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EDITORIAL

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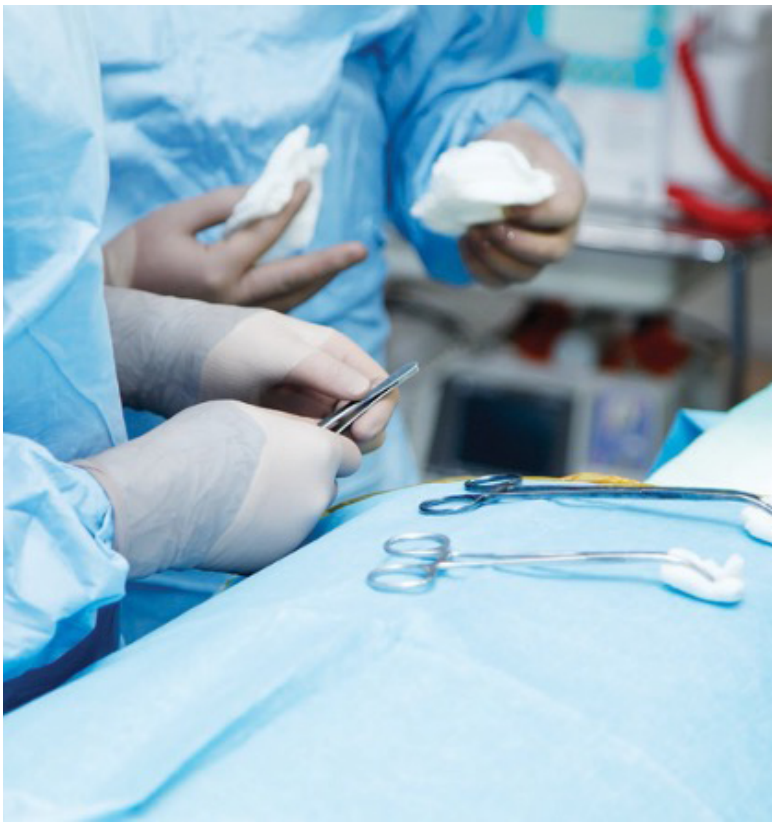

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The theoretical crisis of trust in science is becoming science's practical crisis: Perspective through the eyes of citations

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Abstract

The claimed crisis in science has many origins that, when observed uniquely, might got give the impression of a widespread problem. However, when their integrated networks are appreciated, the crisis then begins to take on a form and life of its own. This letter looks at the basis for a potential crisis in any field of research through the prism of citations, specifically the citation of articles that may become invalidated through retraction, or whose integrity may be weakened through an associated expression of concern (EoC). Fields of research, or bodies of literature of individual researchers, that are weakened by an excessive volume of retractions or EoCs face intellectual and scientific implosion.

Key words: expressions of concern; integrity; network; retractions; transparency; trust.

Dear *Journal of Clinical Medicine of Kazakhstan* Editors,

The crisis of trust in science – including as a factor of replication – has been building over the past few years, as has the evidence to support that theorem [1]. While much has been said about the crisis itself, its agents of induction, and the reasoning for why this crisis has emerged at this time in the history of science – research and publishing, even – is beyond the objectives of this brief note, but are issues that require a thoughtful debate nonetheless. Rather, in this brief note, the citation factor is highlighted. A citation, or the reliance on a paper by another document – whether it be published in a peer-reviewed outlet or in grey literature such as preprints – to support a statement or claim, serves as the bedrock upon which larger scientific, technological and socio-political decision-making frameworks are built, including the use or abuse of citation-based metrics [2].

The science of how information is connected via citations, or bibliometric analyses of citing and cited papers, allows for an appreciation of clues – via patterns – that may point towards possible ethical issues with papers, such as plagiarism, invalid authorships, or editorial abuses [3]. When a citation's central thesis is challenged or disproved, or when complementary explanations are provided that might nullify existing concepts or theorems [4], then the work that constitutes the citation – and thus the citation itself – may become invalidated by retraction.

Building slightly on these theses, using a visually simplistic manner, I note how doubtful findings, which may lead to expressions of concern (EOCs) or retraction of the literature [5], might not impact the intellectual security of that paper alone and, through citation – and thus a physical and meta-physical link – will impact neighboring and/or surrounding papers (or citations) (Figure 1). When a large portion of literature in a field of study becomes associated with EoC-annotated papers, then that field of study may start to become unreliable, and when the majority of the literature in it becomes unreliable (EoCs) or invalidated (retractions), then it risks collapsing the scientific basis of that entire field of research.

While the temporal framework in which the collapse of science's integrity – as measured by its citation integrity – might differ, as a result of multiple factors (e.g., community receptivity to correcting the literature, speed of investigations, editorial biases, etc.), the structural framework's degradation becomes exponential because of the physical link of a paper with any volume of papers (Figure 1). Science might very well be in steps

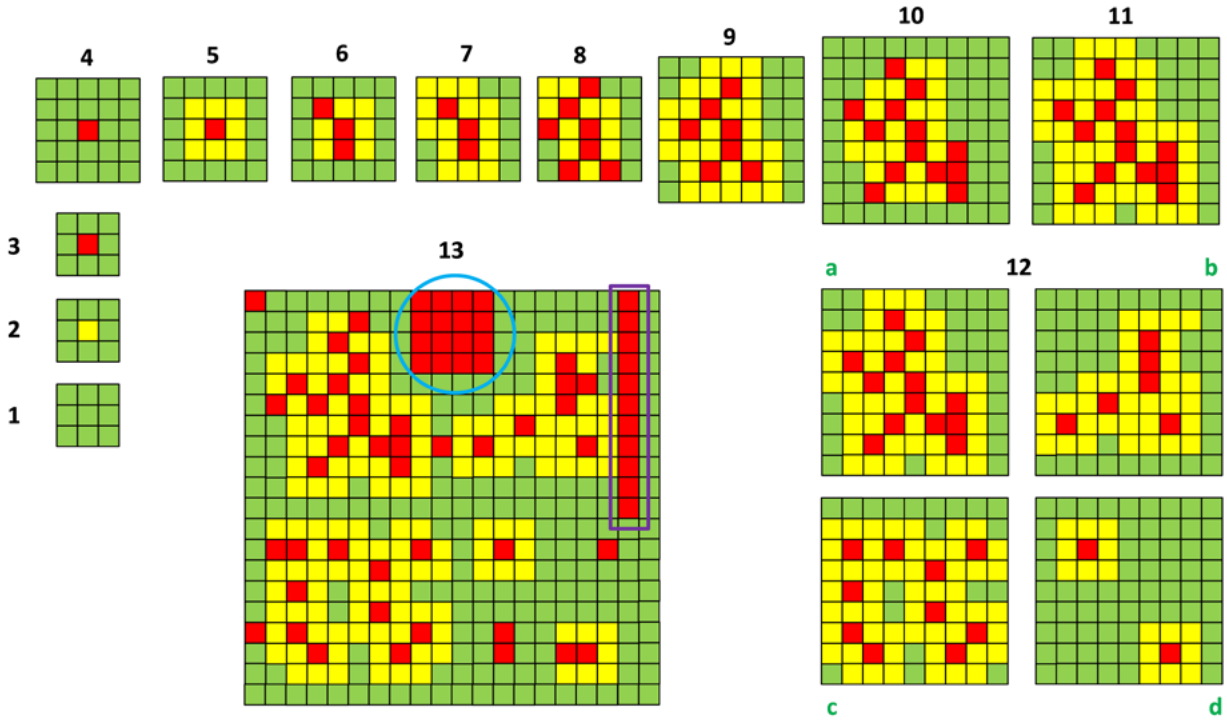

Figure 1 – Simplistic diagram to demonstrate the citation-based fallibility of the scientific literature

5 and 6 (Figure 1), but in just a few years, it is not impossible to envision a situation where the scientific integrity of entire fields of study might face collapse and thus invalidation (step 12, a and c in Figure 1).

A detailed explanation of Figure 1 is warranted. A paper becomes a citation the minute that it is relied upon for whatever reason, and is cited for that purpose. The most prevalent form of citation would be of one paper (peer-reviewed or not) by another, represented in this figure as a square. Thus, in this square, the limit is set that any one paper (i.e., square) can influence – via citation – another four papers (on horizontal and vertical axes), or eight papers (when diagonal directions are also considered), each of which has the ability to then influence other papers – again, via citation. Ultimately, a network of citations forms as a natural (or manipulated) link between papers. A paper (and its citable intellect) is considered to be intact and thus "safe" unless proved otherwise (step 1). However, when a doubt is raised, and an EoC is issued, a doubt is cast on that paper, and this initially places focus on that paper alone (step 2). However, should that paper be retracted, thereby invalidating that citation (via the invalidation of the paper), then the papers (or other media, such as social or news media) that have cited it – or otherwise relied upon it, become negatively impacted by their reliance or dependence on, or association with, that invalidated paper (retracted citation). In this figure, impact is the line that is in contact with the EoC-associated paper (yellow squares) or with retracted papers (red squares), and that contact can be vertical, horizontal, or diagonal. In a micro-field of research in which the retracted paper might only impact 1/8 papers (step 3), the impact is tangibly larger than a slightly larger field of research, such as 1/24 papers (step 4). Evidently, in real science, a field of research is not made up of just 8 or 24 papers, so in this figure, due to size restrictions, a square is merely a theoretical construct, so one square could actually represent dozens, hundreds or even thousands of papers. However, a paper invalidated by retraction – exceptions to that rule are not debated here – might invalidate statements, claims or facts in papers that have cited it, and doubts might then be raised about those papers "in contact with" the retracted paper, leading to a "ring" of potentially "tainted" papers around an invalidated paper (step 5). Each of those "tainted" papers might then be scrutinized, and be – to some degree or another – invalidated, leading to EoCs being issued for neighboring citing papers, or even retractions (step 6). Over an undefined period of time, challenged (yellow) and invalidated (red) papers begin to form a widening mass that then becomes, in the same theoretical cluster of 25 papers, the majority (steps 7 and 8). And, as the field of research – or the field of influence – widen, impacting a wider network of papers and citations (49 in step 9, or 81 in step 10), the intellectual impact of the flaw that was originally restricted to just one paper (step 1), now could – again, theoretically – impact a minority (33/91 in step 10) or a majority (64/91 in step 11) of the associated literature. If this situation is taking place in four fields of study (a, b, c, d) (step 12), each of which – when observed singly – appear to exist independent of each other, then it can be argued that they might be weakly (d), mildly (b) or strongly (a, c) negatively impacted by a network of papers that have been subjected to EoCs or retractions. Given the interdisciplinary nature of science, the negative impact in one field of research might not necessarily be restricted to that field of research, and may eventually begin to encroach on the literature of other fields of research (step 13, where the four fields of study in step 12 become linked, or amalgamated). Entire chunks of literature (e.g., of a scientist, or of a very specific micro-segment of a field of study) might be entirely invalidated when all literature is retracted (blue circle or purple rectangle in step 13).

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Side effects and efficacy of low-dose amiodarone in rhythm disorders

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Abstract

Amiodarone is one of the most widely used antiarrhythmic drugs, which is the most effective drug for maintaining sinus rhythm. Taking this drug correlates with side effects such as pulmonary toxicity, thyroid dysfunction, neurotoxicity, hepatotoxicity, and skin manifestations. In addition, in some cases, amiodarone remains as a first-line therapy to maintain sinus rhythm. The side effects of amiodarone depend on the dose and duration of the drug. Systematic reviews and meta-analyses have shown the safety profile of a low dose of amiodarone, defined as 200 mg and a very low dose of amiodarone 100 mg. Due to the use of catheter ablation, the use of a low dose of amiodarone is sufficient. In this literature review, we have cited the side effects of a low dose of amiodarone. In addition, although there is evidence of a safer low-dose spectrum, it is not free from side effects and needs to develop an algorithm for early detection of adverse events, as well as studying the effectiveness according to modern research methods, such as an implantable heart monitor, which in turn is of undoubted interest.

Keywords: low doses of amiodarone, side effects, safety, amiodarone.

Introduction

Amiodarone, a dilodinated benzofuran derivative similar in structure to thyroxine, contains two iodine atoms [1]. Amiodarone is originally known since 1967 as an antianginal drug, later antiarrhythmic effects were identified. Amiodarone is characterized by the Vaughn-Williams classification as having "Class III" properties [2]. Its mechanism of action involves blocking potassium, sodium channels, delaying intracellular calcium and non-competitive blocking alpha and beta adrenoreceptors. These pharmacological properties make amiodarone effective for both therapy of supraventricular and ventricular arrhythmias, and prevention of recurrent AF [1, 2, 3]. Oral bioavailability of amiodarone is approximately 30-50%, due to the benzene ring, amiodarone has a high lipophilicity. In view of which when taken with food rich in fats absorption of the drug is increased by 2.4-3.8 times in comparison with fasting intake [4]. Its side effects are related to its pharmacodynamics and pharmacokinetics, as the highest amiodarone content is found in the liver, lungs, fatty tissues, thyroid gland, kidneys, heart, skin, adrenal glands, testes, eyes and lymph nodes [5].

The dose and duration of administration of amiodarone are the most important factors of adverse events. Previously, the maintenance dose for the treatment of arrhythmias ranged from 200 mg / day to 800 mg / day. After detecting dose dependence and side effects, a lower dosage was taken, which ranges from 100 mg/day to 200 mg/day [6]. Therefore, it is sufficient to prescribe a low dose of antiarrhythmic drugs to maintain sinus rhythm in atrial fibrillation [7, 8, 9].

This drug has been studied for a long time, which, although it is an effective drug, has a wide range of side effects and leads to damage to the thyroid gland, lungs, liver, and nervous system, depending on the dose and duration of use [10].

Despite studies researching standard-dose amiodarone therapy, the severity of side effects with low-dose amiodarone remains incompletely investigated.

Purpose: to evaluate the range of application and safety of low-dose amiodarone in patients with cardiac rhythm disorders.

Objective: to analyze the use and evaluation of the side effects of a low dose of amiodarone according to literature sources.

Methods: A literature search was conducted in the Pubmed, Medline, Cochrane databases by October 2023 for the keywords low doses of amiodarone, safety, side effects. Studies have been included that have reported side effects of amiodarone. These studies included systematic reviews and meta-analyses, randomized controlled trials (RCTs), clinical cases, and a series of clinical cases with 95% confidence intervals (CI). We have reviewed more than 519 articles. After the deletion of 484 articles, 35 articles were retained for further review.

Results

A systematic review and meta-analysis of 2 studies showed that the use of a low dose of amiodarone, defined as 200 mg, showed clinical safety in comparison with higher doses as a second-line treatment after catheter ablation [6, 8, 11]. Similar systematic reviews report complications even with a low dose of amiodarone, defined as 200 mg and a very low dose of 100 mg [10]. On the contrary, Blackman et al. conducted a survey among cardiologists in European countries and concluded that very low doses of amiodarone are used daily by cardiologists and have a low side effect profile [12].

A study by G E Kochiadakis in 2000 compared the effectiveness of drugs such as amiodarone, propafenone and sotalol in patients with atrial fibrillation. As well as a similar study conducted in 2004 comparing low doses of amiodarone (200 mg) and propafenone (450 mg) in patients with AF. In both studies, the authors concluded that amiodarone is the most effective drug, but most often causes side effects, including non-cardiac ones [13, 14]. In 2020, a retrospective study by RongDa Huang studied the comparison of amiodarone and propafenone in patients with AF after catheter ablation. According to the results of this study, it was revealed that amiodarone was associated with a lower frequency of rhythm disruptions [15].

Jong et al indicated the lowest dose of amiodarone in 2006 in a study examining the effectiveness of low doses of amiodarone in maintaining sinus rhythm after cardioversion in atrial fibrillation. In this study, there was no withdrawal of the drug, and therefore it was concluded that there was a low profile of NSAIDs requiring drug withdrawal [16].

In the studies of Mahrian et al., the parallel administration of a very low dose of amiodarone 100 mg and 50 mg compared with placebo in patients with unstable ventricular tachycardia (VT) was studied. During which, in the group receiving 100 mg, complete suppression of unstable VT was revealed, which shows the clinical efficacy of a very low dose of amiodarone [17].

In a retrospective study in patients with coronary heart disease with tachyarrhythmias, such as supraventricular tachycardia and VT, the use of a low dose of AMD less than 200 mg showed that no recurrence of tachyarrhythmia was observed for 2.9 years with SVT and 3.2 years with VT in 36% and 65% of patients, respectively, for 3 years. In 23% of cases, the frequency of side effects was associated with thyroid dysfunction [18].

Next, consider a series of adverse events associated with taking a low dose of 200 mg amiodarone.

There is a description of cases in patients taking AMD at a dose of 200 mg for 2 to 5 years, the appearance of hemoptysis, acute respiratory distress syndrome, which also proves that the duration of administration is important. Exclusion of other potential diseases and improvement after discontinuation of the drug are important in diagnosis [19, 20, 21, 22]. In another description of a series of cases, there is a report of three patients who received AMD at a dose of 200 mg for an average of 6.6 months. The patients were male, 75, 93 and 85 years old, with a history of smoking, whose first complaints were shortness of breath without signs of heart failure. According to the CT scan, alveolar pneumonitis was exposed. The treatment of this complication was the withdrawal of AMD and the administration of corticosteroids with complete recovery [23].

There are descriptions of cases with changes in the skin of a blue-gray, semi-matte skin tone [24, 25, 26].

Some life-threatening side effects have been reported in patients treated with amiodarone only briefly, although such extremely undesirable events occur very rarely [27].

In a meta-analysis conducted by Ruzieh et al., eliminating amiodarone and placebo, they concluded that low doses of amiodarone were not associated with a statistically significant increase in the incidence of adverse events from the lungs, but were still associated with adverse events from the thyroid gland and liver [28].

A very rare case of a woman having a hallucination for the first time after taking AMD for AF paroxysm is described. After the drug was replaced, the side effects were leveled [29].

Amiodarone is known to have non-cardiac side effects, including hepatotoxicity. Among the least common are pseudoalcoholic cirrhosis. The cases of patients with these complications when taking a dose of amiodarone 200 mg per day for several years with the possible exception of other causes of cirrhosis are presented [30, 31, 32].

Since the release of the systematic review by Chokesuwattanaskul et al., articles have been published, clinical cases describing the more frequent detection of side effects when using low AMD. But there is no unified assessment of side effects and their detailed identification, as well as the frequency of these examinations are not described. They also demonstrated the conclusions that, compared with amiodarone at a dose of 200 mg/day, the cumulative estimated frequency of common side effects was 0.11 (95% CI: 0.04–0.27), while the frequency of side effects requiring drug withdrawal was 0.02 (95% CI: 0.01–0.06) for a dose of 100 mg/day [11]. Another point of view was expressed by the author A. Reiffel, that low doses of amiodarone are not quite as safe as they seem [33].

In our literature review, we can note the weaknesses that do not reflect all the side effects that AMD has.

Conclusion

There are very few randomized studies examining the efficacy and safety of a low dose of amiodarone after catheter ablation. Currently, there are no systematic reviews and meta-analyses, controlled studies confirming the effectiveness of a particular treatment, the clinical safety profile is evaluated everywhere, which is also not fully disclosed. Based on the pharmacokinetics study the principal finding is that a very low dose of amiodarone (100 mg every day) is effective in maintaining sinus rhythm in patients with AF. Amiodarone is commonly utilized for treating both supraventricular and ventricular arrhythmias. While this drug is a very effective antiarrhythmic agent, it also leads to many well-known side effects involving a variety of organs such as the thyroid, liver, lungs, and eyes including many that are dose- and duration-dependent.

Table 1 Side effects of a low dose of amiodarone

№	The title of the article	Authors	Design	Indications for the use of amiodarone	The dose and duration of taking amiodarone	Side effects	The authors' conclusions
1	Amiodarone-induced Hemoptysis: A Rare Presentation of Amiodarone-induced Pulmonary Toxicity Occurs at a Low Dose	Busch, Clayton D et al, 2019 [19]	Case report	AF	200 mg/day, 5 years	Hemoptysis, diffuse alveolar hemorrhage	The manifestation of the side effect of amiodarone can be detected at any dose.
2	Acute respiratory failure on a low dose of amiodarone – is it an underdiagnosed and undertreated condition?	Mijo Meter et al, 2021 [20]	Case report	AF	200 mg/day, 5 years	Acute respiratory distress syndrome	It is important in making a diagnosis to exclude other potential diseases and improve after discontinuation of the drug
3	Amiodarone-related pneumonitis	Sheng-Nan Chang, 2007 [23]	Case report	AF	200 mg/day, 6.6 months	Shortness of breath without signs of heart failure	The treatment of this complication was the withdrawal of AMD and the administration of corticosteroids with complete recovery
4	New-onset hallucinations with amiodarone: a case report.	Jessica Molinaro, 2022 [29]	Case report	AF	200 mg twice a day, 7 days	Visual and auditory hallucinations	The hallucinations disappeared on the third day after the withdrawal of amiodarone, which may be due to the two-phase elimination of amiodarone from the body and an improvement in the condition
5	A low dose of amiodarone-indused sinoatrial node dysfunction: a case report	Ayurzana et al, 2022 [34]	Case report	AF	100 mg/day, 2 month	A long sinus pause (4-7,9 seconds)	Amiodarone decline palpitations, but develop sinoatrial node dysfunction
6	"Blue-grey syndrome" – A rare adverse effect of amiodarone	Hana Kuncipálová, 2018 [35]	Case report	AF	200 mg/day, 6 years	blue-gray discoloration of the face, neck, earlobe and back of the hands	Prolonged use of even a low dose of amiodarone can lead to the appearance of skin pigmentation with subsequent disappearance after discontinuation of the drug

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Influence of Genetic Polymorphisms in CYP3A5, CYP3A4, and MDR1 on Tacrolimus Metabolism after kidney transplantation

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Abstract

Kidney transplantation stands as the ultimate recourse for restoring vital organ functions, particularly in cases of end-stage kidney disease where alternative treatments, such as dialysis, prove less effective. With over 102,000 kidney transplants conducted globally in 2022, the demand for organ transplantation is ever-increasing, fueled by a rising incidence of end-stage renal disease attributed to causes like diabetes and hypertension.

Despite significant advancements in kidney transplantation, immunosuppressive therapy remains crucial to preventing graft rejection. Tacrolimus (TAC), a calcineurin inhibitor, plays a pivotal role in this regard. Discovered in 1984, TAC inhibits T-lymphocyte activation, preventing acute rejection by disrupting the transcription of crucial genes involved in early T-cell activation. However, the use of TAC is not without challenges. The drug exhibits serious side effects, a narrow therapeutic index, and unpredictable pharmacokinetics. Therapeutic drug monitoring (TDM) becomes imperative in daily practice to maintain TAC blood concentrations within the therapeutic range. This literature review delves into the genetic aspects influencing TAC metabolism, focusing on key polymorphisms in CYP3A5, CYP3A4, and ABCB1 genes. Genetic variations in CYP3A5, a major enzyme in TAC metabolism, impact enzyme activity, necessitating personalized dosing strategies. CYP3A4 polymorphisms, especially CYP3A4*22, demonstrate associations with altered TAC clearance and dose requirements. The ABCB1 gene, encoding P-glycoprotein, another player in TAC pharmacokinetics, also exhibits polymorphisms influencing drug absorption and distribution. The ABCB1 3435C>T variant, in particular, shows potential implications on Tacrolimus bioavailability. Understanding these genetic variations aids in the development of personalized dosing regimens. Studies suggest that tailoring TAC doses based on CYP3A5 genotypes significantly improves the proportion of patients achieving therapeutic concentrations. Additionally, incorporating genetic information, particularly CYP3A4*22, into dosing strategies enhances the precision of TAC therapy, reducing the risk of adverse effects. .

Keywords: kidney transplantation, tacrolimus, immunosuppressive therapy, genetic polymorphisms, pharmacogenetics, pharmacokinetics.

Introduction

Transplantation is the last resort to restore vital organ functions when there are no other options that offer similar effectiveness. Hence, kidney transplantation stands as the sole remedy for end-stage kidney disease. An effective kidney transplant enhances life quality and diminishes the mortality hazard for the majority of patients in contrast to ongoing dialysis treatment [1].

The inaugural kidney transplant took place in a canine at the Vienna Medical School in Austria. In 1954, a significant breakthrough occurred when Joseph Murray achieved the first long-term successful human kidney transplantation; the procedure involved monozygotic twins, and remarkably, the transplanted organ endured for 8 years [2].

Nowadays, the kidney is the most transplanted organ worldwide. In 2022, a total of 102,090 kidneys were transplanted in Americas, Europe, the Western Pacific, Southeast Asia, the Eastern Mediterranean, and Africa [3].

The prevalence of end stage renal disease is experiencing a swift increase. Diabetes and hypertension stand as the leading causes of renal failure. Other factors contributing to chronic kidney disease or end stage renal disease are categorized into prerenal causes (chronic or acute ischemia), intrinsic renal causes (such as glomerulonephritis and focal-segmental glomerulosclerosis), or postrenal causes (including reflux nephropathy and obstruction) [4].

Despite the huge growth in the field of kidney transplantation, which is reflected in a fairly large number of successful long-term outcomes, kidney transplantation from a donor who is not an exact match, without the introduction of immunosuppressants, invariably leads to rejection and loss of the allograft. Thus, almost all the patients with renal allograft require ongoing immunosuppressive treatment.

The optimal ongoing immunosuppressive treatment for kidney transplantation remains uncertain. Various combinations of significant immunosuppressive agents accessible [1]. Treatment plans typically involve combinations of these immunosuppressive agents. A carefully selected regimen aims to minimize the morbidity and mortality correlated with each class of agent, all the while striving to enhance overall efficacy.

The choice of regimen depends not only on the knowledge and on experience of the attending physician, but also on many other factors such as age, weight, ethnicity, as well as the organs function responsible for drugs metabolism. That is why pharmacogenetics has gained special importance in recent decades, playing a critical role in interindividual variability in drug disposition and effects.

In this work, a literature review will be conducted regarding Tacrolimus (TAC), as the main immunosuppressive drug after kidney transplantation, from the point of view of the genetic characteristics of its metabolism.

Aim of the review: The purpose of the review is to study the genetic aspects affecting the metabolism of TAC as the main immunosuppressive drug in patients undergoing kidney transplantation. Special attention is paid to key genetic polymorphisms such as CYP3A5, CYP3A4 and ABCB1, which are considered crucial in the metabolism and pharmacokinetics of TAC. The review highlights the effect of genetic variations on the activity of enzymes encoded by the named above genes. The review presents data that can be used to develop personalized dosage regimens for TAC. As a result, it can increase the accuracy of TAC therapy, optimize the timing of achieving therapeutic concentrations, and reduce the manifestation of side effects for each individual patient.

Tacrolimus (TAC) in Kidney Transplantation

TAC serves as a pivotal immunosuppressive agent, crucial in preventing organ transplant rejection. This calcineurin inhibitor was identified in 1984 through the fermented solution derived from a soil sample obtained in Japan, containing the bacterium Streptomyces tsukubaensis [5].

Research has shown that TAC hinders T-lymphocyte activation by initially binding to an intracellular protein called FKBP-12. This binding forms a complex comprising tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin, which subsequently inhibits the phosphatase activity of calcineurin. Consequently, this inhibition prevents the dephosphorylation and translocation of the nuclear factor of activated T-cells (NF-AT), a nuclear component believed to trigger gene transcription necessary for lymphokine formation. Additionally, TAC suppresses the transcription of genes encoding IL-3, IL-4, IL-5, GM-CSF, and TNF-α, all of which play roles in the initial stages of T-cell activation and, consequently, in the development of acute rejection [5].

Despite the enormous benefits that TAC brings to patients with kidney allograft, it is still a medical drug with a number of quite serious adverse effects, a limited therapeutic range, and pharmacokinetics that are variable and difficult to predict. Therefore, Therapeutic Drug Monitoring (TDM) is essential in routine clinical practice. Patients who have undergone renal transplantation typically start with a standard weight-dependent dosage of TAC, which is then corrected according to TDM to keep TAC blood levels within the desired therapeutic range [6]. Nonetheless, owing to variances in individual first-pass effects, attaining the target TAC concentration might be subject to a relative delay. Furthermore, reaching the desired concentration does not guarantee the intended therapeutic outcome or prevent adverse reactions [7].

CYP3A5, CYP3A4 and ABCB1 polymorphisms characteristic

The CYP3A subfamily responsible for the phase I metabolism of more than half of the drugs administered, is primarily found in hepatocytes, biliary epithelial cells of the liver, and the villous columnar epithelial cells of the jejunum [8]. CYP3A5 and CYP3A4, constituting around 30% of hepatic cytochrome P450, are crucial in metabolizing TAC [8-10]. Genetic polymorphisms in CYP3A5 and CYP3A4 genes contribute to variations in drug metabolism, including TAC [11].

The CYP3A5*1 allele encodes the functional form of CYP3A5, which is associated with elevated enzyme expression, whereas the nonfunctional *3 allele leads to the lack of gene expression [9, 12]. The prevalence of these alleles varies across populations, with CYP3A5*3/*3 genotype being prevalent in Caucasians and African Americans, influencing enzyme expression levels [13-16].

The CYP3A4*22 allele, characterized by the C>T substitution (rs35599367) in intron 6 of the CYP3A4 gene, correlates with reduced mRNA levels and enzyme activity within the liver, this allele could account for differences in individual reactions to drugs metabolized by CYP3A4 [17, 18].

The ABCB1 gene is responsible for encoding P-glycoprotein, which plays a role in multidrug resistance by expelling drugs from cells, variations in the ABCB1 gene, notably in exon 26 (C/T at position 3435), impact the expression levels of P-glycoprotein [19]. Carriers of the T-allele exhibit lower levels of P-glycoprotein compared to C/C homozygotes.

These genetic variations play a crucial role in individual responses to drugs, emphasizing the importance of pharmacogenomics in personalized medicine. In the Table 1 a summary overview of the alleles, associated reference single nucleotide polymorphisms (SNPs), and the functions of the SNPs in the specified genes (CYP3A5, CYP3A4, and ABCB1) is provided.

Table 1 Genotype variants and SNP effect of alleles [9, 17]

Allele	Reference SNP (dbSNP)	Function of SNP
CYP3A5*1	Wild type	Normal function
CYP3A5*2	rs28365083	missense
CYP3A5*3	rs776746	cryptic splice site
CYP3A4*1	Wild type	Normal function
CYP3A4*22	rs35599367	changes the folding of sin-gle-stranded DNA and RNA
ABCB1:c.1236T>C	rs1128503	Exon skipping

The CYP3A5 polymorphisms influence on TAC metabolism

Review, that studied several published data on CYP3A5 influence on TAC metabolism in kidney transplant recipients, performed an information on two meta analyses which included 56 studies in summary [15, 21, 22]. Individuals with the *3/*3 genotype consistently displayed considerably elevated trough concentrations adjusted for dosage, with a mean difference adjusted by weight of 63.57 ng/mL per mg/kg (95% confidence interval [CI]: 50.85–76.30) [21]. This difference was observed when compared to a combined group of *1/*3 and *1/*1 patients. The effect was consistent across diverse ethnic groups (Caucasian and Asian) and different time intervals following transplantation (≤1 month, 3–6 months, 12–24 months) [20]. Similar findings were reported, reinforcing the outcomes. TAC dose-adjusted trough concentrations were significantly lower in individuals expressing CYP3A5 [22].

In a retrospective study, a weight-based initial dose of 0.1 mg/kg targeted a therapeutic range of 4–8 mcg/mL, revealing that while 50% of individuals with the CYP3A5 non-expressor genotype reached the target concentration within three days, only 35.3% of expressors achieved the same, with TDM aiding in dose adjustments, leading to 64.2% of expressors and 55.4% of non-expressors attaining therapeutic trough concentrations by the 7th day, suggesting potential benefits of CYP3A5 genotyping prior to kidney transplantation [23]. These results imply that performing CYP3A5 genotyping before kidney transplantation may offer benefits [15].

In a prospective randomized controlled trial, that compared the standard and genotype-based dosage of TAC, the majority of patients (78.8%) had the CYP3A5 *3/*3 genotype (as Caucasian population was predominant 89,9%), with 16.9% being *1/*3 heterozygotes and 4.2% *1/*1 homozygotes [24]. There was no disparity in allele frequency between standard and genotype-based dosing groups. By day 3, the genotype-based dosing group exhibited a significantly higher proportion of patients who achieved therapeutic TAC concentrations compared to the standard dosing group ($p<0.05$) [24]. The results of the study are presented in Table 2.

Table 2 Results of genotype-based dosing and standard dosing [24]

	CYP3A5*1/*1	CYP3A5*1/*3	CYP3A5*3/*3
Standard dosing (mg/kg/d)	0.200	0.200	0.200
Tacrolimus concentrations within the therapeutic range (percentage)	29.1		
Genotype-based dosing (mg/kg/d)	0.3	0.3	0.15
Tacrolimus concentrations within the therapeutic range (percentage)	43.20		

In a retrospective study on a Kazakh population comprising 80 kidney transplant recipients, participants were divided into homozygous (*3/*3) and heterozygous (*1/*3) groups, all administered TAC at an initial dose of 1 mg/kg body weight; TAC concentrations were measured at various intervals up to the 14th day, revealing higher concentrations in *3/*3 heterozygous carriers with significant differences observed on the 2nd, 5th, 7th, and 10th days in both groups ($p = 0.02$, 0.01, 0.12, and 0.016, respectively), while no statistically significant differences were noted on the 14th day post-surgery and at discharge ($p = 0.085$ and 0.171, respectively), with TAC nearing the target level in both groups by the end of the second week [16].

The Clinical Pharmacogenetics Implementation Consortium issued guidelines in 2015, providing recommendations for the genotype-based dosing of TAC with respect to CYP3A5 [25]. According to the recommendations, recipients after kidney transplantation with the CYP3A5*1/*1 or CYP3A5*1/*3 genotype experience notably lower dose-adjusted trough concentrations of TAC compared to those with the CYP3A5*3/*3 genotype. Carriers of the *1 alleles typically require 1.5–2 times higher dosage to achieve similar blood concentrations as *3 carriers, as shown in the Figure 1 (see the next page).

The CYP3A4 polymorphisms influence on TAC metabolism

The impact of the CYP3A4*22 genetic polymorphism on C0/D was assessed through a meta-analysis that involved eight cohort studies with data of 2,624 patients [26-33]. This analysis included a comparison of C0/D in 6 time periods during the first year after transplantation. Combining data across all study periods revealed that CYP3A4*22 carriers exhibited a significantly higher C0/D than CYP3A4*1/*1 recipients, with considerable differences observed in C0/D, except during the first 2 weeks post-transplantation. Despite substantial heterogeneity ($I2 = 76\%$, $p < 0.00001$), no subgroup differences were reported across time periods [34].

Among this meta-analysis six studies assessed the impact of the CYP3A4*22 variant on the daily TAC dose [26, 27, 29, 30, 32, 33]. The combined data indicated that CYP3A4*22 carriers required a 2.02 mg/day lower dose to achieve the optimal trough level compared to non-carriers ($p < 0.00001$), except for 1-year post-transplantation. Substantial heterogeneity was present

CYP3A5 phenotype	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations	Classification of recommendations
Extensive metabolizer (CYP3A5*1/*1 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.d Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5*1/*3 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.a Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5*3/*3 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Figure 1 – Consortium dosing recommendations for TAC based on CYP3A5 phenotype [25]

(I2 = 75%, p < 0.00001), with no significant subgroup differences. Sensitivity analyses were conducted, revealing reduced heterogeneity when excluding data from the first week and 1 year after transplantation.

To evaluate the individual influence of CYP3A422 while accounting for CYP3A53, the effect of CYP3A4*22 in individuals lacking CYP3A5 expression was examined in four studies conducted within 3 to 6 months post-kidney transplantation [26, 29, 35, 36]. After adjusting for CYP3A5*3, CYP3A4*22 carriers showed a 0.67 ng/mL/mg higher C0/D (p < 0.00001) and a 1.83 mg/day lower dose requirement (p < 0.00001) compared to CYP3A4*1/*1 carriers, indicating a significant effect of CYP3A4*22 on TAC pharmacokinetics and dose requirement even after adjusting for CYP3A5*3, what is shown in the Table 3.

the remaining subgroups. The 3435CT variant did not have a discernible impact on TAC dosage within subgroups categorized by various initial doses.

The findings revealed no significant difference in dosage between ABCB1 3435CC and ABCB1 3435CT, however, ABCB1 3435TT exhibited a notably lower dosage than ABCB1 3435CC [37].

This review of fifteen studies examined the association between the genetic variant ABCB1 3435C>T and the C0/D ratio at different time points post-transplantation. The results revealed a significantly higher C0/D ratio in ABCB1 3435T carriers compared to ABCB1 3435CC carriers at 1 and 6 months post-transplantation, with a trend towards higher ratios observed at 7 days, 3 months, and 1 year post-transplantation. Subgroup analysis based on initial TAC dosage showed that ABCB1 3435T

Table 3 Comparative Analysis of CYP3A4*22 and CYP3A4*1/*1 in Tacrolimus Pharmacokinetics and Dosing [26-36]

Analysis	Comparison	Outcome	Result (95% CI)	p-value	Heterogeneity (I2, p)
CYP3A4*22 vs. CYP3A4*1/*1 [26-33]	C0/D in Various Post-Transplant Periods	Higher C0/D in CYP3A4*22 carriers	0.57 ng/mL/mg (0.28 to 0.86)	0.0001	I2 = 76%, p < 0.00001
CYP3A4*22 vs. CYP3A4*1/*1 [26,27,29,30,32,33]	Daily Dose Re-quirement	Lower dose requirement in CYP3A4*22 carriers	-2.02 mg/day (-2.55 to -1.50)	< 0.00001	I2 = 75%, p < 0.00001
CYP3A4*22 vs. CYP3A4*1/*1 (Adjusted for CYP3A5*3) [26,29,35,36]	C0/D and Dose Requirement in CYP3A5 Non-Expressers	Higher C0/D and Lower Dose Re-quirement in CYP3A4*22 carriers	C0/D: 0.67 ng/mL/mg (0.44 to 0.89), Dose: -1.83 mg/day (-2.59 to -1.06)	< 0.00001	Not specified

ABCB1 polymorphisms influence on TAC metabolism

Based on a review encompassing 16 studies focusing on the influence of ABCB1 polymorphisms on TAC dose and concentration (C0/D), recipients were categorized into two groups: ABCB1 3435CC and ABCB1 3435T (comprising CT and TT variants), with their dose and C0/Dose ratio compared across various post-transplantation timeframes, ethnicities, and initial TAC doses [37].

The findings indicated that ABCB1 3435CC carriers required a dosage increase compared to 3435CT variant carriers, however, there were no notable variances observed in carriers had a higher C0/D ratio than ABCB1 3435CC carriers in both the 0.08-0.14 mg/kg per day and 0.15-0.2 mg/kg per day subgroups [37].

The meta-analysis revealed that the genetic variant ABCB1 3435C>T influences the pharmacokinetics of TAC in adult renal transplant recipients during the first year post-transplantation. Patients with the ABCB1 3435T variant showed a higher dosage ratio compared to those with the ABCB1 3435CC genotype. Notably, individuals homozygous for ABCB1 3435TT demonstrated significantly higher TAC dosage and a lower dosage ratio compared to those with ABCB1 3435CC.

Genotype tests cost-effectiveness

A study examining TAC administration, TDM, and hospitalization costs for kidney transplantation across CYP3A5*1/*1, *1/*3, and *3/3 genotypes found that CYP3A51/1 patients had the highest median combined costs for TAC and TDM ($1062) and hospitalization ($9097), followed by CYP3A51/3 patients with costs of $859 for TAC and TDM and $6467 for hospitalization, while CYP3A53/3 patients incurred the lowest costs, with $761 for TAC and TDM and $5604 for hospitalization, moreover the analysis revealed that CYP3A51/1 patients had significantly higher hospitalization costs compared to CYP3A51/3 patients (by $2787), though this difference had marginal significance, and they also incurred significantly higher costs for TAC and TDM (by $309) and hospitalization (by $3275) compared to CYP3A53/*3 patients.

Other studies on the cost-effectiveness of genotyping have indicated that conducting genotyping for all transplant recipients is currently financially prohibitive in numerous countries due to the elevated expenses associated with pharmacogenetic tests. Nevertheless, there is optimism regarding potential changes in the future, driven by the generation of valuable data from pharmacogenetic studies and advancements in genotyping analyses leading to cost reductions [39-42].

For example, genetic tests for determining CYP2D6 and CYP2C19 polymorphisms, crucial for drug metabolism, cost around $350 to $400. Although most genetic tests are priced in a few hundred dollars, they are expected to become less expensive in the future [38]. However, to justify these costs, genotypic analyses must demonstrate a significant improvement in transplant patient outcomes and cost savings [38].

The scenario regarding the expenses and insurance provisions for pharmacogenetic testing varies greatly. Multigene panel-based tests are typically not covered by insurance, with patients facing a median cost of approximately $700. Single-gene tests may receive coverage for specific genes like CYP2C19, CYP2D6, and HLA-B, depending on the indication. The highest mean cost billed to a patient for a single-gene pharmacogenetic test exceeded $1200, with an average insurance coverage of $160. Coverage for CYP3A5 testing for TAC dosing is infrequent, resulting in a median patient cost of approximately $300 [38].

The cost-effectiveness of genotype testing for kidney transplant recipients hinges on the ability of genotypic analyses to significantly enhance patient outcomes and demonstrate cost savings, while the current costs and insurance coverage for pharmacogenetic testing remain variable and may evolve in the future.

Conclusion

In conclusion, the integration of pharmacogenetics into clinical practice holds promise for refining TAC therapy in kidney transplantation, optimizing dosing regimens, and ultimately improving patient outcomes. As research in this field progresses, the vision of personalized medicine in transplant care may move closer to realization, offering tailored approaches that enhance efficacy while minimizing adverse effects.

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Prevalence, incidence, gender and age distribution, and economic burden of psoriasis worldwide and in Kazakhstan

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Abstract

Aim: This study aimed to conduct a literature review on the prevalence, incidence, gender and age distribution of psoriasis, as well as the economic burden of psoriasis worldwide, including Kazakhstan.

Material and methods: A literature review was conducted using keywords in PubMed, Scopus, Web of Science, eLibrary.ru databases, and Google Scholar to identify relevant articles.

Results: The prevalence of psoriasis varies by geographic location and race. However, psoriasis is predominantly common in Western countries and among people of European descent: in Norway (4.6%), France (4.42%), Portugal (4.4%), and the United States of America (3.0%). Significant differences in the prevalence of this disease were identified in Kazakhstan, ranging from 0.86% to 2.5%. In many Western countries, the incidence rate of psoriasis is significantly higher than the global incidence rate (57.8 cases per 100,000 population): in Denmark (199.5), Italy (230.62), and Israel (280), respectively. In Kazakhstan, the incidence rate is 35.0 per 100,000 population, which is almost 1.7 times lower than the global rate. Psoriasis affects both genders. There is a bimodal pattern of manifestation of psoriasis with early (type I) and late (type II) onset, which occurs in the age range of 30–40 years, and about 60 years. In addition, treating and providing medications to patients with psoriasis represents a significant economic burden for both the government and the patients themselves.

Conclusion: The study made it possible to determine the current epidemiological situation of psoriasis worldwide, including Kazakhstan, as well as to assess the economic burden of this disease.

Keywords: psoriasis, prevalence, incidence, gender and age distribution, economic burden.

Introduction

Psoriasis is a common chronic, non-infectious, immune-mediated systemic disease caused by polygenic inheritance and induced by multiple environmental factors [1]. Psoriasis affects about 125 million people worldwide [2,3]. Along with skin manifestations, in 30% of patients with psoriasis, joints are also affected [3,4]. According to many studies, the most common clinical phenotype of psoriasis is plaque psoriasis. For instance, in Ethiopia – 62.9% [5], Egypt – 84.1% [6], Nigeria – 88.1% [7], Australia – 89% [8], Russia – 89.5% [9], India – 90% [10], Japan – 97.4% [11], and China – 97.06% [12], at the same time, mortality rates from all cases in patients with psoriasis are 20% higher than in patients without psoriasis [13].

