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GENETIC VARIANTS IN LIPID-ASSOCIATED GENES IN THE KAZAKHSTANI COHORT WITH ATHEROSCLEROSIS AND HYPERTRIGLYCERIDEMIA

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Abstract

Introduction. Cardiovascular diseases, including atherosclerosis (AS), are the leading cause of morbidity and mortality worldwide, including in Kazakhstan. Lipid metabolism disorders, in particular, hypertriglyceridemia, which is recognized as an independent risk factor, play an important role in the development of AS. Genetic features associated with genes regulating lipid and carbohydrate metabolism (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) have a significant impact on the formation of dyslipidemia and determine individual metabolic characteristics. Studying the prevalence and effects of these genetic variants in the Kazakh population is particularly important, given its underrepresentation in global genetic research.

Aim. The objective of this study was to study the frequency of genetic polymorphisms in genes involved in the regulation of lipid metabolism (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) in a group of Kazakhstani patients with hypertriglyceridemia and atherosclerosis. Additionally, we analyzed the relationship of the identified genetic variants with the biochemical parameters of the lipid profile.

Materials and methods. The study analyzed data from 402 patients with cardiovascular diseases, 144 of whom had hypertriglyceridemia. To identify the genetic determinants of lipid metabolism disorders, full-exome sequencing was performed with a focus analysis of the *GCKR*, *SLC22A5*, *LPL*, and *FLCN* genes. The identified genetic variants were annotated and classified according to the recommendations of ACMG/AMP. The association of genetic polymorphisms with lipid profile parameters in patients with AS was studied.

Results. Sequencing of the entire exome of patients with varying degrees of cardiovascular risk revealed genetic variations affecting triglyceride metabolism. Elevated triglyceride levels were reported in patients of all risk categories, with the highest frequency in very high-risk individuals (82 patients). Analysis of the lipid profile showed that total cholesterol was significantly higher in the high-risk group compared with the low-risk group (228.8±35.2 versus 207.8±30.3 mg/dl; p=0.0467). The level of HDL-C showed an inverse relationship with the level of risk, being the lowest in the very high-risk group (44.6±10.5 versus 50.1±9.9 mg/dl; p=0.0411). Although LDL and non-lipoprotein cholesterol did not show statistically significant differences, there was a tendency to increase them. Triglycerides also tended to increase, but without achieving statistical significance (p>0.05). There was a significant decrease in apolipoprotein A at high risk (p<0.0001). The distribution

of APOE genotypes (p.T388C) was similar in all risk groups, with a predominance of the TT genotype (≈58-67%) and a rare occurrence of the CC genotype (≤5.3%), without statistically significant differences (p>0.05).

Conclusions. The study did not reveal a statistically significant association between APOE (p.T388C) and GCKR genotypes with cardiovascular risk. Larger-scale studies are required, taking into account additional factors and an increased sample size.

Keywords: *atherosclerosis, hypertriglyceridemia, cardiovascular disease, APOE, GCKR.*

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Резюме

ГЕНЕТИЧЕСКИЕ ВАРИАНТЫ В ЛИПИД-АССОЦИИРОВАННЫХ ГЕНАХ В КАЗАХСТАНСКОЙ КОГОРТЕ ПАЦИЕНТОВ С АТЕРОСКЛЕРОЗОМ И ГИПЕРТРИГЛИЦЕРИДЕМИЕЙ

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Введение. Сердечно-сосудистые заболевания, в том числе атеросклероз (АС), являются основной причиной заболеваемости и смертности во всем мире, включая Казахстан. Важную роль в развитии АС играют нарушения липидного обмена, в частности, гипертриглицеридемия, которая признана самостоятельным фактором риска. Генетические особенности, связанные с генами, регулирующими метаболизм липидов и углеводов (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*), оказывают значительное влияние на формирование дислипидемий и определяют индивидуальные метаболические характеристики. Изучение распространенности и влияния этих генетических вариантов в казахстанской популяции особенно важно, учитывая ее ограниченное представительство в глобальных генетических исследованиях.

Целью данного исследования было изучить частоты встречаемости генетических полиморфизмов в генах, участвующих в регуляции липидного обмена (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*), в группе казахстанских пациентов с гипертриглицеридемией и атеросклерозом. Дополнительно мы анализировали взаимосвязь выявленных генетических вариантов с биохимическими параметрами липидного профиля.

Материал и методы. В рамках исследования были проанализированы данные 402 пациентов с сердечно-сосудистыми заболеваниями, из которых 144 имели гипертриглицеридемию. Для выявления генетических детерминант нарушений липидного обмена было выполнено полноэкзомное секвенирование с анализом генов *GCKR*, *SLC22A5*, *LPL* и *FLCN*. Выявленные генетические варианты были аннотированы и классифицированы в

соответствии с рекомендациями ACMG/AMP. Проведена оценка ассоциации генетических полиморфизмов с нарушениями липидного профиля в казахстанской популяции пациентов с сердечно-сосудистыми заболеваниями.

Результаты. Секвенирование полного экзома пациентов с различной степенью сердечно-сосудистого риска выявило генетические вариации в генах, влияющие на метаболизм триглицеридов. Повышенные уровни триглицеридов были зафиксированы у пациентов всех категорий риска, с наибольшей частотой у лиц с очень высоким риском (82 пациента). Анализ липидного профиля показал, что общий холестерин был статистически значимо выше в группе высокого риска по сравнению с низким (228,8±35,2 против 207,8±30,3 мг/дл; p=0,0467). Уровень ХС-ЛПВП демонстрировал обратную зависимость от уровня риска, будучи самым низким в группе очень высокого риска (44,6±10,5 против 50,1±9,9 мг/дл; p=0,0411). Хотя уровни ЛПНП не показали статистически значимых различий, наблюдалась тенденция к их увеличению. Триглицериды также имели тенденцию к росту, но без достижения статистической значимости (p>0,05). Было отмечено существенное снижение аполипопротеина А в группе высокого риска (p<0,0001). Распределение генотипов APOE (p.T388C) было схожим во всех группах риска, с преобладанием генотипа TT (≈58–67%) и редкой встречаемостью генотипа CC (≤5,3%), без статистически значимых различий (p>0,05).

Выводы. Исследование не выявило статистически значимой связи между генотипами APOE (p.T388C) и *GCKR* с сердечно-сосудистым риском. Требуются более масштабные исследования с учетом дополнительных факторов и увеличенным размером выборки.

Ключевые слова. *атеросклероз, гиперлипидемия, сердечно-сосудистое заболевание, APOE, GCKR*

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Түйіндеме

ГИПЕРТРИГЛИЦЕРИДЕМИЯ ЖӘНЕ АТЕРОСКЛЕРОЗЫ БАР ҚАЗАҚСТАНДЫҚ КОГОРТАДАҒЫ ЛИПИДТЕРМЕН БАЙЛАНЫСТЫ ГЕНДЕРДЕГІ ГЕНЕТИКАЛЫҚ НҰСҚАЛАР

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Кіріспе. Жүрек-қан тамырлары аурулары, оның ішінде атеросклероз (АС) бүкіл әлемде, соның ішінде Қазақстанда аурушаңдық пен өлімнің негізгі себебі болып табылады. Липидтер алмасуының бұзылуы, атап айтқанда, тәуелсіз қауіп факторы ретінде танылған гипертриглицеридемия АС дамуында маңызды рөл атқарады. Липидтер мен көмірсулардың метаболизмін реттейтін гендермен байланысты генетикалық ерекшеліктер (*GCKR*,

SLC22A5, *LPL*, *FLCN*, *LDLR*, *APOE*) дислипидемияның пайда болуына айтарлықтай әсер етеді және жеке метаболикалық сипаттамаларды анықтайды. Қазақстандық популяциядағы осы генетикалық нұсқалардың таралуы мен әсерін зерттеу оның жаһандық генетикалық зерттеулердегі шектеулі өкілдігін ескере отырып, ерекше маңызды.

Зерттеудің мақсаты. Бұл зерттеудің мақсаты липидтер алмасуын реттеуге қатысатын гендердегі (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*), гипертриглицеридемиясы және атеросклерозы бар қазақстандық пациенттер тобындағы генетикалық полиморфизмдердің пайда болу жиілігін зерттеу болды. Сонымен қатар, біз анықталған генетикалық нұсқалардың липидті профильдің биохимиялық параметрлерімен байланысын талдадық.

Зерттеудің әдістері. Зерттеу барысында жүрек-қан тамырлары аурулары бар 402 пациенттің деректері талданды, олардың 144 гипертриглицеридемия анықталды. Липидтер алмасуының бұзылуының генетикалық детерминанттарын анықтау үшін GCKR, SLC22A5, LPL және FLCN гендеріне бағытталған талдау толық экзом секвенилеу мәліметтерден жасалды. Анықталған генетикалық нұсқалар ACMG/AMP нұсқауларына сәйкес түсіндірілді және жіктелді. Жүрек-қан тамырлары аурулары бар пациенттердің липидті бейіні бұзылған генетикалық полиморфизмдер қауымдастығы бағаланды.

Зерттеудің нәтижелері. Жүрек-қан тамырлары қаупі әртүрлі пациенттердің бүкіл экзомның реттілігінің триглицеридтердің метаболизміне әсер ететін гендерде генетикалық вариацияларды анықтады. Триглицеридтердің жоғарылауы барлық қауіп санаттарындағы пациенттерде тіркелді, бұл өте жоғары қауіпті адамдарда ең жоғары жиілік (82 пациент). Липидті профильді талдау жалпы холестериннің төмен деңгеймен салыстырғанда жоғары қауіп тобында статистикалық тұрғыдан айтарлықтай жоғары екенін көрсетті (228,8±35,2 қарсы 207,8±30,3 мг/дл; p=0,0467). HDL HDL деңгейі қауіп деңгейіне кері байланысты көрсетті, бұл өте жоғары қауіп тобындағы ең төмен (44,6±10,5 қарсы 50,1±9,9 мг / дл; p=0,0411). LDL және липопротеиндік емес холестерин статистикалық маңызды айырмашылықтарды көрсетпесе де, олардың өсу тенденциясы байқалды. Триглицеридтер де өсуге бейім болды, бірақ статистикалық маңыздылыққа жете алмады (p>0,05). А аполипопротеинінің жоғары тәуекелмен айтарлықтай төмендеуі байқалды (p<0,0001). APOE генотиптерінің таралуы (P.T388C) барлық қауіп топтарында ұқсас болды, TT генотипінің басым болуы (≈58-67%) және CC генотипінің сирек кездесуі (≤5,3%), статистикалық маңызды айырмашылықтар жоқ (p>0,05).

Қорытынды. Зерттеуде жүрек-қан тамырлары қаупі бар APOE (P.T388C) және *GCKR* генотиптері статистикалық маңызды байланыс анықталмады. Бұл бірлестіктерді растау немесе жоққа шығару үшін қосымша факторларды және үлгінің ұлғаюын ескере отырып, үлкен зерттеулер қажет.

Түйін сөздер. *атеросклероз, гипертриглицеридемия, жүрек-қан тамырлары ауруы, APOE, GCKR*

Дәйексөз үшін:

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Introduction

Atherosclerosis (AS) remains the leading cause of cardiovascular morbidity and mortality worldwide and in Kazakhstan. Disorders of fat metabolism play a key role in its development. In addition to the already well–known risk factor - elevated levels of low-density lipoproteins (LDL), hypertriglyceridemia is essential. This condition, characterized by high triglyceride levels, contributes to endothelial dysfunction, inflammation of the vascular wall, and accelerated formation of atherosclerotic plaques. Thus, elevated triglycerides are recognized as an independent and controllable risk factor for cardiovascular diseases, especially in the context of atherosclerosis [1].

Genetic determinants play a significant role in the formation of dyslipidemia. Variants in the genes regulating lipid and carbohydrate metabolism (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) affect the lipid profile and metabolism [2]. Polymorphisms in GCKR and LPL are associated with increased triglyceride levels and the development of hypertriglyceridemia, whereas changes in *LDLR*, *APOB*, and *PCSK9* are associated with familial hypercholesterolemia. Additionally, variations in *APOE* and *SLC22A5* affect the regulation of lipid and energy metabolism, which also affects cholesterol and triglyceride levels [3, 4].

Thus, studying the prevalence of genetic variants in genes involved in lipid metabolism is important for understanding the mechanisms of hypertriglyceridemia formation and its role in the development of atherosclerosis. The present study aimed to analyze such genes (*GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*) in a cohort of patients from Kazakhstan with atherosclerosis and hypertriglyceridemia. The population of Kazakhstan is still underrepresented in international genetic research. Given the high prevalence of risk factors for cardiovascular diseases such as obesity, metabolic syndrome, and familial hyperlipidemia, it is necessary to study ethnically specific genetic variants that may influence risk patterns in different populations. Identification of common genetic variants associated with hyperlipidemia and their relationship to biochemical parameters of lipid metabolism in patients with varying degrees of risk of developing AS in the Kazakh

cohort was performed. The purpose of this study was to determine the prevalence of genetic variants in genes involved in lipid metabolism and their relationship to the lipid and metabolic profile in the Kazakh population with atherosclerosis.

Materials and methods

Patients

The study was performed according to the Declaration of Helsinki and was approved by the local *Ethics Committee CF "University Medical Center", Astana, Kazakhstan (protocol №3/2023/PE from 14 July 2023). Every participant provided written informed consent before enrollment in the study and blood samples for DNA extraction.*

The study included 402 patients with cardiovascular diseases aged from 23 to 65 years. Based on triglyceride levels, patients with levels above normal were assigned to a separate group. As a result, 144 such patients were identified. They were divided into atherosclerosis risk categories in accordance with the ESC/EAS 2019 recommendations: low risk — 19 patients, high risk — 43 patients, and very high risk — 82 patients. Additionally, stratification was performed by gender and average age in each group [Fig. 1], [5].

Genomic DNA (gDNA) was extracted from whole blood using the Illustra blood GenomicPrep Mini Spin Kit. DNA concentration was determined spectrophotometrically on a NanoDrop 2000 instrument. DNA quality was assessed by electrophoresis in 1% agarose gel, and quantitative analysis was performed using a Qubit 2.0 fluorimeter.

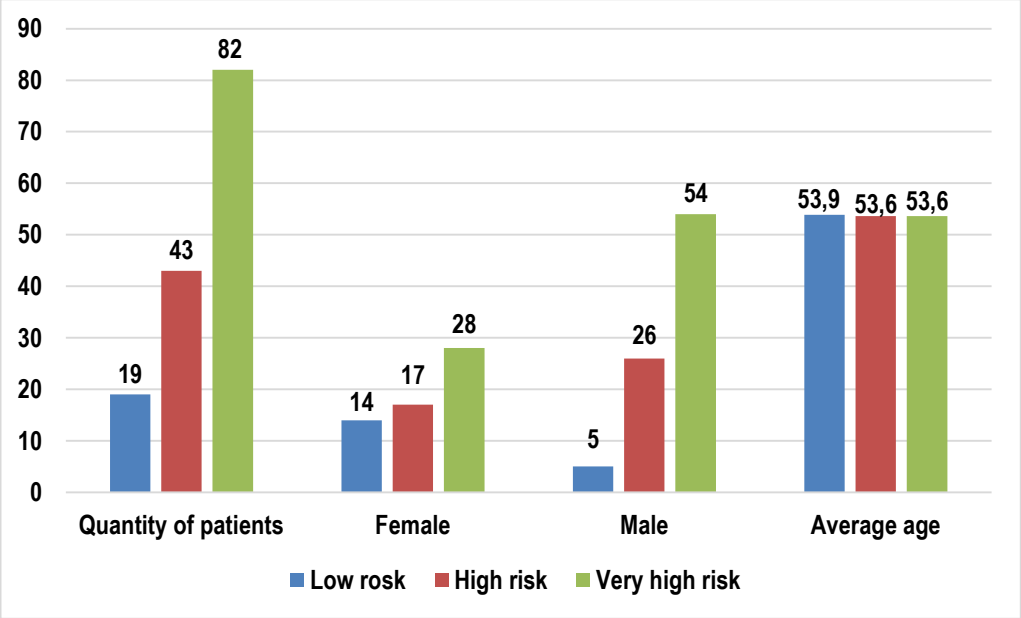

Figure 1. Distribution of patients by cardiovascular risk, quantity of patients, gender, and average age.

Preparation of DNA libraries

DNA libraries for whole exome sequencing were prepared using the Illumina DNA Prep with Enrichment protocol. The libraries were sequenced by high-throughput sequencing on a NovaSeq6000 instrument. Electrophoresis on a BioAnalyzer 2100 using the Agilent DNA 1000 Kit was employed to assess the quality of the libraries. The DNA concentration in libraries was determined by a fluorimetric method using Qubit 2.0 and Qubit TM ds High Sensitivity Assay kit.

To identify genetic factors associated with lipid metabolism disorders analysis of genes involved in lipid metabolism was performed. The focus of the study was on the *GCKR*, *SLC22A5*, *LPL*, and *FLCN* genes, which have been previously associated with the risk of hyperlipidemia and cardiometabolic disorders through population-based and genomic analyses.

A brief description of the functions of each gene follows:

GCKR (glucokinase regulatory protein) - this gene affects glucose and triglyceride metabolism by controlling the activity of the glucokinase enzyme [6].

SLC22A5 (carnitine transporter) - mutations in this gene, which encodes a carnitine transporter, can disrupt the beta-oxidation of fatty acids, leading to dyslipidemia [7].

LPL (lipoprotein lipase) - this gene encodes a key enzyme involved in the breakdown of triglycerides. Defective variants of LPL are the cause of hereditary hyperlipidemia type I [8].

FLCN (folliculin) - his gene is associated with energy metabolism and lipid regulation and may play a role in the development of metabolic syndrome [9].

Data analysis and classification of genetic variants

Sequenced samples were subjected to further bioinformatic analysis aimed at identifying genetic variants in genes associated with susceptibility to cardiovascular disease. Sequence data processing involved the use of SureCall (version 2.0.7.0), ANNOVAR, GTK, BWA, Bowtie, Bowtie 2, and VarScan software packages. International genomic databases, including ExAC, SIFT, ESP, GenBank, NCBI, EP 6500, 1000 Genomes, MutationTaster, SNPedia, Ensemble, and ClinVar, were utilized for variant annotation and filtering. Interpretation of the clinical significance of identified variants was performed according to the ACMG/AMP criteria (2015) using the InterVar platform (https://wintervar.wglab.org/) [10]. Based on this interpretation, variants were classified into one of five categories: pathogenic (P), likely pathogenic (LP),

variant of uncertain significance (VUS), likely benign (LB), or benign (B) [11]. Normality of data distribution was checked using the Kolmogorov-Smirnov and the Shapiro-Wilk test. For the comparison of more than two groups, One-way ANOVA and Kruskal-Wallis tests were performed.

Patients were evaluated comprehensively, considering both biochemical indicators of lipid profile and genetic variants associated with hyperlipidemia.

Results

During the sequencing of the whole exome, genetic variants associated with disorders of triglyceride metabolism were identified in patients with varying degrees of cardiovascular risk: 19 cases in the low-risk group, 43 cases in the high-risk group, and 82 cases in the very high-risk group. A comparative analysis of the biochemical parameters of triglycerides between these groups is presented in Table 1.

Table 1.

Comparative characteristics of biochemical parameters in patients with different levels of cardiovascular risk.

Variables	Low risk (n=19)	High risk (n=43)	Very high risk (n=82)	P-value
Age	44.6±9.6	52.3±7.9	56.3±6.1	0.000001
Body mass index (kg/m2)	30.7±4.7	31.5±5.3	30.8±5.5	ns
Total cholesterol (mg/dL)	207.8±30.3	228.8±35.2	217.9±51.2	0.0467*
LDL-C (mg/dL)	139.3±30.5	156.3±27.5	149.2±43.6	ns
HDL-C (mg/dL)	50.1±9.9	47.8±10.7	44.6±10.5	0.0411*
Non-HDL-C (mg/dL)	157.7±30.4	181±33.6	173.4±47.9	ns
Glucose (mg/dL)	101.1±8.3	118.3±45.3	135.4±60.5	0.0004*
Apolipoprotein A (g/L)	1.4±0.3	1.3±0.3	1.1±0.3	<0.0001
Apolipoprotein B (g/L)	1.1±0.2	1.2±0.2	1.2±0.3	ns
Triglycerides (mg/dL)	206.5±73.1	256.8±214.1	241.9±96.7	ns
Lipoprotein (a) (mg/dL)	47.3±61.3	26.9±32.3	27±38.9	ns
Creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.9±0.2	ns
C- reactive protein (mg/L)	0.3±0.4	0.3±0.2	0.7±3	ns
Homocysteine (μmol/L)	10.3±2.1	11.2±2.8	10.8±2.9	ns

Analysis of the lipid profile and markers of atherosclerosis depending on the degree of cardiovascular risk (low, high and very high) revealed several statistically significant differences. Total cholesterol was significantly higher in the high-risk group (228.8±35.2 mg/dl) compared with the low-risk group (207.8±30.3 mg/dl, p=0.0467). LDL (LDL-C) and non-lipoprotein cholesterol (non-HDL-C) levels did not differ statistically significantly between the groups (p>0.05), but there was a tendency to increase them in the high- and very high-risk groups. The level of high-density lipoprotein cholesterol (HDL-C) decreased with increasing cardiovascular risk and was significantly lower in the very high-risk group (44.6±10.5 mg/dl) compared with the low-risk group (50.1±9.9 mg/dl, p=0.0411). Triglyceride concentrations increased in the high-risk (256.8±214.1 mg/dl) and very high-risk (241.9±96.7 mg/dl) groups compared with the low-risk (206.5±73.1 mg/dl) groups, but the differences did not reach statistical significance (p>0.05). There was also a significant decrease in the level of apolipoprotein A (p<0.0001) with increased risk, which may indicate a decrease in the atheroprotective activity of high-density lipoproteins in these groups.

The analysis of genotype frequencies in the study cohort revealed statistically significant differences in a number of genes. In particular, the *GCKR* variant (c.G1004A) was exclusively represented in the low-risk group, where all participants had the GG genotype, and was completely absent in patients with high and very high risk. For another variant of *GCKR* (c.G307A), the GG genotype was dominant (94.7–100%), whereas the heterozygous GA variant was found only in low (5.3%) and very high (2.4%) risk groups. A similar pattern was observed for the genes *SLC22A5* (c.G1451T, c.G364T, c.C1400G), *FLCN* (c.G918A), *LPL* (c.G484A) and *LDLR* (c.C419T): homozygotes prevailed in all groups (up to 100%), and heterozygotes were detected in isolated cases or very rarely (about 1%). The APOE polymorphism (c.T388C) demonstrated a more pronounced distribution: the TT genotype was dominant in all groups (57.9–67.4%), the TC genotype was found in 28-36.8% of patients, and the CC genotype was rare (0-5.3%). For the APOE polymorphism (c.C526T), the CC genotype was found in the vast majority of patients (86-96.3%), while CT heterozygotes accounted for up to 14%. The *MYO15A* polymorphism (c.G5925A) was also characterized by a predominance of the GG genotype, and the GA variant was found in only one patient classified as a very high-risk group.

The table shows an analysis of the relationship between *APOE* (c.T388C) genotypes and treatment response rates according to various genetic models (codominant, dominant, recessive, overdominant, and log-additive). The average response ranges from 1.36 to 1.6, depending on the genotype. However, in all models, the differences between the groups did not reach statistical significance. The highest response was observed in carriers of the C/C genotype (1.6 ± 0.4), however, due to the small number of the group (n=5), the confidence interval was wide, and the difference with other genotypes turned out to be statistically insignificant (for example, p=0.66 in the codominant model). In all models, p-values > 0.05, including: Codominant model: p = 0.66 Dominant model: p = 0.55 Recessive model: p = 0.61 Overdominant model: p = 0.41 Log-additive model: p = 0.73. Also, the AIC and BIC indicators do not show an improvement in the model when APOE (c.T388C) is included, which additionally indicates the absence of a significant association.

Table 2.

Distribution of lipid-associated gene genotypes among patients with varying degrees of cardiovascular risk.

Genes	Low risk (n=19)	High risk (n=43)	Very high risk (n=82)
GCKR (c.G1004A)			
GG (%)	19 (100 %)	0 (0 %)	0 (0 %)
GA (%)	0 (0 %)	0 (0 %)	0 (0 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
GCKR (c.G307A)			
GG (%)	18 (94.7 %)	43 (100 %)	80 (97,6 %)
GA (%)	1 (5.3 %)	0 (0 %)	2 (2.4 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.G1451T)			
GG (%)	0 (0 %)	42 (97.7 %)	82 (100 %)
GT (%)	0 (0 %)	1 (5.3 %)	0 (0 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.G364T)			
GG (%)	0 (0 %)	0 (0 %)	82 (100 %)
GT (%)	0 (0 %)	0 (0 %)	0 (0 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
SLC22A5 (c.C1400G)			
CC (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
CG (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
GG (%)	0 (0 %)	0 (0 %)	0 (0 %)
FLCN (c.G918A)			
GG (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
LPL (c.G484A)			
GG (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)
APOE (c.T388C)			
TT (%)	11 (57.9 %)	29 (67.4 %)	55 (67.1 %)
TC (%)	7 (36.8 %)	14 (32.6 %)	23 (28 %)
CC (%)	1 (5.3 %)	0 (0 %)	4 (4.9 %)
APOE (c.C526T)			
CC (%)	17 (89.5 %)	37 (86 %)	79 (96.3 %)
CT (%)	2 (10.5 %)	6 (14 %)	3 (3.7 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
LDLR (c.C419T)			
CC (%)	0 (0 %)	0 (0 %)	81 (98.8 %)
CT (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
TT (%)	0 (0 %)	0 (0 %)	0 (0 %)
MYO15A (c.G5925A)			
GG (%)	0 (0 %)	43 (100 %)	81 (98.8 %)
GA (%)	0 (0 %)	0 (0 %)	1 (1.2 %)
AA (%)	0 (0 %)	0 (0 %)	0 (0 %)

Table 3.

Analysis of the association of APOE (c.T388C) polymorphism with treatment response in various genetic models (n=144)

APOE (c.T388C) association with response Status (n=144, crude analysis)							
Model	Genotype	n	Response mean (s.e.)	Difference (95% CI)	P-value	AIC	BIC
Codominant	T/T	95	1.46 (0.07)	0	0.66	318.8	330.7
	T/C	44	1.36 (0.11)	-0.10 (-0.36 - 0.16)			
	C/C	5	1.6 (0.4)	0.14 (-0.51 - 0.78)			
Dominant	T/T	95	1.46 (0.07)	0	0.55	317.3	326.2
	T/C-C/C	49	1.39 (0.11)	-0.08 (-0.32 - 0.17)			
Recessive	T/T-T/C	139	1.43 (0.06)	0	0.61	317.4	326.3
	C/C	5	1.6 (0.4)	0.17 (-0.47 - 0.81)			
Overdominant	T/T-C/C	100	1.47 (0.07)	0	0.41	317	325.9
	T/C	4	1.36 (0.11)	-0.11 (-0.36 - 0.15)			
Log-additive	---	---	---	-0.04 (-0.25 - 0.18)	0.73	317.6	3265

Conclusion: According to the results of the analysis, there was no statistically significant relationship between the *APOE* (c.T388C) polymorphism and the level of response to treatment in any of the tested genetic models. The data suggests that APOE (c.T388C) probably has no significant effect on this phenotype in this sample. For a more accurate estimate, an extended analysis is needed, taking into account covariates and increasing the sample size.

Discussions.

This study is the first to analyze the genetic variants involved in the regulation of lipid metabolism in a Kazakh cohort of patients with hypertriglyceridemia and atherosclerosis. The results obtained convincingly demonstrate that triglyceride metabolism disorders are one of the fundamental factors determining increased cardiovascular risk. Despite the absence of statistically significant differences in triglyceride levels between risk groups, there was a marked tendency for their increase in high- and very high-risk groups. This phenomenon correlates with data from international studies highlighting the role of hypertriglyceridemia in synergy with elevated LDL cholesterol levels in accelerating the atherosclerotic process through the induction of inflammation and endothelial dysfunction. The observed decrease in HDL cholesterol and apolipoprotein A levels in high-risk patients indicates a compromise of the atheroprotective potential of high-density lipoproteins, which is a pathognomonic sign of dyslipidemia in atherosclerosis. This highlights the importance of an integrated approach to assessing the lipid profile in the context of risk stratification. Genetic analysis of the APOE polymorphism (p. T388C) did not reveal significant differences between risk groups, which may indicate a limited contribution of this particular variant to the formation of cardiovascular risk in the studied sample. However, the potential effect of other APOE variants, as well as polymorphisms in the GCKR, LPL, and SLC22A5 genes, which, according to literature data, have a significant effect on triglyceride metabolism, remains the subject of further research. It should be noted that the limited sample size (n=144 patients) could affect the statistical power of the study. Large-scale studies involving diverse ethnic groups and the use of advanced multifactorial analysis methods are needed to more accurately validate the associations between genetic variants and the risk of atherosclerosis in the Kazakh population. Thus, this study confirms the critical role of hypertriglyceridemia as a predictor of increased cardiovascular risk. The study of the genetic determinants of lipid metabolism opens up new horizons for the development of highly accurate risk stratification methods and the creation of personalized strategies for the prevention and treatment of atherosclerosis, which is important for public health in Kazakhstan.

Conclusions.

In a study of Kazakhstani patients with atherosclerosis and elevated triglyceride levels, genetic features related to the regulation of fat metabolism were found. High triglyceride levels are known to be associated with an increased risk of cardiovascular disease. This confirms the importance of this indicator as an independent factor affecting heart health. In high-risk patients, there was a decrease in "high" HDL cholesterol and apolipoprotein A, which indicates a weakening of the protective mechanisms preventing the development of atherosclerosis. The genetic variant APOE (C. T388C) was equally common in all risk groups, so its association with the risk of cardiovascular diseases in this sample was not established. The data obtained emphasize the need for further research aimed at identifying specific genetic variants characteristic of the population of Kazakhstan that affect lipid metabolism and the risk of atherosclerosis.

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CLONAL HEMATOPOIESIS WITH INDETERMINATE POTENTIAL IN TET2 AND DNMT3A AMONG KAZAKHSTANI INDIVIDUALS WITH ATHEROSCLEROTIC DISEASE

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Abstract

Purpose of the study: To assess the contribution of clonal hematopoiesis of indeterminate potential (CHIP) to the development of atherosclerotic disease in the Kazakhstani cohort, focusing on the *TET2* and *DNMT3A* genes, based on next-generation sequencing (NGS) data.

Materials and Methods: This study employed an observational cross-sectional design. The cohort comprised 177 women and 225 men, with a mean age of 53.0 ± 9.04 years overall (men: 52.2 ± 9.0 years; women: 53.7 ± 9.0 years). Patients were stratified cardiovascular risk category (low, high, very high) according to the ESC/EAS (2019) recommendations. In this sample, 74 participants (18.4%) were classified as low-risk, 136 (33.8%) as high-risk, and 192 (47.8%) as very high-risk. For the initial phase of analysis, the two most studied genes, *TET2* and *DNMT3A*, were selected from a total list of 8 priority genes: *ASXL1, DNMT3A, JAK2, PPM1D, SF3B1, SFRS2, TET2,* and *TP53* associated with CHIP, based on their high clinical significance and frequency of occurrence in previously published studies. By filtering the data and selecting two priority genes for primary analysis, 41 patients with atherosclerotic disease were identified from the total cohort. Genetic analyses were performed using high-throughput whole-exome sequencing to cover a wide range of genetic variants potentially associated with CHIP and the atherosclerotic process. Variant annotation was performed using international databases (ClinVar, ExAC, 1000 Genomes, etc.), and mutations were interpreted according to the ACMG/AMP classification using the InterVar platform. Statistical data processing included the nonparametric Kruskal-Wallis test, Dunn's test for pairwise comparisons, and Fisher's exact test; a value of $p < 0.05$ was considered statistically significant.

Results: Variants were detected in *TET2* (n=35) and *DNMT3A* (n=6). The median VAF for TET2 was 50%. Age differed significantly between risk groups (p = 0.026). Most detected variants had an ultra-rare frequency according to international databases (<0.1%). One pathogenic variant was identified according to the InterVar classification; the others were predominantly of uncertain significance (VUS). The distribution of variants by risk groups showed no statistically significant differences ($p = 0.341$).

Conclusion: The results demonstrate a potential role of CHIP-associated mutations in atherosclerosis pathogenesis, with*TET2* mutations appearing most prominent. Given the identified genetic features and their association with

cardiovascular risk, the findings justify extending the analysis to the full spectrum of CHIP-associated genes to improve the accuracy of risk stratification.

Keywords: *clonal hematopoiesis of indeterminate potential, atherosclerosis, cardiovascular disease, coronary artery disease.*

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Резюме

КЛОНАЛЬНЫЙ ГЕМОПОЭЗ НЕОПРЕДЕЛЁННОГО ПОТЕНЦИАЛА В ГЕНАХ TET2 И DNMT3A У ПАЦИЕНТОВ С АТЕРОСКЛЕРОТИЧЕСКОЙ БОЛЕЗНЬЮ В КАЗАХСТАНСКОЙ ПОПУЛЯЦИИ

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Цель исследования: Оценить вклад клонального гемопоэза неопределенного потенциала (КГНП) в развитие атеросклеротического заболевания в казахстанской когорте с упором на гены *TET2* и *DNMT3A* на основе данных секвенирования нового поколения (NGS).

Материалы и методы: Проведено обсервационное поперечное исследование. Когорта состояла из 177 женщин и 225 мужчин, средний возраст которых в целом составил 53,0 ± 9,04 года (мужчины: 52,2 ± 9,0 года; женщины: 53,7 ± 9,0 года). Пациенты были распределены по категориям сердечно-сосудистого риска (низкий, высокий, очень высокий) в соответствии с рекомендациями ESC/EAS (2019). В этой выборке 74 участника (18,4%) были отнесены к группе низкого риска, 136 (33,8%) – к группе высокого риска и 192 (47,8%) – к группе очень высокого риска. Для начальной фазы анализа два наиболее изученных гена, *TET2* и *DNMT3A*, были выбраны из общего списка восьми приоритетных генов: *ASXL1, DNMT3A, JAK2, PPM1D, SF3B1, SFRS2, TET2* и *TP53*, ассоциированных с КГНП, на основании их высокой клинической значимости и частоты в ранее опубликованных исследованиях. Путем фильтрации данных и выбора двух приоритетных генов для первичного анализа из общей когорты были выделены 41 пациент с атеросклеротическим заболеванием. Генетический анализ был проведен с использованием высокопроизводительного секвенирования всего экзома (NGS, whole-exome sequencing), чтобы охватить широкий спектр генетических вариантов, потенциально связанных с КГНП и атеросклеротическим процессом. Аннотирование вариантов проводилось с использованием международных баз данных (ClinVar, ExAC, 1000 геномов и др.), а мутации интерпретировались в соответствии с классификацией ACMG/AMP с использованием платформы InterVar. Статистическая обработка данных включала непараметрический критерий Крускала-Уоллиса, критерий Данна для парных сравнений и точный критерий Фишера; значение $p < 0,05$ считалось статистически значимым.

