional blocks is considered one of the promising techniques. Thoracic paravertebral block (TPVB) is a proven technique considered at par with epidural analgesia. But its blind landmark-based technique has a potential risk of pneumothorax. Ultrasound gives advantage of real time visualization which decreases complications and enhance its success rate. So, we conducted this study to gauge the efficacy and utility of ultrasound guided thoracic paravertebral block.

Material and methods: Twenty patients were administered TPVB under ultrasound guidance with 15 milliliters of 0.25 % inj bupivacaine and 2 mg per kg fentanyl who had multiple rib fractures of unilateral hemithorax. For prolonged pain relief a catheter was left in place to administer recurring boluses. The parameters noted were superior costotransverse ligament (SCTL), skin to SCTL distance, skin to pleura distance, VAS at rest & at cough, respiratory rate arterial blood gas parameters at various time intervals.

Results: Thoracic paravertebral space was easily identified in each patient with ultrasound. We discovered significant pain relief in terms of VAS score at rest & at cough at different time intervals. Respiratory rate and arterial blood gas parameters improved with the use of ultrasound guided thoracic paravertebral block.

Conclusion: Sonographic out of plane sagittal thoracic paravertebral block is a successful technique in rib fracture patients to provide effective pain relief and also ameliorates respiratory rate and oxygenation.

Keywords: ultrasound, pain relief, rib fracture, thoracic paravertebral block

Introduction

Majority of rib fractures are consequence of road traffic accidents, and it results in 10 % of total trauma hospitalization. It is an important indicator of severe injury resulting in increased morbidity and mortality [1].

Multiple rib fractures can cause severe pain, which in turn limits the respiratory functions. The mainstay of treatment is to manage pain, airway, oxygenation, intravascular volume support and tube thoracostomy and infection control [2].

Different methods of pain management include nonsteroidal anti-inflammatory agents, narcotics, intercostal nerve blocks, intrapleural catheters and thoracic epidural. NSAIDS and narcotics are rarely effective during the acute phase. Intercostal nerve blocks require frequent repetitions. Thoracic epidurals pose a risk of haemodynamic instability[3].

Thoracic paravertebral block (TPVB) leads to somatic motor and sensory blockage of multiple thoracic dermatomes in ipsilateral hemithorax above and below the block site. Moreover, its analgesic efficacy is equivocal to epidural analgesia [4].

Multiple approaches have been described to the paravertebral space; ultrasound guided paravertebral block is popular now a days due to real time sonographic visualization compared with traditional technique. Due to limited literature availability, we conducted this study with the aim to estimate the efficacy and effectiveness of ultrasound guided out of plane sagittal approach of thoracic paravertebral block in unilateral rib fracture patients for pain relief.

Material and methods

This prospective randomized study was conducted in Department of Anaesthesia and Critical Care at Pt BDS PGIMS, Rohtak. All procedures performed were within the ethical standards and formal ethical approval was obtained from the institutional board for the same. After written informed consent a total of 20 patients of age group 18 to 75 years who suffered from blunt trauma chest and had unilateral hemithorax fracture ribs with visual analogue score (VAS) $\geq$ 3 received ultrasound guided thoracic paravertebral block. Those who had local

site infection, liver and kidney disease, coagulation disorder and patients who refused to participate in study were excluded.

Routine investigations including haemoglobin, bleeding and clotting time, X ray chest and electrocardiography were done. The number of rib fractured, arterial blood gas analysis and respiratory rate were noted. All the participating patients were explained about the use of Visual analogue score (VAS). VAS was noted at rest and at cough. The ability to cuff and breathe deeply was noted and graded as one - no difficulty, two -mild difficulty, three - moderate difficulty and four who had severe difficulty.

The thoracic paravertebral block was performed in preoperative area. Intravenous access was established and midazolam 2 mg/kg and fentanyl 2 µg/kg were administered. Monitoring included ECG, Spo2 and non-invasive BP. After cleaning and draping of thoracic vertebral, paravertebral area and the ultrasound probe, Initial ultrasound scanning of required vertebral and paravertebral region was done. Patient position was either sitting or lateral according to patients convenience with affected side up.

Site of injection was chosen two segment below the most cephalad fractured rib.

Linear ultrasound probe of 6-13 MHz probe (Sonosite M Turbo) was used for all sonographic assessments. The appropriate thoracic level was identified by cephalad to caudal ultrasound scanning starting from first rib onwards. Afterwards the spinous process and the transverse process of the appropriate thoracic vertebrae and the rib were identified. The midpoint of the transducer was placed in a longitudinal paramedian plane between two transverse processes of chosen vertebral level. Both transverse processed were visualized with the superior costotransverse ligament (SCTL) and the pleura in between (Figure 1).

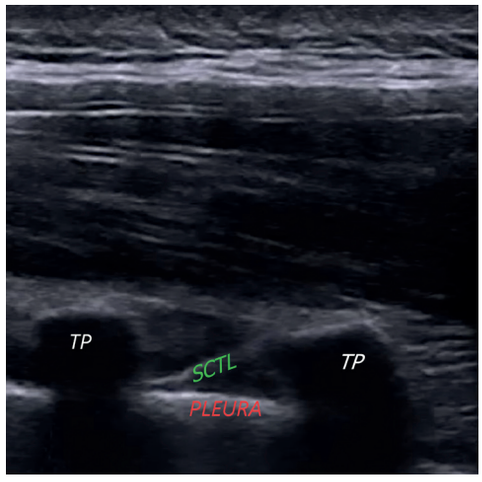

Figure 1 - Ultrasonographic anatomy for thoracic paravertebral block

The image was frozen and the distance of transverse process to the skin was noted.

The following measurements were noted at the appropriate vertebral levels.

i) Ultrasound appearance of the SCTL in percentage visibility [5]:

1	No visibility	0 % Visibility
2	Poor	<25 % Visibility
3	Moderate	26-50 % Visibility
4	Good	51-75 %Visibility
5	Excellent	>75 % Visibility

ii) Skin to SCTL distance in mm from lateral border of upper transverse process.

iii) Skin to pleura distance in mm from lateral border of upper transverse process.

An 18 G needle was introduced using out of plane technique. The tip of the needle was advanced under direct visualization till it pieces the SCTL. 5 ml of bupivacaine 0.25% was injected after negative aspiration, while the spread of local anaesthetic and simultaneously anterior pushing of the pleura was observed (Figure 2).

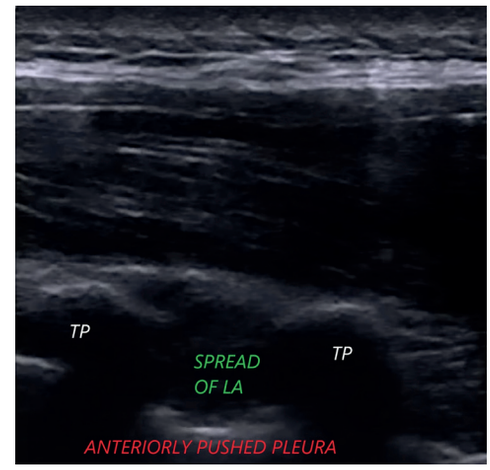

Figure 2 - Thoracic paravertebral block with spread of local anaesthetic and anteriorly pushed pleura

Afterwards an additional 10 ml bupivacaine 0.25% with one µg per kg of fentanyl was injected. A catheter was threaded 2-3 cm into the paravertebral space after the block and was secured with adhesive dressing. The threading of the catheter was graded as easy, some resistance, difficult and not possible. The distance travelled by needle was noted.

Haemodynamic parameters were noted at 3 minutes interval for the first 15 minutes up to 45 minutes. Block was defined successful at loss of cold sensation in greater than or equal to three homolateral dermatomes.

VAS was evaluated at rest and at cough on baseline, 1st hour, 2nd hour, 4th hour, 8th hour, 24th hour, 36th hour, 48th hour, 60th and 72th hour post procedure. If VAS $\geq$ 3 patient were administered 15 ml of 0.25% bupivacaine with 1 µg per kg fentanyl with lock in period of 4 hours. Total number of top-ups doses were noted. During the study if VAS $\geq$ 3 even after top-ups i.v. inj tramadol 100 mg was given as rescue analgesic. Patients were actively stimulated to perform deep breathing exercises. Arterial blood gas analysis was done on day 2 and 3. Catheter was removed after 72 hours.

Discussion and Results

Our study was a male dominated study where 95% of patents were males with a mean age of 47±15.61 years. The mean number of ribs fractured were 3±0.56. Road side trauma was the cause of injury in all the patients. Patients characteristics are depicted in Table 1.

Table 1 Patients' characteristics

Age (Mean ±SD)	47±15.61
Range	18-83 years
Sex (F/M)	1 (5%) / 19 (95 %)
Number of rib fractures (Mean ±SD)	3±0.56
Site involved (Left/Right)	9 (45 %) / 11(55 %)

The technical parameters are depicted in Table 2. Block was performed at T5-T6 in 9 patients and T3-T4 in 6 patient. Superior costotransverse ligament visibility was excellent in seven patients and it was graded as good in thirteen patients. The mean depth from skin to SCTL was 2.99±0.51 cm (range 2.32 4.1 cm). Grade of catheter insertion was easy in ten patients while some resistance was faced in seven patients and it was impossible in three patients.

Table 2 Technical parameters of block

Technical Parameters	
Level of thoracic paravertebral block T2-T3 T3-T4 T4-T5 T5-T6	 3 (15 %) 6 (30 %) 2 (10%) 9 (45%)
Mean depth of Needle insertion (Range 2.8- 4.2 cm)	3.42±0.44 cm
Visibility of SCTL Excellent Good	 7 (35%) 13(65 %)
Distance between skin to transverse process (Range 1.45-3.91 cm)	2.32 ± 0.65 cm
Distance between skin to parietal pleura (Range 3.04-4.4 cm)	3.66± 0.42 cm
Skin to SCTL distance (Range 2.3-4.1 cm)	2.99± 0.51 cm
Grading of catheter insertion Easy Some resistance encountered Not possible	 10 (50%) 7 (35 %) 3 (15 %)

Significant augmentation in pain score was observed both at rest and at cough ($p<0.001$) during different time intervals when matched to baseline (Figure 3).

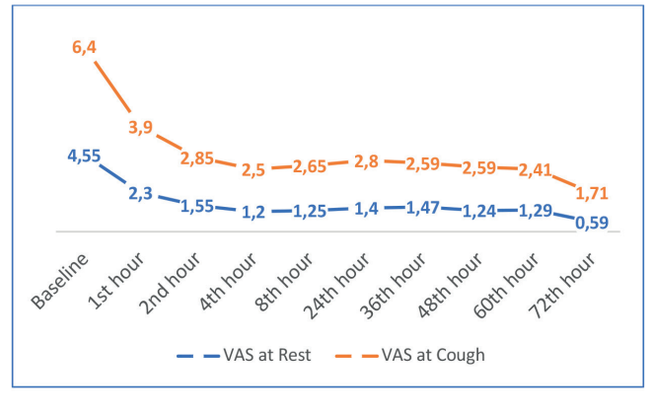

Figure 3 - Comparison of VAS at rest and VAS at cough from baseline

Respiratory function recovered significantly with decrease in respiratory rate ($p<0.001$) as shown in Figure 4. Blood gas analysis shows significance of Po2 and oxygen saturation at 48 and 72 hours compared to baseline as depicted in Table 3. While mean PaCo2 and pH did not alter much after initial block.

Ability to breathe and cough deeply. Twelve patients had severe difficulty in breathing and eight patients had moderate difficulty in breathing which improved after block, although mild difficulty persisted in few patients as shown in Figure 5.

Table 3 Mean of arterial blood gas analysis at day 1, day2 and day 3.

	Day 1	Day 2	Day 3	P value
pH	7.40±0.10	7.42±0.03	7.41 ±0.04	0.549
Po2 in mm Hg	77.45±24.59	89.82±25.76*	95.96±20.71*	<0.001
PCo2 in mm Hg	40.54±7.08	37.58±5.31	38.77±3.96	0.354
HCo3 in mmol/L	25.41±5.52	25.92±1.76	26.06±2.45	0.991
Spo2 in %	87.66±5.78	91.76±2.63**	92.64±1.93**	0.004

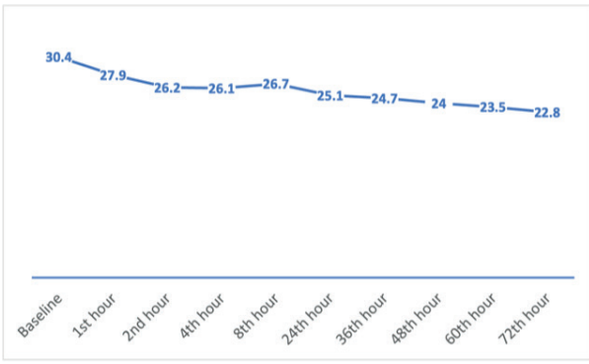

Figure 4 - Mean comparison of respiratory rate from baseline

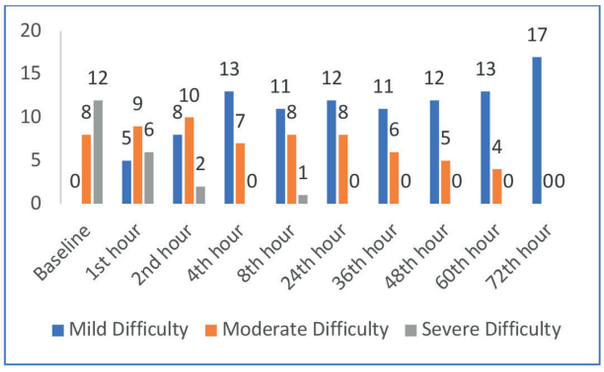

Figure 5 - Ability to breathe and cough deeply

Discussion

TPVB commensurate with epidural analgesia in terms of abatement of pain relief with fewer complications [6,7]. The improvement in pain scores, respiratory functions in our study is similar to Mohta et al who used classical landmark guided approach for paravertebral block [4].

In our study we had improvement in respiratory functions and oxygenation till 3 days after continuous paravertebral block, our results are like Karmakar et al who assessed efficacy of continuous infusion of bupivacaine for pain management in unilateral multiple fracture using blind technique [8].

Out of 20 patients catheter insertion was easy in 10 patients (50%), with some resistance 7 (35%) and it was not possible in 3 (15%) patients which can be either due to narrow thoracic paravertebral space or impediment of catheter into endothoracic fascia and these results are similar to Rianin etal [9] and Luyet et al's cadaveric study [10].

An out of plane technique used in our study which had lower needle penetration depth when compared to in plane technique. Once the needle tip penetrated with SCTL and local anaesthetic was administered, the spread of drug was confirmed by the anteriorly pushed pleura.

The ultrasound appearance of SCTL, skin to pleura distance in our study is comparable to the study by Marhofer et al [11] who used out of plane technique for TPVB at T3 and T6 levels in patients with mastectomy.

The use of ultrasound gives great assistance to determine needle insertion site and depth of paravertebral space. Due to superficial location of paravertebral space, TPVB is apt for sonographic assistance. Hence it should be preferred over loss of resistance technique and additional of using ultrasound is avoidance of pleural puncture.

The fundamental step to achieve a successful TPVB using ultrasound guidance by sagittal approach is correct identification of superior costo transverse ligament and pleura. Factors which compromise successful performance in intercostal approach include blood in intercostal space or presence of subcutaneous air due to pneumothorax. During the procedure the practitioner must always view the tip of needle to prevent inadvertent pleural puncture. Small saline infiltration may help in needle localization.

Limitation of study

Absence of control group, pulmonary functions were not evaluated in detail. More studies are required to assess the effectiveness of the sonographic technique as compared to the conventional loss of resistance technique.

Conclusion

Ultrasound guided thoracic paravertebral block using sagittal approach in out of plane technique is an easy and applicable method of providing significant pain relief in patients with rib fractures which also helps to improve respiratory functions and oxygenation. The benefit of using ultrasound helps in guidance of needle and visualize the depth of insertion hence prevents the chances of inadvertent pleural puncture.

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Can chest computed tomography be useful to emergency residents in the diagnosis of COVID-19 pneumonia?

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Abstract

Aim: During the novel coronavirus disease (COVID-19) pandemic, the workload of emergency department residents (ER) has increased since emergency departments (EDs) are among the first health units to which patients apply. The aim of this study was to investigate the diagnostic value of chest computed tomography (CT) interpretations of emergency department residents in the diagnosis of COVID-19 pneumonia.

Material and methods: Patients who admitted to the tertiary ED between 30.03.2020 and 30.12.2020 with suspected COVID-19 pneumonia and underwent chest CT imaging were retrospectively analyzed. Chest CT images previously reported by the radiologist were reinterpreted by the ER and the diagnostic performance of the ER for COVID-19 pneumonia was calculated.

Results: The study included 2045 patients with suspected COVID-19 pneumonia. Chest CT images of all patients were interpreted and compared by a radiologist and the ER In this study, interpretation by a radiologist was considered as the gold standard. In all patients, the diagnostic performance capacity of ER for COVID-19 pneumonia included a low sensitivity of 66%, a high specificity of 92%, a positive predictive value (PPV) of 83% and a negative predictive value (NPV) of 82%. When patients with positive COVID-19 RT-PCR test results were analyzed, the highest sensitivity, specificity, PPV and NPV of ER were 96%, 82%, 95%, 95% and 86%, respectively.

Conclusion: ER detected COVID-19 pneumonia in COVID-19 (+) patients with high diagnostic value and excluded inconsistent findings. Chest CT interpretation in the ER has a high diagnostic value. It is as important as any other radiologist in outbreak management in the ED.

Keywords: chest computed tomography, emergency department, emergency resident interpret

Introduction

The novel coronavirus disease (COVID-19), which causes acute respiratory syndrome coronavirus-2 (SARS-CoV-2), caused an epidemic that started in Wuhan, China, and affected the whole world [1]. While the effects of the pandemic were not completely finished, emergency departments (ED) of hospitals were often the first unit where patients encountered the healthcare system during this process.