Psoriasis can begin at any age. However, data on the incidence of psoriasis show a clear bimodal age pattern of the onset of the disease; according to some data, the first and second peaks occur at 20-30 and 50-69 years [14,15], and according to other sources, at 30-39 and 60-69 years [16]. In 75% of cases, the disease manifests itself before the age of 40 [17]. Psoriasis affects both men and women equally, but is more common in non-Hispanic whites [14,15]. The disease leads to long-term physical and psychological complications [18] and entails significant costs since it mainly affects

people of working age, which leads to decreased productivity and significant indirect costs [19]. To date, there is no cure for psoriasis [20].

The prevalence of psoriasis varies around the world. Approximately 2-4% of the population in Western countries suffers from this disease [21]. The global age-standardized prevalence rate of psoriasis is 811 cases per 100,000 population, which is approximately 0.84% of the world's population, or about 64.6 million people. The highest prevalence rates of psoriasis have been reported in North America and Western Europe, and the lowest in the Asia and Western Pacific regions [22]. In particular, more than 4.5 million cases of psoriasis were registered worldwide in 2019.

The global age-standardized incidence rate of psoriasis is 57.8 cases per 100,000 population. The highest incidence rate of psoriasis was observed in Western Europe (204.5 cases per 100,000 people), followed by the region of Australasia (145.4) and North America (92.0) (with a high level of income), and the lowest incidence rate was detected in Southeast Asia (20.1), followed by central Latin America (20.7) and Eastern Sub-Saharan Africa (25.1) [23]. According to some estimates, the regional incidence of psoriasis varies from 0.4% in Asian countries to 11.43% in Norway, and among children and adolescents, from 0% in Taiwan to 2.1% in Italy [24,25]. In the United States of America, the prevalence of psoriasis among adults is about 3.0-3.2% [24,26]. The age distribution shows that the increase in the incidence of psoriasis begins at the age of 20, reaching a peak at 55-60 years. As reported, women are susceptible to this disease more often than men [22], and according to others, the incidence of psoriasis is the same in both genders [23].

Aim of the study

To study the prevalence, incidence, gender and age distribution of psoriasis by country of residence and racial origin and determine its financial burden.

Material and methods

The literature search was conducted using keywords in PubMed, Scopus, Web of Science, eLibrary.ru and cyberleninka.ru databases and the web search engine Google Scholar to identify articles relevant to the aim. The geography of the search covered all continents. The global prevalence of psoriasis among adults, in addition to reviewing the literature data, was estimated using the Prevalence Heat Map of the Global Psoriasis Atlas (https://www.globalpsoriasisatlas.org). The adaptation of heat maps was carried out using the program MapChart.net. Graphs on the dynamics of the incidence of psoriasis and dermatoses in Kazakhstan were compiled using Microsoft Excel 2021.

Results

The prevalence of psoriasis

Psoriasis' prevalence varies by geographic location and race. Meanwhile, the prevalence of psoriasis does not vary depending on patients' marital status, education, income, or health insurance status [24]. For instance, a high prevalence of psoriasis among adults in North America was registered in Canada at 2.44% [27] and in the United States of America at 3.0%, which indicates that approximately 7.55 million Americans suffer from this disease. In the United States of America, the highest prevalence of psoriasis was diagnosed among white individuals at 3.6%, followed by other racial and ethnic groups (non-Hispanic, including multiracial) at 3.1%, Asian individuals at 2.5%, Hispanic individuals (including Mexican Americans and other Hispanics) at 1.9%, and African Americans at 1.5% [24]. According to available data, the prevalence of psoriasis in Brazil is 1.31-1.6% [28,29]. Moreover, the prevalence rate of this disease varies from 0.92% to 1.88%, which depends on the geographical region. The highest prevalence rates of psoriasis were recorded in the south (1.86%) and southeast (1.88%) of Brazil, where the local population is represented by immigrants from European countries, while in the north (0.92%) of the country, predominantly Indians live [28]. At the same time, there are many reports that psoriasis is rare in population with colored skin. The actual prevalence may be underestimated due to the lack of large-scale epidemiological studies. However, in Africa, especially in West Africa, psoriasis is indeed considered a relatively rare disease. The prevalence of psoriasis varies from 1.9% to 3.5% in East African countries (Kenya, Uganda, Tanzania) and from 0.025% to 0.9% in West African countries (Nigeria, Ghana, Mali, Angola) [7,30,31]. The prevalence of psoriasis in Australia varies widely, from 0.3 to 2.5% [32]. Interestingly, psoriasis is rare or absent among fool-blood Australian Aborigines. A survey of about three thousand such people in central, northern, and southern Australia found no cases of psoriasis [33]. Data on the prevalence of psoriasis in several countries are presented in Table 1 (see the next page).

From Table 1, it can be seen that the highest prevalence rates of psoriasis are observed in Western countries, in particular: in Norway: 11.4% [36]; Italy: 4.8% [46]; France: 4.42% [41]; Portugal: 4.4% [45]; Romania: 4.2% [47]; the United Kingdom: 2.8% [13]; Germany: 2.78% [39]; Spain: 2.69% [43]; and the lowest in Asian countries, such as Malaysia: 0.34% [53]; China: 0.47% [12]; South Korea: 0.54% [51]; Japan: 0.57% [52]; and Russia: 0.24% [35].

At the same time, according to the Global Psoriasis Atlas (GPA), the prevalence of psoriasis among adults in Europe ranges from 0.11% in Switzerland to 2.36% in Norway (Figure 1, see the next page) [34].

As can be seen from Figure 1, darker colors correspond to higher rates of psoriasis prevalence, while lighter colors correspond to lower rates. In Europe, according to the Global Psoriasis Atlas, the highest prevalence rates of psoriasis among adults are observed in the following countries: Norway (2.36%); Denmark (2.26%); Romania (2.24%); Germany (2.2%); Sweden (2.1%); Poland (2.06%); Italy (2.0%); France (1.94%); Finland, Iceland, the United Kingdom, Ireland, Belgium, Austria, and Greece (1.92%). At the same time, the lowest prevalence rates of psoriasis were recorded in Estonia, Latvia, Lithuania (0.59%), Switzerland (0.11%) [34].

One study reported that the prevalence rate of psoriasis in the United Kingdom (UK) was 2.8% (2815 cases per 100,000 population). Moreover, a significant relationship has been found between the prevalence of psoriasis and latitude; in particular, in the United Kingdom, there are about 6.5 new cases of psoriasis per 100,000 population for every degree increase in latitude. This finding supports the hypothesis that the prevalence of psoriasis varies depending on geographic location. In this regard, in countries more distant from the equator, psoriasis is more prevalent [13]. Several epidemiological studies from different regions of Spain showed the prevalence of psoriasis in the range of 2.3-2.69% and psoriatic arthritis at 0.75% (939 cases of psoriasis or psoriatic arthritis per 100,000 population) [42,43], and among children at 0.30% [44]. For instance, in the province of Lleida in northeastern Spain, the prevalence of

Table 1 Data on the prevalence of psoriasis in several countries

Country	Year	Diagnosis method	Population, n	Age, years	Prevalence of psoriasis (%)	Prevalence among men (%)	Prevalence among women (%)	Prevalence under 18 years (%)	Literature
Kazakhstan	2017	Database	18.2 million	All ages	0.86	-	-	0.1	[34]
Russia	2010-2019	Analysis of statistic surveillance data	-	All ages	0.24	-	-	0.1	[35]
The United Kingdom	January 1, 1999–December 31, 2013	Database	15,436,637	All ages	2.8	2.81	2.83	-	[13]
Norway	1979-2008	Population-based study	33,803	20-79	4.8-11.4	-	-	-	[36]
	2004-2020	Database	272,725	All ages	3.8-4.6 (2015-2020)	-	-	-	[37]
Denmark	2003-2012	Database	5.7 million	All ages	2.22	1.03	1.18	0.4 (<19)	[38]
Germany	2009	Database	1,642,852	18>	2.78	2.94	2.59	-	[39]
	2009	Database	293,181	<18	-	-	-	0,45	[40]
France	September 01 – November 30, 2016	Survey (filling out a digital questionnaire)	20,012	15>	4.42	4.49	4.36	-	[41]
Spain	2013	Computerized telephone survey	12,711	All ages	2.3	2.7	1.9	0.5 (<16)	[42]
	June-September 2016	Computerized telephone survey	7,980	16>	2.69	2.78	2.61	-	[43]
	2010-2016	Database	398,701	All ages	1.72	1.88	1.56	0.30 (<18)	[44]
Portugal	May-November 2021	Phone questionnaire	6,381	15>	4.4	-	-	-	[45]
Italy	-	Review of articles	-	-	1.8-4.8	-	-	-	[46]
Romania	2018-2019	Questionnaire	1500	18>	4.2	-	-	-	[47]
Canada	2008-2012	Database	325,618	18>	2.44	-	-	-	[27]
The United States of America	2011-2014	Database	12,625	20>	3.0	2.8	3.2	-	[24]
Brazil	2015-2016	Telephone survey	8,947	All ages	1.31	1.47	1.15	-	[28]
	2008-2010	Prospective cohort study	15,105	35-74	1.6	-	-	-	[29]
China	2003	Questionnaire and dermatological examination	17,345	All ages	0.47	0.54	0.44	0.18	[12]
Taiwan	2000-2006	Database	5,864	All ages	0.19	0.23	0.16	-	[48]
	2006	Database	23 million	All ages	0.235	-	-	-	[49]
	2006-2017	Database	23.5 million	All ages	0.86	-	-	-	[50]
South Korea	January 2006 – December 2015	Database	51 million	All ages	0.54	-	-	-	[51]
Japan	2012-2018	Database	487,835	40>	0.57	-	-	-	[52]
	April 2010 – March 2011	Database	565,903	All ages	0.34	-	-	-	[11]
Malaysia	2010-2020	Database	1,164,724	All ages	0.34	0.39	0.29	-	[53]
India	-	Review of articles	-	All ages	0.44-2.2	-	-	-	[10]
Israel	2011-2017	Population-based study (analysis of electronic medical records)	71,094	All ages	3.8	-	-	-	[54]
	1999-2014	Population-based cross-sectional retrospective study	887,765	16-18	-	-	-	0.35	[55]
Australia	-	Review of articles	-	All ages	0.3-2.5	-	-	-	[32]
Nigeria	2001-2021	Retrospective review	39,047	All ages	0.6	-	-	-	[7]

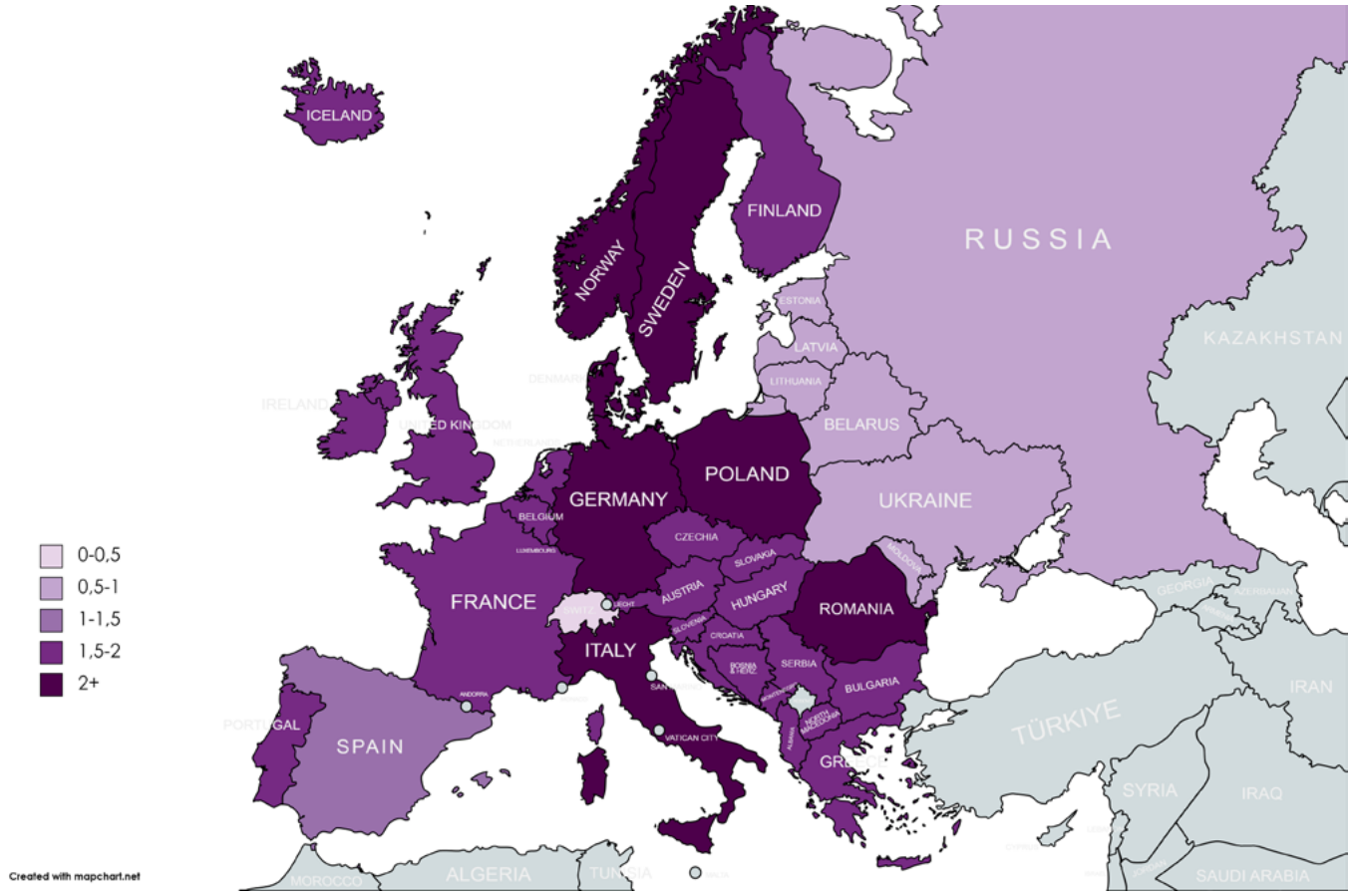

Figure 1 – Map of the prevalence of psoriasis among adults in Europe. Adapted from the Prevalence Heat Map of the Global Psoriasis Atlas. Created by MapChart.net

psoriasis was 1.72% [44]. At the same time, a comparatively higher prevalence was registered in Central Spain (2.5%), the region with the coldest and driest climate [42].

In Germany, over 1.5 million people suffer from psoriasis [56], and the prevalence of this disease among the adult population was 2.78% [39], and among children and adolescents, 0.45% [40]. By comparison, in Denmark, this rate is 2.2% [38]. Psoriasis is also a common disease in Italy, where the prevalence rate of psoriasis varies from 1.8% to 4.8% [46]. Also, a fairly high prevalence of psoriasis was identified in France (4.42%) [41], and Portugal (4.4%) [45]. Among Eastern European countries, a high prevalence rate of this disease was recorded in Romania – up to 4.2% [47].

A high population frequency (up to 4%) of the prevalence of psoriasis is observed in Scandinavian countries and among indigenous residents of the Far North in Russia [57]. Population-based studies conducted in Northern Norway among people aged 20 to 79 years showed an increase in the prevalence of psoriasis from 4.8% in 1979-1980 to 11.4% in 2007-2008. It was found that psoriasis developed as a result of the following precipitating factors: a higher body mass index, less physical activity during work and leisure, a lower level of education, and smoking [36]. Another study reports that the prevalence of psoriasis in Norway is 4.6%. At the same time, there is a difference in the prevalence of the disease depending on the geographical region. For instance, the prevalence of psoriasis in the west and middle of the country was 4.3%, in the south-eastern part, 4.6%, and in the north of the country, 6.1% (6140 patients per 100,000 population). According to the researchers, one possible explanation for the higher prevalence of psoriasis in northern Norway may be less sunlight and a colder climate. This circumstance limits the use of natural sunlight to reduce skin inflammation and, in addition, can lead to decreased vitamin D levels. In addition, factors such as genetics and lifestyle may be involved [37].

Compared to some countries in Western Europe and North America with the relatively high prevalence of psoriasis, in many Asian countries, in particular Malaysia (0.34%) [53,58], China (0.47%) [12], Taiwan (0.19-0.86%) [49,50], South Korea (0.54%) [51], and Japan (0.34-0.57%) [11,52], the prevalence of the disease remains at a comparatively low level [59,60]. Geographical differences in the prevalence of this disease can be explained by the fact that psoriasis has a multifactorial etiology, resulting from a complex interaction between genetic and non-genetic factors [61].

According to GPA, the prevalence of psoriasis among adults ranges from 0.07% in Taiwan to 2.28% in Israel (Figure 2, see the next page) [34].

As can be seen from Figure 2, the following Asian countries have the highest prevalence rates of psoriasis: Israel (2.28%); Cyprus (1,92%); Kazakhstan, Uzbekistan, Kyrgyzstan, Turkmenistan, Tajikistan, and Mongolia (0.86%), Brunei (0.76%); Saudi Arabia (0.73%), and South Korea (0.7%). According to the GPA, in Russia, this rate is 0.51%. The lowest rates of psoriasis are observed in the following Asian countries: Taiwan (0.07%); North Korea (0.14%); China (0.21%); India (0.34%); Nepal (0.35%) [34]. It should be noted that, according to the developers of this resource, only 19% of countries have data on the prevalence and incidence of psoriasis. Accordingly, this resource cannot guarantee absolutely correct data on the epidemiological situation of psoriasis in particular countries [58].

One recent study reported that the prevalence of psoriasis in Malaysia was 0.34%. In a multi-ethnic Malaysian population, the prevalence of psoriasis was higher in patients of Indian

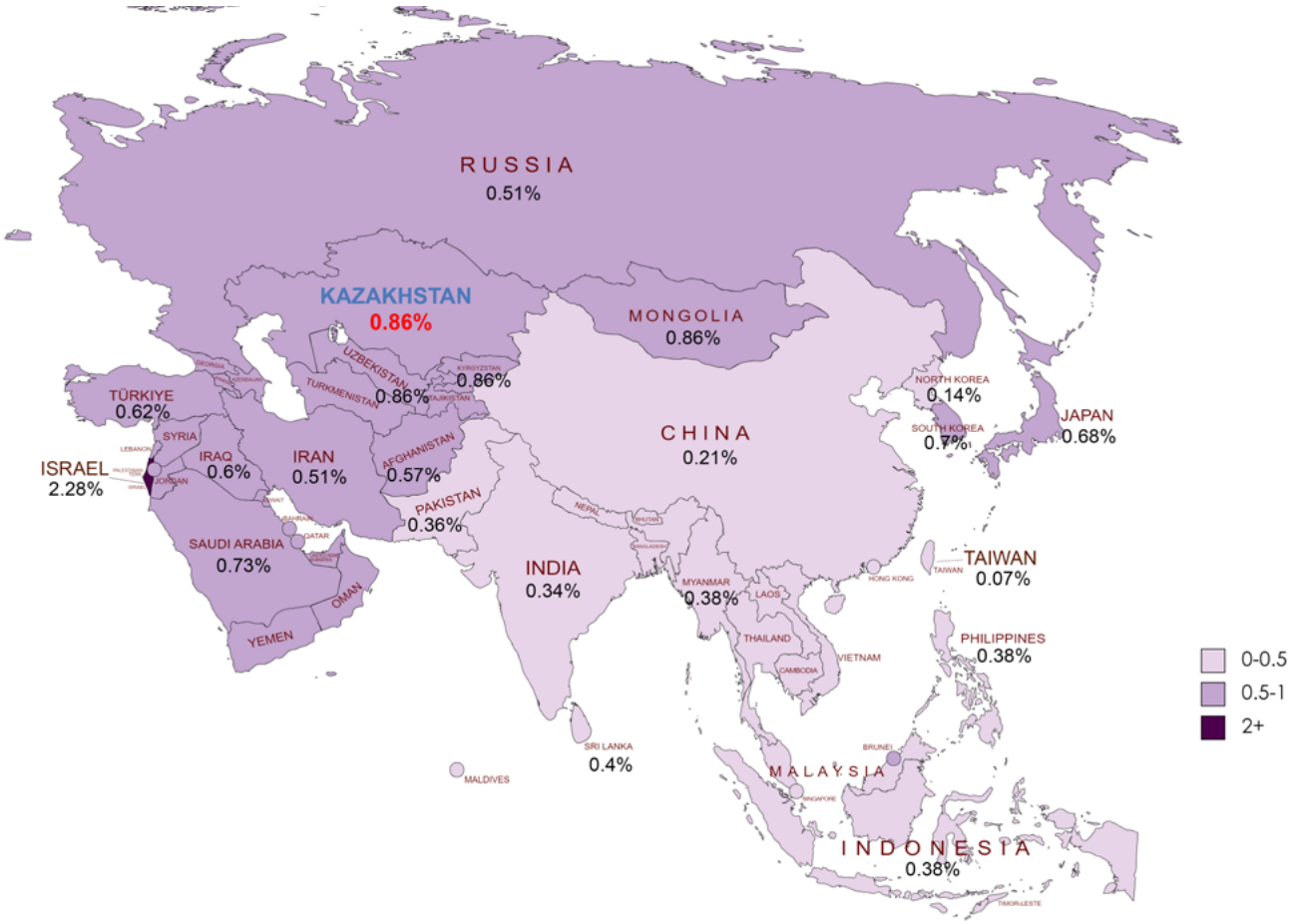

Figure 2 – Map of the prevalence of psoriasis among adults in Asia. Adapted from the Prevalence Heat Map of the Global Psoriasis Atlas. Created by MapChart.net

origin (0.54%) than in Chinese (0.38%) and Malay (0.29%) patients [53,58]. The prevalence of psoriasis in Japan varies from 0.34% to 0.57% [11,52]. According to various data, in Taiwan, this figure varies widely from 0.19% to 0.86% [48-50,62]. In China, the prevalence rate of psoriasis is 0.47% and affects more than 7 million people [12]. Among Asian countries, the highest prevalence rate of psoriasis was registered in Israel: 3.8% [54], while among adolescents (16-18 years old), this figure is 0.35% [55]. In India, the prevalence of psoriasis among all skin patients ranges from 0.44% to 2.2%, with an overall prevalence of 1.02% [10]. According to various data, the prevalence rate of psoriasis in Kazakhstan ranges from 1.0-1.5% [63,64] up to 2.5% [65]. However, according to the GPA, the prevalence rate of psoriasis among the adult population is 0.86%, and among children, it is 0.1% [34].

In Russia, most of whose territory is in Asia, more than 360 thousand cases of psoriasis have been registered. The prevalence rate of psoriasis among the entire population was 247.2 cases per 100,000 population (0.24%). A higher prevalence rate of psoriasis was found in adults of working age: 302.1 cases per 100,000 population (0.30%), and among adults over working age: 243.0 cases per 100,000 population (0.24%). The prevalence of psoriasis among children (0-17 years old) is 109.8 cases per 100,000 population (0.10%) [35]. For example, in the city of St. Petersburg, the prevalence of this disease is 233 cases per 100,000 population (0.23%), and among children (0-14 years old), 77 cases per 100,000 population (0.07%) [66]. There are significant geographical differences in the prevalence of psoriasis among the adult population of Russia. Thus, psoriasis is mostly registered in the northern territories of Russia (Oryol Region, Republic of Karelia and Komi, Pskov Region, Udmurt Republic, Kirov and Sverdlovsk Regions, Yamalo-Nenets Autonomous Okrug, Altai Republic, Republic of Sakha (Yakutia), Magadan, and Sakhalin Regions), and, to a lesser extent, in the regions of the Southern, North Caucasus, and Central Federal Districts (FD). The highest prevalence of psoriasis was registered in the Altai Republic: 453.92 cases per 100,000 population (0.45%). This pattern corresponds to the opinion of some scientists that populations in northern latitudes are more susceptible to psoriasis. In general, the prevalence rate of psoriasis in Russia is 0.2% [67], which is an order of magnitude lower than the global prevalence rate (about 2%) according to the World Health Organization (WHO) [68].

The incidence of psoriasis

The incidence of psoriasis is increasing and varies depending on age, gender, and ethnicity. The incidence of psoriasis is generally lower in Asian populations and in children [53]. The registered incidence rate of psoriasis in the United States of America is 63.8 cases per 100,000 population [69], in the United Kingdom (129) [13], in Italy, according to various data, ranging from 107.742 to 230.62 [46], and in Denmark (199.5) [38], respectively. In the United States of America, the standardized incidence rate was higher in whites (75.3 cases per 100,000 population) than in Hispanics (52.2 cases per 100,000 population), other races (54.3 cases per 100,000 population), and African Americans (24.9 cases per 100,000 population) [69]. Interesting data were obtained in one of the studies conducted in Germany, in which the incidence rate of psoriasis was 17.4-26.31 cases per 100,000 population in men and 19.05-26.39 cases per 100,000 population in women, which is significantly lower than incidence rates in other Western European countries

[56]. A comparatively low incidence of psoriasis was identified in Chile, where the national incidence rate of psoriasis is 22.7 cases per 100,000 population. At the same time, there was a high variation in incidence rates throughout the country, from 0.75 (central region) to 164.9 (below southern region) cases per 100,000 population [70].

In Asian countries, with the exception of Israel, where the average annual incidence rate is 280 cases per 100,000 population, including 92 cases per 100,000 among children (0-14 years) [54], the incidence of psoriasis is generally significantly lower than in Western countries. For instance, according to the latest data in Malaysia, the incidence rate was 34.2 cases per 100,000 population. Due to the fact that Malaysia is a multi-ethnic country, the incidence rate among ethnic groups of the population varies significantly: Indians: 52.5 cases per 100,000 population; Chinese: 38.0 cases per 100,000 population; and Malays: 30.0 cases per 100,000 population [53,58]. In Taiwan, this rate is 62-65 cases per 100,000 population [50].

It is reported that in Russia, the incidence rate of psoriasis is 65.3 cases per 100,000 population [67]. For comparison, in Israel, this rate reaches 305 new cases per 100,000 population (among individuals over 65 years old) [54]. In the city of St. Petersburg, the incidence rate of psoriasis is 75 cases per 100,000 population [66]. In Russia, the lowest incidence rates of psoriasis were noted in the Astrakhan region of the Southern Federal District (SFD), the Republic of Adygea SFD and the Belgorod region of the Central FD – 7.3; 12.6 and 14.8 cases per 100,000 population, respectively. At the same time, the highest incidence rates of psoriasis were recorded in the Khabarovsk Territory of the Far-Eastern FD, the Kurgan Region of the Ural FD and the Udmurt Republic of the Volga FD – 169.8; 163.0 and 143.4 cases per 100,000 population, respectively [71].

A study carried out in the Central Asian country of Kyrgyzstan showed that the incidence rate of psoriasis was 47.7 cases per 100,000 population. An uneven distribution of the disease, depending on the region, was revealed. The highest incidence of psoriasis was identified in Batken (110.5 cases per 100,000 population), Issyk-Kul (91.7 cases per 100,000 population), Naryn (65.9 cases per 100,000 population), and Jalal-Abad (48.5 cases per 100,000 population) regions, and the lowest in Chui (36.9 cases per 100,000 population), Osh (34.3 cases per 100,000 population) and Talas (10.6 cases per 100,000 population) regions. Also, low incidence rates registered in the cities of Osh (17.2 cases per 100,000 population) and Bishkek (32.9 cases per 100,000 population) [72].

According to 2023 data, the incidence rate of psoriasis in the population of Kazakhstan is 35.0 cases per 100,000 population [73]. Compared to other countries, the incidence of psoriasis in Kazakhstan is relatively low (Table 2).

Table 2 – Psoriasis incidence rate per 100,000 population in Kazakhstan in comparison with several countries

Country	Incidence rate per 100,000 population, n	Literature
Kazakhstan	35,0	[73]
The global age-standardized incidence rate of psoriasis	57.8	[23]
Chile	22.7	[70]
Malaysia	34.2	[53]
Kyrgyzstan	47.7	[72]
The United States of America	63.8	[69]
Taiwan	65.0	[50]
Russia	65.3	[35]
The United Kingdom	129.0	[13]
Denmark	199.5	[38]
Italy	230.62	[46]
Israel	280.0	[54]

Table 2 shows that in Kazakhstan, the incidence rate of psoriasis is almost 1.7 times lower than the global incidence rate (57.8 cases per 100,000 population) and is also significantly lower than the incidence rates of a number of countries: Russia – 1.9 times, the United Kingdom – 3.7 times, Denmark – 5.7 times and Israel – 8 times.

The dynamics of the incidence of psoriasis in Kazakhstan in the period from 2012 to 2023 are presented in Figure 3.

From Figure 3, it is clear that during this period, the incidence of psoriasis had a «wavy» trend with periods of both a stable decrease (2012-2015, 2019-2021) and an increase (2017-2019, 2021-2023) [73-78]. At the same time, in 2021, there was an increase in the number of hospitalized patients with psoriasis by 22.2%, from 333 patients in 2020 to 378 patients in 2021 [79]. According to data from the Kazakh Scientific Center of Dermatology and Infectious Diseases, in 2023, the diagnosis of psoriasis in Kazakhstan was confirmed for 6,925 patients, with an incidence rate of 35.0 cases per 100,000 population (Figure 4) [73].

As can be seen from Figure 4, in 2023, psoriasis (33.8% of the total number of dermatoses) was second after atopic dermatitis (51.5%) in terms of incidence among chronic dermatological diseases in Kazakhstan [73].

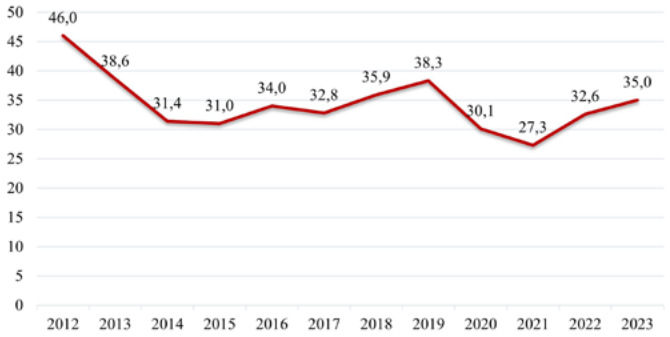

Figure 3 – Dynamics of psoriasis incidence in the population of Kazakhstan in 2012-2023 per 100,000 population. The X-axis represents the period from 2012 to 2023. The Y-axis represents the incidence rate of psoriasis per 100,000 population

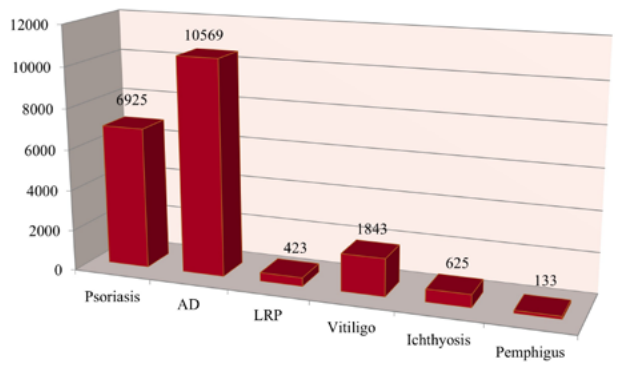

Figure 4 – Incidence of dermatoses in Kazakhstan in 2023. AD – atopic dermatitis; LRP – lichen ruber planus

Psoriasis and eczema are the most common diseases in all regions of Kazakhstan, especially in environmentally unfavorable regions [80]. For instance, in the city of Turkestan in the South Kazakhstan region (now Turkestan), in the period from 2014 to 2016, there was an increase in the incidence of psoriasis from 12.6% to 16.7%, respectively [81]. Psoriasis affects urban residents more often than residents living in rural areas [78]. Possible factors for the development of psoriasis include neuropsychic disorders, previous infectious diseases, pathologies of the gastrointestinal tract and endocrine system, alcohol consumption, unfavorable climatic conditions, and hereditary factors. At the same time, a strong correlation was found between the seasonality of relapses and the allergic syndrome [74].

There is an increase in the number of severe forms of psoriasis that are resistant to various treatment methods, an increase in cases of joint involvement in the pathological process, which causes an increase in cases of long-term incapacitation and disability, as well as the formation of iatrogenic complications and a pronounced deterioration in the quality of life of patients [74]. In Kazakhstan, about 30% of patients have moderate or moderate-severe forms of psoriasis [82]. For comparison, in Japan, in most cases (86.2%), patients were diagnosed with mild psoriasis while 13.8% were diagnosed with moderate to severe psoriasis [52]. Moderate and severe psoriasis, was diagnosed in 7.27% of all patients with psoriasis in Spain [44]. It was revealed that in Kazakhstan, severe forms of psoriasis are most common among residents of the Atyrau, Almaty, and Kyzylorda regions, with a continuously relapsing course in patients in the Kostanay, Akmola, and Almaty regions [74].

Gender distribution of psoriasis

As mentioned earlier, psoriasis affects both genders. However, in some populations, psoriasis is diagnosed more often in women than in men, and vice versa. In some countries, there is an almost equal distribution of psoriasis by gender.

A situation with the gender distribution of psoriasis, when women suffer from psoriasis slightly more often than men, was identified in Germany [56], Norway [37], and Denmark [38] – 53.2%, 54%, and 54%, respectively. In the United States of America, the prevalence of psoriasis was also found to be slightly higher in women (3.2%) than in men (2.8%) [24], but practically equal incidence was recorded in men (62.8 cases per 100,000 population) and women (64.8 cases per 100,000 population) [69].

A higher prevalence and incidence of psoriasis in men have been identified in countries such as Brazil [28], Israel [54], Kazakhstan [74,75], Russia [9], Malaysia [53,58], Taiwan [48,50], China [12], Japan [11], Nigeria [7], Egypt [6], and Ethiopia [5]. In particular, psoriasis in Brazil is more often diagnosed in men (1.47%) than in women (1.15%) [28]. In Israel, psoriasis is slightly more prevalent among men (4.0%) than women (3.7%) [54]. The prevalence of psoriasis in Malaysia is 0.39% in men and 0.29% in women. At the same time, the incidence rate in this country is 40.7 per 100,000 population in men and 28.3 per 100,000 population in women [53,58]. In Taiwan, there is also a higher prevalence of psoriasis in men (0.23%) than in women (0.16%) [48]. Interestingly, in Taiwan, in patients under 30 years of age, psoriasis is diagnosed with almost the same frequency in both genders. However, the incidence rate increases substantially in male patients aged 30 years and older [50]. In China, a higher prevalence of the disease was also reported in men (0.54%) than in women (0.44%) [12]. The same situation occurs in Japan, where psoriasis is more common in men (59.1%) than in women (40.9%) [11]. In India, psoriasis occurs twice as often in men than in women in the ratio (2.46:1) [10]. The trend in which psoriasis affects men more often is also observed in African countries. Specifically, in Nigeria [7], Egypt [6], and Ethiopia [5], men are more susceptible to psoriasis than women – 64.2%, 56.3%, and 54.4%, respectively. In Kazakhstan, a higher susceptibility to psoriasis in men was revealed in Mangistau (64.9%), North Kazakhstan (61.5%), Karaganda (59.7%), Akmola (58.5%), East Kazakhstan (56.1%), Kyzylorda (56.0%), West Kazakhstan (55.7%), South Kazakhstan (now Turkestan) (51.2%) regions, and women in Almaty (59.4%) and Pavlodar (58.8%) regions [74]. For comparison, in Russia, 60.5% of patients with psoriasis are men [9].

An almost equal distribution of psoriasis between both genders was observed in France (men – 4.49%; women – 4.36%) [41], the United Kingdom (men – 2.81%; women – 2.83%) [13], and Spain (men – 2.78%; women – 2.61%) [43]. But, according to other data, the prevalence of psoriasis in Spain is higher in men (1.88-2.7%) than in women (1.56-1.9%) [42, 44].

Age distribution of psoriasis

Psoriasis can develop at any age. However, the average age at which psoriasis occurs is 33 years. In women, psoriasis usually manifests at the ages of 16-22, or 55-60 years, and in men, 30-39, or 60-79 years [83,84]. This bimodal pattern of psoriasis is associated with two distinct subtypes of psoriasis: type I with onset before the age of 40 years and type II with onset after 40 years [85].

A study conducted in the United Kingdom revealed a clear bimodal pattern in the incidence of psoriasis depending on the age of the patient. In women, early-onset psoriasis (type I, diagnosed before the age of 40 years) is more often diagnosed at an earlier age than in men, and late-onset psoriasis (type II, diagnosed after the age of 40 years), on the contrary, is more often diagnosed in men [13]. A bimodal pattern of psoriasis manifests in Israel, with peaks at the ages of 30 and 60. In 48.9% of cases, psoriasis had an early onset and was diagnosed before 40 years of age (the average age of patients was 24.9 years). However, in 51.1% of cases, psoriasis had a late onset and was diagnosed after 40 years of age (mean age 59.7 years). Thus, the average age of onset of psoriasis was 42.4 years. The same gender distribution was observed both with the early and late onset of the disease [54]. Malaysia also revealed a bimodal trend in the age of onset of psoriasis, with the first and second peaks at the ages of 20-29 and 50-59 years. At the same time, in women, the disease begins much earlier (36.8 years) than in men (42.0 years) [53,58]. Interestingly, in Taiwan, the second peak of psoriasis development occurs at the advanced age of 80-89 years (type II, late onset), and the first peak is also observed at the age of 30-39 years (type I, early onset) [50]. A study carried out in Chile found that women had two peaks in incidence of psoriasis, one in childhood and adolescence (5-15 years) and a second in middle age (45-65 years), whereas men had one later peak (56-65 years) [70]. Another study showed that in Nigeria, 25% of patients developed psoriasis before age 20, and 71.4% developed psoriasis before age 40. Moreover, the average age at onset of the disease is 30.5 years. More than 60% of all patients with psoriasis are under 40 years of age. In women, psoriasis begins earlier than in men, with the average age of onset being 27.6 and 32.3 years, respectively [7]. Similar to Nigeria, in Egypt, the average age of onset is 30.5 years [6]. In all regions of Kazakhstan, the onset of psoriasis occurs at a young age: from

14±2.5 years in the Atyrau region and up to 28±4.0 years in the Kyzylorda region, which refers to type I psoriasis with early onset [74].

A Brazilian study noted an age-related increase in the prevalence of psoriasis: under the age of 30 years: 0.58%; from 30 to 60 years: 1.39%; and over 60 years, 2.29% [28]. A study conducted in Denmark revealed the following distribution of psoriasis prevalence depending on the age of patients: 0-19 years – 0.4%; 20-29 years – 1.4%; 30-39 years – 2.1%; 40-49 years – 2.7%; 50-59 years – 3.4%; 60-69 years – 4.1% and over 70 years – 3.8% [36]. A similar trend of increasing prevalence of psoriasis with age was revealed in the study conducted in Spain: up to 16 years – 0.5%; 16-29 years – 1.4%; 30-39 years – 2.7%; 40-49 years– 3.0%; 50-59 years – 3.2%; 60-69 years – 3.4% and over 70 years – 2.6% [42]. In Germany, there was a tendency for the prevalence of juvenile psoriasis to increase with age: from 0.13% at the age of 0-2 years to 0.67% at the age of 14-18 years [40]. In Chile, the minimum incidence of psoriasis was registered in the demographic age group 0-5 years: 4.9 cases per 100,000 population, and the maximum incidence rate was in the age group 55-65 years – 39.4 cases per 100,000 population. A decrease in incidence was observed in the age group over 75 years – 16.5 cases per 100,000 population [70]. An increase in the incidence of psoriasis has also been detected in the United States of America, where the peak incidence occurs in persons in the age group 70-79 years (92.3 cases per 100,000 population) [69]. In Ethiopia, psoriasis most often affects young people aged 18 to 34 years (48.9%), followed by children from 0 to 17 years (26.3%) and adults from 35 to 55 years (24.6%) [5]. Among patients with psoriasis in Kazakhstan, adults (18 years and older) predominate – 77.3% of cases of the total number of patients with psoriasis, followed by children (0-14 years old) – 16.0%, and adolescents (15-17 years old) – 6.7 % [78].

Data from multiple studies show that the highest prevalence rates of psoriasis are observed in older people (Table 3).

As can be seen from Table 3, the highest prevalence rates of psoriasis are observed in the following age groups: in Germany – 60-69 years (4.15%) [39]; Denmark – 60-69 years (4.1%) [38]; Spain – 60-69 years (2.90-3.4%) [42,44]; Malaysia – 50-59 years (0.67%) [53,58]; China – age groups 40-49 (0.92%) and over 70 years (0.92%) [12]. In France, a high prevalence of psoriasis was found in the age groups 35–49 and 50-64 years [41]; in Japan, 75-79 years [11]; and in Taiwan, 70-79 years, regardless of gender [50]. Moreover, in Taiwanese patients in the age group 70-79, there was an increase in the prevalence of the disease by more than 50% compared with patients in the age group 60-69 years [48-50].

Table 3 The highest prevalence rates of psoriasis by age groups in several countries

Country	Age group, years	Prevalence, %	Literature
Germany	50-59	3.62	[39]
	60-69	4.15	
	70-79	3.94	
Denmark	50-59	3.4	[38]
	60-69	4.1	
	Over 70 years	3.8	
Spain	50-59	3.2	[42]
	60-69	3.4	
	Over 70 years	2.6	
Malaysia	50-59	0.67	[53,58]
	60-69	0.66	
China	40-49	0.92	[12]
	50-59	0.91	
	Over 70 years	0.92	

The mean age of patients with psoriasis also varies between countries, for instance: in India – 33.6 years [10], Egypt – 39.3 years [6], Kazakhstan – 43,8 years [86], Denmark – 45 years [38], Russia – 46.1 years [9], Brazil – 49.1-52 years [28,86], Chile – 49.2 years [86], Norway – 47-53 years [37], Spain – 52.08 years [44], Australia – 52.3 years [8] and Japan – 56.7 years [11], respectively. In Kazakhstan, psoriasis is more often diagnosed in men of young working age (21-50 years) – 68.1% [74,75], while the age of onset of the disease is 23.4 years [87]. For comparison, the first symptoms of psoriasis in Romanians usually appear around the age of 50 [47]. In Russia, every fourth patient with psoriasis is a person over working age, that is, men aged 60 years and older and women aged 55 years and older [35].

The economic burden of psoriasis

Psoriasis is a serious disease that significantly deteriorates patients' quality of life. According to the National Psoriasis Foundation, 65% of surveyed patients with psoriasis noted that they experienced discrimination at work, at school, and in other public places [88]. Moreover, psoriasis is a disease that most people recognize as causing considerable morbidity and expense to patients. According to the Psoriasis Disability Index (PDI), two-thirds of respondents said that psoriasis had caused them to change the way they performed their usual daily activities; more than 50% wore clothes of different types and colors; more than 50% said their home became dirtier or unkempt; and more than a third had trouble going to the hairdresser or had difficulty playing sports [89].

The costs associated with decreased quality of life, disability, and absenteeism from work can be significant, increasing the overall costs associated with treating the disease [90,91]. Therefore, it is worth mentioning the economic burden of psoriasis associated with the significant costs of treatment and providing medications to patients with psoriasis. In particular, in the United States of America in 2020, the total medical and pharmacy care for 230,056 patients with psoriasis was about US$1.7 billion, or over US$7,000 per patient [92]. In Italy, the cost of treating psoriasis is estimated to range from €500 to €15,000, depending on the severity of the disease, the treatment used, and hospitalization [46]. In Australia, annual out-of-pocket expenditure on medical products was approximately AUD$250 per person, or US$162.79 (1999). However, costs ranged from zero to more than AUD$2,000, or US$1,292 per person, over a two-year period. The highest costs were for over-the-counter products purchased without a prescription [89].

In Kazakhstan, treatment of psoriasis is included in the List of Free Outpatient Medication Coverage and is financed within the framework of Compulsory Social Medical Insurance (CSMI) [82]. According to the annual report for 2021 of the Health Insurance Fund, psoriasis is among the 10 most costly diseases within the framework of CSMI, along with: mucopolysaccharidosis, hematological blood diseases, multiple sclerosis, muscular dystrophy, hypofunction, and other pituitary disorders; pituitary dwarfism; Shereshevsky-Turner syndrome;

unspecified Turner syndrome; primary pulmonary hypertension; Fabry disease; other sphingolipidoses; hormonally active pituitary tumors; acromegaly; and acute respiratory infections of the lower respiratory tract. 19.1 billion tenge, or US$44.8 million, was spent on the purchase of medications and medical products for 309,977 patients with a confirmed diagnosis of this group of diseases. From this amount, 7.3%, or 1.4 billion tenge (about US$3.3 million), were spent on providing 916 patients with psoriasis (about 3.6 thousand US dollars per patient) [93]. In 2022, according to the National Report on Primary Health Care in the Republic of Kazakhstan, psoriasis will also be among the highest-cost diseases in the CSMI. The amount prescriptions provided amounted to over 2.9 billion tenge (US$6.3 million) [94].