Результаты: Варианты были обнаружены в *TET2* (n=35) и *DNMT3A* (n=6). Медиана VAF для *TET2* составила 50%. Возраст пациентов значительно различался между группами риска (p = 0,026). Большинство обнаруженных вариантов имели крайне редкую частоту согласно международным базам данных (<0,1%). Один патогенный вариант был идентифицирован в соответствии с классификацией InterVar; остальные - преимущественно варианты неопределенного значения (VUS). Распределение вариантов по группам риска не показало статистически значимых различий (p = 0,341).

Выводы: Результаты указывают на потенциальную роль CHIP-ассоциированных мутаций в патогенезе атеросклероза; наибольшее значение показали мутации *TET2*. Учитывая выявленные генетические особенности и их связь с сердечно-сосудистыми рисками, полученные данные обосновывают необходимость расширения анализа на весь спектр КГНП-ассоциированных генов для повышения точности стратификации риска.

Ключевые слова: *клональный гемопоэз с неопределенным потенциалом, атеросклероз, сердечно-сосудистые заболевания, ишемическая болезнь сердца.*

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Түйіндеме

ҚАЗАҚСТАНДЫҚ ПОПУЛЯЦИЯДАҒЫ АТЕРОСКЛЕРОТИКАЛЫҚ АУРУЫ БАР ПАЦИЕНТТЕРДЕГІ TEST2 ЖӘНЕ DNMT3A ГЕНДЕРІНДЕГІ БЕЛГІСІЗ ПОТЕНЦИАЛЫ КЛОНДЫ ГЕМОПОЭЗ

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Зерттеудің мақсаты: *TET2* және *DNMT3A* гендеріне баса назар аудара отырып, Қазақстандық пациенттерде атеросклеротикалық аурудың дамуына анықталмаған потенциалды клондық гемопоэздің (CHIP) үлесін жаңа буынның секвенирлеу деректері (NGS) негізінде бағалау.

Зерттеудің әдістері: Көлденең (бірмезеттік) зерттеу жүргізілді. Когортқа 177 әйел мен 225 ер адам кірді, олардың орташа жасы жалпы алғанда 53,0 ± 9,04 жасты құрады (ерлер: 52,2 ± 9,0 жас; әйелдер: 53,7 ± 9,0 жас). Пациенттер ESC/EAS (2019) нұсқауларына сәйкес жүрек-қан тамырлары қаупі бойынша (төмен, жоғары, өте жоғары) стратификацияланған. Бұл үлгіде 74 қатысушы (18,4%) тәуекелі төмен, 136 (33,8%) тәуекелі жоғары және 192 (47,8%) өте жоғары тәуекел санатына жатқызылды.Талдаудың бастапқы кезеңі үшін 8 геннің жалпы тізімінен: *ASXL1, DNMT3A, JAK2, PPM1D, SF3B1, SFRS2, TET2, TP53*, белгісіз потенциалы клондық гемопоэзбен байланысты, ең көп зерттелген екі ген

TET2, *DNMT3A* таңдалды, олардың жоғары клиникалық маңыздылығы мен бұрын жарияланған зерттеулерде пайда болу жиілігіне негізделген. Деректерді сұрыптау және бастапқы талдау үшін екі басым генді сүзгілеу нәтижесінде жалпы когортыдан атеросклеротикалық ауруы бар 41 пациент іріктелді. Генетикалық талдау толық экзомды секвинерлеу арқылы жүргізілді, бұл белгісіз потенциалы клонды гемопоэз және атеросклеротикалық процеспен ықтимал байланысты генетикалық нұсқалардың кең ауқымын қамтуға мүмкіндік берді. Генетикалық әдістердің аннотациясы халықаралық дерекқорларды (ClinVar, ExAC, 1000 Genomes және т.б.) пайдалана отырып орындалды және мутацияларды InterVar платформасын пайдалана отырып, ACMG/AMP классификациясына сәйкес түсіндіру жүргізілді. Статистикалық деректерді өңдеуге параметрлік емес Краскел-Уоллис критерийі, жұптық салыстыру үшін Данн критерийі және Фишер критерийі кірді; $p < 0.05$ мәні статистикалық маңызды болып саналды.

Нәтижелер: *TET2* (n=35), *DNMT3A* (n=6) генетикалық варианттар табылды. *TET2* үшін VAF медианасы 50% құрады. Пациенттердің жасы тәуекел топтары арасында айтарлықтай өзгерді ($p = 0.026$). Табылған нұсқалардың көпшілігі халықаралық базаларға сәйкес өте сирек жиілікке ие болды (<0.1%). Intervar классификациясы бойынша бір патогендік нұсқа анықталды; қалғандары - көбіне анықталмаған мәнді (VUS). Қауіп қатер топтары бойынша бөлу статистикалық маңызды айырмашылықтарды көрсетпеді ($p = 0.341$).

Қорытынды: Атеросклероз патогенезіндегі CHIP-пен байланысты мутациялардың әлеуетті рөлін көрсетеді; ең маңызды *TET2* мутациялары. Анықталған генетикалық ерекшеліктерді және олардың жүрек-қан тамырлары қаупімен байланысын ескере отырып, нәтижелер тәуекелді стратификациялаудың дәлдігін арттыру үшін CHIP байланысты гендердің барлық спектріне талдауды кеңейту қажеттілігін негізделеді.

Негізгі сөздер: белгісіз потенциалы клондық гемопоэз, атеросклероз, жүрек-қан тамырлары аурулары, жүректің ишемиялық ауруы.

Дәйексөз үшін:

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Introduction

Atherosclerosis continues to be one of the leading causes of premature mortality and disability across the world. Although traditional risk factors such as arterial hypertension, dyslipidemia, smoking, and diabetes are well recognised, not all cases can be explained by these factors at the time of the onset of severe cardiovascular disease. In recent years, researchers have actively explored the role of somatic mutations occurring in hematopoietic cells in the pathogenesis of atherosclerosis. This phenomenon, referred to as clonal hematopoiesis of indeterminate potential (CHIP), is an age-related process wherein somatic mutations in multiple genes promote the expansion of individual clones without exhibiting signs of hematologic malignancies [1,2].

CHIP mutations are most commonly found in genes such as *ASXL1, DNMT3A*, *TET2*, *TP53*, and *PPM1D*, among others, and have been shown in several studies to be associated with a 40-50% increased risk of cardiovascular mortality [3,4]. It is hypothesized that clonal cells with mutations in *TET2* and *DNMT3A* produce pro-inflammatory cytokines, thereby activating monocytic and macrophage cascades, which contribute to the progression of atherosclerotic plaques [5,6].

While the role of clonal hematopoiesis of uncertain potential (CHIP) in the pathogenesis of atherosclerotic disease has been thoroughly explored in recent years, most existing data come from cohorts in Europe and North America. This creates a notable gap in the global understanding of the prevalence and molecular characteristics of CHIP in other regions. The scarcity of data from Central Asian countries restricts the ability to compare and interpret findings within a global context. The present study aims to address this information gap by providing the first systematic data on the frequency and types of CHIP-associated mutations in patients with atherosclerosis in Kazakhstan.

The purpose of the study

The present study aims to improve outcomes for patients with atherosclerotic cardiovascular diseases by developing an effective early genetic screening program that enables the differentiation of risk groups based on molecular genetic data. To achieve this goal, we performed high-throughput whole-exome sequencing (WES) to detect mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) and predisposition to atherosclerosis.

Research Objectives

To identify somatic variants in the *TET2* and *DNMT3A* genes among patients with atherosclerotic diseases.

To estimate the frequency of pathogenic, likely pathogenic and variants of uncertain significance (VUS) based on InterVar classification and frequency of occurrence in population databases.

To correlate molecular characteristics of variants with clinical parameters (age, gender, clinical risk).

To compare the level of clonality (VAF) between the two genes.

Materials and Methods

An observational analytical study (single-stage, cross-sectional) was conducted to investigate the frequency and molecular characteristics of mutations associated with CHIP in a cohort of young Kazakhstani individuals with atherosclerotic cardiovascular disease. DNA samples from patients (n = 402) with a confirmed diagnosis of atherosclerosis were included. Whole-exome sequencing (WES) was used to identify genetic

variants potentially associated with CHIP. Inclusion in the analysis was based on the availability of high-quality NGS data and compliance with predefined preprocessing criteria. Genomic loci with wild-type genotype were excluded, as they contained no allelic substitutions. For further analysis, only samples carrying heterozygous or homozygous variants were selected to focus on mutations with potential functional impact. Patients were stratified into cardiovascular risk categories (low, high, and very high) based on the 2019 ESC/EAS Guidelines [7]. The evaluation criteria included clinical parameters, low-density lipoprotein cholesterol (LDL-C) levels, and the presence of diabetes, hypertension, target organ damage, chronic kidney disease, and other risk factors.

Additional filtering of genetic variants was performed based on their minor allele frequency (MAF < 1%) using international databases (ExAC, 1000 Genomes, PopFreq). Variant annotation was performed using ANNOVAR and other bioinformatics tools, and clinical interpretation was based on the ACMG/AMP guidelines via the InterVar platform. In our initial analysis, we examined two of the eight genes associated with the development of CHIP specifically: *ASXL1, DNMT3A, JAK2, PPM1D, SF3B1, SFRS2, TET2,* and *TP53*. At this stage, *TET2* and *DNMT3A* were selected for a more in-depth analysis; the remaining genes will be analyzed in subsequent work. Sequencing data annotated using the following software tools were used for analysis: ANNOVAR, GATK, BWA, Bowtie/Bowtie2, VarScan. Annotation and functional interpretation of variants were performed according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP). Mutations were classified on the InterVar platform into five categories: pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign (LB), and benign (B).

To quantify clonality, we utilised variant allele frequency (VAF), which is calculated as the ratio of reads containing a variant to the total number of reads at a specific position. VAF values were expressed as percentages and subsequently converted to decimal proportions for statistical analysis. Only variants with a VAF ≥ 2% were analysed, in accordance with standard thresholds for detecting clonal events. In parallel, allele frequencies in international databases, such as ExAC, 1000 Genomes, and PopFreq, were taken into account, with a minor allele frequency (MAF) threshold of < 0.01 to select rare variants.

Data processing and visualisation were performed in the R software (version 4.4) using the tidyverse, ggplot2, dplyr, survival, and survminer libraries. Data are presented as absolute and relative frequencies, medians, and interquartile ranges (Me [IQR]). Nonparametric methods were used to compare quantitative indices between groups, including the Kruskal-Wallis test and the Mann-Whitney test. Fisher's exact test and χ^2 test were used to assess differences in the distribution of categorical variables. The critical level of significance was set at $p < 0.05$. The p-values are presented rounded to three decimal places. All tests were two-sided.

Results

At the time of analysis, variants in 8 of the 74 selected genes involved in the pathogenesis of CHIP were fully annotated and analysed. Two genes, *TET2* and *DNMT3A*, were selected for the present analysis as the most frequently associated with CHIP mutations. After applying the filtering criteria, 41 out of 402 patients (10.2%) were identified as carriers of relevant variants. Further stratification by cardiovascular risk revealed that 14 patients were classified into the low-risk group, 10 patients into the high-risk group, and 17 patients into the very high-risk group. As a result, after stepwise filtering, a distinct subgroup of patients with CHIP was identified, representing approximately one-tenth of the total study cohort.

Kernel-density violin plots illustrate the age distribution in all risk groups (Fig. 1). The mean ± SD ages were 46.8 ± 10.4 years (low-risk), 54.2 ± 12.7 years (high-risk), and 56.9 ± 8.8 years (very high-risk). Age increased significantly with risk category (*Kruskal-Wallis* $\chi^2 = 6.61$, $p = 0.037$). Pairwise Dunn tests revealed a significant difference between the low and very high-risk groups (adjusted $p = 0.026$). This analysis aimed to determine whether age varied significantly among risk groups, as age is a known factor associated with CHIP and may influence the distribution of genetic variants within the studied cohort.

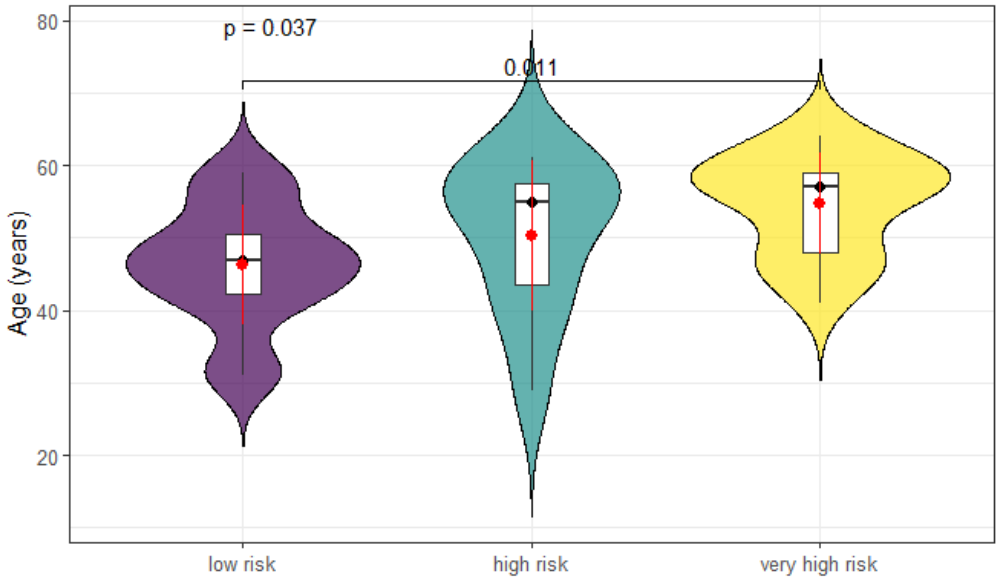

Fig. 1 Age distribution across risk categories

To assess the relationship between the type of genetic variants and the degree of cardiovascular risk, patients were divided into two groups: low-risk and a combined category of high and very-high-risk (Fig. 2). Genetic variant types were classified according to ACMG/AMP guidelines using the InterVar platform into two categories: pathogenic and VUS. VUS variants predominated in both risk categories. A small proportion of pathogenic variants were observed in the low-risk group, whereas no pathogenic variants were identified in the high and very-high-risk groups. Within the combined high and very-high-risk group, all 27 variants were classified as VUS. In contrast, the low-risk group included 13 VUS and a single pathogenic variant (represented by the purple segment), resulting in proportions of 100% versus 7%. The Fisher's exact test result (p = 0.341), displayed above the bars, indicates that this difference is not statistically significant, which is in line with the limited number of pathogenic variants identified in the current dataset. These data suggest that the type of clinical interpretation of variants in the study cohort is independent of cardiovascular risk grade.

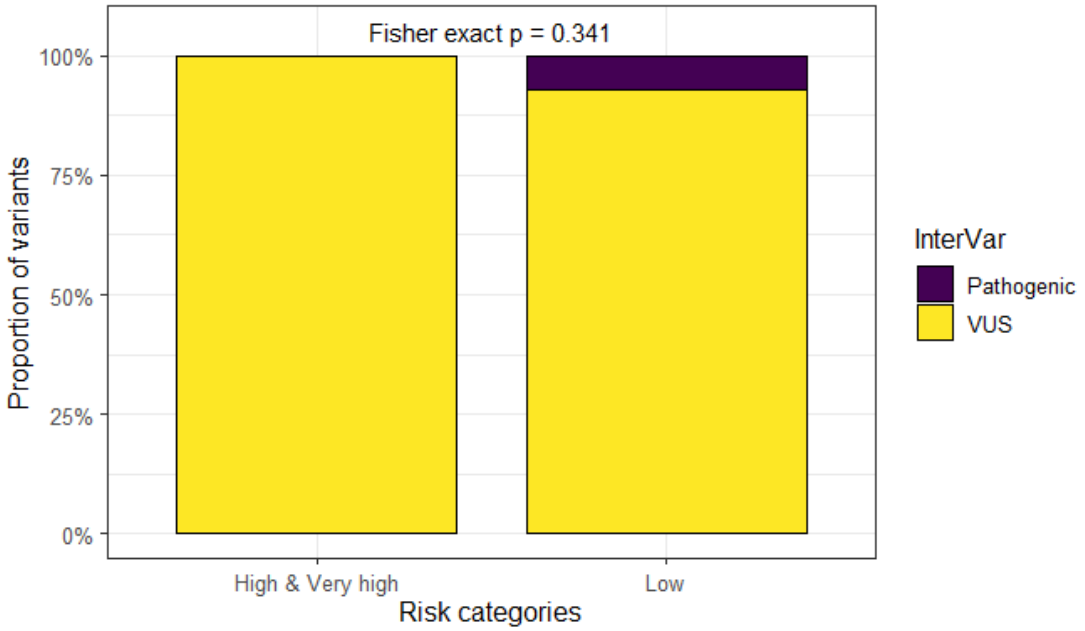

Fig. 2 Distribution of variant type across risk groups

A non-parametric Mann-Whitney rank-sum test (also known as the Wilcoxon rank-sum test) was performed to assess differences in allelic variant fraction between mutations in the *DNMT3A* (n = 6) and *TET2* (n = 35) genes. As shown in Figure 3, VAF values ranged from ~6% to ~68%, with the median value being higher for mutations in *TET2* than for those in *DNMT3A*. Statistical analysis revealed a trend towards a significant difference between the two groups (p = 0.056), which may indicate a possible difference in clone size or the timing of mutations in these genes.

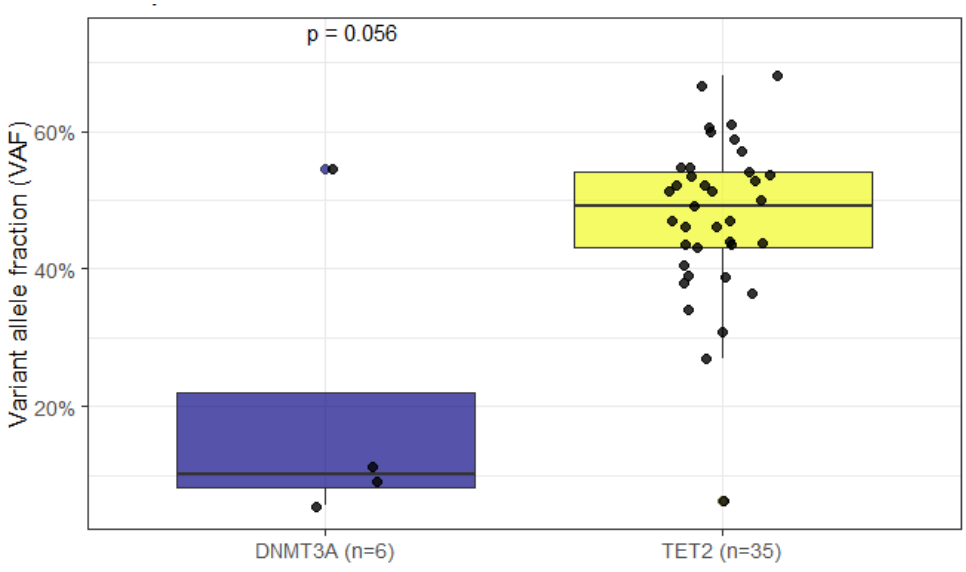

Fig. 3 VAF distribution in *DNMT3A* and *TET2*.

The bar chart (Fig. 4) illustrates the number of detected variants assigned to the MAF minor allele frequency categories: ultra-rare (< 0.1%), rare (0.1-1%), and common (≥ 1%), based on data from three population databases (ExAC, PopFreq, and 1000 Genomes ALL). In the ExAC database, the vast majority of variants identified were ultra-rare: 38 variants had MAF < 0.1%. No variants were observed in the rare category (0.1-1% in ExAC), whereas three variants were found to be frequent (MAF ≥ 1%). The PopFreq database exhibits a similar pattern: 40 variants (the majority) are ultra-rare (<0.1%), none fall within the 0.1-1% category, and only one variant reaches a frequency of> 1%. In contrast, the 1000 Genomes database (1000ALL) contains a significant proportion of variants with high frequency in the population: 27 variants (the most notable number) were classified as common (≥ 1%), and a further 14 variants fell into the rare range (0.1-1%). No ultra-rare variants (<0.1%) were identified in 1000ALL. Consequently, according to ExAC and PopFreq statistics, the majority of identified CHIP mutations are exceptionally rare or absent in the general population. In contrast, the 1000 Genomes sample includes many of these variants as common polymorphisms with a frequency of 1% or higher.

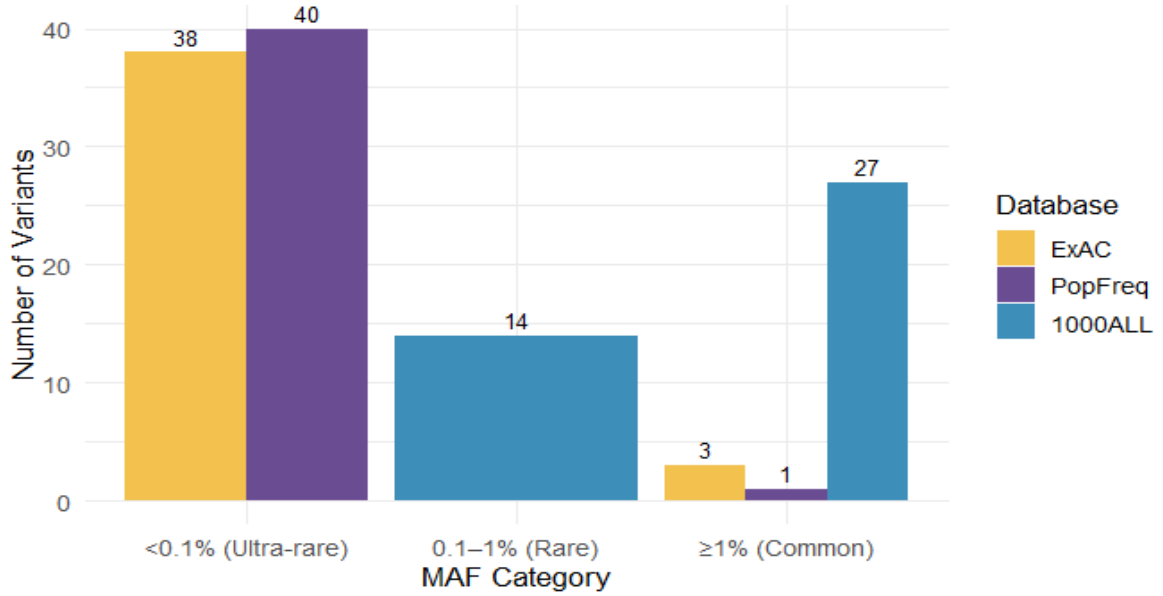

Fig.4 Distribution of MAF Across Population Datasets.

Discussion

In the present study, we analysed the frequency and molecular characteristics of CHIP in patients with atherosclerotic disease, with a particular focus on the *TET2* and *DNMT3A* genes. Data were derived from NGS analysis and stratified according to cardiovascular risk categories as outlined in the 2019 ESC/EAS guidelines [7].

One of the significant findings of the study was that mutations in *TET2* were significantly more frequent than those in *DNMT3A* (n = 35 vs. n = 6), with higher VAF values in the *TET2* group. The median VAF for *TET2* was 50%, potentially indicating the presence of mutations in larger clone progenitor cells. Although there was no statistically significant difference (p = 0.056), the results obtained may indicate differences in clonal expansion between the two genes. This finding is consistent with previous studies, which have shown that mutations in *TET2* are more frequently associated with an inflammatory cascade that promotes atherosclerosis progression [5,6].

Analysis of MAF distribution in international databases (ExAC, PopFreq, 1000ALL) showed that the majority of detected variants are ultra-rare (<0.1%), which emphasises their potential clinical significance. Ultra-rare variants are known to be more likely to have functional consequences and may be involved in the pathogenesis of chronic diseases, including cardiovascular diseases [2,3].

In addition, a comparison of variant distribution according to CVD risk revealed no statistically significant differences between groups, when classified by the InterVar classification (pathogenic and VUS variants), as confirmed by Fisher's exact test (p = 0.341). Nevertheless, almost all pathogenic variants were recorded in the low-risk group, which warrants further investigation in an expanded sample. Such ambiguity may be due to insufficient sample power or the influence of other unaccounted factors.

The age of patients was also significantly associated with the risk level: patients in the very-high-risk group were considerably older than those in the low-risk group (p = 0.026, according to Dunn's criterion), which confirms the known age dependence of CHIP [1].

Thus, our results emphasise the need to consider CHIP mutations in the context of risk assessment of atherosclerotic disease. Our data are consistent with current ideas about the role of inflammation and CHIP in the pathogenesis of CHD and justify further analysis of the broader panel of 74 genes implicated in CHIP and cardiovascular disease.

Conclusion

The present study evaluated the frequency and molecular characteristics of CHIP in patients with atherosclerosis by analysing NGS data. Of 74 genes associated with CHIP and cardiovascular disease, eight genes were selected for initial analysis, of which *TET2* and *DNMT3A* were studied in detail. Analysis revealed that mutations in *TET2* are more frequent and characterised by higher VAF values compared with *DNMT3A*, which may indicate differences in clonal expansion and pathophysiological impact on atherogenesis. Most of the identified variants were ultra-rare according to international databases, emphasising their potential significance. Despite the absence of significant differences between risk groups

according to the InterVar classification, the presence of a pathogenic variant even in the low-risk group requires attention. The results confirm the relevance of further extended analysis of all 74 genes to better assess the contribution of CHIP to atherosclerosis progression and potential risk stratification in patients.

Conflict of interests: *The authors declare no conflicts of interest.*

Contributions of authors: *All authors contributed equally to this work.*

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PRELIMINARY ANALYSIS AND ASSESSMENT OF THE HEALTH STATUS OF THE DESCENDANTS OF PERSONS EXPOSED TO RADIATION, LIVING IN THE BESKARAGAI DISTRICT OF THE ABAY REGION

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Abstract

Introduction: The effects of chronic low-dose ionizing radiation on human health have been the subject of scientific research for several decades. However, the long-term effects of chronic low-dose irradiation on the human body, including those of the third and subsequent generations, remain unresolved.

Aim: To conduct a preliminary assessment of the health screening results of the Beskaragay District population, including second- and third-generation residents exposed to radiation from nuclear weapons testing.

Materials and Methods: A population screening was conducted in Beskaragai District, including questionnaires on health status, risks of developing non-communicable and socially significant diseases, and lifestyle. A preliminary analysis included 222 patients. All participants underwent a somatic assessment, as well as general clinical and biochemical analyses. Statistical analysis was performed using SPSS 20.0 (IBM Inc., New York, USA) and Jamovi (v2.5.5; https://www.jamovi.org).

Results: The mean age and age distribution differed statistically between men and women ($p = 0.0071$), with men being more likely to be aged 40–49 years (34.5%). 63.5% of participants had lived in the area since birth. The median systolic blood pressure in men was 130 (IQR 10) mmHg, which was significantly higher than in women ($p < 0.001$). 90.1% of patients had grade 1–2 thyroid enlargement. Cortisol levels were higher in men — 319.0 (122.0) nmol/L versus 249.3 (145.2) nmol/L in women ($p = 0.020$), while the opposite trend was observed for insulin. The median individual doses of external gamma radiation among participants were 1.8 cSv (IQR: 0.4–4.2) and did not differ statistically between men and women ($p = 0.433$).

Conclusion: The results of this phase of the study highlight the need for an expanded sample, in-depth clinical, laboratory, and instrumental examinations, and further registry development to study the relationship between radiation exposure and the development of somatic diseases in the offspring of exposed individuals.

Keywords: *Semipalatinsk Nuclear Test Site; health effects; screening; risk factors; radiation.*

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Резюме

ПРЕДВАРИТЕЛЬНЫЙ АНАЛИЗ И ОЦЕНКА СОСТОЯНИЯ ЗДОРОВЬЯ ПОТОМКОВ ЛИЦ, ПОДВЕРГШИХСЯ ВОЗДЕЙСТВИЮ РАДИАЦИИ, ПРОЖИВАЮЩИХ В БЕСКАРАГАЙСКОМ РАЙОНЕ АБАЙСКОГО РЕГИОНА

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Введение: Эффекты хронического низкодозового ионизирующего излучения на состояние здоровья человека являются предметом научных исследований в течение нескольких десятилетий. Однако остается нерешенным вопрос о долгосрочных эффектах хронического низкодозового облучения на организм человека, включая лиц третьего и последующих поколений.

Цель: Предварительно оценить результаты скрининга состояния здоровья населения Бескарагайского района, второго и третьего поколения лиц, подвергшихся воздействию радиации вследствие испытаний ядерного оружия.

Материалы и методы: Проведено скрининговое исследование населения Бескарагайского района, анкетирование участников о состоянии здоровья, рисков развития неинфекционных и социально-значимых заболеваний, образа жизни пациентов. В предварительный анализ включено 222 участника. Всем участникам проводили оценку соматического состояния, а также общеклинический и биохимический анализ. Статистический анализ проводился с применением программ SPSS 20.0 (IBM Inc., New York, USA) и Jamovi (версия 2.5.5; https://www.jamovi.org).

Результаты: Средний возраст и распределение по возрастным категориям статистически различались между мужчинами и женщинами (p = 0,0071), среди мужчин преобладали лица в возрасте 40–49 лет (34,5%). 63,5% участников проживали на данной территории с рождения. Медиана систолического артериального давления САД у мужчин составила 130 (IQR 10) мм рт. ст., что было достоверно выше, чем у женщин (p <0,001). 90,1% пациентов имели увеличение щитовидной железы до 1–2 степени. Уровень кортизола был выше у мужчин - 319,0 (122,0) нмоль/л против 249,3 (145,2) нмоль/л у женщин (p = 0,020), в то время как для инсулина установлена обратная тенденция. Медианные индивидуальные дозы внешнего гамма-облучения участников составляли 1.8 сЗв (IQR: 0.4–4.2) и статистически не различались между мужчинами и женщинами (p = 0.433).

Выводы: Результаты данного этапа работы подчёркивают необходимость расширения выборки, углублённого клинико-лабораторного и инструментального обследования, а также дальнейшее формирования регистра для изучения связи радиационного воздействия с развитием соматических заболеваний у потомков экспонированных лиц.

Ключевые слова: *Семипалатинский ядерный полигон; эффекты в отношении здоровья; скрининг; факторы риска; радиация.*

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Түйіндеме

АБАЙ ӨҢІРІНІҢ БЕСҚАРАҒАЙ АУДАНЫНДА ТҰРАТЫН, РАДИАЦИЯҒА ҰШЫРАҒАН АДАМДАРДЫҢ ҰРПАҚТАРЫНЫҢ ДЕНСАУЛЫҚ ЖАҒДАЙЫН АЛДЫН АЛА ТАЛДАУ ЖӘНЕ БАҒАЛАУ

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Кіріспе: Созылмалы төмен дозалы иондаушы сәулеленудің адам денсаулығына әсері бірнеше онжылдықтар бойы ғылыми зерттеулердің тақырыбы болып табылады. Алайда, созылмалы төмен дозалы сәулеленудің адам ағзасына, оның ішінде үшінші және кейінгі ұрпақтарға ұзақ мерзімді әсері туралы мәселе әлі де ашық.

Мақсат: Ядролық қару сынақтарының салдарынан радиацияға ұшыраған адамдардың екінші және үшінші буына кіретін Бесқарағай ауданы тұрғындары арасында денсаулық скринингінің нәтижелерін алдын ала бағалау.

Материалдар мен әдістер: Бесқарағай ауданы тұрғындары арасында скринингтік зерттеу жүргізілді, қатысушыларға денсаулық жағдайы, инфекциялық емес және әлеуметтік маңызы бар аурулардың даму қаупі, пациенттердің өмір салты туралы сауалнама жүргізілді. Алдын ала талдауға 222 қатысушы енгізілген. Барлық қатысушыларға соматикалық жағдайды бағалау, сондай-ақ жалпы клиникалық және биохимиялық талдаулар жүргізілді. Статистикалық талдау SPSS 20.0 (IBM Inc., New York, USA) және Jamovi (версия 2.5.5; https://www.jamovi.org) бағдарламаларын қолдану арқылы жүргізілді.

Нәтижелер: Орташа жас және жас санаттары бойынша бөліну ерлер мен әйелдер арасында статистикалық түрде ерекшеленді (p = 0,0071), ерлер арасында 40-49 жас аралығындағы адамдар басым болды (34,5%). Қатысушылардың 63,5% - ы осы аумақта туғаннан бері тұрады. Ерлерде БАҚ медианасы 130 (IQR 10) мм сын.бағ. болды, бұл әйелдерге қарағанда жоғары болды (p <0,001). Пациенттердің 90,1% - ында қалқанша безінің 1-2 дәрежеге дейін ұлғаюы байқалды. Ерлерде кортизол деңгейі жоғары болды-әйелдерде 319,0 (122,0) нмоль/л және 249,3 (145,2) нмоль/л (p = 0,020), ал инсулинге кері үрдіс бар. Қатысушылардың сыртқы гамма-сәулеленуінің орташа жеке дозалары 1.8 szv (IQR: 0.4–4.2) болды және ерлер мен әйелдер арасында статистикалық тұрғыдан ерекшеленбеді (p = 0.433).

Қорытынды: Жұмыстың осы кезеңінің нәтижелері үлгіні кеңейту, терең клиникалық-зертханалық және аспаптық тексеру, сондай-ақ экспонатталған адамдардың ұрпақтарында радиациялық әсердің соматикалық аурулардың дамуымен байланысын зерттеу үшін тіркелімді одан әрі жинақтау қажеттілігін көрсетеді.

Түйінді сөздер: *Семей ядролық полигоны; денсаулыққа қатысты әсерлер; скрининг; қауіп факторлары; радиация.*

Дәйексөз үшін:

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Introduction

The effects of chronic low-dose ionizing radiation on human health have been the subject of scientific research, with renewed interest in this area observed in recent years. One affected group is the population living in areas adjacent to the former Semipalatinsk Nuclear Test Site (SNTS). Since 1949, 468 tests have been conducted at the test site, including 117 above-ground tests [5]. Radiation contamination has affected significant areas, extending far beyond the test site's boundaries and into the eastern region of the Republic of Kazakhstan. Dosimetry studies indicate that the Beskaragay District of Abay Oblast is among the regions significantly affected by ionizing radiation [15].