COVID-19 is an infectious disease with a high incidence and infectivity with a poor prognosis, causing 81% mild, 14% severe, and 5% critical illness, resulting in sepsis and multi-organ failure [2]. Although the epidemiology and clinical features of the disease have been widely described, there are no specific reports on the clinical course and virus spread of COVID-19 patients with mild to moderate symptoms. Therefore, early diagnosis of the disease is important to reduce the risk of community spread and ensure prompt treatment [3-7].

In the initial months of the pandemic and during the pandemic control process, the broad spectrum of new clinical symptoms, the detection of variant viruses and the need for inexpensive, rapid, highly sensitive and specific diagnostic tests have been prioritized. During this period, COVID-19 pneumonia had to be detected

quickly and the decision to hospitalize or discharge patients had to be made as quickly as possible, due to the increased volume of patients in ED. Chest Computed Tomography (CT) is typically used to detect COVID-19 pneumonia with peripherally located ground-glass pulmonary infiltrates. Rapid and accurate interpretation of chest CT is critical in helping to identify patients who will be discharged or followed up and treated as inpatients. A study about the role of chest CT in the diagnosis and management of COVID-19 showed that chest CT has a low rate (3.9%) of missed diagnoses and is a useful method for rapid diagnosis and outbreak management [8]. In light of all this information, this study aimed to investigate the diagnostic value of chest CT interpreted by the emergency department residents (ER) in the diagnosis of COVID-19 Pneumonia.

Materials and methods

Study design

This study was designed as a retrospective observational study. Approval for the study was obtained by the local ethics committee of our institution with decision number KAEK-149. The records of all patients who admitted to the third-level ED between March 30, 2020 and December 30, 2020 and underwent chest CT imaging were reviewed. All patients aged ≥18 years who underwent COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) test and chest CT imaging with suspected COVID-19 pneumonia were included in the study. All patients with missing RT-PCR data and those who underwent chest CT imaging for other reasons were excluded (Figure 1).

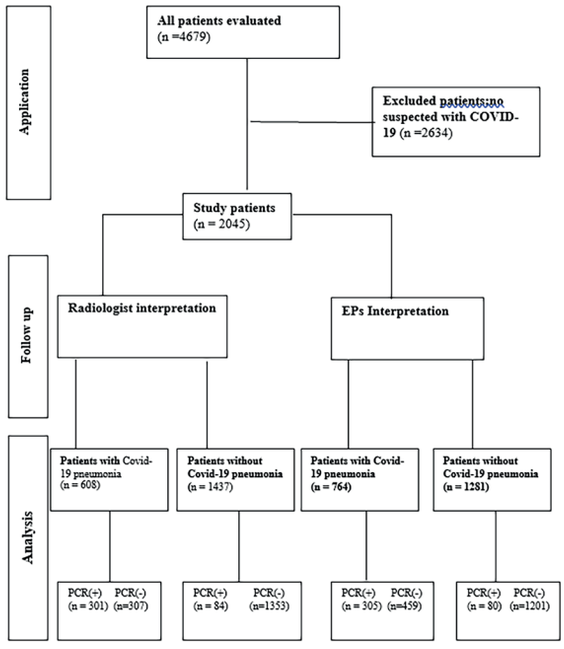

Figure 1 - Study flow chart.

All CT images were interpreted by an expert radiologist at our institution and recorded as a report in the hospital's patient record management system. Chest CT images previously reported by the radiologist specialist were considered the gold standard and compared with ER interpretation of COVID-19 pneumonia. All chest CT images, were re-interpreted by 21 postgraduate-year (PGY) 2-4 and 19 PGY 0-2, for a total of 40 ERs whose were randomized, blinded to radiology reports. Emergency medicine education is given on a regular, full-day basis every Tuesday by academic staff. The post-graduate training programs prepared annually and consisted theoretical and bedside practical training on radiological imaging. This education was given to each ER who was included in the study at least one season a year. For radiologic evaluation, the findings in the CORADS (COVID-19 Reporting and Data System) classification, which evaluates the suspicion of pulmonary involvement of Covid-19 developed by the Dutch Society of Radiology, were used [9]. According to this, chest CT images were classified as follows: CORADS 0-1 "non-pathologic radiologic findings", CORADS 2-3 "pathologic findings incompatible with Covid-19 pneumonia" and CORADS 4-5 "pathologic findings compatible with Covid-19 pneumonia" and recorded in the study protocol form.

Data collection and measurement of variables

Vital signs, complaints and other socio-demographic data of the patients were retrospectively analyzed and recorded via the electronic patient file system at the time of admission to the ED. The results of RT-PCR tests performed on nasopharyngeal swab samples were reviewed according to the Republic of Turkey Ministry of Health SARS-CoV-2 infection COVID-19 pneumonia diagnosis and treatment guidelines. Patients with positive RT-PCR test results were diagnosed with COVID-19. Whole chest CT imaging with Toshiba ACTIVION 16 (TSX-031A, Japan) and multislice chest CT scan were performed in the emergency department.

Statistical analysis

All variables were evaluated using descriptive statistics. Statistical analyzes were performed with SPSS 25 (Statistical Package for Social Sciences) and MedCalc statistical software. Normality analysis was performed with the Kolmogorov-Smirnov test. Numbers and percentages are reported for all categorical variables, and mean, standard deviation and median values are reported for continuous variables. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive odds ratio (PLR), negative odds ratio (NLR) and Kappa (K) coefficients of ER were calculated for the diagnosis of COVID-19 pneumonia based on radiology chest CT reports. Agreement was graded according to the coefficient. (K) greater than 0.75 was considered excellent agreement. A range of 0.75 to 0.40 was considered moderate agreement, and below 0.40 was considered poor agreement [10]. Chi-Square test was used to compare categorical data. $p<0.05$ was considered statistically significant.

Results

A total of 4679 patients who admitted to the emergency department and underwent chest CT were evaluated during the study. After excluding 2634 patients according to the exclusion criteria, 2045 patients with suspected COVID-19 were included in the study (Figure 1). 1206 (59%) patients were male. The mean age of all patients was 59.84±17.45 years. Dyspnea was the main complaint in 932 (45.5%) patients admitted to the ED. Other demographic data of the patients are shown in Table 1.

Chest CT radiologic images of patients diagnosed with COVID-19 were interpreted by ERs and radiologists and the results were compared. In CTs evaluated by ERs, COVID-19 pneumonia findings were detected in 764 (37.4%) patients, non-COVID-19 findings in 933 (45.6%) patients and non-pathologic results in 348 patients. In chest CT images interpreted by radiologists, 608 (29.7%) patients had COVID-19 pneumonia findings, 1147 (56.1%) had non-COVID-19 findings, and 290 (14.2%) had non-pathologic results. When the interpretations of

Table 1 Baseline characteristics of patients

Patient Characteristic	
Age (years) (mean±SD)	59.84±17.45
Male gender n(%)	1206 (59)
Main compliant n(%)	
Dyspnea	932 (45.5)
Fever	624 (30.5)
Cough	495 (24.2)
Sore troat	112 (5.4)
Chest pain	106 (5.1)
Diarrhea	102 (4.9)
Fatigue	93 (4.5)
Genaralizated pain	55 (2.6)
Vomiting	35 (1.7)
Loss of taste or anosmia	27 (1.3)
Vital signs at ED admission, median (min-max)	
Heart rate (beat/min)	100 (55-228)
Respiratory rate	22 (4-60)
SBP (mm/Hg)	130 (60-238)
DBP (mm/Hg)	76 (30-165)
Temperature (°C)	36.8 (34.1-41.9)
SpO2	95 (32-100)
SpO2: Oxygene saturation; DBP, diastolic blood pressure; ED, emergency department; SBP, systolic blood pressure.	

Table 2 Assessment of all patients with Chest CT by ERs and radiologist for the diagnosis of COVID-19 pneumonia

	ERs interpretations	Radiologist interpretations	Kappa Value	p
Covid-19 pneumonia	764 (37.4)	608 (29.7)	0.610	<.001
Non Covid-19 findings	933 (45.6)	1147 (56.1)	0.470	<.001
Non-pathological results	348 (17)	290 (14.2)	0.562	<.001
Total	2045	2045		

CT: Computed Tomography; **EPs:**Emergency residents; **COVID-19:** Coronavirus disease 2019

Table 3 Assessment of PCR positive patients with Chest CT by ERs and radiologist for the diagnosis of COVID-19 pnemonia

	ERs interpretations	**Radiologist interpretations**	**Kappa Value**	**p**
Covid-19 pneumonia	305 (95.1)	301(78.2)	0.799	<.001
Non Covid-19 findings	57 (4.6)	63 (16.4)	0.605	<.001
Non-pathological results	23 (17)	21 (5.5)	0.518	<.001
Total	385	385		

CT: Computed Tomography; **ERs:**Emergency residents; **Covıd-19:** Coronavirus disease 2019

ERs and radiologists were compared, a statistically significant difference was found between the two groups (p<.001). COVID-19 RT-PCR test results were analyzed for the definitive diagnosis of the patients. Chest CT images of patients with positive COVID-19 RT-PCR tests were interpreted and compared by radiologists and ERs. Among the patients evaluated by ERs, 305 (95.1%) had COVID-19 pneumonia findings, 57 (4.6%) had non-COVID-19 findings, and 23 (17%) had non-pathologic results. Among patients who were evaluated by radiologists, 301 (78.2%) had COVID-19 pneumonia findings, 63 (16.4%) had non-COVID-19 findings, and 21 (5.5%) had non-pathologic results. When the interpretations of ERs and radiologists were compared, a statistically significant difference was found between the two groups (p<.001).

The interpretation of radiologists was considered the gold standard. In all patients, the diagnostic performance ability of ERs for COVID-19 pneumonia was low sensitivity 66%, high specificity 92%, positive predictive value (PPV) 83% and negative predictive value (NPV) 82%. In patients with positive COVID-19 RT-PCR test results, ERs had the highest sensitivity, specificity, PPV, and NPV of 96%, 82%, 95%, and 86%, respectively (Table 4).

Table 4 Accuracy of the interpretation of ERs about Chest CT in the diagnosis of COVID-19

	Sensitivity	**Specifity**	**PLR**	**NLR**	**PPV**	**NPV**
All patients with Covid-19 pneumonia	66	92	8	0.3	83	82
Covid-19 PCR (+) pneumonia	96	82	5	0.04	95	86

CT: Computed Tomography; **PPV:** positive predictive value; , **NPV:** negative predictive value **PLR:** Positive Likelihood Ratio; **NLR:** Negative Likelihood Ratio; **Covıd-19:** Coronavirus disease 2019

Discussion

The results of the study were found to be significant since there is no study in the literature showing the diagnostic efficiency of the ER for COVID-19 pneumonia in chest CT. Chest CT interpreted by the ER is beneficial in the ED for the management of the COVID-19 epidemic, especially for patients with positive COVID-19 RT-PCR result in university hospitals in which crowded emergency services are present.

Previous studies have shown that chest CT performs well in the diagnosis of COVID-19 pneumonia, according to the review of the literature [11, 12]. It was reported in a prospective study conducted with 319 suspected COVID-19 patients in the ED that chest CT had a sensitivity, specificity, PPV and NPV of 90.2%, 88.2%, 84.5% and 92.7%, respectively, based on initial RT-PCR results [13]. Similar to our study with 135 COVID-19 RT-PCR positive patients, another study investigating the diagnostic performance of chest CT by radiology residents found a high diagnostic accuracy, specificity, PPV and NPV of 97.22%, 88.89%, 90.91% and 96.55%, respectively [14]. A rapid diagnosis is essential while waiting for RT-PCR results in crowded EDs facing the COVID-19 pandemic. In a study that was conducted in an ED, the diagnostic performance of chest CT in triage of symptomatic patients with suspected COVID-19 was shown to have a high sensitivity of 99%, specificity of 76%, PPV of 90% and NPV of 97%, similar to our study [15]. In another study with 287 definite positive patients among 694 patients in multicenter EDs during the COVID-19 pandemic, chest CT was shown to have high diagnostic performance with 90.2% sensitivity, 88% specificity, 84.1% PPV and 92.7% NPV [16]. Although chest CT has high sensitivity in patients with suspected COVID-19

pneumonia, it may cause specificity problems when overlaps with the findings of other viral pneumonia agents [17]. In this study, we also examined the diagnostic performance of chest CT in RT-PCR-confirmed COVID-19 patients and showed that it has higher specificity. Indeed, from previous studies, Bai et al., reported in a retrospective study with 213 positive COVID-19 patients, that chest CT differentiated COVID-19 pneumonia from viral pneumonia with high specificity and moderate sensitivity. In a study of W. Guan et al., pathological findings were found in 2.9% of chest CT imaging of RT-PCR-positive COVID-19 patients with severe disease [7]. The differences in elapsed time may be due to the presence of similar CT findings with other viral agents. Therefore, the American College of Radiology and SIRM (Società Italiana di Radiologia Medica e Interventistica) recommended that chest CT should not be used as a primary diagnostic screening tool in the radiological management of COVID-19, but can be used in suspected symptomatic patients with clinical indications or positive COVID-19 patients [19]. In the related literature, there are some studies evaluating the effectiveness of chest CT as a COVID-19 diagnostic screening tool. When the full texts of 28 studies were reviewed and 4486 patients were evaluated, it was shown in one review that a total of 3164 patients had positive chest CTs and 3014 had positive PCR results. Results from this review suggest that chest CT should not be used as a screening tool but can be used in inpatients and symptomatic patients [20]. Therefore, the recommendations in the guideline for radiological management have been confirmed by the conducted studies.

In light of all this, this study showed that ER has low sensitivity for diagnosing COVID-19 pneumonia on chest CT in all patients with suspected COVID-19, but high specificity for excluding the diagnosis of COVID-19. In COVID-19 patients who were RT-PCR positive, ER was found to have high sensitivity and specificity on chest CT and diagnostic value for COVID-19 pneumonia.

Limitations

This study has some limitations. First, this study was retrospectively designed and the number of RT-PCR positive patients was relatively small. The second important limitation was that only the registered data of patients with RT-PCR test results from the hospital electronic file system were included in the study. Therefore, the radiologic findings on chest CT at admission of patients with missing RT-PCR results are unknown. In addition, since the clinical duration of pneumonia was not known, only chest CT scans at admission were interpreted and some patients may not have had radiologic pneumonia findings.

Conclusion

In conclusion, this study showed that ER has sufficient diagnostic value and knowledge to diagnose COVID-19 pneumonia using chest CT in patients with suspected COVID-19 for epidemic management.

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Comparative effectiveness-safety of conventional versus newer antiepileptics in epileptic patients in a tertiary care hospital, India

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Abstract

Background: As initial monotherapy, individuals with epilepsy are treated with both conventional and newer antiepileptic drugs (AEDs). The differences in their relative effectiveness and safety as a group, however, have not been thoroughly studied.

Objective: To evaluate and compare the effectiveness and safety of conventional and newer anti-epileptic drugs in epileptic patients.

Material and methods: A prospective comparative study was done in 126 epileptic patients. Patients divided into two groups Group A and B of 63 each received conventional and newer antiepileptic drugs respectively. Patients were allocated the AED based on type of epilepsy, patient characteristics and drug characteristics by the treating physician. Patients maintained a seizure diary which they filled weekly and this seizure diary was evaluated at 6 weeks and 12 weeks of follow up. Patients were assessed for adverse drug reactions (ADRs) at 0, 6 and 12 weeks of follow up and also for spontaneous reported ADRs at any time during the study.

Results: In both group A and group B, our study demonstrated that seizure freedom, seizure severity, and time before first seizure did not differ significantly ($p>0.5$). Except for cognitive dysfunction, impaired memory, and swollen gums, which were more frequent in the conventional anti-epileptics group, the ADR profiles of both group of medications were similar. Phenytoin was found to cause gum swelling and cognitive impairment. No subject experienced a serious adverse event.

Conclusion: Newer Antiepileptics as monotherapy are equally efficacious as conventional antiepileptics but may offer a better safety profile to epileptic patients.

Keywords: newer, conventional, antiepileptic drugs, effectiveness, safety

Introduction

A brain function disease known as epilepsy is characterised by the unpredictable and recurrent occurrence of seizures [1]. A comprehensive review and meta-analysis of incidence data revealed that epilepsy has a pooled incidence rate of 61.4 per 100,000 person-years [2]. People of all ages, genders, races, social backgrounds, and geographic areas can develop epilepsy. In India, there are reportedly around 10 million PWE (persons with epilepsy). In our demographic, it affects roughly 1% of people [3].

The widespread familiarity, established effectiveness, typically inexpensive cost, and well-documented ADRs of conventional AEDs have led to their widespread use. However, the 20–25% of patients who experience treatment failure have sparked intense research to create new AEDs [4]. In the treatment of epilepsy, monotherapy is preferred over polytherapy since it is equally or more effective, cost-efficient, and has fewer ADRs [5]. In addition to seizure freedom and control, the safety profile of the medications used for therapy is crucial when it comes to epilepsy [6]. To

prevent seizure recurrence, the AEDs are frequently given orally over a lengthy period of time. To treat their crippling illness and improve their quality of life, epileptic patients will receive the best care possible if their safety profiles are better understood [7].

The AEDs have been divided as per the year of market introduction before or after 1990 into newer and conventional [8]. Numerous studies on the effectiveness of conventional and newer AEDs have failed to show a significant difference. The assertion of an improved safety profile is largely to blame for the current trend of preferring newer AEDs [9]. Before the study's foundation was laid, there were relatively few research evaluating the effectiveness and safety of older and newer AEDs both internationally and among Indian populations. Therefore, the goal of the current study was to examine the safety and effectiveness profiles of conventional and newer AEDs in individuals with epilepsy.