Discussion

Psoriasis is predominantly common in Western countries and among people of European descent. This may be due to the fact that countries located closer to the equator (Malaysia (0.34%) [53], Nigeria (0.6%) [7] and others) may suffer from insufficient diagnosis and underreporting, and countries further north (Norway (4.6%) [37], France (4.42%) [41], Portugal (4.4%) [45], the United States of America (3.0%) [24], the United Kingdom (2.8%) [13], Germany (2.78%) [39], Canada (2.44%) [27] and others) suffer from colder temperatures, which may affect the epidemiology and symptomatology of psoriasis [95, 96]. Analysis of available data shows significant differences in the prevalence of psoriasis in Kazakhstan, which varies widely from 0.86% [34] to 2.5% [65]. Such significant differences in the prevalence of psoriasis can probably be explained by the lack of large-scale population studies assessing the prevalence of this socially significant disease among the entire population of the country.

The global age-standardized incidence rate of psoriasis in the world is 57.8 cases per 100,000 population [23]. However, in many Western countries, the incidence rate is significantly higher than the global indicator; for example, in the United Kingdom – 129 cases per 100,000 population [13], Denmark – 199.5 [38], Italy – 230.62 [46], Israel – 280 [54], respectively. Compared to countries of the Western world with a high incidence of psoriasis, in many Asian countries this indicator is significantly lower or almost equal to the global incidence rate; for example, in Kazakhstan – 35.0 cases per 100,000 population [72], Malaysia – 34.2 [53,58], Kyrgyzstan – 47.7 [72], Taiwan – 65.0 [50], and Russia – 65.3 [35], respectively. The incidence rate of psoriasis in Kazakhstan is almost 1.7 times lower than the global incidence rate. Therefore, we can draw the encouraging conclusion that the incidence of psoriasis in the country is at a fairly low level.

Psoriasis affects both the male and female half of the world's population. However, studies show that in some Western countries (the United Kingdom, France), men and women suffer from psoriasis almost equally, or there is a slight predominance of psoriasis in women (Denmark, Germany, Norway, the United States of America). The opposite situation in terms of gender differences in the prevalence of psoriasis is observed in Asia (Malaysia, China, Taiwan, and Japan), as well as in countries located closer to the equator (Brazil, Spain, Egypt, Ethiopia, and Nigeria), where psoriasis is much more common in the male half of the population. As in many countries in Asia and Africa, in Kazakhstan, psoriasis is more often diagnosed in men.

Psoriasis is characterized by a bimodal pattern of psoriasis manifestation with early (type I) and late (type II) onset [13,54,85]. The first peak of manifestation occurs at the age of 30-40 years [13,54], and the second at about 60 years [53,58]. At the same time, the highest prevalence rates of psoriasis are observed in people over 60 years old.

The economic burden of psoriasis is associated with the significant costs of treatment and providing medications to patients with psoriasis. This burden falls on both the government and the patients themselves and is associated with the need to visit a dermatologist, prescription or physician treatment, and hospitalization [19]. At the same time, in Kazakhstan, treatment of patients with psoriasis is carried out at the expense of the government within the framework of CSMI.

Conclusion

An analysis of literature data was carried out on key epidemiological indicators, including the prevalence, incidence, gender and age distribution of psoriasis in the world and in Kazakhstan, and the economic burden of this disease was assessed.

Limitations: One of the limitations of the study is the lack of data on the epidemiology of psoriasis in all regions of Kazakhstan in recent years, which does not allow an accurate assessment of the prevalence of this disease in the country.

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Assessing the impact of COVID-19 on renal health in recovered patients: a multi-center longitudinal study

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Abstract

The coronavirus pandemic of 2019 has become a global health problem. This article presents an analysis of the scientific literature focusing on the pathogenetic and clinical parallels between the kidneys and SARS-CoV-2, as well as the state of kidney health in patients who have recovered from treatment. The goal is to analyze the effects of COVID-19 on kidney health in recovered patients amid an unprecedented flow of scientific data. This study was conducted in 2020-2023 using modern scientific databases such as Scopus, PubMed, Google and others to examine the impact of COVID-19 on kidney health in recovered patients. The analysis of studies included data from analytical reviews, meta-analyses, and scientific reports of clinical trials, using the following keywords: "kidney disease", "health impact of SARS-CoV-2", "acute kidney injury". The majority of patients infected with coronavirus had kidney damage, comorbidities, and insufficiency of many organs. Deterioration of kidney function after COVID-19 is observed not only in patients with urological diseases, but also in those patients who have not previously had kidney problems. Despite the fact that nephrologists have developed rapid response methods and defined emergency tactics for the management of patients with kidney damage in COVID-19, cases of kidney disease continue to increase, and the percentage of patients in intensive care units is increasing. For better medical outcomes, careful monitoring of renal function and early laboratory diagnostics to determine biochemical markers, both serum, and urine, in patients with COVID-19 and continuous monitoring of these indicators after recovery are recommended.

Keywords: coronavirus, COVID-19, renal function, kidney health, urological diseases.

Introduction

The pandemic has spread to more than 160 countries, with million people have been infected with the coronavirus disease. COVID-19 initially affects the lungs and is accompanied by damage to other organs [1, 2, 3]. Symptoms associated with coronavirus infection can last for more than a month and affect primarily the respiratory system, as well as gastrointestinal, cardiovascular, urinary, bone and muscle, and other multiple organ damage [2, 4, 5].

An increasing number of patients with the virus are reported to have a list of urological symptoms that should not be ignored by nephrologists today. In SARS-CoV-2 disease, the most common symptoms of urological complications are increased urination. The course of coronavirus infection may have its own characteristics in patients with renal failure, including kidney disease, renal transplant recipients and those on haemodialysis.

The onset of viral damage occurs due to the effect on angiotensin-converting enzyme-2 (ACE-2)

receptors, no less important mechanisms of viral damage are reactions of complement system dysfunction, immunological and inflammatory reactions, leading to multiorgan failure. Post-COVID syndrome has been described in patients on the kidneys are manifested by increased creatinine concentration, proteinuria, microhaematuria (Figure 1).

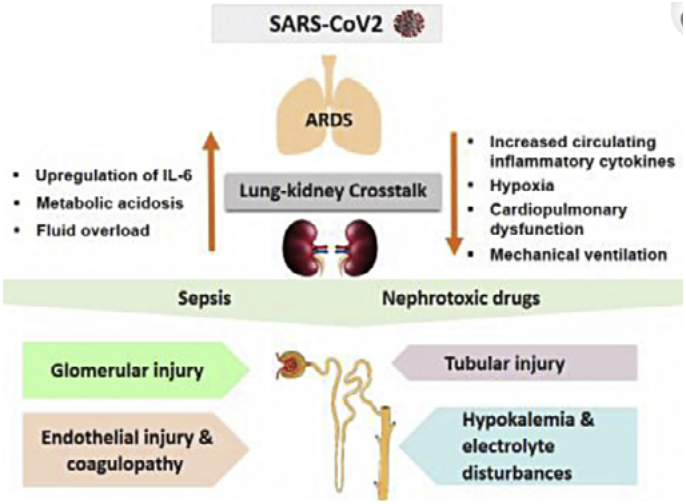


Figure 1 – Crosstalk in the lungs and kidneys, pathomechanism of kidney damage in COVID-19 (2021) [3]

Despite the fact that most patients feel recovered after a coronavirus infection, there is a lot of evidence that raises the problem of post-COVID damage to various organs and tissues, including the kidneys, which leads to impaired physiological functions and problems in the social sphere.

People with COVID-19 have a significantly risk of significant deterioration in kidney function, patients who have not been to hospital with COVID-19 have a nearly 200% risk of end-stage renal disease compared to people who have not had the coronavirus [6].

The depth of post-COVID renal damage depends on the severity of the disease and the presence of acute renal injury before COVID-19. Researchers have shown that patients with acute renal injury (AKI) associated with COVID-19 had a significant decrease in GFR, increased creatinine concentration, proteinuria, microhaematuria in the long-term period, and required renal replacement therapy. Other risk factors for severe damage were old age, chronic kidney disease (CKD), diabetes, hypertension, history of coronary heart disease, hospitalisation, and long-term hospital stay [7].

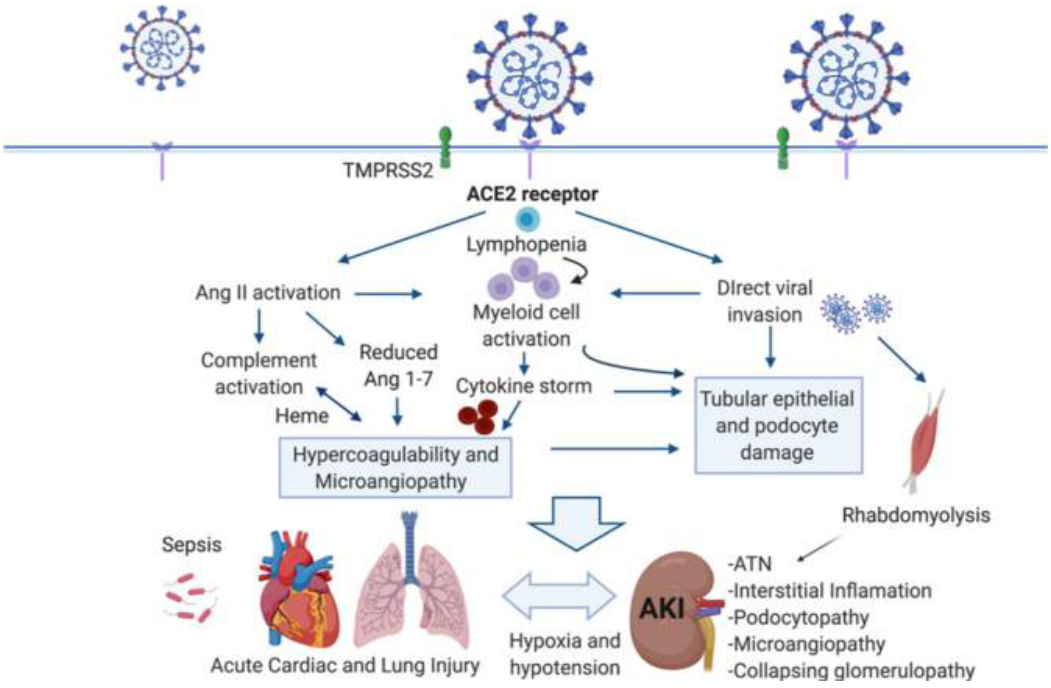
Symptoms of renal dysfunction in patients with infection and SARS range from an increase in the number of red blood cells in the urine (hematuria) to AKI with the development of dialysis [8]. Kidney damage in patients increases dramatically with a decrease in the number of lymphocytes in the peripheral blood and a significant increase in the concentration of procalcitonin, C-protein and interleukins in the blood serum.

Activation of the cytokine pathway in urological diseases leads to the development of multiple organ failure, which often causes death. Researchers have shown that the highest level of T-cell stimulation, which occurs under the influence of the virus, is observed in the exudative stage. At this stage, humoral immunity cells are not detected. At the next stage (proliferation), there is a decrease in the levels of T cells. As a result of autoimmune damage and inadequate immune response, prolonged lymphopenia, and atrophy of lymphoid organs, the number of T-suppressors (CD8+) is increased over T-helper cells (CD4+) [6, 7].

The purpose of this review is to analyse the literature on the impact of COVID-19 on kidney health in recovered patients amidst an unprecedented flow of scientific data.

Material and methods

This study was conducted by analyzing the literature for 2020-2023 using modern well-known scientific databases such as Scopus, PubMed, Google, and others to study the impact of COVID-19 on kidney health in recovered patients. Data from analytical reviews, meta-analyses, and scientific reports of clinical trials were included in our analysis of studies. In this regard, the following keywords were used in the search and analysis: “kidney disease”, “impact of SARS-CoV-2 on health”, “acute kidney injury”. Short and promotional messages were not used in the analysis of the scientific literature. The scientific publications Soliman NA., 2021 (Figure 1); Batlle D, 2020 (Figure 2) were used to create the charts.



Ang 1-7 – angiotensin 1-7.
ATN – acute tubular necrosis.
ACE2 – angiotensin converting enzyme 2.
SARS-CoV-2 – severe acute respiratory syndrome, coronavirus 2.
TMPRSS2 – transmembrane protease, serine 2.

Figure 2 – Pathogenesis of kidney damage in COVID-19 (2020) [9]

Results and discussion

Impact of COVID-19 on kidney health in patients who have recovered

Urological problems are one of the many complications of coronavirus and a significant risk factor for death. During the pandemic, the number of reports of AKI increased in line with the rise of this severe complication, which followed lower respiratory tract infections and respiratory failure (Figure 2) [9].

Targeting ACE2 with SARS-CoV-2 leads to angiotensin dysregulation, activation of the innate and adaptive immune pathway, and hypercoagulability, resulting in organ damage and ARF associated with COVID-19. Crosstalk between the damaged lungs, heart and kidney can further spread the damage. CD8+ T cells and natural killer cells can inhibit macrophage activation and are potential targets for SARS-CoV-2.

It was found that coronavirus RNA in the kidneys of patients with AKI, compared to the lower incidence of SARS-CoV-2 renal failure in patients without the virus, and RNA was detected in a small number of patients [10]. Researchers have confirmed the link between kidney disease and mortality in hospitalized patients. [11]. It was shown that those patients who had signs of renal dysfunction and who were diagnosed with AKI during treatment in inpatient units had a poor clinical picture against the background of elevated serum creatinine, proteinuria, and hematuria compared to patients with normal levels of these parameters; patients with AKI at stage II had an increased risk of mortality, and at stage III - critical kidney injury with a fatal outcome [11].

In another single-centre study in Wuhan (China), among the total number of patients with confirmed pneumonia, AKI was reported in 4 %, the incidence of AKI continued to increase throughout the study [11].

Kidneys and COVID-19: mechanisms of damage

Scientists suggest the following pathomechanisms of kidney damage in COVID-9:

1) destructive metabolic changes with activation of catabolic processes, cell damage leading to electrolyte disturbances [12]. The accumulation of ACE2 caused by the virus can contribute to an imbalance and activation of the renin-angiotensin system, which leads to inflammation, vasoconstriction, and fibrosis.

Based on reports that virus RNA was identified in kidney tissue in a patient with SARS, data were presented on the isolation of the virus in the patient's urine; the accumulated nucleocapsid antigen of SARS-CoV-2 was found by immunohistochemistry and was identified in renal tubular cells, confirming that the kidneys are a target of the coronavirus [13, 14].

Recently, RNA sequencing of human tissues demonstrated the accumulation of the following genes in the kidneys: CTSL, TMPRSS2, and ACE2, which contribute to SARS-CoV-2 infection [15, 16].

2) Activation of the inflammatory and immune response, enhanced by the release of circulating immune complexes. In this case, the patient has elevated plasma levels of pro-inflammatory cytokines; MIP1A; GCSF and MCP1, indicating the presence of an excessive proinflammatory state in the progression of the disease [17]. High concentrations of circulating pathological mediators interact with renal cells, leading to microcirculatory disorders, tubular damage, and endothelial dysfunction [18].

3) COVID-19 infection leads to coagulopathy, a procoagulant state with vascular damage, patients have microvascular thrombosis, acute renal necrosis, accompanied by glomerular ischaemia and fibrinoid necrosis, i.e., irreversible renal damage [9]. The virus leads to chronic reactive endotheliitis with disseminated vascular damage and is one of the significant causes of clinical symptoms [19]. All this gives grounds for choosing a treatment aimed at stopping viral replication and simultaneously restoring the endothelial state for patients with comorbidities [20].

4) In patients in serious condition with prolonged stay in the hospital, there are a number of factors that further aggravate urological problems, including haemodynamic disorders, nephrotoxic drugs, mechanical ventilation, and sepsis [21].

SARS-CoV-2 and kidney health

Lippi G, 2019, confirmed that the severity of COVID-19 is associated with decreased levels of blood electrolytes in both patients with severe and acute disease [22]. De Carvalho H, in his study, demonstrated the presence of hyponatremia, hypokalemia in patients with infection during treatment in the emergency department [23].

Sarwal [24] followed 1570 patients with COVID-19 and showed that half of the cases had ESRD, 71.8% had recovery of renal function, while 28.2% of patients were discharged with AKI. These patients had grade III kidney disease, congestive heart failure, and the use of non-invasive mechanical ventilation. Early detection and proper treatment of patients at risk of progression of AKI can improve the results of therapy, reduce the long-term consequences of CKD and have a positive impact on health status [24].

A study of 201 people (average age 45 years) conducted in 2020 [25] found the average time to organ damage in people aged 18 years with severe clinical symptoms after treatment and recovery compared to a control group of the same age and gender. Among those examined, 19% were hospitalised and had a low risk of mortality. It should be noted that 42% of the subjects had 10 or more long-term symptoms of COVID within 4 months after recovery, and 60% of people had serious long-term symptoms, namely shortness of breath, mild heart failure, headache, fatigue and myalgia, lung function, liver and kidney dysfunction [25].

Lumlertgul N and colleagues showed in their study that 7.5% of patients had AKI; stage I was characteristic of 45.7% of these patients of the disease 3 weeks after the onset. Compared to patients with ESRD, there was a higher recovery rate for ESRD. Careful statistical analysis allowed us to identify patients who recovered from AKI, with data showing that half of the early AKI in patients with COVID-19 was mild and patients recovered easily [11].

According to another study of 198 patients followed for 12 days, 118 (59.6%) of patients with COVID-19 had remission of pneumonia [2], and urine tests were negative in the long-term period. It was shown that 4 patients with AKI achieved full recovery of renal function during follow-up, but there was a pattern that patients with severe AKI had more adverse outcomes after severe pneumonia [2, 11]. At the time of hospital discharge, not a significant number of patients were on dialysis, and a greater percentage of patients recovered renal function, with one-third of patients experiencing major adverse renal events at 90 days (MAKE90) [11].

Liberali [7] found a partial deterioration in renal function after coronavirus infection in patients with advanced CKD and transplant recipients, but the short follow-up period did not allow for any firm conclusions in this regard.

Due to the complexity of determining the treatment tactics for patients with chronic nephropathy after COVID-19, they require an individualized approach.

In the therapeutic treatment of patients in this group, more extensive data on the average time to achieve viral clearance and patient's immune response (antibody production) can help adjust

treatment regimens and the logistical components required for this. Patients with urological disease have been shown to have slower viral clearance than the general population, with an average of 32.4 days [7, 26]. It was found that patients' recovery time after infection was longer due to sporadic cases or high viral load.

In summary, infection is a serious medical problem for patients with nephropathy. The results of the Liberali M study [7] show delayed clearance of the virus in this challenging cohort of patients, although there is a satisfactory immune response (presence of specific antibodies). The role of immunological pathomechanisms in urological diseases remains unknown, and elucidation of their peculiarities in the body during the disease will enable the development of relevant vaccines. For those patients who are at risk of morbidity with possible development of pathological conditions of the urological system, it is necessary to take all measures to prevent infection and detect the disease at an early stage [7].

Conclusion

The COVID-19 pandemic has become a public health crisis that has created numerous unprecedented challenges for global health systems. Exposure to COVID-19 continues to lead to kidney disease as more and more reports emerge, so this issue is attracting nephrologists who are actively working on early diagnosis and conceptual treatment. The pandemic is harming patients with urological diseases by disrupting their conservative follow-up care. The ultimate impact of COVID-19 infection on patients with urological diseases remains to be seen. AKI is common among patients hospitalised with COVID-19, the disease occurs in the early stages and is preceded by lung damage.

Recommendations

To optimize treatment, physicians are advised to closely monitor renal function and early urine sediment testing, as well as to determine urinary biochemical markers in patients with COVID-19 and monitor these parameters after recovery. Continuous updating of preventive, diagnostic, and therapeutic strategies is crucial to improve clinical outcomes and reduce morbidity. Researchers need to continuously monitor scientific data in patients with kidney disease after COVID-19 to determine the current state of the problem and to identify unresolved issues. The healthcare system needs to review and improve treatment guidelines for these patients in order to implement a personalized approach.

Prospects for further research

It is important to continue studying the impact of coronavirus on kidney function and the effectiveness of treatment. The next step may be to develop diagnostic guidelines and criteria for identifying those at risk of developing renal dysfunction in COVID-19 and personalised treatment.

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Knowledge and perceptions of infectious disease physicians about epidemiology, causes, diagnosis, treatment and prevention of Q fever in the Republic of Kazakhstan: results of online survey

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Abstract

Q fever is a significant zoonotic infectious illness triggered by the pathogen known as Coxiella burnetii and may cause complications as pneumonia, hepatitis or myocarditis, and some patients may develop chronic Q fever due to incomplete treatment and the topical resistance of C.burnetii. Poor awareness of clinicians about the disease can be one of the reasons for delay in treatment. In view of the above, a survey has been carried out to collect information on the approach of modern Kazakhstan doctors to the problem of Q fever.

Methods: The electronic survey was conducted among infectious disease physicians from different cities of Kazakhstan, based on convenient sampling through social network platforms. Data were collected anonymously between November 14, 2022 and December 14, 2022 among infectious disease doctors.

Results: The majority of the respondents (91.7%) considered themselves to have knowledge of information; however 80.2% of physicians showed satisfactory level of knowledge.

Conclusions: According to the results of the study, the level of experience of infectious disease physicians about Q fever can be assessed as satisfactory. We found that the level of registration of its' diagnosis is low due to the lack of diagnostic testing systems and poor knowledge about the disease in Kazakhstan. As a consequence, we consider it advisable to enhance the level of knowledge about Q fever among young specialists by including comprehensive information in training programs, seminars, conferences in the field of infectiology, epidemiology and public health, as well as expanding diagnostic opportunities in Kazakhstan.

Keywords: Coxiella burnetii; Q fever; Infectious disease physicians; awareness; Kazakhstan; Surveys and questionnaires.

Introduction

Q fever is an essential zoonotic disease having a global spread caused by Coxiella burnetii, a narrow cellular Gram-negative bacterium [1]. The primary descriptions of Q fever in humans were made in 1937 by Burnet. He investigated several cases of Australian abattoir workers who suffered from indistinguishable fever [2, 3]. The pathogen affects individuals and a widespread array of animals, both feral and domestic, including ovines, cattle, goats, pigeons and others [4]. Infected animals disseminate C.burnetii to the surrounding area through their milk, colostrum, birthing products, and urine. In

addition, C.burnetii is highly tolerant to dryness, low and high pH and ultraviolet radiation, so it can remain infectious in soil for many months [5, 6].

People are highly sensitive to C.burnetii, and infection may occur as a result of only a few hosts. The majority of cases are not symptomatic (60%), but some may induce acute flu-like symptoms and atypical pneumonia. Chronic episodes include endocarditis, chronic hepatitis and osteomyelitis with a fatality incidence of up to 11%. The disease is an occupational risk often for people working with domestic livestock who can be affected by highly contagious sprays from the birth products, contaminated particles of dust, or fur. Workers in slaughterhouses, veterinarians and ranchers are also susceptible to it [6].

Q fever has a broad spectrum of symptom that is often nonspecific. They can last from a few days to more than a year, is frequently misdiagnosed. This causes inadequate therapy, and prolonged illness can lead to severe debilitating disease and the patients may get disabled. Affected people may develop serious changes in their different organs and systems. The infection not only results in enormous economic damage to society by affecting livestock production, but also threatens physical and mental health. The prevalence of Q fever in both humans and animals cannot be estimated in most countries, remains unrecognized and there is no epidemiological surveillance of it. In Kazakhstan, there is a similar trend of under-diagnosis of Q fever and a gap in the treatment and prevention of the disease. Currently, there is limited information on knowledge and experience on Q fever among Kazakhstan doctors [7]. Therefore, this study aimed to investigate the level of Q fever awareness of in infectious disease physicians in various regions of Kazakhstan in further to address existing research questions and problems in knowledge and practice.

Methods

Study design

The present descriptive questionnaire has been constructed to explore the current knowledge and perceptions of infectious disease physicians from different areas of Kazakhstan about the epidemiology, etiology, diagnostics, treatment and preventive measures of Q fever. The survey was conducted among infectious disease doctors. A pre-designed online questionnaire for self-completion in Kazakh and Russian languages, developed in Google Forms, was analyzed to collect data.

Survey items

Three experts reviewed the questions to finalize the wording and ensure content validity. Once finished, the survey included 24 questions. The first part of the survey (Q1-Q6) was used to collect demographic characteristics (age, gender) one response had to be selected, it also included background characteristics of respondents (degree, duration of experience and type of institution working at) only a numeric value had to be entered. The second part of the survey (Q6-Q14) focused on general knowledge and epidemiology of the disease. Finally, the third and last part of the questionnaire (Q15-Q24) converged on symptoms, diagnosis, differential diagnosis, treatment, complications and prevention of Q fever, the questions were multiple choice. Respondents could change answers before submission but not afterward. All questions were made mandatory so that partial answers were automatically discarded by the Google Forms platform.

Sampling strategy and confidentiality

We used convenient sampling strategy and distributed questionnaire on social network, through Whats up chats, between November 14, 2022 and December 14, 2022. Respondents were anonymous and only one response from each participant was accepted. The survey link was open from the moment it was distributed to the professional social network.

Statistical analysis

The normality of the data was checked by means of the Shapiro-Wilk test. Mostly descriptive statistics are presented. Microsoft Excel was used to construct graphical representations.

After the data were extracted, they were translated, edited, coded, entered into statistical software and analyzed with help of SPSS version 26. Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as mean and standard deviation. The Kraskal-Wallis, Mann-Whitney U criterion was used to assess the statistical relationship between categorical variables. A value of $P \leq 0.05$ was considered statistically significant.

Table 1 Base line demographics

Variables	Response
Education	
Higher education 4-5 years	47(38.8)
Postgraduate education (master's / residency) 1-2 years	42(34.7)
Postgraduate education (PhD) from 3 years	6(4.9)
Other	26(21.4)
Experience (years)	
0–10	49(40.4)
11–20	19(15.7)
21–30	35(28.9)
31–40	17(14)
>40	1(0.8)
Type Of Workplace	
Outpatient type (outpatient clinics, polyclinics, consultations, dispensaries, medical-sanitary units and ambulance stations)	57(47.1)
Inpatient type (hospitals, clinics, hospitals, maternity hospitals)	60(49.5)
Other	4(3.3)
Location	
City	90(74.3)
Rural location	31(25.6)
Age	
18–23	1(0.8)
24–29	32(26.4)
30–35	13(10.7)
36–40	11(9.1)
41–45	14(11.5)
46–49	7(5.7)
50–55	26(21.4)
>55	17(14.1)
Gender	
Female	105(86.7)
Male	16(13.2)

Values are presented as number (%).

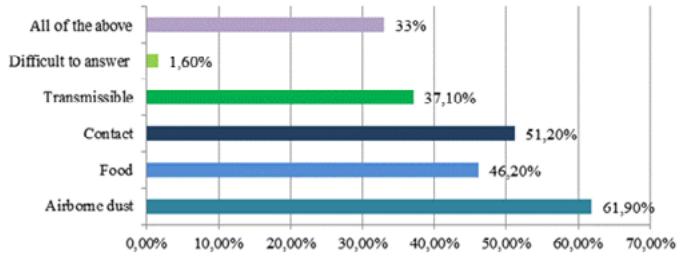

Figure 1 – Answer results about the main routes of transmission of Q fever

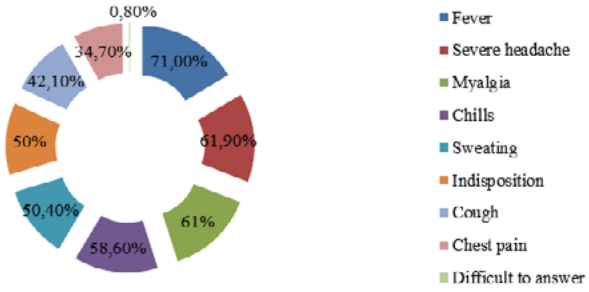

Figure 2 – Results of responses about the clinical symptoms of Q fever

Results

Out of total 121 respondents, majority (86.7%) were female infectious disease specialists, age group 24-29 years (26.4%). More than half of the respondents resided in the city (74.3%), almost half of the participants (49.5%) were working in hospital, with an experience of 1-10 years (40.4%). The detailed demographics of the respondents are presented in Table 1.

Presentation of the features of Q fever

Majority (91.7%) of the respondents answered that they are familiar with Q fever. Based on the respondents' answers, the main routes of transmission of Q fever showed (61.9%) airborne, (51.2%) contact and (46.2%) alimentary routes (Figure 1). More than two thirds reported that animals (71.9%) were the main source of C.burnetti, this followed by mosquitoes (14.8%), humans (4.9%) and others. Just over ½ (52%) reported that ticks are the main vectors of the disease, while 17% of respondents thought humans and mosquitoes as the main vectors. The most common way to contract Q fever is in spring and summer (65.2%). Also 14, 8% answers of respondents were summer time, 9% answered fall and winter, and 7% of the doctors could not answer this question. More than ¾ of the infectious disease specialists think that the main risk factor for Q fever is (77.6%) a contact with infected animals, 64.4% of respondents think that traveling and living in endemic areas affect the risk of the disease. 55.3% selected occupational risk. Above ½ of the respondents (63.6%) answered that the risk of contracting Q fever for all contingents is the same, the same number of answers were for pregnant, about 20% for elderly people, about ¼ of the respondents (23.1%) selected male contingents, a small proportion (7.4%) thought that women are more likely to get infected with Q fever. The specific signs of Q fever reported were fever in 71% of answers, severe headache and myalgia in 61.9%. They were followed by chills (58.6%), sweating and malaise (50.4%), and cough (42.1%) (Figure 2).

The level of awareness of specialists about diagnosis of Q fever

Among the tests used to examine patients with Q fever for diagnosis, serologic testing methods were most commonly used (75.2%), followed by bacteriologic testing methods (15.7%), microscopic testing methods (3.3%) and others. The majority of respondents (76.8%) chose blood as the material to confirm the diagnosis of Q fever, followed by sputum (33.8%), urine (31.4%), liquor (24.7%), bronchial lavage (21.4%), and feces (19%), only (1.6%) found it difficult to answer. However, more than 1/3 (46.2%) reported that due to the lack of special tests for confirming Q fever, the diagnosis is not made in Kazakhstan. Almost all respondents believe that the differential diagnosis of Q fever should be made with all listed diseases, such as influenza, brucellosis, tuberculosis and others.

The level of awareness of specialists about treatment of Q fever

Doxycycline, an antibiotic of tetracycline group, was the most commonly (76.8%) selected as a drug for treatment of Q fever, then it was followed by Ceftriaxone (8.2%), Interferon (7.4%), Metronidazole (2.4%), Chloramphenicol (0.8%). 4.1% of participants found it difficult to answer.

The level of awareness of specialists about complications and prevention of Q fever

The majority of interviewees considered veterinary sanitary control (84.2%) as the main preventive measure against Q fever, followed by other measures such as consumption of milk after thorough boiling (63.6%), vaccination (57.8%), the need to treat fields and places (47.9%), only (1.6%) doctors found it difficult to answer. The majority of participants (71.9%) think that pneumonia is the main complication of the disease. More than ½ of respondents (59,5%) think endocarditis, almost half of participants answered hepatitis (47,9%), a small part of participants think that complications of this disease are peritonitis (14%) and bleeding (19,8%).

Discussion

We conducted this survey due to the high risk of Q fever infection in our country, as a large number of residents are engaged in animal production, which increases the risk of Q fever in the communities.

According to Hamad G. and et al. [8] investigations a total of 15 articles were analyzed. These articles published on surveys and interviews conducted with farmers, veterinary practitioners and nurses, medical practitioners, policy makers, researchers, industry representatives, animal science students, cat breeders, wildlife rehabilitators, and agriculture show attendees. Two investigations [9, 10] that involved practicing physicians revealed a low level of awareness of Q fever. In our survey involved only infectious disease physicians, the majority of the surveyed interviewees (91.7%) felt that they had good knowledge of information, with 80.2% demonstrating a satisfactory level of knowledge. In study Lindsay P. J. et al. investigated 43 hospital and community-based doctors, 72% accurately identified that Q fever is caused by a bacteria; less than half (47%) of clinicians were aware of long-term complications of Q fever, with few clinicians being aware of the variable clinical presentations and suggesting underestimation of disease burden [9]. According to Rahaman M. R. et al. study that included general practitioner as one of many stakeholders recognized the important role general practitioners have in diagnosing, reporting and treating

Q fever; however limited knowledge and awareness among general practitioner was acknowledged [10]. Participants from four additional studies [11-14] raised concern about general practitioners in certain locations. This included: identifying at risk populations, symptoms, and vaccination provision of Q fever [11]; lack of awareness including vaccination administration and advocation to higher-risk populations [12]; failure to recommend vaccination and lack of knowledge around Q fever [14]; and general practitioners expressing low levels of awareness [13]. In our study, the lowest level of knowledge in the categories is the knowledge of transmission routes (32.2%), risk factors of the disease (19.8%), materials used for diagnosis (27.3%), prevention (43.8%), outcomes and complications (27.3%) of the disease. In consequence, awareness in these domains of knowledge needs to be increased. In the categories of knowledge possession, the highest knowledge levels were knowledge about sources of infection (71.9%), vector (52.1%), seasonality of the disease (65.3%), symptoms (52.1%), differential diagnosis (60.3%), diagnostic methods (75.2%), and treatment (76.9%).

We also, assessed the relationship of knowledge level with different socio-demographic characteristics of the respondents. A statistically significant difference was found for work experience (*P<0.05) and for age (*P<0.05). Namely, the higher is the work experience, the more is knowledge about the disease (Figure 3). When comparing the level of knowledge in different age groups, it was found that age groups 50-55, over 55 years demonstrated significantly more "good" knowledge than other age groups (Figure 4). There were no statistically significant differences in the knowledge level of participants according to education level, gender, place of residence and type of institution (P> 0.05). That is, the distribution of knowledge level was the same for these categories, indicating that the knowledge level of participants on Q fever is independent of gender, education, place of residence, and type of institution.

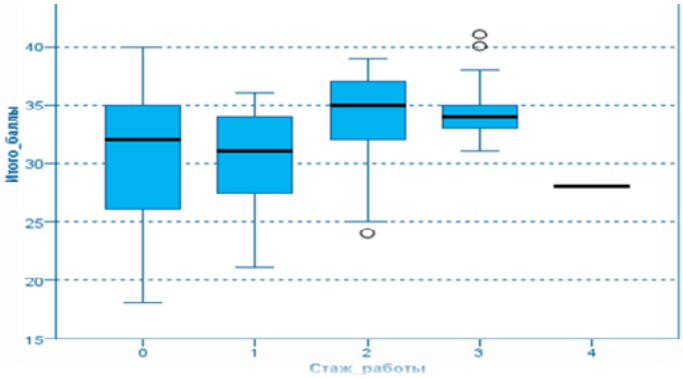

Figure 3 – Level of knowledge by Work experience

(Kraskal-Wallis criterion for independent samples. The horizontal line shows the work experience, the vertical line shows the total score)

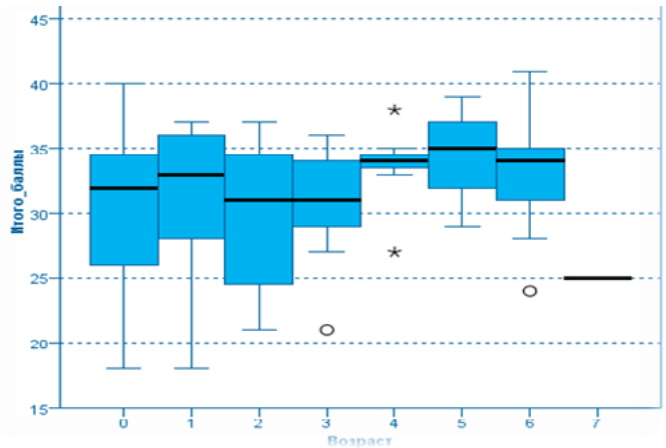

Figure 4 – Level of knowledge by age

(Kraskel-Wallis criterion for independent samples. The horizontal line shows the age, the vertical line shows the total score)

Conclusion

In our study, most of the respondents in the sample were aware of Q fever; the level of knowledge about the pathology was satisfactory. However, among specialists in the age groups of 24-45 years old there was a lack of knowledge about transmission, risk factors, diagnosis, prevention, outcomes and complications of Q fever; therefore, we recommend to increase the level of knowledge about Q fever in these sections for this age group. Consequently, we consider it advisable to include comprehensive information on the previously mentioned categories in training programs, seminars, conferences in the field of infectiology, epidemiology and public health, to create online video courses on available platforms, educational videos, publications in the media to attract attention and talk about the discussed disease among young professionals and the population.

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The effect of mindfulness-based psychoeducation on automatic thinking, pain beliefs, and pain coping of nursing students with dysmenorrhea: a quasi-experimental study

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Abstract

Aim: Dysmenorrhea has a high prevalence among university students and affects important aspects of daily activity, psychological health, quality of life, and academic performance. This study aimed to evaluate the effect of mindfulness-based psychoeducation program on automatic thinking, pain beliefs and coping of nursing students with dysmenorrhea.

Material and methods: This study was a quasi-experimental study using a nonrandomized control group pretest and posttest design. The study included 72 nursing students with primary dysmenorrhea. The experimental group received psychoeducation for 75 minutes per week for nine sessions. Data were collected using the Automatic Thoughts Questionnaire, Pain Beliefs Questionnaire, and Pain Coping Inventory.

Results: The automatic thinking, organic pain beliefs, and passive pain coping total scores in the experimental group significantly decreased after program compared with those in the control group ($p < 0.05$). Moreover, there was a significant increase in psychological pain beliefs and active pain coping total scores in the experimental group ($p < 0.05$).

Conclusions: These findings indicate that the program was effective in addressing automatic thinking, pain beliefs and coping of nursing students with dysmenorrhea. The mindfulness-based psychoeducation program can be easily applied to students suffering from dysmenorrhea.

Keywords: dysmenorrhea, mindfulness, psychoeducation, automatic thinking, pain beliefs, pain coping.

Introduction

Dysmenorrhea is the painful cramps of uterine origin that occur during menstruation; it is a common cause of pelvic pain and menstrual disorder [1]. It occurs as primary and secondary. Primary dysmenorrhea generally appears in women under 20 years old and is a painful uterine contraction caused by endometrial laceration. However, there is pathology in secondary dysmenorrhea, and it is a common problem among those over 20 years [2]. It usually comes with several physical symptoms such as headache, dizziness, fatigue, diarrhea, cramps, and sweating [3]. The most typical symptom is painful involuntary contraction and often accompanying symptoms such as backache, nausea, vomiting, and diarrhea [4].

Dysmenorrhea has a high prevalence (61.2%-85.1%) among university students and affects important aspects of daily activity, psychological health, quality of life, and academic performance [5-8]. Female university students in Ethiopia reported school absence, lack of interest in class, lack of attention, unwillingness to participate in an activity involving physical exertion and group activities, and loss of motivation for homework [9]. Turkish university students reported that they had difficulty attending classes, had low concentration, and did not continue their daily life activities [10].

Primary dysmenorrhea prevalence in nursing students in Turkey was 94%, and severe primary dysmenorrhea was high among students who used medication for pain, used complementary and alternative treatments, had other accompanying symptoms, and had a family history of painful menstruation [11]. In another study, 67.7% of Turkish nursing students experienced dysmenorrhea and severity of pain was 9.07 ± 3.42 [12]. Karabulutlu [13] reported that 86.4% of nursing students had dysmenorrhea, and it was associated with family history.

Nursing students experienced physical or mental features that worsen the pain severity, such as dizziness, gastrointestinal system complaints, worry, exhaustion, fatigue, distension, idleness, anorexia, musculoskeletal system pain, and recurrent throbbing headaches [14]. Al-Zahrani et al. [15] revealed that dysmenorrhea had negatively affected nursing students' academic performances, such as absenteeism from school, loss of concentration, and inability to fulfill school-related responsibilities and participate in social life. Turkish midwifery students experienced problems with family, school, and social life and problems with school attendance and exams due to dysmenorrhea [16].

Şahin et al. [17] determined that university students coping with dysmenorrhea preferred hot application to the feet, rest/sleep, analgesics, hot bath, health institution application, and physical activity. According to Karabulutlu [13], Turkish nursing students preferred resting, hot bathing, applying a heat pack to the abdomen, walking, taking analgesics, listening to music, and exercising. As can be seen, students mostly use physical methods to cope with dysmenorrhea. However, psychosocial interventions may be beneficial as pain has a psychosocial dimension. This study aimed to determine the effect of mindfulness-based psychoeducation program (MBPP) on automatic thinking, pain beliefs, and pain management of nursing students with dysmenorrhea.

Material and methods

Design

This quasi-experimental study with a nonrandomized control group was performed in February and May 2019.

Setting and Sample

The study population consisted of 243 nursing students registered in the nursing department at a state university in Turkey. Purposive sampling method was used and students with primary dysmenorrhea were included in the study. Inclusion criteria for the study were nursing students who volunteered to participate and experienced primary dysmenorrhea. The exclusion criterion was to participate previously in a mindfulness-based or psychoeducation program. It was determined that 164 students had primary dysmenorrhea. The inclusion criteria for primary dysmenorrhea were: 1) Onset of pain within 6–12 hours after menstruation, and 2) Menstrual pain accompanied by pain such as waist, leg, and abdominal pain [18].

The sample size of the study was 52, with a 0.80 effect size, 0.80 power, and 0.05 type margin of error. Of students, 72 were included in the study, and 36 students each for the experimental group (EG) and control group (CG) were selected. After the data for the study was collected, post hoc power analysis was performed in the G*Power 3.1.9.7 software. In this study, when the mean scores obtained from the Automatic Thoughts Questionnaire were entered, the alpha value was 0.05, the theoretical power was 95%, and the effect size was 0.7. Students who wanted to participate in psychoeducation were included in the experimental group. Those who did not want to participate in psychoeducation were assigned to the control group.

Instruments

Student information form (SIF)

The SIF which was developed by the researchers in line with the literature [11-16]. It consisted of ten questions including the sociodemographic characteristics of the students, such as age, residence place, perceived economic status, chronic disease presence, smoking and alcohol use, regular eating habits, social activity status, body weight, and height.

Automatic thoughts questionnaire (ATQ)

The ATQ was developed by Hollon and Hollon [19] and adapted into Turkish by Aydın and Aydın [20]. It was a five-point Likert-type scale and it consisted of 30 items. It was scored from "all the time = 5" to "not at all = 1," and scores from the scale varied between 30 and 150 [19]. A high score indicated more frequent negative thoughts. The Cronbach alpha of the scale in original study was 0.93 [20]. In this study, the Cronbach alpha values were 0.96 (pretest) and 0.98 (posttest).

Pain beliefs questionnaire (PBQ)

The PBQ was developed by Edwards et al. [21] and adapted into Turkish by Sertel-Berk [22]. It was a six-point Likert scale that was scored as "6 = always" to "1 = never," but the subscale scores were calculated from the organic belief subscale (OBS) and psychological belief subscale (PBS) [21]. There are no cut-off values for the scores, but the higher subscores indicate the high pain beliefs, respectively. The Cronbach alpha coefficients were 0.71 for the PBS and 0.64 for the OBS [22]. In this study, the Cronbach alpha coefficients were 0.81 (pretest) and 0.72 (posttest) for the PBS and 0.63 (pretest) and 0.82 (posttest) for the OBS.

Pain coping inventory (PCI)

The PCI was developed by Kraaimaat and Evers [23] and adapted into Turkish by Hocaoglu et al. [24]. It had two subscales: active coping (ACS) and passive coping (PCS) [23]. The scale consisted of 22 items and was scored from "1 = never" to "4 = frequently." The Cronbach alpha coefficient for internal consistency reliability in the original study was between 0.53 and 0.77 [24]. In this study, the Cronbach alpha coefficients were 0.85 (pretest) and 0.86 (posttest) for ACS and 0.81 (pretest) and 0.82 (posttest) for PCS.