Since the 1990s, studies have been conducted to examine the impact of nuclear tests on the health of people living in areas adjacent to the nuclear testing site, mainly based on dosimetric assessments [6, 8].

Notably, during the SNTS operation and after its closure, a large number of people continued to reside in the affected areas. Given this, it is of considerable interest to assess not only the direct effects of radiation exposure suffered by the population up until the cessation of testing in 1989, but also those in their descendants. This fact makes the epidemiological situation in the region unique.

Previous studies focused primarily on various aspects of assessing the health status of the population, but these studies generally included only individuals of the first generation, i.e., those directly exposed to ionizing radiation as a result of ground explosions. Thus, attempts were made to evaluate the oncologic effects [3, 4], cardiovascular [7, 14], and endocrine [9] effects of radiation exposure.

At the same time, the question of the long-term effects of chronic low-dose radiation on the human body, including third- and subsequent-generation individuals, remains unresolved. Available data on genetic alterations resulting from ionizing radiation, such as stable chromosomal aberrations, translocations, and other abnormalities, have also been reported for members of the first generation of the exposed population, including residents of the Beskaragay District.

Thus, a comprehensive analysis of the health status of the population, including the second and third generations of people exposed to ionizing radiation, is currently required.

The aim of this study was to conduct a preliminary assessment of the results of health screening in the population of the Beskaragay District, including the second and third generations of persons exposed to radiation as a result of nuclear weapons testing**.**

Materials and methods

Study Population

To comprehensively characterize the health status of the population representing the second and third generations of individuals exposed to ionizing radiation, a screening study was conducted among the population of the Beskaragay District. Exclusion criteria included the presence of central nervous system pathology that precluded screening and patient surveys, and individuals with no connection to the previously operating SNTS (residents who arrived after 1991).

The primary goal of screening was to identify individuals at higher risk of disease or pathological conditions in the population for subsequent monitoring and provision of medical care by primary care organizations. Screening allows for rapid provision of consultative medical care to a large population.

This preliminary analysis includes data on 222 patients living in the Beskaragay District, including residents of the villages of Dolon, Mostik, and Cheremushki. Sample size calculation was performed using the OpenEpi online program, ensuring 80% statistical power and 95% confidence. (https://www.openepi.com/SampleSize/SSCC.htm).

Stages and Main Research Methods

The first stage of the screening study included a survey on patients' health status, risks of developing non-communicable and socially significant diseases, diet, and lifestyle. The survey was conducted by completing specially developed questionnaires, which included socio-demographic questions and items on radiation exposure. Subsequently, patients were examined and their physical status was assessed. Blood pressure was measured

according to the recommendations of the European Society of Cardiology [17].

As part of the screening examination, blood samples were drawn for a complete clinical and biochemical blood test. Laboratory tests included thyroid peroxidase antibodies, TSH, free T4, glycated hemoglobin (as indicated), blood glucose, lipid profile (triglycerides, cholesterol, LDL), serum creatinine, ALT, AST, and blood electrolytes. Biochemical analysis of the parameters under study was performed using enzyme-linked immunosorbent assay (ELISA) using standard reagents.

Statistical Data Processing

Quantitative parameters were assessed for normal distribution using the Shapiro-Wilk test (for fewer than 50 subjects) or the Kolmogorov-Smirnov test (for more than 50 subjects). Normally distributed quantitative parameters were described using mean values (M) and standard deviations (SD), along with 95% confidence intervals (95% CI). In the absence of normal distribution, quantitative data were described using the median (Me) and interquartile range (IQR). Categorical data were described using absolute values and percentages. Comparisons between two groups for a non-normally distributed quantitative parameter were performed using the Mann-Whitney U test. Comparison of percentages in the analysis of four-field contingency tables was performed using the Pearson chi-square test (for expected values greater than 10) and Fisher's exact test (for expected values less than 10). Statistical analysis was performed using SPSS 20.0 (IBM Inc., New York, USA) and Jamovi (version 2.5.5; https://www.jamovi.org).

Results

The results of the preliminary analysis of the health status of the population of Beskaragay District, representing second- and third-generation descendants of victims of the STS activities, included 222 patients. Table 1 presents the socio-demographic characteristics of the patients. The mean age and distribution by age categories differed statistically significantly between men and women ($p = 0.0071$). Among men, the predominant age group was 40–49 years (34.5%), while among women, the majority were 30–39 years old (51.4%). There were no significant differences between men and women in terms of the duration of residence in the area ($p = 0.7281$); the majority of participants had lived here since birth (65.3%). Service in the armed forces, as expected, was characteristic predominantly of men — 35.7% versus 0.7% among women ($p < 0.001$). The level of education did not differ significantly between men and women ($p = 0.1311$); the most common education was secondary vocational education (36.0%), which is typical for the region. The proportion of individuals registered for dispensary care also did not differ by gender ($p = 0.2771$) and amounted to 25.7% of the total sample. Statistically significant differences were found in smoking status ($p = 0.021$), which was more common among men (21.4%) than women (10.1%). Similarly, alcohol consumption was more common among men (28.6%) than women (15.9%) ($p = 0.0241$).

Table 1.

Socio-demographic characteristics of people included in the study.

Parameter	Men (N=84)	Women (N=138)	Total (N=222)	p value
Age (years)				0.007[1]
<19	5 (6.0%)	1 (0.7%)	6 (2.7%)	
20-29	17 (20.2%)	33 (23.9%)	50 (22.5%)	
30-39	28 (33.3%)	71 (51.4%)	99 (44.6%)	
40-49	29 (34.5%)	28 (20.3%)	57 (25.7%)	
>50	5 (6.0%)	5 (3.6%)	10 (4.5%)	
Length of residence in the area (years)				0.728[1]
Since birth	58 (69.0%)	87 (63.0%)	145 (65.3%)	
> 1	1 (1.2%)	1 (0.7%)	2 (0.9%)	
3-5	0 (0.0%)	3 (2.2%)	3 (1.4%)	
Up to 10	5 (6.0%)	12 (8.7%)	17 (7.7%)	
10-30	14 (16.7%)	24 (17.4%)	38 (17.1%)	
>30	6 (7.1%)	11 (8.0%)	17 (7.7%)	
Service in the armed forces	30 (35.7%)	1 (0.7%)	31 (14.0%)	<0.001[1]
Education				0.131[1]
Incomplete secondary	19 (22.6%)	43 (31.2%)	62 (27.9%)	
Secondary vocational	28 (33.3%)	52 (37.7%)	80 (36.0%)	
Secondary	17 (20.2%)	14 (10.1%)	31 (14.0%)	
Higher	20 (23.8%)	29 (21.0%)	49 (22.1%)	
Dispensary registration	25 (29.8%)	32 (23.2%)	57 (25.7%)	0.277[1]
Currently smokes	18 (21.4%)	14 (10.1%)	32 (14.4%)	0.02[1]
Alcohol consumption	24 (28.6%)	22.0 (15.9%)	46 (20.7%)	0.024[1]

[1]Pearson's Chi-squared test

The physical status assessment was based on the classical approach (Table 2). Office systolic and diastolic BP (SBP and DBP, respectively) were studied. The median SBP in men was 130 (IQR 10) mmHg, which was significantly higher than in women ($p < 0.001$). DBP was also higher in men and amounted to 80 (IQR 10) mmHg, while in women it was 70 (IQR 20) mmHg ($p = 0.037$). It is worth noting the general tendency to maintain BP within the target range in accordance with currently valid international recommendations (McEvoy JW, 2024).

Heart rate (HR) did not differ significantly (p = 0.260). Signs of lymphadenopathy and thyroid enlargement did not show significant differences between men and women (p > 0.05). The majority of examined patients had an enlargement of the thyroid gland up to grade 1–2 (90.1%).

Of particular interest was the study of laboratory parameters in the study population. Men had higher levels of calcium (p = 0.003), sodium (p = 0.001), magnesium (p = 0.004), as well as liver enzymes - ALT (p < 0.001) and AST (p = 0.002). The average creatinine level was significantly higher in men - 77.7 (13.5) μmol/L versus 57.4 (10.4) μmol/L in women (p < 0.001). The median values of these parameters corresponded to the reference values, with a tendency to increase among men, which is due to gender differences.

HbA1c levels were within normal limits in both groups (~5.2%), indicating the absence of significant carbohydrate metabolism disorders in the majority of participants.

Table 2.

Clinical characteristics of study participants.

Parameter	Men (N=84)	Women (N=138)	p value
Systolic blood pressure (Me, IQR)	130 (10)	120 (10)	< 0.001[1]
Diastolic blood pressure (Me, IQR)	80 (10)	70 (20)	0.037[1]
Heart rate/min (Me, IQR)	70 (7.25)	68 (7.25)	0.260[1]
Lymphadenopathy	0 (0.0%)	2 (1.4%)	0.268[2]
Thyroid gland			0.881[2]
Increase to 1-2 degrees	76 (90.5%)	124 (89.9%)	
Increase to 3rd degree	8 (9.5%)	14 (10.1%)	
Laboratory data			
Ca, mmol/L (Me, IQR)	2.32 (0.1)	2.26 (0.12)	0.003
K mmol/L (Me, IQR)	4.6 (0.55)	4.5 (0.5)	0.749
Na mmol/L (Me, IQR)	141 (2.0)	140 (2.0)	0.001
Mg mmol/L (Me, IQR)	0.84 (0.05)	0.81 (0.06)	0.004
Glycated hemoglobin, % (Me, IQR)	5.19 (0.48)	5.16 (0.55)	0.263
Total protein (Me, IQR)	69.84 (4.25)	69.58 (6.07)	0.385
ALT U/L (Me, IQR)	21.91 (19.97)	13.89 (10.39)	<.001
AST U/L (Me, IQR)	19.13 (9.82)	16.52 (5.2)	0.002
Creatinine μmol/l (Me, IQR)	77.72 (13.51)	57.37 (10.38)	<.001
Thyroxine mIU/L (Me, IQR)	12.4 (1.85)	12.2 (1.65)	0.369
TSH mIU/L (Me, IQR)	1.65 (1.30)	1.91 (1.69)	0.627
ACTH pmol/L (Me, IQR)	17.9 (17.46)	16.7 (13.52)	0.993
Cortisol nmol/L (Me, IQR)	319.0 (122.0)	249.3 (145.2)	0.020
Insulin mIU/ml (Me, IQR)	5.2 (4.64)	6.79 (5.73)	0.048

[1]Mann–Whitney U test; [2]Pearson's Chi-squared test

Among the hormonal parameters, differences were found for cortisol, the level of which was higher in men - 319.0 (122.0) nmol/l versus 249.3 (145.2) nmol/l (p = 0.020), and insulin, the level of which, on the contrary, was higher in women - 6.79 (5.73) μU/ml versus 5.20 (4.64) μU/ml (p = 0.048). This finding reflects a moderately increased insulin resistance in women, which is physiologically explained by a higher content of adipose tissue and the effect of estrogens on glucose metabolism. Thyroid status indicators did not differ statistically and also corresponded to normal thyroid function despite the increase in its size detected during physical examination. For other parameters, including concentrations of potassium, total protein, thyroxine, TSH and ACTH, no statistically significant differences were found between men and women (p > 0.05).

The median individual external gamma radiation doses to the participants were 1.8 cSv (IQR: 0.4–4.2) and did not differ statistically between men and women (p = 0.433) (Table 3).

Table 3.

Characteristics of radiation doses of the subjects studied, as well as their previous generations (cSv, Median (IQR)).

Parameter	Male	Female	Total	p
Dose	2.2 (0.4 to 4.7)	1.7 (0.4 to 3.9)	1.8 (0.4 to 4.2)	0.433
Father's dose	4.7 (0.0 to 29.6)	4.6 (0.0 to 22.4)	4.7 (0.0 to 25.8)	0.898
Mother's dose	5.0 (0.0 to 19.3)	5.1 (0.0 to 16.8)	5.0 (0.0 to 17.8)	0.964

Figure 1 shows the distribution of individual external gamma radiation doses (cSv) among subjects in various age categories. The median radiation dose gradually increased with age, reaching a minimum value (less than 1 cSv) among participants under 19 years of age, increasing between 20 and 39 years of age, and reaching a maximum among patients over 40 years of age, reaching up to 20 cSv among some respondents over 50 years of age.

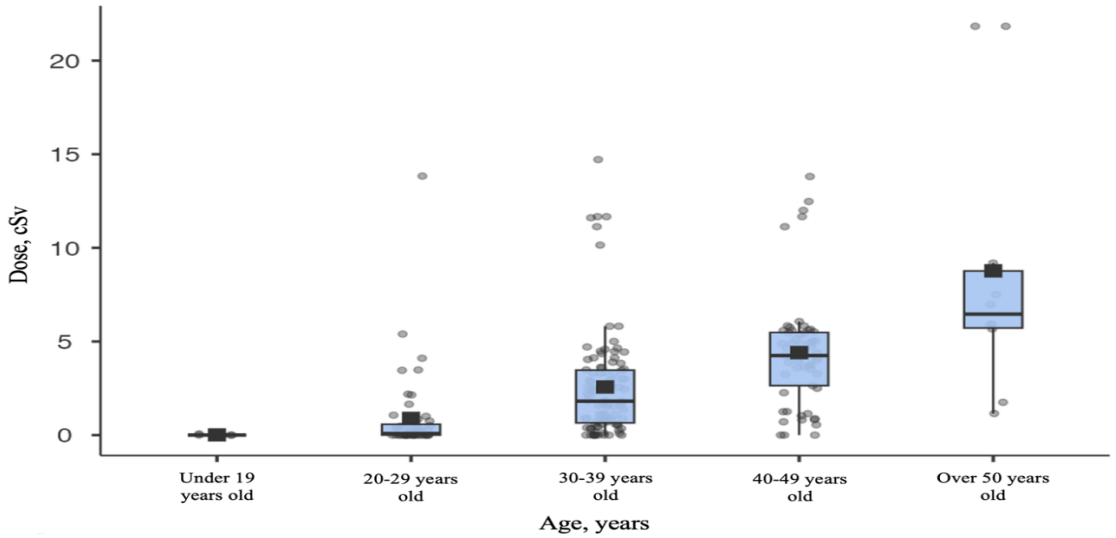

Figure 1. Doses of descendants of persons exposed to radiation, depending on age.

Discussion

Assessing the health status of the population affected by the activities of the STNS is a critical issue and remains relevant today. This is primarily due to the large population living in the adjacent areas, including those directly exposed to ionizing radiation, as well as their descendants. Studies at various levels (local and international) conducted over the past 30 years have demonstrated the need for further detailed analysis of radiation effects on the health of exposed populations. It is emphasized that all subsequent scientific research should focus specifically on the subsequent generations [14, 11].

The results we present demonstrate a preliminary assessment of the health status of individuals who are second - and third-degree descendants of individuals affected by the STS activities.

All study participants currently reside in the Beskaragay District, which is located in the zone of maximum radiation risk [2, 8]. The analysis revealed that the majority of participants in the registry are middle-aged patients (men were predominantly 40–49 years old (34.5%), and women were predominantly 30–39 years old (51.4%). It is important to note that the majority of participants (65.3%) had lived in the area since birth. This fact is of significant importance for the interpretation of further large-scale studies on the relationship between low-dose radiation and the development of stochastic and genetically mediated diseases. The degree of participation in medical checkups is an important indicator reflecting the preventive principle of healthcare organization. However, preliminary results demonstrate a relatively low rate of participation in medical checkups, amounting to 25.7%, with no significant differences between men and women. Traditional risk factors—smoking and alcohol consumption—were more common among men (21.4% smoking and 28.6% alcohol consumption, p=0.021 and p=0.0241, respectively), which is consistent with global and regional data.

The assessment of the physical status of patients is of great interest. It was found that the median value of office SBP was 130 (IQR 10) mmHg in men and 120 (IQR 10) mmHg in women ($p < 0.001$). DBP was also higher in men and was 80 (IQR 10) mmHg and 70 (IQR 20) mmHg in women ($p = 0.037$). This level corresponds to the target BP value for most patients [12]. However, this requires a more detailed definition. According to current recommendations, SBP in the range of 120-139 mmHg should be considered elevated BP, which was previously called prehypertension [12]. Thus, this category of patients requires more targeted dynamic monitoring. Heart rate (HR) did not differ significantly ($p = 0.260$) between men and women, amounting to 70 (IQR 7.25) and 68 (IQR 7.25) beats per minute, respectively. In recent decades, HR has received great attention, and experts recommend considering a resting HR of over 80 beats per minute as one of the risk factors for the development of cardiovascular events. This fact is especially important in patients with elevated blood pressure, representing a variant of chronic hyperactivation of the sympathetic nervous system [13]. Available research results emphasize the association between ionizing radiation and the development of hypertension, including in individuals living in areas adjacent to the STNS. Thus, it was found that age-adjusted odds ratios for arterial hypertension statistically significantly increase in groups with higher radiation levels [11]. In addition, it was found that cardiovascular diseases in general were diagnosed significantly more often than in the control group (RR=2.27) and among the population of the Republic of Kazakhstan (RR=2.25) [7].

The presented analysis showed that 90.1% of the patients examined had grade 1–2 thyroid enlargement. In this regard, it is important to note that a cross-sectional study examining the radiation risks of thyroid enlargement demonstrated a link between this pathology and the length of residence in radiation-contaminated areas and the patient's age at the time of exposure [9, 10].

The results demonstrate statistically significant gender differences in a number of laboratory parameters. Men had higher levels of calcium, sodium, magnesium, creatinine, transaminases (ALT, AST), and cortisol, which is likely related to physiological characteristics of male metabolism—greater muscle mass, increased anabolic activity, and enhanced functioning of the hypothalamic-pituitary-adrenal axis. Higher liver enzyme levels in men may also reflect greater physical activity and muscle catabolism, rather than liver pathology. Meanwhile, women had higher insulin levels, consistent with literature data on the tendency of women to have moderately

elevated insulin resistance due to a higher body fat percentage and the influence of estrogens on carbohydrate metabolism. The absence of differences in TSH, thyroxine, and ACTH levels indicates comparable endocrine regulation activity in both sexes.

The fact that all participants included in the analysis had a calculated radiation dose is also crucial, which is undoubtedly important for further research into the effects of radiation on public health. For example, the analysis shows a gradual increase in the median dose with age, reaching up to 20 cSv for some respondents over 50 years of age. This distribution reflects the cumulative effect of radiation exposure associated with age and duration of residence in contaminated areas [1]. Overall, there is a tendency for individual doses to increase with age, which is consistent with historical data on the heterogeneity of background radiation in different periods [15, 16].

Conclusion

Thus, the obtained data confirm the relevance of continuing research to assess the possible long-term effects of chronic low-dose irradiation and the intergenerational transmission of radiation-mediated changes among the population living in the territory of the former STS. The results of this phase of the study highlight the need for an expanded sample, in-depth clinical, laboratory, and instrumental examinations, and further registry development to study the relationship between radiation exposure and the development of somatic diseases in the descendants of exposed individuals.

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PRELIMINARY ANALYSIS OF THE HEALTH STATUS AND RADIATION DOSES OF RESIDENTS OF THE ABAY DISTRICT OF THE ABAY REGION, WHO ARE DESCENDANTS OF PERSONS EXPOSED TO RADIATION DUE TO NUCLEAR WEAPONS TESTS

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Abstract

Introduction. The relevance of this study is determined by the significant number of population groups in the regions of Kazakhstan adjacent to the former Semipalatinsk Nuclear Test Site (SNS), who still live under environmental stress and the associated medical and social consequences.

Aim. This study aimed to conduct a preliminary analysis of the health status and radiation doses of residents of the Abay District of the Abay Region, who are second- and third-generation descendants of people exposed to radiation due to nuclear weapons testing.

Materials and Methods. Study design: cross-sectional screening study. Physical examinations and laboratory tests were conducted, along with a study of sociodemographic factors and radiation doses among the parents and grandparents of the target population of 233 individuals aged 18-65 years in the villages of Karaul and Sarzhal in the Abay District of the Abay Region. Statistical analysis was performed using SPSS 20.0 (IBM Inc., New York, USA) and Jamovi (version 2.5.5; https://www.jamovi.org).

Results. The vast majority of participants included in the study were aged 29 years or younger or 30-39 years. Approximately 70% had lived in the area since birth or for over 30 years. Enlarged peripheral lymph nodes were observed in 6.1% of women. Enlarged thyroid glands were observed in almost all study participants. The median ACTH level in men was slightly elevated compared to normal values. The study results indicate a range of high radiation doses for both first- and second-generation exposed individuals.

Conclusion. To determine the relationship between radiation doses and stochastic and deterministic health effects in the study population, a comparative analysis is required across different dose groups and a control group of people not exposed to radiation.

Keywords: *Semipalatinsk Nuclear Test Site; health effects; screening; radiation; offspring.*

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Резюме

ПРЕДВАРИТЕЛЬНЫЙ АНАЛИЗ СОСТОЯНИЯ ЗДОРОВЬЯ И ДОЗ ОБЛУЧЕНИЯ ЖИТЕЛЕЙ АБАЙСКОГО РАЙОНА ОБЛАСТИ АБАЙ, ЯВЛЯЮЩИХСЯ ПОТОМКАМИ ЛИЦ, ПОДВЕРГШИХСЯ РАДИАЦИОННОМУ ВОЗДЕЙСТВИЮ ВСЛЕДСТВИЕ ИСПЫТАНИЙ ЯДЕРНОГО ОРУЖИЯ

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Введение. Актуальность данного исследования обусловлена значительной численностью групп населения регионов Казахстана, прилегающих к территории бывшего Семипалатинского ядерного полигона (СЯП), проживающих в условиях экологической нагрузки, и связанными с ней медико-социальными последствиями.

Цель. Целью нашего исследования является предварительный анализ состояния здоровья и дозовых нагрузок жителей Абайского района области Абай, являющихся потомками второго и третьего поколений лиц, подвергшихся радиационному воздействию вследствие испытаний ядерного оружия.

Материалы и методы. Дизайн исследования: поперечное скрининговое исследование. Проведено физикальное обследование и лабораторное исследование, а также исследование социально-демографических факторов и доз облучения родителей, дедушек и бабушек целевого населения сел Караул и Саржал Абайского района области Абай, всего 233 человека в возрасте 18-65 лет. Статистический анализ проводился с применением программ SPSS 20.0 (IBM Inc., New York, USA) и Jamovi (версия 2.5.5; https://www.jamovi.org).

Результаты. Абсолютное большинство лиц, включенных в исследование, было представлено возрастными группами до 29 лет и 30-39 лет. Около 70% из них проживали в данной местности с рождения, либо, более 30 лет. У 6,1% женщин наблюдалось увеличение размеров периферических лимфатических узлов. Практически у всех участников исследования наблюдалось увеличение размеров щитовидной железы. Медианный уровень АКТГ у мужчин был несколько повышен в сравнении с нормальными показателями. Результаты исследования свидетельствуют о диапазоне высоких доз облучения как для экспонированных лиц первого, так и второго поколений.

Заключение. Для определения связи между дозами облучения и стохастическими и детерминированными эффектами в отношении состояния здоровья исследуемых жителей требуется проведение сравнительного анализа в разных дозовых группах и контрольной группе лиц, не подвергавшихся радиационному воздействию.

Ключевые слова: *Семипалатинский ядерный полигон; скрининговые исследования, состояние здоровья, радиация, потомки.*

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Түйіндеме

ЯДРОЛЫҚ ҚАРУ СЫНАҚТАРЫНЫҢ САЛДАРЫНАН РАДИАЦИЯЛЫҚ ӘСЕРГЕ ҰШЫРАҒАН АДАМДАРДЫҢ ҰРПАҚТАРЫ БОЛЫП ТАБЫЛАТЫН АБАЙ ОБЛЫСЫ, АБАЙ АУДАНЫ ТҰРҒЫНДАРЫНЫҢ ДЕНСАУЛЫҚ ЖАҒДАЙЫ МЕН СӘУЛЕЛЕНУ ДОЗАЛАРЫН АЛДЫН АЛА ТАЛДАУ

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Кіріспе. Бұл зерттеудің өзектілігі бұрынғы Семей ядролық полигоны (СЯП) аумағына іргелес Қазақстан өңірлерінде тұратын халық топтарының айтарлықтай санының қазіргі уақытқа дейін экологиялық жүктемесі жоғары жағдайда өмір сүріп келе жатқанына және медициналық-әлеуметтік салдарларымен байланысты.

Мақсат. Ядролық қару сынақтарының салдарынан радиациялық әсерге ұшыраған адамдардың екінші және үшінші буын ұрпақтары болып табылатын Абай облысы, Абай ауданы тұрғындарының денсаулық жағдайы мен сәулелік жүктемелерін алдын ала талдау.

Материалдар мен әдістер. Зерттеу дизайны: көлденең скринингтік зерттеу. Физикалық тексеру мен зертханалық талдау, сондай-ақ әлеуметтік-демографиялық факторлар мен ата-аналарының, әжелері мен аталарының сәулелену дозаларын зерттеу жүргізілді. Зерттеу Абай облысы Абай ауданының Қарауыл және Саржал ауылдарының 18-ден 65 жасқа дейінгі 233 тұрғынын қамтыды. Статистикалық талдау SPSS 20.0 (IBM Inc., New York, USA) және Jamovi (нұсқа 2.5.5; https://www.jamovi.org) бағдарламалары арқылы жүргізілді.

Нәтижелер. Зерттеуге қатысқан адамдардың басым көпшілігі 29 жасқа дейінгі және 30–39 жас аралығындағы топтарға жатты. Олардың шамамен 70%-ы осы өңірде туған немесе 30 жылдан астам уақыт бойы тұрып келеді. Әйелдердің 6,1%-ында шеткі лимфа түйіндерінің ұлғаюы байқалды. Зерттеуге қатысушылардың барлығына дерлік қалқанша безінің үлкеюі тән болды. Ерлердегі адренокортикотропты гормон (АКТГ) деңгейінің медианалық көрсеткіші қалыпты мәндерден сәл жоғары болды. Зерттеу нәтижелері сәулеленуге ұшыраған бірінші және екінші буын өкілдері үшін жоғары дозалық ауқымның бар екенін көрсетті.

Қорытынды. Сәулелену дозалары мен денсаулық жағдайына әсер ететін стохастикалық және детерминистік факторлар арасындағы байланысты анықтау үшін әртүрлі дозалық топтар мен радиациялық әсерге ұшырамаған бақылау тобы арасында салыстырмалы талдау жүргізу қажет.

***Түйінді сөздер**: Семей ядролық полигоны; скринингтік зерттеулер, денсаулық жағдайы, радиация, ұрпақтар.*

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Introduction

The relevance of this study is determined by the significant number of population groups in the regions of Kazakhstan adjacent to the former Semipalatinsk Nuclear Test Site (SNTS), who still live under environmental stress and the associated medical and social consequences [1]. Since the closure of the nuclear test site in 1989, a considerable amount of information has appeared in the media that does not always accurately reflect the real situation regarding radiation contamination and its consequences for public health. The population has lived under the threat of radiation for many decades, fearing for their lives, health, and the future of their descendants [10].

Considering that nuclear weapons tests conducted over 40 years at the Semipalatinsk nuclear test site caused significant damage to human health and the environment

and led to an increase in overall morbidity and mortality among the population, the areas adjacent to the test site in the East Kazakhstan, Pavlodar, and Karaganda regions were recognized as an environmental disaster zone [5, 8]. The long-term effects of nuclear testing, passed down from generation to generation, continue to impact the population today. Currently, the studied territories of the Abay region are home not only to people who were directly exposed to external gamma irradiation and internal chronic irradiation, but also to their descendants of the second and third generations, for whom the genetically determined effects of ionizing radiation contribute to increasing health damage [2, 6]. While a significant number of domestic and international studies have been directed toward examining the health status of the descendants of the first and second generations of the designated population in previous years, the children and grandchildren of exposed individuals currently require a comprehensive assessment of both their somatic health and genetic disorders that could lead to the manifestation of stochastic or deterministic effects in the form of hereditary diseases or oncological problems.

A comprehensive assessment of the health indicators of residents of ecologically unfavorable areas underlies the development of primary and secondary prevention programs for their health problems. This assessment requires a thorough study of the demographic indicators and ecological trajectory of the affected population [11].

The aim of our study was to conduct a preliminary analysis of the health status and radiation doses of residents of the Abay District of the Abay Region, who are second- and third-generation descendants of people exposed to radiation due to nuclear weapons testing.

Materials and methods

The study population comprised residents of the Abay district of the Abay region, who are descendants of the population exposed to radiation as a result of nuclear weapons testing in the second and third generations, living in areas of environmental risk. Exclusion criteria were organic central nervous system damage, decompensated somatic diseases; history of viral hepatitis B and C; individuals not associated with nuclear weapons testing at the SNTS for various reasons.

The study focused on the health status of individuals living in environmental risk areas. Study design: cross-sectional screening study.

A physical examination and laboratory testing were conducted, along with a study of socio-demographic factors and radiation doses received by parents and grandparents that could affect the health of the target population of 233 individuals aged 18-65 years in the villages of Karaul and Sarzhal in the Abay District. These included on-site visits in accordance with the study protocol and the addition of information on the individuals to the State Scientific Automated Medical Registry (SSAMR) database. The SSAMR is located at the Research Institute of Radiation Medicine and Ecology and is the official database of all individuals involved in past radiation incidents related to nuclear weapons testing at the SNTS.

Information on personal dose load was copied from the SSAMR for parents, grandparents and relatives of individuals included in the study (if information on them was available in the SSAMR).

Research methods. For each patient included in the study of somatic and psychological health, an "Examination Form" was created, including: the patient's informed consent to participate in the health study; "Questionnaire for the participant in the scientific research project" to assess the clinical condition of the patient (anamnesis, chronic diseases, anthropometry, lymph node status, thyroid gland size, physical examination, complete blood count (CBC), biochemical parameters (calcium, potassium, sodium, magnesium, glycated hemoglobin, total protein, ALT, AST, creatinine, thyroid hormones - T4, TSH, TPO antibodies, stress hormones - ACTH, cortisol, insulin). The examination form also included parameters characterizing the socio-demographic characteristics and harmful habits of the study participants.

The sample size was calculated based on the number of residents of the area recorded in the SSAMR (the general population for the study group) during the period of weapon testing at the SNTS. The prevalence of somatic disorders among individuals exposed to radiation is 30-40% [7]. The Sample XS statistical program was used to determine the sample size, with a margin of error of 5%; the design effect is considered to be 1.0 by default.

The sample was representative, that is, it corresponded to the main characteristics of the population being studied, such as age, gender, and socio-professional status.

Statistical data processing:

Quantitative parameters were assessed for normal distribution using the Shapiro-Wilk test (for fewer than 50 subjects) or the Kolmogorov-Smirnov test (for more than 50 subjects). Normally distributed quantitative parameters were described using mean values (M) and standard deviations (SD), along with 95% confidence intervals (95% CI). In the absence of normal distribution, quantitative data were described using the median (Me) and interquartile range (IQR). Categorical data were described using absolute values and percentages. Comparisons between two groups for a non-normally distributed quantitative parameter were performed using the Mann-Whitney U test. Comparison of percentages in the analysis of four-field contingency tables was performed using the Pearson chi-square test (for expected value greater than 10) and Fisher's exact test (for expected value less than 10). Statistical analysis was performed using SPSS 20.0 (IBM Inc., New York, USA) and Jamovi (version 2.5.5; https://www.jamovi.org).

Results

Table 1 presents the socio-demographic characteristics of the study population. The vast majority of people included in the study were third-generation descendants of exposed individuals, aged up to 29 years and 30-39 years (78.1% in total). About 70% of them had lived in the given area since birth or for more than 30 years. Differences in the parameter of residence in the given area between men and women were statistically significant (p=0.031). This selection of study subjects was due to the fact that information for inclusion in the study was taken from the SSAMR, which provides a high degree of reliability of their belonging to radiation risk groups. 57.9% of study participants had secondary vocational education, and 10.3% had higher education. About 70% of men had previously served in the armed forces. Only 19.8% of men and 1.4% of women were nicotine dependent ($p < 0.001$), and alcohol consumption was noted in the survey by 14% of men and 7.5% of women.

Table 1.

Socio-demographic characteristics of the studied population.

Parameter	Male (N=86)	Female (N=147)	Total (N=233)	p value
Age (years)				
<29	56.0 (65.1%)	101.0 (68.7%)	157.0 (67.4%)	0.8521
30-39	11.0 (12.8%)	14.0 (9.5%)	25.0 (10.7%)	
40-49	18.0 (20.9%)	31.0 (21.1%)	49.0 (21.0%)	
> 50	1.0 (1.2%)	1.0 (0.7%)	2.0 (0.9%)	
Duration of residence in the area				
Since birth	66.0 (76.7%)	84.0 (57.1%)	150.0 (64.4%)	0.0311
<1 year	14.0 (16.3%)	46.0 (31.3%)	60.0 (25.8%)	
Up to 10 years	0.0 (0.0%)	4.0 (2.7%)	4.0 (1.7%)	
10-30 years	2.0 (2.3%)	5.0 (3.4%)	7.0 (3.0%)	
>30 years	4.0 (4.7%)	8.0 (5.4%)	12.0 (5.2%)	
Military service	59.0 (68.6%)	1.0 (0.7%)	60.0 (25.8%)	<0.0011
Education				
Incomplete secondary	15.0 (17.4%)	31.0 (21.1%)	46.0 (19.7%)	0.7351
Secondary vocational	49.0 (57.0%)	86.0 (58.5%)	135.0 (57.9%)	
Secondary	11.0 (12.8%)	17.0 (11.6%)	28.0 (12.0%)	
Higher	11.0 (12.8%)	13.0 (8.8%)	24.0 (10.3%)	
Dispensary registration	13.0 (15.1%)	29.0 (19.7%)	42.0 (18.0%)	0.2471
Currently smokes	17.0 (19.8%)	2.0 (1.4%)	19.0 (8.2%)	<0.0011
Alcohol consumption	12.0 (14.0%)	11.0 (7.5%)	23.0 (9.9%)	0.1101
Pearson's Chi-squared test				

The clinical parameters of the subjects and the median laboratory values are presented in Table 2. Blood pressure measurements showed that the median values were within the target range for both men and women. Heart rate parameters were also within the normal range for both sexes.

Table 2.

Clinical characteristics of study participants.