Material and methods

Patients who visited the Neurology Outpatient Department were the subjects of this study. In this prospective, open-label study, 120 individuals were enrolled who were classified as having epilepsy by the International League Against Epilepsy (ILAE) [10] The institutional ethics committee gave its approval to the project.

Inclusion criteria

People of either gender aged 18 to 75 years, classified as epileptics as per the ILAE [10]. Patients who were ready to provide written, fully informed consent.

Exclusion criteria

Patients with progressive or uncontrolled diseases involving central nervous system, heart like progressive encephalopathy, cardiac dysrhythmia, recent myocardial infarction (MI), or congestive heart failure (CHF) or mental illness [11]. Also, people with known hypersensitivity to any study medication or those participating in another study within 8 weeks of study's start date or at any point in the study were excluded. People with known abnormal liver or kidney function (AST (Aspartate transaminase) and ALT (Alanine transaminase) levels above 2 times the upper normal limit) or known abnormal renal function (serum creatinine > 1.5 mg/dL). Pregnant and lactating mothers or people with drug or substance of abuse induced seizures.

According to the ILAE classification, patients with epilepsy (both new and old) were enrolled and split into two groups. Each group had 63 patients in it. It is recommended to discontinue the medication, post two years of seizure freedom [12]. Keeping this in mind, our study, did not have a washout period as we considered it unethical. Moreover, this research was a baseline study and a larger scale research is to be planned with a possible consideration of washout period keeping in mind the frequency of seizures. Each patient got a thorough physical examination and laboratory evaluation. We assessed the heart rate and blood pressure while sitting. Patients in group A were given the conventional AEDs (sodium valproate, carbamazepine, and phenytoin) as monotherapy, whereas those in group B were given the newer AEDs (levetiracetam, oxcarbazepine, and lamotrigine). Based on the type of epilepsy, the patient's features, and the drug's qualities, the treating physician administered the necessary AED to the patient.

Using a patient particular sheet and data from the patient's seizure diary, the patient's specifics and details of the disease and medications were acquired at baseline, six weeks, and twelve weeks of follow up. Patients kept a seizure journal that they updated weekly, and this seizure diary was assessed at the halfway point and the final point of the follow-up period. At 0, 6, and 12 weeks of follow-up, patients had their adverse medication reactions evaluated. They were also evaluated for spontaneously reported adverse drug reactions at any point during the study.

Statistical analysis: Student's t-test and chi-square tests were applied. A p value of less than 0.05 was considered as statistically significant.

Results

The baseline demographic profile of patients in both the groups was comparable and is depicted in Table 1. The mean age of patients in group A and group B was 34.58±1.8 years and 30.02±1.62 respectively while median age was 27 years. Occupation wise, majority of the patients were employed in group A i.e., 50.7% while Group B had 47.6% patients as students. Considering education wise both the groups A and B had maximum patients who were educated more than 10th standard i.e., 60.35 and 79.3% respectively. The baseline clinical and epilepsy characteristics of the patients in both the groups A and B were comparable as depicted in Table 2.

Table 1 Demographic profiles of patients at the baseline

Characteristics	Group A	Group B
Total no. of patients	63	63
Age in years	34.58±1.8	30.02±1.62
Sex (M: F)	37:26	30:33
Occupation		
Employed	50.7%	28.5%
Housewives	22.2%	22.2%
Unemployed	1.5%	1.58%
Students	25.3%	47.6%
Education		
< 10th standard	39.6%	20.6%
>10th standard	60.3%	79.3%
Smokers	1.6%	1.6%
Alcoholics	15.9%	7.9%

Table 2 Clinical and epilepsy characteristics of the patients at baseline

Characteristics	Group A	Group B
Clinical Characteristics		
Pulse rate (Beat/minute)	79±8.2	80±6.3
Weight (Kilograms)	65.92±1.78	63.28±1.9
Blood pressure (mm of Hg)		
Systolic BP	114±1.9	113±1.7
Diastolic BP	72.6± 1.3	73±1.3
Newly diagnosed cases	68.3%	65.1%
Old diagnosed cases	31.7%	34.9%
Epilepsy Characteristics		
Generalised tonic-clonic	65.07%	55.5%
Partial	34.9%	36.5%
Unclassified	0%	55.5%
Mean duration of illness (years)	6.01±7.2	6.01±8.4
Mean duration of seizure episode (min)	2.5±0.19	2.3±0.14
Post ictal confusion	73%	66.7%
Status epilepticus	3.2%	7.9%
Positive family history	14.3%	12.7%

Values expressed as percentages and mean ± SE

The baseline pattern and characteristics of epilepsy such as type of seizure, mean duration of illness (in years), mean duration of seizure episode (in minutes), post-ictal confusion, status epilepticus and positive family history were comparable in both the groups A and B.

The Seizure characteristics including freedom from seizure, total number of seizures and time to first seizure are depicted in Table 3. The patients who achieved freedom from seizure did not vary significantly in both the groups A and B (p >0.5) As depicted in Table 4, in group A as well as group B, 21 (33.3%) patients each had freedom from seizure in 1st month of treatment. 14 (22.2%) patients in group A while 15 (23.8%) had freedom from seizures in 2nd month in group B. In 3rd month of treatment 8 (12.6%) patients in group A and 14 (22.2%) patients in group B had freedom from seizures. The number of patients who could not achieve freedom from seizure in group A was 20 (31.7%) and 13 (20.6%) in group B. The total number of seizures during the three-month treatment period. The total number of seizures did not vary significantly in both conventional and new AED groups (p>0.05).

The time to first seizure in both the groups i.e., group A and group B. In group A 25 (39.6%) patients had their first seizure in 1st month of treatment while in group B, 34 (53.9%) had first seizure in 1st month (p>0.05). Twenty (31.74%) patients experienced 1st seizure episode during second month of treatment whereas 10 (15.8%) patients in group B experienced 1st seizure in second month of treatment (p<0.05). In third month of treatment, 3 (4.76%) patients in group A while 4 (6.34%) patients in group B experienced their first seizure (p>0.05). 15 patients in each group did not experience seizures during the study period (p>0.05).

Table 3 Seizure characteristics in group A and group B

Seizure Characteristics	Group A	Group B
Freedom from Seizure		
1st month	21 (33.3%)	21 (33.3%)
2nd month	14 (22.2%)	15 (23.8%)
3rd month	8 (12.6%)	14 (22.2%)
No freedom	20 (31.7%)	13 (20.6%)
Total Number of Seizures		
0	15	15
1	24	24
4	15	10
3	4	4
4	1	6
5	2	1
6	1	0
7	1	2
11	0	1
Time to first seizure		
1st month	25(39.6%)	34(53.9%)
2nd month	20(31.74%)	10(15.8%)*
3rd month	3(4.76%)	4(6.34%)
No seizure	15(23.8%)	15(23.8%)

Values are expressed as percentages
**p value<0.05 as compared to group A*

The findings of the seizure diary maintained by the patient are depicted in Table 4. No patients in the study experienced seizures which came more often. The severity of seizures in terms of coming being same in severity did not vary significantly between the two groups (p>0.05). In terms of improvement in the severity of seizures also not a statistically significant difference was seen (p>0.05). Worsening of seizures or an emergence of a new type of seizure also did not vary significantly among the two groups (p>0.05). Also, there was no statistical difference in both groups regarding post ictal confusion (p>0.05), injury related to seizure (p>0.05), loss of consciousness (p>0.05), or presence of aura (p>0.05).

Table 4 Seizure diary findings in group A and group B

Parameter	1st month	2nd month	3rd month
More often			
@Group A	0	0	0
$Group B	0	0	0
Same			
Group A	24	20	16
Group B	23	10	12
Improving			
Group A	0	5	1
Group B	7	10	6
Worse			
Group A	2	5	3
Group B	2	6	3
New type			
Group A	1	1	0
Group B	1	1	0
Lasting longer			
Group A	2	7	5
Group B	2	4	0
Post ictal confusion			
Group A	7	9	7
Group B	1	0	0
Injury			
Group A	0	2	3
Group B	3	3	2
Loss of consciousness			
Group A	13	15	9
Group B	20	7	8
Aura			
Group A	1	6	3
Group B	3	1	1

*pvalue <0.05 as compared to group A
@ number of patients in group A=36
$ number of patients in group B=36

Table 5, shows the ADRs observed in both the groups A and B. The most common adverse drug reaction observed in patients in the group A was irritability which was reported by 33 (52.3%) patients followed by sleepiness which was observed in 31 (49.2%) patients out of the total of 63 patients. In the group B the most common ADR observed was again irritability observed in 30 (47.65%) followed by sleepiness seen in 21 (33.3%) patients out of total 63 patients. The ADR profile of both the drugs was similar except cognitive impairment, poor memory and swollen gums which were more common in the group A. The cognitive impairment as well as swelling of gums was seen with phenytoin. There was no serious adverse effect noted in any patients.

Table 5 Adverse drug reactions observed in group A and group B

Adverse drug reaction	Group A (n = 63)	Group B (n = 63)
Weight loss	9 (14.2%)	6 (9.5%)
Weight gain	18 (28.5%)	13 (20%)
Sleepiness	31 (49.2%)	21 (33.3%)
Tiredness	23 (36.5%)	15 (23.8%)
Irritability	33 (52.3%)	30 (47.6%)
Tremor	5 (7.9%)	2 (3.17%)
Rash	6 (9.5%)	2 (3.17%)
Concentration difficulty	23 (36.5%)	3 (4.7%)
Hair loss	13 (20%)	10 (15.8%)
Acne	6 (9.5%)	10 (15.8%)
Facial hair growth	0 (0%)	0 (0%)
Swollen gums	10 (15.8%)	1 (1.58%)
Poor memory	28 (44.4%)	10 (15.8%)
Slow speech	8 (12.6%)	0 (0%)
Headache	21 (33.3%)	13 (20%)

Discussion

Effectiveness of the conventional drugs and newer drugs are studied many a times but hardly generated some gross difference. The recent trend of choosing newer drugs is mostly due to the claim of better safety profile. In our study, the findings of the seizure diary suggested that the seizure severity did not vary significantly in the conventional and newer AED groups. Our findings are similar to another study where there was no difference in seizure severity [13]. Time to first seizure in both the groups i.e., the conventional and new AED group did not vary significantly between the two groups. The time to first seizure did not vary between the two groups in another study [14]. In contrast in another study the conventional group of drugs for the time to first seizure depicted better results than the newer group of drugs [15]. The seizure severity as well as time to first seizure was not expected to differ between the two groups as the effectiveness in controlling seizures of the AEDs in both the groups is well documented to be same.

In our study, the safety of patients was assessed by adverse drug reaction check list and by voluntary reporting for any adverse drug reaction during the entire study period. The adverse drug reactions did not vary between the two groups. This is in accordance with findings of a study which compared the conventional and newer AEDs and did not find a statistical difference in the adverse drug reactions [16].

In the present study, the most common adverse effect was irritability in both the conventional and newer AEDs followed by sleepiness. This is in accordance with findings from another study where irritability followed by sleepiness was the most common ADR encountered with antiepileptics [17]. In contrast another study done in India with antiepileptics demonstrated loss of appetite as the most common ADR encountered during the study [18].

There was a higher incidence of cognitive impairment and poor memory with the conventional AEDs as per the adverse drug reaction profile. This is in accordance with a number of studies which suggest that cognitive impairment is well documented with conventional AEDs [19]. In contrast another study suggested that cognition can be adversely affected by both conventional and newer AEDs [20]. In our study, the AED which caused maximal cognitive impairment was phenytoin. This finding is similar to a number of studies where phenytoin is associated with cognitive impairment [21,22]. Also swollen gums were more frequently seen in the conventional AED group. This finding is also well documented by the fact that conventional AEDs mainly phenytoin is implicated in gum hypertrophy [23]. There was no serious adverse effect noted in any patient. This finding is similar to another study [24,25]. Extensive literature search yielded only a few studies comparing effectiveness-safety of conventional and newer antiepileptic drugs in Indian population as well as globally. However, these studies have compared a few drugs only and not conventional and newer drugs as a group. Although, the study carries a limitation of washout period not being included, it was a step to provide a baseline data which will act as a scaffold for future studies to be built on.

Conclusion

In conclusion, our study found that newer AED have a comparable effectiveness yet they offer better safety profile as monotherapy for epilepsy. Hence, they can be considered as monotherapy in epileptic patients since they are required lifelong or long-term basis and safety of these medications is of prime importance.

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Incidence and functional outcome of inter-carpal ligament injuries associated with fractures of distal radius

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Abstract

Introduction: Although the prevalence of intercarpal ligament injuries with distal radius fractures ranges from 0.5 to 75 percent, these injuries are often missed by the untrained eye. Currently, wrist arthroscopy is considered gold standard for diagnosis and treatment, but in Indian setting it is an impractical proposition. Scapho-lunate and luno-triquetral injuries can be identified on X rays easily by Gilula's arc, scapholunate distance and angle, carpal height ratio etc. The aim of this study is to estimate the prevalence of intercarpal ligament injuries in distal radius (DER) fractures and determine their functional outcome at one year.

Material and methods: The study was conducted over 18 months at VMMC and Safdarjung Hospital. Patients with distal radius fractures were subjected to wrist X rays in 100% magnification and earlier mentioned parameters were measured. Patients who needed surgery were operated for fracture DER. Immediate post-operative X rays and X rays at 1 year were compared with that of the contralateral wrist. Patients' clinical outcomes like range of motion, grip strength, quick DASH score and pain on VAS were measured at one year to assess the clinical outcome.

Results: The study population was of 103 patients. Prevalence of intercarpal injuries in patients with DER fractures was 11.7%. Out of these 12 patients, 50% had broken Gilula's arc, 66.6% had increased scapho-lunate distance and 42% had increased scapho-lunate angle. Carpal height ratio was significantly less in patients with intercarpal ligament injuries at one year. Similarly, functional outcome was worse in these patients at one year.

Conclusion: Intercarpal injuries are associated with worse outcomes in patients with fracture DER. These injuries can reliably diagnosed on X rays using the parameters mentioned. Since the prevalence is quite high, we should learn to diagnose them early, so that patients can be explained about the prognosis of their injury.

Keywords: intercarpal ligament, distal radius fracture, scapho-lunate

Introduction

Distal Radius Fractures (DRF) are one of the commonest injuries encountered in clinical practice [1] and one sixth of all fractures managed in the emergency department. The incidence is 20-40 per 10000 persons per year [2,3].

There has been an increasing concern regarding the incidence of various soft tissue injuries that are associated with DRF, their association with the type of fracture, treatment of these injuries and their effect on the final outcome of the patient.

The prevalence of intercarpal ligament injuries and distal radius fractures ranges from 0.5-75% [4,5,6]. The incidence of these injuries is higher with intra-articular DRF [4,7]. But there is scarcity of studies documenting their incidence and outcome in Indian population.

There are 2 types of ligaments in the wrist; extrinsic and intrinsic. Extrinsic ligaments connect the forearm bones with the carpals while intrinsic ligaments are the functional inter carpal stabilizers. The intercarpal ligament injuries commonly associated with distal radius fractures are scapholunate ligament

and lunotriquetral ligament. Scapholunate ligament injuries cause Dorsal Intercalated Segment Instability (DISI deformity) while Lunotriquetral ligament injuries cause Volar Intercalated Segment Instability (VISI deformity).

The association of the intercarpal ligament injuries has shown to affect the future outcome of the injury in terms of range of motion at the wrist joint, grip and pinch strength, pain in wrist as well as the ability in doing daily activities [8]. Therefore, there is a need for diagnosing these injuries early to know their natural history opt for early treatment. Presently wrist arthroscopy is considered the gold standard procedure for their diagnosis and treatment [9,10].

We have studied these injuries using radiographs of wrist due to our limited resources. Our study has tried to identify these injuries and their future outcome at 1 year on X-rays in the Indian diaspora. We aim to help understand these injuries so that early diagnosis is possible in a limited resource setting.

Material and methods

Our study was conducted over a period of 18 months in Central Institute of Orthopedics, Safdarjung Hospital, New Delhi. We included all the patients coming to our emergency with unilateral distal end radius fractures, both intra-articular and extra-articular, between the age of 18-50 years. All these patients were explained about the study and patients were enrolled after taking written informed consent. All the patients were subjected to preoperative X-ray of bilateral wrist: PA & Lateral views in 100% magnification. Radiographic parameters visualized were:

1) Gilula's Arc- 3 uniform arcs were visualized on the PA view of the wrist to assess carpal alignment. First arc outlines the proximal articular surface of scaphoid, lunate and triquetrum. Second arc outlines the concave distal surface of scaphoid, lunate and triquetrum. Third arc outlines the proximal surface of capitate and hamate. Any disruption of these arcs is suggestive of abnormality at that site [11] (Figure 1).

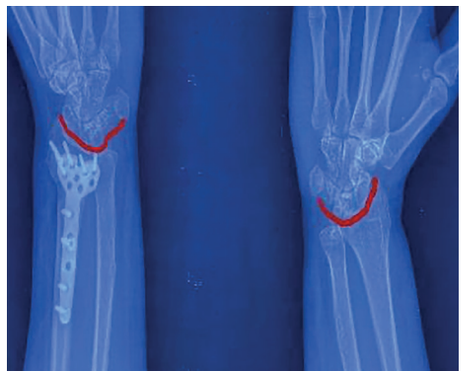

Figure 1 - Post op X- Ray: PA view B/L wrist at 1 year showing broken Gilula's arc (Arc1) as compared to the uninjured side.

2) Scapholunate distance- it is the distance between scaphoid and lunate measured at a midpoint between first and second Gilula's arc [12]. Distance > 2 mm is suggestive of SL dissociation leading to Terry Thomas Sign on the PA view (Figure 2A and 2B).

3) Scapholunate Angle: it is the angle between the long axis of scaphoid and mid axis of lunate on lateral view. Angle >60 degree indicates DISI while angle <30 degree suggests VISI [13] (Figure 3A and 3B).