Data Collection and Procedure

The study was conducted from February 25, 2019, to May 3, 2019. Intervention and control groups were created. A mindfulness-based psychoeducation program (MBPP) consisting of nine sessions was applied to the intervention

group. The MBPP comprised weekly sessions and each session lasted about 75 minutes. Participants practiced mindfulness exercises together with the first author. Table 1 shows the titles and contents of the sessions. Figure 1 shows the flow diagram of the data collection and procedure. First author conducted the sessions. She had a PhD in psychiatric nursing and certifications in cognitive-behavioral therapy and mindfulness.

Table 1 The content of mindfulness-based psychoeducation program

Session 1:	Providing information about the program, applying pre-tests, and discuss-ing the concept of mindfulness.
Session 2:	Explaining the cognitive model (relationship between emotion, thought and behavior).
Session 3:	Breath awareness and determining the cognitive distortions.
Session 4:	Breath anchor meditation and awareness concept.
Session 5:	Compassionate acceptance meditation, mountain meditation and pleasure treasure meditation.
Session 6:	Body scan meditation, developing new perspectives and valuing "mo-ments" in daily life.
Session 7:	Silence day (practice all meditations without speaking at all).
Session 8:	Awareness kit and self-letter writing activity.
Session 9:	Assessment, receiving feedback about the program, and applying post-tests.

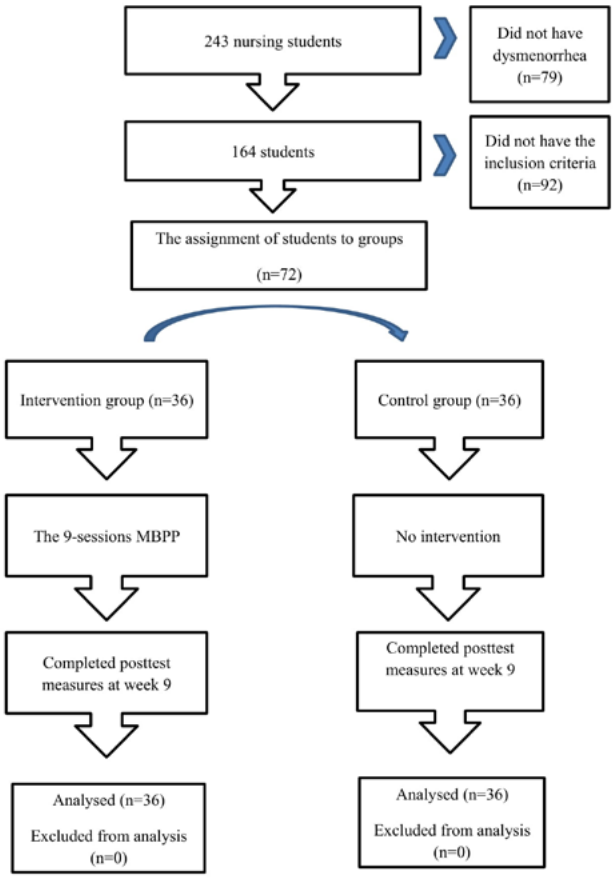

Figure 1 – The flow diagram of the data collection and procedure

Data Analysis

The study data were analyzed using the SPSS 24 package program. Descriptive statistics were used to analyze the descriptive characteristics of the students. The distribution of the data was evaluated with the Shapiro-Wilk test. The chi-square test was used to compare the descriptive characteristics of the groups, and the Mann–Whitney U test was used to compare automatic thoughts, pain beliefs and pain coping scores between the groups. Bonferroni-corrected Wilcoxon signed-rank test was used to compare the mean scores of the scales in the group. An alpha value of 0.05 was considered statistically significant.

Ethics Approval

Written approvals were obtained from the Department of Nursing and the University Human Research Ethics Committee (No: 2019/65). The students were informed about the research and their written consent for participating voluntarily was obtained. All principles of the Helsinki Declaration were followed. There is no conflict of interest with the students and that participating or not participating in the study has no positive or negative impact on course grades.

Results

The average ages for the EG and CG were 21.38 ± 1.39 and 21.38 ± 1.07 years, respectively (Table 2). When the groups were compared, there was no difference according to descriptive characteristics, such as age, residence place, perceived economic status, chronic disease presence, smoking, alcohol use, regular eating habits, social activity status, sporting status, body weight, and height ($p > 0.05$).

Table 2 The sociodemographic characteristics of the students

Characteristics		Experimental Group (n=36)		Control Group (n=36)		t/p value
		n	%	n	%	
Place of residence	City	22	61.1	22	61.2	$x^2 = 0.583$ $p = 0.747$
	Town	9	25.0	7	19.4	
	Village	5	13.9	7	19.4	
Perceived economic status	High	6	16.7	6	16.7	$x^2 = 0.480$ $p = 0.787$
	Moderate	26	72.2	24	66.6	
	Low	4	11.1	6	16.7	
Chronic disease	Yes	3	8.3	4	11.1	$x^2 = 0.158$ $p = 0.691$
	No	33	91.7	32	88.9	
Smoking	Yes	5	13.9	6	16.7	$x^2 = 0.107$ $p = 0.743$
	No	31	86.1	30	83.3	
Alcohol use	Yes	0	0.0	2	5.6	$x^2 = 2.057$ $p = 0.151$
	No	36	100.0	34	94.4	
Regular eating habits	Yes	22	61.1	17	47.2	$x^2 = 1.399$ $p = 0.237$
	No	14	38.9	19	52.8	
Social activity status	Yes	13	36.1	15	41.7	$x^2 = 0.234$ $p = 0.629$
		23	63.9	21	58.3	
Sporting status	Yes	4	11.1	9	25.0	$x^2 = 2.347$ $p = 0.126$
	No	32	88.9	27	75.0	
Body weight	42-52 kg	12	33.3	11	30.6	$x^2 = 2.735$ $p = 0.603$
	53-63 kg	20	55.6	21	58.3	
	64-74 kg	2	5.6	4	11.1	
	75-85 kg	1	2.8	0	0.0	
	≥ 86 kg	1	2.8	0	0.0	
Height	1.50-1.60 cm	15	41.7	8	22.2	$x^2 = 3.785$ $p = 0.151$
	1.61-1.71 cm	18	50.0	26	72.2	
	≥ 1.71 cm	3	8.3	2	5.6	
Age (mean ± SD)		21.38 ± 1.39		21.38 ± 1.07		$x^2 = 4.100$ $p = 0.535$

SD: Standard deviation. x^2= The chi-square test

Table 3 compares the mean pretest and posttest scores of the EG and CG in the ATQ, OBS, PBS, ACS, and PCS categories.

Table 3 The pre-test and post-test mean scores of ATQ, OBS, PBS, ACS and PCS of the experimental and control groups

Scales		Experimental Group (n=36) Mean±SD	Control Group (n=36) Mean±SD	t/p value
ATQ	Pre-test	56.25 ± 19.08	54.86 ± 18.90	z = -0.344 p = 0.731
	Post-test	41.19 ± 10.78	55.63 ± 23.72	z = -2.654 p = 0.008
	t/p value	z = -4.472 p = 0.000	z = -0.346 p = 0.729	
OBS	Pre-test	3.47 ± 0.58	3.30 ± 0.55	z = -1.101 p = 0.271
	Post-test	2.63 ± 0.66	3.53 ± 0.71	z = -4.796 p = 0.000
	t/p value	z = -4.543 p = 0.000	z = -1.525 p = 0.127	
PBS	Pre-test	4.38 ± 0.66	4.39 ± 0.92	z = -0.351 p = 0.725
	Post-test	4.85 ± 0.27	4.41 ± 0.67	z = -2.794 p = 0.005
	t/p value	z = -3.748 p = 0.000	z = -0.207 p = 0.836	
ACS	Pre-test	2.24 ± 0.60	2.43 ± 0.58	z = -1.701 p = 0.089
	Post-test	2.97 ± 0.60	2.40 ± 0.48	z = -3.878 p = 0.000
	t/p value	z = -4.700 p = 0.000	z = -0.054 p = 0.957	
PCS	Pre-test	2.57 ± 0.46	2.47 ± 0.38	z = -0.926 p = 0.355
	Post-test	2.23 ± 0.40	2.61 ± 0.47	z = -3.638 p = 0.000
	t/p value	z = -3.426 p = 0.000	z = -1.871 p = 0.061	

SD: Standard deviation. ATQ= Automatic thoughts questionnaire, OBS= organic belief subscale, PBS= psychological belief subscale, ACS= active coping subscale, and PCS= passive coping subscale.

The pretest ATQ mean score did not differ significantly between the EG (56.25 ± 19.08) and CG (54.86 ± 18.90; $p > 0.05$). However, the posttest ATQ mean score of the EG (41.19 ± 10.78) was statistically lower than that of the CG (55.63 ± 23.72; $p < 0.05$). In this study, the average ATQ scores of students were 56.25 ± 19.08 at the beginning and 41.19 ± 10.78 at the end of MBPP. The difference between the pretest and posttest score averages was significant ($p < 0.05$).

The pretest mean scores of OBS and PBS did not differ significantly between the EG and CG ($p > 0.05$). But the posttest OBS mean score of the EG (2.63 ± 0.66) was statistically lower than that of the CG (3.53 ± 0.71; $p < 0.05$). Also, the posttest PBS mean score of the EG (4.85 ± 0.27) was statistically higher than that of the CG (4.41 ± 0.67; $p < 0.05$). In the study, the OBS average scores of students were 3.47 ± 0.58 at the beginning of MBPP and 2.63 ± 0.66 at the posttest. The PBS average scores of students were 4.38 ± 0.66 for the pretest and 4.85 ± 0.27 for the posttest. The difference between the two score averages in the EG was statistically significant ($p < 0.05$).

According to Table 3, the pretest mean scores of ACS and PCS did not differ significantly between the EG and CG ($p > 0.05$). But the posttest ACS mean score of the EG (2.97 ± 0.60) was statistically higher than that of the CG (2.40 ± 0.48; $p < 0.05$). Also, the posttest PCS mean score of the EG (2.23 ± 0.40) was statistically lower than that of the CG (2.61 ± 0.47; $p < 0.05$).

In the study, the ACS average scores of students in the EG were 2.24 ± 0.60 at the beginning of MBPP and 2.97 ± 0.60 at the end. The PCS average scores of students were 2.57 ± 0.46 for the pretest and 2.23 ± 0.40 for the posttest. The difference between the two score averages was statistically significant ($p < 0.05$).

Discussion

This study aimed to determine the effect of mindfulness-based psychoeducation program (MBPP) on automatic thinking, pain beliefs, and pain management of nursing students with dysmenorrhea. Dysmenorrhea is a very common health problem in university students and affects their social life as well as their academic success [11-16]. Yılmaz and Şahin [25] applied a cognitive-behavioral approach to support students with dysmenorrhea and found that primary dysmenorrhea symptoms, pain levels, and analgesic use decreased after the program. Kırca and Sis Çelik [26] also applied a yoga program to students with dysmenorrhea and found that menstrual pain decreased after the program. Hassan et al. [27] applied cognitive-behavioral therapy to students with dysmenorrhea and found that the program was effective on depression, anxiety, stress, and coping strategies. In this study, mindfulness-based psychoeducation, including the cognitive-behavioral approach, was applied and after the program, the students' automatic thoughts decreased, and their pain beliefs and pain management improved positively.

The study found that automatic thinking in nursing students decreased after MBPP. They had a lower level of negative thoughts after than before the program. Similarly, nursing students' scores of automatic thoughts were significantly lower at the end of a 12-session cognitive-behavioral group counseling program [28]. Also, psychoeducation based on a cognitive-behavioral approach did not show significant differences between the intervention group and CG in depressive thoughts among nursing and midwifery students with premenstrual syndrome symptoms [29]. In this study, psychoeducation intervention was effective on automatic thoughts. Also, psychoeducation was based on both mindfulness and some cognitive behavioral therapy-based interventions. Like this study, another study found that mindfulness training decreased significantly automatic thoughts in female students [30].

Elvery et al. [31] found that pain catastrophizing, mindfulness, and pain acceptance were related in undergraduate students reporting chronic or intermittent pain. Considering this information, the present study found that MBPP showed significant differences between the intervention group and CG in the organic and psychological pain beliefs. After MBPP, passive pain coping in nursing students decreased and active pain coping increased. Similar to this study, Payne et al. [32] evaluated the effect of a mind–body intervention on young adult women with primary dysmenorrhea. After the intervention, participants reported significantly lower menstrual pain and pain catastrophizing improved over time. Ball et al. [33] reported the most important effect of mindfulness meditation on affective pain and sensory pain in individuals with chronic pain.

Başoğul et al. [29] carried out a 5-week psychoeducation for female nursing and midwifery students. The psychoeducation reduced fatigue and anger levels but not in pain. Asgari et al. [34] improved a protocol of 3-week psychoeducational intervention based on a self-regulation model. They aimed to cope with dysmenorrhea pain and menstrual distress but did not yet explain the outcomes of the intervention. Borji-Navan et al. [35] found that cognitive-behavioral therapy decreased premenstrual

syndrome symptoms and increased perimenstrual quality of life of university students.

As can be seen, in these studies, either mindfulness-based practice or cognitive-behavioral theory-based psychoeducation were applied. Moreover, different results were obtained. For this study, we can say that this is the first study in which MBPP was applied to nursing students with dysmenorrhea. This program was found to be effective on pain coping with both automatic thoughts and pain beliefs.

There are several strengths and limitations. The most important strength of this study is that it is one of the limited number of studies in which mindfulness-based psychoeducation was applied. It has brought a valuable application to the field by positively affecting students' automatic thoughts, pain beliefs and pain coping. The effectiveness of the MBPP was evaluated in a small sample size. The study had a lack of follow-up measurements and the lack of randomization. Data collection tools based on self-report were also used.

Conclusion

The mindfulness-based psychoeducation program was effective on the automatic thoughts, pain beliefs, and coping with pain of students with dysmenorrhea. It increased psychological pain beliefs and active pain coping in nursing students with dysmenorrhea. Nursing students' automatic thinking, organic pain beliefs, and passive pain coping levels decreased after the program.

The mindfulness-based psychoeducation program should be implemented with the goal of improving the automatic thoughts, pain beliefs and pain coping of students with primary dysmenorrhea. The mindfulness-based psychoeducation practices, such as giving information about mindfulness, understanding relationship between emotion, thought and behavior, improving breath awareness, and determining the cognitive distortions can be useful in decreasing negative pain beliefs and passive pain coping strategies. Psychiatric nurses should apply the randomized controlled mindfulness-based interventions and assess their effects on cognitive distortions and pain coping. They should monitor the effects of a longer-term MBPP on physiological and psychological symptoms of dysmenorrhea.

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Long-term outcomes of myocardial revascularization in patients with multivessel coronary artery disease and comorbid pathology

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Abstract

Objective. To assess the long-term outcomes of myocardial revascularization in patients with multivessel coronary artery disease and varying degrees of comorbidity.

Materials and methods. 406 patients with low and moderate Syntax scores (SS) (<33) underwent primary percutaneous coronary intervention (PCI) (n=200) with a drug-eluting stent, and coronary artery bypass grafting (CABG) (n=206). Patients were stratified by the Charlson Comorbidity Index (CCI) into 2 groups: 1) CCI ≤ 3(n=108/26.6%); 2) CCI ≥ 4(n=298/73.4%). The mean follow-up period was 9±1.9 years. The endpoints of the study were as follows: major adverse cardiac and cerebrovascular events (MACCE), a repeat revascularization, decreased left ventricular ejection fraction, and high SS in dynamics.

Results. An increase in CCI of more than 4 points was significantly associated with the risk of developing a combination of MACCE (HR 1.3, 95% CI 1.2 – 1.4, p<0.001), all-cause mortality (HR 1.25, 95% CI 1.2 – 1.4, p<0.001), and cerebrovascular accidents (CVA) (HR 2.2, 95% CI 1.4 – 3.4, p=0.001). Patients with CCI ≥4 required repeat revascularization more frequently after PCI than after CABG (HR 2.6, 95% CI 1.8 – 3.7, p<0.001). Among patients with varying degrees of comorbidity, the risk of progression of coronary atherosclerosis (SS≥33) was higher after CABG compared with PCI.

Conclusion. A CCI score of more than 4 points was associated with an increased risk of developing of MACCE, all-cause mortality, and CVA. Among patients with varying degrees of comorbidity, PCI and CABG did not demonstrate significant advantages in terms of MACCE.

Keywords: Coronary Artery Disease, Percutaneous Coronary Intervention, Coronary Artery Bypass Grafting, Comorbidity.

Introduction

Despite the achievements in the diagnosis and treatment of coronary artery disease (CAD) in recent decades, it continues to occupy a prominent position in the morbidity and mortality statistics in most countries worldwide [1]. Coronary revascularization is undeniably the most important treatment strategy for CAD, and the choice of the optimal revascularization method, whether it be coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), remains a current challenge [2, 3]. In recent years, patients are more frequently presenting with complex multivessel CAD and a wide range of comorbidities [4]. In these conditions, clinicians face a growing population of patients with unique clinical profiles and challenges in both interventional and surgical treatment. In cases of more complex multivessel coronary lesions, CABG achieves more complete revascularization than PCI [5]. As a consequence, the majority of prior studies comparing the long-term outcomes of surgical and interventional treatment in patients with multivessel disease have demonstrated the superiority of CABG over PCI in several aspects, including survival [2,6,7]. However, it is worth noting that, despite advances in surgical techniques, CABG remains a more invasive revascularization method compared to PCI.

Consequently, it is evident that surgery for comorbid patients is associated with additional risks of adverse events.

In recent years, interventional procedures have become the most frequently performed treatments for CAD. The introduction of advanced drug-eluting stents (DES) questions the relevance of earlier research in today's context. Some more recent long-term randomized clinical trials (RCTs) fail to find a significant difference in outcomes between PCI and CABG [8-10]. In modern conditions, when selecting the optimal revascularization method, it is necessary to consider not only the anatomical characteristics of coronary arteries but also to understand the impact of comorbidities on clinical outcomes [11]. Over the past decades, various long-term and short-term studies have been conducted to compare the outcomes of CABG and PCI in different patient groups while assessing the influence of comorbid pathologies [12-19]. Mostly, the impact of individual pathologies was evaluated, such as diabetes mellitus (DM) [12-14], renal pathology [15,16], prior cerebrovascular accidents (CVA) [17], Chronic Obstructive Pulmonary Disease (COPD) [18], infections [19]. However, the impact of the general burden of comorbid diseases on revascularization outcomes has been relatively understudied in recent decades and has been separately analyzed for each strategy [11, 20, 21]. Therefore, analyzing the results of both revascularization methods in comorbid patients is believed to be of significant interest. The Charlson Comorbidity Index (CCI) is a widely recognized and convenient tool for assessing the prognostic impact of comorbid conditions on survival [22, 23]. In our study, we used CCI to analyze the impact of comorbidity on long-term revascularization outcomes in general and in relation to the each strategy.

Material and methods

Study Design and Patients

The process of selecting patients for the study was described in detail earlier [24]. However, let's clarify key points. Our study is a retrospective, two-center clinical cohort study. Based on the archives of the medical records from two clinics, we selected 406 patients who underwent primary PCI with DES (n = 200) or primary CABG (n = 206) between 2010 and 2013. The study included patients with stable forms of CAD and stabilized patients with non-ST-segment elevation acute coronary syndrome, featuring multivessel disease and low or intermediate SYNTAX scores (SS) (i.e., ≤ 32). Patients with prior cardiac surgery or stenting were excluded from the study. Additional exclusion criteria from the study were: an acute coronary syndrome with an ST-elevation, left main disease, an SS ≥ 33, age over 65, single-vessel coronary disease, an aneurysm of the left ventricle, severe valvular dysfunction due to CAD, rheumatic or congenital heart defects, a left ventricular ejection fraction (LVEF) of less than 40%, severe chronic renal failure (i.e., a glomerular filtration rate [GFR] using the Cockcroft–Gault equation of less than 30 ml/min/1.73 m^2).

The severity of atherosclerotic coronary artery damage was assessed using the SYNTAX score [25, 26]. The SYNTAX score was not initially utilized during the period 2010–2013 when selecting a revascularization method. We retrospectively conducted the SYNTAX score assessment based on archival angiograms (https://syntaxscore2020.com) [25, 26]. Thus, 200 patients with a low SS and 206 patients with an intermediate SS (i.e., ≤ 32) were selected.

The search for patients and the collection of necessary clinical information occurred from 2020 to 2022 through the clinical electronic databases of participating centers, the Clinical Medical Information System (CMIS, Outpatient National Register; https://pvd.dmed.kz), the electronic register of inpatient (ERIP, National Inpatient Register; www.eisz.kz), as well as the current contact information of patients and their relatives. The mean follow-up period was 9±1.9 years, with a maximum follow-up period of 12 years.

Endpoints and definitions

The clinical endpoints of the study included the following: a combination of major adverse cardiac and cerebrovascular events (MACCE) and their components: all-cause mortality, CVA (transient ischemic attack [TIA] or stroke), myocardial infarction (MI), repeated revascularization, the development of chronic heart failure (CHF) (based on clinical status, decreased LVEF, heart chamber dilation with valvular dysfunction), and a high-degree atherosclerotic lesion of coronary arteries according to the SS (≥33) in dynamics.

The cause of death was classified as definite cardiovascular, definite non-cardiovascular, and undetermined death. If it was not possible to establish the exact cause of death, then the cases were conservatively regarded as cardiovascular. Diagnoses of CVA and MI were recorded when confirming medical documentation. Heart failure development was clinically assessed, considering LVEF and heart chamber dilation, compared with initial echocardiographic parameters. A decrease in LVEF below 50% was considered significant for patients with an initial LVEF above 50%. For patients with primary LVEF in the range of 40-50%, a decrease of 5 points from the baseline was considered significant. Dilation of heart chambers with valve dysfunction was additionally recorded when echocardiography showed dilation of all heart chambers with the development of mitral and/or tricuspid valve insufficiency. Out of the 334 surviving patients, 238 patients (71.3%) underwent repeat angiography at participating centers and other hospitals in Kazakhstan and foreign clinics. Protocols and electronic media of angiograms were obtained from electronic databases of participating hospitals and from patients. The SYNTAX score was recalculated for patients who underwent repeat angiography (https://syntaxscore2020.com). If a patient had multiple angiography during the follow-up period, the SS was assessed on the last angiogram.

Patient comorbidity was assessed using the Charlson Comorbidity Index (CCI) [22, 23]. The CCI is a scoring system evaluating age and the presence of 16 comorbidities. Each condition is assigned 1, 2, 3, or 6 points based on the associated mortality risk. An additional point is added for each decade of life after the patient reaches the age of fifty (i.e., 50-59 years – 1 point, 60-69 years – 2 points, etc.) (Table 1, see the next page). The CCI was calculated for all patients (https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci). The study population was divided into two groups: the first group comprised patients with mild/moderate comorbidity (CCI≤3), and the second group included patients with severe comorbidity (CCI≥4). The maximum CCI value was 12 points.

Our retrospective cohort study was conducted in accordance with the principles of the Declaration of Helsinki, and approval was obtained from the Local Ethical Commission of NJSC "Semey Medical University" (minutes no. 2, dated October 28, 2020) and the Committees of the participating centers.

Statistical Analysis

All calculations were performed using IBM SPSS Statistics 23.0 (IBM Corporation, Armonk, New York, USA), and a p-value <0.05 was considered statistically significant. Continuous variables were compared using the Student's t-test or Mann-Whitney U test. Categorical variables were presented as percentages and numbers and compared using the χ 2 test, Fisher's exact test, or Kendall-Stewart test. The survival function of patients was assessed using Kaplan-Meier method, and the

Table 1 Clinical variables and definitions used to calculate Charlson co-morbidity index [22, 23]

Clinical Variables	Points
Age <50 years 50–59 years 60–69 years 70–79 years ≥80 years	 0 +1 +2 +3 +4
CHF Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	+1
Peripheral vascular disease Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)	+1
CVA or TIA History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	+1
Dementia Chronic cognitive deficit	+1
COPD	+1
Connective tissue disease	+1
Peptic ulcer disease Any history of treatment for ulcer disease or history of ulcer bleeding	+1
Liver disease Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)	None 0 Mild +1 Moderate to severe +3
Diabetes mellitus	None or diet-controlled 0 Uncomplicated +1 End-organ damage +2
Hemiplegia	+2
Moderate to severe CKD Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.265 mmol/L)	+2
Solid tumor	None 0 Localized +2 Metastatic +6
Leukemia	+2
Lymphoma	+2
AIDS	+6

CHF = Congestive heart failure, COPD= Chronic obstructive pulmonary disease, CKD = Chronic kidney disease, CVA = cerebrovascular accident, TIA= Transient ischemic attack.

Cox proportional regression method with the determination of the Hazart ratio (HR) and 95% confidence interval (CI). Multivariate analysis was fulfilled to assess whether CCI is an independent predictor of adverse events. The Cox regression model included the following covariates: CCI, gender, age, smoking status, body mass index (BMI), dyslipidemia, arterial hypertension, diabetes, previous MI, previous CVA, peripheral vascular disease, atrial fibrillation (AF), COPD, primary LVEF, type of revascularization (PCI/CABG), initial SYNTAX score. Receiver-operating characteristic (ROC) curves were used to assess the diagnostic significance of CCI.

Results

Baseline characteristics

The baseline characteristics of the groups are presented in Table 2. In terms of their baseline characteristics, patients with severe comorbidity were, on average, 5 years older compared to patients with mild/moderate comorbidity (58 [53-61] years and 53 [48-57] years, respectively, p<0.001). There was no significant difference in the gender composition of the two groups; both groups were predominantly composed of males, over 80% in each group. Patients with severe comorbidity compared with the group patients with mild/moderate comorbidity, respectively, had a higher prevalence of the following conditions: a high degree of hypertension (66% vs. 49%, p=0.046), diabetes (41.3% vs. 10.2%, p<0.0001), and more often suffered from previous MI (71.8% vs. 37%, p<0.001), previous CVA (9.4% vs. 1.9%, p=0.012), were more likely to have peripheral vascular disease (19.8% vs. 8%, p=0.006), and more often had an abnormal lipid

Table 2 Baseline patients characteristics by level of comorbidity

Parameter	Mild/Moderate, CCI≤3 (n=108/26.6%)	Severe, CCI≥4 (n=298/73.4%)	p-value
Age, years	53(48-57)	58(53-61)	<0.0001
Gender			0.095
Women	13(12%)	57(19%)	
Men	95(88%)	241(80.9%)	
Family history of heart disease	31(28.7%)	76(25.5%)	0.52
History of smoking	41(38%)	92(30.9%)	0.18
Body-mass index (BMI), kg/m^2	29.2(±5)	29.8(±4.7)	0.26
Dyslipidemia	74(68.5%)	250(83.9%)	0.001
GFR, ml/min/1.73m^2	97(82-108.75)	91(75-102)	0.003
Hypertension	105(97.2%)	294(98.7%)	0.39
Degrees of hypertension			0.046
Mild hypertension	13(12%)	7(2.3%)	
Moderate hypertension	39(36%)	90(30.2%)	
Severe hypertension	53(49%)	197(66%)	
Diabetes mellitus	11(10%)	123(41.3%)	<0.0001
Previous myocardial infarction	40(37%)	214(71.8%)	<0.0001
Previous CVA	2(1.9%)	28(9.4%)	0.02
Atrial fibrillation	17(15.7%)	63(21%)	0.23
Peripheral arterial disease	9(8.3%)	59(19.8%)	0.006
Chronic obstructive pulmonary disease	0	50(16.8%)	<0.0001
Left ventricular ejection fraction (%)	57(53.2-60)	55(49-59)	<0.0001
SYNTAX Score			
Mean	19.7(±7.1)	21.2(±6.65)	0.04
Conventional category			0.13
SYNTAX Score, ≤22	60(55.6%)	140(47%)	
SYNTAX Score, 23-32	48(44.4%)	158(53%)	
Disease extent			0.35
Two-vessel disease	59(54.6%)	147(49.3%)	
Three-vessel disease	49(45.4%)	151(50.7%)	
Type of revascularization			0.08
PCI	61(56.5%)	139(46.6%)	
CABG	47(43.5%)	159(53.4%)	

Values are shown as mean ± SD (n), Me (Q1-Q3) or % (n/N).
CCI= Charlson Comorbidity Index; CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention; SS = SYNTAX Score; CVA = cerebrovascular accident; GFR = glomerular filtration rate according to the Cockcroft-Gault formula.

Table 3 Clinical Outcomes According to level of comorbidity and Revascularization Treatment

Events	Mild/ Moderate, CCI≤3 (n = 108/26.6%)	Severe, CCI≥4 (n = 298/73,4%)	Hazard ratio (95% CI)	P value
MACCE	51 (47.2%)	206(69%)	0.57 (0.42 – 0.78)	<0.0001
Repeat revascularization	41(38%)	141(47.3%)	0.7 (0.5 – 0.99)	0.04
All-cause-Death / MI/Stroke/TIA	20(18.5%)	129(43.3%)	0.38 (0.24 – 0.6)	<0.0001
Death, all-cause	12(11%)	65(21.8%)	0.5 (0.27 – 0.9)	0.024
Cardiac death	10(9.3%)	40(13.4%)	0.67 (0.34 – 1.34)	0.26
Non-cardiac death	2(1.9%)	25(8.4%)	0.2 (0.05 – 0.9)	0.034
Myocardial infarction	7(6.5%)	49(16.4%)	0.37 (0.17 – 0.8)	0.01
Stroke/TIA	5(4.6%)	47(15.8%)	0.27 (0.1 – 0.7)	0.006
LVEF during follow-up (%)*	58(53-61)	51.9(44-58)		<0.0001
Decrease in LVEF	12(15.6%)	102(41.3%)	0.3 (0.18 – 0.6)	<0.0001
Heart chambers dilatation + valvular insufficiency	4(5.2%)	48(19.4%)	0.2 (0.08 – 0.65)	0.005
SYNTAX Score during follow-up*	20(8-27.5)	24.5(15.5-33.5)		0.005
SYNTAX Score, ≥33, during follow-up	11(18.6%)	51(28.5%)	0.56(0.3-1.08)	0.08

Values are number of events (%), unless otherwise indicated
*- Values are shown as mean ± SD (n), Me (Q1-Q3) or % (n/N). CCI= Charlson Comorbidity Index; CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention; MACCE-major adverse cardiac and cerebrovascular events = All-cause-death +MI+Stroke/TIA+ Repeat revascularization; MI = myocardial infarction; TIA = transient ischemic attack; LVEF = Left ventricular ejection fraction

profiles (83.9% vs. 68.5%, p=0.001). Notably, there were no reported cases of COPD among patients with mild/moderate comorbidity. The groups did not differ significantly in terms of BMI, with an average of 29.2 ± 5 for the first group and 29.8 ± 4.7 for the second (p=0.26). There were also no significant differences in the proportion of smoking patients (38% and 31%, p=0.18) or the prevalence of AF (15.7% vs. 21%, p=0.23) in the first and second groups, respectively.

On average, patients in both groups had a similar distribution of coronary artery lesions: two-vessel disease - 54.6% vs 49.3%; three-vessel disease - 45.4% vs 50.7% (p=0.35); low gradation of SS (≤22)- 55.6% vs 47%; intermediate SS category (23-32) - 44.4% vs 53% for the first and second groups, respectively. In addition, both groups had an even distribution of revascularization strategies: CABG or PCI (Table 2).

Outcomes

Patients with different degrees of comorbidity did not show significant differences in the risk of developing cardiac death and the likelihood of developing a high degree of atherosclerotic damage to the coronary arteries based on SS (≥33). However, for other endpoints, patients with severe comorbidity predictably had a higher risk of experiencing adverse events compared to patients with mild/moderate comorbidity (Table 3).

When analyzing revascularization outcomes with stratification by CCI, patients with severe comorbidity had a greater risk of requiring repeat revascularization after PCI compared to CABG (68% and 29%, HR 2.6, 95% CI 1.8 – 3.7, respectively; p<0.001). Among patients with different levels of comorbidity, undergoing CABG was associated with a higher likelihood of developing severe coronary artery lesions based on SS (≥33) compared to PCI (37.5% and 5.7%, HR 14.3, 95% CI 1.8-114, p=0.012; vs 45.9% and 12.8%, HR 3.1, 95% CI 1.6-5.9, respectively, for the first and second groups). Regarding other endpoints, no significant advantages were found between CABG and PCI (Table 4).

Table 4 Clinical Outcomes According to level of comorbidity and Revascularization Assignment

Events	Mild/Moderate, CCI≤3				Severe, CCI≥4 (n=298/73.4%)				
	(n=108/26.6%)	CABG (n=47)	Hazard ratio (95% CI)	P value	PCI (n=139)	CABG (n=159)	Hazard ratio (95% CI)	P value	P value interaction
MACCE	33(54%)	18(38.3%)	1.2 (0.66-2.2)	0.54	116(83.5%)	90(56.6%)	1.6 (1.2-2.1)	0.001	0.001
Repeat revascularization	29(47.5%)	12(25.5%)	1.5 (0.75 -3)	0.24	95(68.3%)	46(28.9%)	2.6 (1.8-3.7)	<0.0001	<0.0001
All-cause-Death /MI/ Stroke/TIA	10(16.4%)	10(21.3%)	0.8 (0.33-1.9)	0.6	63(45.3%)	66(41.5%)	1.2 (0.8 – 1.6)	0.39	0.55
Death, all-cause	4(6.6%)	8(17%)	0.4 (0.12-1.3)	0.14	31(22.3%)	34(21.4%)	1.1 (0.68-1.8)	0.69	0.8
Cardiac death	3(4.9%)	7(14.9%)	0.34 (0.09-1.3)	0.12	17(12.2%)	23(14.5%)	0.88 (0.47-1.6)	0.68	0.27
Non-cardiac death	1(1.6%)	1(2%)	0.8 (0.05-13.4)	0.9	14(10.1%)	11(6.9%)	1.6 (0.7 – 3.5)	0.25	0.28
Myocardial infarction	6(9.8%)	1(2%)	4.6 (0.55-38)	0.16	29(20.9%)	20(12.6%)	1.75 (0.99-3)	0.055	0.02
Stroke/TIA	3(4.9%)	2(4.3%)	1.2 (0.2-7.3)	0.8	21(15%)	26(16.4%)	0.94 (0.53-1.7)	0.8	0.9
LVEF during follow-up (%)*	56.5(±6.8)	56.7(±6.6)		0.87	50.9(±10.9)	48.2(±11)		0.049	
Decrease in LVEF	8(18.2%)	4(12%)	1.3 (0.37-4.4)	0.7	38(32.2%)	64(49.6%)	0.7 (0.47-1.01)	0.09	0.13
Heart chambers dilatation + valvular insufficiency	2(4.5%)	2(6%)	0.4 (0.04- 4.5)	0.47	18(15.3%)	30(23.3%)	0.74 (0.4 – 1.3)	0.3	0.2
SYNTAX Score during follow-up*	12(5-21.5)	26.5(20-39.5)		<0.0001	18.5(9.8-26)	31.5(24-35.8)		<0.0001	
SYNTAX Score, ≥33, during follow-up	2(5.7%)	9(37.5%)	0.07 (0.01-0.56)	0.012	12(12.8%)	39(45.9%)	0.33 (0.17-0.6)	0.001	<0.0001

Values are number of events (%), unless otherwise indicated
*- Values are shown as mean ± SD (n), Me(Q1-Q3) or % (n/N). CCI= Charlson Comorbidity Index; CABG = coronary artery bypass grafting; CI = confidence interval; PCI = percutaneous coronary intervention; MACCE-major adverse cardiac and cerebrovascular events = All-cause-death +MI+Stroke/TIA+ Repeat revascularization; MI = myocardial infarction; TIA = transient ischemic attack; LVEF = Left ventricular ejection fraction.

We conducted a multivariate Cox regression analysis for all study endpoints, including the following covariates: CCI, gender, age, smoking, BMI, dyslipidemia, hypertension, DM, previous MI, previous CVA, peripheral atherosclerotic vascular disease, AF, COPD, primary LVEF, type of revascularization (CABG/PCI), and initial SYNTAX Scores. As a result, CCI was significantly associated with the risk of developing MACCE (All-cause-Death/MI/CVA) (HR 1.3, 95% CI 1.2 – 1.4, p<0.001), all-cause mortality (HR 1.25, 95% CI 1.2 – 1.4, p<0.001), and CVA (HR 2.2, 95% CI 1.4 – 3.4, p=0.001). However, CCI did not have a significant impact on the other endpoints in our study (Table 5).

Table 5 Results of multivariate analysis for Charlson comorbidity index

Events	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI) *	P value
All-cause-Death /MI/Stroke/TIA	1.3 (1.2 – 1.4)	<0.0001	1.3 (1.2 – 1.4)	<0.001
Death, all-cause	1.3 (1.2 – 1.5)	<0,0001	1,25 (1,12-1,4)	<0.001
Cardiac death	1.2 (1.06 – 1.4)	0.004	1,1 (0,9 - 1,2)	0.42
Myocardial infarction	1.13 (1.002 – 1.28)	0.045	1.12 (0.98 – 1.3)	0.09
Stroke/TIA	1.4 (1.3-1.6)	<0,0001	2.2 (1.4 – 3.4)	0.001
Heart failure with decrease in LVEF	1.2 (1.14-1.35)	<0.0001	1.12(0.9 - 1.37)	0.27
Heart failure with heart chambers dilatation and valvular insufficiency	1.3 (1.1-1.4)	<0,0001	1.13 (0.98 – 1.3)	0.1
SYNTAX Score, ≥33, during follow-up	1.1 (0.95 -1.24)	0.25	-	
Repeat revascularization	1.05 (0.98 -1.14)	0.17	-	

* Adjusted for sex, age, smoking status, body mass index, dyslipidemia, arterial hypertension, diabetes mellitus, myocardial infarction, peripheral vascular disease, atrial fibrillation, COPD, CVA, primary LVEF, type of revascularization (PCI/CABG), initial SYNTAX score
CABG = coronary artery bypass grafting; CI = confidence interval COPD = Chronic obstructive pulmonary disease; CVA = cerebrovascular accident; HR = Hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; LVEF = Left ventricular ejection fraction.

To assess the diagnostic significance, sensitivity, and specificity of CCI, a Receiver Operating Characteristic (ROC) analysis was conducted. The area under the ROC curve (AUC) showed good predictive capability for CCI in influencing the development of MACCE and CVA (AUC 0.73, 95% CI 0.68-0.78; and AUC 0.76, 95% CI 0.68-0.8; respectively, p<0.001). For all-cause mortality, the AUC was 0.69 (95% CI 0.62-0.76, p<0.001), indicating a moderate model quality. The cut-off value was determined to be 4.5 (Figure 1).

Discussion

The treatment of patients with comorbid conditions is always accompanied by difficulties. The higher frequency of adverse outcomes in patients with comorbidities is well recognized. Meanwhile, researchers have reported an increasing burden of comorbidities among patients undergoing CABG and PCI [11]. It is important to note that despite the increasing prevalence of comorbid conditions, many studies have shown improvements in outcomes, reflecting the progress in surgical and interventional treatments [11, 27, 28]. Determining the optimal revascularization strategy for patients with comorbidities is a challenging task. It is also important to note that high-risk patients were often excluded from revascularization studies [4, 11]. Therefore, the conclusions drawn from these studies may not be directly applicable to high-risk patients. This presents a challenging dilemma for practicing physicians when it comes to choosing the optimal revascularization method, especially considering the limited availability of reliable information to guide decision-making. Over the last decade, most research in the field of revascularization has focused on evaluating the impact of individual pathologies on revascularization outcomes [12-19], while the influence of general comorbidity burden has been separately studied for each revascularization strategy [11, 20, 21].

Our findings regarding the impact of comorbid conditions on the development of adverse events partially coincide with previous studies. Earlier studies indicated a connection between the CCI and the development of MACCE (All-cause Death/MI/CVA) in patients after PCI and those with acute coronary syndrome [21, 29, 30]. In our study, for each additional point increase in CCI, the risk of developing MACCE in the general cohort and in the PCI group increased by 1.3 times (HR 1.3, 95% CI 1.2 – 1.4, p<0.0001), and in the surgical group, it increased by 1.36 times (HR 1.36, 95% CI 1.2-1.5, p<0.0001). In a multifactorial analysis in the general cohort, other covariates

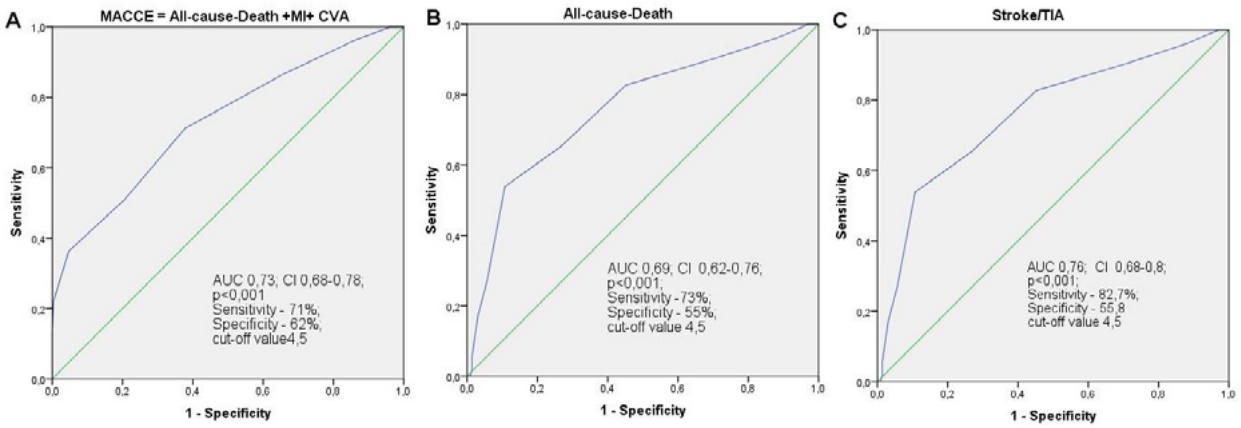

Figure 1 – Receiver operator characteristic (ROC) curve of the Charlson comorbidity index to predict MACCE.

Receiver-operating characteristic (ROC) curves for (A) MACCE (All-cause-Death/MI/CVA); (B) death from any cause; and (C) stroke/TIA based on the Charlson comorbidity index are shown. AUC = area under the ROC curve; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; CVA = cerebrovascular accident; TIA = transient ischemic attack.

besides CCI did not significantly impact the development of MACCE. However, for stented patients, along with CCI, persistent and permanent AF and smoking became significant predictors of MACCE [HR 1.9, 95% CI 1.13 – 3.3, p=0.015 and HR 2.7, 95% CI 1.6 – 4.4, p<0.0001, respectively]. This aligns with previous research results. According to the largest-scale SYNTAX study comparing outcomes of PCI and CABG, 5-year results showed a significant influence of smoking on the development of the composite endpoint of death/MI/stroke [31]. The 10-year results indicated more than a twofold higher adjusted risk of all-cause mortality in current smokers compared to those who never smoked [32]. In our study, smoking was associated with MACCE but did not significantly impact on all-cause and cardiovascular mortality. Our analysis also assessed the impact of persistent/permanent AF on revascularization outcomes. It is reported correlation between AF and CAD [33]. Unfortunately, we did not find reliable information on the impact of persistent/permanent AF on myocardial revascularization outcomes in the last 10 years. However, based on the HORIZONS-AMI study, new-onset AF after PCI in patients with ST-segment elevation myocardial infarction was associated with higher 3-year rates of adverse events and mortality [34]. Rashid M et al., in their review, reported an increased risk of death with the presence and increasing number of comorbidities in patients with acute coronary syndrome, stable CAD, and patients who underwent PCI [35]. In our study, a multivariate analysis revealed that an increase in CCI raised the risk of all-cause death in the general cohort (HR 1.25, 95% CI 1.12-1.4, p<0.0001). However, there was no significant impact of CCI on the development of cardiac death in our observation. Besides CCI, for the development of all-cause mortality in our study, an increase in BMI (HR 1.05, 95% CI 1.002-1.1, p=0.04) and prior CVA (HR 2.3, 95% CI 1.2 – 4.2, p=0.008) had a significant influence. For cardiac mortality, only BMI and prior CVA were significant predictors (HR 1.1, 95% CI 1.02 – 1.15, p=0.01 and HR 2.9, 95% CI 1.4 – 5.9, p=0.004, respectively). In the SYNTAX study, prior cerebrovascular disease was associated with a significantly increased risk of all-cause death over 10 years for both PCI and CABG patients [17]. It is noteworthy that we did not find a significant link between prior CVA and subsequent development of stroke/TIA in our study. The increase in BMI predictably had a significant impact on the development of cardiac mortality in our analysis, aligning with recent findings on the influence of obesity on PCI outcomes [36], but not CABG outcomes [37].