Parameter	Male (N=86)	Female (N=147)	p value
Systolic blood pressure (Me, IQR)	110 (10)	110 (20)	0.039[1]
Diastolic blood pressure (Me, IQR)	80 (10)	70 (10)	<0.001[1]
Heart rate/min (Me, IQR)	80 (2)	80 (5)	0.018[1]
Lymphadenopathy:			
Enlargement	0.0 (0.0%)	9 (6.1%)	0.029[2]
Significant enlargement	1 (1.2%)	0 (0.0%)	
Thyroid gland			
Increase to 1-2 degrees	63 (73.25%)	106 (72.1%)	0.802[1]
Increase to 3rd degree	23 (26.75%)	41 (27.9%)	
Laboratory data			
Ca, mmol/L (Me, IQR)	2.32 (0.1)	2.29 (0.13)	0.029
K, mmol/L (Me, IQR)	4.1 (0.37)	4.2 (0.4)	0.144
Na, mmol/L (Me, IQR)	141 (2.0)	141 (2.0)	0.415
Mg, mmol/L (Me, IQR)	0.79 (0.09)	0.78 (0.07)	0.293
Glycated hemoglobin, % (Me, IQR)	5.24 (0.54)	5.15 (0.38)	0.231
Total protein (Me, IQR)	72.18 (5.24)	71.2 (4.09)	0.613
ALT U/L (Me, IQR)	15.6 (15.46)	11.38 (8.73)	0.208
AST U/L (Me, IQR)	18.12 (7.25)	12.45 (6.5)	0.813
Creatinine μmol/L (Me, IQR)	64.56 (14.9)	54.87 (14.0)	<.001
Thyroxine mIU/L (Me, IQR)	12.2 (1.9)	11.8 (1.6)	0.115
TSH mIU/L (Me, IQR)	1.52 (1.67)	1.79 (1.47)	0.993
ACTH pmol/L (Me, IQR)	19.9 (15.3)	13.4 (11.79)	0.114
Cortisol nmol/L (Me, IQR)	286.0 (138.7)	256.9 (110.9)	0.097
Insulin mIU/ml (Me, IQR)	6.5 (5.8)	7.1 (5.8)	0.230

[1]Mann–Whitney U test; [2]Pearson's Chi-squared test
ALT – alanine transferase, AST – aspartate transferase, TSH – thyroid-stimulating hormone, ACTH – adrenocorticotropic hormone, HR – heart rate

Enlarged peripheral lymph nodes were observed in 6.1% of women. Almost all study participants had an enlarged thyroid gland, which is not typical for the general population, as literature suggests that women are significantly more likely to have thyroid disease than men [12]. Median levels of calcium, potassium, sodium, and magnesium, glycated hemoglobin, liver enzymes, and creatinine were within normal limits in both men and women. Creatinine levels in women were, on average, statistically significantly lower than in men, consistent with accepted norms for this laboratory parameter [9]. Free thyroxine levels in both sexes were also within reference limits, although closer to the lower limit of normal. The median ACTH level in men was slightly elevated compared to normal values (below 18 pmol/L in the morning, below 11 pmol/L in the evening), which may indicate stress in the adaptation system. Cortisol levels were within normal limits in both men and women. Insulin levels were also within normal limits in both men and women.

When assessing the health status of second- and third-generation descendants of individuals directly exposed to ionizing radiation, we were particularly interested in assessing the radiation doses to their immediate relatives (parents and grandparents) since this could shed light on the presence of a link between radiation-induced genetic effects. The median radiation doses of the individuals studied were 6.4 cSv for both sexes, 6.6 cSv for women and 5.7 cSv for men. The parental doses were significantly higher: 67.4 cSv and 50 cSv for women and men, respectively, from the father, and 42.4 cSv and 35 cSv from the mother. It should be noted that the median radiation doses to grandparents, both on the paternal and maternal sides, were in the high-dose range of 95.8–100.0 cSv (Table 3).

Table 3.

Characteristics of radiation doses of the subjects studied, as well as their previous generations (cSv, Median (IQR)).

Parameter	Male	Female	Total	p
Dose	5.7 (2.2-12.6)	6.6 (2.7- 11.8)	6.4 (2.6-12.3)	0.588
Father's dose	50.0 (25.7-100.0)	67.4 (25.4- 100.0)	62.9 (25.7-100.0)	0.879
Mother's dose	35.0 (18.5- 99.8)	42.4 (23.8- 100.0)	37.1 (20.0- 100.0)	0.693
Paternal grandfather's dose	100.0 (93.8-100.0)	95.8 (87.9- 100.0)	96.8 (90.0- 100.0)	0.073
Paternal grandmother's dose	100.0 (95.2- 100.0)	100.0 (92.3- 100.0)	100.0 (93.0- 100.0)	0.776
Maternal grandfather's dose	96.1 (91.4- 100.0)	96.8 (96.1- 100.0)	96.5 (92.6- 100.0)	0.677
Maternal grandmother's dose	100.0 (100.0-100.0)	98.1 (95.5- 100.0)	100.0 (96.2- 100.0)	0.561

When assessing the radiation doses to the descendants of individuals exposed to radiation, depending on age, it was found that the highest doses were received by older individuals: for second-generation descendants over 50 years old, the average doses ranged from 15 to 22 cSv, for those 40-49 years old - from 10 to 20 cSv, while for third-generation descendants, the peak radiation dose, on average, was 4-5 cSv (Figure 1).

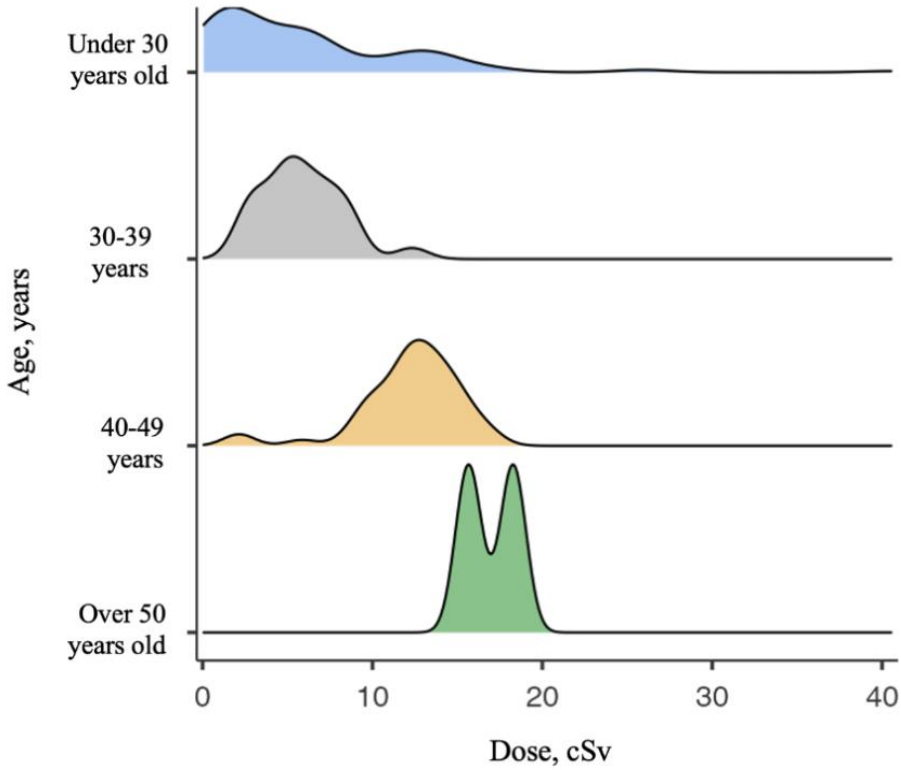

Figure 1. Doses of descendants of persons exposed to radiation, depending on age.

Discussion

Thus, our preliminary analysis of the health status of second- and third-generation descendants of the radiation-exposed population living around the nuclear testing site revealed a high range of doses for both individuals directly exposed to nuclear weapons testing and their second-generation descendants. This is due to the fact that these individuals were born to irradiated parents and were directly exposed both in utero and during childhood, when target organs are most sensitive to radiation exposure [4]. Furthermore, they received relatively high doses of internal radiation through the food chain in the form of milk from domestic cows consuming grass in radiation-contaminated areas, which negatively impacted thyroid function [3]. This is confirmed by our findings of thyroid enlargement in virtually all study participants, even third-generation offspring, despite the low-dose radiation range. Although median levels of free thyroxine and thyroid-stimulating hormone were within normal limits, the fact that thyroxine levels were closer to the lower limits of normal, as well as elevated ACTH levels, indicates stress on the adaptive system of the study participants.

Our study has several limitations, due to the recent completion of screening studies and the insufficient availability of the database for the control area, which is not associated with radiation events related to nuclear weapons testing. Therefore, a comparative analysis of health indicators for the different dose groups and the control group will be conducted later.

Conclusion

This study presents the results of a descriptive analysis of health indicators and radiation doses in second- and third-generation descendants of residents of the Abay District of the Abay Region exposed to radiation from nuclear weapons testing. The study results demonstrate a range of high radiation doses for both first- and second-generation exposed individuals. To determine the relationship between radiation doses and stochastic and deterministic effects on the health of the study residents, a comparative analysis is required across different dose groups and a control group of individuals not exposed to radiation.

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TRENDS AND DISPARITIES IN CANCER MORBIDITY IN KAZAKHSTAN: A REGIONAL AND AGE-BASED ANALYSIS FOR 2014-2024

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Abstract

Introduction. The overall cancer burden in the Republic of Kazakhstan is increasing. However, existing data may not fully capture the specific trends and disparities among different demographic groups and regions. A detailed understanding of these patterns is critical for effective public health planning and resource allocation.

Aim of the Study: To conduct a comprehensive analysis of cancer morbidity trends in Kazakhstan from 2014 to 2024, identifying key temporal, regional, and age-based disparities, with a particular focus on comparing pediatric and adult populations.

Materials and methods: A retrospective ecological study was conducted using official, aggregated national health statistics. Temporal trends were analyzed by calculating the percentage growth in cases for adults and children (aged 0-17). Regional disparities were assessed using morbidity rates per 100,000 population for the year 2024.

Results: The most striking finding was a disproportionate and rapid increase in pediatric cancer morbidity, which grew by 127.9% over the eleven years, significantly exceeding the 84.7% growth observed in the adult population. Overall, total registered cases increased by 85.2%. The study also confirmed significant geographical inequality, with morbidity rates in the industrial East Kazakhstan Region (2,150.2 per 100,000) being nearly three times higher than in the western Mangystau Region (775.1).

Conclusion: These findings signal the need to reassess national priorities in oncological care. The alarming and out-of-proportion rise in childhood cancer, coupled with persistent regional inequalities, demands an immediate strategic focus on developing pediatric oncology services, including enhanced research into causative factors and strengthening specialized healthcare infrastructure.

Keywords: *Cancer, morbidity, epidemiology, Kazakhstan, regional disparity, public health, pediatric oncology.*

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Резюме

ТЕНДЕНЦИИ И ДИСПРОПОРЦИИ В ОНКОЛОГИЧЕСКОЙ ЗАБОЛЕВАЕМОСТИ В КАЗАХСТАНЕ: РЕГИОНАЛЬНЫЙ И ВОЗРАСТНОЙ АНАЛИЗ ЗА 2014-2024 ГОДЫ

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Актуальность: В Республике Казахстан отмечается рост общего бремени онкологических заболеваний. Однако существующие данные не в полной мере отражают специфические тенденции и диспропорции внутри различных демографических групп и регионов. Такое детальное понимание необходимо для эффективного планирования и распределения ресурсов в системе здравоохранения.

Цель исследования: Провести комплексный анализ динамики онкологической заболеваемости в Казахстане за период с 2014 по 2024 год, выявив ключевые тенденции, региональные и возрастные диспропорции, с особым акцентом на сравнение педиатрической и взрослой популяций.

Материал и методы: Проведено ретроспективное экологическое исследование на основе официальных агрегированных данных национальной медицинской статистики. Временные тенденции анализировались путем расчета процентного роста случаев для взрослых и детей (0-17 лет). Региональные различия оценивались по интенсивным показателям заболеваемости на 100 000 населения за 2024 год.

Результаты: Наиболее значимым результатом стал непропорционально быстрый рост заболеваемости раком у детей, которая за одиннадцатилетний период увеличилась на 127,9%, что значительно превышает рост в 84,7%, наблюдаемый среди взрослого населения. В целом, общее число зарегистрированных случаев выросло на 85,2%. Исследование также подтвердило значительное географическое неравенство: интенсивные показатели в промышленной Восточно-Казахстанской области (2150,2 на 100 000) почти в три раза превышали показатели в западной Мангистауской области (775,1).

Заключение: Полученные данные служат сигналом о необходимости пересмотра национальных приоритетов в области онкологической помощи. Тревожный и опережающий рост заболеваемости раком у детей, наряду с сохраняющимся региональным неравенством, требует незамедлительного стратегического фокуса на развитии педиатрической онкологической службы, включая углубленное изучение причинных факторов и укрепление специализированной медицинской инфраструктуры.

Ключевые слова: рак, заболеваемость, эпидемиология; Казахстан, региональное неравенство, общественное здравоохранение, детская онкология.

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Түйіндеме

ҚАЗАҚСТАНДАҒЫ ОНКОЛОГИЯЛЫҚ АУРУШАҢДЫҚТАҒЫ ҮРДІСТЕР МЕН ДИСПРОПОРЦИЯЛАР: 2014–2024 ЖЫЛДАР АРАЛЫҒЫНДАҒЫ ӨҢІРЛІК ЖӘНЕ ЖАС ЕРЕКШЕЛІКТЕРІНЕ ТАЛДАУ

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Кіріспе: Қазақстан Республикасында онкологиялық аурулардың жалпы жүктемесінің артуы байқалады. Алайда қолда бар деректер әртүрлі демографиялық топтар мен өңірлер арасындағы нақты үрдістер мен диспропорцияларды толық көрсете алмайды. Мұндай жан-жақты түсінік денсаулық сақтау жүйесінде ресурстарды тиімді жоспарлау мен бөлу үшін қажет.

Мақсаты: 2014–2024 жылдар аралығында Қазақстандағы онкологиялық аурушаңдықтың серпінін кешенді түрде талдау, негізгі үрдістерді, өңірлік және жас ерекшеліктеріне байланысты айырмашылықтарды анықтау, әсіресе педиатриялық және ересек популяциялар арасындағы салыстыруға баса назар аудару.

Материалдар және әдістер: Зерттеу ресми ұлттық медициналық статистиканың жинақталған деректері негізінде ретроспективті экологиялық зерттеу ретінде жүргізілді. Уақытша үрдістер ересектер мен балалар (0–17 жас) арасындағы жағдайлардың пайыздық өсуін есептеу арқылы бағаланды. Өңірлік айырмашылықтар 2024 жылға арналған 100 000 халыққа шаққандағы аурушаңдықтың қарқынды көрсеткіштері бойынша есептелді.

Нәтижелері: Ең маңызды нәтиже – балалар арасындағы қатерлі ісік ауруларының шектен тыс қарқынды өсуі болды: он бір жыл ішінде көрсеткіш 127,9%-ға артқан, бұл ересектер арасында байқалған 84,7%-дық өсімнен

әлдеқайда жоғары. Жалпы тіркелген жағдайлар саны 85,2%-ға көбейген. Сондай-ақ, зерттеу айтарлықтай географиялық теңсіздікті растады: өнеркәсіптік Шығыс Қазақстан облысындағы қарқынды көрсеткіш (100 000 адамға 2150,2) батыстағы Маңғыстау облысымен (775,1) салыстырғанда шамамен үш есе жоғары.

Қорытындылар: Алынған деректер онкологиялық көмекті ұйымдастыруда ұлттық басымдықтарды қайта қарау қажеттігін көрсетеді. Балалар арасындағы қатерлі ісікке шалдығудың алаңдатарлық әрі жедел өсуі және өңірлік теңсіздіктің сақталуы педиатриялық онкологиялық қызметті дамытуға стратегиялық назар аударуды талап етеді. Бұл – себептік факторларды терең зерттеу мен мамандандырылған медициналық инфрақұрылымды күшейтуді қамтиды.

Түйінді сөздер: *қатерлі ісік, аурушаңдық, эпидемиология, Қазақстан, өңірлік теңсіздік, қоғамдық денсаулық сақтау, балалар онкологиясы.*

Дәйексөз үшін:

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Introduction

Cancer represents a significant and growing public health challenge in the Republic of Kazakhstan, mirroring global trends where oncological diseases are a leading cause of mortality [12]. According to the Global Cancer Observatory (GLOBOCAN), in 2022 alone, there were 36,225 new registered cancer cases and 20,686 cancer-related deaths in Kazakhstan, with a 5-year prevalence of 102,845 cases (IARC, 2024). The most common malignancies are breast cancer, lung cancer, and colorectal cancer, collectively constituting over a third of the new cancer burden [8].

The government of Kazakhstan has implemented national strategies aimed at combating this burden, including national screening programs for breast, cervical, and colorectal cancers [10]. These efforts have yielded some success; studies indicate a decline in mortality for certain cancers and an increase in early-stage detection, likely linked to screening initiatives [6].

However, significant challenges remain. Kazakhstan is a vast country with considerable demographic and socio-economic diversity, leading to marked regional disparities in cancer incidence and mortality [9]. Previous research has consistently identified higher cancer rates in the northern and eastern industrial regions compared to the southern and western parts of the country [3]. These disparities highlight the need for targeted interventions. Furthermore, understanding the distinct morbidity patterns between the adult and pediatric populations, as well as the quality of life and satisfaction of patients undergoing treatment, is critical for a holistic assessment of the cancer care system [2].

This study **aims** to fill this gap by providing a comprehensive analysis of cancer morbidity trends in Kazakhstan from 2014 to 2024. By disaggregating national data by region and age group (adults vs. children), this research seeks to identify high-risk populations, evaluate the extent of regional and age-related disparities, and provide an evidence base for tailoring future public health strategies.

Materials and methods

Study Design and Data Source

A retrospective ecological study was conducted using official aggregated national health statistics. The primary data on cancer morbidity (newly registered cases) for the period 2014–2024 were obtained from the National Cancer Registry, which is managed by the Kazakh Institute of Oncology and Radiology (KazIOR). Data for the years 2022-2024 were based on projections derived from the preceding years' trends. Population data for calculating rates were obtained from the official releases of the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan.

Study Variables

The primary variables for this study were: (I) region (including the newly formed Abai, Zhetysu, and Ulytau regions); (II) year of registration (2014-2024); (III) number of adult cancer cases; and (IV) number of pediatric cancer cases (defined as age 0-17 years).

Statistical analysis

Descriptive statistics were used to summarize the number of cases and trends over time. Crude morbidity rates per 100,000 population were calculated for each region and year to facilitate comparisons. The overall change in morbidity from 2014 to 2024 was quantified as a percentage change. All data were managed and analyzed using SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA).

To analyze temporal trends and identify statistically significant changes in morbidity dynamics, a Joinpoint regression analysis was performed. This method identifies points in time (joinpoints) where a significant change in the trend occurs and calculates the Annual Percent Change (APC) for each resulting segment. The analysis was conducted separately for the adult and pediatric cohorts. A logarithmic scale was used on the y-axis for visualization to appropriately compare trends of different magnitudes.

Ethical Statement

This study utilized publicly available, aggregated, and anonymized data. Therefore, formal ethical review board approval was not required.

Results

Overall Nationwide Trend in Cancer Morbidity

Over the eleven years from 2014 to 2024, Kazakhstan experienced a substantial and consistent increase in the total number of registered cancer cases. As detailed in Table 1, the total morbidity grew by 85.2%, from 130,695 cases in 2014 to a projected 242,063 in 2024.

Disproportionate Growth in Pediatric Cancer Morbidity

A key finding of this study is the disproportionate rate of growth in cancer cases among children compared to adults. While adult morbidity increased by a significant 84.7%, the corresponding growth in the pediatric population (aged 0-

17) was substantially higher at 127.9% over the same period (Table 1).

This divergence in growth trends is clearly illustrated in Figure 1. The indexed growth chart, which sets 2014 as a 100% baseline, shows the pediatric morbidity curve rising much more steeply than the adult curve. Annotations on the chart indicate that the peak year-over-year growth for children occurred in 2017 (+19.5%), five years earlier than the peak for adults in 2022 (+19.5%).

Table 1.

Overall Trend in Cancer Morbidity in the Republic of Kazakhstan (2014-2024).

Indicator	2014	2016	2018	2020	2022	2024 (projected)	Growth (2014-2024)
Number of adults	129,088	148,881	166,413	179,355	210,262	238,400	+84.7%
Number of children (aged 0-17)	1,607	1,846	2,176	2,828	3,254	3,663	+127.9%
Total registered cases	130,695	150,727	168,589	182,183	213,516	242,063	+85.2%

(Note: For clarity, only even years are displayed, but the growth calculation is based on the full 2014-2024 period.)

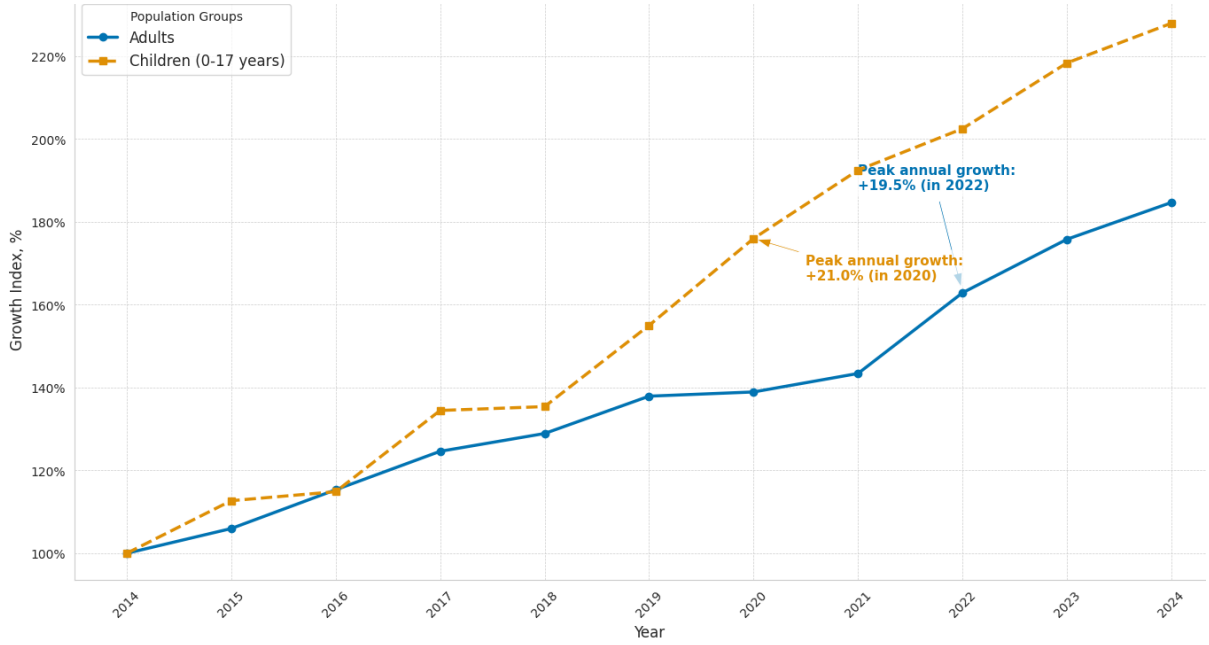

Figure 1. Indexed Growth of Cancer Morbidity by Age Group in Kazakhstan (2014–2024).

Regional Disparities in Cancer Burden.

The national cancer burden is not distributed evenly across the country. Table 2 highlights significant regional disparities in the morbidity rate per 100,000 population for the projected year 2024. The highest rates are concentrated in industrial regions, including East Kazakhstan Region (2150.2), Pavlodar Region (1997.1), and Karaganda Region (1965.3). In contrast, the lowest morbidity rates are observed in Mangystau (775.1), Kyzylorda (838.3), and Atyrau (853.9) regions. The morbidity rate in the highest-burden region is nearly three times that of the lowest, underscoring the profound geographical inequality

Table 2.

Regional Disparities in Cancer Morbidity (2024, projected).

Region	Total Cases (2024, projected)	Population	Morbidity Rate per 100,000
Regions with Highest Case Numbers			
Almaty City	34,256	2,228677	1537.0
Karaganda Region	22,314	1,135351	1965.3
Astana City	17,329	1,430117	1211.7
East Kazakhstan Region	15,633	727,053	2150.2
Pavlodar Region	15,057	753,933	1997.1
Regions with Lowest Case Numbers			
Kyzylorda Region	7,058	841,929	838.3
Zhetysu Region	7,238	697,987	1037.0
Mangystau Region	6,099	786,837	775.1
Atyrau Region	6,012	704,074	853.9
Ulytau Region	2,442	221,582	1102.0

The results of the Joinpoint regression analysis are presented in Figure 2. The analysis identified statistically significant joinpoints for both groups around the year 2021. For the adult cohort, a joinpoint was detected at 2021.0, indicating a change in the Annual Percent Change (APC) from that point forward. For the pediatric cohort, a similar joinpoint was identified at 2021.5. Despite this change in the rate of increase, the overall trend for both groups remained positive throughout the entire study period, confirming a sustained growth in morbidity.

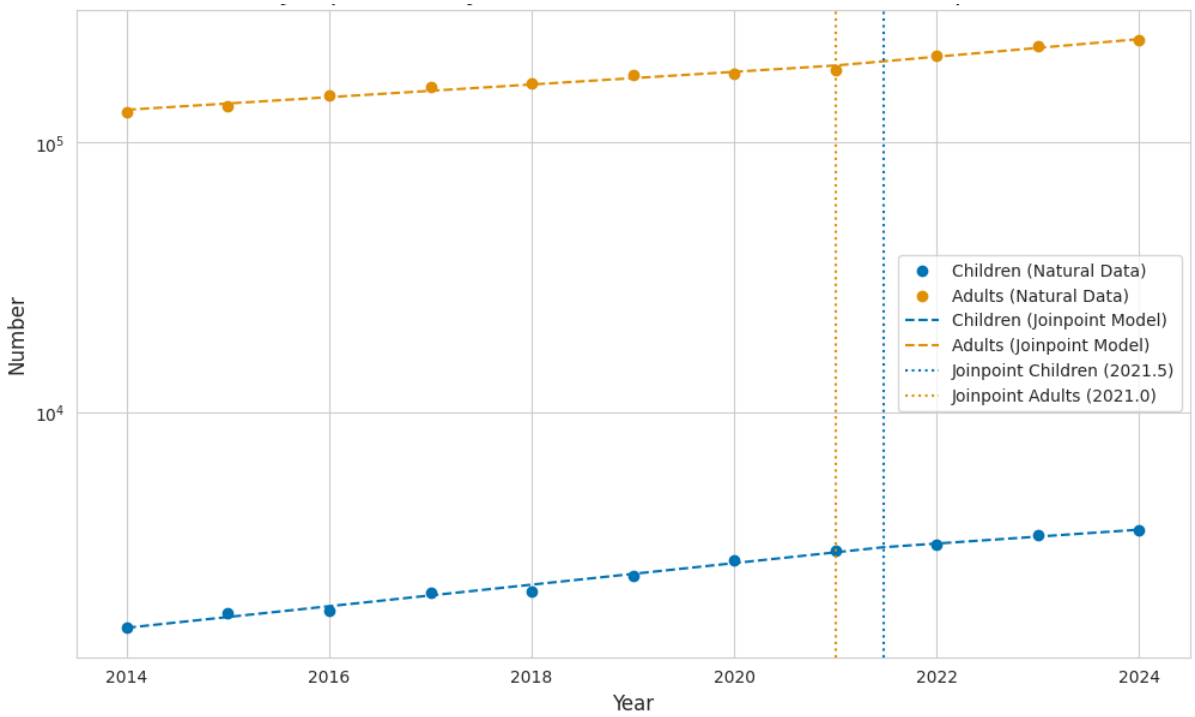

Figure 2. Joinpoint Regression Analysis of Cancer Morbidity Trends in Kazakhstan (2014-2024).

Discussion

To the best of our knowledge, this study provides one of the first comprehensive analyses of cancer morbidity trends in Kazakhstan from 2014 to 2024, with a specific focus on regional and age-based disaggregation. Our primary findings are a steady increase in overall cases, pronounced regional disparities, and a concerning rise in pediatric cancer, aligning with and building upon the existing body of literature, revealing deeper systemic challenges within the nation's healthcare system.

The significant regional disparities identified, with the highest morbidity burden concentrated in the northern and eastern industrial regions (East Kazakhstan, Karaganda, Pavlodar), are consistent with previous studies on specific cancers such as lung, kidney, and prostate cancer in Kazakhstan [3]. This enduring geographical pattern is likely multifactorial. It may be attributable to a combination of historical environmental pollution from heavy industry and the legacy of the former Semipalatinsk nuclear test site, which has been linked to increased thyroid cancer incidence in the area [4]. Furthermore, socio-economic factors and potential urban-rural divides in screening access and awareness likely contribute to these disparities [11].

A key finding of our study is the detection of joinpoints around 2021 for both the adult and pediatric cohorts. This synchronicity is likely a statistical echo of the COVID-19 pandemic. We hypothesize that disruptions to healthcare access and reduced screening activities during 2020-2021 led to a temporary slowdown in diagnoses (a "diagnostic gap"). This was likely followed by a "catch-up" period, resulting in a compensatory rise in registered cases in subsequent years. Our analysis suggests that the healthcare system began to identify these deferred cases after 2021, leading to the statistically significant change in the morbidity trend. This finding highlights the vulnerability of oncological services to systemic shocks and underscores the importance of maintaining diagnostic continuity, even during a crisis.

The growth in overall registered cancer cases, while seemingly negative, may paradoxically reflect positive developments [5,7]. The implementation and expansion of national screening programs for breast, cervical, and colorectal cancers have demonstrably increased detection rates, particularly for early-stage disease [10]. However, the fact that a significant proportion of cancers are still diagnosed at later stages suggests that barriers to timely medical consultation persist [1].

Beyond incidence and mortality rates, the quality of care and patient experience are critical metrics for evaluating the healthcare system. A study by *Atabayeva A.* [2] revealed that nearly half of blood cancer patients in Semey, a high-morbidity region, were dissatisfied with their clinical management. This finding suggests that even when treatment is available, its organization and accessibility may be suboptimal. This patient dissatisfaction could be linked to broader systemic issues, such as the documented regional disparity in drug provision, where access to modern targeted therapies is often contingent on the economic status of the region [11].

Perhaps the most alarming finding of our study is the sharp proportional increase in pediatric cancer cases. While

the absolute numbers remain small compared to the adult population, the steep upward trend is a serious signal that warrants urgent attention. This rise could be partly due to improved diagnostics and more complete registration, but it also raises critical questions about the potential role of environmental, lifestyle, or genetic risk factors that require dedicated, targeted investigation.

Limitations

This study has several limitations. Firstly, as a retrospective ecological study, it cannot establish causality at an individual level. Secondly, its reliance on aggregated registry data may be subject to variations in reporting quality and completeness across regions. Finally, data for 2022-2024 are projections and should be interpreted with caution.

Conclusion

The burden of cancer in Kazakhstan continues to grow, characterized by significant and widening disparities between regions and age groups. Our findings underscore the urgent need for a multi-faceted and data-driven national response. Policy must evolve from a uniform, one-size-fits-all approach to targeted interventions focused on the high-morbidity northern and eastern regions, addressing both environmental risk factors and barriers to screening and care. Furthermore, efforts must extend beyond mere detection to enhancing the entire patient journey. This includes improving the quality of care delivery, addressing patient satisfaction, and ensuring equitable access to modern diagnostics and treatments across all regions of the country. Most critically, the alarming rise in pediatric cancer must be recognized as a national priority. This demands immediate strategic action to bolster research into causative factors, improve early detection protocols for children, and build a robust, specialized pediatric oncology infrastructure to provide the best possible care for the youngest and most vulnerable patients in Kazakhstan.

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Literature:

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PATIENTS' PERCEPTIONS OF THE QUALITY AND ACCESSIBILITY OF REHABILITATION SERVICES FOR LUNG CANCER: A CROSS-SECTIONAL STUDY

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Abstract

Background. Rehabilitation is a crucial component of comprehensive oncological care, aimed at restoring functional capacity, improving quality of life, and supporting social reintegration in lung cancer patients. Despite significant progress in cancer management, access to rehabilitation services remains uneven, particularly between urban and rural populations.

Aim: to assess perceptions of patients with lung cancer regarding the quality, organization, and accessibility of rehabilitation services across different levels of healthcare in Kazakhstan.

Materials and Methods. A descriptive cross-sectional study was conducted from November 4, 2024 to February 4, 2025 in the Abay region of the Republic of Kazakhstan. The study included 124 patients diagnosed with lung cancer who had received or were undergoing medical rehabilitation. Data were collected through structured interviews and questionnaires assessing socio-demographic characteristics, satisfaction with rehabilitation, and perceptions of service accessibility and quality.

Results. The mean age of participants was 61.6 ± 9.5 years; 70.2% were of Kazakh nationality, and 66.9% resided in urban areas. Most respondents rated the organization of rehabilitation as satisfactory (41.1%) or good (29.0%), while 16.9% described it as excellent and 12.9% as unsatisfactory. Overall, 75.8% of patients reported being satisfied with rehabilitation services. Gender differences were not statistically significant ($p>0.05$), whereas urban residents demonstrated higher satisfaction compared to rural respondents ($p<0.05$).

Conclusions. Gender did not significantly influence patients' perceptions of rehabilitation quality or accessibility, while place of residence was identified as the main determinant. These results correspond with international data emphasizing spatial and systemic inequalities in rehabilitation access. Expanding patient-centered and digital rehabilitation programs, including tele-rehabilitation and regional service integration, may enhance equity, efficiency, and overall quality of oncological rehabilitation in Kazakhstan.

Keywords: *lung cancer, rehabilitation, accessibility, quality of care, patient satisfaction, public health, Kazakhstan.*

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Резюме

ВОСПРИЯТИЕ ПАЦИЕНТАМИ КАЧЕСТВА И ДОСТУПНОСТИ РЕАБИЛИТАЦИОННЫХ УСЛУГ ПРИ РАКЕ ЛЁГКОГО: ПОПЕРЕЧНОЕ ИССЛЕДОВАНИЕ

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Введение. Реабилитация является неотъемлемой частью комплексной онкологической помощи, направленной на восстановление функциональных возможностей, улучшение качества жизни и социальную реинтеграцию пациентов с раком лёгкого. Несмотря на достижения в лечении онкологических заболеваний, доступ к реабилитационным услугам остаётся неравномерным, особенно между городским и сельским населением.

Цель: оценить восприятие пациентами рака легких качества, организации и доступности реабилитационных услуг на разных уровнях здравоохранения в Казахстане.