4) Carpal Height Ratio (CHR): it is measured by dividing carpal height by the length of the third metacarpal on the PA view. Carpal height is measured from articular surface of base of 3rd metacarpal to the distal articular surface of radius and 3rd metacarpal length was measured along its longitudinal axis from distal to proximal articular surface. Normal value ranges from 0.45-0.63 [14] (Figure 4A and 4B).

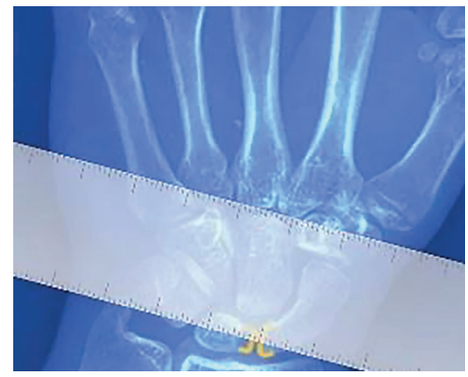

Figure 2A - X- Ray showing normal SL (<2 mm) Distance on PA view

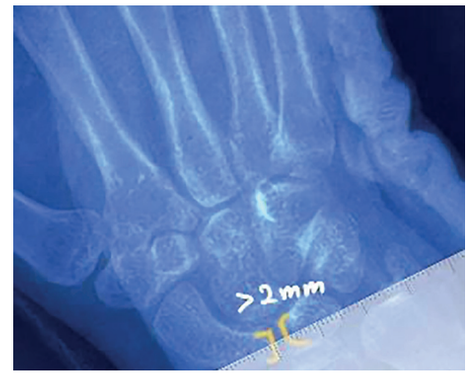

Figure 2B - X- Ray showing increased SL Distance (>2 mm) on PA view.

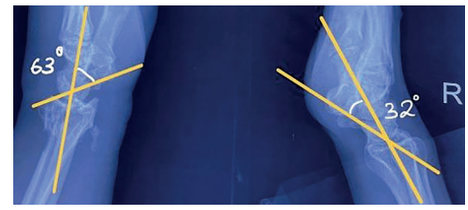

Figure 3A - X- Ray B/L wrist: Lateral view showing increased SL Angle (DISI).

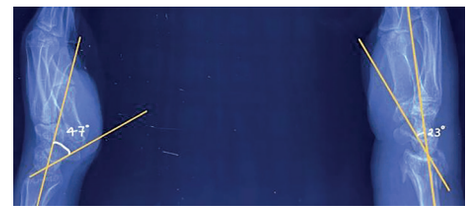

Figure 3B - X-Ray B/L wrist: Lateral view showing decreased SL Angle (VISI).

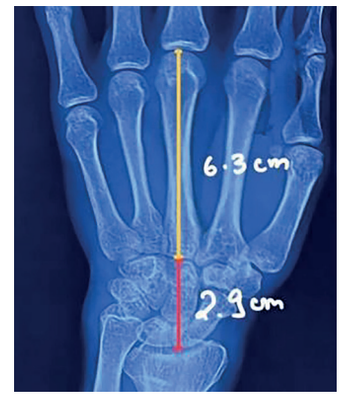

Figure 4A -X-Ray at 1 year showing CHR on affected side (0.46).

Figure 4B - X-Ray at 1 year showing CHR on normal side (0.5).

All patients were then evaluated for swelling and skin condition and those patients who were found to have healthy skin were managed by surgical intervention for distal radius fractures by either of the following methods:

1) ORIF with plating
2) K wire pinning
3) External fixator

Repeat X-Rays of bilateral wrist: PA & Lateral view in 100% magnification were taken at post op day 1, at 6 weeks and at 1 year. X-rays were visualized for various radiographic parameters and were compared with contralateral wrist between immediate post-operative day 1 x-ray and at 1 year.

The patients were also evaluated for functional and clinical outcomes for bilateral wrist joints with normal wrist acting as a control at one year. Parameters assessed were;

1) Range of Motion: It is the extent of osteokinetic motion available for movement activities, functional or otherwise, with or without assistance [15]. It is assessed using a Goniometer. Movements assessed included wrist flexion-extension, supination-pronation and radial deviation-ulnar deviation.

2) Grip Strength: It is the measure of maximum force generated by one's forearm muscle. It is measured using the Hand Dynamometer of the bilateral side for comparison. An average of 3 readings was taken.

3) Visual Analog Scale: It is used to measure severity of pain at the wrist joint of the affected side while doing day-to-day activity as compared to the opposite normal side. It consists of a numerical rating scale with numbers marked at regular intervals from 0 to 10 with 0 representing no pain and 10 representing severe debilitating pain [16].

4) Quick DASH Score: It is a self-reported outcome measure for physical function and symptoms in persons with any or multiple musculoskeletal disorders of the upper limb on a 5-point Likert scale [17,18]. It consists of 11 questions for which the patient selects an appropriate number according to his/her function level [19]. It cannot be measured if more than 1 question is missing. Quick DASH Scoring Formula= ([(sum of n responses)/n] -1)(25), where n is the number of answered questions. Higher score indicates more disability and vice-versa.

The entire study was conducted after taking the Institutional Ethics Committee (IEC) approval from our Institution (IEC/ VMMC/SJH/Thesis/ 2020-11/CC-201).

Results

The study population consisted of 103 patients out of which 71 were males and 32 were females with a mean age of 28.13+/-5.56 years (range 20 to 50 years).

The radiographic parameters were evaluated in all the patients at the time of presentation which showed that the incidence of intercarpal ligament injuries associated with distal radius fractures was 11.7% (12 out of 103 patients) (Table 1). These 12 patients consisted of 9 men and 3 women. The Gilula's arc was broken in 6 out of 12 patients, 8 patients had increased scapholunate distance. The scapholunate angle was abnormal in 5 out of 12 patients with 4 patients having SL angle > 60 degree while 1 patient having SL angle < 30 degree (Table 2).

Table 1 Incidence of Ligament injury in study subjects (n=103)

Ligament injury	No.	%
Absent	91	88.3
Present	12	11.7

Table 2 Comparison of different radiological and functional parameters between subjects with ligament injury side and normal side at post treatment 1 year.

	Ligament injury		Normal side	P value
	Absent (n=91)	Present (n=12)		
Gilula's line				
Broken	0	6 (50%)	0	**<0.001**
Unbroken	91 (100%)	6 (50%)	103 (100%)	
Scapholunate distance				
<2	91 (100%)	4 (33.3%)	103 (100%)	**<0.001**
>2	0	8 (66.7%)	0	
Scapholunate angle	49.78±10.67	60.92±16.79	50.88±10.42	**0.03**
Carpel height ratio	0.53±0.11	0.49±0.02	0.53±0.04	**<0.01**
Quick DASH score	30.39±8.06	76.97±6.53	0.40±1.30	**<0.001**
Grip strength	19.12±4.42	10.92±4.27	26.38±4.16	**<0.001**
VAS score	1.15±1.39	3.50±1.83	0.0±0.0	**<0.001**

Table 3 Comparison of Carpal height ratio between both groups.

	Ligament injury		P value intergroup
Carpal height ratio	**Absent (n=91)**	**Present (n=12)**	
Post -treatment at day 1	0.53±0.11	0.53±0.03	0.56
Post -treatment 1 year	0.53±0.11	0.49±0.02	**<0.01**
P value between post & 1 year	0.76	**<0.01**	

Carpal height ratio (CHR) was measured in all the patients at 1 year. The mean carpal height ratio in patients without ligament injuries was 0.53±0.11 at day and it was unchanged in one year. It was 0.53+/-0.03 at post op day 1 and 0.49+/-0.02 at 1 year in patients with associated ligament injuries. The difference in the values in two groups was significant at 1 year (p value <0.01) (Table 3).

Functional outcome was significantly poor in patients with associated ligament injuries. The mean Grip Strength measured at 1 year was 10.92+/-4.27kg and 19.12+/-4.42kg in patients with and without ligament injury, respectively and that on the

normal side was 26.38+/-4.14 kg which showed a significant reduction of grip strength with a p value<0.001. Range of motion was assessed at 1 year and was compared to the opposite normal wrist which also showed significant reduction in patients with ligament injury which affected their normal daily activities.

Clinical outcomes were assessed using quickDASH score and VAS score at 1 year time. The quickDASH score was 76.97+/-6.53 and 30.39+/-8.06 in patients with and without ligament injuries, respectively. The patients also had a poorer VAS score of 3.50+/-1.83. Both quickDASH and VAS score had a significant difference in both groups with a p value <0.001 signifying that the patients had restricted and painful daily activities.

Discussion

The purpose of this study was to estimate the incidence of intercarpal ligament injuries associated with distal radius fractures and determine the functional outcome at one year.

Age: The mean age associated with intercarpal ligament injuries in distal radius fractures was 32.5+/-8.5 in our study. While the mean age of patients with distal radius fractures was 28.13/-5.56 years.

Sex: The intercarpal ligament injuries were found more commonly in males (75%) than females due to the predominant male population being affected.

Incidence: In our study, the incidence of intercarpal ligament injuries was found 11.7% in patients with distal radius fractures on X-rays. In the study by Rosenthal et al [4] the incidence of intercarpal lesions was found to be 7.4% on X-rays which is similar to our study. Laulan et al [8] took all patients with intra and extra articular distal radius fractures and found the incidence to be 43% on X-rays. The incidence of various intercarpal ligament lesions on radiographs was found between [8] 1-32% [10,20]. Later arthroscopic studies showed the incidence ranging from 7-64% in association with DRF [9,21-24]. All the patients with intercarpal ligament injuries were diagnosed early at the immediate post op period. The incidence of these lesions increases with intra-articular distal radius fractures. These lesions can be detected on radiographs with proper understanding of intercarpal alignment, angles and measurements on initial presentation.

Radiographic parameters: Of the patients diagnosed with an associated intercarpal ligament injury, the Gilula's arc was broken in 50% patients, SL angle was affected in 41.7% patients while the SL distance was abnormal in 66.7% patients. Out of 12 patients, 7 had more than one parameter affected. Also, no significant change in affected parameters was seen at 1 year follow up that was present at post op day 1.

At 1 year, the mean CHR showed significant reduction in 41.67% patients with ligament injury from 0.55+/-0.3 to 0.47+/-0.21 which shows significantly affected carpal height. The mean CHR in patients without ligament injuries was 0.53+/-0.11 at post op day1 and at 1 year. Laulan et al [8] also showed similar progression in CHR reduction using revised CHR measurement [25] method in 61% of cases with intercarpal ligament lesions with rCHR value decreasing from 1.56+/-0.07 at post op day 1 to 1.51+/-0.09 at 1 year follow up.

Functional outcome: All range of motions i.e., wrist flexion and extension, radial and ulnar deviation, supination and pronation were significantly affected in patients with ligament injuries as compared with the contralateral normal wrist and also with the patients without ligament injuries. In patients with intercarpal ligament lesions in our study, average wrist flexion was 20.5+/- 6.36 and 82.81+/- 4.64 degrees, wrist extension was 16.83+/-3.97 and 74.56+/-4.35 degrees, radial deviation was 10.08+/-3.23 and 30.06+/-2.94 degrees, ulnar deviation was 20+/-4.71 and 34.96+/-4.61 degrees, pronation was 17.92+/-5.31 and 69.64+/-5.28 degrees and supination were 25.17+/-7.69 and 81.60+/-5.64 degrees on affected and the normal side respectively. Similar results of poor wrist function were seen by Tang et al [20] in all patients with ligament injuries. In contrast to our study, Forward et al [21] showed no significant difference in ROM of affected and normal wrist.

The grip strength in the affected wrist was 10.92+/-4.27 kg which was significantly lower than in patients without ligament injury (19.12+/-4.42 kg) and that on the normal side 26.38+/-4.14 kg. Kaspinova et al [26] also found poor grip strength in patients with associated ligament injuries using hydraulic hand dynamometer. This was in contrast with results shown by Laulan et al [8] And Forward et al [21] in their studies.

Clinical outcome: The quick DASH score was also significantly higher in patients with ligament injuries 76.97+/-4.27 as compared to those without associated ligament injury showing that these patients had more difficulty in doing day-to-day activities. Similar results were seen by Kaspinova et al [26] where patients with associated ligament injury had greater disability with high Dash score.

The subjective pain was assessed using VAS score which showed significant pain in patients with associated ligament injuries at 1 year with mean value of 3.50+/-1.83 compared to 1.15+/-1.39 in patients without ligament injuries. Similar results were seen by Forward et al21 with VAS score of 1.1 in patients with ligament injuries. In contrast with this, Laulan et al [8] 86% showed no wrist pain, 12% had pain after strenuous activities and 2% had severe pain.

Conclusion

In this study, "Incidence and functional outcome of intercarpal ligament injuries associated with fractures of the distal radius" by evaluating the result and statistics we concluded that patients with intercarpal ligament injuries associated with distal radius fractures had poor functional and clinical outcome at 1 year.

Following advantages were seen with our study:

Intercarpal ligament injuries associated with distal radius fractures can be diagnosed on x rays.

X-rays can be done as a routine procedure in all patients and are inexpensive.

Abnormality of Radiographic parameters such as Gilula's arc, SL distance, SL angle, and carpal height ratio can help in early diagnosis of intercarpal instabilities.

Arthroscopy of wrist to diagnose intercarpal ligament injuries cannot be carried out routinely.

Patients with intercarpal ligament injuries had poor functional outcome evaluated by ROM and Grip strength.

These patients also had poor clinical outcomes evaluated as high VAS score for pain and high quick DASH score suggesting more disability.

It is important to diagnose these injuries early on X rays because when left alone, the outcome is generally unsatisfactory.

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Changes in blood oxygen transport function and body energy expenditure during anaesthesia during coronary artery bypass grafting in adults: A randomized clinical study

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Abstract

Introduction: Cardiac surgery is a dangerous and complex field of medicine with significant morbidity and mortality. Quality anesthetic care with specific attention to detail can greatly enhance patient safety and outcome.

Objectives: Comparison of the effects of anesthetics on oxygen consumption, transport and energy expenditure during coronary artery bypass grafting in adults.

Material and methods: A total of 90 patients were assigned randomly into three groups according to the type of anaesthesia: the first group with propofol (P), the second group with sevoflurane, and the last one was with isoflurane. All patients underwent coronary artery bypass grafting under cardiopulmonary bypass. To determine oxygen delivery and oxygen consumption were determined using the formulas ((DO_2 = CI* CaO_2), (VO_2 = Cardiac index (CI)) and a spirometric device during anaesthesia.

Results: the cardiac index remained at the same level in the propofol and sevoflurane groups (2.5±0.6 l/min/m2 and 2.3±0.5 l/min/m2), while in the isoflurane group it was decreased to 2.3±0.5 l/min/m2. The oxygen transport index was 421.6±57.0 ml/min/m2 in the propofol group, 396.4±63.2 ml/min/m2 in the sevoflurane group, and 376.7±68.0 ml/min/m2 in the isoflurane group. Propofol reduced oxygen consumption to 101.5±23.5 ml/min/m2, while sevoflurane and isoflurane anesthesia reduced it to 106.6±22.3 ml/min/m2 and 116.4±21.4 ml/min/ m2. All anaesthetics reduced energy expenditure, but propofol anaesthesia significantly reduced it from 1491.4 to 1188.3 kcal/day.

Conclusion: In conclusion, isoflurane significantly reduced cardiac index compared to propofol and sevoflurane. Oxygen transport was higher in the propofol group than volatile anesthetics, and propofol reduced oxygen consumption more than inhalational anesthetics. In addition, energy expenditure was lowest in the propofol group than in the other anesthetics.

Keywords: oxygen consumption, energy expenditure, sevoflurane, isoflurane, propofol, oxygen transport, metabolic status

Introduction

Cardiac surgery is done under general anaesthesia, which means the patient is in a state of carefully controlled, medication-induced unconsciousness and will not respond to pain. Anesthesia of patients undergoing cardiac surgery is challenging and requires responsibility. The goals of anesthesia for cardiac surgery include avoidance of perioperative cardiac ischemia, tight hemodynamic control, early extubation. General anesthesia in cardiac surgery should also attempt to preserve myocardial function, prevent ischemia, and maintain stable hemodynamics.

Indirect calorimetry can be an indicator of homeostatic changes during surgery. Stress increases oxygen consumption (VO2) and during anaesthesia there is a decrease in VO_2 [1].

Resting oxygen consumption is influenced by several factors including the consumption and digestion of food, environmental temperature, the performance of muscular work, pregnancy, and hormones [2,3]. Increased

post-operative oxygen consumption is driven by a systemic inflammatory response to tissue trauma sustained during surgery [4-8]. The primary goal of the cardiorespiratory system is to deliver adequate oxygen to the tissues to meet their metabolic demands [9].

Tissues vary considerably in their sensitivity to hypoxia. Neurons tolerate hypoxia for only a few minutes, whereas the smooth muscles of the bladder go several days without oxygen. This has important implications for oxygen transport and monitoring of tissue hypoxia in patients [10]. Increased oxygen extraction, the ratio of consumption to transport, has been associated with poor outcome after surgery [11]. Researchers [12,13] found that surgery and anaesthesia did not significantly affect oxygen consumption and energy expenditure during anaesthesia. General anaesthesia reduced VO_2 by approximately a third in elderly patients undergoing major abdominal surgery. The relevance of these changes needs future assessment in relation to outcomes and haemodynamic interventions. [14]. Oxygen delivery (DO_2) is an important marker of O_2 transport than arterial blood oxygen saturation (SaO_2). Anaesthetics (propofol or sevoflurane) had no significant effect on DO_2. In addition, no correlation was found between SaO_2 and DO_2. DO_2 data may provide useful additional information about the patient's condition, especially with low SaO_2 [15]. Progressive hypothermia in anesthetized patients reduces metabolic rate but does not change DO_2. The significant decrease in oxygen extraction ratio may partly be related to a leftward shift of the oxyhemoglobin dissociation curve, as evidenced by the decrease in P50 [16]. Oxygen consumption during general anaesthesia was independent of the type of anaesthetics. General anaesthesia leads to a marked decrease in oxygen consumption, but during recovery the O_2 uptake can increase dramatically [17]. Indirect calorimetry can be an indicator of homeostatic changes during surgery. Stress increases oxygen consumption and during anaesthesia there is a decrease in VO_2 due to lack of kinetic energy as a cellular metabolic response to surgical trauma and anaesthesia. More research is needed to find out which oxygen consumption measurement system is the most appropriate for anaesthesia and what the VO_2 limit values might be [18].