Interestingly, COPD in our study was associated with the risk of developing MI in the general cohort (HR 2.2, 95% CI 1.2 – 4.2, p=0.014) and with a high degree of atherosclerotic coronary artery damage in stented patients (HR 3.9, 95% CI 1.15 – 13, p=0.03). In this regard, it is worth noting that according to Li Y et al., COPD was independently associated with adverse outcomes after PCI or CABG [38], and in the SYNTAX Extended Survival study, COPD was associated with a higher risk of 10-year all-cause death after revascularization for complex coronary artery disease [18].

The most closely associated comorbidity with CAD is diabetes mellitus, which is linked to worse outcomes of coronary revascularization [39]. Results of revascularization indicate that CABG surpasses PCI for this patient group [40]. In our study, DM did not have a significant impact on the development of MACCE, and neither revascularization method showed advantages in patients with diabetes.

Thus, myocardial revascularization in patients with CAD and comorbid conditions requires an individualized and detailed approach. The integration of interdisciplinary expertise, advancements in PCI and CABG technologies, and understanding the complex relationships between CAD and comorbidities are crucial in optimizing the choice of revascularization method for this patient population.

Often in clinical practice, many patients with severe comorbidity receive a justified refusal to undergo CABG. In our study, we excluded patients with severe coronary lesions and clear indications for surgery. We included patients with multivessel coronary artery disease and varying levels of comorbidity with low-to-intermediate SS, making both CABG and PCI feasible. Our analysis did not reveal any advantages for CABG or PCI in terms of the MACCE (All-cause Death/MI/CVA). Consequently, improvements in CABG and PCI techniques may lead to their consideration in broader population groups, including patients with severe comorbidity.

Limitation

Our findings should be interpreted in light of the following limitations:

Firstly, due to the modest sample size, this analysis may lack sufficient statistical power.

Secondly, despite the measures taken and corrections applied, due to the retrospective observational nature of the study, there was a possibility of systematic selection bias.

Thirdly, our study included stable patients with multivessel CAD without left main disease and with low to intermediate SS who underwent primary PCI or CABG before the age of 65. Therefore, these results cannot be extrapolated to other coronary heart disease patients.

Conclusion

An increase in the Charlson Comorbidity Index of more than 4 points was significantly associated with the risk of developing a combination of MACCE, all-cause mortality, and cerebrovascular accident. Patients with severe comorbidity significantly more frequently required repeat revascularization after PCI than after CABG. In patients with varying degrees of comorbidity, the risk of developing severe coronary atherosclerotic lesions (≥33) was higher after surgery than after stenting. In other aspects, PCI and CABG did not show significant advantages in patients with varying degrees of comorbidity.

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Comprehensive pharmacoepidemiological and clinical-economic analysis of antibacterial drugs consumed during the pandemic at the hospital level in Aktobe, Kazakhstan

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Abstract

Aim: The study aimed to analyze the frequency and structure of antibacterial drug consumption during the COVID-19 pandemic at a dispensary hospital in Aktobe, Kazakhstan. It sought to identify the most frequently used and most costly antibacterial drugs, assessing their economic impact and usage patterns.

Methods: This descriptive, retrospective clinical, economic, and pharmacoepidemiological study was conducted using data from the dispensary hospital's pharmacy and patient records between March 13, 2020, and December 31, 2020. The ABC/VEN analysis and ATC/DDD methodology were applied to evaluate the consumption of antibacterial drugs. Antibiotics were classified according to WHO AWARe criteria.

Results: The study found that 27 different antibacterial drugs were used, representing 2.2% of all medications. The ABC/VEN analysis revealed that the majority of the budget was spent on a few high-cost drugs. Ceftriaxone was the most commonly used antibiotic, with a significant financial impact. According to the WHO AWaRe classification, most antibiotics fell into the Access and Watch categories.

Conclusion: The study highlights a high rate of antibacterial drug usage, with significant financial implications for the hospital. The predominance of certain high-cost antibiotics, like ceftriaxone, indicates a need for more rational and cost-effective use of these medications. The findings call for improved adherence to clinical guidelines, enhanced education for medical professionals, and optimized antibiotic utilization to prevent resistance development and ensure better patient outcomes, especially in pandemic situations.

Keywords: antibacterial drugs, COVID-19, clinical and economic research, pharmacoepidemiology, WHO AWaRe methodology.

Introduction

In 2020, humanity faced a new pandemic of coronavirus infection (COVID-19), which has claimed the lives of millions of people to date. According to many data, the majority of hospitalized COVID-19 patients used extensive empirical antibiotic use during the pandemic [1-5].

Over-prescribing antibiotics can have significant financial consequences for individuals and health systems. When antibiotics are over-prescribed, not only can they become less effective due to the development of resistance to them, but they can also cause side effects that lead to further medical expenses. As antibiotic resistance increases, the cost of treating infections increases as more expensive and effective drugs are required. The World Health Organization (WHO) recommends reducing the global number of antibiotic prescriptions by 20% to combat the development of antibiotic resistance [6]. In recent years, numerous awareness-raising activities have been undertaken to educate both the public and medical professionals about the problem of unjustified consumption of antibiotics, which remains a serious public health problem. Kazakhstan, as part of the global community, adheres to WHO recommendations. Despite a slight decrease in the consumption of antibiotics for systemic use, the irrational use of these drugs is still widespread in Kazakhstan. This is due to the availability of 27.5% of over-the-counter antibiotics and over-prescribing by medical professionals, while 29.9% of all prescribed drugs are antibiotics [7]. At the same time, practical healthcare requires the most rational use of funds, which dictates effective, but also cost-effective treatment [8].

During the COVID-19 pandemic, clinical practice guidelines were constantly changing to reflect the best available evidence for the existence of a new virus. In Kazakhstan, national clinical guidelines for the care of patients with COVID-19 have been regularly modified, and it is unknown whether or to what extent these recommendations have been followed in practice. Given the ongoing tensions over COVID-19 in the world and in the Republic of Kazakhstan, we believe that it is necessary to conduct a clinical, economic and pharmacoepidemiological study of an antibacterial drug.

The purpose of the study: to study the frequency and structure of consumption of antibacterial drugs during the pandemic of the outpatient hospital in Aktobe, to identify the most frequently consumed and most expensive antibacterial drugs.

Research objectives:

- To study the structure of antibacterial drugs used in 2020.
- To conduct a clinical and economic assessment of the consumption of antibacterial drugs in a dispensary hospital in Aktobe in 2020.
- To conduct a pharmacoepidemiological assessment of the consumption of antibacterial drugs in a dispensary hospital in Aktobe in 2020.
- Evaluation of antibacterial drugs according to the WHO AWaRe classification.

Material and methods

The study was performed on the basis of a dispensary hospital in Aktobe using data on the movement of medicines in the organization for the period from March 13, 2020 to December 31, 2020 from a pharmacy for medicines and medical records of patients. To analyze the consumption of antibacterial drugs (J01), a comprehensive pharmacoepidemiological and clinical-economic study was conducted and antibiotics were classified according to WHO AWARe.

ABC/VEN analysis

A clinical and economic ABC/VEN analysis was performed, which is the method of choice for calculating the financial needs of organizations. At the same time, all antibiotics were divided by cost, taking into account their international nonproprietary names (INN), into three classes: class A - for which 80% of the funds were spent, Class B - for which 15% of the funds were spent, and Class C - for which 5% of the funds were spent (Figure 1).

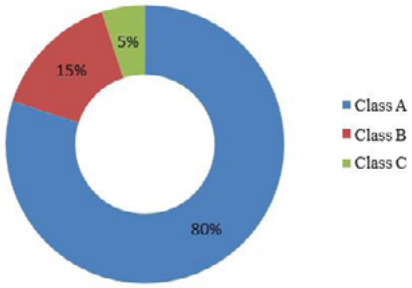

Figure 1 – Separation of antibiotics by cost

At the same time, 3 indices were used V (Vital) - important for saving lives; having life-threatening withdrawal syndrome, constantly necessary to maintain life; E (Necessary / Essential) – effective in the treatment of less dangerous but serious diseases; importance is high, but not absolute; N (Secondary/ Non-essential) – for the treatment of mild diseases, medicines with questionable effectiveness, expensive medicines for symptomatic indications [9].

ATC/DDD analysis

Pharmacoepidemiological assessment was performed using the ATC/DDD methodology (English anatomical therapeutic chemical (ATC) classification system – anatomical therapeutic chemical classification) recommended by the World Health Organization, according to the DDD indicator for 100 bed days, which allows aggregating data on the use of drugs, taking into account differences in dosages and activity of the active substance [10].

Classification AWaRe

The AWaRe Antibiotic Classification was developed in 2017 by the WHO Committee of Experts on the Selection and Use of Essential Medicines as a tool to support efforts for the rational use of antibiotics at the local, national and global levels. The consumption of antibiotics was classified into categories: available (Access), observational (Watch), Reserve (Reserve) [11].

Study design: a descriptive, retrospective clinical, economic and pharmacoepidemiological study.

Statistical processing: The data was processed using a computer program

Excel (Microsoft, USA). The program was used to distribute LP into ABC analysis groups. Using the program, an ATC/DDD analysis was performed, calculating the DDD index for 100 bed days.

Criteria for inclusion in the study:

- inpatient records of patients over the age of 18
- patients with COVID -19 positive and negative results
- identified bacterial pneumonia

Criteria for exclusion from the study:

- children (under 18 years old)
- pregnant and birthing women
- cancer patients

Results

According to the results of our study, in 2020, a total of 27 antibacterial drugs (J01) were used in the outpatient hospital in Aktobe. Antibiotics accounted for 2.2% of the total number of 1,283 medicines. According to the results of ABC/VEN analysis, 80% of the total cost of group A includes 9 antibacterial drugs: meropenem (21.2%), ceftriaxone (13.2%), cefepim (11.5%), amoxicillin sodium and potassium clavulanate (7.5%), ertapenem (7.4%), metronidazole (5.9%), clarithromycin (5.6%), cefotaxime (4.2%), levofloxacin (3.9%) (Figure 2).

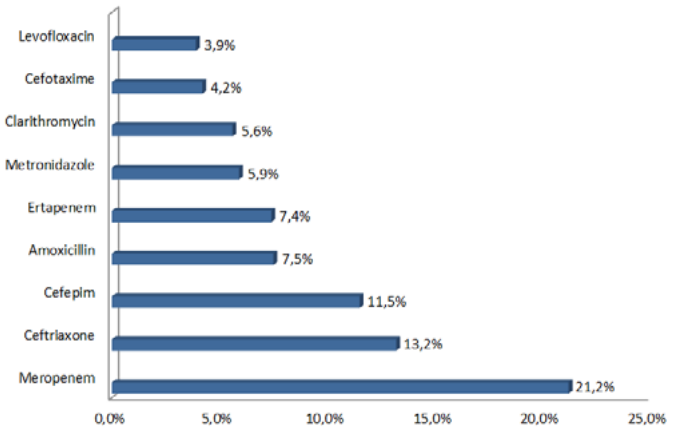

Figure 2 – Costs of class A antibacterial drugs

5 antibacterial drugs were used in the group of 15% of the total cost of antibiotics: doripenem (3.6%), ciprofloxacin (2.5%), cefuroxime (2.4%), cefazolin (2.3%), piperacillin (2.2%) (Figure 3).

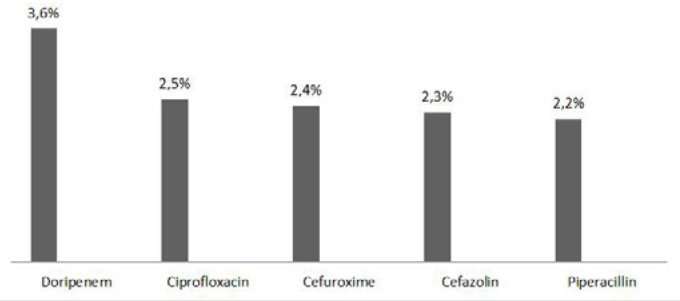

Figure 3 – Costs of class B antibacterial drugs

14 antibacterial drugs included in group "C" 5% of funds were spent: caspofungin (2.1%), fluconazole (1.2%), azithromycin (1.0%), moxifloxacin (0.63), vancomycin (0.6%), ampicillin (0.4%), amikacin (0.3%), gentamicin (0.1%), imipenem cilastatin (0.1%), ofloxacin (0.09%), thiamphenicol glycinate acetylcysteinate (0.03%), erythromycin (0.02%), amoxicillin (0.005%), lincomycin (0.003%).

All antibacterial drugs were classified as category V (Vital) – important for saving lives. Category N (Secondary/Non-essential) included caspofugin, erythromycin, thiamphenicol glycinate acetylcysteinate, lincomycin, i.e. included in group C.

According to the results of the pharmacoepidemiological analysis of the most commonly used antibiotics, the following drugs were identified (Table 1).

To optimize the rational use of antibiotics and support monitoring, in March 2017, WHO presented a detailed classification of antibiotics, designated "Access", "Surveillance" and "Reserve". According to the WHO AWaRe classification as a result of our study: 7 -to the Access group, 19 - to the Watch group, to the Reserve group - it was not revealed. 16 are included in the WHO List of Essential Medicines, and 10 are not included in the WHO List of Essential Medicines.

Table 1 Commonly used antibiotics

1	Ceftriaxone	19,043 DDD/100 bed days
2	Metronidazole	6,906 DDD/100 bed days
3	Cefotaxime	6,001 DDD/100 bed days
4	Cefosalin	4,204 DDD/100 bed days
5	Levofloxacin	3,389 DDD/100 bed days
6	Ciprofloxacin	2,872 DDD/100 bed days
7	Amoccicillin clavulanic acid	2,026 DDD/100 bed days
8	Gentamicin	1,811 DDD/100 bed days
9	Cefuroxime	0.688 DDD/100 bed days
10	Meropenem	0.404 DDD/100 bed days

Discussion

For the first time in Aktobe, the structure of antibacterial drugs used during the pandemic was studied in a dispensary hospital, and a comprehensive clinical, economic, pharmacoepidemiological study was conducted for the first time. According to the results of our study shown above, it can be noted that the drug meropenem, which was the most expensive in 2020, was used infrequently. But the drug ceftriaxone, which accounted for 80% of the costs, ranked first among the most commonly used in 2020. As we can see, more than half of the hospitalized patients in our study received antibiotics, and cephalosporin antibiotics were most often prescribed. As well as the antibiotic levofloxacin, which is not included in the List of medicines of the World Health Organization, was often used.

That is, during the pandemic, 72% of the "Observation" group of patients were prescribed antibiotics in antibacterial therapy. These figures are high, but below the global estimate of 75% of patients with COVID-19 who received prescriptions for antibiotics [12]. Overuse of antibiotics can contribute to the development of resistance to antibacterial drugs, which is a global public health problem. This finding is consistent with other studies highlighting problems in the management of antibacterial drugs during the pandemic. And, as in our study, in 2020, cephalosporin antibiotics were the most commonly prescribed antibacterial drugs in Almaty, followed by fluoroquinolones [13].

A study in Pakistan, Jordan, and South Asian countries showed that ceftriaxone and azithromycin, ciprofloxacin were often used during the pandemic [14-16]. SARS-CoV-2 was detected in our country in March 2020. Since that moment, on the basis of the order of the regional health department of Aktobe region No. 68-5 dated 2020, the multidisciplinary hospital in Aktobe has been redesignated into a 400-bed dispensary hospital for the treatment of patients with severe pneumonia. On the basis of a multidisciplinary dispensary, 2,223 patients with severe pneumonia in combination with various concomitant diseases COVID-19 received inpatient treatment.

2020 is the first year of the outbreak of the pandemic in the country. The first version of the COVID-19 diagnostic and treatment protocol was developed on February 3, 2020 and has been revised several times since then. Kazakhstan, as part of the global community, adheres to WHO recommendations.

However, despite a slight decrease in the consumption of systemic antimicrobials in recent years, the irrational use of antibiotics continues to persist in Kazakhstan. In addition, we are concerned that this trend will increase as a result of the widespread empirical use of antibiotics during the COVID-19 pandemic [17].

In conclusion, this study highlights the need for more effective implementation of developing clinical practice guidelines for people hospitalized with COVID-19 in Aktobe, Kazakhstan. Efforts are needed to improve communication, education, and support for physicians to ensure the continued and consistent use of evidence-based therapies, promote the proper use of medicines, and optimize patient outcomes in any pandemic response.

Conclusion

A comprehensive analysis of ABP in a dispensary hospital during the pandemic showed that the highest proportion of costs during the study period and the most commonly used antibiotics during the pandemic came from the group of carbapenems, cephalosporins, as well as the group of fluoroquinolones.

Antibiotic abuse was noticeably high throughout the period. Monitoring the consumption of antibacterial drugs in a dispensary hospital allows you to make strategic decisions to optimize antibiotic therapy and bring the number and assortment of antibiotics used in line with the profile of the hospital units. The comprehensive ABC analysis and DDD analysis allows us to compare the data on the priority of financial costs and the level of consumption of ABP, which makes it possible to optimize the use of antibiotics in a multidisciplinary medical facility.

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Investigation of the effects of cilostazol on the myocardial ischemia-reperfusion injury of rats

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Abstract

Background. Myocardial ischemia, occurring as a consequence of imbalance between oxygen supply and demand, causes a rapid metabolic and structural impairment within the tissue. After a period of ischemia, sudden onset of reperfusion causes a transition to aerobic metabolism within living cells. Afterwards, emerging substrates initiate a chain of reactions leading to tissue injury. This situation is called "ischemia reperfusion injury". Despite all technical advancements in anesthesia, myocardial protection and cardiac surgical techniques, we still face the clinical reflections of ischemia reperfusion (IR) injury.

Materials and methods. The protective effect of cilostasole on IR injury in an animal model of experimental myocardial ischemia and reperfusion was investigated. In this regional myocardial ischemia model, male Wistar-Albino rats were used as subjects and they were allocated into three groups; ischemia (n=8), sham (n=8), and cilostazole (n=8). LAD was occluded for 45 minutes, and then reperfused for three hours. Rats received Cilostazole 20 mg/kg/day by gastric gavage once daily. During IR hemodynamic parameters were recorded. Serum analysis for CK-MB and Troponin T were analysed at 180th minute of ischemia.

Results. Before the onset of LAD occlusion, as well as at 25th, 60th and 120th minutes of occlusion, all groups were similar in terms of blood pressure and pulse rate.

This study evaluated biochemical markers, energy metabolism, and the antioxidant system in rats with myocardial ischemic damage. Acute ischemia followed by reperfusion led to significant increases in Troponin I and CK-MB levels, indicating myocardial injury. Cilostazol did not significantly affect this process, but it notably inhibited Neopterin synthesis, potentially reducing inflammation. Moreover, cilostazol intake inhibited ADMA synthesis, increasing NO levels, which could alleviate microcirculation disturbances. Cilostazol also weakened lipid peroxidation by enhancing GSH-Px enzyme levels, reducing MDA levels. Overall, cilostazol shows promise in increasing myocardial tolerance to ischemia and protecting against reperfusion damage, suggesting its potential clinical utility.

Conclusion. This study explored how cilostazol affects myocardial ischemia-reperfusion injury in rats, finding that cilostazol administration during

reperfusion may protect against such injury. Through various analyses, we observed positive outcomes associated with cilostazol treatment, suggesting its potential in reducing myocardial damage. Further research is needed to understand the underlying mechanisms and optimize therapeutic strategies, but our findings highlight cilostazol's promise in improving clinical outcomes in cardiac interventions.
Keywords: cilostazol, Myocard, İschemia reperfusion injury.

Introduction

Cardiac surgery is usually performed under bloodless and motionless conditions of the heart. To achieve such conditions, there is a need for global ischemia of the heart. However, while performing global ischemia of the heart, unwanted events can occur. After 20 minutes of a bloodless period, irreversible myocardial damage (ischemic necrosis) occurs [1]. Histopathological examinations of myocardial tissue have revealed that 4 hours after myocardial infarction, coagulative necrosis, edema, and neutrophil infiltration can be detected. Death of myocardial cells occurs during myocardial infarction and also in the reperfusion period when blood flow is restored to the infarction area. Such cell damage can cause arrhythmias, myocardial stunning, and an increase in damaged tissue (infarction). Myocardial damage can be considered an important cause of low cardiac output, which can lead to mortality [2].

The main reasons for ischemia-reperfusion damage include the occurrence of free oxygen radicals, imbalance of Ca2+ ions in myocytes, stimulation of neutrophil accumulation, and formation of adhesion molecules as a result of the release of cytokines and interleukins by endothelial cells or macrophages [3, 4].

Cilostazol, chemically known as 6-[4-(1-cyclohexyl-5-tetrazole) butoxy]-1, 2, 3, 4-tetrahydro-2-oxoquinoline, has the abilities of vasodilation and anti-platelet aggregation. It mainly increases the concentration of cyclic adenosine monophosphate (cAMP) or releases adenosine diphosphate (ADP) and 5-hydroxytryptamine (5-HT) by inhibiting the activity of phosphodiesterase (PDE) in platelets and vascular smooth muscle or the production of thromboxane A2 (TXA2) in the phospholipid membranes [5, 6].

Cilostazol is commonly employed for treating intermittent claudication and occasionally for intracranial atherosclerosis or stroke prevention. Accumulating evidence suggests that cilostazol may serve as a safeguard against ischemia-reperfusion injury in diverse organ systems. Another study indicated the utility of cilostazol pre-treatment in cold hepatic ischemia-reperfusion injury, attributing its efficacy to the prevention of endothelial inflammation and apoptotic death. Additionally, cilostazol pre-treatment enhanced neurological functional outcomes [7, 8].

The purpose of this investigation is to study the effects of cilostazol in ischemia-reperfusion injury and to investigate biochemical, hemodynamic, and histopathological data.

Materials and methods

In the study, 24 male Wistar Albino rats, bred in Gulhane Military Medical Academy Multi-Discipline laboratories, were utilized. General physiological information is provided in Table 1. Rats were selected as experimental animals due to their utility in myocardial ischemia-reperfusion models and their low myocardial coronary collateral circulation [9].

Table 1 Physiologic values of rats.

Physiological charasterictics	Mean value
Average lifespan	2.5-3.5 years
Weight	200-300gr
Body temperature	35.9 - 37.5 ^{0}C
Respiratory rate	100-150/ min
Blood pressure	88-184 mmHg
Blood volume	1/20 of body weight
Heart rhythm	250-450 (240)/min
Hemoglobin	16-19
Hematocrit	0.1gr/100ml
Sodium	320mgr/100mg
Potassium	17.5-22.0 mgr/100ml

The rats were housed at room temperature, with five rats per cage, in a clean environment, under standard laboratory conditions, and were provided with pellet feed. Feeding was halted 12 hours before the surgical procedure, and access to water was removed. After the experiment, the rats were euthanized, and no postoperative care was administered.

Experimental Groups

Group 1 (8 pieces): Sham group. These animals have been fed with water for 14 days with the help of gavage. After the intervention and surgical procedure performed on the subjects, an intramyocardial suture passed on the left anterior descending (LAD) coronary artery but was not occluded with the help of a snare.

Group-2 (8 pieces): Ischemia-reperfusion group. These animals have been fed with water for 14 days with the help of gavage. After the intervention and surgical procedure performed on the subjects, an intramyocardial suture passed on the LAD artery and was occluded with the help of a snare. After 45 minutes of occlusion of the LAD artery, the snare was taken out and reperfusion was performed for 180 minutes.

Group-3 (8 pieces): cilostazol group. These animals have been fed with cilostazol 20 mg/kg/day for 14 days with the help of gavage. After the intervention and surgical procedure performed on the subjects, an intramyocardial suture passed on the LAD coronary artery and was occluded with the help of a snare. After 45 minutes of occlusion of the LAD artery, the snare was taken out and reperfusion was performed for 180 minutes

We neutralized the effects of all interventions and surgical procedures on the hemodynamic, biochemical, and pathological data examined in the study by using a sham group.

Anesthesia and Monitoring

Anesthesia was induced with 35mg/kg ketamine (Ketalar® vial 100mg/mL Alfasan International Holland) and 5mg/kg Xylazine (Alfazyne® 20mg/mL Alfasan International Holland). The dose was repeated when necessary.

The neck and anterior chest wall were shaved and the surgical field was stained with 10% povidone-iodine solution (Isosol Solution Merkez Labaratuvarı A.Ş). Tracheostomy was opened through the neck incision and intubated. They were connected to a mechanical animal respirator (Datex-Ohmeda Excell 410) at 60 respiratory rate/min, 40% oxygen supply, 1,5 mL/150 gr tidal volume.

The carotid artery was for continuous pressure monitoring and the jugular vein was catheterized with a 24G branula.

Surgical Procedure

A left thoracotomy was performed to access the heart. The thorax was entered through the 4th intercostal space. The surgical manipulation area was widened with a mini thorax retractor and the heart was accessed by cutting the pericardium (Figure 1).

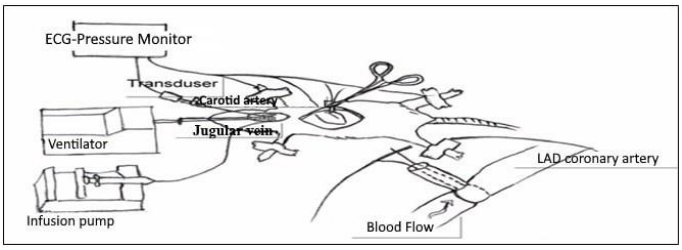

Figure 1 – Schematic drawing of the operation site

A 5-0 10 mm atraumatic needle prolene suture was passed intramyocardially through the LAD branch of the left main coronary artery, which continues in the interventricular septum, proximal to the diagonal side branch.

At the beginning of the 15-min equilibration period, 150IU/kg heparin (Nevparin® vial 5000IU/mL Mustafa Nevzat İlaç San. A.Ş.) was administered intravenously to prevent thrombosis in the coronary artery. At the end of this period, the suture needles were passed through the pledget and the suture threads were tightened with the help of a sner to prevent LAD compromise and to achieve complete occlusion and ischemia. Before suture tightening, 0.5mL of blood was collected for cardiac enzymes (creatine kinase-myocardial band – (CK- MB)). Fluid administration was replaced with Ringer's lactate, 3 times the blood lost during the procedure. During the 45-minute ischemia period, arrhythmias were recorded. At the end of this period, the singer was loosened and reperfusion of the ischemic area was achieved. The experimental animal was kept in reperfusion by a respirator for 3 hours. During this time, the thoracotomy incision was approximated with a temporary prolene suture to minimize insensible loss. At the end of three hours, the rat heart was removed and placed in an empty pathology dish. The pathology container was placed in a cold water-ice mixture and taken to the laboratory of the Department of Pathology without losing time (within 3-4 minutes).

Biochemical Measurements

For the measurement of the cardiac enzyme creatinine kinase-MB (CK-MB), blood was collected before (0 min) and after (45 min) coronary artery occlusion, as well as at the first and third hours following reperfusion. Blood was centrifuged at 5000g at 4°C for 15 minutes. The serum portion was removed and stored at -71°C. After samples were taken from all animal groups for biochemical studies, the Immulite® Turbo CK-MB kit (EURO/DPC Ltd. UK) was used in the Gulhane Military Medical Academy Central Biochemistry Laboratory.

Statistical Method

SPSS for Win. Ver. 15.0 (SPSS Inc. Chicago II., USA) program was used for statistical analysis. Kruskal-Wallis Test was used for statistical comparison between groups, Mann-Whitney U Test was used when a statistical difference was found and Wilkcoxon Signed Ranks Test was used to compare the differences of intragroup values according to baseline values. Statistical results with $p<0.05$ (95% confidence interval) were considered significant.

Results

Since cardiomyocytes lack reserves of energetic substrates, including macroergic energy sources, this study aimed to objectively evaluate the depth of pathological changes in the structural proteins of the myocardium subjected to acute anoxic ischemia. Changes in the levels of creatine phosphokinase (CK-MB) and Troponin I, which are major cardiospecific enzymes, in the blood of rats included in all three groups were studied and comparatively analyzed (Table 2). During this process, it was determined that the levels of CK-MB in the IR and Cilostazol groups, respectively rising to 0.95±0.125 and 0.90±0.010 ng/l, were 4 times higher than the value in the Control group (0.23±0.025 ng/l) (X2=15.905; P<0.001). Notably, despite the equal increase in CK-MB levels in both groups, there was no statistically significant difference between them (P>0.05). A similar trend was recorded in the levels of Troponin I. Although the amount of Troponin I in the blood of animals in the IR and Cilostazol groups increased 10-fold compared to the control, reaching 81.13±2.13 and 82.18±4.69 ng/l (X2=15.560, P<0.001), it was found that there was no statistically significant difference between the comparison groups (P>0.05).

Table 2 Dynamics of CK-MB, Troponin I, Neopterin, and ADMA indicators in the experimental groups.

	Control group (n=8)	İ/R group (n=8)	Silostazol group (n=8)	Statistical indicators
CK-MB (ng/ml)	0.23±0.025) (0.10–0.30)	0.95±0.125 (0.80–1.80)	0.90±0.010 (0.80–1.40)	X^2=15.905 P<0.001
Troponin I (ngr/l)	8.89±0.78 (7.13–13.35)	81.13 ± 2.13 (44.12-61.18)	82.18± 4.69 (53.63–91.21)	X^2=15.560 P<0.001
Neopterin (ng/l)	8.60 ± 0.63 (5.90–11.00)	30.24 ± 2.33 (8.40-26.26)	19.71 ± 1.17 (6.40-15.80)	F=89.019 P<0.001
ADMA (□mol/l)	0.83 ±0.05 (0.57–0.96)	4.80 ± 0.15 (3.76–4.96)	2.38±0.25 (2.46–4.47)	X^2=16.409 P<0.001

Note: *Here and in subsequent tables, X2 denotes Kruskal-Wallis non-parametric variation, F denotes one-way analysis of variance (ANOVA) results, and t denotes Student's t-test criterion. Differences between comparison groups were considered statistically significant at P<0.05 or less.*

Thus, the sharp increase in the levels of CK-MB and Troponin I (respectively 4 and 10 times) in the blood of animals with the IR model created indicates that these indicators are highly informative markers for objectively evaluating the changes occurring in the myocardium subjected to acute ischemia and reperfusion. The absence of a significant difference between the

groups suggests that cilostazol does not have a significant effect on this process.

According to literature data, Neopterin is synthesized by macrophages in the vascular endothelium and plays a significant role in the formation of inflammatory reactions due to its strong immunomodulatory effect. It has the property of increasing the tolerance and viability of cells subjected to acute ischemia and reperfusion. Our studies showed that the amount of Neopterin in the blood of rats in the IR and Cilostazol groups increased to 30.24±2.33 and 19.71±1.17 ng/l, respectively (F=89.019, P<0.001), exceeding the level in the control group by 3.5 and 2.3 times. The fact that the level of Neopterin in the Cilostazol group was 10.53 ng/l lower than in the IR group (P<0.001) could be explained by the inhibition of its synthesis by cilostazol. However, the milder manifestation of histomorphological changes in the myocardium in the Cilostazol group compared to the IR group suggests that this decrease is better explained by the enhanced uptake and rapid elimination of Neopterin by cells subjected to anoxic ischemia. The increased tolerance and viability of cells to hypoxia provided by Neopterin may be achieved in this way.

In addition, the dynamics of asymmetric dimethylarginine (ADMA) in the blood of rats with the IR model were studied. As is known, ADMA is an inhibitor of the enzyme NO synthase, which regulates the synthesis of nitric oxide (NO) from arginine. Considering that NO has strong vasodilator, antiplatelet, antiadhesive, and antioxidant effects, it is clear how important it is to study the effect of cilostazol on the level of ADMA. The results of our studies (Table 2) showed that the amount of ADMA in animals with the IR model increased more than 6 times (up to 4.80±0.15 mmol/l) compared to the control. In contrast, it was observed that this increase was more moderate in rats treated with cilostazol (up to 2.38±0.25 mmol/l) (P<0.001). This means that during the creation of the myocardial IR injury model, a sharp increase in the amount of ADMA in the blood, by inhibiting the synthesis of NO, leads to spasm of microcirculatory vessels in the damaged area, aggregation of platelets, adhesion of monocytes and erythrocytes, thereby creating a basis for severe histomorphological disorders. Moreover, the use of cilostazol before the creation of the IR model significantly prevented the dangerous increase in the amount of ADMA in the blood, thereby eliminating the inhibition of NO synthesis.

The study of the amount of NO in myocardial tissue exposed to IR injury confirmed this conclusion once again (Table 3). It was observed that in the myocardial tissue taken from rats with the IR model, the amount of NO was more than twice that of the control group (15.46±6.25 mmol/l), while in the Cilostazol group, this amount was recorded to be 5.5 times higher, at 84.37±11.12 mmol/l (X2=12.635, P=0.02). In our opinion, this significant difference between the randomized groups based on the main parameters can only be attributed to the effect of cilostazol. As we have shown above, this is based on the effective inhibition of the synthesis of ADMA, an inhibitor of NO synthase, due to the prior use of cilostazol.

If the basis of irreversible myocardial damage during anoxic ischemia is the disruption of membrane permeability and the breakdown of structural proteins, then in reperfusion injuries, endothelial dysfunction, disturbances in the microcirculatory system, and the acceleration of the process of free radical oxidation of lipids come to the forefront. Considering this, the activity of the enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), which play a leading role in regulating lipid peroxidation, and the level of malondialdehyde (MDA), the final product of this process, were comparatively studied in myocardial tissue taken from rats in all three groups (Table 3).

As we know, SOD is an enzyme with antioxidant effects, catalyzing the dismutation of superoxide radicals into oxygen and hydrogen peroxide, thus protecting the organism from their toxic effects. Our studies showed a significant increase in the level of SOD in the myocardial tissue of animals in both the IR and Cilostazol groups. Specifically, while the amount of SOD in the Control group animals was 67.28±4.77 ng/l, in the comparison groups, this indicator increased to 118.26±5.75 and 100.64±6.90 ng/l, respectively (F=5.910, P=0.009). The lack of a statistically significant difference in SOD levels between the comparison groups (P>0.05) indicates that the increase in SOD levels in the blood during extreme conditions is part of the body's universal defense system and is not influenced by the effect of cilostazol.

Table 3 Dynamics of key indicators of free radical oxidation of lipids in the comparison groups.

	Control group (n=8)	İ/R group (n=8)	Silostazol group (n=8)	Statistical indicators
NOx (□mol/l)	6,34±2,27 (0,21–20,11)	15,46±6,25 (4,22–54,33)	84,37±11,12 (9,88–98,76)	X^2=12.635 P=0,02
SOD (ng/ml)	67,28±4,77 (53,60–91,80)	118,26±5,75 (93,77–139,8)	100,64±6.90 (69,86–125,18)	F=5.910 P=0,009
GSH-Px (ng/l)	9,94±0,40 (8,65–11,88)	11,41±1,13 (7,59–16,60)	24,27±4,38 (10,28–45,42)	X^2=7.440 P=0,02
MDA (ng/l)	0,14±0,022 (0,09–0,27)	0,88±0,027 (0,76–0,98)	0,34±0,04 (0,17–0,49)	X^2=19.046 P<0.001

In contrast, the changes in the level of MDA, the final product of lipid peroxidation, were more striking (Table 3). Specifically, the amount of MDA in the blood of rats with the IR model increased more than 6 times (from 0.14±0.022 to 0.88±0.027 ng/l) compared to the control group (X2=19.046, P<0.001), which we evaluated as a result of the dangerously accelerated processes of free radical oxidation of lipids under the influence of acute ischemia and reperfusion. In this case, considering that the increase in the amount of MDA observed in the Cilostazol group was significantly weaker (up to 0.34±0.04 ng/l) and 2.6 times lower than the level in the IR group (P<0.001), it can be concluded that the use of cilostazol before creating the IR model prevents the dangerous acceleration of the free radical oxidation process of lipids.

While there was no significant difference in the level of SOD between the comparison groups, when investigating the mechanism behind the amount of MDA in the Cilostazol group being 2.6 times lower than that in the IR group, our attention was

drawn to the changes in the level of the enzyme glutathione peroxidase (GSH-Px), another important element of the antioxidant system. It was found that while the amount of this enzyme in the blood of rats with the IR model did not differ from the level in the control group (9.94±0.40 and 11.41±1.13 ng/l, P>0.05), it increased to 24.27±4.38 ng/l in animals treated with cilostazol (X2=7.440, P=0.02). It can be assumed that the significantly lower amount of MDA in the Cilostazol group compared to the IR group is due to the more than twofold increase in the level of this enzyme in the blood under the influence of cilostazol. While SOD breaks down superoxide radicals into hydrogen peroxide and water molecules, the primary function of the GSH-Px enzyme is to inactivate hydrogen peroxide by breaking it down into water and molecular oxygen, thereby completing the process. Therefore, the prevention of excessive MDA increase in the Cilostazol group is due to this enzyme (Table 3).

Discussion

Transient ischemic attacks for myocardial ischemia-reperfusion injury may occur during severe coronary artery spasm, atherosclerotic plaque rupture, or unmet O2 demand during exertion. The return of myocardial systolic-diastolic function within hours or even days, as in the case of thrombolytic therapy, cessation of exertion, restoration of cardiac circulation after cardiopulmonary bypass, or resolution of coronary artery spasm, is called "myocardial stunning" [10]. Myocardial stunning is associated with prolonged low-output cardiac syndromes and precipitates heart failure.

The molecular events of ischemia-reperfusion injury are complex and multifactorial. In many studies, free oxygen radicals, excessive intracellular calcium accumulation, and the inflammatory response cascade, especially neutrophils, have been shown as possible mechanisms [11-15].

Many agents have been used in experimental studies to prevent myocardial ischemia-reperfusion injury. The main ones are Ca channel blockers, ACE inhibitors, prostaglandins, glutathione, N-acetylcysteine, pentoxifylline, and anesthetic agents.

In the liver ischemia model of Wakabayoshi et al., laser Doppler and histological studies showed that cilostazol given 30 minutes before warm ischemia rapidly restored perihepatic microcirculation. In this study, cilostazol was shown to exert its effect by inhibiting the expression of endothelin 1, a potent vasoconstrictor [16].

Sarc et al. reported that cilostazol given before ischemia prolonged survival and improved the restoration of hepatic ATP content in a model of liver ischemia and hepatectomy in rats [17].

Zini et al. showed that cilostazol inhibited two different complexes (complex 3 and complex 5) in the electron transport chain in studies on mitochondria in a rat brain ischemia model. These are responsible for free oxygen radical formation [18].

The rapid decrease in cellular ATP content during ischemia compromises the electrolyte gradient between intracellular and extracellular compartments. Intracellular Ca+2 is a critical indicator. Dhar et al. showed that intracellular Ca+2 accumulation and hepatocellular damage decreased after reperfusion in a canine liver ischemia model by administering cilostazol [19].

Thus, the comparative analysis of some biochemical markers, energy metabolism, and the state of the antioxidant system in the blood samples of rats subjected to ischemic damage of the myocardium in experimental groups, including those created with IR model and those that received cilostazol two weeks prior, provided important scientific and experimental results. It was found that the myocardial damage due to acute ischemia for 45 minutes and reperfusion for 180 minutes leads to a sharp increase in the levels of Troponin I and CK-MB in the blood compared to the control group. At this time, the lack of significant difference between the IR and Cilostazol groups suggests that cilostazol does not effectively protect against structural damage from ischemia and reperfusion. However, the significant inhibition of Neopterin synthesis by cilostazol can be considered as a positive quality, weakening the inflammatory response in the endothelium and myocardial tissue exposed to acute ischemia and reperfusion. Additionally, the inhibition of ADMA synthesis, an inhibitor of NO synthase, by cilostazol intake facilitates a significant increase in blood NO levels compared to the IR group (by 5.5 times), thus providing a substantial basis for the milder character of microcirculation and rheology disturbances observed under reperfusion.

Given that structural lipid oxidation is one of the main contributing factors to ischemia-reperfusion injury, understanding how cilostazol affects this process has yielded promising results. It was found that pre-administration of cilostazol in animals with the IR model does not prevent the increase in SOD levels in the blood but significantly weakens the peroxidation process by increasing the level of GSH-Px enzyme, which is capable of breaking down and neutralizing peroxide radicals by more than 2 times. The lower level of MDA, the end product of this process, in the blood of animals receiving cilostazol compared to the IR group by 2.6 times clearly confirms this result.

Comparative analysis of the results of experimental research leads to the conclusion that cilostazol may be a promising and effective drug for increasing myocardial tolerance to anoxic ischemia and protecting against reperfusion damage during "open-heart" surgeries, thus warranting its widespread clinical application.

Since the formation of ischemia-reperfusion injury is a complex mechanism that triggers each other, more detailed studies with cilostazol and other active substances are needed.

Conclusion

In this study, we investigated the effects of cilostazol on myocardial ischemia-reperfusion injury in rats. Our findings suggest that cilostazol administration during reperfusion may confer protective effects against myocardial ischemia-reperfusion injury. Through biochemical analyses, we observed favorable outcomes associated with cilostazol treatment. These results indicate the potential of cilostazol in attenuating myocardial damage induced by ischemia-reperfusion injury.

While our study adds valuable insights into the protective effects of cilostazol, further investigations are warranted to elucidate the underlying molecular mechanisms and optimize therapeutic strategies. Overall, our findings underscore the importance of exploring novel pharmacological agents, such as cilostazol, to mitigate the detrimental effects of myocardial ischemia-reperfusion injury and improve clinical outcomes in cardiac surgery and related interventions.

Limitations

The study utilized a relatively small sample size of 24

male Wistar Albino rats. While this sample size was suitable for conducting the experiment, larger sample sizes could provide more robust and generalizable results.

Cilostazol was administered at a fixed dosage to the experimental group. Variations in dosage levels or administration regimens could yield different results, and exploring a range of doses may provide a more comprehensive understanding of cilostazol's effects.

While the study provides valuable insights into cilostazol's effects in a controlled experimental setting, correlating these findings with clinical data from human trials is essential to validate its therapeutic potential in patients undergoing cardiac surgery or experiencing myocardial ischemia-reperfusion injury.

Author Contributions: Conceptualization, formal analysis, investigation, methodology, project administration, supervision; validation, visualization, roles/writing – original draft, writing – review and editing, A. A. The author has read and agreed to the published version of the manuscript.

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Mid-term outcome of the hybrid method of ventricular septal defect closure in children

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Abstract

Objective: To describe the clinical experiences and mid-term follow-up results of the hybrid method of ventricular septal defect closure in children.

Methods: This study was a combined - multidirectional cohort. Between May 2016 and December 2020, 250 patients with isolated VSD (or residual VSD after a previous repair) underwent surgery by the hybrid method at the pediatric cardiac surgery department in the National Scientific Medical Center. This study adopted a combined and multidirectional cohort approach, initially starting as a retrospective cohort and later transitioning into a prospective cohort.

Results: A total of 250 patients in this cohort underwent hybrid VSD closure, of which 233 (93.2%) patients were successful, 16 (6.4%) patients were converted to the traditional method and 1 (0.4%) death occurred. New trivial or mild tricuspid regurgitation was detected in 35 patients (15%) and aortic regurgitation in 9 patients (3.9%) by intraoperative TEE. For the remaining 10 patients with incomplete right bundle branch blocks the sinus rhythm was restored in follow-up. In addition, the left ventricular ejection fraction improved over time. One of the important points after surgery is the deformation of the chest. In 122 (91%) patients, there is no deformation; unfortunately, in 12 (9%) patients, there is deformation.

Conclusions: The hybrid method is a rapidly developing technique that has been safe and effective in a selected group of patients in recent years. The advantages of this method are minimum incision namely the size and length of the postoperative scar from 2 to 4 cm. Also, no myocardial injury, and reduces operation time, intensive care unit stay, and hospital stays.

Keywords: congenital heart disease; ventricular septal defect; hybrid method; Kazakhstan.

Introduction

Currently, the development of minimally invasive cardiac surgery is underway, with one notable approach being the hybrid method [1]. The term "hybrid method", as used in contemporary cardiology and cardiac surgery, refers to a combination of surgical and interventional techniques aimed at optimizing the therapy for congenital and acquired heart defects while reducing their limitations. The hybrid method involves minimally invasive ventricular septal defect (VSD) closure on a beating heart [2,3]. This approach offers advantages such as a shortened duration of hospitalization, reduced rehabilitation time, no X-ray exposure, and favorable cosmetic effects. However, there are drawbacks, including the potential development of arrhythmias and the risk of device dislocation after implantation [4-6].