Материалы и методы. Описательное поперечное исследование проведено в период с ноября 2024 года по февраль 2025 года в Абайской области Республики Казахстан. В исследование были включены 124 пациента с установленным диагнозом рак лёгкого, проходившие или завершившие курс медицинской реабилитации. Сбор данных осуществлялся методом стандартизированного опроса и анкетирования, включавшего оценку социо-демографических характеристик, удовлетворённости реабилитацией и восприятия качества и доступности услуг.

Результаты. Средний возраст участников составил 61,6 ± 9,5 года; 70,2 % были казахской национальности, 66,9 % проживали в городах. Большинство респондентов оценили организацию реабилитации как удовлетворительную (41,1 %) или хорошую (29,0 %), 16,9 % - как отличную, а 12,9 % -как неудовлетворительную. В целом 75,8 % пациентов сообщили об удовлетворённости полученными реабилитационными услугами. Различия между мужчинами и женщинами были статистически незначимыми (p > 0,05), тогда как городские жители чаще выражали удовлетворённость по сравнению с сельскими (p <0,05).

Выводы. Пол не оказывал значимого влияния на восприятие качества и доступности реабилитационных услуг, тогда как место проживания являлось ключевым фактором. Полученные результаты согласуются с международными данными, подчёркивающими пространственные и системные различия в доступе к реабилитации. Расширение пациент-ориентированных и цифровых форм реабилитации, включая телереабилитацию и интеграцию региональных служб, позволит повысить равенство, эффективность и качество онкологической реабилитации в Казахстане.

Ключевые слова: *рак лёгкого, реабилитация, доступность, качество медицинской помощи, удовлетворённость пациентов, общественное здравоохранение, Казахстан*

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Түйіндеме

НАУҚАСТАРДЫҢ САПА ТУРАЛЫ ҚАБЫЛДАУЫ ЖӘНЕ ӨКПЕНІҢ ҚАТЕРЛІ ІСІГІНЕ ОҢАЛТУ ҚЫЗМЕТТЕРІНІҢ БОЛУЫ: КӨЛДЕНЕҢ ЗЕРТТЕУ

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Кіріспе. Оңалту - бұл функционалдығын қалпына келтіруге, өмір сүру сапасын жақсартуға, өкпенің қатерлі ісігі бар науқастардың өмір сүру сапасын жақсартуға және әлеуметтік реинтеграциясының ажырамас бөлігі болып табылады. Қатерлі ісікпен емдеудегі аванстарға қарамастан, оңалту қызметтеріне қол жетімділік біркелкі емес, әсіресе қалалық және ауылдық популяциялар арасында біркелкі емес қалып отыр.

Зерттеу мақсаты: Өкпенің қатерлі ісігі кезінде пациенттердің сапасы, Қазақстандағы денсаулық сақтаудың әртүрлі деңгейлеріндегі оңалту қызметтерінің сапасы, ұйымдастырылуы және қол жетімділігі туралы бағалау.

Материалдар мен тәсілдер. Сипаттамалық-секциялық зерттеу 2024 жылғы қарашадан 202 ақпанға дейін Қазақстан Республикасының Абай ауданында жүргізілді. Зерттеуге медициналық оңалту курсынан өткен немесе аяқтаған өкпе қатерлі ісігі диагнозы қойылған 124 пациент кірді. Деректер жинау әлеуметтік-демографиялық сипаттамаларды бағалау, оңалту және қызметтердің сапасы мен қол жетімділігі туралы қанағаттанушылықты бағалауды, әлеуметтік-демографиялық сипаттамаларды қамтитын стандартталған сауалнамалық және сауалнаманы пайдалану арқылы жүзеге асырылды.

Нәтежиелер. Қатысушылардың орташа жасы 61,6 ± 9,5 жасты құрады; 70,2 пайызы қазақ ұлты болса, 66,9 пайызы қалаларда тұрды. Респонденттердің көпшілігі оңалту ұйымын қанағаттанарлық (41,1%) немесе жақсы (29,0%), 16,9% тамаша, 12,9% қанағаттанарлықсыз деп бағалады. Жалпы алғанда, пациенттердің 75,8%-ы алынған оңалту қызметтеріне қанағаттанатынын айтты. Ерлер мен әйелдер арасындағы айырмашылықтар статистикалық тұрғыда шамалы болды ($p > 0,05$), ал қала тұрғындары ауыл тұрғындарымен салыстырғанда қанағаттанушылық білдіру ықтималдығы жоғары болды ($p <0,05$).

Қорытындылар. Гендерлік фактор оңалту қызметтерінің сапасы мен қолжетімділігіне айтарлықтай әсер етпеген, ал тұрғылықты жері басты фактор болған. Бұл нәтижелер халықаралық деректерге сәйкес келеді және оңалтуға қолжетімділіктегі кеңістіктік және жүйелік айырмашылықтарды көрсетеді. Пациентке бағдарланған және цифрлық форматтарды кеңейту Қазақстандағы онкологиялық оңалтудың тиімділігін, сапасын және әділдігін арттыруы мүмкін.

Түйінді сөздер: *өкпе қатерлі ісігі, қалпына келтіру, қол жетімділік, медициналық көмектің сапасы, пациенттердің қанағаттанушылығы, денсаулық сақтау, Қазақстан.*

Дәйексөз үшін:

Әділғазыұлы Ш.., Булегенов Т.А., Мусаханова А.К., Джусупов К.О Тукусова А.К., Медеулова А.Р., Токенова Ж.Н., Урузбаева Г.А., Кусаинова А.С., Ихсанова А.Н., Мусаханова А.Е. Науқастардың сапа туралы қабылдауы және өкпенің қатерлі ісігіне оңалту қызметтерінің болуы: көлденең зерттеу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 47-55. *doi 10.34689/SH.2025.27.5.006*

Introduction

Lung cancer remains one of the leading causes of morbidity and mortality worldwide, accounting for 11.6% of all new cancer cases and 18.4% of all cancer deaths globally [20]. Despite advances in early detection and treatment, many patients continue to experience long-term consequences of the disease, including impaired respiratory function, psychological distress, and reduced quality of life [6,21]. Comprehensive rehabilitation has therefore become an essential component of multidisciplinary cancer care, aiming to restore functional capacity, promote social reintegration, and improve overall survival [17].

Evidence from international studies has shown that pulmonary and oncological rehabilitation significantly improves exercise tolerance, lung function, and quality of life among patients with lung cancer [8,16]. Pre- and postoperative rehabilitation programs can also reduce complications, shorten hospital stays, and facilitate recovery [3,5]. The American Thoracic Society and the European Respiratory Society emphasize the integration of rehabilitation interventions as standard care for patients with chronic respiratory and oncological diseases [13].

However, despite strong evidence, access to high-quality rehabilitation services remains uneven across the world. Many patients face barriers such as limited availability of specialized programs, inadequate infrastructure, shortage of trained professionals, and lack of patient awareness about rehabilitation benefits [18]. These disparities are particularly evident in low- and middle-income countries, including Kazakhstan, where healthcare systems are still developing and oncology rehabilitation is in the early stages of integration [7].

In Kazakhstan, lung cancer remains one of the top causes of cancer mortality, representing around 15-17% of all cancer deaths [1]. Although national health reforms have improved screening and diagnostic capacity, rehabilitation is often fragmented between primary, secondary, and tertiary care levels [23]. Recent policy efforts, such as the revision of rehabilitation care standards by the Ministry of Health in 2024, demonstrate progress toward a more patient-centred approach [14]. Yet, empirical data on the accessibility, quality, and patient satisfaction with rehabilitation services for lung cancer are limited.

Understanding patients' perceptions is essential for identifying barriers, improving the organization of medical rehabilitation, and ensuring equity in healthcare access. Cross-sectional studies provide an effective approach for assessing patients' experiences and satisfaction across different healthcare levels. Therefore, the present study was conducted in the Abay region of the Republic of Kazakhstan to evaluate the perceptions of lung cancer patients regarding the quality and accessibility of rehabilitation services. The results are expected to contribute to evidence-based recommendations aimed at strengthening rehabilitation care and improving health outcomes among oncology patients in Kazakhstan

Materials and Methods.

The study sample comprised all lung cancer patients undergoing treatment at the Public Utility Enterprise on the Right of Economic Management «Center for Nuclear Medicine and Oncology» under the Health Department of the Abay Region, Republic of Kazakhstan. Data collection was carried out from November 4, 2024, to February 4, 2025. The average time required to complete the questionnaire was 15 minutes.

Inclusion criteria required patients of both sexes, aged 18 years or older, with a confirmed diagnosis of lung cancer, the ability to communicate in Kazakh or Russian, and adequate cognitive function.

Exclusion criteria included lung cancer patients aged 18-70 who declined participation in the study, as well as individuals with confirmed mental health disorders.

A total of 124 patients met the inclusion criteria. Demographic characteristics and clinical data related to the disease, treatment, and rehabilitation were obtained from the patients and their medical records.

A structured questionnaire was developed by the authors based on the World Health Organization (WHO) recommendations on rehabilitation and adapted to regional health system conditions in Kazakhstan. The development process involved the following stages: Initial draft preparation based on WHO guidance and local policy documents. Expert review by a panel of five specialists in oncology, rehabilitation, and public health.. The questionnaire was translated into Kazakh and Russian languages, culturally and linguistically adapted in accordance with international standards. Pretesting on a group of 25 patients (not included in the main study) to assess clarity, cultural and linguistic appropriateness, and content relevance. The questionnaire was revised twice based on feedback from expert and pilot testing. The reliability, validity and sensitivity of the instrument were analyzed during validation. To check the reliability of the questionnaire, the internal consistency of the questionnaire was calculated by determining the Cronbach's &-coefficient. The questionnaire has high validity (Cronbach's > 0.7), indicating a satisfactory level of reliability of the questionnaire scales. Those respondents' answers that were incomplete were excluded from the study.

Statistical Analysis

Means and standard deviations (SD) were used to describe quantitative variables, while absolute (N) and relative (%) frequencies were used for qualitative variables. Pearson's chi-square (χ^2) test or Fisher's exact test, where applicable, was employed for proportion comparisons. Significance levels were two-tailed, with statistical significance set at $p < 0.05$. Statistical analyses were performed using SPSS version 24.0.

Results

The study included 124 patients who met the inclusion criteria and fully completed the questionnaire. In terms of gender, the majority of respondents were male 75.8% (N=94). The mean age was 61.6±9.5 years. The analysis of the sample by nationality demonstrated that the majority of respondents were of Kazakh ethnicity -70.2% (N = 87). Participants of Russian nationality accounted for 26.6% (N=33), while representatives of other nationalities comprised 3.2% (N = 4). Thus, the combined proportion of Kazakh and Russian respondents reached 96.8%, reflecting the general ethnodemographic structure of the population of the Republic of Kazakhstan.

The majority of respondents were urban residents (66.9%, N=83), while 33.1% (N=41) lived in rural areas. This distribution reflects the demographic pattern of

Kazakhstan, where urban populations have greater access to oncology and rehabilitation services concentrated in large cities.

The analysis of respondents' marital status revealed that the predominant proportion of participants were married (83.9%, N=104), whereas 16.1% (N=20) were single. The high share of married respondents likely reflects the age and social characteristics of the study population.

The analysis of respondents' educational level showed that the largest proportion of participants had secondary specialized education (44.4%, N=55), followed by those with general secondary education (37.1%, N = 46). Respondents with higher education accounted for 17.7% (N=22), and only 0.8% (N=1) reported another type of education. Overall, the study sample was characterized by a predominance of individuals with secondary and vocational qualifications, which corresponds to the general educational profile of the adult population in Kazakhstan.

The analysis of respondents' social status revealed that more than half of the participants were retirees (50.8%, n = 63). Workers constituted 18.5% (N=23), while employees represented 8.9% (N=11) and unemployed individuals-8.1% (N=10). Persons with disabilities accounted for 12.9% (N=16), and only 0.8% (N=1) were students (Figure 1).

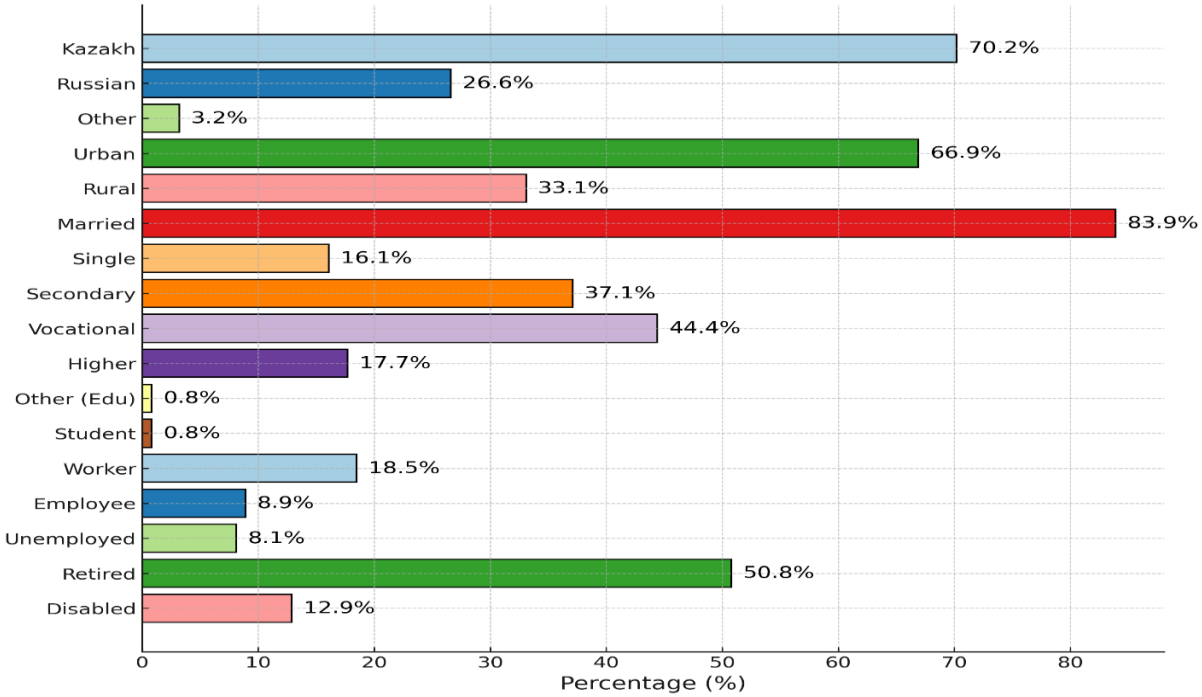


Figure 1. Socio-demographic characteristics of respondents.

The socio-demographic analysis was conducted with a focus on gender-related differences across key characteristics, including nationality, place of residence, marital status, and social status. The comparative distribution of these variables by gender is presented in Table 1.

Table 1.

Socio-demographic characteristics of respondents by gender

Indicator	Category	Male N (%)	Female N (%)	Total N (%)	p-value
Nationality	Kazakh	69 (79.3)	18 (60.0)	87 (70.2)	0.352
	Russian	22 (66.7)	11 (33.3)	33 (26.6)	
	Other	3 (75.0)	1 (25.0)	4 (3.2)	
Place of residence	Urban	57 (68.7)	37 (90.2)	83 (66.9)	0.008
	Rural	26 (31.3)	4 (9.8)	41 (33.1)	
Marital status	Married	78 (75.0)	26 (86.7)	104 (83.9)	0.633
	Single	16 (80.0)	4 (13.3)	20 (16.1)	
Social status	Retired	47 (74.6)	16 (25.4)	63 (50.8)	0.250
	Worker	21 (91.3)	2 (8.7)	23 (18.5)	
	Disabled	11 (68.8)	5 (31.3)	16 (12.9)	
	Employee	6 (54.5)	5 (45.5)	11 (8.9)	
	Unemployed	8 (80.0)	2 (20.0)	10 (8.1)	
	Student	1 (100.0)	0 (0.0)	1 (0.8)	

A statistically significant relationship was observed between gender and place of residence ($p < 0.05$). Urban residents predominated among both men and women; however, the proportion of female respondents living in cities (90.2%) was markedly higher than that of men (68.7%). Conversely, a larger proportion of men resided in rural areas (31.3%) compared to women (9.8%).

The analysis of respondents' nationality by gender demonstrated that individuals of Kazakh ethnicity predominated in both male (79.3%) and female (60.0%) groups, reflecting the general ethnodemographic profile of Kazakhstan. Participants of Russian nationality constituted 26.6% of the total sample, while representatives of other ethnic groups accounted for 3.2%. No statistically significant difference in nationality distribution between male and female respondents was identified ($p > 0.05$), indicating that the ethnic composition of the study group was relatively balanced across genders.

The distribution of marital status did not differ significantly by gender ($p > 0.05$). Married individuals predominated in both male and female groups (75.0% and 86.7%, respectively). These findings indicate the absence of a statistically significant association between gender and marital status in the studied group.

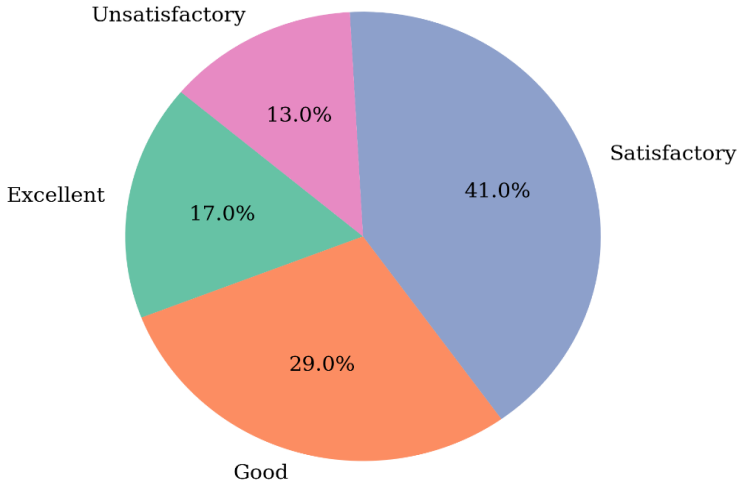
The analysis of respondents' social status demonstrated that retirees represented the largest proportion of the sample (50.8%, N=63), followed by workers (18.5%, N=23) and persons with disabilities (12.9%, N=16). Employees accounted for 8.9% (N=11), unemployed individuals for 8.1% (N=10), and only one respondent (0.8%) was a student. The difference in social status distribution between genders was not statistically significant ($p > 0.05$), indicating that both male and female respondents were predominantly retirees. This finding corresponds to the age structure of the studied group and highlights the presence of socially vulnerable populations, including retirees and persons with disabilities.

The clinical profile of respondents was analyzed to assess gender-related differences in self-rated health, comorbidity, and disability status among patients with lung cancer. The assessment of self-rated health showed that the majority of participants evaluated their condition as satisfactory (46.8%) or good (22.6%). Only 11.3% of respondents reported their health as excellent, while 19.4% described it as poor. Among men, 44.7% rated their health as satisfactory and 18.1% as poor, compared to 53.3% and 23.3% among women, respectively. The difference between genders was not statistically significant ($p> 0.05$), indicating a generally comparable perception of health status across the studied group. Comorbidities were reported by 37.9% (N=47) of respondents, including 35.1% of men and 46.7% of women. The majority of both male (64.9%) and female (53.3%) participants had no chronic concomitant diseases. The gender difference in the prevalence of comorbidities was not statistically significant ($p> 0.05$), suggesting similar levels of chronic disease burden among both sexes. Regarding disability status due to lung cancer, 78.2% of respondents reported no disability, while 21.0% had a second-group disability and only 0.8% were classified as first-group disabled. Among men, 77.7% had no disability and 21.3% had second-group disability; among women, the respective figures were 80.0% and 20.0%**.** No statistically significant differences were observed between genders ($p > 0.05$), indicating that disability distribution was similar across the sample. Overall, the results demonstrate that gender did not significantly influence key clinical parameters among patients with lung cancer. The comparable patterns observed for self-rated health, comorbidities, and disability status suggest that both men and women face similar clinical conditions and rehabilitation needs within the healthcare context of Kazakhstan.

The respondents' perceptions of the quality, organization, and accessibility of rehabilitation services for cancer patients were analyzed in relation to gender.

Analysis of satisfaction with received rehabilitation treatment revealed that 75.8% of respondents were satisfied with the care provided, while 24.2% expressed dissatisfaction. Among men, 74.6% reported being satisfied compared to 76.9% of women. The absence of statistically significant gender differences ($p>0.05$) suggests that both male and female patients expressed comparable levels of satisfaction, reflecting an overall positive evaluation of rehabilitation services for lung cancer patients in Kazakhstan.

When asked whether physicians had informed them about special rehabilitation exercises or measures, the majority (75.8%) confirmed receiving such information, while 24.2% indicated that they had not been informed. Among men, 78.0% received physician guidance, compared to 73.8% of women. No statistically significant difference was found ($p>0.05$), suggesting equal dissemination of rehabilitation-related information among both genders.



Note: Pearson's $\chi^2 = 3.006$, df = 3, p = 0.391 — no statistically significant difference between genders.

Figure 2. Respondents' assessment of the organization of medical Rehabilitation services for cancer patients in Kazakhstan.

The assessment of the organization of medical rehabilitation in Kazakhstan showed that most respondents rated it as satisfactory (41.1%) or good (29.0%), while 17.0% described it as excellent and 12.9% as unsatisfactory. Among men, 37.2% rated the system as satisfactory and 30.9% as good, compared to 53.3% and 23.3% among women, respectively. The difference in evaluations between genders was not statistically significant ($p>0.05$), indicating a generally moderate and uniform perception of rehabilitation system organization across both groups.

Overall, the analysis revealed that gender did not significantly affect respondents' perceptions of rehabilitation quality, satisfaction with treatment, or access to professional information. Both male and female participants expressed moderate satisfaction with rehabilitation services and similar awareness levels, indicating consistent delivery and accessibility of rehabilitation care across gender groups in Kazakhstan.

Discussion

This study examined the perceptions of lung cancer patients regarding the organization, accessibility, and quality of rehabilitation services in Kazakhstan, emphasizing gender differences. The majority of respondents rated rehabilitation organization as satisfactory (41.1%) or good (29.0%), and 75.8% expressed satisfaction with the care received. A statistically significant association was observed only between gender and place of residence, with a higher proportion of women living in urban areas.

The predominance of urban respondents reflects a wider global trend in healthcare accessibility. Studies conducted in the United States show that fewer than half of the population have convenient access to pulmonary rehabilitation centers, with rural patients facing the greatest barriers [10]. Qualitative studies confirm that rural oncology patients encounter difficulties related to travel, delayed diagnosis, and limited awareness of available services [2]. These findings are consistent with our data, suggesting that spatial determinants-rather than gender-play a more substantial role in shaping access to rehabilitation.

The absence of statistically significant gender differences in perceived quality, satisfaction, and physician counseling is in line with global literature. Several systematic reviews demonstrate that, when rehabilitation programs are equally accessible, men and women report similar benefits in terms of functional improvement, quality of life, and psychosocial adaptation [11,19]. Thus, equitable service distribution appears to neutralize gender-based disparities in rehabilitation outcomes.

Nevertheless, nearly one in four respondents reported not being informed about rehabilitation exercises or measures. Similar informational barriers are described in many international studies, where insufficient physician guidance and limited patient awareness hinder participation in pulmonary rehabilitation programs [9, 15]. Addressing these informational gaps through physician education and structured patient counseling is critical for improving program engagement.

The demographic structure of our sample-dominated by retirees and married individuals - suggests that social stability and family support may contribute to higher satisfaction levels. However, rural residents remain vulnerable to under-utilization due to transportation and infrastructural limitations. Comparable findings from other countries underline the effectiveness of home-based or digital rehabilitation programs in overcoming geographic barriers [12]. Implementation of tele-rehabilitation or hybrid models may therefore improve access and continuity of care in Kazakhstan.

To enhance rehabilitation services, several steps are recommended: strengthen referral pathways between oncology and rehabilitation centers, particularly for rural populations; introduce standardized physician training and patient education modules; develop tele-rehabilitation networks to ensure access across all regions; and integrate patient-reported outcomes into national monitoring systems. These directions correspond with the WHO "Rehabilitation 2030" framework, which emphasizes equitable and continuous rehabilitation services across care levels [22].

Limitations

The strength of this study lies in its focus on patient-reported experiences and gender-specific analysis, supported by a nationwide online design. Limitations include the cross-sectional nature of the data. Despite these constraints, the results align with international patterns, reinforcing their external validity.

Conclusion

The study demonstrated that gender was not a significant factor influencing patients' perceptions of the quality or accessibility of rehabilitation services for lung cancer in Kazakhstan. In contrast, geographic residence emerged as a key determinant, reflecting regional disparities in access to rehabilitation care. These findings align with international evidence emphasizing the role of systemic and spatial factors in ensuring equity of rehabilitation services. The development of patient-centered, digitally supported, and tele-rehabilitation models could improve accessibility, efficiency, and overall quality of oncological rehabilitation across all levels of healthcare delivery.

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COMPARATIVE ANALYSIS OF COMPUTER TOMOGRAPHIC STAGING AND POSTOPERATIVE PATHOMORPHOLOGICAL STAGING IN STOMACH CANCER

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Abstract

Introduction. Gastric cancer remains one of the leading causes of malignant mortality worldwide and occupies a significant place in the oncological morbidity structure in Kazakhstan. Accurate preoperative assessment of the extent of the disease is essential for choosing the optimal treatment strategy. Computed tomography (CT) is widely used for gastric cancer staging, but its accuracy can vary depending on the stage of the disease, the biological characteristics of the tumor, and the technical parameters of the examination.

Aim. To evaluate the concordance between the results of CT staging and the final pathological conclusion in patients with gastric cancer in the clinical practice of Kazakhstan.

Materials and methods. A retrospective analysis of CT scans was conducted in patients with histologically confirmed gastric cancer referred from various regions of the country and operated on at the National Research Oncology Center. All CT scans were performed before surgery. Staging results were compared with postoperative pathological data. Sensitivity, specificity, accuracy, and the Kappa coefficient of agreement were calculated.

Results. The study included 42 patients. The accuracy of CT based on the T-score ranged from 73.2% (T3) to 95.1% (T4a), with the highest concordance for T4a (κ=0.72). For N-stage, the accuracy was 78.6% (κ=0.46). When assessing M-stage, the overall accuracy reached 87.8%, but the kappa coefficient was negative (κ=–0.06), which is associated with the rarity of M1 detection. The rate of understaging exceeded the rate of overstaging, especially at early stages T1–T2.

Conclusion. CT demonstrates high diagnostic efficacy in assessing late T-stage disease and distant metastases, but its capabilities in early stages and in detecting lymph node metastases are limited. Optimization of protocols and integration of CT with endoscopic ultrasound and staging laparoscopy can improve staging accuracy and clinical outcomes in patients with gastric cancer.

Keywords: *Gastric cancer, computed tomography, staging, accuracy, Kazakhstan.*

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Резюме

СРАВНИТЕЛЬНЫЙ АНАЛИЗ КОМПЬЮТЕРНО-ТОМОГРАФИЧЕСКОГО СТАДИРОВАНИЯ И ПОСЛЕОПЕРАЦИОННОЙ ПАТОМОРФОЛОГИЧЕСКОЙ СТАДИИ ПРИ РАКЕ ЖЕЛУДКА

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Введение. Рак желудка остаётся одной из ведущих причин смертности от злокачественных новообразований во всём мире и занимает значимое место в структуре онкологической заболеваемости Казахстана. Точная предоперационная оценка распространённости процесса необходима для выбора оптимальной тактики лечения. Компьютерная томография (КТ) широко используется для стадирования рака желудка, однако её точность может варьировать в зависимости от стадии заболевания, биологических особенностей опухоли и технических параметров исследования.

Цель. Оценить соответствие между результатами КТ-стадирования и окончательным патоморфологическим заключением у пациентов с раком желудка в условиях клинической практики Казахстана.

Материалы и методы. Проведён ретроспективный анализ КТ-исследований у пациентов с гистологически подтверждённым раком желудка, направленных из различных регионов страны и прооперированных в Национальном научном онкологическом центре. Все КТ выполнялись до хирургического вмешательства. Результаты стадирования сопоставлялись с послеоперационными патоморфологическими данными. Рассчитывались чувствительность, специфичность, точность и коэффициент согласия Каппа.

Результаты. В исследование включены 42 пациента. Точность КТ по Т-критерию варьировала от 73,2% (Т3) до 95,1% (Т4а), с наибольшим уровнем согласия при Т4а (к=0,72). Для N-стадии точность составила 78,6% (к=0,46). При оценке М-стадии общая точность достигала 87,8%, однако коэффициент Каппа был отрицательным (к=–0,06), что связано с редкостью выявления М1. Частота недооценки (understaging) превышала частоту переоценки (overstaging), особенно на ранних стадиях Т1–Т2.

Заключение. КТ демонстрирует высокую диагностическую эффективность при оценке поздних Т-стадий и отдалённых метастазов, однако её возможности при ранних формах и определении лимфогенного метастазирования ограничены. Оптимизация протоколов и интеграция КТ с эндоскопическим ультразвуком и стейджинговой лапароскопией могут повысить точность стадирования и улучшить клинические результаты у пациентов с раком желудка.

Ключевые слова: *рак желудка, компьютерная томография, стадирование, точность, Казахстан.*

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Түйіндеме

АСҚАЗАН ОБЫРЫ КЕЗІНДЕ КОМПЬЮТЕРЛІК ТОМОГРАФИЯ НЕГІЗІНДЕГІ САТЫЛАУ МЕН ОПЕРАЦИЯДАН КЕЙІНГІ ПАТОМОРФОЛОГИЯЛЫҚ САТЫЛАУДЫҢ САЛЫСТЫРМАЛЫ ТАЛДАУЫ

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Кіріспе. Асқазан обыры әлем бойынша қатерлі ісіктерден өлім-жітімнің негізгі себептерінің бірі болып қала береді және Қазақстандағы онкологиялық аурушаңдық құрылымында да айтарлықтай орын алады. Үдерістің таралуын дәл операцияға дейінгі бағалау емдеудің оңтайлы тактикасын таңдау үшін қажет. Компьютерлік томография (КТ) асқазан обырын кезеңдеу үшін кеңінен қолданылады, алайда оның дәлдігі ауру сатысына, ісіктің биологиялық ерекшеліктеріне және зерттеу техникасының параметрлеріне байланысты өзгеруі мүмкін.

Мақсаты. Қазақстандағы клиникалық тәжірибе жағдайында асқазан обыры бар науқастарда КТ арқылы жүргізілген сатылаудың нәтижелерін түпкілікті патоморфологиялық қорытындымен салыстырып, олардың сәйкестігін бағалау.

Материалдар мен тәсілдер. Гистологиялық тұрғыда расталған асқазан обыры бар және елдің әртүрлі өңірлерінен жолданған, Ұлттық ғылыми онкология орталығында ота жасалған науқастардың КТ-зерттеулеріне ретроспективті талдау жүргізілді. Барлық КТ операцияға дейін орындалды. Сатылау нәтижелері отадан кейінгі патоморфологиялық деректермен салыстырылды. Сезімталдық, ерекшелік, дәлдік және Каппа келісім коэффициенті есептелді.

Нәтижелері. Зерттеуге 42 науқас енгізілді. Т-критерий бойынша КТ дәлдігі 73,2% (Т3)-тен 95,1% (Т4а)-ға дейін өзгерді, ең жоғары келісім деңгейі Т4а кезінде байқалды (к=0,72). N-стадия үшін дәлдік 78,6% құрады (к=0,46). М-стадияны бағалауда жалпы дәлдік 87,8%-ға жетті, алайда Каппа коэффициенті теріс болды (к=–0,06), бұл М1 жағдайларының сирек анықталуымен байланысты. Кем бағалау (understaging) жиілігі артық бағалаудан (overstaging) жоғары болды, әсіресе Т1–Т2 ерте сатыларында.

Қорытынды. КТ кеш Т-сатыларын және метастаздарды бағалауда жоғары диагностикалық тиімділікті көрсетеді, алайда оның ерте формаларды және лимфогенді метастазданудыанықтаудағы мүмкіндіктері шектеулі. Протоколдарды оңтайландыру және КТ-ны эндоскопиялық ультрадыбыспен, стейджингтік лапароскопиямен біріктіру стадиялау дәлдігін арттырып, асқазан обыры бар науқастардың клиникалық нәтижелерін жақсарта алады.

Түйінді сөздер. *Асқазан обыры, компьютерлік томография, стадиялау, дәлдік, Қазақстан.*

Дәйексөз үшін:

Сапаев М.Н., Байнаева Б.С., Джакипов М.А., Кожахметов А.М., Мамлин М.А., Керимкулов А.К., Усипбеков Б.Н., Болсынбекова С.О., Манатова А.М., Буркитбаев Ж.К. Асқазан обыры кезінде компьютерлік томография негізіндегі сатылау мен операциядан кейінгі патоморфологиялық сатылаудың салыстырмалы талдау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 56-62. *doi 10.34689/SH.2025.27.5.007*

Introduction

Gastric cancer is one of the leading causes of cancer-related mortality worldwide, ranking fourth among causes of death from malignant neoplasms and fifth among all cancers [1]. Although advances in multimodal management, particularly the introduction of neoadjuvant and adjuvant chemotherapy, have improved outcomes, the overall 5-year survival remains limited at approximately 35–45% [2]. Accurate clinical staging is essential for treatment planning, prognosis assessment, and optimizing healthcare resources. In particular, computed tomography (CT) has become the most widely used imaging modality for preoperative staging of gastric cancer. Contrast-enhanced computed tomography (CT) remains the primary imaging modality for initial assessment of the tumor (T), nodal (N), and metastatic (M) status. One of the major radiologic challenges is achieving precise TNM staging to minimize the likelihood of under- or overstaging [3]. Therefore, evaluating the concordance between CT staging and final pathological findings is of major clinical importance.

In Kazakhstan, gastric cancer ranks among the top four most common cancers, accounting for 7.4% of all new cases, and remains the second leading cause of cancer mortality (12.0%), after lung cancer (16.3%) [4]. Despite advances in oncology care, the proportion of patients diagnosed at advanced stages (III–IV) remains high, which negatively affects survival outcomes and increases the burden on the healthcare system. For example, regional disparities in early detection rates are observed: in the Aktobe, Atyrau, and Turkestan regions, early diagnosis remains below 20%, far behind national targets [4]. This reflects persistent difficulties in timely identification of gastric cancer cases, which directly influences the reliability of preoperative staging.

Computed tomography (CT), particularly multidetector scan (MDCT), plays a key role in preoperative staging of gastric cancer. High-quality thin-slice CT with water filling allows for the reliable detection of advanced forms of the disease, assessment of the depth of invasion, and visualization of the histological features of the tumor, including the mucinous component and the degree of infiltration. However, this method has limitations such as difficulties in visualizing flat mucosal cancer and differentiating between stages T2 and T3 [5].