Objectives: Comparison of the effects of anesthetics on oxygen consumption, transport and energy expenditure during coronary artery bypass grafting in adults.

Material and methods

Study design: Single-centre prospective randomized controlled clinical study.

This study was approved by NJSC "Astana Medical University" No. 3, Session No. 10. Republic of Kazakhstan, Astana. And written informed consent was obtained from all subjects. This manuscript adheres to the applicable CONSORT guidelines. The study includes data from 90 patients operated on at the Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan. All patients underwent coronary artery bypass grafting under cardiopulmonary bypass (CPB). This research work was conducted between 2021 and 2022. To calculate the sample size, we used the formula n=t2*D*N/confidence interval*N+t2*α, which will allow to identify the statistical significance of the study. Clinicaltrials.gov. NCT05693428, first trial registration date 22/01/2022.

Inclusion criteria for the main study phase

- The age is between 40-60 years old.
- coronary revascularization or >50% stenosis on coronary angiography
- CHD. Multivessel coronary lesions.
- Participants of both sexes will be included in the study
- Signed informed consent

Exclusion criteria

- pregnancy (risk to the baby and the mother)
- allergenic patients (anaphylactic shock).
- vulnerable groups.
- current congestive heart failure;
- current unstable angina pectoris;
- preoperative hemodynamic instability, defined as the use of vasopressors;

All patients were divided into 3 groups: 1 (control group) (n=30) consisted of patients who underwent anaesthesia with propofol (P). The second group (n=30) were patients who received sevoflurane inhalation anaesthesia (S). Group 3 (n=30) with isoflurane (I).

The study was conducted in 5 stages:

1) determined the patient's baseline values before anaesthesia;

2) after tracheal intubation;

3) before the cardiopulmonary bypass;

4) after the cardiopulmonary bypass;

5) The post-operative period.

Before induction into anaesthesia, haemodynamic monitoring with Nihon Kohden monitors (Japan) was initiated on admission to the operating theatre. The right radial artery was catheterised for invasive systemic pressure monitoring and arterial blood sampling, then a catheter was inserted into the central jugular vein (under ultrasound machine control) and guided into the right atrium for mixed venous blood sampling.

Cardiac stroke volume was determined by transthoracic echocardiography (CS=end diastolic volume - end systolic volume). Cardiac output (CO=CS x heart rate), cardiac index (CI=CB/body surface area) were determined. Blood oxygen content was determined using the formula CaO_2 (arterial blood gas ABG) and CvO_2 (central mixed venous BG) = [(1.34 × Hb × SO2) + (PO2 × 0.031)] / 100, arteriovenous difference = CaO_2-CvO_2. Oxygen delivery was determined using the formula (DO_2 = CI* CaO_2), oxygen consumption (VO_2 = Cardiac index (CI)*AVD or VO_2 = CB × (CaO_2 - CvO_2) ~ CB × Hb × 1.34 × (SaO_2 - SvO_2) / 100).

In the second stage, GE Datex Ohmeda Aisys CS2 (USA) machine was used for anesthesia, after tracheal intubation, indirect calorimetry was used to determine VO2, energy expenditure during anaesthesia, using a "Spirometry" (GE DATEX OHMEDA E-CAiOV USA), which was connected to an endotracheal tube and continuously showed oxygen demand and energy expenditure. Additionally, cardiac output was determined using Fick's formula. In the third and fourth stages of anaesthesia the same tests (cardiac output, cardiac index, consumption, oxygen delivery and energy expenditure) were determined. In the last stage to assess the pharmaco-efficiency of anaesthetics, the consumption of muscle relaxants and opioid analgesics was calculated. The time of extubation and the time of transfer of the patient to the specialist department were determined.

All patients were given the same type of premedication: 30-40 minutes before surgery, 0.3 mg/kg promedol was administered intramuscularly. Patients continued to take their usual baseline drugs both before and on the day of surgery to prevent withdrawal syndrome and to reduce the risk of myocardial ischaemia in the perioperative period.

All patients in both groups were given fentanyl in a dose of 5-7 μg/kg, ketamine 1.5-2 mg/kg, and propofol 1-1.5 mg/kg intravenously fractionally. Pipecuronium bromide 0.04-

0.07 mg/kg was used as muscle relaxant in all patients. To maintain anaesthesia in Group 1 P, propofol was used as an anaesthetic in a dose of 5 mg/kg/h intravenously on a perfusor (BBRAUN). In Group 2, sevoflurane was used as an anaesthetic in a dose of - 1.7-1.9 MAC. In Group 3 isoflurane was used as anaesthetic in a dose of - 1.1-1.2 MAC. In all groups fentanyl 100 µg intravenously was administered fractionally to increase heart rate and blood pressure, also pipecuronium bromide 2 mg intravenously for muscle relaxation. During CPB in all patients in all groups, propofol was used at a dose of 4-5 mg/kg/h intravenously via perfusion, analgesic regimen: fentanyl 100 µg intravenously every 30 min; myorelaxant piperonium bromide 2 mg every 40-60 min. Norepinephrine solution was administered at a dose of 0.05 µg/kg/min intravenously on perfusor after CPB in all patients at the same dosages in all groups.

Aim to use cardiotonic drugs:

1. In order to maintain mean arterial perfusion pressure (CPB causes cytokine storm and vasodilation).

2. For inotropic support (for reperfusion syndrome, resulting in a lower ejection fraction).

The depth of anaesthesia was monitored with a processed electroencephalogram, such as a BIS.

Statistical analysis was performed using IBM SPSS Statistics 20 package using one-factor analysis of variance for independent samples and nonparametric Kraskel Wallis test. The Kraskel-Wallis test was applied only to myorelaxant consumption, as the distribution was non-normal on this parameter. A Pearson and Spearman correlation analysis was also performed to determine the significance of the association between cardiac index and oxygen consumption, as well as energy expenditure.

Results

Patients in the study subgroups were comparable at baseline, with tables showing demographic, anthropometric, operative volume, cardiac index, consumption, oxygen delivery (Table 1).

Table 1 Demographic, anthropometric, operative volume, cardiac index, consumption, oxygen delivery. Parameters.

Indicator	Propofol (n=30)	Sevoflurane (n=30)	Isoflurane (n=30)
Sex M F	 25 (83,3%) 5 (16,7%)	 27 (90%) 3 (10%)	 22 (73,3%) 8 (26,7%)
Age, years	62,4 ± 7,7	61,5 ± 8,4	62,5 ±8,1
Weight, kilograms	81,5 ± 10,8	86 ± 9,6	81,4 ± 10,9
Height, centimetre	169,8±9,6	168,4±7,9	167,6±9,9
Duration Operation, hour	3,8±0,5	3,7±0,4	3,9±0,5
Cardiac index, l/min/m2	2,5 ± 0,6	2,4 ± 0,5	2,5 ± 0,6
Oxygen consumption, ml/min/m2	125,0±34,4	118,2 ± 38,3	114,9 ± 37,4
Oxygen delivery, ml/min/m2	415,4±62,2	403,9±76,2	398,7±70,4
Oxygen recovery, %	27,4±7,0	26,4±6,6	28,1±6,9
Note: P>0.05.			

At the beginning, before the start of anesthesia, the heart index was almost the same in all 3 groups, there was no statistical difference. But after tracheal intubation, it was observed that the cardiac index increased by 2.6±0.5 L/min/m2 in the propofol group and decreased by 2.3±0.5 L/min/m2 in the sevoflurane and isoflurane groups. However, propofol decreased the cardiac index by 2.5±0.5 l/min/m2 before entering the artificial circulatory system, while inhalation anesthetics remained almost at the same level in the sevoflurane and isoflurane groups (2.3±0.5 l/min/m2 and 2.3±0.6 l/min/m2) (p=0.4). There was no statistical difference. After weaning from the artificial circulation device, the cardiac index remained at the same level in the propofol and sevoflurane groups (2.5±0.6 l/min/m2 and 2.3±0.5 l/min/m2), while in the isoflurane group it was decreased to 2.3±0.5 l/min/m2 (p=0.04) (Figure 1).

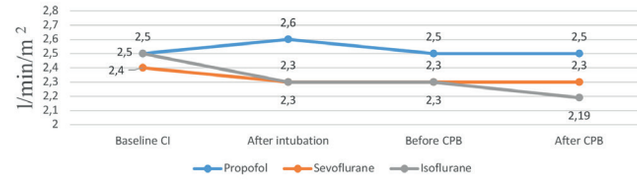

Figure 1 - Changes in cardiac index during surgery.

There was no significant difference between groups in terms of oxygen transport before induction of anesthesia. After tracheal intubation, oxygen transport increased slightly to 429.0±83.4 ml/min/m2 in the propofol group, on the contrary, inhaled anesthetics slightly decreased it (398.6±74.0 ml/min/m2 and 395.1±82, 4 ml/min/m2) (p=0.2). However, it was observed that propofol reduced oxygen transport by 425.0±68.4 ml/min/m2 before entering the artificial blood circulation machine, while oxygen transport in the sevoflurane and isoflurane groups was 397.5±69.6 ml/min/m2 and 387.7±60.6 ml/min/m2 (p=0,096). After leaving the artificial blood circulation device, the oxygen transport index was 421.6±57.0 ml/min/m2 in the propofol group, 396.4±63.2 ml/min/m2 in the sevoflurane group, and 376.7±68.0 ml/min/m2 in the isoflurane group (p=0,025) (Figure 2).

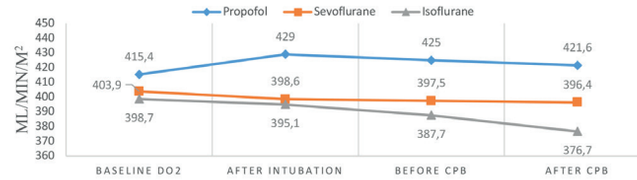

Figure 2 - Changes in oxygen transport during surgery.

There was no difference between groups in terms of oxygen consumption before the onset of anesthesia. After induction of anesthesia, oxygen consumption decreased in all groups, with propofol decreasing oxygen consumption by 111.7±23.7 ml/min/m2, sevoflurane by 109.2±35.6 ml/min/m2, and isoflurane by 121.0±26.4 ml/min/m2 (p=0.2). Before weaning, propofol reduced oxygen consumption by 109.5±23.6 ml/min/m2, while sevoflurane and isoflurane anesthesia reduced it by 108.3±23.8 ml/min/m2 and 118.3±26.9 ml/min/m2 (p=0.2). At the end of surgery, propofol reduced oxygen consumption to 101.5±23.5 ml/min/m2, while sevoflurane and isoflurane anesthesia reduced it to 106.6±22.3 ml/min/m2 and 116.4±21.4 ml/min/ m2 (p=0.037) (Figure 3).

After intubation and connection of a spirometer (UK, Oxford) to the intubation tube, energy expenditure (EE) was found to be 1491.4±199.7 kcal/day in the propofol group, 1497.1±196.6 kcal/day in the sevoflurane group and 1453.5±207.2

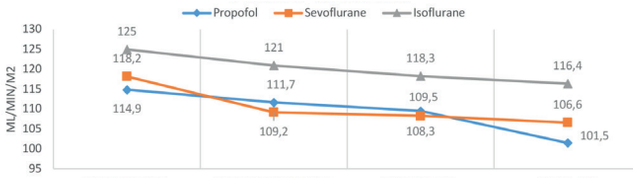

Figure 3 - Changes in oxygen consumption during surgery.

kcal/day in the isoflurane group. All anaesthetics reduced energy expenditure, but propofol anaesthesia significantly reduced it from 1491.4 to 1188.3 kcal/day. However, anaesthesia with sevoflurane did not significantly reduce energy expenditure, energy consumption was decreased to 1389.2 kcal. However, in anesthesia with isoflurane the decrease of energy expenditure was noticeable after CPB, i.e. before CPB it was 1414.9 kcal, and after CPB it decreased to 1289.6 kcal (Figure 4).

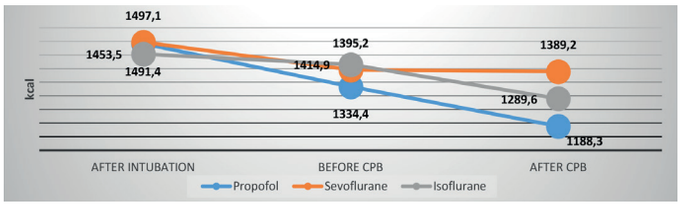

Figure 4 - Changes in energy expenditure during surgery.

Discussion

Traditionally, TIVA and inhalation anaesthesia are used for anaesthesia. The choice of anaesthesia method often depends on the possession of a particular ward tradition, etc. However, there are few studies which have comparatively evaluated their advantages and disadvantages, especially there are no indicators such as O transport2, its utilisation, consumption, energy expenditure.

Anaesthesia has a significant effect on blood circulation and oxidative metabolism, which are closely linked. During prolonged anaesthesia, increased oxygen demand can have adverse effects on haemodynamics. There is an ongoing controversial debate in the literature about the role of different types of anaesthesia in relation to blood oxygen-transport function, O2 uptake and utilisation.

In the immediate postoperative period, the use of sevoflurane prevents the occurrence of bradycardia and a decrease in cardiac index [19]. Increases in propofol blood concentrations decrease vascular stressed volume without a change in cardiac output. The absence of an effect of propofol on cardiac output can be explained by the balance between the decrease in effective, or stressed, volume, the decrease in resistance for venous return, and slightly improved heart function [20]. Anesthesia and surgery have a wide range of effects on the cardiovascular system. Even in healthy patients having minor operations, anesthetic agents can cause significant cardiac depression and hemodynamic instability [21]. Sevoflurane appears to be similar to isoflurane and desflurane with a few exceptions. Sevoflurane was not associated with increases in heart rate in adult patients and volunteers, whereas higher MACs of isoflurane and desflurane and rapid increases in the inspired concentrations of these two anesthetics have been associated with tachycardia. Increasing concentrations of sevoflurane progressively decrease blood pressure in a manner similar to the other volatile anesthetics, and in unstimulated volunteers this decrease may be slightly less than with isoflurane at a higher MAC [22]. Anesthetics have cardiac depressant effects that decrease myocardial oxygen demand and may have a beneficial role on myocardial oxygen balance during ischaemia [23].

According to the results of our research, the effect of anesthetics on cardiac index during coronary artery bypass graft surgery, anesthesia with propofol in a dose 5-6 mg/kg/h increased the cardiac index after tracheal intubation, while inhalational anesthetics decreased it. However, after cardiopulmonary bypass, the heart index was lowered to the initial level and kept at the same level until the end of the operation. And sevoflurane in a dose of - 1.7-1.9 MAC slightly lowered the cardiac index and kept it at the same level until the end of the operation. In anesthesia with isoflurane in a dose of - 1.1-1.2 MAC, after tracheal intubation, the heart index was slightly reduced and it was at the same level after leaving cardiopulmonary bypass, but when we recalculated the cardiac index at the end of the operation, we noticed that its level decreased again.

According to the authors [24] DO_2 did not significantly differ between sevoflurane and propofol. But other researchers [25] observed sevoflurane and propofol had similar effect on PaO_2 during one-lung ventilation when their administration is titrated to maintain BIS between 40 and 60.

Although oxygen transport was initially the same in all groups, after tracheal intubation, its increase was observed in the propofol group, but at this time, on the other hand volatile anesthetics sevoflurane and isoflurane slightly reduced oxygen transport. Also we observed a decrease in oxygen transport in the propofol group before entering cardiopulmonary bypass, while no significant change was observed in the sevoflurane group. However, we noticed that isoflurane further reduced oxygen transport. At the end of the operation, oxygen transport was reduced by propofol to baseline, and sevoflurane had almost no effect on it. Anesthesia with isoflurane significantly reduced DO_2.

The author [17] states that oxygen consumption is independent of the type of anaesthetic. In addition, the researchers [13] argue that further investigation is necessary. VO2 decreased after anaesthesia induction by – 65 ml/min [10].

After induction of anesthesia, oxygen consumption decreased in all anesthetic groups, but sevoflurane reduced oxygen consumption significantly more than the other anesthetics. Isoflurane steadily reduced oxygen consumption from the beginning to the end of the operation. However, sevoflurane had almost no effect on oxygen consumption after tracheal intubation.

A significant decrease in oxygen consumption under propofol anesthesia was observed after cardiopulmonary bypass.

Median energy expenditure under general anesthesia is about one-quarter lower than preoperative awake resting energy expenditure in patients having noncardiac surgery [26].

Energy expenditure was decreased significantly before entering the cardiopulmonary bypass under sevoflurane anesthesia, but its decrease slowed down towards the end of the operation. However, isoflurane significantly reduced energy expenditure from the beginning to the end of anesthesia. In addition, compared to inhalation anesthetics, propofol significantly reduced energy expenditure.

Limitations of the study

This study has 2 limitations. The first limitation is that it was a single-center study. The second limit of our study is the sample size. Because the sample size affects the statistical significance of the study. But we believe that randomized controlled trials with a large number of patients are needed.

Conclusion

In conclusion, isoflurane significantly reduced cardiac index compared to propofol and sevoflurane. Oxygen transport was higher in the propofol group than volatile anesthetics, and propofol reduced oxygen consumption more than inhalational anesthetics. In addition, energy expenditure was the lowest in the propofol group than in the other anesthetics.