Our study aimed to describe the clinical experiences evaluating the safety, efficacy, and mid-term follow-up results of the hybrid method of ventricular septal defect closure in children.

Methods

Patient population

Between May 2016 and December 2020, 250 patients with isolated VSD (or residual VSD after a

previous repair) aged 2 months to 18 years with a body weight of 4.7 to 100 kg, underwent surgery by the hybrid method at the pediatric cardiac surgery department in the National Scientific Medical Center. This research protocol was approved by the Ethics Committee of National Scientific Medical Center, Astana, Kazakhstan (Protocol number: 081/CR-75; Assigned number: 053/CT-63) and carried out by the principles set out in the Declaration of Helsinki 1964.

Study methods

This study adopted a combined and multidirectional cohort approach, initially starting as a retrospective cohort and later transitioning into a prospective cohort. Patient recruitment was conducted retrospectively, relying on medical documentation. For the prospective phase, a questionnaire designed for parents of children with congenital heart disease, specifically "ventricular septal defect" after surgical treatment, was created and secured with a copyright certificate. An online survey was administered to the enrolled patients.

The indications for the hybrid method:

- Patients with isolated VSD (perimembranous, muscular, inlet, outlet and residual);
- Clinical manifestations: symptoms of heart failure, recurrent respiratory infection, developmental delay, and history of bacterial endocarditis [7].

Echocardiographic Inclusion Criteria:

- Distance to the pulmonary, tricuspid, aortic (subaortic rim)valve >2 mm;
- no prolapse of the aortic valve into the defect [8];
- defect size from 4 to 12 mm;
- for perimembranous defects, the ratio of the size of the VSD and the weight of the patient was taken into account: a) ≤6 mm with a weight of 4-8 kg; b) ≤8 mm with a weight of 9–12 kg; c) ≤10 mm over 13 kg [9].

Exclusion Criteria:

- Heart arrhythmias (in particular, AV block);
- large non-restrictive VSDs;
- infective endocarditis;
- complex congenital heart disorder requiring correction using cardiopulmonary bypass;
- aortic dextraposition;
- aortic and tricuspid valve regurgitation (more than mild);
- aneurysm of the interventricular septum [7-11].

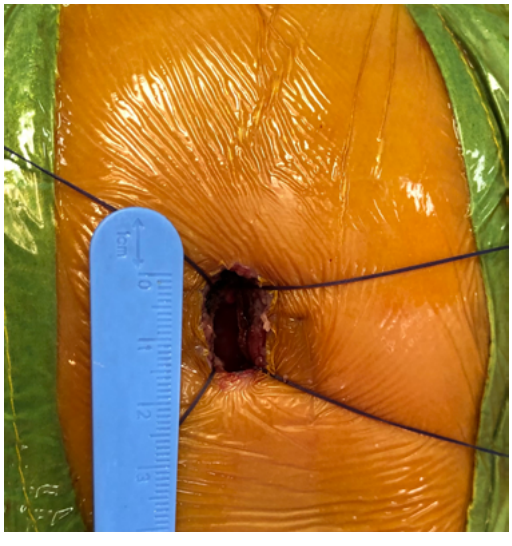

Figure 1 – Wound size with the hybrid method

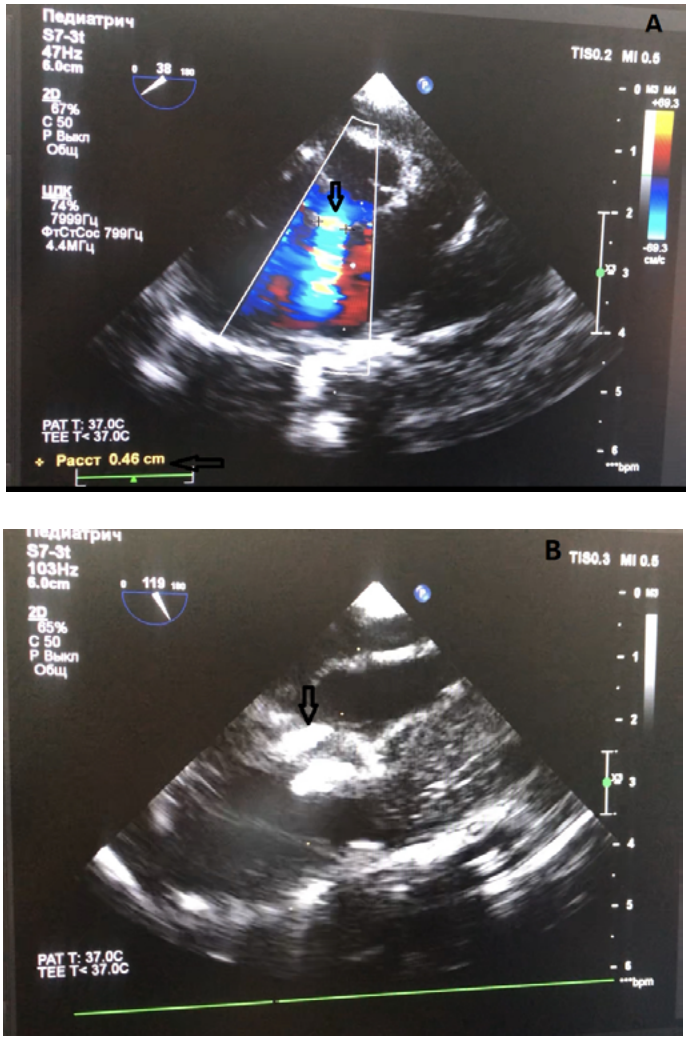

Figure 2 – A- Short-axis view of VSD from TEE and B- muscular occlude installed (long-axis view)

Surgery stages of the hybrid method

After the induction of general anesthesia, patients were positioned supine. The entire operation was guided by transesophageal echocardiography (TEE). Before the procedure, TEE meticulously assessed the location and size of VSDs (Figure 2A). Based on TEE measurements, occluders, including symmetric, asymmetric, eccentric, and muscular types, were selected.

A 2- to 4-cm inferior median sternotomy and a pericardiotomy were executed (Figure 1). Following the exposure of the right ventricular free wall, the puncture site was identified under continuous TEE control. A purse-string suture was placed around the chosen location, and a trocar was used for puncture.

A 0.035-inch guide wire was introduced into the right ventricle (RV) and passed through the defect into the left ventricle (LV) using the trocar. After trocar removal, the delivery sheath was introduced along the guide wire to the LV. Subsequently, the occluder was deployed through the loading sheath under TEE guidance (Figure 2B).

Following the removal of the inner sheath of the delivery sheath and the guide wire, TEE was employed to assess for residual shunt and valve dysfunction, particularly focusing on the aortic valve. If TEE evaluation revealed indications such as atrioventricular block, residual shunt exceeding 2 mm, or new aortic or tricuspid regurgitation, patients were converted to traditional on-pump treatment.

Description of Device and Delivery System

The occluder employed in this study was the CeraTM Occluder from LifeTech Scientific Co., China (12). It is a self-expandable, double-disc device crafted from nitinol wire mesh. The two discs are interconnected by a short cylindrical waist tailored to match the size of the ventricular septal defect (VSD). Both the discs and the waist feature polytetrafluoroethylene (PTFE) membranes securely sewn to the device using nylon threads [12] (Figures 3A and B).

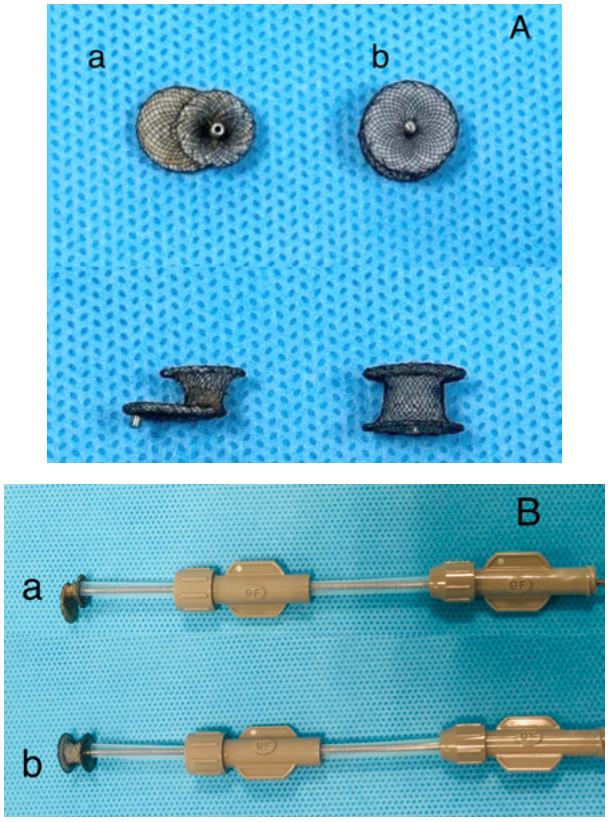

Figure 3 – Types of occluders: A – muscular(symmetric) and B – eccentric(asymmetric)

Physicians selected the occluder size based on anatomical conditions, considering factors such as the VSD's position, diameter, and the thickness of the interventricular septum.

To advance the VSD occluder to the correct position, it was used in combination with the delivery system (Figure 4).

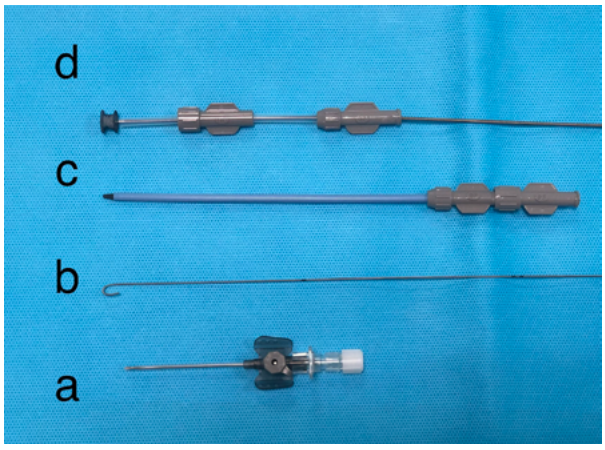

Figure 4 – Delivery system: a – trocar, b –guidewire, c – delivery sheath and dilator, d – loading sheath with a muscular occluder

Follow-up

Based on the results of a retrospective analysis, we estimate:

Efficiency: total hospital stay, preoperative and postoperative hospitalization, duration of stay in intensive care, time of mechanical ventilation, duration of operation, amount of intraoperative blood loss, number of residual shunts, number of atrioventricular blocks, insufficiency of the aortic, tricuspid valves, ejection fraction up to and postoperative period.

Safety: hospital mortality, the success rate of VSD closure, conversion rate, and reason for conversion.

Based on the results of the prospective analysis:

Long-term results: long-term safety assessment from 36 months to 84 months. To assess safety, a questionnaire was created for parents of children with congenital heart disease "ventricular septal defect" after surgical treatment. A copyright certificate has been received. An online survey was conducted among patients included in the study. Next, the patients underwent cardiac echocardiography at their place of residence, followed by remote consultation.

Results

Intraoperative and Early Postoperative Period

A total of 250 patients in this cohort underwent hybrid VSD closure, of which 233 (93.2%) patients were successful, 16 (6.4%) patients were converted to the traditional method and 1 (0.4%) death occurred. The 2 types of occluders were used: the membranous occluders were implanted in 200 patients (80%) and the muscular were implanted in the remaining patients (Figure 5). Hospital mortality was 0.4% of patients (1\234). According to the conclusion of pathological autopsies cause of death was a pulmonary hypertensive crisis.

In 16 patients who were converted to open surgery, 8 symmetric, 5 eccentric, and 3 muscular occluders were used.

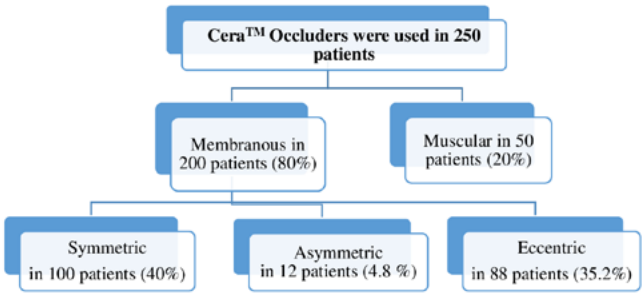

Figure 5 – Types of occluders were used for closure VSD in 250 patients (CeraTM Occluders, LifeTech Scientific Co., China)

New trivial or mild tricuspid regurgitation was detected in 35 patients (15%) and aortic regurgitation in 9 patients (3.9%) by intraoperative TEE. The absence of more than a mild degree of regurgitation and the lack of worsening with pre-existing tricuspid and aortic regurgitations before surgery in patients. Echocardiography upon discharge from the hospital showed that 16 (6.84%) patients were found with residual shunts (<2mm).

In 20 patients (8.6%) were detected the incomplete right bundle branch block while in hospital. After a short course of corticosteroid therapy (3-5 days) the sinus rhythm was restored in 10 patients. The remaining 10 patients were discharged with recommendations for observation by a pediatric cardiologist and arrhythmologist at the place of residence. Also, complete atrioventricular block (AVB) was found in 3 patients during the postoperative period: after 2 weeks (1 patient) and 5 months (2 patients) after discharge. These patients were implanted

with permanent pacemakers and under the supervision of a cardiologist and arrhythmologist at their place of residence. The average intraoperative blood loss was 27 ml. Pericardial drainage was removed on the first day after surgery in all patients, and none of the patients had repeated pericardial drainage.

The total operative time was 84 (31 min.; 160 max.) minutes, and the time for occluder implantation ranged from 10 to 80 minutes. All patients were extubated from 6 to 10 hours after the operation and the average stay in the Intensive care unit was 1.03 days.

The average stays (days): before operation-3.12, after the operation -6.76, and total hospital stay with first step rehabilitation -9.88 days.

Cases of Conversation to the Traditional Method with the heart-lung machine in 16 Patients

Nine patients (3.6%) had residual shunts <2mm. Regardless of the complete release of disks of the occluder, the residual shunt remained. The cause of interventricular shunts were multiple defects and membranous aneurysms, which were found during open surgery. Inadequate assessment resulted from a difference between preoperative TEE data and intraoperative data.

Severe arrhythmia appeared in two patients (0.8%) upon deployment of the disks at the defect, the cessation of arrhythmia was after removing the occluder. There were several attempts, however, the arrhythmia returned, which led to the decision to open surgery. The resolution of arrhythmia upon releasing the aortic clamp is an interesting observation, although the reason behind the heart's reaction remains unknown.

New aortic regurgitation in 2 patients (0.8%) and new tricuspid regurgitation in 1 patient (0.4%) occurred. Any new regurgitation, regardless of severity, indicates that the occluder is hurting the function of the aortic and tricuspid valves, considering data TEE, patients were converted to traditional surgical closure.

Two patients (0.8%) were dislocation occluder. The causes of dislocation were underestimation of the anatomical features of the defect (difference between preoperative TEE findings and intraoperative findings), and incorrect positioning of the occluder into the defect and this arose at the stage of mastering this method.

Table 1 Before and after surgery and follow-up data of patients

	Hybrid method (n=233)	Follow-up from 36 to 72 months (n=134)
Sex (male), n	106	61
Size of device used, range (mm)	4-14	4-14
Defect diameter (mm)		
Up to 5 mm, n (%)	127 (54.5)	70 (52.2)
From 5 to 10 mm, n (%)	103 (44.2)	63 (47,05)
Over 10 mm, n (%)	3 (1.3)	1 (0.75)
Left ventricular ejection fraction (%) (before surgery) (min; max)	65.5 (59; 78)	-
Left ventricular ejection fraction (%) (after surgery) (min; max)	60.7 (55;68)	62 (55; 78)
New trivial or mild tricuspid regurgitation, n (%)	35 (15%)	12 (9%)
New trivial or mild aortic regurgitation, n (%)	9 (3.9%)	3 (2.2%)
Incomplete right bundle branch block, n (%)	10 (4.3%)	0
Permanent pacemakers	3 (1.3%)	3 (2.2%)
Residual shunts	16 (6.84%)	2 (1.5%)

Table 2 Questionnaire for parents of children with congenital heart disease "ventricular septal defect" after surgical treatment

Questions	Age (year) (n=134)		
	<6 year (n=30)	6–12 years (n=65)	>12 year (n=39)
Does your child go to or did you go to kindergarten? (n)			
• Yes	20	25	-
• No	5	-	
• Haven't gone yet	5	-	
• Not suitable age		40	
Does your child go or did you go to school?			
• Yes	-	45	30
• No		0	0
• Haven't gone yet		0	0
• Not suitable for age		20	9
Exercise tolerance:			
• Weak	0	2	1
• Regular	30	61	33
• Sports	0	2	5
Visiting sports sections:			
• Yes	0	25	29
• No	20	25	7
• Haven't gone yet	10	15	3
Did you as a parent and/or your child receive psychological help if they needed it?			
• Yes	5	10	8
• No	25	55	31
Does your child have any difficulties communicating with healthy peers?			
• Yes	3	2	0
• No	27	63	39
Has your child been granted disability and for how long?			
• Yes			
- 1 year	5	10	5
- 2 years		3	3
- 3 years	0	2	1
• No	20	30	20
• Removed from disability	5	20	10
Did you develop chest deformity after heart surgery?			
• Yes	5	5	2
• No	25	60	37
• Deformation of the chest was present from birth	0	0	0
Indicate whether the child had a heart rhythm disturbance in the postoperative period (dizziness, loss of consciousness, interruptions in heart function).			
• Yes	2	3	4
• No	28	62	35
Was it necessary to implant a pacemaker (pacemaker)?			
• Yes	3	0	0
• No	27	65	39
How often did the child suffer from colds in the postoperative period about the preoperative period?			
• more often	5	3	1
• rarely	20	60	37
• also	5	2	1
During what period did your child take antiplatelet therapy (ThromboASS, Aspirin Cardio, Thrombopol, Acetylsalicylic acid)?			
• did not take	2	4	3
• 1 month	4	8	7
• 6 month	19	43	28
• 1 year	5	10	1
Were there any complaints while taking antiplatelet therapy, such as nosebleeds, stool problems, or stomach pain?			
• Yes	3	6	3
• No	27	59	36

Follow-ups

Of the 234 patients who underwent surgery, 100 patients were lost to follow-up, leaving 134 (57%) patients. This is primarily due to the lack of a unified basis for the management and monitoring of patients with congenital heart defects. In the postoperative period, patients are recommended to undergo echocardiography 4 times (1, 3, 6, and 12 months) within 1 year in our hospital, and then according to the treatment protocol, further observation at the place of residence. To analyze mid-term results, a retrospective analysis was carried out based on the patient's medical history and echocardiography data (which were carried out within 1 year in the postoperative period) (Table 1). Next, for a prospective analysis, all patients were called by doctors, and all echocardiography data that were performed at their place of residence was sent to us by mail. Later, an online survey was conducted (Table 2), with a subsequent recommendation to undergo echocardiography at the place of residence. After completion, all patients were consulted online and recommendations.

For the remaining 10 patients with incomplete right bundle branch blocks the sinus rhythm was restored in follow-up (p=0,000). In addition, the left ventricular ejection fraction improved over time (p=0.465) (Table 1).

According to the results of the examination, exercise tolerance in children after surgery was good: 124/134 (92.5%), and in 7 (5.2%) patients it was athletic; only in 3 (2.3%) patients it was weak. One of the important points after surgery is the deformation of the chest. In 122 (91%) patients, there is no deformation; unfortunately, in 12 (9%) patients, there is deformation. In addition, 129 patients did not have difficulties communicating with healthy peers; this is one of the big advantages of the minimal incision, which is not visible in the jugular notch. 10 patients had complaints while taking antiplatelet therapy, in the form of nosebleeds, black stools, and stomach pain; therefore, the dose of antiplatelet therapy was adjusted, and in 124 patients, these symptoms were not observed.

Discussion

Nowadays, it is fascinating to note the dynamic evolution in surgical techniques, especially with the increasing popularity of minimally invasive procedures. It's essential to weigh the pros and cons of each method to determine the most suitable approach for each patient, considering factors such as age, overall health, and the specific characteristics of the VSD. Advances in medical technology and techniques may continue to shape the landscape of VSD correction methods.

Traditional Open Surgery:

- Open surgery with the heart-lung machine has been a long-standing and effective approach.
- Despite its effectiveness, it may be associated with larger incisions and potential cosmetic concerns.
- The use of the heart-lung machine in this procedure is associated with various complications [13,14].

Transcatheter Closure:

- This is a minimally invasive approach where catheters are guided through blood vessels to the site of the defect.
- X-ray control is used to guide the closure device to the precise location of the VSD.
- There is a noted high risk of vascular damage, particularly in early-age patients.
- Transcatheter closure is associated with shorter recovery times and reduced postoperative pain compared to open surgery [15-17].

Hybrid (Transventricular) Approach:

- The hybrid approach combines elements of both traditional open surgery and transcatheter techniques.
- It involves a combination of surgical and catheter-based interventions, often performed in collaboration between cardiac surgeons and interventional cardiologists.
- This method aims to leverage the benefits of both approaches while minimizing the drawbacks [18-20].

This study included a group of patients with VSD of various localizations. Most of the patients had perimembranous defects and used 3 types of membranous occluders: symmetric occluders in 100 patients, eccentric in 88, and asymmetric in 12 patients (Figure 3).

Based on the results of a survey and echocardiography of the heart, the hybrid technique appeared safe and efficacious during a 36- to 84-month follow-up period (Tables 1 and 2). The residual shunts were in 16 patients and now only 2 patients. New trivial or mild tricuspid and aortic regurgitation was 35(15%),9(3.9%), and now 12(9%),3(2.2%) (Tables 1). After the operation, the majority of children went to kindergarten, and school, played sports, and had no health problems related to the heart.

Considering all this data the hybrid method:

- Less trauma to tissues, which reduces pain, immune suppression, inflammation, and swelling
- Less risk of infection, bleeding, and bruising, as there are no large incisions or damage to blood vessels
- Shorter duration of surgery and anesthesia, which reduces the risk of complications associated with anesthesia and pain relief
- Shorter length of hospital stay and rehabilitation, which reduces treatment costs and improves the patient's quality of life
- Better cosmetic results as there are no large scars or deformities [21-28]

The hybrid method is not a panacea, but only one of the tools in the hands of an experienced and qualified surgeon who strives for the best result for his patient.

Limitations

We acknowledge that this study is limited by its multidirectional cohort and single-center design. We would like to distribute a significant report about the experience of our medical center, the National Scientific Medical Center, located in Astana, the Republic of Kazakhstan. The hybrid method appears to be safe in the mid-term follow-up, but its long-term safety —particularly regarding the late complication of complete AVB and heart function — is unknown. More experience and long-term follow-up are necessary to assess the true safety and effectiveness of this treatment as an alternative to traditional surgery and transcatheter intervention. This is a novel approach to treating VSD that is becoming better with time. Moreover, this is not a summary derived from a lab but rather from experience. The experience gained from using three-dimensional echocardiography should help refine this method.

Conclusions

The hybrid method is a rapidly developing technique that has been safe and effective in a selected group of patients in recent years. The advantages of this method are minimum

incision namely the size and length of the postoperative scar from 2 to 4 cm. Moreover, no myocardial injury, and reduces operation time, intensive care unit stay, and hospital stays. Although, like other methods, it also has disadvantages, such as the development of arrhythmia and, dislocation of the occluder after implantation. Further use of the hybrid method and the accumulation of experience will clarify the indications for the use of this technique and the incidence of late complications, such as complete AV block. The presence of the latter implies long-term, perhaps even lifelong, follow-up of patients who have undergone this operation.

Author Contributions: Conceptualization, A.A and N.B.; methodology, A.A., N.B., M.Sh. and K.S.; validation, A.A and N.B.; formal analysis, A.A., N.B., M.Sh.; investigation, A.A and N.B.; resources, A.A and N.B.; data curation, M.Sh. and K.S.; writing – original draft preparation, A.A and N.B.; writing – review and editing, N.B., M.Sh. and K.S.; visualization, A.A., N.B., M.Sh. and K.S.; supervision, M.Sh. and K.S.; project administration, M.Sh. and K.S.; funding acquisition, M.Sh. and K.S. All authors have read and agreed to the published version of the manuscript.

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Ethical Statement: This research protocol was approved by the Ethics Committee of National Scientific Medical Center, Astana, Kazakhstan (Protocol number: 081/CR-75; Assigned number: 053/CT-63) and carried out by the principles set out in the Declaration of Helsinki 1964.

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Clinicopathological analysis of pediatric posterior fossa tumors: insights from a National neurosurgical center

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Abstract

Background. Pediatric posterior fossa tumors are the significant cause of morbidity and mortality in children and adolescents. This study aimed to investigate the characteristics of the patient population and report the experience in managing and treating children with these tumors, as well as their survival outcomes in Kazakhstan.

Methods. This retrospective study analysed data from the archives of the Pediatric Neurosurgery Department and included 214 pediatric patients with PFT in the period from January 2015 to December 2020.

Results. The study included 214 patients with a mean age of 7.29 ± 4.26 years. The most common tumor pathology observed in this study was medulloblastoma (33.18%). Grade I tumors showed a notable median survival of 56.64 months (95% CI, 53.93-59.35), surpassing Grade II tumors at 50.38 months (95% CI, 40.57-60.2). Grade III and IV tumors had median survivals of 38.64 months (95% CI, 31.11-46.17) and 38.76 months (95% CI, 33.96-43.56). Multivariate analysis using Cox regression model revealed significant predictors of overall survival. Grade III-IV tumors (RR = 0.577, 95% CI 0.462-0.720, p = 0.000), delayed resection (RR = 0.950, 95% CI 0.717-1.104, p = 0.000), and brainstem tumors (RR = 2.454, 95% CI 1.791-5.751, p = 0.000) had poorer survival. Tumor volume, age, and adjuvant chemotherapy were not significant predictors of 5-year survival (p > 0.05).

Conclusions. The study found similar death rates in children with pilocytic astrocytoma compared to other population studies. Regrettably, the 5-year survival rate for medulloblastoma and ependymoma indicates a poorer outcome compared to previous reports.

Keywords: pediatric tumor, posterior fossa tumor, surgical treatment, survival.

Introduction

Pediatric posterior fossa tumors (PFT) are a major cause of morbidity and mortality in children and adolescents less than 14 years of age. According to the Central Brain Tumor Registry of the United States (CBTRUS) and the American Cancer Society, PFT of the central nervous system (CNS) is the second leading cause of death in this age group [1–3]. The most common histological type of PFT in children is pilocytic astrocytoma, followed by medulloblastoma, ependymoma, and brainstem glioma [1, 4–15]. Pilocytic astrocytomas alone account for 33.2% of all childhood gliomas. In infants under 1 year of age, gliomas (37.2%) and embryonic tumors (24.9%) are the most frequent types [1, 5, 8, 16–21]. Embryonic PFT are predominantly composed of medulloblastomas (61.9%), atypical teratoid/rhabdoid tumors (ATRT) (15.0%), and primitive neuroectodermal tumors (PNEO) (14.9%). High-grade gliomas are responsible for the greatest number of deaths (43.8%).

PFT are characterized by their rapid growth and the anatomical features of the posterior cranial fossa, which can lead to the rapid onset of symptoms in affected children. Symptoms associated with PFT include headache (31%), vomiting (31%), convulsions (21%), and behavioral changes (11%). At the time

of diagnosis, the most common symptoms observed were headache (51%), vomiting (51%), visual impairment (37%), and seizures (24%) [20, 22]. The timely diagnosis and management of these tumors are critical for improving patient outcomes. Neuroimaging, including CT and MRI, is an essential diagnostic tool for the differential diagnosis of pediatric PFT [23]. Access to accurate and timely neuroimaging data is critical for the timely diagnosis and effective management of these tumors in children.

Despite significant advancements in neuroimaging, surgical techniques, and the development of a multidisciplinary approach to therapy, the survival rate of patients with pediatric PFT remains relatively low due to the aggressive nature of embryonal tumors. The American Cancer Society reports a 5-year survival rate of 74% for children under the age of 14 with CNS tumors and 76% for patients aged 15 to 19 [3]. Despite this, there have been no targeted epidemiological studies conducted on the morbidity and mortality rates of brain tumors, including PFT, in Kazakhstan. In this retrospective study, we aimed to investigate the characteristics of our patient population and report our experience with managing and treating children with PFT, as well as their survival outcomes.

Methods

This retrospective study is based on the archives of the Department of Pediatric Neurosurgery and includes a total of 214 pediatric patients who underwent primary tumor resection for PFT and were included in the study with permission from the Ethics Committee. Inclusion criteria consisted of patients under 18 years of age diagnosed with a PFT after the primary histopathological examination. All patients were admitted to the National Centre for Neurosurgery between January 2015 and December 2020 (Figure 1). This study excluded patients with missing data records, those with secondary tumors (metastases), cranial nerve tumors, and those with tumors located in other areas.

All patients underwent primary tumor resection: gross total resection (GTR) (no residual tumor), subtotal resection (STR) (90% tumor size reduction), partial resection (50–90% tumor size reduction), and biopsy (<50% tumor size reduction). The biopsy specimens from all 214 patients were analyzed and

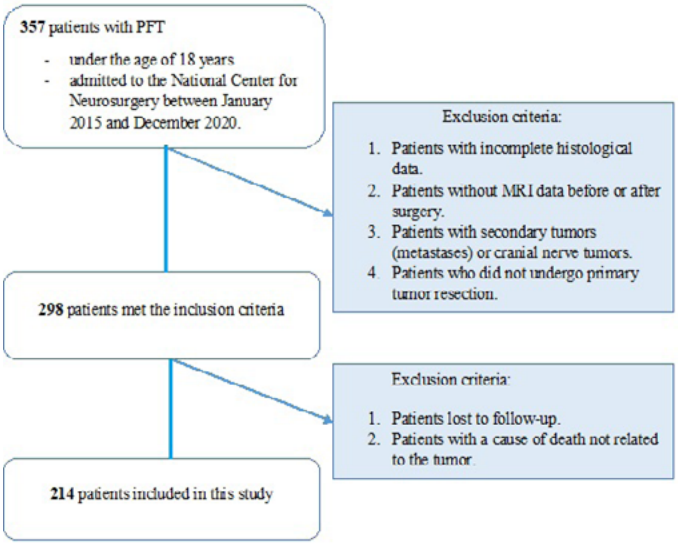

Figure 1 – Types of occluders: A – muscular(symmetric) and B – eccentric(asymmetric)

categorized based on the World Health Organization (WHO) classification of central nervous system tumors for 2007 and 2016. The tumors were classified as either low-grade or high-grade CNS tumors. The extent of resection was assessed through post-operative imaging review in each case.

The study analyzed the post-surgical mortality rate and its correlation with demographic data, clinical characteristics, tumor histology, and the extent of resection. The patients were followed up until September 30th, 2022, which was the date of the last follow-up for surviving patients.

The statistical analysis was performed using the statistical package StataCorp LP (College Station, Texas, 77845, USA). Continuous nonparametric variables are reported as medians (ranges), while categorical variables are reported as numbers and percentages. For categorical data, the Chi-square test was used to evaluate group differences, while the Mann-Whitney U test was used for continuous nonparametric variables. The Kaplan-Meier method was employed to determine overall survival curves. Overall survival was measured from the time of diagnosis to the time of death. Patients without events were censored for PFS at the last follow-up or death. To calculate the hazard ratio and 95% confidence interval for predictors of progression, the Cox proportional hazard model was used, and a p value ≤ 0.05 was considered significant.

Results

From 2015 to 2020, 214 children under the age of 18 underwent primary PFT resection at our clinic. Table 1 displays the patients' characteristics. The median age at diagnosis was 7.29 ± 4.26 years (ranging from 4 months to 17 years). Only six children (2.8%) were infants (less than 1 year of age). Sixty-seven patients (31.31%) were aged between 4 and 7 years, making it the largest proportion within the study population.

Table 1 Patient characteristics (N-214)

Variable		N	%
Age	≤3	50	23.36%
	4-7	67	31.31%
	8-12	57	26.64%
	>13	40	18.69%
Sex	Male	128	59.81%
	Female	86	40.19%
Tumor grade	Grade I	71	33.18%
	Grade II	16	7.48%
	Grade III	38	17.76%
	Grade IV	89	41.59%
Location	Brainstem	25	11.68%
	Cerebellopontine angle	14	6.54%
	Cerebellar hemispere	71	33.18%
	Ventricle+cerebellar vermis	104	48.60%
CSF diversion	Preoperative CSF diversion	147	68.69%
	Intraoperative CSF diversion	3	1.40%
	Postoperative CSF diversion	13	6.07%
	Without CSF diversion	51	28.83%

A significant number of 57 patients (26.64%) were aged between 8 and 12 years. Additionally, the age group comprising patients older than 13 years accounted for 40 individuals (18.69%) of the total participants. Out of the total 214 patients, 128 (59.81%) were male.

Table 2 Clinical Features of Patients with posterior fossa tumors.

Average symptom duration, month	3.78 ± 2.61	
Intracranial hypertension symptoms	192	89.72%
Seizures	10	4.67%
Vision	51	23.83%
Cranial nerves palsy	86	40.19%
Focal weakness	70	32.71%
Cerebellar deficit	176	82.24%

All children were symptomatic, and most had symptoms of intracranial hypertension, such as headache and vomiting (Table 2), which were observed in 192 of 214 children (89.72%). A gait disturbance was present in 176 (82.24%) of the patients. Eighty-six (40.19%) of all cases were associated with cranial nerve palsy, such as strabismus (16.82%), facial nerve palsy (19.16%), hypoacusis (2.80%), and bulbar signs (22.90%). In 23.8% of cases, it was associated with visual impairment. The median time from onset of symptoms to tumor resection was 3.78 ± 2.61 months. In our study, the most prevalent tumor location was the cerebellar vermis and fourth ventricle, accounting for 48.60% of cases. Additionally, the tumor was frequently found in the cerebellar hemisphere in 33.18% of cases. In 25 patients (11.68%), the tumor involved the brainstem, and in 14 cases (6.54%), it was located in the cerebellopontine angle.

Of the 214 children, 87 (40.65%) had CNS WHO low-grade tumors, while 127 (59.24%) were diagnosed with high-grade tumors (Table 3). The most prevalent histologic types were medulloblastoma and pilocytic astrocytoma, which accounted for 33.18% and 32.71% of all cases, respectively, followed by ependymoma (15.42%). The majority of medulloblastoma cases (19.16% of all children) presented as desmoplastic/nodular type. Additionally, 11 incidences (5.14%) of diffuse midline glioma were recorded. Other histologic types in our study include atypical teratoid rhabdoid tumor, pilomyxoid astrocytoma, other high-grade gliomas, and primitive neuro-ectodermal tumor. Of the 214 children, 172 (80.37%) exhibited clinical and radiological findings of hydrocephalus.

Table 3 Histology types of presented tumors

Hystologic types	N=214	%
Pilocytic astrocytoma	71	32.17%
Pilomyxoid Astrocytoma	7	3.27%
Diffuse astrocytoma	6	2.80%
Subependymal giant cell astrocytoma	1	0.47%
Anaplastic Astrocytoma	4	1.87%
Oligoastrocytoma	2	0.93%
Glioblastoma	1	0.47%
Diffuse midline glioma	11	5.14%
Atypical papilloma	1	0.47%
Choriocarcinoma	1	0.47%
Anaplastic ependymoma	33	15.42%
Desmoplastic / nodular medulloblastoma	41	19.16%
Large cell/anaplastic medulloblastoma	4	1.87%
Classic medulloblastoma	14	6.54%
Medulloblastoma NOS	12	5.61%
Atypical teratoid/rhabdoid tumor	3	1.40%
PNET	1	0.47%

Before tumor resection, a total of 147 children (68.69%) underwent hydrocephalus surgery, while 3 patients (1.40%) received CSF diversion surgery at the time of tumor resection. At the time of admission, five patients underwent endoscopic third ventriculostomies (ETV). In most cases, CSF draining operations were performed in regional hospitals before the patients were referred to our clinic. Nevertheless, of the 15 children who received external ventricular drain (EVD) or ETV, 13 had persistent hydrocephalus after tumor resection, requiring the placement of a ventriculoperitoneal shunt (VPS).

All patients underwent primary tumor resection, with subtotal resection (STR) being performed in the majority of cases (77.10%). Gross total resection (GTR) was achieved in 41 children (19.16%). 17 children required a tracheostomy during the postoperative period. After surgery, 120 (56.07%) children received adjunctive radiotherapy, and 131 (61.21%) patients underwent chemotherapy (Table 4).

Table 4 Summary of Patient Characteristics in each Grade group

Treatment	Grade I (N-71)	Grade II (N-16)	Grade III (N-38)	Grade IV (N-89)
Mean age, years (p = 0.018)	8.39±4.14	5.21±3.11	5.69±4.39	7.51±4.17
Average time from onset of symptoms to tumor resection, days (p = 0.000)	144.36 ± 136.52	129 ± 73.75	96.86 ± 91.85	107.25 ± 110.04
Extend of tumor resection (p = 0.000)				
Gross total resection	10 (14.08%)	2 (12.5%)	7 (18.42%)	22 (24.72%)
Subtotal resection	59 (83.1%)	12 (75%)	31 (81.58%)	63 (70.79%)
Partial resection	1 (1.4%)	0	0	3 (3.37%)
Biopsy	1 (1.4%)	2 (12.5%)	0	1 (1.12%)
Intraoperative Blood loss, ml	218.73±120.23	350±310.37	277.02±177.01	267.07± 196.94
Duration of surgery, hours	4.19±1.05	4.62±1.14	4.72±1.34	4.58±1.12
Tracheostomy	3 (4.23%)	1 (6.25%)	5 (13.16%)	8 (8.99%)
Complications				
Neurologic	7 (9.86%)	2 (12.50%)	10 (26.32%)	18 (20.22%)
Non-neurologic	1 (1.41%)	0	1 (2.63%)	6 (6.74%)
Radiotherapy (p = 0.004)	24 (33.8%)	11 (68.75%)	25 (65.79%)	60 (67.42%)
Chemotherapy (p = 0.021)	18 (25.35%)	8 (50%)	30 (78.95%)	75 (84.27%)
Metastasis	2 (2.82%)	2 (12.5%)	0	18 (20.22%)
Tumor progression	8 (11.27%)	4 (25%)	12 (31.58%)	17 (19.1%)

The study included a follow-up period ranging from 21-60 months, during which recurrence or progression was observed in 41 (19.16%) cases, resulting in reoperation for 9 patients. Metastasis was reported in 22 (10.8%) cases. A total of 75 deaths were reported after 60 months from diagnosis.

The study findings reveal distinct survival trends among patients based on tumor grade and histological group. Patients with Grade I tumors demonstrated a notable median survival time of 56.64 months (95% CI, 53.93-59.35 months), surpassing the median survival time of 50.38 months (95% CI, 40.57-60.2 months) observed in patients with Grade II tumors. The median survival time was 38.64 months (95% CI, 31.11-46.17 months) for patients with Grade III tumors, compared with a median survival time of 38.76 months (95% CI, 33.96-43.56 months) for patients with Grade IV tumors. The impact of various risk factors on overall survival rates was analyzed using Kaplan-Meier analyses stratified for each variable (Figure 2).

In the pilocytic astrocytoma group, patients exhibited a median survival time of 56.59 months (95% CI, 53.84-59.34 months), accompanied by an impressive 5-year survival rate of 91.43%. Patients diagnosed with medulloblastoma faced a median survival time of 43.01 months (95% CI, 38.01-48.00 months) and a 5-year survival rate of 56.34%. Within the Anaplastic ependymoma category, the median survival time was 38.13 months (95% CI, 30.03-46.24 months), while the 5-year survival rate stood at 42.42%.

Utilizing a multivariate analysis approach employing the Cox proportional hazards regression model, significant predictors of overall survival emerged. Patients with grade III-IV tumors (RR = 0.577, 95% CI 0.462-0.720, p = 0.000), delayed time to tumor resection (RR = 0.950, 95% CI 0.717-1.104, p = 0.000), and tumors located in the brainstem (RR = 2.454, 95% CI 1.791-5.751, p = 0.000) experienced poorer overall survival rates, as highlighted in Table 5.

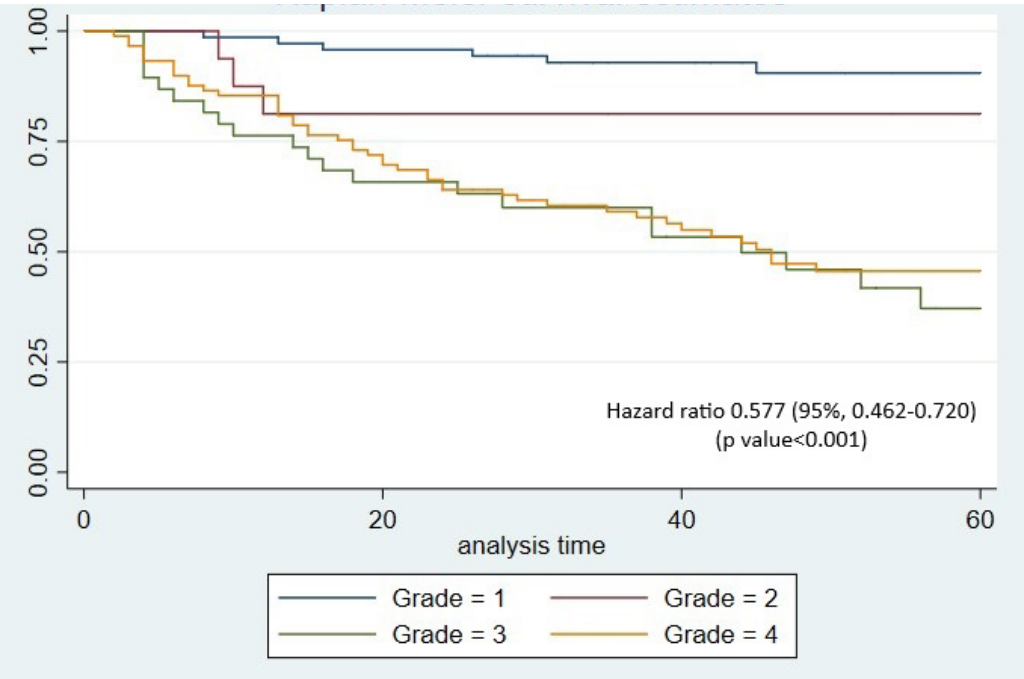

Figure 2 – Kaplan-Meier Survival Estimates

Table 5 Cox regression hazard ratio for poor outcome

	Unadjusted hazard ratio (95% CI)		Adjusted hazard ratio (95% CI)	
Variable	Confidence interval	P value	Confidence inter-val	P value
Tumor volume	0.987(0.973-1.001)	0.079		
Histology	0.577(0.462-0.720)	0.000	0.514(0.406-0.651)	0.000
Pilocytic astrocytoma			0.081(0.031-0.211)	0.000
Medulloblastoma			0.646(0.364-1.148)	0.137
Anaplastic ependy-moma			0.415(0.250-0.581)	0.018
Other			0.585(0.297-1.153)	0.000
Sex	1.816(0.836-2.185)	0.218		
Age	0.933(0.881-0.988)	0.018		
Time to surgery				
(Low-grade/ High-grade)	0.950(0.717-1.104)	0.000		
Radiotherapy	0.792(0.304-0.796)	0.004	0.481(0.297-0.779)	0.003
Chemotherapy	1.824(1.093-3.044)	0.021		
Location-CPA	1.784(1.049-2.903)	0.032	1.714(1.030-2.852)	0.038
Location-brainstem	2.454(1.791-5.751)	0.000	2.549(1.362-4.771)	0.003
Extent of tumor re-section	0.095(0.030-0.300)	0.000	0.098(0.034-0.281)	0.000

The extent of tumor resection demonstrated a substantial impact on overall survival, with a noteworthy relative risk (RR) of 0.098 and a tight 95% confidence interval (CI) of 0.034 to 0.281 ($p < 0.001$). Notably, tumor volume (RR = 0.987, 95% CI 0.973-1.001, p = 0.079), age (RR = 0.933, 95% CI 0.881-0.988, p = 0.018), and adjuvant chemotherapy (RR = 1.824, 95% CI 1.093-3.044, p = 0.021) did not emerge as significant predictors of 5-year survival.