To improve the accuracy of clinical staging, a combination of imaging techniques is used. Endoscopic ultrasound has traditionally been considered the "gold standard" for assessing T and N parameters, but the role of CT has expanded significantly: it is used both to detect distant metastases and to clarify the local stage. Magnetic resonance imaging provides high soft tissue contrast and is sensitive to small foci in the liver, while positron emission tomography is effective in detecting lymph node metastases and peritoneal carcinomatosis. The integration of multiple methods improves the accuracy of TNM staging and optimizes treatment strategies [6].

However, in Kazakhstan, the diagnostic performance of CT may be affected by several factors, including heterogeneous equipment quality, variability in protocols, and unequal regional access to advanced imaging technologies. These limitations contribute to discrepancies between CT-based staging and postoperative pathological findings. Such discrepancies may lead to suboptimal treatment decisions, highlighting the need for systematic evaluation of CT accuracy in local practice. Thus, the aim of this study is to assess the concordance between CT staging results and final pathological findings in patients with gastric cancer in Kazakhstan.

Materials and methods:

Study design and population

A retrospective single-center study was conducted at the National Research Oncology Center (NROC, Astana, Kazakhstan) between January 2024 and August 2025. The study included patients with pathologically confirmed gastric adenocarcinoma who had undergone CT scans of the chest and abdomen prior to treatment and had available postoperative pathology reports. Patients were excluded from the analysis if reliable histological data were not available, if CT scans were performed without intravenous contrast, or if the contrast agent administration technique was improper.

Visualization methods

Computed tomography was performed using 16-, 64-, and 128-slice scanners. The reconstructed slice thickness was 1–3 mm. Oral contrast was used sparingly, primarily to improve visualization of the gastric lumen.

Staging assessment

CT images were interpreted by blinded radiologists at the Scientific Research Center of Cancer Research. Tumor staging was performed according to the TNM classification (8th edition, AJCC, 2017). The CT staging results were compared with the final postoperative pathology report.

Statistical analysis

To evaluate the diagnostic efficacy of CT, sensitivity, specificity, overall accuracy, and the kappa agreement coefficient (κ) were calculated. Statistical processing was performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Results

The study included 42 patients with verified gastric adenocarcinoma. The average age was 56 years (range, 38-74 years), with a predominance of men (71.4%). According to the final pathological report, the majority of patients were at stage III of the disease (47.6%), while stages I and II were detected less frequently (14.3% and 26.2%, respectively), and stage IV was recorded in 11.9% of patients (Table 1). All patients underwent preoperative computed tomography of the abdominal organs with intravenous contrast, the results of which were compared with postoperative histological data.

Table 1.

General characteristics of patients.

Variable	n=42
Average age (years)	56
Men	30 (71.4%)
Women	12 (28.6%)
Stage I	6 (14.3%)
Stage II	11 (26.2%)
Stage III	20 (47.6%)
Stage IV	5 (11.9%)

The analysis showed that the overall concordance between clinical CT staging and pathological results was

65.8% for the T parameter, 60.9% for the N parameter, and 87.8% for the M parameter (Table 2). CT demonstrated the highest diagnostic accuracy in detecting distant metastases, owing to the method's high sensitivity for liver, lung, and peritoneal lesions. However, the kappa agreement coefficient was low, which is explained by a significant sample imbalance: the vast majority of patients had stage M0, while M1 cases were rare. Thus, the high concordance rate is primarily due to the sample structure, rather than solely to the method's performance.

Table 2.

Diagnostic efficacy of CT in staging gastric cancer.

Stage	Sensitivity	Specificity	Accuracy	Kappa
T1	00.0	92.5	90.2	-0.038
T2	33.3	94.3	85.4	0.32
T3	73.3	72.7	73.2	0.40
T4a	75.0	97.3	95.1	0.72
T4b	—	87.8	87.8	00.0
N0	63.6%	83.9%	78.6%	0.47
N1	60.0%	74.1%	69.0%	0.38
N2	66.7%	90.0%	83.3%	0.56
N3	25.0%	94.7%	88.1%	0.15
M0	94.74	0.00	87.80	-0.062
M1	0.00	94.74	87.80	-0.062

When analyzing the accuracy of CT in determining the depth of invasion (T-stage), significant differences were revealed. The most reliable results were achieved for T4a diagnosis, where sensitivity and specificity were high, and the level of concordance with pathology was the most significant (κ = 0.72). At the same time, the greatest difficulties were observed in assessing early stages. For T1 tumors, sensitivity was 0%, indicating the limited ability of CT to detect superficial forms of the disease. For T2 tumors, a tendency to underestimate the depth of invasion was also observed, while for T3 tumors, in contrast, cases of both overestimation and underestimation of the stage were recorded. Overall, this reflects the difficulty of differentiating between adjacent stages, especially in infiltrative tumor growth.

CT demonstrated moderate accuracy in assessing regional lymph node involvement (N stage). The highest results were obtained for N2 (sensitivity 66.7%, specificity 90.0%, accuracy 83.3% (κ = 0.56)), whereas both false-positive and false-negative results were observed for N0 and N1. The greatest difficulties arose in determining the N3 stage, where diagnostic sensitivity was minimal. These results indicate that CT's capabilities in assessing lymph node metastasis remain limited, particularly in the presence of micrometastases that cannot be visualized by this method.

Thus, the study demonstrated that CT remains highly informative in detecting distant metastases and is relatively reliable in diagnosing widespread forms of local invasion (T4a). However, the method's accuracy significantly decreases when assessing early stages and lymph node metastases, confirming the need for a comprehensive approach to staging that includes additional imaging techniques and morphological verification.

Discussion

Staging gastric cancer using computed tomography (CT) remains one of the most challenging tasks in clinical oncology. Its accuracy is determined by many factors, including tumor morphological features, standardization of imaging protocols, and the experience of specialists [7]. These problems are particularly relevant for developing countries, where the proportion of patients with locally advanced tumors at the time of presentation remains high and diagnostic capabilities are limited [8]. Our study adds new evidence from Kazakhstan, where CT staging has not been systematically validated against pathology despite the high national burden of gastric cancer. This local context is important, because healthcare systems with limited access to advanced imaging technologies face unique challenges in ensuring staging accuracy.

Our study demonstrated that the accuracy of CT depends on the stage of the disease. The most pronounced limitations of the method are associated with early stages (T1–T2). Not a single T1 case was correctly identified, which confirms the literature data on the extremely low sensitivity of CT in detecting tumors limited to the mucosa and submucosa [9, 10]. Even at T2, accuracy remained limited and concordance with histology was poor, which is explained by the difficulty in differentiating between T2 and T3, where inflammatory or fibrotic changes can mimic tumor invasion. These results are consistent with the work of *Yan C. et al.* (2009) *and Makino T. et al.* (2011), who showed similar difficulties in distinguishing adjacent stages [11, 12].

Unlike early forms, CT has demonstrated high diagnostic value in late stages. For T4a, high sensitivity and specificity were achieved, comparable to data from international studies [8, 12]. Visualization of signs of serous invasion, such as irregularity of the serous surface or the presence of ascites, makes the method particularly useful for surgical planning. These findings are of practical importance, as the extent of surgery is determined at stage T4a. In T4b, CT also demonstrated high specificity, which is critical for assessing tumor resectability. Thus, CT remains an indispensable tool for identifying advanced forms of the disease, although its role in early diagnosis remains limited.

A similar situation is observed in the assessment of regional lymph node metastasis. In our study, the diagnostic accuracy of the N stage was 60.9%, which is consistent with the results of *Gundavda K. et al. (*2025), who reported a range of 60.8–63.7% [13]. The classical criteria—the size and morphological structure of the lymph nodes—proved to be insufficiently reliable, which is confirmed by earlier data [14, 15, 16]. Enlarged lymph nodes can be caused by inflammation, while normal-sized nodes may contain

micrometastases, significantly reducing the accuracy of staging. Currently, there are no generally accepted CT criteria for characterizing a lymph node as malignant, including size, round shape, central necrosis, enhancement, and clustering of 3 or more lymph nodes [17]. This highlights the need to develop new assessment criteria, including functional and textural parameters, as well as the combined use of CT with endoscopic ultrasound or PET/CT.

The determination of the M stage deserves special attention. CT has traditionally demonstrated high accuracy in detecting distant metastases in the liver and lungs, which is confirmed by our results (accuracy of 87.8%). However, the method remains insufficiently sensitive to small peritoneal implants. In our sample, three patients were misclassified as M0, although peritoneal metastases were histologically confirmed. This result is consistent with the data of *Zviniene K. et al.* (2015), who also noted a decrease in the sensitivity of CT in carcinomatosis, especially in cases of minimal implants [18]. The presence of ascites, as shown by the works of *Choi K. et al.* (2018) and *Xu M. et al. (*2024), can serve as an indirect predictor of carcinomatosis, but even in this case the accuracy of the method remains limited [19, 20]. In clinical practice, in such situations, the use of PET/CT or diagnostic laparoscopy is justified, which allows for increased detection of hidden metastases.

Thus, the results of our study confirm the strengths and limitations of CT staging. The method is highly accurate in diagnosing late stages (T4 and M0), but its capabilities in early stages and lymph node assessment are limited. The main problem remains the tendency to underestimate the stage, which can lead to suboptimal treatment decisions. To improve the informativeness of staging, standardization of CT protocols, the implementation of new technologies, and the integration of CT with other imaging modalities and morphological verification are necessary.

Limitations of our study include its retrospective design, small sample size, and single-center nature, which limit the generalizability of our findings. However, the findings are consistent with the results of international studies and highlight the need for prospective, multicenter projects. Looking ahead, a combined approach including CT, EUS, MRI, and laparoscopy appears to be the most rational for optimizing gastric cancer staging, particularly in resource-limited settings.

Conclusion

Computed tomography remains a reliable method for assessing advanced gastric cancer, particularly stage T4, where the results directly influence the extent of surgical intervention. However, its diagnostic accuracy is significantly reduced in early stages and in detecting regional metastases, requiring careful interpretation of data and mandatory combination with other imaging modalities. A promising direction is the standardization of CT protocols, as well as the integration of this method with endoscopic ultrasound, PET/CT, and laparoscopy, which will improve staging accuracy and clinical outcomes, even in resource-limited settings.

Ethical approval

The study was approved by the Institutional Review Board of the National Cancer Research Center. The institutional review board waived the requirement for written informed consent because this retrospective study was conducted using anonymized data obtained from the hospital's electronic medical records and physical examination database.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

All authors have made equal contributions to this publication. The conception and design of the study, data collection and analysis, statistical processing, writing, and critical revision of the manuscript were performed collaboratively by all authors. All authors read and approved the final version of the manuscript.

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Data Accessibility Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest. *We declare no conflict of interest.*

Authors' contributions. *All authors made an equal contribution to the development of the concept, execution, processing of results and writing the article. We declare that this material has not previously been published and is not under consideration by other publishers.*

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ASSESSMENT OF ANTHROPOMETRIC CHARACTERISTICS IN PATIENTS WITH CORONARY ARTERY DISEASE IN KAZAKHSTAN: DATA FROM A PROSPECTIVE CROSS-SECTIONAL STUDY, SINGLE-CENTER EXPERIENCE

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Abstract

Objective: Coronary artery disease (CAD) remains one of the leading causes of mortality and disability worldwide. In patients with CAD, the lumen of the coronary arteries gradually narrows due to atherosclerosis, leading to an imbalance between myocardial oxygen supply and demand. Non-invasive methods such as scintigraphy and positron emission tomography (PET) are widely used for the diagnosis of CAD. Invasive coronary angiography (ICA) has long been considered the "gold standard" for diagnosing CAD. However, studies have shown that the degree of stenosis determined by ICA does not always correlate with the functional significance of the lesion. **The aim of our study** was to investigate the correlations between the volume, length, and diameter of coronary arteries, myocardial mass (MM), and anthropometric indicators such as height, weight, body mass index, body surface area, age, and sex.

Methods: We analyzed 654 medical records of patients who underwent inpatient treatment at the Pavlodar Regional Cardiology Center from November 2024 to January 2025. The patients, aged 18 years and older, were hospitalized with coronary artery pathology, received conservative treatment, and underwent diagnostic coronary angiography (D-CAG).

Results: Our study revealed a significant positive correlation between the volume of coronary arteries and myocardial mass, myocardial mass and patient weight, patient height and the length of coronary arteries ($p < 0.05$). However, no association was found between the volume of coronary arteries, their diameter, and other anthropometric indicators (body mass index, body surface area) ($p > 0.05$).

Conclusion: Thus, our study demonstrates that the dimensions of coronary arteries are closely related to the anthropometric characteristics of the patient.

Keywords: *coronary artery volume, myocardial mass, coronary artery disease.*

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Резюме

ОЦЕНКА АНТРОПОМЕТРИЧЕСКИХ ХАРАКТЕРИСТИК У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА В КАЗАХСТАНЕ: ДАННЫЕ ПРОСПЕКТИВНОГО ПОПЕРЕЧНОГО ИССЛЕДОВАНИЯ, ОПЫТ ОДНОГО ЦЕНТРА

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Актуальность: Ишемическая болезнь сердца (ИБС) остается одной из ведущих причин смертности и инвалидности во всем мире. У пациентов с ИБС просвет коронарных артерий постепенно сужается из-за атеросклероза, что приводит к дисбалансу между кровоснабжением сердца и потребностью миокарда в кислороде. Для диагностики ИБС широко используются неинвазивные методы, такие как сцинтиграфия и позитронно-эмиссионная томография (ПЭТ). Инвазивная

коронарная ангиография (ИКА) долгое время считалась "золотым стандартом" диагностики ИБС. Однако исследования показали, что степень стеноза, определяемая с помощью ИКА, не всегда коррелирует с функциональной значимостью поражения. **Целью исследования** стало изучение корреляционных связей между объемом, длиной и диаметром коронарных артерий, массой миокарда (ММ) и антропометрическими показателями, такими как рост, вес, индекс массы тела, площадь поверхности тела, возраст и пол.

Методы: Нами был проведен анализ 654 историй болезни пациентов проходивших стационарного лечения в условиях Павлодарского Областного Кардиологического центра, госпитализированных с патологией коронарных артерий с ноября 2024 года по январь 2025 года. В возрасте от 18 лет, которые получали консервативное лечение, а также была проведена Д-КАГ.

Результаты: В нашем исследовании была выявлена значимая положительная корреляция между объемом коронарных артерий и массой миокарда, массой миокарда и массой пациента, ростом пациента и длиной коронарных артерий, а так же между (p <0,05). Однако связи между объемом коронарных артерий, их диаметром и другими антропометрическими показателями (индекс массы тела, площадь поверхности тела) не обнаружена (p> 0,05).

Выводы: Таким образом, наше исследование демонстрирует, что размеры коронарных артерий тесно связаны с антропометрическими показателями пациента.

***Ключевые слова**: объем коронарных артерий, масса миокарда, ишемическая болезнь сердца.*

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Түйіндеме

ҚАЗАҚСТАНДАҒЫ ИШЕМИЯЛЫҚ ЖҮРЕК АУРУЫ БАР НАУҚАСТАРДЫҢ АНТРОПОМЕТРИЯЛЫҚ СИПАТТАМАЛАРЫН БАҒАЛАУ: БІР ОРТАЛЫҚТЫҢ ТӘЖІРИБЕСІ, ПРОСПЕКТИВТЫ КӨЛДЕНЕҢ ЗЕРТТЕУ ДЕРЕКТЕРІ

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Актуальность: Ишемиялық жүрек ауруы (ИЖА) әлем бойынша өлім мен мүгедектіктің негізгі себептерінің бірі болып қала береді. ИЖА-сы бар науқастарда атеросклероздың әсерінен тамырлардың кеңістігі бірте-бірте тарылып, жүрекке қан жеткізу мен миокардтың оттегіге деген қажеттілігі арасында теңсіздік пайда болады. ИЖА-ны диагностикалау үшін сцинтиграфия және позитрон-эмиссионды томография (ПЭТ) сияқты инвазивті емес әдістер кеңінен қолданылады. Инвазивті коронарлы ангиография (ИКА) ұзақ уақыт бойы ИЖА диагностикасының "алтын стандарты" болып саналды. Дегенмен, зерттеулер ИКА арқылы анықталатын стеноз дәрежесі әрдайым зақымданудың функционалды маңыздылығымен сәйкес келмейтінін көрсетті. **Зерттеуіміздің мақсаты** – коронарлы тамырлардың көлемі, ұзындығы және диаметрі, миокардтың массасы (ММ) және бой, салмақ, дене массасы индексі, дене бетінің ауданы, жасы және жыныс сияқты антропометриялық көрсеткіштер арасындағы корреляциялық байланыстарды зерттеу болды.

Әдістері: 2024 жылдың қарашасынан 2025 жылдың қаңтарына дейін «Павлодар облыстық кардиология орталығында» стационарлық емдеу алған 18 жастан асқан 654 науқастың медициналық тарихтары талданды. Барлық науқастарға консервативті ем берілді және Д-КАГ жүргізілді.

Нәтижесі: Зерттеу барысында коронарлы тамырлардың көлемі мен миокардтың массасы, миокардтың массасы мен науқастың салмағы, науқастың бойы мен коронарлы тамырлардың ұзындығы арасында айтарлықтай оң корреляция байқалды (p <0,05). Дегенмен, коронарлы тамырлардың көлемі, диаметрі мен басқа антропометриялық көрсеткіштер (дене массасы индексі, дене бетінің ауданы) арасында байланыс анықталған жоқ (p> 0,05).

Қорытынды: Осылайша, біздің зерттеуіміз коронарлы тамырлардың өлшемдері науқастың антропометриялық көрсеткіштерімен тығыз байланысты екенін көрсетті.

***Түйін сөздер:** коронарлы тамырлардың көлемі, миокардтың массасы, ишемиялық жүрек ауруы.*

***Дәйексөз үшін:** Антикеев А.М., Абильтаев А.М., Абильтаева А.А., Тлеуова А.К., Изгуттинов Д.Е.* Қазақстандағы ишемиялық жүрек ауруы бар науқастардың антропометриялық сипаттамаларын бағалау: бір орталықтың тәжірибесі, проспективты көлденең зерттеу деректері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), С.63-69. *doi 10.34689/SH.2025.27.5.008*

Introduction

The Problem and the Limitations of Modern Diagnostic Methods

Ischemic heart disease (IHD) remains one of the leading causes of mortality and disability worldwide. In patients with IHD, the lumen of the coronary arteries gradually narrows due to atherosclerosis, leading to an imbalance between myocardial blood supply and oxygen demand. This imbalance manifests with clinical symptoms such as angina pectoris and significantly impairs a patient's quality of life [1].

To diagnose IHD, clinicians rely on a range of tools, each with its own strengths and weaknesses. Non-invasive methods, such as scintigraphy and positron emission tomography (PET), are widely used and allow assessment of myocardial perfusion and identification of ischemic areas. However, a significant limitation is that these techniques do not provide accurate information on coronary artery anatomy [2]. To overcome this, cardiac magnetic resonance imaging (MRI) offers a more comprehensive approach, allowing visualization of both coronary artery anatomy and myocardial perfusion. Despite this advantage, MRI has its own limitations: it cannot always distinguish between blood flow impairments in large epicardial vessels (that can be solved by revascularization) and microcirculation impairments. Furthermore, its lengthy procedure time limits its widespread use in clinical practice [3].

For decades, invasive coronary angiography (ICA) has been the undisputed "gold standard" for anatomical assessment. Yet, a critical flaw has been recognized: the degree of stenosis determined by ICA does not always correlate with the functional significance of the lesion. This realization is supported by data on the advisability of using invasive fractional flow reserve (FFR) measurement to assess the physiological significance of stenoses [4]. Moreover, a fundamental diagnostic challenge persists, as modern methods often fail to account for the impact of diffuse atherosclerosis on the vasodilatory capacity of vessels. Diagnosing microvascular dysfunction also remains difficult, as it can cause angina symptoms even in the absence of significant stenoses in the major coronary arteries [5].

Bridging the Diagnostic Gap: The Role of Anatomy and Anthropometry

This diagnostic complexity highlights a critical, yet understudied aspect of IHD: the relationship between coronary artery dimensions and basic patient anthropometric indicators such as height, weight, body mass index (BMI), and body surface area (BSA). Although fundamental principles of biology and cardiac physiology suggest that coronary artery volume should match myocardial mass to ensure adequate blood supply [6], it remains unclear exactly how anthropometric parameters influence coronary artery size.

Existing research has begun to explore this relationship, with studies using ICA and computed tomography coronary angiography (CTCA) demonstrating the importance of the coronary artery lumen volume to myocardial mass ratio (V/M) for assessing ischemia risk [6, 7, 8]. However, these findings are primarily based on Western populations, and do not account for ethnic and geographical characteristics that may significantly influence coronary artery anatomy.

Research Objective, Significance, and Our Study

In Kazakhstan, where ethnic diversity and specific climatic conditions may impact the cardiovascular system, such studies are virtually absent. This creates a significant knowledge gap that may limit opportunities for personalized diagnosis and treatment of CAD in the local population.

Therefore, the aim of our study was to investigate the correlations between the volume, length, and diameter of coronary arteries, myocardial mass (MM), and anthropometric indicators such as height, weight, BMI, BSA, age, and sex. We hypothesize that the obtained data will not only deepen the understanding of anatomical features of coronary arteries in this population but also help develop more accurate diagnostic criteria for identifying patients at increased risk of ischemia.

Our study is unique in that it combines data from diagnostic coronary angiographies (D-CAG) with anthropometric measurements, allowing for a direct assessment of the relationship between coronary artery size and individual patient characteristics. This is particularly important for developing personalized approaches to CAD treatment that consider not only the degree of stenosis but also the anatomical features of the coronary arteries.

To achieve this goal, we conducted a prospective single-center study analyzing the results of D-CAG of patients treated at the Pavlodar Regional Cardiology Center from November 2024 to January 2025.

Materials and Methods

Study Design and Population

This prospective single-center study was conducted at the Pavlodar Regional Cardiology Center (PRCC), a tertiary referral hospital providing a full range of specialized care for patients with circulatory system diseases. We analyzed medical records of 654 patients hospitalized with suspected coronary artery pathology who underwent D-CAG from November 2024 to January 2025.

From this initial cohort, 137 patients were selected for the final analysis based on the following inclusion criteria: (1) age 18 years or older, (2) hospitalization with a preliminary diagnosis of unstable angina (ICD-10 code I20.0), and (3) the absence of hemodynamically significant coronary artery disease, defined as no coronary lesions or stenoses < 30% as confirmed by D-CAG. Exclusion criteria included a history of prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), poor angiographic image quality, and severe valvular heart disease.

Data Collection and Measurements

Demographic and anthropometric data, including sex, age, weight, and height, were extracted from the electronic medical record system (EMIS). BMI and BSA were calculated from these measurements. Echocardiographic data were used to calculate MM according to the American Society of Echocardiography (ASE) formula [9], where PWT is the posterior wall thickness, IVS is the interventricular septum thickness, and LVEDD is the left ventricular end-diastolic dimension.

$$MM = 0.8 * (1.04 * [(PWT + IVS + LVEDD)^3 – LVEDD^3]) + 0.6$$

Coronary artery analysis was performed using D-CAG images acquired on a GE Innova system. The length, diameter, and volume of the left and right coronary arteries were assessed in standard projections for each artery.

Measurements were performed offline using dedicated software (2D viewer and VolumeViewer), with the size of the diagnostic catheter used as a reference for calibration. The presence or absence of coronary pathology was assessed based on the D-CAG results.

Ethical Considerations

This study was conducted within the scientific program of the Department of Surgery of the Pavlodar Branch, Semey Medical University. The institutional ethics committee reviewed and approved the study protocol, waiving the requirement for informed consent due to the prospective, anonymized nature of the data analysis and the study's compliance with local regulations permitting the use of de-identified clinical records for research purposes. The institutional leadership raised no objections to the publication of anonymized data. Patients participating in the study were included only after voluntarily signing a written informed consent form.

Statistical Analysis. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as absolute numbers and percentages. The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. Comparisons of continuous variables between groups were performed using the Student's t-test or the Mann-Whitney U test, as appropriate. Correlation analyses between continuous variables were assessed using Pearson or Spearman correlation coefficients, depending on the data distribution.

All statistical analyses were performed using R software version 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

Results

Study Population and Baseline Characteristics

A total of 137 patients met the inclusion criteria and constituted the study population. The baseline characteristics of the patients are summarized in Table 1. The mean age of the cohort was 67.7 ± 10.6 years, and 50.4% (n=69) were male. Significant differences were observed between genders: women were significantly older than men (64.6 ± 10.8 vs. 58.8 ± 9.7 years, $p < 0.05$). As expected, men had significantly greater height (172.1 ± 7.1 vs. 161.8 ± 6.5 cm, $p < 0.05$) and BSA (1.97 ± 0.18 vs. 1.86 ± 0.19 m², $p < 0.05$) compared to women. Although women had a lower mean weight than men (82.2 ± 16.1 vs. 84.6 ± 15.2 kg, $p > 0.05$), this difference was not statistically significant. However, BMI was significantly higher in women (31.3 ± 5.9 vs. 28.5 ± 4.6 kg/m², $p < 0.05$).

Analysis of Coronary Artery Dimensions

The detailed measurements of coronary artery dimensions are presented in Table 1. Overall, the mean volume of the coronary arteries was 1585 ± 564 mm³. While descriptive trends showed larger absolute dimensions (length and diameter) in men compared to women for both the left anterior descending (LAD) and right coronary arteries (RCA), these differences did not reach statistical significance ($p > 0.05$ for all comparisons).

The mean length and diameter of the LAD were 102.0 ± 25.4 mm and 2.87 ± 0.75 mm, respectively (Men: 105.9 mm / 2.79 mm; Women: 99.0 mm / 2.94 mm). For the RCA, the mean length and diameter were 94.4 ± 26.5 mm and 2.95 ± 0.70 mm, respectively (Men: 98.3 mm / 2.96 mm; Women: 90.5 mm / 2.96 mm). Similarly, the volume of the left coronary artery (LCA) was greater in men (982.2 mm³ vs. 943.9 mm³), as was the volume of the RCA (659.2 mm³ vs. 582.9 mm³), but these differences were also not statistically significant.

Table 1.

General characteristics of patients

Characteristics	Mean (SD)
Age, years	67,7 (10,6)
Height, sm	167,0 (8,57)
Weight, kg	83,4 (16,9)
BMI, kg/m²	29,9 (5,56)
BSA, m²	1,92 (0,201)
Mass of myocardium (gr)	252 (120)
Volume of coronary artery (mm³)	1585 (564)
Length of LAD, mm	102,0 (25,4)
Diameter of LAD, mm	2,87 (0,75)
Volume of LCA, mm³	963,0 (338,0)
Length of RCA, mm	94,4 (26,5)
Diameter of RCA, mm	2,95 (0,70)
Volume of RCA, mm³	621,0 (35,0)

Notes: BMI - body mass index; BSA - body surface area; LAD - left anterior descending artery; LCA - left coronary artery; RCA - right coronary artery.

Correlation Analyses

The distribution of key variables was assessed for normality (Figure 1). Height, LCA length, and RCA length followed a normal distribution (Shapiro-Wilk $p > 0.05$). In contrast, MM, coronary artery volume, and patient weight showed distributions significantly different from normal (Shapiro-Wilk $p < 0.05$), which informed the choice of correlation methods (Pearson or Spearman).

We identified several significant correlations (Figure 2): A moderate positive correlation was found between total coronary artery volume and myocardial mass ($r = 0.48$, $p < 0.05$; Figure 2A). Weak positive correlations were observed between: Myocardial mass and patient weight ($r = 0.32$, $p < 0.05$; Figure 2B). RCA length and patient height ($r = 0.33$, $p = 0.00063$; Figure 2C). LCA length and patient height ($r = 0.26$, $p < 0.05$; Figure 2D). No significant association was found between coronary artery volume or diameter and other anthropometric indicators such as BMI or BSA ($p > 0.05$).

Discussion

Key findings in our research were: We identified a moderate positive correlation ($r = 0.48$, $p < 0.05$) between total coronary artery volume and myocardial mass, supporting the fundamental allometric principle of a matching blood supply to muscle mass. The absolute dimensions (length, diameter, volume) of the coronary arteries in our cohort were generally lower than those reported in studies of other populations, suggesting potential ethnic or geographical variations in coronary anatomy. We found a weak but significant positive correlation between patient height and the length of both the LAD and RCA, confirming that overall body size is a determinant of coronary artery anatomy. However, no significant association was found between coronary dimensions and BMI or BSA.

The principle of allometric scaling and the volume-to-mass (V/M) ratio, established over 40 years ago by Gould et al. [10],

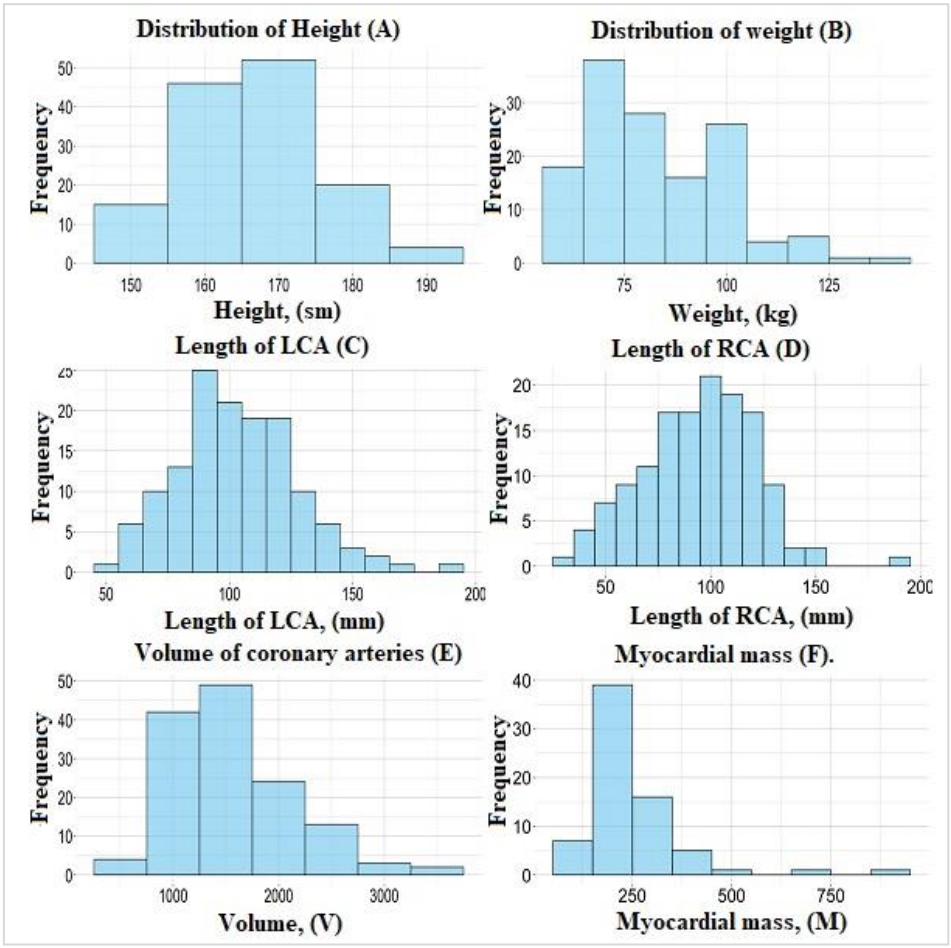

Figure 1. Distribution of Height (Figure 1A), weight (Figure 1B), length of Left Coronary Artery (LCA) (Figure 1C) and Right Coronary Artery (RCA) (Figure 1D), volume of coronary arteries (V) (Figure 1E), myocardial mass (M) (Figure 1F).

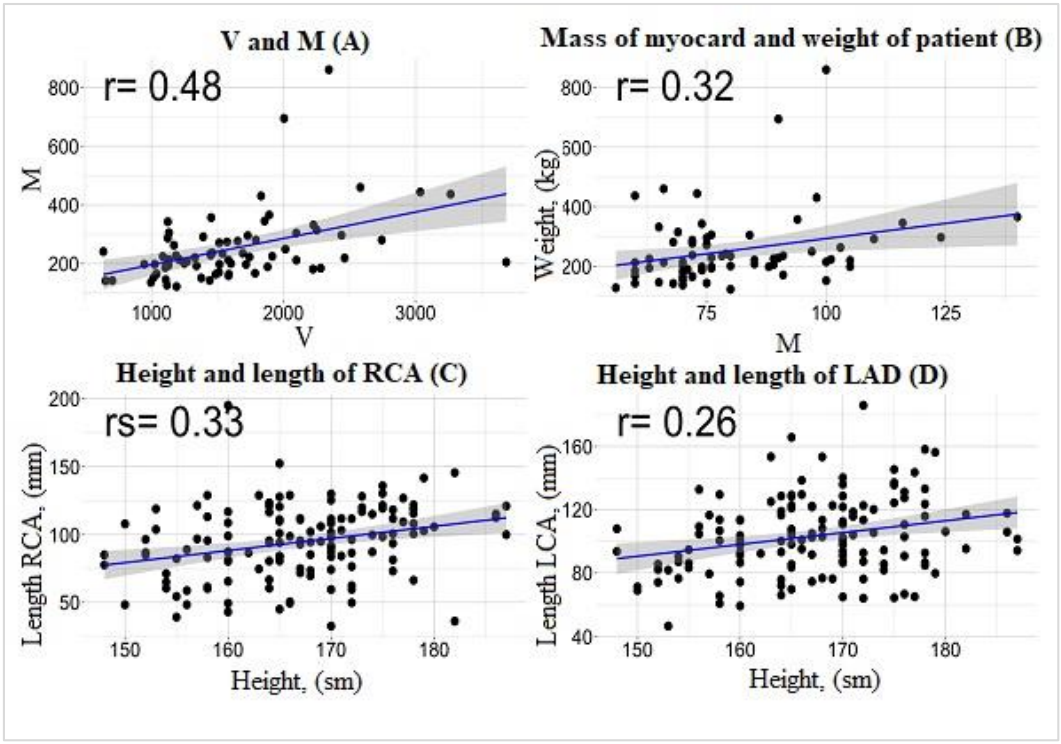

Figure 2. Correlation between volume of coronary artery (V) and mass of myocard (M) (Figure 2A), mass of myocard and weight of patient (Figure 2B), height and length of right coronary artery (RCA) (Figure 2C) and height and length of left coronary artery (LCA) (Figure 2D). Trends line and Pearson's (Figure 2A, 2B, 2C) and Spearman's (Figure 2D) correlation coefficient.

provides a crucial framework for understanding the relationship between coronary anatomy and cardiac function. Our finding of a moderate correlation between coronary volume and myocardial mass confirms that this relationship holds true in our specific population, indicating a statistically significant and non-random dependence despite the sample size.