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Actual issues of secondary prevention of liver cancer in Kazakhstan

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Abstract

Liver cancer is characterized by high mortality and low survival rates in most countries of the world. According to the WHO data, more than 1.3 million people with liver cancer die annually in the world and according to the data of the 9th volume of "Cancer on five continents" - the highest standardized incidence rates are in Korea - 44.9 per 100 thousand population as well as in Thailand, Japan, China. Low rates were in Algeria, India, Belgium and the Netherlands. In Russia 61.5% of patients die of liver cancer progression in the first year after diagnosis [1,2].

Information on the global burden of cancer in 2018 showed that the specific weight of liver cancer in the structure of malignant neoplasms (MN) is 8.2%, and in 2020 - 8.3% [3].

The worldwide peculiarity of liver cancer is its late diagnosis. Several evidence-based treatment options for liver cancer are currently available: liver transplantation for hepatocellular liver cancer (HCC) (according to the Milan criteria), radiofrequency ablation as a radical treatment option (RFA), chemoembolization for intrahepatic cholangiocarcinoma (TACE), and the administration of Sorafenib as systemic therapy [4].

Current approaches for the treatment of early-stage primary liver cancer are represented by hepatic RFA, and the efficacy of this approach depends on the subjective attentiveness and visual acuity of the clinician. The latest technique used in liver RFA is the hyperspectral imaging which utilize objective assessment [2].

Ultrasound is usually used to detect liver lesions, but the detection rate is low for many reasons, such as clinician skills and technical capabilities. Modern approaches of diagnostic capabilities, such as contrast-enhanced ultrasound integrated imaging (CEUS) and comprehensive ultrasound imaging - contrast-enhanced CT (CECT) or contrast-enhanced MRI (CEMRI) for visualization of focal liver lesions (FLL) - increase the confidence of the interventional physician so it should be recommended for use as a routine procedure [5-6].

The ratio of morbidity and mortality in many countries reaches 91.6%, which represents the third most important cause of cancer deaths [7-9].

Keywords: liver cancer, prevalence, incidence, regions of Kazakhstan

Introduction

Late diagnosis is the peculiarity of liver cancer worldwide. Information on the global burden of cancer in 2018 showed that the specific weight of liver cancer in the structure of malignant neoplasms (MN) - 8.2%, and in 2020 - 8.3%. In Kazakhstan in 2021 - 2.8%.

The incidence of liver cancer in the world reaches up to 44.6 per 100 thousand population and in Kazakhstan - 4.7 in 2021.

Objective: To study the prevalence of liver cancer in Kazakhstan.

Material and methods

A search in the databases of PubMed, GoogleScholar, Rinz, statistical and analytical indicators materials of oncological service of Kazakhstan for 2019-2021 was conducted. The method of research is desk-based, retrospective.

Results and discussion

In 2021, the incidence of malignant neoplasms (MN) increased by 7.6% and amounted to 170.3, compared to 2020 - 157.3. The growth rate increased over two years +8.3%. In the structure of malignant neoplasms, liver cancer ranked 15th with a positive growth rate of +3.1% (Table 1).

Table 1 — Incidence of liver cancer in the structure of MNs of the population in Kazakhstan

Localization	Indicators					Growth rate, %	
	abs. number		to 100 000.			2020	2021
	2020	2021	2019	2020	2021		
All MNs, including	29701	32572	174,8	157,3	170,3	-10,3	8,3
Mouth	76	119	0,7	0,4	0,6	-42,9	54,6
Oral cavity	481	520	2,8	2,5	2,7	-4,8	6,7
Salivary gland	112	143	0,6	0,6	0,7	-	26,1
Nasopharynx	70	76	0,4	0,4	0,4	-	7,2
Throat	164	169	0,8	0,9	0,9	-20,0	1,7
Esophagus	1082	1130	6,3	5,7	5,9	-7,3	3,1
Stomach	2497	2576	14,4	13,2	13,5	-8,5	1,9
Colon	1645	1686	9,2	8,7	8,8	-4,9	1,2
Rectum	1471	1604	8,7	7,8	8,4	-11,5	7,7
Liver	861	899	5,4	4,6	4,7	-16,3	3,1
Pancreas	1143	1128	6,0	6,1	5,9	1,9	-2,6
Larynx	339	365	2,3	1,8	1,9	-20,0	6,3
Lungs	3375	3615	20,1	17,9	18,9	-11,6	5,8
Bones	141	143	0,8	0,7	0,7	-12,5	0,1
Soft tissues	381	439	2,2	2,0	2,3	-5,0	13,8
Skin melanoma	283	360	1,9	1,5	1,9	-23,5	25,6
Mammary gland	4307	5021	26,6	22,8	26,3	-14,9	15,1
Uterine cervix	1672	1804	9,6	8,9	9,4	-8,1	6,5
Uterine corpus	1074	1240	6,4	5,7	6,5	-11,9	14,0
Ovary	1010	1249	6,2	5,3	6,5	-12,0	22,1
Prostate	970	1169	6,6	5,1	6,1	-23,6	19,0
Kidneys	1029	1292	6,7	5,5	6,8	-18,3	24,0
Bladder	667	737	4,1	3,5	3,9	-13,5	9,1
Nervous system	785	765	3,8	4,2	4,0	11,4	-3,8
Thyroid	612	712	4,3	3,2	3,7	-25,6	14,9
Blood	1702	1713	8,3	9,0	9,0	9,1	-0,6
Lymphoma	837	886	4,4	4,4	4,6	9,1	4,5
Leukemia	865	827	3,8	4,6	4,3	9,1	-0,6

For economically developed countries the standardized indicator of the population morbidity with MN is within 250-350, for developing countries - 100-120. According to these benchmarks, Kazakhstan is striving to reach the levels of indicators of economically developed countries in recent years.

Graphical analysis of the growth rate of liver cancer in the structure of MN in Kazakhstan showed that liver cancer is characterized by low intensity of detection compared to the previous year, despite the positive growth rate (Figure 1).

Analysis of regional peculiarities of 2021 in the structure of MN in Kazakhstan allowed to single out regions with high morbidity rates - the highest rate of MN is breast cancer in Pavlodar region - 48.0, East Kazakhstan (EKR) - 40.0 and lung cancer in North Kazakhstan - 39.0 (SKR) (Table 2).

Regions with high liver cancer incidence rates are Pavlodar region - 7.0, East-Kazakhstan - 6.8 and Atyrau region - 6.3; with low rates - Turkestan region - 2.6, Kostanay region - 2.7, North Kazakhstan - 3.7 (Figure 2).

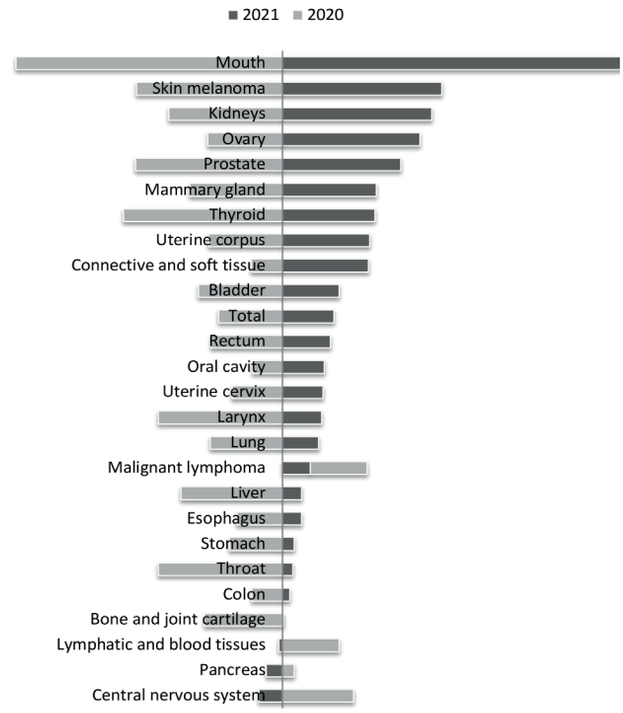


Figure 1 - Growth rate of liver cancer incidence in the structure of the population in Kazakhstan, *Gr.*

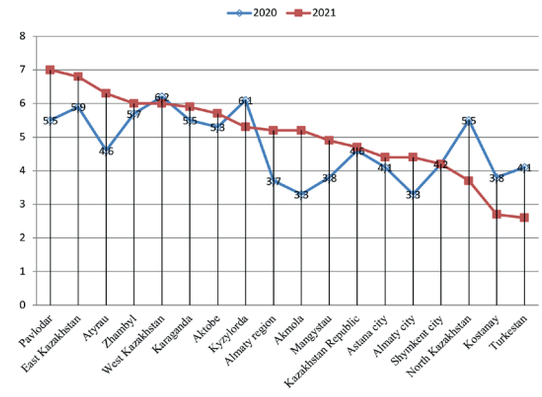


Figure 2 - Liver cancer incidence in the regions of Kazakhstan

The analysis of regional peculiarities in 2021 of MN structure in Kazakhstan showed that the highest specific weight of liver cancer in Zhambyl and Mangystau regions - 4.9% and 4.5%, Atyrau region 4.1% and Kyzylorda region - 3.9%, and less specific weight in Kostanay region -1.1%, North Kazakhstan - 1.3% (Figure 3).

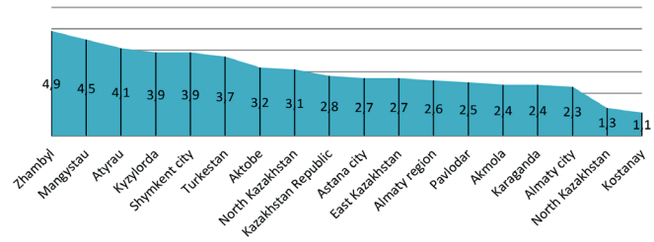


Figure 3 - Specific weight of liver cancer in the structure of MN by regions of Kazakhstan, 2021, %

Analysis of regions with a high proportion of stage 4 liver cancer in 2020-2021 showed that the most disadvantaged region is Akmola region - 38.9/61.1%, SKO - 38.9%, and Pavlodar region - 27.7% (Figure 4).

Table 2 Incidence of liver cancer in the structure of MN in the population of the Republic of Kazakhstan in 2021, per 100 thousand population.

MN localization	Name of regions																	
	Kazakhstan Republic	Akmola	Aktobe	Almaty region	Atyrau	East Kazakhstan	Zhambyl	West Kazakstan	Karaganda	Kyzylorda	Kostanay	Mangystau	Pavlodar	North Kazakhstan	Turkestan	Nur-Sultan city	Almaty city	Shymkent city
Total	170	216	177	119	152	255	123	192	244	137	245	110	281	287	71	166	193	109
Oral cavity	2.7	4.1	3.4	1.6	3.4	4.7	2.3	3.0	3.1	1.8	4.4	1.1	5.2	6.9	0.9	2.3	2.6	1.3
Esophagus	5.9	6.5	10	4.1	8.1	5.3	5.9	11	6.6	12	6.3	8.1	5.0	6.3	4.5	4.1	3.6	4.2
Stomach	13	17	19	11	14	18	10	19	18	12	16	9.7	17	25	6.7	13	12	7.4
Colon	8.8	10	9.0	4.7	8.7	13	5.8	10	15	4.6	16	4.9	15	13	2.7	9.0	12	4.0
Rectum	8.4	13	8.1	5.6	6.3	14	5.1	9.8	12	5.3	16	2.8	18	15	2.7	9.0	7.8	5.0
Liver	4.7	5.2	5.7	3.1	6.3	6.8	6.0	6.0	5.9	5.3	2.7	4.9	7.0	3.7	2.6	4.4	4.4	4.2
Pancreas	5.9	9.1	6.3	3.8	5.8	8.7	5.4	6.9	9.0	5.1	8.4	3.2	9.8	7.1	2.3	5.6	6.4	3.6
Lungs	19	32	20	10	21	31	14	25	29	15	25	9	35	39	7	17	17	10
Bones	0.7	1.1	1.3	0.5	1.0	0.2	0.6	0.8	0.6	2.2	0.7	0.4	0.8	2.0	0.3	0.8	0.8	0.4
Connective tissues	2.3	1.5	2.4	1.9	1.5	2.3	3.0	3.5	2.8	2.8	4.7	1.2	4.1	3.9	0.9	1.5	2.4	1.7
Melanoma	1.9	2.0	1.1	1.1	0.7	3.8	0.9	0.9	3.1	1.0	3.7	1.5	3.9	5.4	0.4	1.1	2.9	0.6
Mammary gland	26	30	24	17	16	40	15	28	40	14	36	17	48	38	12	28	35	22
Uterine cervix	9.4	12	12	9.5	12	11	5.7	11	12	8.2	11	10	17	10	5	7	8	7
Uterine corpus	6.5	9.3	6.1	4.7	4.2	10	4.6	5.7	9.6	4.8	9.4	3.1	10	15	1.3	6.5	8.5	4.3
Ovary	6.5	6.9	6.4	5.4	6.7	7.2	4.3	7.2	7.5	8.3	9.6	3.2	9.4	6.3	3.5	7.7	9.3	4.1
Prostate	6.1	7.1	3.6	4.3	1.6	14	4.4	5.6	10	1.0	12	2.7	11	16	1.0	4.3	7.6	3.1
Kidneys	6.8	0.4	6.6	4.0	6.9	9.4	4.1	4.5	9.5	3.9	10	4.9	12	14	2.5	9.4	8.4	3.1
Bladder	3.9	5.7	3.2	2.8	2.1	7.0	2.8	3.6	6.4	2.7	5.7	2.0	6.4	7.6	1.1	2.6	4.8	2.3
CNS	4.0	4.8	5.2	4.1	3.3	4.1	4.2	4.1	3.1	4.5	3.6	3.1	6.3	5.2	2.3	4.3	5.7	1.7
Thyroid	3.7	3.8	3.4	3.0	0.6	5.8	2.1	3.8	4.8	4.1	2.9	1.9	5.2	8.0	0.5	6.3	5.9	2.6
Blood	9.0	6.9	6.7	6.3	7.2	13	5.0	8.1	16	6.8	11	6.9	14	19	5.0	9.3	12	4.8

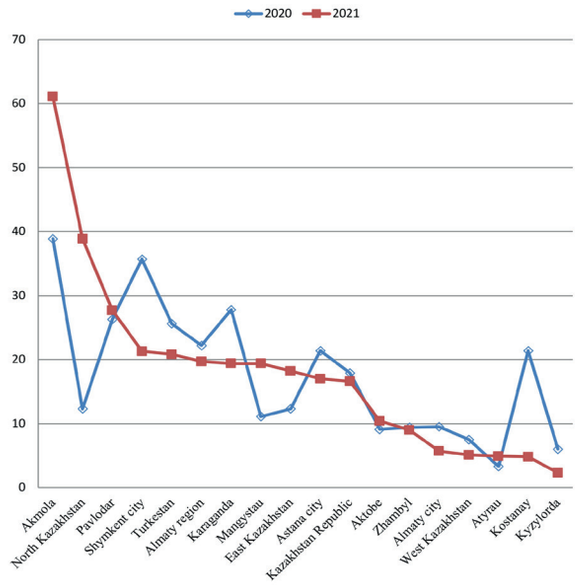


Figure 4 - Specific weight of stage 4 liver cancer in Kazakhstan, %

Analysis of regions with low specific weight of stage 1 liver cancer in 2020-2021 showed that the most unfavorable region is Akmola - 38.9/61.1%, North Kazakhstan - 38.9%, and Pavlodar region - 27.7% (Figure 5).

Regions with high mortality rate from liver cancer in 2020: East Kazakhstan and West Kazakhstan - 4.8; Pavlodar region - 4.4. In 2021: East Kazakhstan - 5.4; Pavlodar region - 4.7; West Kazakhstan - 4.2 per 100 thousand population (rough indicators).

Regions with low mortality rate from liver cancer in 2020: Almaty city - 1.8; Atyrau region - 2.1; Aktobe region - 2.2. In 2021: Kostanay region - 1.6; Kyzylorda region - 1.7; Almaty region - 1.9 per 100 thousand population (rough indicators) (Figure 5).

For the indicator by regions: morbidity, mortality, post-mortem (Figure 6).

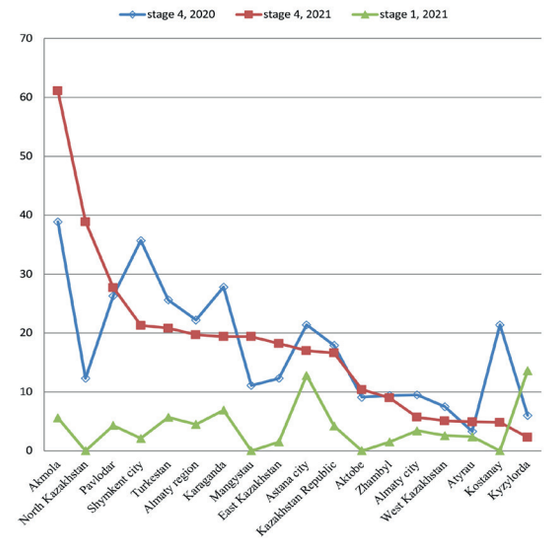


Figure 5 - Specific weight of stage 1 and 4 liver cancer in Kazakhstan, %

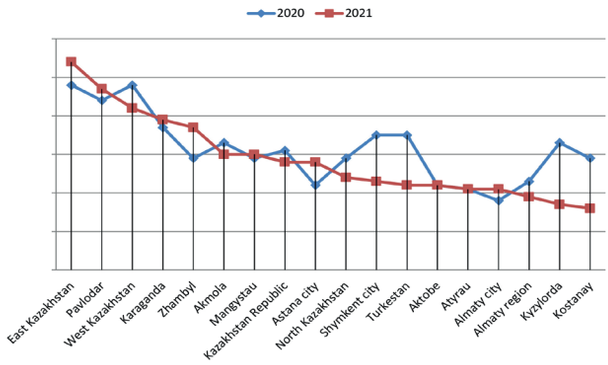


Figure 5 - Mortality of Kazakhstan population from liver cancer by regions, per 100 thousand population.