Postoperative neurologic complications were observed in 17.29% of patients, comprising oculomotor nerve palsy (2.33%), facial nerve palsy (0.93%), bulbar sign (3.27%), ataxia (0.46%), limb weakness (3.74%), and Posterior fossa syndrome (0.93%). Non-neurologic complications, predominantly pneumonia, observed in 3.74% cases.

Discussion

Brain tumors account for a significant proportion of cancer cases in Kazakhstan, with an estimated prevalence of 15.7% on average and ranking second in malignant tumors affecting children [24,25]. Despite this, no targeted epidemiological studies have been conducted on the morbidity and mortality rates of brain tumors, including PFT, in Kazakhstan.

To address this gap in knowledge, our study provides a comprehensive analysis of a large cohort of PFT patients, represented by data collected from the National Center of Neurosurgery database, which caters to over 90% of Kazakhstan children with this pathology who receive surgical care. Our study evaluated the demographics, clinical data, histological types, and surgical treatment of children with PFT. To the best of our knowledge, this is the first analysis of the incidence and survival of children with PFT in Kazakhstan.

In our study, the three most prevalent histological types of PFT were pilocytic astrocytomas (32.71%), medulloblastomas (33.17%), and anaplastic ependymomas (15.42%). These findings are consistent with previous studies, indicating that these types of tumors are the most commonly occurring in the posterior fossa [1, 6, 23, 26–29].The prevalence of other tumor types, such as atypical rhabdoid/teratoid tumors, hemangioblastomas, vestibular schwannoma, gangliocytomas of the cerebellum, and meningiomas, was relatively low, accounting for 18–19% of cases.

Several investigators have reported that embryonal tumors are more commonly found in infants [1, 4, 5]. This is consistent with our findings that infants under the age of one have the highest incidence of central nervous system malignancies (6.22 per 100,000) and PFT is the most prevalent tumor in children aged 1-4 years (22.1%), especially in the cerebellum [1, 23, 30].

Our study found that the median age at the time of diagnosis of PFT in children in Kazakhstan was 7.29 ± 4.26 years, which is consistent with previous studies [16, 30, 31]. However, we observed that the median age of children with grade II and grade III tumors was lower, at 5.21 and 5.69 years, respectively. This difference in age may be attributed to the tumor's location and earlier manifestation of hydrocephalus symptoms.

There have been conflicting reports regarding the gender distribution of PFT in children across various studies. In line with the findings of some earlier studies [32], we discovered that there were more male children than female children in our study. Though more female patients with PFT were reported by Picariello et al.[11, 30]. Certain types of PFT have been reported to be more common in either males or females. For example, Ostrom et al. discovered that medulloblastomas and ependymomas are more common in males than in females [1, 9]. Pilocytic astrocytoma, on the other hand, impacts both genders equally [33].

The reasons for these gender distribution differences are unclear and require further investigation. For patients to receive a successful course of treatment, early PFT diagnosis is essential. However, the diagnosis of PFT is frequently difficult because of the early nonspecific clinical signs, particularly in infants. The most typical signs of tumors in the cerebellum are increased intracranial pressure and symptoms of cerebellar dysfunction. The most common clinical signs of PFT in our study, as well as earlier studies, were intracranial hypertension symptoms like headache, vomiting, and vision impairment, as well as anorexia, behavioral abnormalities, irritability, and lethargy [21-22, 30, 34, 35]. A neurologist is consulted because of these symptoms, which are present in about 89.72% of patients. Other clinical manifestations of cranial nerve involvement are less frequent and more prevalent in older kids [23].

The influence of the duration of time between symptom onset and tumor diagnosis on survival prognosis in patients with pediatric brain tumors is a topic of ongoing debate. In our study, the average time from symptom onset to tumor removal was 3.78 ± 2.61 months, which is longer than the 4 weeks reported in a previous study [22]. The longer diagnostic delay in our study may be attributed to the level of knowledge of malignant brain tumors among the general population and healthcare professionals, as well as the availability of diagnostic tools such as CT and MR examinations of the brain.

In our study, an extended diagnostic delay was found to exert a substantial impact on the overall survival of patients. The lack of availability of CT and MR examinations of the brain in many regional centers is a significant challenge that further delays tumor detection in our country. Strategies to improve access to diagnostic tools and increase awareness of malignant brain tumors among healthcare professionals and the general population are needed to facilitate early diagnosis and improve overall survival in patients with pediatric brain tumors.

In our study, the majority of deaths were observed in children under 5 years old, which is consistent with the findings of Aras et al. [20]. This highlights the importance of early detection and timely treatment to improve survival outcomes, particularly in young children who may be more vulnerable to the effects of these tumors.

Previous research has shown that the histological type, tumor size, and location are all important factors in predicting mortality rates for brain tumors [32, 36, 37]. In our study, we found that while tumor size did not significantly affect survival rates (p=0.079), tumors located in the brainstem had a higher mortality rate compared to tumors in the ventricle and cerebellum, consistent with previous findings [1]. This underscores the importance of accurate diagnosis and prompt treatment, especially for tumors in critical brain regions.

Embryonic tumors and ependymomas are known for their aggressive biology and high lethality, despite advancements in diagnosis and treatment [3]. Previous studies have shown a strong correlation between tumor histology and patient outcomes [18, 32, 38, 39]. Surgery and adjuvant therapies, such as chemotherapy and radiation, are the mainstay of treatment for these tumors. Achieving maximum safe resection through surgery is critical for successful treatment, and the extent of resection is directly related to patient outcomes [20, 21, 31, 40-43].

Pilocytic astrocytomas are generally associated with favorable outcomes in pediatric patients. Previous studies have reported 10-year survival rates exceeding 90% [44]. Our analysis of 5-year overall survival rates for pilocytic astrocytomas aligns with these findings, showing a promising 91.43% survival rate. Prior research has indicated that the 10-year overall survival of pediatric ependymoma was around 50 ± 5% [45]. In our study, we observed a 5-year overall survival rate of 42.42%. These results highlight the persistent challenge in achieving favorable outcomes for patients with posterior fossa ependymoma. Long-term survival rates for Medulloblastoma have been reported to be approximately 70-85% [21]. However, our study's 5-year overall survival rate (56.34%) for Medulloblastoma indicates a poorer outcome compared to these previous reports.

The significant effect of postoperative adjuvant radiotherapy on patient survival is also highlighted by our study. However, we were unable to locate any solid proof supporting the necessity of postoperative chemotherapy. Due to this, chemotherapy regimens for ependymomas and embryonic tumors in our country may need to be revised.

Our research emphasizes the value of early detection, aggressive surgical resection, and suitable adjuvant therapy for the treatment of PFT. The results of this study can help clinicians and researchers better understand the clinical and pathological characteristics of PFT in the pediatric population of Kazakhstan. A more thorough and systematic epidemiological analysis of brain tumors in the Kazakh pediatric population is also required, as our study's findings show.

The main limitation of this study is its retrospective design. In addition to survival, the variety of tumors and the limited sample size restricted us from doing a thorough investigation of prognostic factors in this carefully chosen cohort of children. Despite these drawbacks, we offer a large descriptive sample of PFT diagnosed in our country. These findings highlight the necessity of additional study as well as the application of present knowledge and clinical practice.

Conclusion

In this study, we have analyzed data from the National Center of Neurosurgery database, providing insights into pediatric brain tumors, particularly those located in the posterior fossa. Our findings indicate that pilocytic astrocytomas exhibit favorable outcomes, with a 5-year survival rate comparable to data from other population studies. Unfortunately, our study's findings reveal that the 5-year survival rate for medulloblastoma and ependymoma is less favorable when compared to earlier documented reports. These results highlight the need for further research and improved treatment strategies to enhance survival rates for this aggressive tumor. Modern oncology urgently needs to do a systematic epidemiological analysis of the morbidity and mortality from malignant tumors in the Kazakh children's population.

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EVALUATION OF GENITAL HYGIENE BEHAVIORS OF FEMALE SECONDARY SCHOOL STUDENTS: VIZE EXAMPLE

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Abstract

Aim: The study was conducted to evaluate the genital hygiene behaviors and habits of female secondary school students in the adolescent period.

Methods: The study was conducted in a descriptive and correlational design between February and June 2022 to determine.

The study population consisted of 355 female students studying in all high schools affiliated with the Ministry of National Education in Vize district of Kırklareli province in Turkiye. It aimed to reach the entire population without determining the sample size. As a result, 194 female students who volunteered to participate in the study were included in the sample. In data collection, the "Personal Information Form" and "Genital Hygiene Behavior Scale" were applied using the face-to-face interview method.

Results: It was found that the mean age of the students was 15.74±1.1, the majority of them lived with their parents, more than half of them (67.5%) didn't receive information about genital care and hygiene, almost all of them (92.3%) used materials for cleaning the genital area, their genital hygiene behaviors were positive, and they thought that they were given inadequate education about hygiene at school or in classes. It was determined that the genital hygiene behaviors and menstrual hygiene of the students living with only a mother or father were more positive, and the use of materials for genital hygiene was higher in the students living in the city center and district compared to the students living in the village.

Conclusion: As a result, it was observed that the mother's education level, family income level, and the person living with her positively affected general hygiene and menstrual hygiene habits.

Keywords: Adolescent, hygiene, genital hygiene, behavior, nursing.

Introduction

Personal hygiene and self-care practices are essential in every period of life to protect and improve health. One of these practices is genital hygiene. Genital hygiene is a broad term that includes various hygiene behaviors and care practices necessary to protect the organs in the urogenital region from infectious agents, maintain physical integrity, and improve functional health [1, 2]. The meaning of genital hygiene is affected by individual differences. It is affected by factors such as low socio-economic level, lack of education, lack of knowledge about perineal hygiene, improper genital hygiene, not paying attention to hygiene during menstruation, and using unhygienic materials during menstruation [3, 4].

The genital area is the most humid, warmest, and sensitive body part. Various excretions such as menstrual blood, urine, and sweat can accumulate in this area, which may increase the susceptibility to genital infections. Genital infections are an essential health problem with adverse effects, especially for women, and are among the main reasons that push women to the gynecology outpatient clinic for medical help [5]. In the literature, it is reported that approximately one million women worldwide experience genital infections every year, and 75% have a history of vaginal infection [6,

7]. These infections can be easily treated and prevented, or their complications can be reduced when diagnosed early. In this context, acquiring correct genital hygiene habits is a fundamental reason [8].

Adolescence is when the individual begins to manage their hygiene in the light of information obtained from their family, school, peers, or the internet. With the new education system in our country, the secondary education age coincides with the generations of students between 10-13. Management of menstrual hygiene should be a critical issue, especially for adolescent girls, but it is often neglected [9, 10]. Lack of adequate information about genital hygiene from early adolescence can lead to misinformation and misapplication. Schools ' inadequate cleaning and hygiene areas may also cause students to have an uncomfortable menstruation process [9]. Therefore, evidence-based data on adolescents' menstrual hygiene management is essential to take steps to protect them from future genital infections. It is vital for nurses, who play a crucial role in achieving and maintaining health, to analyze the genital hygiene behaviors of adolescents, to recognize abnormal vaginal secretions, and to provide counseling to ensure that people apply to the health institution for early diagnosis.

Methods

Study design and sample size

The study was conducted to evaluate the genital hygiene behaviors and habits of female secondary school students in the adolescent period. The population of the study consisted of all female students (N:355) studying in all high schools affiliated with the Ministry of National Education in Vize in Turkiye province between February and June 2022 Since it aimed to reach the entire population, no sampling calculation was made to determine the number of samples. For this study, the estimated sample size is derived from the online Raosoft sample size calculator. The sample size was calculated based on a response rate of 50%, a confidence interval of 95%, and a margin of error of 5%, the largest required sample size is 355. The recommended sample size has found minimum 185. Accordingly, this study included of 194 students. The response rate was 54.64 per cent of the sample population.

During data collection, schools were visited by the researcher to interview students studying in the institutions within the scope of the sample. The times when the students were available were determined by the school administration. At these times, students were first informed about the purpose of the study and that the data obtained would remain confidential and not be shared. After the students' verbal consent to participate in the study was obtained, written permission was obtained from their parents with the "Informed Voluntary Consent Form". The data collection forms were filled out in the library or the available classrooms the school administration planned during the students' free time. The data collection process took an average of 25 minutes for each class.

Data collection tools

"Personal information form" and "Genital Hygiene Behaviors Scale" were used for data collection. The personal information form consisted of 18 questions related to genital hygiene behaviors, such as the students' socio-demographic characteristics (age, class, school, parents education, income status, the people with whom she lives) the status of receiving education about genital hygiene, the presence of materials used in genital area cleaning, and the status of experiencing genital infections.

"Genital Hygiene Behaviors Scale"; The scale developed and validated by Karahan (2017) is a five-point Likert-type scale consisting of 23 items. The scale has 3 sub-dimensions: general hygiene habits, menstrual hygiene, and awareness of abnormal findings. High scores obtained from the scale indicate that genital hygiene behavior is positive [6]. In the study, the Alpha value of the scale was determined to be 0.81.

Ethical approval

"Ethics Committee Approval" (Decision no:2021/50-38, Date:09.04.2021) was obtained from XXX University Non-Interventional Clinical Research Ethics Committee to conduct the study. After the ethics committee's approval, institutional permission numbered E-81588373-605.01-44240020 was obtained from the Ministry of National Education of Kırklareli, Republic of Turkiye, to conduct the study. Consent was obtained from the parents of the students participating in the study with the "Informed Voluntary Consent Form."

Study Limitations

- Conducting the research on limited dates.
- The research covers all high schools in Vize district of Kırklareli and cannot be generalized to the whole Kırklareli.
- Only students with parental consent can participate in the study.

Data analysis

The data obtained in the study were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 22.0 program. The Kolmogorov-Smirnov test examined the normal distribution of the data. Normality distribution histograms of the mean scores of the Genital Hygiene Behaviour Scale of the students were also examined (Figure 1). Descriptive statistical methods were used in the evaluation of the data. Mann Whitney U test and Kruskal-Wallis H tests were used as nonparametric tests. The chi-square test (Pearson Chi-Square, Fisher's Exact test) was used to compare qualitative data. The results were evaluated at a 95% confidence interval and $p<0.05$ significance level.

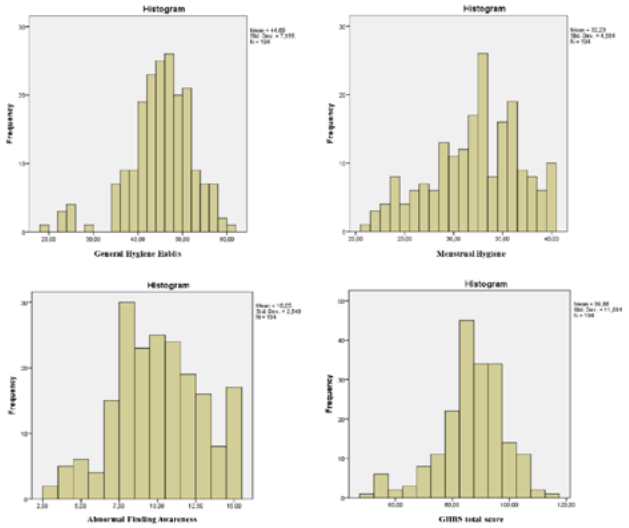

Figure 1 – Normality Distribution of Mean Scores of Students' Genital Hygiene Behaviours Scale

Table 1 Findings Related to Genital Hygiene Habits of Students (N: 194)

Genital Hygiene Habits of Students	n	%	
Receiving information about genital care and hygiene	Receiving information	63	32.5
	Not receiving information	**131**	**67.5**
*Sources used to obtain information on genital care and hygiene (n:131)	Mother	**129**	**66.5**
	Mom and Dad	23	11.9
	Sister, aunt, etc.	12	6.2
	Teacher	6	3.1
	Friend	4	2.1
	Internet, TV	20	10.2
Presence of material used for cleaning the genital area	Using	179	**92.3**
	Not using	**15**	7.7
Materials Used in Genital Area Cleaning	Water	25	12.9
	Shower Gel	**59**	**30.4**
	Soap	27	13.9
	Waxing	33	17.0
	Razor blade	9	4.6
	Depilatory cream	15	7.7
	Other (pads, wipes, napkins)	11	5.7
	Not using	15	7.7
How to bathe during menstrual bleeding	Standing shower	**177**	**91.2**
	Sitting	17	8.8
Experiencing genital infections	Never experienced	**172**	**88.7**
	Experienced	22	11.3
Thinking that sufficient training on hygiene is provided at school or in classes	Thinking they are sufficient	39	20.1
	Thinking they are insufficient	**155**	**79.9**
Thinking that the school has sufficient facilities to ensure menstrual hygiene	Thinking they are sufficient	26	13.4
	Thinking they are insufficient	**168**	**86.6**
Total		**194**	**100**

*More than one option is marked.

Results

The average age of the students participating in the study was 15.74±1.1. 42.3% of the students were in the 10th grade, 61.8% were studying at an Anatolian High School in Vize, 70.6% of the student's mothers, and 59.8% of the students' fathers had primary education. It was found that 70.6% of the participants lived in the district, 70.6% had an income equal to their expenses, 88.1% lived with their parents, 41.8% of their mothers, and 88.1% of their fathers were employed.

It was determined that 67.5% of the students did not receive information about genital care and hygiene, and 66.5% of those who received information received it only from their mothers. It was determined that 92.3% of the students used materials for cleaning the genital area, 12.9% of the students used water, 30.4% shower gel, 13.9% soap, 17% waxing, 4.6% razor, 7.7% depilatory cream and 5.7% other products (pads, wipes, napkins) for cleaning the genital area. It was observed that 91.2% of the students took a standing shower during menstrual bleeding, 88.7% had never experienced genital infections, 79.9% thought that insufficient education was given about hygiene in school activities or lessons, and 86.6% believed that the facilities available at school to ensure menstrual hygiene were inadequate (Table 1).

The students who participated in the study scored an average of 44.60±7.1 points in the General Hygiene Habits Subscale, 32.23±4.6 points in the Menstrual Hygiene Subscale, and 10.05±2.8 points in the Abnormal Finding Awareness Subscale of the Genital Hygiene Behaviors Scale. The mean total score of the Genital Hygiene Behavior Scale was 86.88±11.6. It was determined that the students scored above the mean value in the Genital Hygiene Behaviors Scale (min:50; max:113), and their genital hygiene behaviors were positive (Table 2).

It was determined that the student's grades, the school they attended, the father's educational status (except for the menstrual hygiene sub-dimension of the scale), and the place where they lived did not affect their genital hygiene behaviors ($p>0.05$). It was observed that students whose mothers were illiterate had lower mean scores in the total and General Hygiene Habits and Menstrual Hygiene Sub-dimension of the Genital Hygiene Behaviors Scale, and students whose fathers were illiterate had lower mean scores in the Menstrual Hygiene Sub-dimension of

Table 2 Clinical Features of Patients with posterior fossa tumors.

Genital Hygiene Behavior Scale		Mean±SD	Min.-Max
Genital Hygiene Behavior Scale General		86.88±11.6	50-113
Scale Sub-Dimensions	General Hygiene Habits	44.60±7.1	19-60
	Menstrual Hygiene	32.23±4.6	21-40
	Abnormal Finding Awareness	10.05±2.8	3-15

Mean: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum

the Genital Hygiene Behaviors Scale than the others, and these situations showed significance (p=.019, p=.014, p=.004, p=.021; p<0.05, respectively). It was observed that the student's general hygiene and menstrual hygiene habits were negatively affected as the educational level of their mothers decreased, and menstrual hygiene habits were negatively affected as the academic level of their fathers decreased (Table 3).

It was found that those whose income was higher than their expenditures scored higher on the overall Genital Hygiene Behaviors Scale (except the mean scores on the Awareness of Abnormal Findings Subdimension) and on the General Hygiene Habits and Menstrual Hygiene Subdimension, and there was a significant difference between the groups (p=.005, p=.017, p=.000; p<0.05, respectively) (Table 3).

Table 3 Comparison of Students' Descriptive Characteristics with Mean Scores of Genital Hygiene Behaviors Scale (N:194)

Descriptive Characteristics of the Students		General Hygiene Habits				Menstrual Hygiene				Abnormal Finding Awareness				GHBS total score			
		Mean ±SD	Med	Int. ran	U/ χ^2 P	Mean ±SD	Med	Int. ran	U/ χ^2 P	Mean ±SD	Med	Int. ran	U/ χ^2 P	Mean ±SD	Med	Int. ran	U/ χ^2 P
Grade	9th grade	**43.39±8.9**	**44.00**	**10.00**	**3.455& .327**	31.69±5.1	33.00	8.00	**1.312& .726**	9.61±2.5	9.00	3.00	7.004& .072	84.69±14.3	87.00	18.00	4.289& .232
	10th grade	**44.35±6.2**	**45.00**	**6.25**		32.13±4.1	32.00	7.00		9.83±2.8	10.00	4.00		86.32±9.7	87.00	8.50	
	11th grade	45.65±6.6	46.50	9.00		32.74±4.9	33.00	5.25		10.52±3.0	11.00	4.25		88.91±11.3	89.50	13.00	
	12th grade	46.87±6.4	47.00	8.00		33.00±4.1	33.00	5.00		11.27±3.2	11.00	5.00		91.13±10.7	91.00	20.00	
The school you are studying at	An Anatolian High School in Vize	45.15±5.9	45.00	8.00	1.371& .712	32.88±4.0	33.00	6.00	4.746& .191	10.05±2.9	10.00	4.00	1.409& .703	88.08±9.8	88.00	12.00	.732& .866
	A Vocational and Technical Anatolian High School in Vize	43.74±10.7	47.00	9,25		30.92±5.7	32.00	9.25		9.66±2.9	10.00	3.00		84.31±16.3	87.00	16.50	
	An Anatolian Imam Hatip High School in Vize	43.83±6.6	45.00	7.50		31.12±4.7	32.00	7.75		10.25±2.5	10.00	3.75		85.21±11.1	88.50	16.00	
	Another Anatolian High School in Vize	43.42±5.8	**45.50**	**6.75**		32.00±4.8	32.00	7.25		10.83±2.3	10.50	4.00		86.25±10.1	87.00	11.25	
Mother's education level	Illiterate	**34.33±7.7**	35.00	13.00	**15.322& .004****	25.83±3.7	24.50	7.00	**12.56& .014***	9.33±2.2	8.00	3.50	1.600& .809	69.50±12.2	68.00	21.75	**11.840& .019***
	Can read and write	51.00±6.0	51.00	-		31.00±6.9	27.00	-		10.33±0.6	10.00	-		92.33±3.8	94.00	-	
	Primary education	**44.34±7.1**	**45.00**	**8.00**		32.26±4.4	33.00	5.00		10.09±2.8	10.00	4.00		86.70±11.5	87.00	12.50	
	High School	46.30±6.2	46.50	7.00		32.85±4.5	33.00	7.25		9.91±3.1	10.00	4.25		89.06±10.4	90.00	10.50	
	University and above	**44.50±9.2**	**44.50**	**-**		36.50±0.7	36.50	-		11.50±0.7	11.50	-		92.50±10.6	92.50	-	
Father's education level	Illiterate	26.50±3.5	26.50	-	7.168& .127	24.00±0	24.00	-	**11.563& .021***	8.00±0	8.00	-	2.478& .649	58.50±3.5	58.50	-	8.145& .086
	Can read and write	40.00±0	40.00	-		29.00±0	29.00	-		9.00±0	9.00	-		78.00±0	78.00	-	
	Primary education	**44.60±7.3**	**45.00**	**8.00**		31.80±4.7	32.50	6.00		10.09±2.9	10.00	4.00		86.49±11.9	87.00	11.75	
	High School	45.01±6.6	45.50	9.00		32.94±4.2	33.00	6.00		10.11±2.9	10.00	4.00		88.07±10.4	88.50	13.25	
	University and above	**47.00±2.9**	**47.00**	**5.00**		36.00±3.0	37.00	5.50		9.20±2.2	10.00	4.00		92.20±6.7	92.00	12.50	
Place of residence	City Center	**45.57±6.4**	**46.00**	**9.00**	.766& .682	32.29±4.7	34.00	8.00	.233& .890	9.28±2.9	10.00	5.00	1.296& .523	87.14±9.5	86.00	13.00	.247& .884
	District	**44.83±7.3**	**45.00**	**9.00**		32.17±4.5	33.00	7.00		10.21±2.8	10.00	4.00		87.21±11.8	88.00	12.00	
	Village	**43.84±6.9**	**45.00**	**7.00**		32.38±4.8	33.00	6.75		9.70±2.9	9.00	4.00		85.9±11.1	87.00	15.25	
Monthly income	Income less than expenditure	**41.65±8.5**	**43.00**	**12.00**	**8.186& .017***	29.43±5.2	29.00	9.00	**16.558& .000*****	9.61±1.8	9.00	3.00	1.327& .515	80.70±13.3	85.00	18.00	**10.682& .005****
	Income equal to expenditure	**44.37±7.2**	**45.00**	**8.00**		32.09±4.5	32.00	6.00		10.15±2.9	10.00	4.00		86.62±11.6	87.00	13.50	
	Income more than expenditure	**47.53±4.4**	**47.00**	**5.00**		34.65±3.4	35.50	5.00		9.91±3.2	10.00	5.25		92.09±7.8	91.50	9.50	
Who do you live with	Together with mom and dad	**44.65±7.2**	**45.00**	**8.00**	2.430& .119	32.08±4.5	33.00	6.00	**5.547& .019***	10.10±2.8	10.00	4.00	.045& .832	86.82±11.5	87.00	12.00	**3.899& .048***
	Only with the mother or only with the father	**47.50±4.5**	**49.00**	**5.75**		35.00±4.4	36.00	5.00		10.08±3.3	10.00	4.75		92.58±9.6	94.00	14.75	
	Other	**40.73±7.9**	**41.00**	**13.00**		31.54±6.1	32.00	9.00		9.18±2.3	9.00	4.00		81.45±13.3	85.00	19.00	

Mean: Mean, SD: Standard Deviation; Med: Median Interquartile range: Int.ran;ΔMann-Whitney U test, &Kruskal-Wallis Test, *p<.05; **p<.001; ***p<.001

It was found that the mean scores of the students who lived with only their mother or only their father were higher than those who lived with their mother and father or other family members, and there was a significant difference between the groups (p=.048, p=.019; p<0.05, respectively). It was determined that the genital hygiene behaviors and menstrual hygiene of the students living with only their mother or only their father were more optimistic (Table 3).

Table 4 Comparison of Findings Related to Genital Hygiene Habits of Students with Genital Hygiene Behaviors Scale (N: 194)

Genital Hygiene Habits		General Hygiene Habits				Menstrual Hygiene				Abnormal Finding Awareness				GHBS total score			
		Mean ±SD	Med	Int. ran	U/χ² P	Mean ±SD	Med	Int. ran	U/χ² P	Mean ±SD	Med	Int. ran	U/χ² P	Mean ±SD	Med	Int. ran	U/χ² P
Receiving information about genital care and hygiene	Receiving information	**45.44±6.8**	**46.00**	**8.00**	3619.50Δ .165	33.03±4.0	33.00	5.00	3573.00Δ .130	9.76±2.7	10.00	4.00	3716.50Δ .260	88.24±10.3	88.00	10.00	3746.50Δ .299
	Not receiving information	**44.20±7.3**	**45.00**	**8.00**		31.84±4.8	32.00	7.00		10.18±2.9	10.00	4.00		86.22±11.6	87.00	15.00	
Resources used to obtain information on genital care and hygiene	Mother	44.57±7.1	45.00	8.50	4.168& .525	32.26±4.4	33.00	7.00	3.171& .674	9.95±2.7	10.00	4.00	10.15& .071	86.77±11.4	88.00	13.00	6.288& .279
	Mom and Dad	45.74±5.9	46.00	8.00		33.39±4.3	33.00	5.00		11.48±2.8	12.00	5.00		90.61±10.1	89.00	14.00	
	Sister, aunt, etc.	43.83±9.9	43.00	13.25		31.67±5.3	31.50	8.25		10.00±2.6	9.50	2.00		85.50±14.7	88.50	18.00	
	Teacher	42.83±11.0	44.00	14.25		31.67±5.0	31.50	6.75		10.00±3.0	9.00	5.00		84.50±15.2	85.00	16.25	
	Friend	49.00±4.7	48.50	8.50		33.50±3.0	32.00	4.50		11.50±3.5	11.50	6.50		94.00±9.9	93.50	18.00	
	Internet, TV	43.65±5.9	**45.00**	**8.25**		30.95±5.6	31.00	10.75		8.75±3.1	8.500	3.75		83.35±11.2	84.00	17.25	
Presence of material used for cleaning the genial area	Using	**44.65±7.3**	45.00	8.00	1249.50Δ .656	32.11±4.6	33.00	7.00	1063.00Δ .180	10.04±2.8	10.00	4.00	1326.50Δ .939	86.81±11.7	87.00	13.00	1250.50Δ .659
	Not using	44.00±5.8	45.00	9.00		33.60±3.6	34.00	3.00		10.07±3.6	9.00	5.00		87.67±10.0	89.00	13.00	
How to bathe during menstrual bleedin	Standing show	**44.64±7.4**	**45.00**	**9.00**	1389.50Δ .602	32.38±4.6	33.00	7.00	1208.00Δ .179	10.09±2.9	10.00	4.00	1371.50Δ .545	87.11±11.8	88.00	13.00	1262.00Δ .272
	Experienced	44.23±4.6	46.00	5.00		30.65±4.8	32.00	6.50		9.59±2.3	9.00	4.00		84.47±9.3	87.00	10.50	
Experiencing genital infections	Never Experienced	**44.65±6.6**	**45.00**	**8.00**	1812.50Δ .748	32.31±4.4	33.00	6.75	1779.50Δ .649	9.95±2.8	10.00	4.00	1613.50Δ .258	86.91±10.8	87.00	12.00	1817.00Δ .762
	Receiving information	44.23±10.5	46.00	13.25		31.54±6.0	32.00	11.25		10.82±2.8	10.00	5.25		86.59±17.0	88.00	22.25	
Thinking that sufficient training on hygiene is provided at school or in classes	Thinking that they are sufficient	45.79±8.3	47.00	8.00	**2404.00Δ .048***	33.15±4.9	34.00	7.00	2498.50Δ .094	11.03±2.8	11.00	5.00	**2309.50Δ .022***	89.97±13.6	94.00	12.00	**2192.50Δ .008**
	Thinking that they are insufficient	**44.30±6.8**	**45.00**	**8.00**		31.99±4.5	32.00	7.00		9.80±2.8	10.00	4.00		86.10±10.9	87.00	12.00	
Thinking that the school has sufficient facilities to ensure menstrual hygiene	Thinking that they are sufficient	44.23±7.9	46.00	7.25	2065.00Δ .655	31.69±4.7	33.00	7.25	2062.50Δ .647	10.96±2.7	11.00	5.00	1743.00Δ .096	87.08±13.0	89.00	11.25	2053.00Δ .623
	Thinking that they are insufficient	**44.63±7.1**	**45.00**	**9.00**		32.31±4.6	33.00	7.00		9.90±2.8	10.00	4.00		86.84±11.4	87.00	13.00	

Mean: Mean, SD: Standard Deviation; Med: Median Interquartile range: Int.ran;ΔMann-Whitney U test, &Kruskal-Wallis Test, *p<.05; **p<.001; ***p<.001

It was found that the status of receiving information about genital care and hygiene, the sources used to obtain information, the material used for cleaning the genital area, the way of bathing during menstrual bleeding, the status of experiencing genital infection, and the status of thinking that there were adequate facilities at school to provide menstrual hygiene did not affect the genital hygiene behaviors of the students participating in the study (p>0.05, Table 4).

It was found that the mean scores of the students who thought that they were given adequate education about hygiene in school activities or lessons were higher than the students who did not know that they were given sufficient education, and there was a significant difference between the groups (p=.008, p=.048, p=.022; p<0.05, respectively). It was observed that genital hygiene behaviors, general hygiene habits, and awareness of abnormal findings were more positive in students who thought they received adequate hygiene education at school and in classes (Table 4).

It was found that the student's grade, mother's education level, mother's employment status, education status about genital hygiene, and frequency of changing underwear did not affect the use of materials in genital hygiene (p>0.05), while the place of residence and the people they lived with affected the use of materials (p<0.05, (Table 3).

It was found that students living in the city center or district and students living with their parents used materials in the genital area cleaning above the expected values, and there was a significant difference between the groups (p=.001, p=.002;

Table 5 Comparison of the Relationship of Descriptive Characteristics with the Presence of Materials Used in Genital Area Cleaning (N: 194)

Descriptive Characteristics		Presence of material used for cleaning the genital area		
		Using n()μ	Not Using n()μ	χ^2 p
Grade	9th grade	48 (47.1)	3(3.9)	3.660□ .301
	10th grade	**78(75.7)**	**4(6.3)**	
	11th grade	**40(42.4)**	**6(3.6)**	
	12th grade	13(13.8)	2(1.2)	
Mother's education level	Illiterate	5(5.5)	1(0.5)	**2.031□ .730**
	Can read and write	3(2.8)	0(0.2)	
	Primary education	125(26)	12(10.6)	
	High School	44(42)	2(3.6)	
	University and above	2(1.8)	**0(0.2)**	
Place of residence	City Center	**7(6.5)**	0(5)	**14.335□ .001****
	District	132(126.4)	5(10.6)	
	Village	**40 (46.1)**	**10(3.9)**	
Who do you live with	Together with mom and dad	160(157.8)	11(13.2)	**12.351□ .002****
	Only with mother or only with father	**8(11.1)**	**4(0.9)**	
	Other	11(10.1)	0(0.9)	
Mother's employment status	Working	77(74.7)	4(6.3)	1.521□ .217
	Not working	**102(104.3)**	**11(8.7)**	
Receiving information about genital care and hygiene	Receiving information	57(58.1)	6(4.9)	.420□ .517
	Not receiving information	**122(120.9)**	**9(10.1)**	
Frequency of changing underwear	I do not agree at all	**3(2.8)**	**0(0.2)**	3.051□ .549
	Disagree	**12(12.0)**	**1(1.0)**	
	Undecided	**22(23.1)**	**3(1.9)**	
	I agree.	**72(69.2)**	**3(5.8)**	
	Completely Agree	**70(72.0)**	**8(6.0)**	

μThe values given in brackets are expected values. □ Pearson Chi-Square, #Fisher's Exact test ** p<.001

p<0.05, respectively). It was observed that students living in the city center or district had higher rates of using materials in genital area cleaning than students living in the village, and students living with their parents had higher rates of using materials in genital area cleaning than those living with a single parent or other family members.

It was found that there was no statistically significant difference between the student's grade, mother's education level, place of residence, cohabitant, mother's employment status, receiving education about genital hygiene, and frequency of changing underwear and experiencing genital infection (p=.673, p=.425, p=.388, p=.223, p=.144, p=.679, p=.774; p<0.05, respectively) (Table 5).

Discussion

It was found that nearly half of student's mothers (41.8%) and all of their fathers (88.1%) were employed. According to Türkiye Demographic and Health Survey (TDHS) 2018 data, it was determined that 32% of married women aged 15-49 and 94% of their husbands worked in the last 1 year before the study [11]. When the findings obtained from the study are compared with the TDHS, it is seen that the employment status of women is slightly higher, and that of men is somewhat lower. This is thought to be due to the higher level of education and the average age at marriage in the western part of the country and the encouragement of women to start working before this period.

Parents are thought to play a role in teaching genital hygiene habits from childhood, particularly concerning the mother's awareness and education level [12]. For this reason, mothers have essential duties in gaining hygiene habits starting from childhood [13]. It was observed that the education level of the mothers of 70.6% and the fathers of 59.8% of the students in the study was primary education; 67.5% did not receive information about genital care and hygiene, and 66.5% received information only from their mothers (Tables 1 and 2). In the literature, it is reported that women received genital hygiene education in a wide range of 40.1%-91.9%. In addition, in this study, it was also reported that 51.5% of those who received education received it from healthcare personnel [14]. In the literature, a study also shows that almost all women have not received training on genital hygiene before [15]. Another study revealed that the most important person who provided education about genital and menstrual hygiene was their mother [16]. Considering social roles and beliefs, mothers are generally seen as responsible for child care, hygiene, and education issues. In parallel with the literature [13, 16], it was observed in this study that mothers gave more information to children about genital hygiene and care, and it is thought that increasing education and information on genital hygiene will benefit both mothers and girls who are thought to educate them.

Since keeping the genital area moist will create a suitable environment for the growth of microorganisms, it is recommended to dry the genital area with soft and perfume-free toilet paper from front to back at once after washing with water [14,17-20]. It is thought that providing genital hygiene after using the toilet only with toilet paper without using water is not sufficient for cleaning the genital area and increases the likelihood of genital infection [21]. When the distribution of the student's answers to

the questions about genital care and hygiene was analyzed, it was determined that almost all (92.3%) used some kind of material for genital hygiene cleaning. When the hygiene materials used by the students were examined, it was seen that shower gel, wax, soap, water only, depilatory cream, pads, wipes, napkins, and razors were the most common. Serhatlıoglu and Yilmaz also reported that soap, washing gel, foam, wet wipes, deodorant, antiseptic solution, moisturizer, depilatory cream, pads, and toilet papers were among the products used in genital hygiene interventions [22]. In the studies in the literature, it has been reported that the rates of the pad, wax, razor, water only, soap or water, and toilet paper use are high, while the use of shower gel is lower [1,3-5,12-17,19,20,23-34]. When the findings of the study are compared with the literature, it's seen that shower gel, wax/razor blade, soap and pads are included in genital hygiene cleaning, although the order is different.

It is recommended that women take a standing shower, especially during menstruation, to eliminate possible foul odors, alleviate pelvic discomfort, and relax the woman. It is stated that showering while sitting may increase the risk of genital infection due to dirty water accumulating in the genital area [23,25]. In this study, it was found that almost all of the students (91.2%) took a standing shower during menstrual bleeding, and the majority of them (88.7%) had never experienced genital infections. Previous studies have also reported high rates of standing showering during menstruation [1, 19, 20, 23]. It is stated that urogenital infections are the leading cause of hospitalization in reproductive health [14]. Unsal (2010) reported that 9.1% of the students had previously experienced genital infections. The results of the study were found to be compatible with the literature. As it is known, bathing is a part of hygiene behaviors and helps to remove sweat, dead cells, oil, and microorganisms from the skin [20]. Showering while standing also prevents genital infections. The fact that the students in the study attached importance to vaginal hygiene and had a high rate of standing showering may have led to a lower likelihood of genital infections.

In the study, it was observed that the majority of the students (79.9%) thought that there was inadequate education about hygiene at school or in classes, and (86.6%) thought that there were not enough facilities at school to ensure menstrual hygiene. In a study conducted by Unsal (2010) with university students, it was found that the majority of students (90.4%) wanted to receive information about genital hygiene from health personnel [16]. When the study results are compared with the literature, it suggests that students are not given adequate education about hygiene in schools. It is thought that it would be beneficial to create information and training programs in hospitals, health institutions, or schools for individuals who want the correct information about genital hygiene. In addition, adding information about hygiene to the curriculum of both pre-service teachers and all educational institutions affiliated with the Ministry of National Education will be beneficial in raising public awareness and reducing infections.

It was found that the mean scores of the students who participated in the study from the Genital Hygiene Behaviors Scale were higher than the mean value (86.88±11.6 points from the overall Genital Hygiene Behaviors Scale; 44.60±7.1 points from the General Hygiene Habits Subscale; 32.23±4.6 points from the Menstrual Hygiene Subscale; and 10.05±2.8 points from the Abnormal Finding Awareness Subscale) and their genital hygiene behaviors were positive. In many studies involving different age groups in the literature, the mean scores of the Genital Hygiene Behaviors Scale were found to be between 68.63±4.83 and 95.25±8.57 points [3, 20, 33, 35]. In studies conducted with adolescent women, the mean scores of the Genital Hygiene Behaviors Scale were 85.3±10.1 and 79.28±6.80 [36, 37]. In studies conducted with students studying in the field of health, it was found that the mean score of general hygiene habits of the Genital Hygiene Behaviors Scale was higher than other students, but the mean scores of menstrual hygiene habits and abnormal finding awareness were similar [12, 20, 33, 38]. Our study result is consistent with other studies. In addition, the fact that the general hygiene scores of students studying health are higher than the others shows that it is directly proportional to their education. These positive hygiene behaviors are thought to be due to increased education levels, ease of access to hygienic products, technological developments, and increased use.

It was observed that the student's grade, school, and place of residence did not affect their genital hygiene behaviors. Still, the student's general and menstrual hygiene habits were negatively affected as their mothers' education level decreased. Menstrual hygiene habits were negatively affected as the education level of their fathers decreased. Looking at the studies conducted in the literature in this field, it was found that the General Hygiene Habits and menstrual hygiene scoring of adolescent female students with high maternal education level was higher than the General Hygiene Habits scoring of adolescent female students with low maternal education level [32, 37]. In many studies, it is also stated that genital hygiene behaviors are not affected by socio-demographic parameters [2, 12, 36].

It was found that 70.6% of the participants' family income was equal to their expenses, and it was determined that the student's general hygiene and menstrual hygiene habits increased positively as the income level of the families increased. As the income status increases, the higher likelihood of meeting the needs in terms of providing hygienic materials, using better quality products, training, and service procurement may support students to manage general hygiene and genital hygiene more healthily.

It was observed that the majority of the students (88.1%) lived with their parents. It was found that genital hygiene behaviors and menstrual hygiene of the students living with one of their parents were more positive than the others. This result may be due to the increased sense of responsibility attributed to a single parent or because the other parent may react to the parent who has custody in case of any illness in the child due to inadequate care and may even use this situation against them.

It was found that the students' status of receiving information about genital care and hygiene, information sources, the type of material used for cleaning the genital area, the kind of bathing during menstruation, the status of experiencing genital tract infection, and the status of thinking that there were adequate opportunities to provide menstrual hygiene at school did not affect general and menstrual hygiene behaviors and awareness of abnormal findings. It was observed that the genital hygiene behaviors, general hygiene habits, and abnormal finding awareness of the students who thought that the education at school was sufficient to provide menstrual hygiene were more positive than the others. To ensure menstrual hygiene, schools should have gender-based toilets; all toilets should be usable, bright, and clean; toilet doors should be lockable; there should be a trash bin and toilet paper in the bathroom; flushing and hand washing faucets should be in working order, water, soap, and paper towels should be sufficient to meet the needs. In addition, there should be posters prepared by the Ministry of Health about proper hand washing in the toilets, and a school health nurse should be on duty in schools. In cases where these conditions are not met, it is shown in the study that students in their menstrual

period do not want to go to school because they do not feel comfortable, cannot manage hygienic practices effectively in this process, and their absenteeism increases [32]. In all schools within the scope of the sample, it was observed that the facilities other than the school health nurse were complete. The availability of adequate facilities supports more positive genital hygiene behaviors and general hygiene habits. In order to further increase this favorable situation, sanitary pad vending machines can be added to schools to meet the urgent need for hygienic pads that may occur due to irregular menstruation bleeding, which can be seen more frequently, especially in adolescence.

No correlation was found between the students' grades, mother's education level, mother's employment status, education about genital hygiene, and frequency of changing underwear and using preferred materials for genital hygiene. It was found that students living in the city center and district had higher rates of using materials for genital hygiene than students living in the village. This is thought to be related to the opportunities in the settlements.

It was observed that the student's experience of genital infection was not affected by class, mother's education, place of residence, cohabitant, mother's employment status, education about genital hygiene, and frequency of changing underwear. Individuals may have difficulty meeting their hygienic needs during the menstrual cycle's first years. As the education level of mothers, who are thought to be responsible for the education of most of them, increases, correct guidance can be given. Considering where individuals live, access to and provision of hygienic facilities also becomes more accessible. Receiving education about genital hygiene also positively affects genital health. Considering all these, it is expected that the likelihood of genital infection will decrease. However, the results of the study showed that these were ineffective. Apart from these, it is reported that changing underwear daily, if possible, is essential in preventing infections. It is also stated that the frequency of changing underwear is negatively correlated with vaginal infection [1, 29]. In a study parallel to our study, contrary to the information in the literature, no relationship between the frequency of changing underwear and the frequency of genital infections was shown [29].