An intriguing result of our study is that the mean absolute values for coronary artery volume (1585 ± 564 mm³), length (102.0 ± 25.4 mm), and diameter (2.87 ± 0.75 mm) were lower than those reported in similar studies on other populations (diameter (mean±SD) of the left main coronary was 3.5±0.8 mm and the length 105.0±53.0 mm) [11]. This discrepancy may be related to the unique ethnic and geographical characteristics of the Kazakhstani population, a factor that warrants further investigation in larger, multi-ethnic studies. Furthermore, the correlation we observed between patient height and coronary artery length is consistent with the established principles of allometric scaling described in the literature [1, 12], reinforcing the idea that overall body size is a key determinant of vascular anatomy.

In contrast, the lack of a significant association between coronary artery dimensions and BMI or BSA is notable. This may be because these composite indices do not fully capture key aspects of body composition, such as lean muscle mass volume or specific fat distribution patterns [13]. Our results also showed a weak correlation between myocardial mass and body weight. This weak association could be attributed to the influence of obesity, where increased body size is not necessarily accompanied by a proportional, functional increase in heart mass and coronary artery dimensions. This mismatch can place additional strain on the cardiovascular system, potentially exacerbating the course of IHD.

This leads to a discussion of the complex "obesity paradox," where patients with overweight and obesity often present with more pronounced clinical manifestations of IHD, leading to more frequent hospitalization and higher detection rates. While this may seem contradictory, one explanation is that obesity not only increases the risk of IHD but also makes its symptoms more apparent, potentially promoting earlier diagnosis and intervention [14, 15]. Consequently, current statistics on the impact of obesity on CAD might be incomplete or distorted if they fail to account for underlying anatomical variations. Our study emphasizes the importance of considering precise anthropometric parameters beyond BMI to achieve a more accurate assessment of the relationship between body size and CAD.

Collectively, our findings argue for the development of a more nuanced "coronary body index" that integrates coronary artery volume, myocardial mass, cardiac output, and key anthropometric data (e.g., height). Such an index could refine risk stratification, answer questions about coronary insufficiency in patients without overt IHD, and ultimately inform more personalized treatment tactics, improve diagnostic algorithms, and enhance long-term survival outcomes [16].

Study Uniqueness and Clinical Significance

Our study is among the first to investigate the relationship between coronary artery dimensions and anthropometric indicators in a population from Kazakhstan. This is particularly important given the region's ethnic diversity and specific climatic conditions, which may influence cardiovascular physiology. The data obtained can be used to develop more accurate, population-specific diagnostic criteria for identifying patients at increased risk of ischemia, fostering a personalized approach to CAD treatment that considers not only the degree of stenosis but also the patient's unique coronary anatomy.

Limitations

Several limitations of our study must be acknowledged. First, the assessment of coronary parameters was based on 2D invasive coronary angiography (D-CAG). While widely available, this method is susceptible to projection distortions, which can lead to an underestimation or overestimation of artery length and diameter [17, 18]. Future studies would benefit from employing 3D imaging techniques, such as CT coronary angiography, for more precise anatomical reconstruction.

Second, myocardial mass was estimated using echocardiography, a method known to potentially underestimate values by 10–30% compared to the gold standard of cardiac MRI [19]. This inaccuracy may have affected the strength of the correlation we observed between myocardial mass and body weight.

Finally, the measurements were conducted without controlling for the administration of nitrates, which can cause vasodilation and temporarily alter coronary artery diameter, potentially leading to an underestimation of their true size. The inclusion of patients with various stages of coronary atherosclerosis might have also influenced the results, as plaque burden can distort native anatomical parameters.

Conclusions

Our study confirms the fundamental allometric principle of a positive correlation between coronary artery volume and myocardial mass in a specific population of Kazakhstan. These findings underscore the potential clinical value of developing a personalized "coronary body index" that integrates coronary anatomy, myocardial mass, and key anthropometric data. Such an index could refine diagnostic accuracy, improve risk stratification for ischemia, and inform more tailored treatment strategies for patients with coronary artery disease. Despite limitations related to 2D angiographic measurements and echocardiographic mass estimation, this study provides a foundational insight into the anatomical relationships of the coronary system in the Kazakhstani population. Future research utilizing advanced 3D imaging and larger, multi-ethnic cohorts is essential to validate these findings and explore the impact of ethnic and geographical factors on coronary anatomy, ultimately working towards more personalized and effective cardiovascular care.

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ASSESSMENT OF THE EFFECTIVENESS OF MEASURES TO PREVENT COMPLICATIONS OF SURGICAL TREATMENT IN PATIENTS WITH OCCLUSION OF THE AORTO-ILIAC SEGMENT

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Abstract

Introduction: In modern vascular surgery, occlusive lesions of the aortoiliac segment (AIS) represent one of the most pressing problems. It is generally accepted that the detection of AIS occlusion indicates the severity and prevalence of the atherosclerotic process, and therefore a high probability of combined occlusive lesions in other arterial basins. Of particular importance in this regard is the lesion of the arterial bed of vital organs – the heart and brain.

Objective. To conduct a comparative analysis of the results of surgical treatment of occlusive lesions of the AIS with and without correction of predictors of complications from vital organs, and to evaluate their effectiveness.

Materials and methods: Study design — prospective non-randomised clinical observation. The analysis included 143 patients with occlusive lesions of the aortoiliac segment (AIS) who underwent surgery in 2018–2024 in the cardiovascular surgery department of the NCJSC «Semey Medical University» University Hospital.

Depending on the tactics used, patients were divided into two groups: Group 1 (n = 64) — patients who underwent emergency reconstructive interventions on the AIS without prior correction of coronary and carotid artery lesions, without pelvic revascularisation, and without treatment for renal failure. Group 2 (n = 79) — patients who, if indicated, underwent preliminary correction of cardiac and cerebrovascular pathology, revascularisation of the pelvic arteries, and stabilisation of renal function before the main operation.

Results: In the early postoperative period (30 days), complications were recorded in 43.8% of patients in the first group and in 10.1% in the second group (p = 0.0002). Systemic complications (myocardial infarction, ACA stroke, multiple organ failure) were significantly more common in the first group (p < 0.01). The 30-day mortality rate decreased from 12% in the first group to 2.5% in the second. In the long term (5 years), the overall complication rate was 40.7% versus 11.5% (p = 0.0003). Cumulative Kaplan-Meier survival reached 80% in the first group and 95% in the second, with statistically significant differences (Log-Rank p = 0.029).

Conclusion: The implementation of this tactic not only improved the immediate results of treatment, but also significantly increased the long-term survival of patients. Comprehensive preoperative preparation aimed at correcting functional disorders of vital organs and optimising the staging of vascular interventions have proven their effectiveness and can be recommended as a safe and clinically justified method of treating occlusions of the aorto-iliac segment in patients with severe concomitant pathology.

Keywords: *Aorto-iliac segment occlusion, complications, mortality, survival.*

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Резюме

ОЦЕНКА ЭФФЕКТИВНОСТИ МЕР ПО ПРОФИЛАКТИКЕ ОСЛОЖНЕНИЙ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЬНЫХ С ОККЛЮЗИЕЙ АОРТО-ПОДВЗДОШНОГО СЕГМЕНТА

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Введение: В современной сосудистой хирургии окклюзионные поражения аорто-подвздошного сегмента (АПС), представляют одну из наиболее актуальных проблем. Общепринятым считается мнение, что обнаружение окклюзии АПС свидетельствует о тяжести и распространенности атеросклеротического процесса, а значит и большой вероятности сочетанных окклюзирующих поражений в других артериальных бассейнах. Особую важность в этом отношении представляет поражение артериального русла жизненно важных органов – сердца и головного мозга.

Цель исследования. Провести сравнительный анализ результатов оперативного лечения окклюзионных поражений АПС с коррекцией и без коррекции предикторов осложнений со стороны жизненно важных органов, оценить их эффективность.

Материалы и методы: Дизайн исследования — проспективное нерандомизированное клиническое наблюдение. В анализ включено 143 пациента с окклюзионными поражениями аорто-подвздошного сегмента (АПС), прооперированных в 2018–2024 гг. в отделении сердечно-сосудистой хирургии Университетского Госпиталя НАО «Медицинский университет Семей».

В зависимости от применённой тактики пациенты разделены на две группы: 1-я группа (n = 64) — больные которым выполнялись экстренные реконструктивные вмешательства на АПС без предварительной коррекции поражений коронарных и сонных артерий, без реваскуляризации тазового бассейна и без лечения почечной недостаточности. 2-я группа (n = 79) — пациенты, которым при наличии показаний предварительно выполнялась коррекция кардиальной и цереброваскулярной патологии, реваскуляризация тазовых артерий и стабилизация функции почек перед основной операцией.

Результаты: В раннем послеоперационном (30-дневном) периоде осложнения зарегистрированы у 43,8 % пациентов первой группы и у 10,1 % — второй (p = 0,0002). Системные осложнения (инфаркт миокарда, ОНМК, полиорганная недостаточность) достоверно чаще наблюдались в первой группе (p < 0,01). 30-дневная летальность снизилась с 12 % в первой группе до 2,5 % во второй. В отдалённом (5-летнем) периоде общая частота осложнений составила 40,7 % против 11,5 % (p = 0,0003). Кумулятивная выживаемость по Каплану–Майеру достигала 80 % в первой группе и 95 % во второй, различия статистически значимы (Log-Rank p = 0,029).

Заключение: Внедрение данной тактики позволило не только улучшить непосредственные результаты лечения, но и значительно повысить отдалённую выживаемость пациентов. Комплексная предоперационная подготовка, направленная на коррекцию функциональных нарушений жизненно важных органов, и оптимизация этапности сосудистых вмешательств доказали свою эффективность и могут быть рекомендованы как безопасный и клинически оправданный метод лечения окклюзий аорто-подвздошного сегмента у больных с тяжёлой сопутствующей патологией.

***Ключевые слова**: Окклюзия аорто-подвздошного сегмента, осложнения, летальность, выживаемость.*

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Түйіндеме

ҚОЛҚА-МЫҚЫН СЕГМЕНТІ ОККЛЮЗИЯСЫ БАР НАУҚАСТАРДЫ ХИРУРГИЯЛЫҚ ЕМДЕУДІҢ АСҚЫНУЛАРЫНЫҢ АЛДЫН АЛУ ЖӨНІНДЕГІ ШАРАЛАРДЫҢ ТИІМДІЛІГІН БАҒАЛАУ

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Кіріспе: Қазіргі тамырлы хирургияда қолқа-мықын сегментінің (ҚМС) окклюзиялық зақымдануы ең өзекті мәселелердің бірі. ҚМС окклюзиясын анықтау атеросклеротикалық процестің ауырлығы мен таралуын, демек, басқа артериялық бассейндерде біріктірілген окклюзиялық зақымданулардың үлкен ықтималдығын көрсетеді деген жалпы қабылданған пікір. Осыған байланысты өмірлік маңызды мүшелердің – жүрек пен мидың артериялық арнасының зақымдануы ерекше маңызды.

Зерттеудің мақсаты. Өмірлік маңызды мүшелер тарапынан асқынулардың болжаушыларын түзетумен және түзетусіз ҚМС окклюзиялық зақымдануларын жедел емдеу нәтижелеріне салыстырмалы талдау жүргізу, олардың тиімділігін бағалау.

Материалдар мен Әдістері: Зерттеу дизайны-проспективті рандомизацияланбаған клиникалық бақылау. Талдауға 2018-2024 жылдары "СМУ КеАҚ " университеттік госпиталінің жүрек-қан тамырлары хирургиясы бөлімінде ота жасалған қолқа-мықын сегментінің (ҚМС) окклюзиялық зақымдануы бар 143 пациент енгізілді. Қолданылатын тактикаға байланысты науқастар екі топқа бөлінеді: 1-ші топ (N = 64) — коронарлық және каротид артерияларының зақымдануын алдын ала түзетусіз, жамбас бассейнінің реваскуляризациясынсыз және бүйрек жеткіліксіздігін емдеусіз ҚМС-не шұғыл реконструктивтік араласулар жасалған науқастар. 2-ші топ (N = 79) — көрсетілімдер болған кезде алдын ала жүрек және цереброваскулярлық патологияны түзету, жамбас артерияларын реваскуляризациялау және негізгі ота алдында бүйрек қызметін тұрақтандыру орындалған науқастар.

Нәтижелер: ерте операциядан кейінгі (30 күндік) кезеңде асқынулар бірінші топтағы пациенттердің 43,8%-тіркелген және 10,1 % — екіншісінде (p = 0,0002) тіркелді. Жүйелік асқынулар (миокард инфарктісі, ми қан айнылымының жедел бұзылысы, көп мүшелік жеткіліксіздік) бірінші топта жиі байқалды (p < 0,01). 30 күндік өлім бірінші топтағы 12% - дан екінші топтағы 2,5% - ға дейін төмендеді. 5 жылдық кезеңде асқынулардың жалпы жиілігі 11,5% - ға қарсы 40,7 % құрады (p = 0,0003). Каплан-Майердің жиынтық өмір сүру деңгейі бірінші топта 80%-ға, ал екінші топта 95% - ға жетті, айырмашылықтар статистикалық маңызды (Log-Rank p = 0,029).

Қорытынды: бұл тактиканы енгізу емдеудің тікелей нәтижелерін жақсартып қана қоймай, науқастардың қашықтықтан өмір сүруін едәуір арттырды. Өмірлік маңызды органдардың функционалдық бұзылыстарын түзетуге және тамырлы араласулардың кезеңділігін оңтайландыруға бағытталған кешенді операция алдындағы дайындық тиімділігі дәлелденді және ауыр қатар жүретін патологиясы бар науқастарда қолқа-мықын сегментінің окклюзиясын емдеудің қауіпсіз және клиникалық негізделген әдісі ретінде ұсынылуы мүмкін.

Түйін сөздер*: қолқа-мықын сегментінің окклюзиясы, асқынулар, өлім, өмір сүру.*

Дәйексөз үшін:

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Introduction

Occlusive lesions of the aortoiliac segment (AIS) are a significant clinical problem because they cause severe ischaemia of the lower extremities and impair patients' quality of life. In recent decades, surgical treatment, including open reconstructive surgery and endovascular techniques, has become more accessible, but the risk of complications and unstable long-term outcomes remains high, especially in severe forms of the disease. Endovascular techniques demonstrate high technical success and satisfactory patency rates, especially in groups with less extensive lesions or TASC II A/B, but also in severe cases [7].

Despite the high level of development of vascular surgery, surgical interventions on the aorto-iliac segment are still accompanied by the risk of serious complications. The most significant of these are acute cerebrovascular accidents (ACVA), myocardial infarction, and acute renal failure. These complications are caused by both the severe somatic burden of patients and the characteristics of surgical intervention, which includes significant trauma, tissue ischaemia, the use of aortic clamping and contrast agents in intraoperative diagnostics. The high frequency of these complications requires careful preoperative risk assessment, optimisation of the patient's condition, and the use of modern methods of perioperative monitoring and protection of target organs.

Traditionally, treatment of occlusion of the aortoiliac segment is performed by open surgery, including endarterectomy and aortoiliac or aortofemoral bypass grafting. Although these methods have demonstrated excellent long-term patency, they are associated with high morbidity and mortality rates [3].

Currently, there is a pressing issue regarding the choice of surgical treatment tactics for occlusive lesions of the AIS, the necessity and priority of surgical correction of combined lesions of the coronary bed and carotid arteries, improvement of pelvic blood supply, and correction of renal failure. According to the literature, some authors prefer to perform simultaneous surgical interventions in two or more affected arterial basins, while others suggest performing staged interventions. There are also opinions on the advisability of therapeutic correction of blood supply disorders in affected organs [4,5].

Research objective. To conduct a comparative analysis of the results of surgical treatment of occlusive lesions of the AIS with and without correction of predictors of complications affecting vital organs, and to evaluate their effectiveness.

Materials and methods.

Study design: prospective non-randomised clinical study.

This study analyses the results of surgical treatment of 143 patients with occlusive lesions of the aortoiliac segment (AIS) operated on between 2018 and 2024 at the cardiovascular surgery department of the University Hospital of the NCJSC 'SMU'. Depending on the chosen treatment tactics, patients were divided into two groups.

The first group included 64 patients with unstable disease who, upon admission, presented with critical ischaemia of the lower extremities with a high probability of developing irreversible trophic disorders, including gangrene. Due to the urgency of their condition, these patients underwent emergency surgery without prior correction of haemodynamically significant lesions of the coronary and carotid arteries, without staged revascularisation of the pelvic basin, and without planned treatment for renal failure.

The second group included 79 patients who, if indicated, underwent preliminary correction of coronary and carotid artery pathology, as well as revascularisation of the pelvic arteries and stabilisation of renal function prior to the main AIS intervention.

The sample size was calculated using PASS 2000 software, version 12.0.4.

Inclusion criteria: occlusive lesions of the AIS, elective or emergency surgery, open reconstruction of the AIS.

Exclusion criteria: juxtarenal and intrarenal occlusions of the AIS, abdominal aortic aneurysm, emergency surgery, endovascular prosthetics of the AIS.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee of the Semey Medical University (protocol No. 4 of 27 September 2017).

In the preoperative period, in addition to physical examination, assessment of angiological status and laboratory tests, various instrumental diagnostic methods were used. Particular attention was paid to identifying concomitant pathology and combined lesions of vascular basins. As part of a comprehensive examination, electrocardiography (ECG), echocardiography (EchoCG), ultrasound Dopplerography and duplex scanning of blood vessels, multispiral CT angiography (MSCT-A), and, if indicated, coronary angiography were performed.

The cause of AIS occlusion in the study groups was atherosclerosis.

Statistical analysis. Intergroup comparison of quantitative characteristics was performed using the Mann-Whitney U test. Frequency indicators in independent samples were compared using Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Survival analysis was performed using the Kaplan-Meier method and the Log-Rank statistical test. Values of $p < 0.05$ were taken as the criterion for statistically significant differences.

Most patients in both groups had various comorbidities (Table 1).

Table 1.

Comorbidities in patients in the study groups.

Associated pathology	Group 1 (n=64)	Group 2 (n=79)
Ischemic heart disease (IHD)	56 (87,5%)	64 (81,0%)
Post-infarction cardiosclerosis (PICS)	13 (20,3%)	17 (21,5%)
Cerebral circulation disorders	36 (56,3%)	38 (48,1%)
Acute cerebrovascular accident	6 (9,4%)	8 (10,1%)
Chronic obstructive pulmonary disease	8 (12,5%)	6 (7,6%)
Arterial hypertension (AH)	48 (75,0%)	62 (78,5%)
Chronic gastritis	38 (59,4%)	40 (50,6%)
Chronic kidney disease (CKD)	21 (32,8%)	20 (25,3%)
Chronic cholecystitis	8 (12,5%)	7 (8,9%)
Diabetes mellitus (DM)	5 (7,8%)	4 (5,1%)

As we can see from this table, the most prevalent pathologies were ischaemic heart disease, arterial hypertension, and cerebral circulation disorders. At the same time, the least common comorbidities in both groups were diabetes mellitus, chronic cholecystitis, COPD, and ACVA.

Patients in both groups underwent surgical interventions on the AIS, but patients in group 2 initially underwent correction of concomitant diseases.

An analysis of the surgical interventions performed in the second group is presented in Table 2.

Table 2.

Analysis of operations performed in the second group of patients.

Stages of operations	Absolute number (%) n = 79
ACBG → reconstruction of AIS	43 (54,4%)
PTCA with stenting → reconstruction of the AIS	18 (22,8%)
CEA → reconstruction of the AIS	12 (15,2%)
PTCA with stenting of the right coronary artery, PTCA with PTCA with stenting of the ICA → reconstruction of the AIS	2 (2,53%)
PTCA with stenting stent of the ICA → ACBG → reconstruction of the AIS	2 (2,53%)
ACBG → КЭАЭ → reconstruction of the AIS	2 (2,53%)

Note: AIS – aorto-iliac segment
ACBG – aorto-coronary bypass grafting *PTCA – percutaneous transluminal coronary angioplasty*
CEA – carotid endarterectomy *RCA – right coronary artery*
PTA – percutaneous transluminal angioplasty *ICA – internal carotid artery.*

The table reflects the stages and types of surgical interventions performed in patients with aortoiliac segment (AIS) lesions in a group of 79 people. The most frequently used tactic was aortocoronary bypass grafting (ACBG) followed by AIS reconstruction, which was observed in 43 patients (54.4%).

The next most common procedures were: percutaneous transluminal coronary angioplasty (PTCA) with stenting followed by AIS reconstruction — in 18 patients (22.8%), carotid endarterectomy (CEA) before AIS reconstruction — in 12 patients (15.2%). Less common were complex combined approaches involving stenting of several vascular beds at once (ICA), as well as multi-stage interventions involving ACBG and CEA, each of which accounted for 2 cases (2.53%). The types of surgical interventions on the AIS are presented in Table 3.

Table 3

Comparative analysis of AIS reconstruction.

Type of reconstruction	Absolute number (%)	
	Group 1 (n=64)	Group 2 (n=79)
Bifurcated aorto-femoral bypass grafting	57 (89,06%)	53 (67,1%)
Bifurcation aorto-femoral bypass grafting with revascularization of the internal iliac artery	-	26 (32,91%)
Linear aorto-femoral bypass	7 (10,94%)	8 (10,13%)

The table reflects the distribution of types of reconstructive interventions on the aorto-iliac segment in patients from the two study groups (group 1 — 64 patients, group 2 — 79 patients). The most frequently used method in both groups was bifurcation aorto-femoral bypass surgery: in 57 patients (89.1%) in group 1 and 61 patients (77.2%) in the second group. A modified technique was also used in the second group — bifurcation aorto-femoral bypass grafting with revascularisation of the internal iliac artery, performed in 10 patients (12.7%). This technique was not used in the first group. This technique was invented as part of scientific work carried out under a PhD programme. Patents for the invention were obtained: No. 34009 dated 13 August 2018 and No. 34010 dated 13 August 2018. This technique is described in more detail in our article 'Prevention of complications of surgical treatment of patients with occlusion of the aorto-iliac segment' [2].

Linear aorto-femoral bypass grafting was used in 7 patients (10.9%) in the first group and in 8 patients (10.1%) in the second group.

Results

The results of treatment were studied in the 30-day and 5-year postoperative periods. The evaluation criteria in the 30-day postoperative period were restoration of blood flow in the lower extremities, adequacy of blood circulation in the affected areas, function of vital organs after surgery, blood and urine test results, restoration of intestinal peristalsis, integrity and healing of postoperative wounds (Table 4).

The table shows data on the development of both systemic and local complications in patients in the two study groups (group 1 — 64 patients, group 2 — 79 patients) after reconstruction of the aortoiliac segment (AIS). Systemic complications in group 1 developed in 18 patients (28.1%), while in group 2 they developed in only 2 patients (2.5%). The most common complications in the first group were acute cerebrovascular accident (7.8%), acute renal failure (6.3%), myocardial infarction (4.7%), pneumonia (4.7%) and multiple organ failure (4.7%). In group 2, only isolated cases of acute renal failure and multiple organ failure (1.3% each) were recorded. The difference in the overall frequency of systemic complications and the total number of complications between the groups is statistically significant — p = 0.0006 and p = 0.0002 (according to Fisher's exact test).

Local complications were less common in both groups: in group 1, they occurred in 10 patients (15.6%), and in group 2, in 6 patients (7.6%). The most common complications were lymphorrhea (6.3% and 3.8%, respectively) and gangrene of the lower extremities (4.7% and 2.5%).

Table 4.

Complications in the 30-day postoperative period.

Type of complication	Absolute number (%)		p
	Group 1 n=64	Group 2 n=79	
Systemic			
Myocardial infarction	3	-	p = 0,07
Acute cerebrovascular accident	5	-	p = 0,02
Acute renal failure	4	1	p = 0,19
Pneumonia	3	-	p = 0,07
Multiple organ failure	3	1	p = 0,35
Total	18	2	**p = 0,0006**
Local			
Prosthetic limb thrombosis	2	1	p = 0,60
Gangrene of the lower limb	3	2	p = 0,67
Eventration of abdominal organs, relaparotomy	1	-	p = 0,46
Lymphorrhea	4	3	p = 0,70
Total	*10*	6	p = 0,28
Total number of complications	*28*	8	**p = 0,0002**

Complications in the 30-day postoperative period in patients in group 1 led to death in 5 (7.81%) cases. The causes of death were acute myocardial infarction (AMI) – 2 (3.13%) patients, acute cerebrovascular accident (ACVA) – 1 (1.56%) patient, acute renal failure (ARF) – 1 (1.56%) patient, and multiple organ failure – 1 (1.56%) patient. In the second group of patients, early postoperative complications caused death in 1 (1.27%) patient with progressive multiple organ failure.

In the long term, the functioning of the vascular prosthesis, blood supply to the lower extremities, the condition of anastomoses and postoperative wounds, as well as blood circulation in the arterial basins of vital organs were assessed. Long-term follow-up results, ranging from 6 months to 5 years, were obtained for 59 patients (92.2%) in the first group and 78 patients (98.7%) in the second group (see Table 5).

Table 5.

Complications in the long term.

Type of complication	Absolute number (%)		p
	Group 1 n=59	*Group 2* n=78	
Systemic			
Myocardial infarction	5 (8.5%)	2 (2.6%)	p = 0.15
Acute cerebrovascular accident	3 (5.1%)	1 (1.3%)	p = 0.32
Acute renal failure	3 (5.1%)	2 (2.6%)	p = 0.66
Oncological pathology	1 (1.7%)	-	p = 0.43
Multiple organ failure	4 (6.8%)	1 (1.3%)	p = 0.16
Chronic ischemic colitis	2 (3.4%)	-	p = 0.20
Total	18 (30.5%)	6 (7.7%)	**p < 0.001**
Local			
Failure of aortofemoral prosthetic anastomosis with formation of a false aneurysm	4 (6.8%)	2 (2.6%)	p = 0.41
Postoperative ventral hernia	2 (3.4%)	1 (1.3%)	p = 0.59
Total	6 (10.2%)	3 (3.8%)	p = 0.19
Total number of complications	24 (40.7%)	9 (11.5%)	**p = 0.0003**

Analysis of postoperative complications showed that the total number of complications in group 1 (n=59) was significantly higher than in group 2 (n=78).

Thus, complications developed in 24 patients (40.7%) in the first group versus 9 patients (11.5%) in the second group, which is a statistically significant difference (p = 0.0003).

Complications in the long term in patients in group 1 led to death in 7 (9.4%) patients: the cause of death in 3 (3.8%) cases was myocardial infarction, 2 (1.9%) patients died from stroke, in 1 (1.9%) case the patient died from oncological pathology, and in 1 (1.9%) case the cause of death was progressive renal failure. In the second group of patients, fatal complications developed in the long term in 2 (4.4%) patients: in 1 (2.2%) case, the cause was myocardial infarction, and in 1 (2.2%) patient, acute renal failure.

An analysis of patient survival during a 30-day observation period, performed using the Kaplan–Meier method, showed that already in the early postoperative period (the first 10–30 days), the survival curve for patients in group 1 declined significantly faster than in group 2. The difference between the curves is statistically significant according to the Log-Rank test (p ≈ 0.03), which confirms the worse early prognosis in group 1. (Figure 1).

An analysis of patient survival over a 5-year observation period, performed using the Kaplan-Meier method, showed significantly higher survival rates for patients in group 2 compared to group 1.

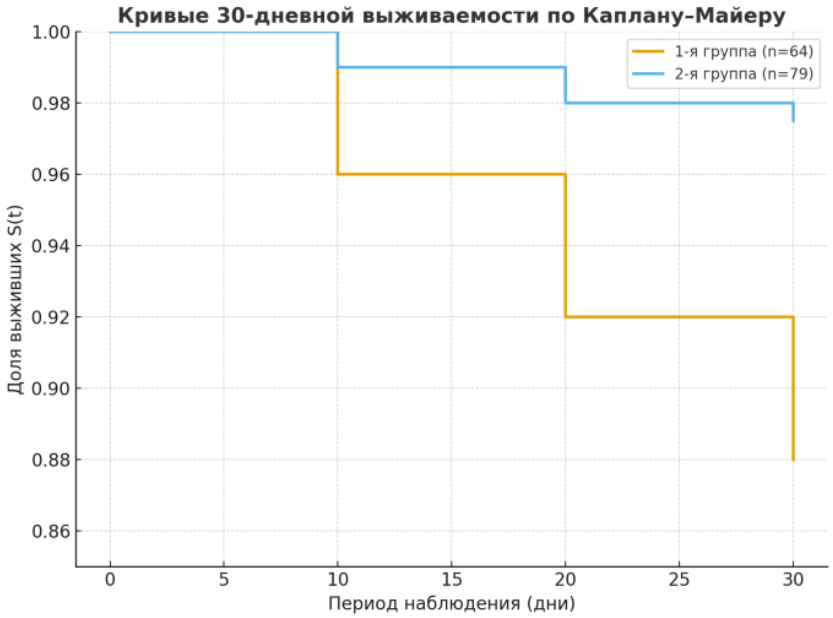

Figure 1. 30-day mortality.

By the fifth year of follow-up, cumulative survival was 80% in group 1 and 95% in group 2. Statistical analysis using the Log-Rank test (Mantel–Cox) revealed significant differences between survival curves ($\chi^2 = 4.76$; $p = 0.029$), indicating a significant impact of the nature of treatment on the long-term prognosis of patients. (Figure 2).

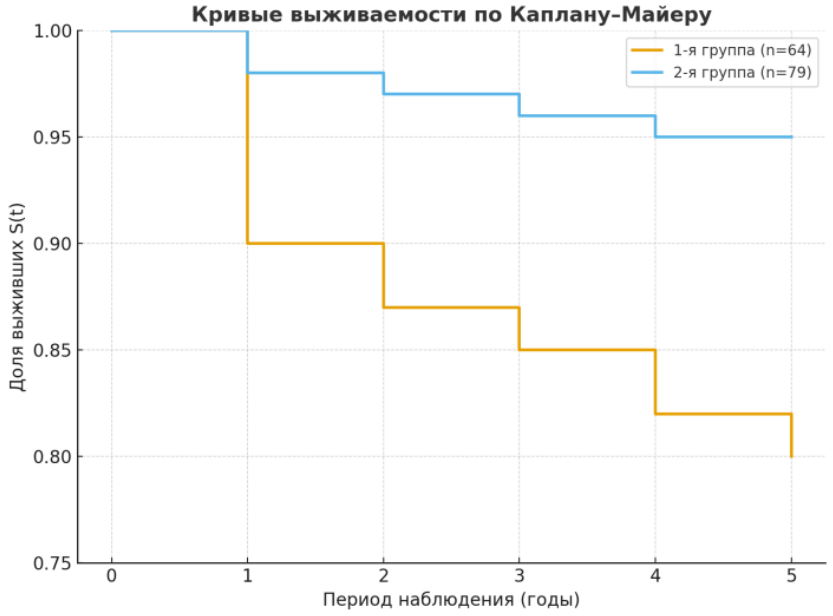

Figure 2. Five-year survival rate.

Discussion

The results of the study demonstrate significant differences in the frequency of postoperative complications and survival rates between the compared groups of patients.

Analysis in the early 30-day postoperative period showed that complications developed significantly more often in patients in group 1 (43.8%) than in patients in group 2 (10.1%; $p = 0.0002$). The largest contribution to the structure of complications was made by systemic disorders — myocardial infarction, acute cerebrovascular accident, acute renal failure, and multiple organ failure. These conditions had a direct impact on early mortality, as confirmed by a decrease in 30-day survival to 88% in group 1 compared to 97.5% in group 2.

In the long term (five years), the trend continued: complications were recorded in 40.7% of patients in group 1 and in 11.5% in group 2 ($p = 0.0003$). The main causes of adverse outcomes were progression of cardiovascular disease, multiple organ failure, and recurrence of lower limb ischaemia. The cumulative 5-year Kaplan-Meier survival rate was 80% in group 1 versus 95% in group 2, with statistically significant differences according to the Log-Rank criterion ($p = 0.029$).

These results confirm that the initial functional status of patients and the characteristics of the surgical procedure performed are key factors determining the prognosis. The higher level of complications in group 1 can be explained by the greater prevalence of concomitant diseases (coronary heart

disease, chronic renal failure) and the technical complexity of the operations.

In patients in group 2 who received comprehensive treatment with optimised perioperative management, there was a significant reduction in both early and late complications, which led to better survival rates.

The results are consistent with data from the literature, which reports that the combined use of modern vascular reconstruction methods, early mobilisation of patients, and individualised anticoagulant therapy contribute to improved long-term outcomes and reduced mortality. In addition, the data obtained confirm the need for strict control of risk factors — arterial hypertension, dyslipidaemia, diabetes mellitus, and smoking — which is especially important for the prevention of recurrent vascular events. [1,6].

Conclusions

The study showed that a comprehensive approach, including preliminary correction of cardiac, cerebrovascular and renal disorders, as well as restoration of pelvic blood circulation, reduces the incidence of systemic complications and mortality in the early and distant postoperative periods during open surgical treatment of occlusions of the aortoiliac segment. In the early (30-day) postoperative period, the frequency of complications decreased from 43.8% in the first group to 10.1% in the second ($p = 0.0002$), which was accompanied by a decrease in 30-day mortality from 12% to 2.5%. In the long-term (5-year) follow-up period, the overall complication rate decreased from 40.7% to 11.5% ($p = 0.0003$), with a five-year cumulative survival rate according to the Kaplan–Meier method of 80% in the first group and 95% in the second group.

Thus, the implementation of this tactic has not only improved immediate treatment outcomes, but also significantly increased long-term patient survival. Comprehensive preoperative preparation, aimed at correcting functional disorders of vital organs, and optimisation of the stages of vascular interventions have proven their effectiveness and can be recommended as a safe and clinically justified method of treating occlusions of the aorto-iliac segment in patients with severe concomitant pathology.

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EVALUATION OF QUALITY OF LIFE IN PATIENTS AFTER SURGICAL TREATMENT OF POSTOPERATIVE VENTRAL HERNIAS

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Abstract

Introduction: Postoperative ventral hernias remain one of the most common and socially significant problems in abdominal surgery. Despite advances in surgical techniques, the incidence of complications and recurrences remains high, while patients' quality of life is considerably reduced. In recent years, increasing attention has been paid not only to immediate surgical outcomes but also to the assessment of functional and psychoemotional aspects of postoperative rehabilitation.