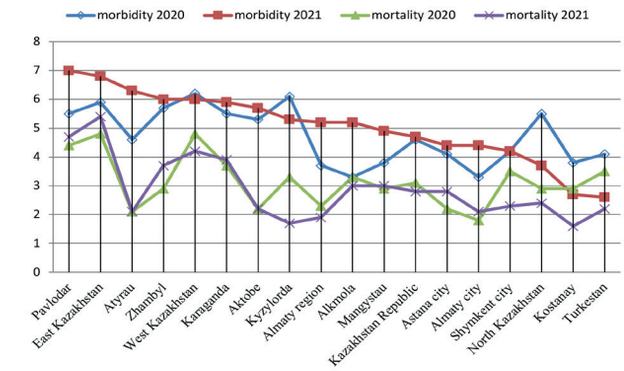


Figure 6 - Morbidity and mortality of liver cancer in Kazakhstan by region.

Analyzing the data of morbidity and mortality rates by regions, attention is drawn to the indicators of high morbidity and low mortality in the regions: Atyrau, Zhambyl, Aktobe and Kyzylorda and North Kazakhstan.

The ratio of incidence and mortality from liver cancer in Kazakhstan in 2020-2021 is 67.4/59.57. By region, this indicator varies from 33.3 to 100: regions with high ratio - Akmola in 2020 100, in 2021 - 57.7; Turkestan 85.4/84.6, East Kazakhstan 81.4/79.4, Pavlodar region 80.0/67.4. With low ratio - Atyrau 45.7/33.3; Aktobe 41.5/38.6; Kyzylorda 54.1/32.1 (Figure 8).

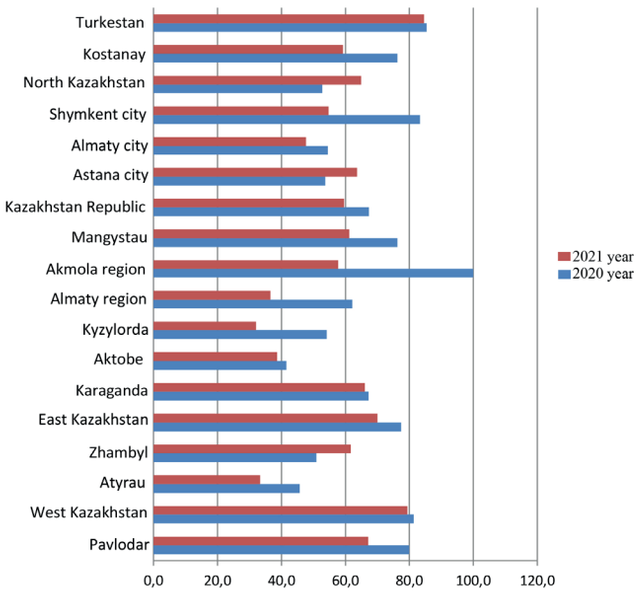


Figure 8 - Ratio of liver cancer incidence and mortality in Kazakhstan by region

In 2020, a high ratio was observed in Akmola region, Turkestan region and Shymkent city, and in 2021 - Turkestan region, East Kazakhstan and Pavlodar region.

It is important to estimate the proportion of postmortem detected patients for the quality indicator of lifetime diagnostics of liver cancer.

The highest share of postmortem-detected cancer patients in Kazakhstan was recorded for 2019-2021 for liver cancer and amounted to - 7.3-7.5-6.2%. The minimum share is within 0-0.9% for 12 localizations, average - from 1 to 3% for localizations and above average from 3-7.5% for 6 localizations (Figure 9).

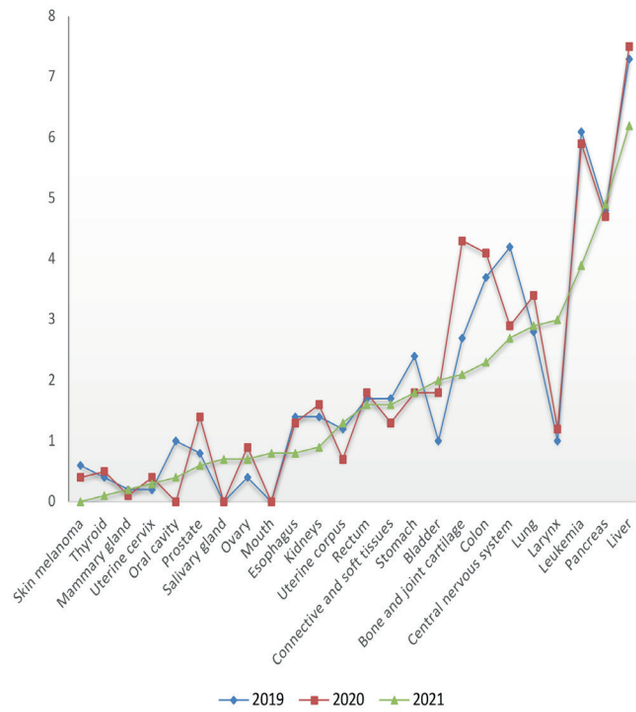


Figure 9 - Share of liver cancer deaths not registered with oncology organizations, %

Full 100% confirmation of the postmortem diagnosis by autopsy in 2020 was provided by oncological organizations of Zhambyl, Karaganda, Kostanay regions and Almaty city. Autopsies were not performed in 2020 and 2021 in Aktobe and Turkestan regions. In Kazakhstan, the overall rate of posthumously detected patients was -1.8% in 2019, 2.0% in 2020, and 1.6% in 2021. If we compare it with the indicators in Russia, the average indicator is 5.3% [The state of oncological care in Russia in 2019].

The ratio of one-year mortality and neglect (stage 4) in the republic in 2019-2021 was 1,9 – 1,8 - 1,7 , the recommended indicator is 1.0. In the first place of the worst indicator was taken by the central nervous system, but, liver cancer was in 6th place (Figure 10).

For the period 2019-2021, liver cancer in the ratio between one-year mortality and stage 4 negatively is ranked sixth place.

Analyzing liver cancer rates by gender for the study period, there is a positive indicator in the decreasing the incidence in men - Increase rate of -14.3% in 2029 and a significant increase in incidence rate of +7.3% in 2021. At the same time, mortality is steadily decreasing by -9.7% (Table 3).

The growth rate of morbidity and mortality shows how fast the indicator is increasing or decreasing in comparison with previous year. The values used for calculation are current value and comparable value according to the formula: current value/ comparable value x 100%. 543/634 x 100% - 100%

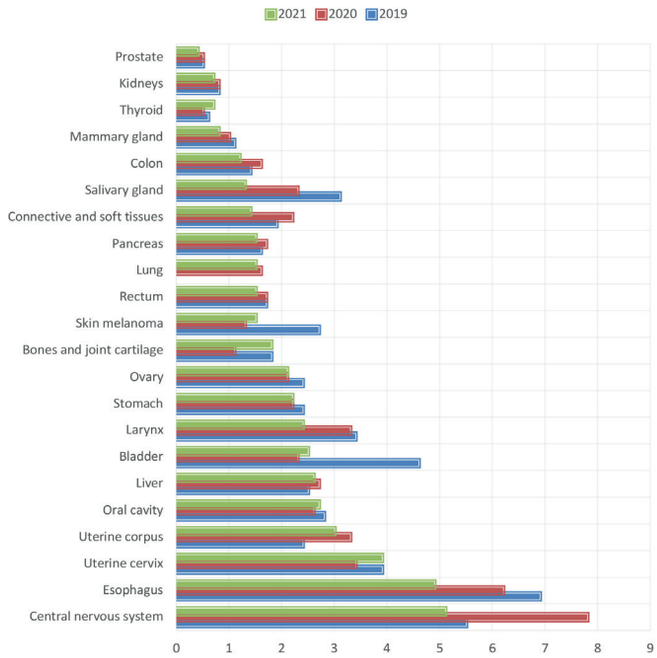
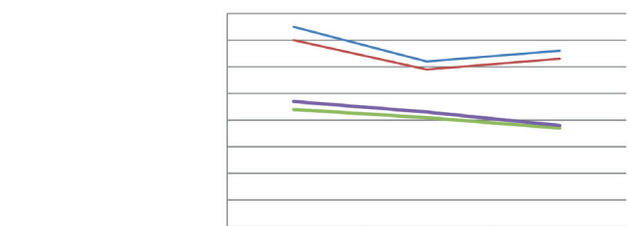


Figure 10 - Correlation between one-year mortality and liver cancer neglect in the structure of MN in Kazakhstan (stage 4).



	2019	2020	2021
male morbidity standardised rates	7,5	6,2	6,6
male morbidity	7	5,9	6,3
mortality	4,4	4,1	3,7
mortality standardised rates	4,7	4,3	3,8

Figure 11 - Features of morbidity and mortality of liver cancer in Kazakhstan in men, per 100 thousand population.

Table 3 — Indicators of first-time diagnosis of liver cancer in Kazakhstan in men, rough indicators

Men								
Indicators	abs. number			to 100 000.			growth rate	
	years							
	2019	2020	2021	2019	2020	2021	2020	2021
Morbidity	634	543	583	7,0	5,9	6,3	-14,3	+7,3
Mortality	397	373	341	4,4	4,1	3,7	-6,8	-9,7

The incidence of MN population in the males was 151.3 or 14048 cases (2020 142.3 - 13036 cases) per 100,000 and in females was 171.5 and 188.3 in 2021.

Liver cancer in males were 7.0 - 5.9 - 6.3 per 100,000 population and in females were 4.4 - 4.1 - 3.7 respectively (Figure 11) in 2019-2021.

For women, growth rate of morbidity decreased -15.9 in 2019, and -0.6% in 2021, and mortality were19.2% and -4.7%, respectively (Table 4).

The morbidity of the male population of MN is 151.3 or 14048 cases (2020 142.3 - 13036 cases) per 100,000 population and in females 171.5 and 188.3 in 2021.

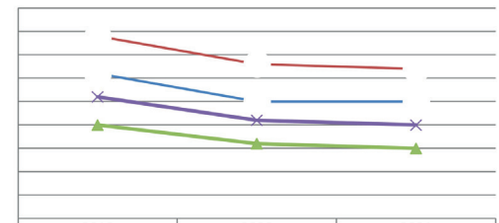
What are the dangers of fast and slow rates? Fast positive rates can lead to unrealistic expectations and negative fast rates

Table 4 — Indicators of diagnosis liver cancer in Kazakhstan among women for the first time their life, rough indicators

Women								
Indicators	abs. number			to 100 000.			growth rate	
	years							
	2019	2020	2021	2019	2020	2021	2020	2021
Morbidity	378	318	316	3,9	3,3	3,2	-15,9	-0,6
Mortality	245	207	197	2,6	2,1	2,0	-19,2	-4,7

can lead to unreasonable funding. To analyze a negative growth rate, other indicators need to be analyzed: the status of liver cancer detection in population screenings and post-mortem liver cancer detection rates.

Liver cancer rates for men were 7.0 - 5.9 - 6.3 per 100,000 population, for women, respectively, 3.9 - 3.3 - 3.2 in 2019-2021 (Figure 12).



	2019	2020	2021
female morbidity in standardised rates	3,1	2,5	2,5
female morbidity	3,9	3,3	3,2
female morbidity in standardised rates 2	2	1,6	1,5
female mortality	2,6	2,1	2

Figure 12 - Features of liver cancer morbidity and mortality in women in Kazakhstan, per 100 thousand population.

By analyzing the data of liver cancer by sex, no significant difference was found in results ($p \leq 0.05$).

The mortality rate from MN decreased in both sexes by 4.5%, from 74.9 to 71.5 per 100,000 population, and the standardized mortality rate decreased by 5.1% in 2021.

The ratio of the standardized mortality rate from MN of men to that of women is stable at 1.6:1.0. The ratio of standardized liver cancer mortality rate is 2.5:1.0 in 2021, while there is a decrease in mortality in women over the three years to 4.4 in 2019, 4.1 in 2020 and 3.7 in 2021. Males also show a decrease in mortality rate of 4.4-4.1-3.7, respectively (Figure 13).

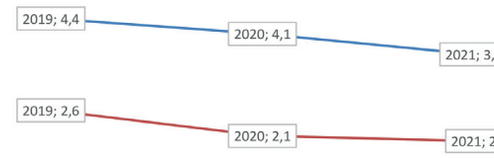


Figure 13 - Liver cancer mortality by sex, per 100,000 population.

In 2021, the number of patients with MN decreased from 647 to 562 deaths, or by 13%, and was 1.6%, in 2020 - 2.0%. Comparatively, in Russia this indicator in 2020 was 6.9%.

By regions of Kazakhstan mortality rates from MN show dependence on the sex and age composition of the population. The specific weight of liver cancer in the structure of MN in Kazakhstan for 2019-2021 ranked 5/8 in men and 12/12 in women.

The most consistently low five-year survival rate of patients with MN in Kazakhstan with liver and pancreatic cancer, and high - MN of bones and articular cartilage and larynopharynx (Figure 14).

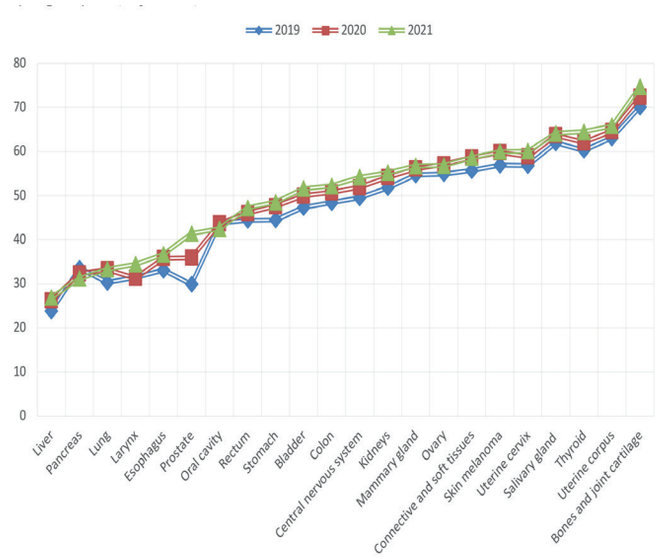


Figure 14 - Five-year survivability of patients with liver cancer in Kazakhstan, %

The five-year survivability of liver cancer is the lowest - this is another factor confirming liver cancer in the early stages. Official statistical compilations do not take into account the coverage of special treatment in oncology. The radical treatment of liver cancer is interventional method in the early stages in Kazakhstan (Figure 15).

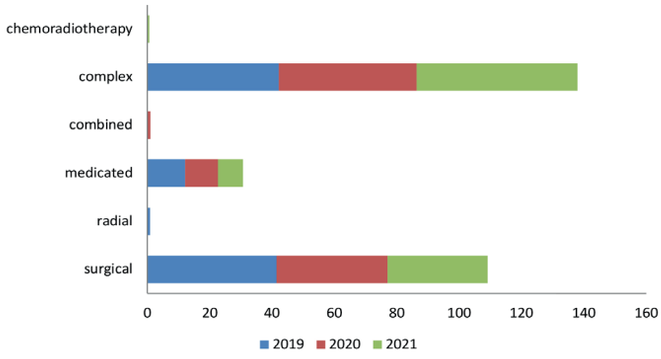


Figure 15 - Coverage of specialized treatment for liver cancer patients in the Republic of Kazakhstan

Results and discussion

For the period 2019-2020, liver cancer ranked 7th in the structure of standardized morbidity rates in men and its specific weight was 7.5% in 2019, and 6.2% and 9th in 2020, growth rate = -17.3 in the structure of malignant neoplasms (MN) morbidity in Kazakhstan. In females it is 3.1/2.5, growth rate = -19.3.

Standardized incidence rates of liver cancer were 4.9 per 100,000 population in 2019 and 4.1 in 2020, growth rate = -16.3.

Mortality from liver cancer was 3.4 per 100,000 population in 2019 and 3.1 in 2020: in men 4.4/4.1 and in women 2.6/2.1 respectively. Place in mortality structure was 10th place - in 2019; and 8th in 2020.

In 2020, the top three regions with high mortality rates from liver cancer were East Kazakhstan - 4.8. West-Kazakhstan - 4.8, Pavlodar - 4.4; the three lowest indicators were identified: Almaty city - 1.8; Atyrau - 2.1; Aktobe and Astana - 2.2.

The number of deaths from malignant neoplasms not registered with oncological organizations - liver cancer in the first place in 2019 and 2020, blood cancer in the second place, pancreatic cancer in the third place.

The top three diseases with the highest one-year mortality rates are pancreatic cancer at 59.6%, liver cancer at 46.9% and oesophageal cancer at 43.4% in 2020. At the same time, compared to 2019, liver cancer showed a worsening of this indicator by 17.7%. The leading negative place over 2 years for the ratio between one-year mortality and neglect (stage 4) belonged to malignant neoplasms of the central nervous system - 5.5 and 7.8 The positive ratio (1.0) was breast cancer in 2019 and bone and articular cartilage cancer - 1.1 in 2020.

In Kazakhstan, the lowest five-year survival rate for liver cancer patients was 23.8 % in 2019 and 26.2 %in 2020. Pancreatic cancer has a slightly better statistics like 33.5% and 32.3%, and also, blood cancer numbers at 53.7% and 54.4%.

Conclusion

In Kazakhstan, standardized indicators of liver cancer incidence are low, and in the structure of morbidity they are not among the top ten of the number of registered malignant diseases, while liver cancer is in first place among the deceased who are not registered at the dispensary during 2019 and 2020. Also, liver cancer is one of the three stable anti-leaders of malignant neoplasms with mortality within a year and low five-year survival

It is necessary to introduce new modern approaches to early diagnosis and modern treatment of liver cancer in Kazakhstan.