Conclusıon

As a result of the study conducted to evaluate the genital hygiene management of female secondary school students, it was found that more than half of the students did not receive information about genital care and hygiene; they thought that the education on hygiene at school and the facilities available to ensure hygiene were insufficient, almost all of them used materials for cleaning the genital area, they showered standing up during menstrual bleeding, the majority of them had never experienced genital infection, and their genital hygiene behaviors were positive. It was found that hygiene behaviors decreased as maternal and paternal education decreased; living with a single parent, thinking that they had received adequate education on hygiene, and increasing income level increased hygiene behaviors. It was found that the place where the students lived and the people they lived with affected the use of materials in genital hygiene cleaning.

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Aminotransferases activity on additional therapy in rheumatoid arthritis patients with liver disease

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Abstract

Aim. Investigate the effect of additional therapy of atorvastatin, essential phospholipids and their combination on activity of aminotransferases in RA patients with NAFLD.

Materials and Methods. We investigated 126 RA patients and 30 in control. 77 RA patients with NAFLD were divided into three groups. I: 25 RA patients received 10 mg of atorvastatin per day. II: 26 RA patients received essential phospholipids 1800 mg per day. III: 26 RA patients received essential phospholipids 1800 mg per day and atorvastatin 10 mg per day for 6 months.

The results. In the I group, a transient increase in ALT and AST activity was observed to 35.11±3.501 U/l and 30.51±2.19 U/l, respectively, and a spontaneous decrease in elevated transaminases was recorded after 6 months of atorvastatin use. In the II group, a decrease in ALT by 25.6% was observed compared to the indicators before treatment, and they remained unchanged even after 6 months. After 3 months of complex use of atorvastatin and essential phospholipids, ALT activity decreased by 33.8% and AST decreased by 8.2%, which was not observed in RA patients with NAFLD of groups I and II.

Conclusions. Use essential phospholipids 600 mg three times a day and atorvastatin 10 mg per day for 6 months in addition to antirheumatic therapy in RA patients with NAFLD allows to avoid a transient increase in aminotransferases, reduce the severity of hepatotoxic reactions, and avoid stopping or canceling antirheumatic therapy.

Keywords: rheumatoid arthritis, nonalcoholic fatty liver disease, aminotransferases, atorvastatin, essential phospholipids.

Introduction

In recent years, the development of nonalcoholic fatty liver disease (NAFLD) in patients with rheumatoid arthritis (RA). RA patients deserve more and more attention since fatty infiltration of the liver of varying intensity is observed in patients [1-2]. Most often, NAFLD develops in RA patients with high clinical and immunological activity of the disease [3]. Vassiliadis E. et al., showed that in the liver of RA patients, structural changes are observed, on which the functioning of this organ directly depends, namely: granular and fatty dystrophy, deposition of amyloid masses, less often - annular cirrhosis and necrosis of hepatocytes. Similar changes were found in the liver tissue of RA patients by other researchers [1,4]. Moreover, Radovanovic-Dinic B. et al., demonstrated a correlation between structural and functional liver disorders and the activity of the rheumatoid process [5]. According to a meta-analysis, 1 in 3 patients with RA had NAFLD, which is comparable to the overall prevalence in the general population [6].

The analysis of scientific information showed that the drugs used in RA – nonsteroidal anti-inflammatory drugs (NSAIDs) and the gold standard of treatment – methotrexate can contribute to liver damage with a high probability. Methotrexate can cause an increase in the activity of liver enzymes, the development of fibrosis and cirrhosis of the liver with long-term treatment [7-10]. However, data on the frequency of development and severity of liver fibrosis and cirrhosis when using antirheumatic drugs are ambiguous.

The clinical data, as well as a high percentage of changes in functional tests of the liver in RA patients, in the absence of a history of liver pathology, may indicate the benefit of the development of steatosis in patients. Currently, there is no specific biochemical marker that can confirm the diagnosis of NAFLD or help differentiate steatosis, non-alcoholic steatohepatitis (NASH) and liver cirrhosis [11-13]. Despite the fact that more than 50% of patients with NAFLD have no complaints, however, they have an increase in the size of the liver and a slight increase in the level of transaminases (2-4 times the upper limit of normal). The cause of liver dysfunction is autoimmune processes on the one hand, and the influence of drugs on the other. Hepatotoxic reactions that occur during the use of RA basic therapy depend on the duration of the disease, the timing of administration and the dose of drugs [14].

Thus, the problem of early diagnosis of NAFLD in RA while ensuring a minimum of negative effects on the body is extremely relevant both from the point of view of scientific and practical medicine.

Materials and methods

The study of laboratory biochemical indicators of blood, which can indicate liver damage, was conducted in a group of RA patients and a control group, compared by age and gender.

Were investigated 126 RA patients who had the following inclusion criteria: had written patient consent to participate in the study; female and male patients were aged 20 to 55 years old; the diagnosis of RA was established according to the criteria of ARA, 1987.

The control group consisted of 30 patients without RA who had the following inclusion criteria: had written patient consent to participate in the study; female and male persons were aged 20 to 55 years old; absence of any autoimmune pathology, inflammatory conditions and diseases; absence of any chronic diseases in the active phase.

The main data on the clinical and demographic characteristics of RA patients and the control group are shown in Table 1.

During the laboratory biochemical examination of blood, the following laboratory syndromes were studied: cytolytic, mesenchymal-inflammatory and cholestatic. To study the cytolytic syndrome, the blood serum level was studied - alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (GGT), the de Ritis index was determined; mesenchymal-inflammatory – total protein, thymol test, cholestatic – total, direct and indirect bilirubin, alkaline phosphatase (ALP).

Table 1 Clinical and demographic characteristics of RA patients and control group individuals

Indicator	Distribution feature	RA patients (n=126)		Control group (n=30)	
		n	%	n	%
Gender	Women	102	80.95	25	83.33
	Men	24	19.05	5	16.67
Age	Young	53	42.06	13	43.33
	Average	73	57.94	17	56.67
Grade of RA activity	I, DAS28≤3.2	7	5.56	-	-
	II, 3.2<DAS28≤5.1	79	62.7	-	-
		40	31.75	-	-

According to the patient selection criteria, RA patients and persons of the control group who had an increase in the level of ALT and AST three times or more from the upper limit of normal were not included in the study. All RA patients included in the study and individuals of the control group had negative results in the examination of markers of hepatitis B (HBsAg, AB-HBcor), hepatitis C (HCV, AB-HCV) and markers of autoimmune hepatitis (ANA - antinuclear (antinuclear) antibodies).

Laboratory biochemical research was carried out on an OLYMPUS AU-400 automatic biochemical analyzer (Japan) using "Beckman Counter" kits (USA) according to the manufacturer's method. For the study, venous blood was collected in the morning, on an empty stomach, from the elbow vein, using disposable sterile material.

Based on the results of a comprehensive clinical, laboratory, and instrumental examination of 126 patients with RA a diagnosis of NAFLD was established in 77 patients with RA.

All patients with RA and NAFLD had a proatherogenic serum lipid profile, which was expressed by a reduced level of HDL-C, a high level of TG, LDL-C, and LDL-C. Presumably, the accumulation of fat in the liver can be an independent factor of dyslipidemia and indicates the possible presence of a direct pathogenetic chain: liver steatosis - dyslipidemia - atherosclerosis. Changes in the lipid profile in blood serum may indicate metabolic disorders, changes in the quantitative and qualitative composition of lipids in the liver, and atherogenic dyslipidemia in patients with RA and NAFLD, in turn, is the most important risk factor for the development and progression of cardiovascular pathology.

For all patients with RA, dyslipidemia and NAFLD were prescribed additional therapy using atorvastatin, essential phospholipids, and their combination.

For dyslipidemia treatment in RA patients with NAFLD, we chose atorvastatin, as a representative of the highly effective class of drugs that inhibit HMG-CoA (3-hydroxy-3-methylglutarylcoenzyme A) reductase and is one of the most studied statins. In the TARA study, 2005 and meta-analysis, 2023, many pleiotropic effects of the use of atorvastatin in RA patients were shown, such as a decrease in RA activity by Disease Activity Score in 28 Joints (DAS28), a decrease in tenderness and swelling of the joints, as well as a decrease in the level of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6).

77 RA patients with NAFLD were divided into three studied treatment groups. All three groups were comparable in terms of age, gender, duration of RA disease, grade of RA activity and grade of fatty infiltration of the liver according to ultrasonography.

The first group consisted of 25 RA patients who received antirheumatic therapy for RA and atorvastatin in a daily dose of 10 mg in the evening, regardless of food intake, for 6 months.

The second group consisted of 26 RA patients who received antirheumatic RA therapy and essential phospholipids at a dose of 600 mg (two capsules) three times a day for 6 months.

The third group consisted of 26 RA patients who, in addition to RA antirheumatic therapy, received essential phospholipids at a dose of 600 mg (two capsules) three times a day and atorvastatin at a daily dose of 10 mg for 6 months.

Control of the effectiveness of the use of essential phospholipids, atorvastatin and their combination were carried out 3 and 6 months after the start of treatment.

The analysis and processing of statistical data of clinical studies was carried out on a personal computer using the STATISTICA 10.0 StatSoft for Windows and MS Excel XP application program package. Using the sampling method, the following were determined: average value, error of the average value and standard deviation. The sample parameters given in the tables of the article have the following designations: M - the average value, m - the error of the average value, SD - the standard deviation, and n - the volume of the analyzed group. With the help of parametric methods, in the case of a normal distribution of signs for unrelated and related groups, the Student's t-test and Fisher's exact test were used, in the case when one of the indicators in the group is less than 5. The level of significance was considered critical at $p<0.05$. The following designations are given in the tables of the article: p – the level of significance reached.

Results

The results of the conducted studies showed that the grade of activity has a small effect on the changes in the enzymatic activities of ALT and AST in blood serum. Thus, in patients with the 1st grade of activity, the enzymatic activity of ALT and AST is 1.3 and 1.2 times higher than that of the control group, respectively. However, as the disease progresses, there is an increase in the activity of transaminases in the blood serum, with the maximum values in patients with the III grade of RA activity (Figure 1).

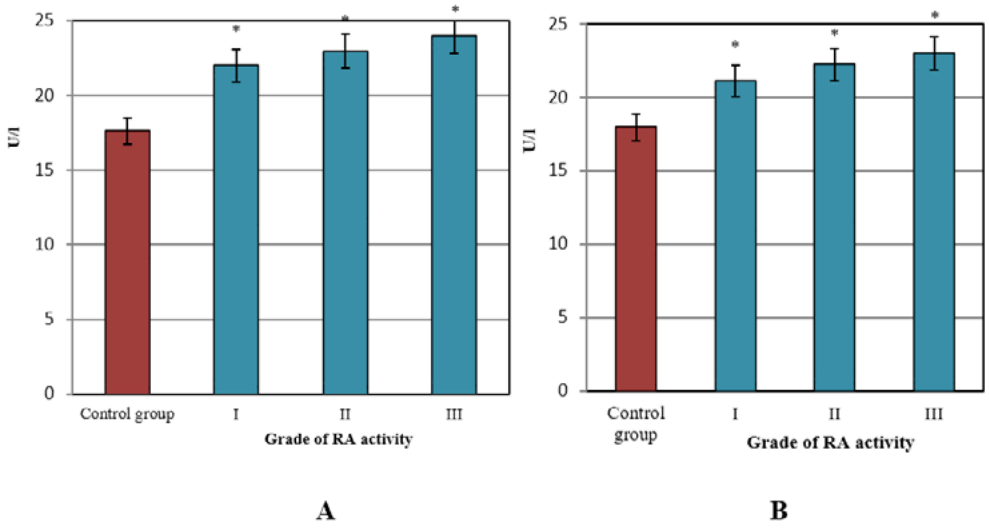

Figure 1 – Alanine aminotransferase (A) and aspartate aminotransferase (B) activity in blood serum of rheumatoid arthritis patients and the control group

* – statistically significant difference compared to the indicators of the control group, $p<0.05$.

Table 2

Dependence of indicators of cytolytic, cholestatic and mesenchymal-inflammatory syndromes in blood serum on the grade of rheumatoid arthritis activity, M±SD

Indicator	Grade of disease activity			Control group (n=30)
	I (n=7)	II (n=79)	III (n=40)	
Indicators of cytolytic syndrome				
LDH, U/l	173.57±6.07	177.80±1.54	178.35±2.24	174.20±1.8
Indicators of cholestatic syndrome				
Total bilirubin, mmol/l	7.03±0.28	6.95±0.09	6.87±0.13	7.64±0.26
direct bilirubin, mmol/l	1.21±0.04*	1.09±0.02*	1.09±0.02*	0.96±0.01
indirect bilirubin, mmol/l	5.81±0.27	5.86±0.09	5.78±0.12	6.68±0.26
ALP, U/l	67.57±5.15*	74.73±1.43*	74.28±2.21*	51.10±0.84
GGT, U/l	26.00±0.85	26.53±0.21	26.58±034	27.83±0.70
Indicators of mesenchymal inflammatory syndrome				
Total protein, g/l	72.00±0.85	69.89±0.24	69.68±0.31	71.23±0.66
Albumin, g/l	41.43±0.65*	41.99±0.15*	42.05±0.20*	33.07±0.42
Thymol test, units	2.80±0.16*	3.11±0.05*	3.35±0.09*	2.43±0.04

* – statistically significant difference compared to the indicators of the control group, $p<0.05$.

Table 2 shows the results of a laboratory study of indicators of cytolytic, cholestatic and mesenchymal-inflammatory syndromes in blood serum in the control group and in RA patients and their dependence on the grade of RA activity.

The next task of our study was to investigate the effect of additional therapy using atorvastatin, essential phospholipids and their combination on the activity of aminotransferases in 77 RA patients with NAFLD.

No differences between the groups were found when evaluating the initial enzymatic activities of ALT and AST in blood serum, which proved their comparability (Table 3).

The analysis of the results of RA patients with NAFLD of the I group showed that after three months of atorvastatin use, the enzymatic activities of ALT and AST in blood serum increased to 35.11±3.50 U/l and 30.51±2.19 U/l, respectively (Table. 3). However, after 6 months of atorvastatin use, there was a spontaneous reduction of elevated transaminases in patients (Table 3).

As for the introduction of essential phospholipids in patients of the II group, already 3 months after their use, a decrease in alanine aminotransferase activity by 25.6% was observed compared to the indicators observed before treatment, ($p<0.05$). The indicators remained at the same level 6 months after the start of the use of essential phospholipids (Table 3). The values of the de Ritis index at the level of 1.03±0.06 - after 3 months and at the level of 1.02±0.10 - after 6 months of the use of essential phospholipids testify to their

Table 3

Enzymatic activity of aminotransferases in blood serum of rheumatoid arthritis patients under the conditions of use of atorvastatin and essential phospholipids, M±m

Term	Treatment indicator		
	ALT, U/l	AST, U/l	de Ritis index
I group (n=25)			
Before treatment	29.72±2.58	24.63±1.93	0.82±0.01
After 3 months	35.11±3.50*	30.51±2.19*	0.87±0.05
After 6 months	26.94±3.93#	26.34±4.09 #	0.98±0.05*,#
II group (n=26)			
Before treatment	28.69±1.83	23.64±3.12	0.82±0.07
After 3 months	21.34±1.12*	22.01±4.03	1.03±0.06*
After 6 months	21.27±2.29*	21.79±3.92	1.02±0.10*
III group (n=25)			
Before treatment	28.71±2.53	23.24±2.10	0.81±0.09
After 3 months	19.01±1.92*	21.34±1.83	1.12±0.07*
After 6 months	17.09±1.25*,#	19.88±1.97*	1.16±0.13*,#

* – statistically significant difference compared to indicators characteristic of treatment, p<0.05; # – statistically significant difference compared to the indicators observed after 3 months of treatment, p<0.05.

protective effect in the treatment of RA patients with NAFLD (Table 3).

As can be seen from Table 3, the most pronounced positive result in the form of the absence of the formation of cytolysis syndrome and faster and more significant normalization of ALT and AST indicators, when comparing the data of the I, II and III comparison groups, was achieved with the simultaneous use of atorvastatin and essential phospholipids. After 3 months of complex use of atorvastatin and essential phospholipids, ALT activity decreased by 33.8% and AST decreased by 8.2%, which was not observed in RA patients with NAFLD of groups I and II.

Discussion

ALT and ACT are considered the most sensitive and specific indicators of hepatocellular damage. Since ALT and AST belong to intracellular enzymes, an increase in their activity in blood serum indicates hepatocyte damage and inflammatory processes in the liver. With deeper hepatocellular damage, an increase in the activity of the mitochondrial isoforms of the studied transaminases is observed in the blood serum, which is due to the damage to the mitochondria [15]. Probably, the metabolic processes that occur in the body of RA patients lead to destructive changes in the liver, as a result of which ALT and AST enter the bloodstream [16]. However, AST in the body is localized not only in the liver but also in the heart, so AST hyperfermentemia may be associated with damage to the liver or heart muscle as a result of cell cytolysis. To identify the origin of hyperenzymatemia of transaminases, the AST/ALT ratio (de Ritis index) is determined, the increase of which indicates a violation of the cardiovascular system, including damage to the myocardium. The de Ritis index value below 1.0 indicates liver damage [17].

Although the indicators of transaminase activities were within the permissible reference values (men less than 41 U/l; women less than 31 U/l), however, changes in the de Ritis index indicate deviations in the work of the hepatobiliary system. Analyzing another indicator of cytolytic syndrome – LDH, its value did not differ from normal indicators (Table 2).

Studies of biochemical markers of cholestatic syndrome showed that the level of enzymatic activity of ALP in blood serum increases compared to the indicators of a control group of individuals, and as RA activity progresses, the enzymatic activity of ALP in blood serum increases (Table 2). Hyperfermentemia of ALP may be associated with obstruction of the intrahepatic or extrahepatic bile ducts or inflammatory processes in the liver. It should be noted that the increase in alkaline phosphatase activity occurs against the background of unchanged indicators of total and indirect bilirubin, that is, before the level of bilirubin increases. Such changes in indicators are observed in liver diseases.

As for direct bilirubin, its value significantly exceeds the indicator of the control group of individuals at all stages of RA development (Table 2). However, in patients with the 1st grade of RA activity, its indicator is higher than in patients with the 2nd and 3rd grades of activity. The established fact indicates that as RA progresses in the liver, the conjugation of indirect bilirubin and its transition to direct bilirubin is disrupted. It is believed that hyperbilirubinemia due to the direct fraction has a hepatic origin and may be associated with impaired excretion of direct bilirubin due to cytolysis of hepatocytes. In addition, an increase in the concentration of bilirubin in the blood can indicate cholestasis or volumetric damage to the liver parenchyma. The level of GGT in the blood serum of RA patients did not statistically differ from the indicators found in the control group (Table 2).

The analysis of indicators of mesenchymal-inflammatory syndrome showed that against the background of a stable level of total protein in the blood serum of patients with the 1st grade of RA activity, the level of albumin increased by 1.3 times and the indicator of thymol test by 1.2 times compared to the indicators of the control group (table 2). As the grade of activity progresses, the values of these indicators increase and reach a maximum in patients with the III grade of RA activity. Thus, the highest level of thymol test was observed at the III grade of disease activity, 3.35±0.09 units, which is 1.2 times higher than at the first grade of disease activity, 2.80±0.16 units, and 1.4 times higher than in the control group – 2.43±0.04 units (p<0.05) (Table 2).

An increase in the level of albumin in the blood can be a consequence of slight dehydration of the body, which will increase the negative course of RA. So, for the normal functioning of the articular cartilage, a sufficient amount of water is needed, which is the basis of the intercellular substance and 75% of the weight of the cartilage tissue. There are no blood vessels in the cartilage, and all the nutrients in the chondrocytes come from the liquid environment of the extracellular matrix, which consists mainly of water. Dehydrated cartilage and joints are gradually destroyed, and in the later stages of arthritis, the process becomes irreversible. At the same time, elevated values of the thymol test indicate an increase in the concentration of α-, β- and γ-globulins and lipoproteins in the blood, which is most often observed in liver diseases.

Therefore, as the grade of RA activity increases, there is a violation of the functioning of the organs of the liver, which is expressed by a violation of the synthetic and, possibly, detoxification function of the liver and the excretory function of the gallbladder. However, since the values of the studied indicators are within the permissible norm, it is difficult to say about violations on the part of hepatobiliary system based only on laboratory biochemical indicators. Therefore, only a comparison of the complaints of RA patients with the data of clinical and

instrumental studies allows us to conclude that in patients with the development of RA, the work of the hepatobiliary system is disturbed, which is expressed by the development of NAFLD.

Therefore, under the conditions of use of atorvastatin, the increase in the level of ALT and AST is transient, since their activities returned to the initial level and even lower without the need to cancel statins. This is confirmed by many studies, the results of which showed the effectiveness and safety of the use of statins in the treatment of NAFLD [18-20].

The correcting ability of phospholipids on the functional state of the disease is obviously related to their amphiphilic properties, which can regulate the penetration of the cell skin. Thus, the use of phospholipids leads to the following hepatotropic effects: reduction of lipid peroxidation processes, restoration of enzyme systems, normalization of protein metabolism, improvement of the metabolism of the disease [21-24]. This contributes to the restoration of plasma membrane cells and the regeneration of damaged cells [25-27].

Therefore, against the background of the liver protective action of essential phospholipids and the use of atorvastatin, antirheumatic therapy drugs do not show a pronounced hepatotoxic effect, as evidenced by a decrease in the activity of transaminases in blood serum.

Conclusion

1. The pathology of hepatobiliary system in RA patients occurs in 61.10% of patients and does not depend on age, duration of the disease, and activity of the inflammatory process.

2. Determining only laboratory biochemical indicators of hepatobiliary system work is not enough to assess the state of the liver and control the progression of liver damage. For a reliable determination of liver pathology, it is necessary to carry out a comprehensive assessment of the patient's complaints, clinical, laboratory and instrumental data.

3. Using the combination of atorvastatin and essential phospholipids helps to avoid the formation of cytolysis syndrome and decreases the activity of ALT by 33.8% and AST by 8.2%, compared to the use of atorvastatin alone.

4. In RA patients with NAFLD recommended to use of essential phospholipids in a dose of 600 mg three times a day and atorvastatin in a daily dose of 10 mg for 6 months in addition to antirheumatic therapy. This will allow for avoiding a transient increase in aminotransferases, reducing the severity of hepatotoxic reactions, to avoid stopping or cancelling the antirheumatic drug therapy.

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Nijmegen breakage syndrome – NBS: a rare clinical case in Kazakhstan

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Abstract

Nijmegen syndrome is a primary immunodeficiency characterized by chromosomal instability, microcephaly, physical retardation, specific disorders of the facial skeleton, as well as a predisposition to cancer. Most patients of Slavic origin have a homozygous mutation with the del5 founder effect in the NBS gene. The frequency of occurrence is 1:100000population. The highest frequency of carriage in the population of the del5 mutation in the NBS gene in the Czech Republic is 1:154, in Ukraine – 1:182, in Poland – 1:190. This pathology is presented in our clinical practice for the first time, and therefore we would like to provide data for a wide review.

Keywords: NBS, autosomal recessive disorder, primary immune deficiency, microcephaly.

Introduction

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive chromosomal disease characterized by a combined, persistent immunodeficiency condition, microcephaly and a tendency to malignant neoplasms [1]. In this case, there is a mutation in the NBN gene (early name NBS1). Gen NBN encodes nibrin, which is necessary for DNA epair and plays a critical role in all situations of double-stranded DNA synthesis. Nibrin, interacting with proteins MRE11 and RAD50, promotes the formation of a protein complex (MRN) that repairs DNA chain breaks [2,3].

As mentioned earlier, the disease manifests itself as microcephaly at birth, according to the literature without neurological disorders. The main symptoms of the disease appear with the age of the child. Children have growth retardation, frequent recurrent diseases against the background of an immunodeficiency condition, early ovarian disorders, a high risk of malignant neoplasms in childhood, more often hematological. The combined type of immunodeficiency condition (cellular, humoral) is a feature of this disease [4]. From the side of mental disorders, clinical symptoms are not very noticeable, despite microcephaly, but with the progression of the disease, cognitive impairment may occur [5].

It is known from historical data that NBS was first described in 1979 in a Dutch boy with growth and development retardation, microcephaly, IgA deficiency and chromosomal changes (chromosomes 7 and 14). The same symptoms were present in the deceased brother of this patient. In 1981, researchers from the University of Nijmegen in the Netherlands first described a new syndrome with chromosomal instability and named it Nijmegen chromosomal breakage syndrome (NBS) [6].

This syndrome is classified as rare, there are more than 150 known cases described in the scientific

literature with the identification of the NBN gene [7-10]. High prevalence of NBS among the population of Central and Eastern Europe (Czech Republic, Poland, Russia and Ukraine) [11,12]. NBS has also been reported in many other European countries [13-15], in South and North America, New Zealand and Morocco [16-18]. There are 3 known cases of NBS in Kazakhstan, in this article we will talk about the case of a child who was being treated in Corporate Fund “University Medical Center”.

An 8-year-old girl complained of cough, lag in physical development, lack of nasal conchae, facial skin lesions, purulent discharge from the nose and ears, pain, swelling in the left knee joint and diarrhea.

She has been ill since the age of 1.6 with manifestations of purulent otitis media, febrile fever, frequent streptococcal tonsillitis, stomatitis, recurrent respiratory infections. She received treatment with antibacterial drugs in the hospital, where some improvement was noted.

In 2 years, 8 months. is primary immunodeficiency, Nijmegen syndrome?, suspected for the first time. Recurrent oral aphthae, other specified anemia. She took normal human immunoglobulin, sulfasalazine, and metronidazole in treatment. There was a positive effect.

At the age of 4, during an examination at Corporate Fund "University Medical Center" the diagnosis was established: "Primaryimmunodeficiency of the humoral type. Delayed physical development, moderate pediatric malnutrition (Z-score -2.0 to -2.9). A contagious mollusk. Microcephaly (there is no data for delayed mental and motor development). Chronic bilateral otitis media. Chronic rhinopharyngitis in remission, bacilli-bearing. Pharyngomycosis. Anemia of mild severity. Recommendations were given.

The patient's condition worsens from 4 years 8 months, when recurrent stomatitis and an increase in body temperature began to bother him again. For the main disease, she received inpatient treatment: normal human immunoglobulin, antibacterial and antifungal therapy.

Before the age of 7, the child was repeatedly observed by many specialists, such as oncohematology, rheumatologists, immunologists, with the above complaints, frequent recurrent infections. The child was consulted by immunologists from Russia, Novosibirsk, where they established a new diagnosis: "Basal cell carcinoma. Secondary immunodeficiency. Protein-energy deficiency of the 2nd degree. Hypostatura".

At the age of 7 and 8 months the patient was consulted by doctors from Hadassah, Israel. Where a skin biopsy was performed twice. In the first coloring, an inflammatory process of the skin was revealed. Atypical cells (granulomatous inflammation and T-cell lymphoproliferative neoplasm) were detected for the second time. Conclusion of the molecular histological test dated 07/04/2023: does not confirm the possibility of a tumor process of lymphocytes. Sequencing of one eczema: the result is a pathogenic variant in the NBS gene according to the autosomal recessive type of inheritance of PID. Nijmegen syndrome.

Upon admission to the department, the child's condition is severe, due to the underlying disease, intoxication, joint syndrome, severe pediatric malnutrition (weight – 12 kg, height – 106 cm, BMI – 10.68 - Z-score -3.0 or greater).

Position: active. Phenotypically: characteristic features of appearance according to the type of "bird" face. The patient has a narrow face with a high forehead, corroding of the external nasal cavity, and a small lower jaw. Skin: pale in color, dry to the touch, there are foci of hyperemia on the face (Figure 1), scars, cracks, as well as the absence of an external nasal cavity (Figure 2). The subcutaneous fat layer is extremely poorly developed. Skin and joint system: swelling of the left knee joint, soreness, restriction of movement. The visible mucous membranes are pale pink, moist. Peripheral lymph nodes are enlarged to 2-3 cm in the cervical, submandibular and inguinal areas up to 1.5 cm (Figure 3).

Figure 1 – Foci of hyperemia on the face with destruction of the nasal cavity

Figure 2 – Photo of the child before and after the destruction of the nasal cavity

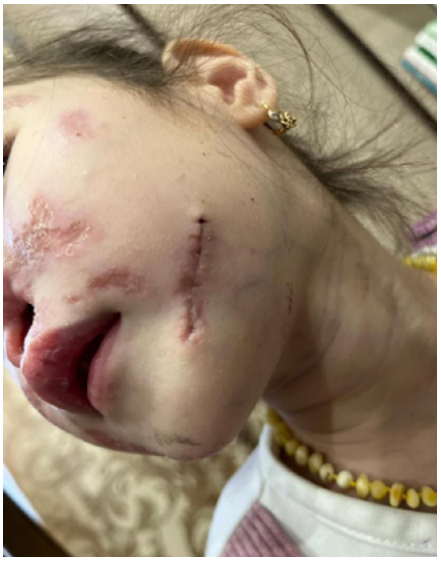

Figure 3 – The figure shows an increase in the cervical, submandibular lymph nodes, as well as a postoperative scar on the face

When examined according to immunophenotyping data, the child has an incomplete defect of the cellular and humoral links of immunity.

Immunophenotyping 10/10/2023: leukocyte count 9.76 10^9/L, lymphocyte count 27.22%, cd3- HLA-dr lymphocytes+ 7.23% (5.00 - 20.00), B-lymphocytes cd19+cd3- abs 0.17 x10^9/L (0.30 - 0.50), B-lymphocytes cd19+cd3- 6.41 % (12.00 - 22.00), mature cd3+cd19 T-lymphocytes- abs 2.08 x10^9/L (1.40 - 2.00), mature cd3+cd19 T-lymphocytes- 78.44% (66.00 - 76.00), NK cells cd3-cd16+/cd56+ abs 0.31 x10^9/L (0.10 - 1.33), NK cells cd3-cd16+/cd56+ 11.73% (4.00 - 26.00), immunoregulatory index (cd4+/cd8+) 0.75 (0.95 - 2.25). 10/10/2023 Compliment C3 1.39 g/l (0.90 - 1.80), Compliment C4 0.47 g/L (0.10 - 0.40), Immunoglobulin A 0.00 g/L (0.34 - 3.05), Immunoglobulin G 3.14 g/L (5.72 - 14.74), Immunoglobulin M 0.23 g/L (0.31 - 2.08) Immunochemical studies 11/10/2023 - TSH 4.82 mMu/ml (0.28 - 4.30), Prolactin 22.98 ng/ml (3.60 - 12.00), T4 free 16.28 pmol/L (12.50 - 21.50).

During hospitalization, the child was consulted by narrow specialists such as a phthisiologist (conclusion: there is no data for the tuberculosis process during the examination), an oncologist, since CT showed signs of polysegmental bilateral pneumonia with signs of atelectasis S5 of the right and S5, S8, S9 of the left lungs, with the presence of traction dilated bronchi in S5 of both lungs and deformity, bronchial dilation in the lower lobe of the left lung. Pronounced intrathoracic lymphadenopathy,

bilateral subclavian, axillary lymphadenopathy (lymphoma?). Further, to exclude the oncological process, a biopsy of the skin and lymph node was performed (conclusion: in the examined bone marrow sample, the population of cells with the immunophenotype: CD 117+/ CD34+ /CD33+/ Hla-DR+/ CD7-/ CD19-/CD10- is 0.63%; B lymphocytes are represented by regenerating cells bone marrow in the amount of 2,14%. Conclusion: Immunophenotypic data for acute leukemia have not been obtained. Myelogram (conclusion: No abnormal cells were found).

Histological examination of 1 block preparation of surgical biopsy material (IV category of complexity) from 20/10/23 were sent to Moscow, to the Dmitry Rogachev National Medical Research Center for Pediatric Hematology, Oncology and Immunology. Where was the conclusion received: The studied material shows signs of polymorphic lymphoproliferative disorder EBV+ in a patient with a congenital abnormality of the immune system. A picture of granulomatous lymphoproliferative disorder rich in CD8 lymphocytes in conditions of congenital abnormality of the immune system was revealed in the skin.

In the hospital, the child underwent immunoglobulin replacement therapy, antibacterial therapy, prevention of pneumocystis pneumonia (sulphanilamide group), and symptomatic therapy.

Discussion

Typical clinical manifestations of NBS are: microcephaly, severe and progressive (from birth or develops progressively in the first months after birth); characteristic facial skull: "bird-like" face (sloping forehead, decreased lower jaw, protruding middle part of the face with a large nose), mongoloid eye incision; skeletal disorders: clinodactyly 5th finger and/or partial syndactyly of the 2nd and the 3rd fingers, polydactyly is observed in half of the described patients; mental retardation in 60% of patients; stunting and delayed physical development; pigmented spots ("coffee with milk"); infectious and autoimmune pathology; predisposition to the development of malignant neoplasms; fibrosis and absence of thymus are also described.

In our clinical case, the patient has frequent recurrent bacterial nasopharyngitis, otitis media, less often bronchitis and pneumonia, phenotypically characteristic features of appearance according to the type of "bird" face. The patient has a narrow face with a high forehead, a small lower jaw, as a complication of repeated abscessing, corroding of the external nasal cavity. There is also a proven result of a genetic examination performed in July 2023. In Israel (see above in the article). Structural changes were also revealed in the MRI of the brain with contrast from October 2023 in the form of microcephaly, however, cognitive impairment was not detected in the psycho-emotional status corresponding to age. The complications of this case are lymphadenopathy and protein-energy malnutrition 3 grade. As a result of the examination, the diagnosis of lymphoma was excluded. Since the radical treatment for Nijmegen syndrome is HSCT, HLA typing was taken to find a donor. According to the results of HLA typing SSP, the patient's parents are not compatible. The result of the patient's HLA typing has been submitted to the international donor database. Currently, the child is at home, receiving human immunoglobulin G subcutaneously once a month on an outpatient basis.

Conclusion

Thus, dynamic monitoring of patients with NBS is mainly carried out by a pediatrician and an immunologist. A specific treatment method is hematopoietic stem cell transplantation and replacement intravenous administration of human immunoglobulin, which in many patients can reduce the frequency of infectious episodes. Patients need to undergo periodic medical examinations for early detection of cancer. Since Nijmegen syndrome is one of the types of chromosomal instability syndromes, it is necessary to use X-ray research methods in a limited way and replace them with other imaging diagnostic methods (ultrasound and nuclear magnetic resonance imaging) [6]. During the examination of this patient, a rare genetic anomaly was revealed in the Kazakh population in the form of Nijmegan syndrome, which had not been previously encountered. HSCT is recommended for this patient in the near future, as it reduces the risk of developing malignancy [19].

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A rare case of sclerosing encapsulating peritonitis secondary to tuberculosis

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Abstract

Sclerosing encapsulating peritonitis is a relatively rare, potentially life-threatening condition that causes intestinal loops to become encapsulated as a fibro-collagen cocoon. Despite advances in treatment, mortality is high. It shows vague clinical signs and is therefore difficult to diagnose clinically. Abdominal Contrast Enhanced CT (CECT) is an excellent modality for diagnosing the condition, for assessing its complications such as perforation, and for guiding the treatment approach to the condition. This case report highlights a rare case of sclerosing encapsulating peritonitis in a young adult secondary to tuberculosis. Although the most common secondary cause of SPE is peritoneal dialysis, consideration of tuberculosis as a cause of such a condition is very important especially in the Indian context.

Keywords: Sclerosing encapsulating peritonitis, CECT abdomen, tuberculosis.

Introduction

SEP is a chronic inflammatory disease that begins as low-grade peritonitis that progresses to sclerosis and membrane formation, eventually forming cocoons. Encapsulation takes place in the form of a membrane made of fibro-collagen [1]. Overall, SEP is more common in men [2]. There are two forms of SEP – primary and secondary. The primary type is generally idiopathic while secondary SEP can occur due to peritoneal dialysis, tuberculosis, sarcoidosis, cirrhosis [3]. The pathogenesis of SEP involves cytokines and fibroblasts in the formation of the fibro-collagen membrane.

Case presentation

A 22-year-old woman presented to the surgical department with abdominal distension and pain since the last 20 days and reduced stool since the last 10 days. She had a mild fever for 10 days. A general examination revealed pallor with a temperature of 100°F. A routine blood test (complete blood count) showed – increase in total leukocyte count, reduced hemoglobin, high ESR. Mantoux test was positive.

Abdominal ultrasound examination was recommended as subacute intestinal obstruction was suspected. Her ultrasound revealed a loculated fluid collection with intraperitoneal internal septations [Fig 1]. Visualized bowel loops were of normal caliber. To find out the cause, a diagnostic evaluation of ascitic fluid was performed. Ascitic fluid analysis revealed high ADA levels and leukocytosis.

She was further evaluated using CECT of the abdomen. CECT showed loculated septate ascites with clustering of small bowel loops toward the center of the abdominal cavity with a surrounding envelope with marked continuous enhancement [Fig 2 & Fig 3]. Several prominent peripherally enhancing necrotic mesenteric lymph nodes were noted.

Based on clinical, laboratory and radiological parameters, a diagnosis of SEP secondary to tuberculosis was made.

The patient was managed conservatively with recommended fluid intake, nutrition and started on anti-tubercular therapy. The patient showed an improvement in symptoms and general condition on conservative therapy. The patient was further advised for a follow up CECT scan abdomen after 6 months.

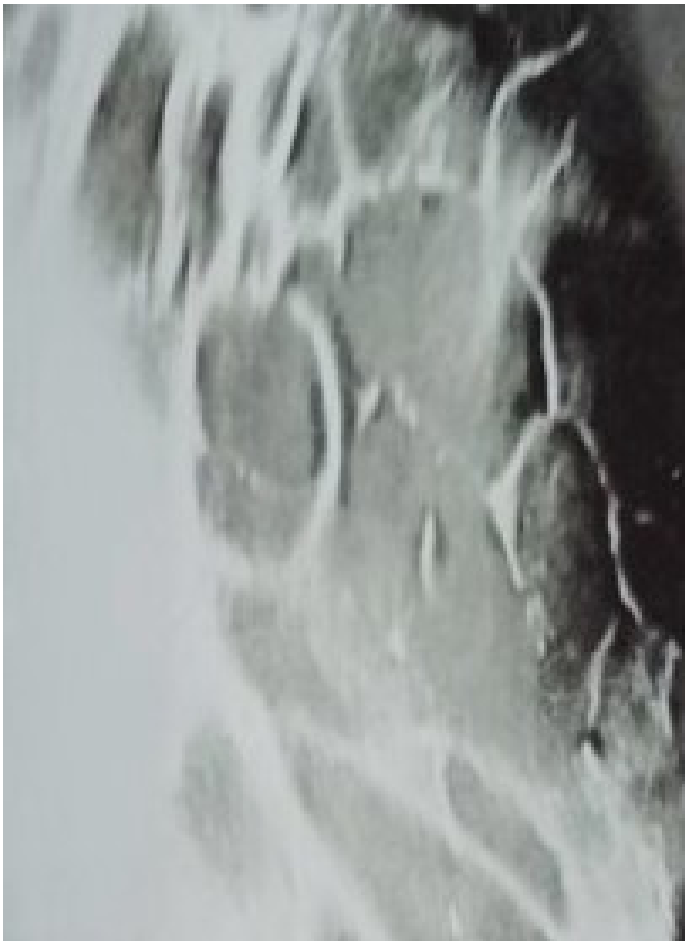

Figure 1 – Ultrasound abdomen showing loculated ascites with intraperitoneal strands

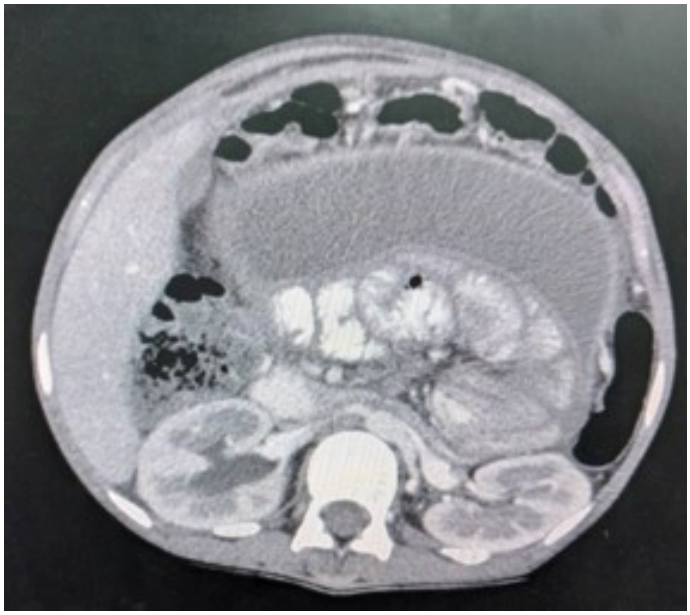

Figure 2 – Axial CECT abdomen showing loculated ascites with clustered bowel loops in the center surrounded by a membrane

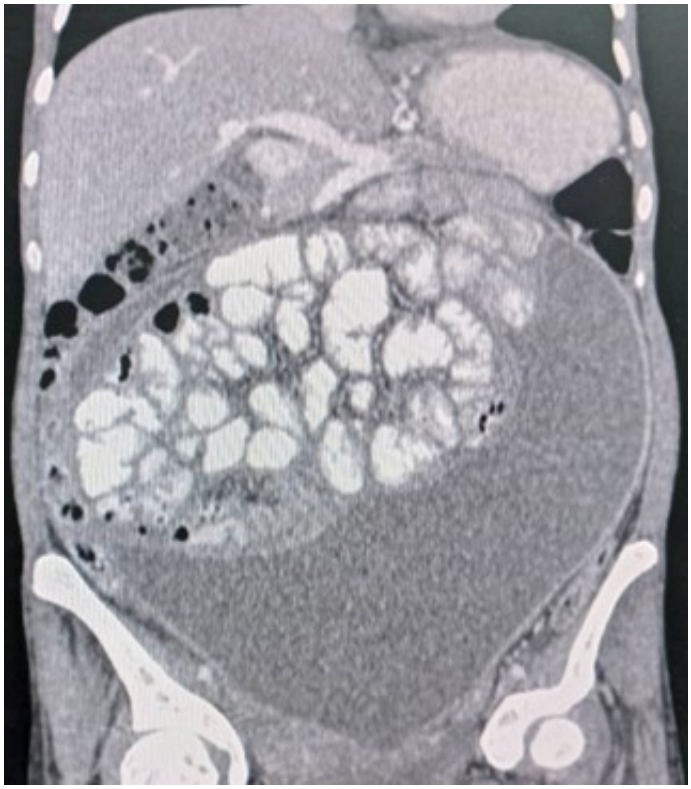

Figure 3 – Coronal CECT abdomen showing loculated ascites with clustered bowel loops in the center surrounded by a membrane

Discussion

SEP generally presents with signs of intestinal obstruction such as pain, nausea, vomiting, and inability to pass stool. The clinical picture is complex, making it difficult to diagnose. Clinicians generally rely on imaging for diagnosis as well as associated complications of the condition, such as perforation and peritonitis, which require immediate surgical intervention.

In terms of imaging, abdominal CECT is the best modality to diagnose the condition and its complications. The small intestine appears to cluster in the middle with a thick variably enhancing capsule [4]. Peritoneal thickening is somewhat

subjective. Other findings include loculated ascites, mesenteric stranding, peritoneal calcification [5]. The formation of complex ascites may indicate an underlying infection [5]. Extraluminal air indicates perforation. Intra-abdominal bleeding is also a feared complication [5].

Abdominal ultrasound may reveal ascites, clusters of intestinal loops with a surrounding membrane [6]. The "cauliflower sign" may be indicated by accumulated and adherent intestinal loops seen in the mid-abdomen during barium passage through the small intestine [7].

The treatment of this condition includes two options - conservative and surgical intervention. Conservative treatment includes decompression, nil orally and a special focus on maintaining the patient's nutrition [8]. Drugs such as tamoxifen, steroids, colchicine, azathioprine, and mycophenolic acid may be used [9]. The standard surgical approach involves excision of the membrane along with anastomosis, either with or without a protective enterostomy[1].

Conclusions

Despite advances in diagnosis and treatment, SEP secondary to tuberculosis, when symptomatic has a high mortality rate ranging between 50-60 percent [10]. The disease has a variable age distribution with unclear clinical symptoms. Diagnosis is largely dependent on CECT, which guides the approach to further management. Peritoneal carcinomatosis mimics SPE on CT, which is easily distinguished by a nodular or sheet pattern of peritoneal enhancement and the absence of a surrounding membrane. On the other hand, interbowel adhesions, omento-mesenteric stranding and necrotic nodes point to tuberculosis.

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