It is necessary to include in the monitoring of liver cancer treatment methods - an interventional method that is used worldwide in routine practice for early diagnosis of liver cancer.

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A rare neurological complication of COVID-19: Pediatric Miller Fisher Syndrome. A case report

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Abstract

The SARS-CoV-2 pandemic has significantly transformed the world. While it was initially viewed as a respiratory virus, it has now been found to cause cardiovascular, gastrointestinal, and psychological complications. Moreover, the nervous system (NS) is also greatly affected. Research has identified dizziness, headaches, as well as disturbances in one's taste and smell abilities as the most frequent symptoms of NS involvement. Even more significant changes may occur in patients who get infected with SARS CoV-2, such as the development of acute cerebrovascular disorders (stroke), multiple sclerosis, acute disseminated encephalitis, Guillain-Barré syndrome, encephalitis, and myelitis. It is important to note these potential complications and monitor patients closely. A retrospective study conducted in Wuhan, China revealed that CNS (central nervous system) involvement occurred three times more frequently than PNS (peripheral nervous system) involvement. This emphasizes the critical importance of studying and describing CNS manifestations. This case report depicts Miller Fisher syndrome in a 5-month-old infant after SARS CoV-2 infection and explores literature on pediatric cases and potential pathogenic mechanisms.

Keywords: SARS-CoV-2, Miller Fisher Syndrome, COVID-19, neurological complications, immune-mediated neuropathy, anti-GQ1b

Introduction

Miller-Fisher Syndrome (MFS) is an acute peripheral neuropathy that is considered a clinical variant of Guillain-Barré syndrome. It arises from the impact of various viral, bacterial, and fungal pathogens. An infectious agent triggers an autoimmune inflammatory response, which results in damage to the peripheral nerves, followed by demyelination and subsequent axonal injury. This syndrome presents a clinical triad consisting of ophthalmoplegia, ataxia, and areflexia, with the potential addition of moderately pronounced peripheral tetraparesis. MFS combines both central nervous system involvement, which affects the cerebellar structures leading to ataxia, and peripheral nervous system involvement, particularly the third, fourth, or sixth cranial nerves, as well as peripheral nerves, resulting in ophthalmoplegia and ataxia [1]. The incidence of MFS generally accounts for a small subset of GBS patients, making up only 5%. However, a study conducted in Asia revealed a higher incidence of GBS in Asian countries [2]. With the increasing incidence of neurological complications associated with SARS CoV-2, there is concern that it could potentially contribute to existing MFS incidence numbers in the future. Typical laboratory findings of Guillain-Barre syndrome (GBS) reveal albumin-cytologic dissociation, which suggests a rise in protein level within the cerebrospinal fluid (CSF), while the cell count remains in the normal range [3]. Additional diagnostic methods that bolster suspicion of GBS include electromyography (EMG) and magnetic resonance imaging (MRI), along with the identification of anti-GQ1b antibodies. However, despite the fact that anti-GQ1b antibodies are positive in the majority of GBS patients (up to 90%), their absence does not exclude the diagnosis [4,5]. We herein report a retrospective case of Miller Fisher syndrome development in a 5-month-old infant subsequent to SARS CoV-2 infection. Possible pathogenic mechanisms related to this case are also discussed.

Case presentation

A 5-month-old infant was admitted to the Pediatric Clinical Infectious Disease Hospital in Almaty with a history of high fever of up to 38.5°C, coughing, sore throat, nasal discharge, and fatigue. The onset of the disease was sudden and manifested as refusal to breastfeed and irritability. On the third day of illness, the child displayed a temperature of up to 38.5°C. The mother initially believed that the symptoms indicated the

emergence of new teeth and she administered her own gingival pain reliever and ibuprofen. On the fourth day of symptoms, the mother scheduled an appointment with a pediatrician at a private medical center. Following examination, the child was diagnosed with acute respiratory viral infection (ARVI), acute pharyngitis, and acute otitis media. The child was then sent for home treatment. However, the next morning the infant's condition rapidly worsened by developing shortness of breath and the emergence of neurological symptoms, including left ptosis, general fatigue, and loss of movement in the extremities, and lethargy. This led to the family calling for an ambulance and seeking care at the Pediatric Infectious Disease Hospital.

Based on the medical history, the child demonstrated age-appropriate developmental milestones. The child only received prophylactic vaccinations at birth, and all other vaccinations were declined due to written parental refusal. There was no family history of autoimmune or neurological disease. The epidemiological history indicates a recent occurrence of acute respiratory viral infection (ARVI), which occurred approximately two weeks ago with mild symptoms that improved within three days. Due to receiving treatment at home, the infant was not seen by a specialist and was not tested for possible causes of ARVI.

Upon admission and objective examination, the infant presented with severe and unstable condition due to type 2 respiratory failure, metabolic acidosis, and neurological impairment. The child appeared lethargic, intermittently restless, and moaning. Pupil examination revealed bilaterally dilated pupils with weak light response. Weak muscle tone and reflexes were found in both upper and lower extremities. No signs of meningeal irritation were noted. The fontanelle measured 2.5x2.5cm with no bulging. The oropharyngeal exam revealed only erythema of the posterior pharyngeal wall and tonsils. Lung auscultation revealed diminished respiratory sounds with crackles in the lower lobes, indicating moderate mixed-type dyspnea at rest with a respiratory rate of 54 bpm. Muffled heart sounds and tachycardia (185 bpm) were noted. Abdominal palpation showed moderate hepatomegaly and splenomegaly but was painless. The patient remained hemodynamically stable. Due to the severity of the infant's condition, he was promptly referred to the pediatric intensive care unit.

A lumbar puncture was conducted upon admission, revealing elevated protein levels and a normal cell count in the cerebrospinal fluid (CSF). The cell count was 3 cells/microliter with 100% lymphocytes and protein levels were 920 g/l. The CSF appeared clear with normal pressure and glucose levels, indicating albumin-cytologic dissociation. Subsequently, an ELISA analysis of the CSF was performed to detect antiGQ1b IgG and IgM antibodies, yielding a negative result (reference range <1700 BTU). After one week, the Gram stain and CSF culture results demonstrated no growth. Furthermore, the respiratory viral PCR panel tests for SARS-CoV-2, flu, and RSV were all negative. A chest X-ray revealed bilateral multifocal pneumonia and first degree thymus enlargement (Figure 1). Notably, the serological panel showed negative results for chlamydia trachomatis, toxoplasma gondii, and herpes simplex, but only CMV IgG antibodies were positive. The general blood count test revealed an increase in leukocytes (22*103/mcL), accompanied by elevated levels of neutrophils (75%) and reduced levels of lymphocytes (14%). The nerve conduction test showed indications of impairments in both sensory and motor nerve conduction, with the absence of both H reflex and F waves.

In the days following admission to the pediatric intensive care unit, the patient's condition deteriorated with the disappearance of the gag reflex, development of swallowing difficulty, and right-side facial muscle paralysis, indicating cranial nerve involvement. A brain CT scan was performed to rule out any other cranial conditions that could be causing these symptoms. The CT scan revealed benign enlargement of the frontoparietal subarachnoid space without signs of hemorrhage or tumor, as shown in Figure 2.

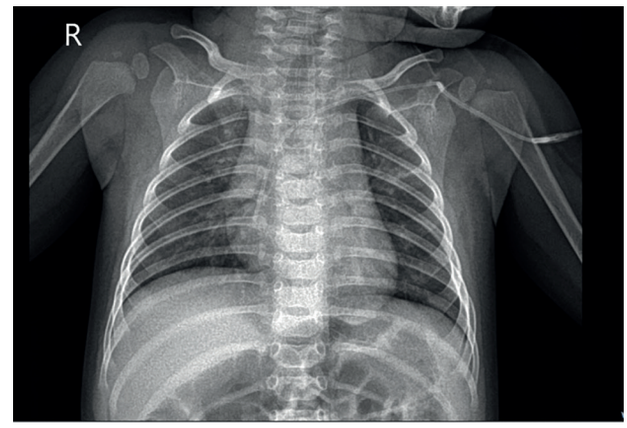

Figure 1 - Chest radiograph showing bilateral multifocal pneumonia with first degree of thymus enlargement.

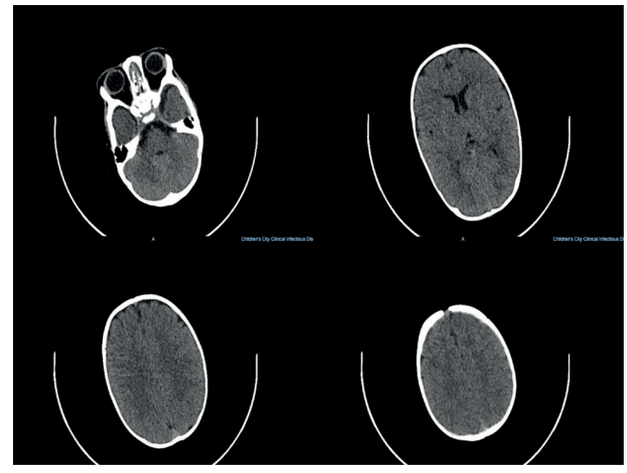

Figure 2 - Cranial CT scan: benign enlargement of frontoparietal subarachnoid space.

Further investigation for possible causes that could have triggered Miller Fisher Syndrome revealed positive IgG to N-protein of SARS-Cov-2 - 4.85s/co while IgM to N-protein of SARS-Cov-2 was negative. Based on patient's symptoms, epidemiological history and laboratory findings a clinical diagnosis of Miller Fisher Syndrome was made. The diagnosis was confirmed by using the Brighton Collaboration GBS Working Group criteria with 1 level of certainty (Figure 3).

	Level of diagnostic certainty			
Symptoms	**1**	**2**	**3**	**4**
Symmetric flaccid limb weakness	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset of signs 12 hours to 28 days	+	+	+	+/-
Cerebrospinal fluid (CSF) cell count <50/ml	+	+/-	-	+/-
CSF protein level is greater than normal value	+	+/-	-	+/-
Absence of alternative diagnosis for weakness	+	+	+	+/-
Nerve conduction test results is consistent with one of the subtypes of Guillain Barre Syndrome	+	+/-	-	+/-

Figure 3 - Brighton criteria for Guillain Barre Syndrome. (+) present, (-) absent, (+/-) present or absent.

Initially prior to ruling out CNS infection empirically ceftriaxone along with acyclovir was given intravenously. In addition to antibiotics and antiviral medicine methylprednisolone was administered. Following completion of differential diagnosis and obtaining laboratory results ceftriaxone and acyclovir were discontinued, and instead, 2g/kg intravenous immunoglobulin (IVIg) was given. Overall, signs of cranial nerve impairment persisted for 6 days. After being monitored and treated in pediatric intensive care unit for 13 days gag reflex, difficulty in swallowing and facial paralysis resolved. Subsequently, the patient was further referred to the pediatric neurology department. Following a total hospital stay of 20 days, the patient was discharged with mild muscle weakness in extremities.

Discussion

Prior to the COVID-19 pandemic, the global incidence of Guillain-Barré Syndrome (GBS) was approximately 1-2 cases per 100,000 people, and the manifestation variant of Miller-Fisher Syndrome (MFS) accounted for only 5% of GBS cases [4,6]. A systematic review conducted on nervous system involvement triggered by SARS CoV-2 shows 25 cases of MFS associated with COVID-19 in adults, and four cases in children [7]. Searching for previously reported relevant scientific articles and literature found no cases of MFS associated with SARS cov-2 in the Republic of Kazakhstan. However, there was only one case of MFS has been described in the Russian Federation [8,9]. Researchers who conducted genetic analyses of COVID-19 recovered patients discovered that Asians and individuals of African descent experienced more severe outcomes. It is essential to note that patients experiencing severe COVID-19 symptoms may suffer from neurological impairment due to rapid clinical deterioration or worsening of their condition [10].

The pathogenesis of CNS involvement in COVID-19 remains variable. In studies describing cases of meningitis and encephalitis, autopsy material exhibited SARS-CoV-2 RNA [11,12]. This finding is explained by the viral particles entering through the endothelial cells of capillaries, similar to how it affects other organs and systems. The mechanism of injury causing MFS-like symptoms is thought to be immune mediated rather than direct viral neurotropism, as SARS-CoV-2 RNA was not detected when examining cerebrospinal fluid (CSF) from affected patients [13,14]. Several studies have shown that the immune-inflammatory response to COVID-19 and the heightened production of IL-1, IL-6, IL-17, IL-22, and TNF-α lead to nervous system involvement that is as significant as that in other organs [15,16].

Furthermore, the hypothesis is supported by the finding that in the majority of cases, the time span between the onset of COVID-19 symptoms and the onset of neurological symptoms exceeded two weeks, suggesting a post-infection autoimmune process [17]. Another crucial point to consider is the prompt and favorable response to treatment observed after the administration of intravenous immunoglobulins. Thus, the immune-mediated neuropathy triggered by COVID-19 could be induced by cross-reactivity and molecular mimicry between SARS-CoV-2 antigenic epitopes and carbohydrate fragments of surface cranial nerve glycoproteins [18]. Given this factor, it is justifiable to examine both the direct neurotropism of SARS-CoV-2 in causing complications like anosmia, encephalitis, and meningitis, as well as the immune-mediated mechanism in the origin of Miller-Fisher Syndrome (MFS) or Guillain-Barré Syndrome (GBS) [19,28]. The diagnosis of MFS cases are based on history of symptoms and physical examination where presentation of classical triad such as ataxia, areflexia, and ophthalmoplegia can be found. Furthermore, indirect changes in cerebrospinal fluid (CSF) or nerve conduction studies corresponding to the polyneuropathy patterns described for MFS when CSF sampling is not accessible is also useful. For CSF analysis, slight pleocytosis, an elevated protein concentration, and the absence of other microorganisms in PCR analysis or bacteria culture test [3,20]. This is also supported by the presence of anti-GQ1b antibodies in some patients, which are commonly associated with Miller Fisher syndrome. Anti-GQ1b antibodies bind to gangliosides on the oculomotor nerve, abducens nerve, vagus nerve, limb muscle spindle, and brainstem network structure by blocking acetylcholine excretion from the motor terminals resulting in symptoms including ataxia, weakness, breathing difficulties, and areflexia [21].

In our patient apart from anti-GQ1b antibodies the classic clinical symptoms and CSF changes were present. The absence of anti-GQ1b antibodies considers the case of MFS to be atypical as the majority of MFS cases (85-90%) are known to have positive anti-GQ1b antibodies particularly in variants with ophthalmoplegia [4,22]. However, despite being positive in majority of the patients with MFS absence of antiGQ1b antibodies does not rule out the diagnosis [23]. Additionally, the systematic review published in 2021 by Martins-Filho et al revealed that significant number of MFS cases were anti-GQ1b antibody negative [24].

We think in our case there were several factors that contributed to patient's condition. Firstly, the history of contracting an acute respiratory infection prior to development of neurological complications which further proved to be SARS-CoV-2 infection by identification of IgG to N-protein of SARS-Cov-2. It is worth noting that according to multicenter study conducted in South Korea among the children to see antibody responses to SARS-CoV-2 revealed that anti-SARS-Cov-2 IgG antibodies become detectable in all children after 14 days from onset of SARS-Cov-2 [25]. Apart from molecular mimicry that is well known in development of cross-reaction against myelin of the host nerves. Another risk factor that could possibly trigger inadequate immune reaction was thymus enlargement identified during chest organ investigation. Given the fact that thymus has a major role in differentiation and maturation of T-cells, thymic enlargement could play an important role in developing many conditions including respiratory distress and autoimmune disorders [26,27]. Finally, the reason for the late hospital admission which led to multifocal pneumonia with type 2 respiratory failure and negative metabolic changes was home treatment and misdiagnosis and underestimation of child's condition. At the time of admission parents could not recall what treatment was prescribed by the private medical center pediatrician and did not present it later.

In conclusion, the case of the 5-month-old infant highlights the challenges in diagnosing and managing neurological complications related to COVID-19. While Miller Fisher Syndrome (MFS) is a rare form of Guillain-Barré Syndrome (GBS), this case emphasizes the importance of increased awareness of unique and less common clinical presentations during the ongoing COVID-19 pandemic.

Several factors contributed to the child's condition. Initially, the respiratory symptoms were misdiagnosed as acute respiratory viral infection (ARVI), leading to a delay in appropriate medical care. Subsequently, the identification of IgG to N-protein of SARS-CoV-2 indicates that the child had previously contracted SARS-CoV-2. This highlights the significance of considering

COVID-19 as a potential trigger for neurological complications, even in young children. The absence of anti-GQ1b antibodies, which are usually related to MFS, in our patient's case highlights the atypical nature of the condition and serves as a reminder that clinical diagnosis should not solely rely on the presence of specific antibodies. The thymus enlargement discovered during chest organ investigation contributes an additional level of complexity to the case. Thymic enlargement can impact immune responses, and its role in contributing to autoimmune disorders and respiratory distress should not be underestimated.

In addition, the rapid and positive response to intravenous immunoglobulin treatment further supports the hypothesis that COVID-19-triggered immune-mediated neuropathy may involve cross-reactivity and molecular mimicry between SARS-CoV-2 antigenic epitopes and cranial nerve glycoproteins. This case adds valuable evidence to the growing body of knowledge regarding the neurological symptoms of COVID-19, emphasizing the significance of timely diagnosis and appropriate treatment. Furthermore, it highlights the necessity for further research to enhance our comprehension of the intricate connection between viral infections, the immune system, and neurological problems. We suggest that healthcare providers should maintain a high level of suspicion for neurological complications, particularly in cases where initial symptoms may be linked to a SARS-CoV-2 infection. This approach can facilitate prompt diagnosis and treatment, which may result in more favorable outcomes among affected individuals.

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CONTENTS

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