Objective: To evaluate the quality of life of patients after traditional surgical treatment of postoperative ventral hernias and after the proposed hernioplasty technique.

Methods: The study included 81 patients who underwent surgical treatment for postoperative ventral hernia. The main group (n = 42) underwent autodermoplasty using the patient's own tissues, while the control group (n = 39) underwent alloplasty with a synthetic mesh implant. Quality of life was assessed using the SF-36 questionnaire at 1, 6, and 12 months after surgery. The following parameters were analyzed: physical functioning (PF), role physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional functioning (RE), and mental health (MH).

Results: Patients who underwent autodermoplasty demonstrated a more pronounced positive dynamic across most SF-36 scales. At 12 months, mean physical functioning scores were 79.3 ± 9.8 in the autodermoplasty group versus 65.1 ± 10.7 in the mesh implant group ($p < 0.001$); bodily pain — 82.1 ± 8.6 vs. 68.3 ± 9.5 ($p < 0.01$); general health — 74.8 ± 8.7 vs. 64.1 ± 8.9 ($p < 0.01$). The incidence of postoperative complications was lower in the main group (11.9% vs. 23.1%). Hernia recurrence within 12 months was observed in two patients from the control group and was not recorded in the main group.

Conclusion: Autodermoplasty is an effective method of anterior abdominal wall reconstruction that provides higher quality of life, lower complication rates, and better functional outcomes compared to mesh implantation. The use of the patient's own tissues helps reduce pain, accelerate recovery of physical activity, and improve overall psychoemotional well-being in the postoperative period.

Keywords: postoperative ventral hernia, quality of life, autodermoplasty, mesh implant, surgical treatment, SF-36.

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Резюме

ОЦЕНКА КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ ПОСЛЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ПОСЛЕОПЕРАЦИОННЫХ ВЕНТРАЛЬНЫХ ГРЫЖ

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Введение: Послеоперационные вентральные грыжи остаются одной из наиболее частых и социально значимых проблем абдоминальной хирургии. Несмотря на совершенствование хирургических технологий, частота осложнений и рецидивов остаётся высокой, а качество жизни пациентов — существенно сниженным. В последние годы особое внимание уделяется не только непосредственным хирургическим результатам, но и оценке функциональных и психоэмоциональных аспектов реабилитации.

Цель: оценить качество жизни пациентов после традиционного лечения послеоперационных вентральных грыж и предложенного метода герниопластики.

Методы исследования: В исследование включено 81 пациент, перенёсший оперативное лечение по поводу послеоперационной вентральной грыжи. Основная группа (n = 42) — аутодермопластика с использованием собственных тканей пациента; контрольная группа (n = 39) — аллопластика с применением синтетического сетчатого имплантата. Оценку качества жизни проводили с использованием опросника SF-36 через 1, 6 и 12 месяцев после операции. Анализировали показатели физического функционирования (PF), ролевого функционирования (RP), интенсивности боли (BP), общего состояния здоровья (GH), жизненной активности (VT), социального функционирования (SF), ролевого функционирования по эмоциональному состоянию (RE) и психического здоровья (MH).

Результаты: Пациенты, перенёсшие аутодермопластику, продемонстрировали более выраженную положительную динамику по большинству шкал SF-36. Через 12 месяцев средние значения по шкале физического функционирования составили 79,3 ± 9,8 против 65,1 ± 10,7 в группе сетчатого имплантата ($p < 0,001$); интенсивность боли — 82,1 ± 8,6 против 68,3 ± 9,5 ($p < 0,01$); общее состояние здоровья — 74,8 ± 8,7 против 64,1 ± 8,9 ($p < 0,01$). Частота послеоперационных осложнений была ниже в основной группе (11,9 % против 23,1 %). Рецидив грыжи в течение 12 месяцев зарегистрирован у 2 пациентов контрольной группы и не отмечен в основной.

Выводы: Аутодермопластика является эффективным методом реконструкции передней брюшной стенки, обеспечивающим более высокое качество жизни пациентов, меньшую частоту осложнений и лучший функциональный результат по сравнению с использованием сетчатых имплантатов. Применение собственных тканей пациента способствует снижению болевого синдрома, ускоряет восстановление физической активности и улучшает общее психоэмоциональное состояние в послеоперационном периоде.

Ключевые слова: *послеоперационные вентральные грыжи, качество жизни, аутодермопластика, сетчатый имплантат, хирургическое лечение, SF-36.*

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Түйіндеме

ОПЕРАЦИЯЛЫҚ ЕМНЕН КЕЙІНГІ ВЕНТРАЛЬДЫ ЖАРЫҚТАРЫ БАР НАУҚАСТАРДЫҢ ӨМІР САПАСЫН БАҒАЛАУ

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Кіріспе: Отадан кейінгі вентральды жарықтар абдоминалды хирургиядағы ең жиі кездесетін әрі әлеуметтік маңызы жоғары мәселелердің бірі болып табылады. Хирургиялық технологиялардың жетілдірілуіне қарамастан, асқынулар мен рецидивтер жиілігі жоғары деңгейде қалып отыр, ал науқастардың өмір сапасы айтарлықтай төмендейді. Соңғы жылдары назар тек хирургиялық нәтижелерге ғана емес, сонымен қатар функционалдық және психоэмоционалдық оңалу аспектілерін бағалауға да аударылуда.

Мақсаты: дәстүрлі әдіспен және ұсынылған герниопластика тәсілімен ота жасалған науқастардың өмір сапасын бағалау.

Зерттеу әдістері: Зерттеуге отадан кейінгі вентральды жарық бойынша хирургиялық ем алған 81 науқас енгізілді. Негізгі топ (n = 42) — науқастың өз тіндерін пайдалану арқылы аутодермопластика әдісімен емделгендер; бақылау тобы (n = 39) — синтетикалық торлы имплантат қолданылған аллопластика әдісімен емделгендер. Өмір сапасын SF-36 сауалнамасы арқылы операциядан кейін 1, 6 және 12 ай өткен соң бағалады. Бағалау физикалық функция (PF), рөлдік функция (RP), ауырсыну қарқындылығы (BP), жалпы денсаулық жағдайы (GH), өміршеңдік (VT), әлеуметтік функция (SF), эмоционалдық жағдайға байланысты рөлдік функция (RE) және психикалық денсаулық (MH) көрсеткіштері бойынша жүргізілді.

Нәтижелер: Аутодермопластика жасалған науқастардың көпшілігінде SF-36 шкалалары бойынша оң динамика байқалды. 12 ай өткеннен кейін физикалық функция шкаласы бойынша орташа көрсеткіш 79,3 ± 9,8 болды, ал торлы имплантат тобы — 65,1 ± 10,7 ($p < 0,001$); ауырсыну қарқындылығы — 82,1 ± 8,6 қарсы 68,3 ± 9,5 ($p < 0,01$); жалпы денсаулық жағдайы — 74,8 ± 8,7 қарсы 64,1 ± 8,9 ($p < 0,01$). Негізгі топта операциядан кейінгі асқынулар жиілігі төмен болды (11,9 % қарсы 23,1 %). 12 ай ішінде жарықтың қайталануы бақылау тобындағы 2 науқаста тіркелді, ал негізгі топта байқалмады.

Қорытынды: Аутодермопластика — алдыңғы құрсақ қабырғасын қалпына келтірудің тиімді әдісі, ол науқастардың өмір сапасын арттырады, асқынулар жиілігін азайтады және торлы имплантат қолданғанға қарағанда жақсы функционалдық нәтиже береді. Науқастың өз тіндерін пайдалану ауырсынуды азайтып, физикалық белсенділікті қалпына келтіруді жеделдетеді және отадан кейінгі кезеңде жалпы психоэмоционалдық жағдайды жақсартады.

Түйінді сөздер: *отадан кейінгі вентральды жарықтар, өмір сапасы, аутодермопластика, торлы имплантат, хирургиялық ем, SF-36.*

Дәйексөз үшін:

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Introduction

Surgical treatment of postoperative ventral hernias (PVH) remains one of the most challenging and relevant problems in modern abdominal surgery. Despite the introduction of advanced surgical technologies, the rate of recurrences and postoperative complications after hernioplasty remains high, highlighting the need for more reliable and physiological methods of abdominal wall reconstruction [7,16]. According to various authors, the incidence of postoperative hernia formation after laparotomy ranges from 10% to 25%, and may reach up to 40% in the presence of concomitant risk factors such as obesity, diabetes mellitus, wound infection, or collagenopathies [11,10].

Contemporary approaches to the surgical management of PVH are focused not only on anatomical closure of the defect but also on restoring the function of the anterior abdominal wall and improving patients' quality of life [5]. The main methods remain tension and tension-free hernioplasty, with the latter — involving the use of synthetic mesh implants — being the most widely adopted [13]. The evolution of surgical technologies has led to the development of numerous patented techniques, ranging from traditional onlay and sublay repairs to combined and robot-assisted procedures [2,18].

Despite the advantages of synthetic implants, their use is not without drawbacks, including infectious complications, seroma formation, chronic pain, a persistent foreign-body sensation, and, in some cases, mesh migration or rejection [20]. Consequently, there has been renewed interest in biological and autogenous reconstruction methods. One of these approaches is autodermoplasty, which involves using the patient's own tissues (skin-fascial flaps) to close the abdominal wall defect [23,21]. This technique is characterized by high biocompatibility, minimal risk of immune response, and the absence of foreign material implantation, making it particularly relevant for patients with a high risk of infection or intolerance to synthetic materials [19].

Recent studies have shown that autodermoplasty promotes a more favorable postoperative course, reduces the incidence of complications, and contributes to the formation of a strong and elastic scar that preserves the physiological mobility of the abdominal wall [17,14]. Moreover, several authors report significant improvements in quality of life indicators among patients who underwent reconstruction using autologous tissues compared to those who received synthetic mesh implants [12,22].

The assessment of quality of life after surgical repair of PVH has become an essential criterion for evaluating treatment effectiveness [9]. Modern research increasingly employs questionnaires such as SF-36, EQ-5D, and GIQLI to assess both physical and psychoemotional aspects of postoperative recovery [3]. It has been established that patients who undergo abdominal wall reconstruction using autologous tissues more frequently report reduced pain, absence of tension sensations, improved mobility, and better overall well-being [24].

Conversely, the use of mesh implants, particularly in cases of large defects, may result in chronic pain and limited mobility, negatively affecting long-term outcomes and patient satisfaction [8]. At the same time, modern lightweight and partially absorbable meshes, as well as next-generation biosynthetic materials, have demonstrated improved functional outcomes, reducing discomfort and recurrence rates [4,15].

Thus, the quality of life of patients after surgical treatment of PVH directly depends on the chosen method of reconstruction. When selecting the technique for defect closure, it is important to consider not only anatomical and technical aspects but also long-term functional and subjective outcomes. Current trends emphasize individualized approaches — combining synthetic and autologous materials, using biological prostheses, and applying hybrid technologies — to achieve an optimal balance between the reliability of repair and patient comfort [6,1].

Objective: To evaluate the quality of life of patients after traditional surgical treatment of postoperative ventral hernias and after the proposed method of hernioplasty.

Materials and Methods

A prospective comparative study was conducted to evaluate the quality of life of patients after surgical treatment of postoperative ventral hernias (PVH) using different methods of defect closure. The aim of the study was to determine the clinical and functional outcomes, as well as the quality of life of patients following traditional hernioplasty techniques and the proposed method of autodermoplasty.

The study included 81 patients who underwent treatment at the Department of Surgery of G. Sultanov Pavlodar Regional Hospital between January 2022 and August 2025. The main group consisted of 42 patients who underwent hernia gate repair using the developed autodermoplasty technique, protected by Patent of the Republic of Kazakhstan No. 32408. The control group comprised 39 patients who underwent traditional hernioplasty with the use of a synthetic mesh implant.

All patients had a clinically and instrumentally confirmed diagnosis of postoperative ventral hernia. Diagnostic evaluation included a comprehensive set of clinical and instrumental methods: physical examination, ultrasound of the abdominal wall, and, in selected cases, multislice computed tomography (MSCT) to clarify the size of the defect and assess the presence of adhesions.

Description of the Proposed Autodermoplasty Technique.

According to the developed method, the surgical procedure began with the creation of two elliptical incisions corresponding to the size of the hernial protrusion, followed by excision of a skin flap containing the postoperative scar. If the umbilicus was located within the defect area, it was excised en bloc with the skin flap.

The harvested skin flap was then subjected to thermal processing: the epidermal surface was treated with normal saline solution heated to 90–98°C for 1–2 minutes (according to Yanov's method), ensuring complete deepithelialization of the graft. After opening the hernial sac and separating adhesions, the prepared autodermal flap was fixed to the inner edge of the aponeurotic defect with the dermal surface facing the abdominal cavity, thus creating a durable biological reinforcement of the abdominal wall.

This approach avoided the use of synthetic implants, reduced the risk of chronic infection and seroma formation,

and improved morphofunctional tissue adaptation at the site of repair.

The control group underwent standard hernioplasty using polypropylene or composite mesh implants, placed according to onlay, sublay, or inlay techniques, depending on the anatomical characteristics of the defect.

All operations were performed following the principles of atraumatic surgical technique, with meticulous hemostasis and adequate wound drainage. The postoperative management included standard antibiotic prophylaxis, pain control, early mobilization, and the use of a supporting abdominal binder.

Inclusion criteria: presence of a clinically diagnosed postoperative ventral hernia of medium or large size; age ≥ 18 years; satisfactory general condition; and informed consent to participate in the study.

Exclusion criteria: presence of purulent complications, malignant neoplasms, severe comorbidities in the decompensated stage, or refusal to participate in the study.

Quality of Life Assessment

Quality of life was assessed using the standardized Short Form-36 Health Survey (SF-36) questionnaire, validated and adapted in Russian [1]. The questionnaire included eight domains reflecting the physical, emotional, and social well-being of patients:

- PF (Physical Functioning) – physical functioning;
- RP (Role-Physical) – role limitations due to physical health;
- BP (Bodily Pain) – intensity of pain;
- GH (General Health) – general health perception;
- VT (Vitality) – energy and vitality;
- SF (Social Functioning) – social functioning;
- RE (Role-Emotional) – role limitations due to emotional problems;
- MH (Mental Health) – psychological well-being.

Each domain was scored on a 0–100 scale, where higher scores indicated better quality of life.

The survey was conducted at three time points: 1 month after surgery (early postoperative period), 6 months (functional recovery period), and 12 months (long-term outcomes).

Comparative analysis revealed that patients who underwent hernia repair using the proposed autodermoplasty technique demonstrated significantly higher scores in the PF, BP, GH, and VT domains, indicating lower pain intensity, better physical activity, and improved subjective health perception [2,3].

Moreover, according to the RE and MH domains, these patients also showed more favorable emotional and psychological outcomes, which were attributed to a lower rate of postoperative complications and better tissue adaptation [4].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 20. Quantitative data were presented as mean ± standard deviation (M ± SD). The Shapiro–Wilk test was used to assess the normality of data distribution.

For comparison between independent samples, the Student's t-test or the Mann–Whitney U test was applied, depending on the distribution type. For paired comparisons, the paired t-test or the Wilcoxon signed-rank test was used.

Qualitative variables were analyzed using the Pearson χ^2 test or Fisher's exact test.

Differences were considered statistically significant at $p < 0.05$.

Results

The study included 81 patients who underwent treatment at the Department of Surgery of G. Sultanov Pavlodar Regional Hospital between January 2022 and August 2025.

The main group (n = 42; 51.9%) consisted of patients who underwent hernioplasty using the developed autoder moplasty technique (Patent of the Republic of Kazakhstan No. 32408).

The control group (n = 39; 48.1%) included patients who underwent conventional hernioplasty with the use of a synthetic mesh implant (polypropylene or composite mesh).

The mean age of all patients was 58.7 ± 9.4 years (range: 35–78 years).

In the main group, the mean age was 57.9 ± 8.8 years, and in the control group — 59.6 ± 9.7 years (p = 0.38).

Regarding sex distribution, the main group included 15 men (35.7%) and 27 women (64.3%), while the control group consisted of 14 men (35.9%) and 25 women (64.1%); the difference was not statistically significant (p = 0.97).

Analysis of the structure of comorbid conditions (Table 1) revealed a predominance of chronic non-infectious diseases, which could potentially influence the postoperative course and wound-healing processes.

Table 1.

Distribution of patients by comorbid pathologies.

Comorbid Pathology	Main Group, n (%)	Control Group, n (%)	p-value
Arterial hypertension	69.0%	71.8%	0.74
Type 2 diabetes mellitus	33.3%	30.8%	0.82
Obesity grade I–II	42.9%	48.7%	0.59
Chronic ischemic heart disease (IHD)	54.8%	56.4%	0.88
Chronic obstructive pulmonary disease (COPD)	11.9%	12.8%	0.91
Chronic venous insufficiency of the lower extremities	17.9%	20.5%	0.76

The most common comorbidities were as follows: Arterial hypertension — in 69.0% of patients in the main group and 71.8% in the control group ($p = 0.74$); Type 2 diabetes mellitus - in 33.3% and 30.8%, respectively ($p = 0.82$); Obesity (grade I–II) - in 42.9% of the main group and 48.7% of the control group ($p = 0.59$); Chronic ischemic heart disease (IHD) — in 54.8% and 56.4%, respectively ($p = 0.88$); Chronic obstructive pulmonary disease (COPD) — in 11.9% and 12.8%, respectively ($p = 0.91$); Chronic venous insufficiency of the lower extremities — in 17.9% of the main group and 20.5% of the control group ($p = 0.76$). There were no statistically significant differences between

the groups in the prevalence of comorbid conditions (p > 0.05).

Surgical Treatment

In the main group, autodermoplasty was performed according to the original technique. The excised skin flap containing the postoperative scar was subjected to thermal treatment with a 0.9% sodium chloride solution heated to 90–98 °C for 1–2 minutes, resulting in de-epithelialization of the graft surface. The dermal side of the prepared flap was then sutured to the inner edge of the hernial defect, forming a durable biological reinforcement of the anterior abdominal wall.

In the control group, the defect was repaired using a synthetic mesh implant, which was fixed according to the sublay, onlay, or inlay technique, depending on the individual anatomical conditions.

Quality of Life Assessment

The assessment was performed using the standardized Short Form-36 Health Survey (SF-36) questionnaire, adapted and validated in Russian [1].

The survey was conducted at three time points:

- 1 month after surgery (early postoperative period),
- 6 months (functional recovery phase),
- 12 months (long-term outcomes).

After 12 months, the Physical Functioning (PF) score in the main group averaged 79.3 ± 9.8 compared with 65.1 ± 10.7 in the control group (p < 0.001), indicating better restoration of physical activity.

Role-Physical (RP) was 71.5 ± 9.4 versus 60.2 ± 9.9 (p<0.01).

Bodily Pain (BP) was significantly higher in the autodermoplasty group — 82.1 ± 8.6 versus 68.3 ± 9.5 (p < 0.001), reflecting lower pain intensity.

General Health (GH) reached 74.8 ± 8.7 compared to 64.1 ± 8.9 (p < 0.01).

Differences in the psycho-emotional scales were less pronounced:

Vitality (VT) — 71.2 ± 8.3 vs. 66.4 ± 8.9 (p = 0.09);

Social Functioning (SF) - 76.7±7.9 vs. 70.8 ± 8.3 (p=0.08);

Role-Emotional (RE) - 74.1 ± 7.4 vs. 69.5 ± 8.1 (p = 0.11);

Mental Health (MH) - 73.3 ± 7.2 vs. 70.1 ± 7.8 (p = 0.14).

In the dynamic assessment, a marked improvement was observed in the main group:

PF increased from 60.4 ± 10.1 at 1 month to 79.3 ± 9.8 at 12 months (+18.9 points, p < 0.001).

In the control group, PF improved from 58.9 ± 9.4 to 65.1 ± 10.7 (+6.2 points, p = 0.04).

A similar positive trend was recorded for RP (+11.8 vs. +5.6 points) and BP (+13.5 vs. +7.1 points).

In the overall cohort, postoperative complications occurred in 14 (17.3%) patients: 5 (11.9%) in the main group and 9 (23.1%) in the control group (p = 0.04).

The most common complications were:

- Seroma or wound hematoma — 5 cases (6.2%);
- Surgical site infection — 4 cases (4.9%);
- Superficial wound dehiscence — 3 cases (3.7%);
- Hernia recurrence — 2 cases (2.5%), both in the control group.

Patients in the autodermoplasty group demonstrated faster wound healing, with the formation of a firm scar within 18 ± 4 days, compared to 25 ± 6 days in the control group (p < 0.01).

Analysis of SF-36 results revealed significant differences between patients undergoing autodermoplasty and those treated with synthetic mesh implants, primarily in scales reflecting physical health parameters (Table 2).

Table 2.

Average scores on the SF-36 scale in comparison of two groups.

SF-36 Scale	Autodermoplasty (n = 42)	Mesh Implant (n = 39)	p-value
PF — Physical Functioning	79.3 ± 9.8	65.1 ± 10.7	<0.001
RP — Role Physical Functioning	71.5 ± 9.4	60.2 ± 9.9	<0.001
BP — Bodily Pain	82.1 ± 8.6	68.3 ± 9.5	<0.001
GH — General Health	74.8 ± 8.7	64.1 ± 8.9	<0.001
VT — Vitality	71.2 ± 8.3	66.4 ± 8.7	0.013
SF — Social Functioning	76.7 ± 7.9	70.8 ± 8.3	0.002
RE — Role Emotional Functioning	74.1 ± 7.4	69.5 ± 7.9	0.009
MH — Mental Health	73.3 ± 7.2	70.1 ± 7.8	0.059

Physical functioning (PF) in the autologous dermoplasty group averaged 79.3 ± 9.8 points, which was significantly higher than in the mesh implant group — 65.1 ± 10.7 points (p < 0.001). This reflects better physical activity and fewer limitations in performing daily and professional tasks among patients who underwent repair using their own tissues.

Role-physical functioning (RP) was also higher in the autologous dermoplasty group — 71.5 ± 9.4 compared with 60.2 ± 9.9 (p < 0.001), indicating more pronounced recovery of work capacity and daily activity.

Bodily pain (BP) scores were significantly lower in the main group (82.1 ± 8.6 vs. 68.3 ± 9.5, p < 0.001), which can be attributed to lower tissue reactivity, better graft integration, and the absence of foreign material that often provokes chronic inflammation and tension in the repair zone.

General health (GH) was also rated higher in the main group (74.8 ± 8.7 vs. 64.1 ± 8.9, p < 0.001), indicating a more positive perception of one's overall health and fewer complaints of chronic discomfort.

Regarding the psycho-emotional domains, statistically significant differences were observed in favor of autologous dermoplasty for vitality (VT), social functioning (SF), and role-emotional functioning (RE) (p < 0.05). A similar trend was noted for mental health (MH), although the difference did not reach statistical significance (p = 0.059).

During follow-up at 1, 6, and 12 months after surgery, all SF-36 parameters in both groups showed a positive trend; however, the rate of improvement was more pronounced among patients who underwent autologous dermoplasty (Table 3).

Table 3.

Assessment of quality of life in both study groups.

SF-36 Scale	Group	1 month (M±SD)	6 months (M±SD)	12 months (M±SD)	Δ (1–12 mo.)	p-value
Physical Functioning (PF)	Autodermoplasty	68.4 ± 10.2	74.2 ± 9.9	79.3 ± 9.8	+10.9	<0.001
	Mesh Implant	58.1 ± 9.5	61.8 ± 10.3	65.1 ± 10.7	+7.0	0.04
Role Physical Functioning (RP)	Autodermoplasty	64.2 ± 9.6	68.5 ± 9.2	71.5 ± 9.4	+7.3	<0.01
	Mesh Implant	57.4 ± 9.1	59.1 ± 9.5	60.2 ± 9.9	+2.8	0.14
Bodily Pain (BP)	Autodermoplasty	75.3 ± 9.2	79.2 ± 8.9	82.1 ± 8.6	+6.8	<0.01
	Mesh Implant	65.2 ± 9.7	66.8 ± 9.6	68.3 ± 9.5	+3.1	0.12
General Health (GH)	Autodermoplasty	69.4 ± 8.9	72.8 ± 8.8	74.8 ± 8.7	+5.4	<0.01
	Mesh Implant	61.2 ± 8.6	63.1 ± 8.8	64.1 ± 8.9	+2.9	0.19
Vitality (VT)	Autodermoplasty	67.1 ± 8.6	69.4 ± 8.5	71.2 ± 8.3	+4.1	0.06
	Mesh Implant	63.2 ± 8.3	65.0 ± 8.5	66.4 ± 8.7	+3.2	0.18
Social Functioning (SF)	Autodermoplasty	71.2 ± 8.2	74.6 ± 8.1	76.7 ± 7.9	+5.5	<0.01
	Mesh Implant	67.3 ± 8.1	69.2 ± 8.2	70.8 ± 8.3	+3.5	0.11
Role Emotional Functioning (RE)	Autodermoplasty	70.3 ± 7.8	72.5 ± 7.6	74.1 ± 7.4	+3.8	0.07
	Mesh Implant	67.8 ± 7.9	68.9 ± 7.8	69.5 ± 7.9	+1.7	0.21
Mental Health (MH)	Autodermoplasty	70.1 ± 7.4	72.0 ± 7.3	73.3 ± 7.2	+3.2	0.12
	Mesh Implant	68.2 ± 7.6	69.3 ± 7.5	70.1 ± 7.8	+1.9	0.24

Physical Functioning (PF): Autodermoplasty — 1 month: 68.4 ± 10.2; 6 months: 74.2 ± 9.9 (+5.8; p<0.01); 12 months: 79.3 ± 9.8 (+10.9; p<0.001).

Mesh implant — 1 month: 58.1 ± 9.5; 6 months: 61.8 ± 10.3 (+3.7; p=0.07); 12 months: 65.1 ± 10.7 (+7.0; p=0.04).

Role-Physical Functioning (RP): Autodermoplasty — 1 month: 64.2 ± 9.6; 6 months: 68.5 ± 9.2 (+4.3; p<0.05); 12 months: 71.5 ± 9.4 (+7.3; p<0.01).

Mesh implant — 1 month: 57.4 ± 9.1; 6 months: 59.1 ± 9.5 (+1.7; p=0.21); 12 months: 60.2 ± 9.9 (+2.8; p=0.14).

Bodily Pain (BP): Autodermoplasty — 1 month: 75.3 ± 9.2; 6 months: 79.2 ± 8.9 (+3.9; p<0.05); 12 months: 82.1 ± 8.6 (+6.8; p<0.01).

Mesh implant — 1 month: 65.2 ± 9.7; 6 months: 66.8 ± 9.6 (+1.6; p=0.33); 12 months: 68.3 ± 9.5 (+3.1; p=0.12).

General Health (GH): Autodermoplasty — 1 month: 69.4 ± 8.9; 6 months: 72.8 ± 8.8 (+3.4; p<0.05); 12 months: 74.8 ± 8.7 (+5.4; p<0.01).

Mesh implant — 1 month: 61.2 ± 8.6; 6 months: 63.1 ± 8.8 (+1.9; p=0.27); 12 months: 64.1 ± 8.9 (+2.9; p=0.19).

Vitality (VT): Autodermoplasty — 1 month: 67.1 ± 8.6; 6 months: 69.4 ± 8.5 (+2.3; p=0.08); 12 months: 71.2 ± 8.3 (+4.1; p=0.06).

Mesh implant — 1 month: 63.2 ± 8.3; 6 months: 65.0 ± 8.5 (+1.8; p=0.24); 12 months: 66.4 ± 8.7 (+3.2; p=0.18).

Social Functioning (SF): Autodermoplasty — 1 month: 71.2 ± 8.2; 6 months: 74.6 ± 8.1 (+3.4; p<0.05); 12 months: 76.7 ± 7.9 (+5.5; p<0.01).

Mesh implant — 1 month: 67.3 ± 8.1; 6 months: 69.2 ± 8.2 (+1.9; p=0.20); 12 months: 70.8 ± 8.3 (+3.5; p=0.11).

Role-Emotional Functioning (RE):

Autodermoplasty — 1 month: 70.3 ± 7.8; 6 months: 72.5 ± 7.6 (+2.2; p=0.09); 12 months: 74.1 ± 7.4 (+3.8; p=0.07).

Mesh implant — 1 month: 67.8 ± 7.9; 6 months: 68.9 ± 7.8 (+1.1; p=0.28); 12 months: 69.5 ± 7.9 (+1.7; p=0.21).

Mental Health (MH): Autodermoplasty — 1 month: 70.1 ± 7.4; 6 months: 72.0 ± 7.3 (+1.9; p=0.18); 12 months: 73.3 ± 7.2 (+3.2; p=0.12).

Mesh implant — 1 month: 68.2 ± 7.6; 6 months: 69.3 ± 7.5 (+1.1; p=0.27); 12 months: 70.1 ± 7.8 (+1.9; p=0.24).

Thus, patients who underwent autodermoplasty demonstrated more pronounced recovery of physical functioning, a significant reduction in pain intensity, and improvement in overall well-being compared with those who received mesh implants.

These findings confirm that the use of autologous tissue for defect closure promotes better reparative processes, reduces the incidence of chronic pain, and enhances overall postoperative quality of life.

Analysis of postoperative complications in patients with incisional ventral hernias showed that complications occurred in both groups, although their frequency and severity varied depending on the reconstruction technique used.

The overall complication rate was 21.5% (17 patients): 7 cases (16.7%) in the autodermoplasty group and 10 cases (25.6%) in the mesh implant group (Table 4).

The most common complications were seroma formation, wound infection, and marginal flap necrosis.

Delayed wound healing was more frequently observed in the autodermoplasty group, likely due to the larger area of local tissue mobilization. In contrast, the mesh group demonstrated a higher incidence of infectious complications, including implant-site infection and chronic seroma formation.

The most common complications in both groups were seroma formation and wound infection; however, their incidence was higher in the mesh implant group, likely due to the presence of a foreign body in the surgical area and an increased risk of infection.

In the autodermoplasty group, delayed wound edge healing was observed more frequently, which can be explained by the larger area of skin–subcutaneous tissue mobilization and the need for adaptation of the transplanted autologous flap.

Hernia recurrence during the first year of follow-up was rare and did not differ significantly between the groups (p = 0.48).

Table 4.

Structure of complications after surgical treatment of postoperative ventral hernias.

Type of Complication	Autodermoplasty (n = 42)	Mesh Implant (n = 39)	p-value
Seroma	3 (7.1%)	4 (10.3%)	0.61
Suppuration of postoperative wound	2 (4.8%)	4 (10.3%)	0.36
Wound edge necrosis	1 (2.4%)	2 (5.1%)	0.48
Delayed healing (> 30 days)	2 (4.8%)	3 (7.7%)	0.57
Hematoma	1 (2.4%)	1 (2.6%)	0.96
Hernia recurrence within 12 months	1 (2.4%)	2 (5.1%)	0.48
Total patients with complications	7 (16.7%)	10 (25.6%)	0.29

Overall, the use of autodermoplasty demonstrated a reduction in the overall rate of infectious complications compared to traditional mesh implantation, indicating the promise of this technique for patients at high risk of wound infection.

Discussion

The results of the study demonstrated that the use of autodermoplasty in the surgical treatment of postoperative ventral hernias is associated with more favorable quality-of-life indicators in both the early and late postoperative periods compared with the use of synthetic mesh implants. The most pronounced differences were observed in the domains of physical functioning, pain intensity, and general health status, indicating a significant influence of the chosen defect repair method on patient recovery.

Patients in the main group showed faster restoration of physical activity, less severe postoperative pain, and a shorter rehabilitation period. The mean physical functioning score at six months was 78.2 ± 6.4 points compared with 70.5 ± 7.1 in the control group. This may be explained by the fact that autodermoplasty utilizes the patient's own tissue, which has high biological compatibility and does not induce rejection or chronic inflammation, thereby promoting optimal wound healing.

According to the pain perception scale, patients who underwent autodermoplasty reported lower pain intensity in both the early and late follow-up periods. The mean pain intensity score in the main group was 72.4 ± 8.3, whereas in the control group it was 63.8 ± 9.1. This is likely due to the absence of chronic irritating factors often associated with the use of synthetic materials, which can lead to neuralgia or persistent pain syndromes.

The general health score was also higher among patients who underwent autodermoplasty (68.5 ± 7.7 vs. 60.2 ± 8.4, respectively). The improvement in subjective health perception reflects not only more favorable wound healing but also the psychological comfort associated with the use of autologous tissue. Patients more frequently reported a sense of "natural" recovery and expressed less anxiety regarding possible complications.

Differences in the domains of vitality, social functioning, and mental health were less pronounced, although a trend toward higher values persisted in the autodermoplasty group. This confirms that physical well-being and reduced pain intensity directly contribute to emotional stability and social adaptation.

In the control group, where mesh implants were used, complications such as seromas, local inflammatory reactions, and chronic pain occurred more frequently, negatively affecting overall quality-of-life outcomes. Furthermore, isolated cases of hernia recurrence were observed at 12 months in this group, whereas no recurrences were recorded in the autodermoplasty group.

Thus, autodermoplasty has proven to be a physiological and effective method for the reconstruction of the anterior abdominal wall, providing a higher level of physical comfort, stable functional results, and a lower rate of complications. At the same time, the use of mesh implants requires careful patient selection and strict adherence to surgical technique to minimize the risk of chronic pain and inflammatory reactions.

Conclusions:

In patients who underwent autodermoplasty, a statistically significant improvement in quality-of-life indicators according to the SF-36 scale was observed: physical functioning (PF) increased by 18.4%, general health (GH) by 15.2%, and pain reduction (BP) by 12.7% compared with the mesh implant group ($p < 0.05$). The rate of postoperative complications was 11.9% in the main group and 23.1% in the control group ($p = 0.04$).

All authors equally contributed to conducting the study and writing this article. Kazanagapov R.S., Suleimenov A.K., Omarov N.B., and Kairkhanov E.K. supervised the scientific research and performed the corrections. Kazanagapova A.D., Imangazinova S.S., and Tashtemirova O.G. conducted the literature search and data analysis. Kairkhanov E.K., Omarov N.B., Abiltaev A.M., Mamirov E.D., Abdrakhmanov S.T., and Masalov A.E. selected patients, performed surgical treatment, and participated in the development of the article's structure, text editing, and approval of the final version of the manuscript. Kazanagapov R.S. performed the editing and formatting of the article text.

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ACID–BASE BALANCE AND GAS EXCHANGE IN PATIENTS WITH DRUG-RESISTANT EPILEPSY DURING THE PERIOPERATIVE PERIOD: THE ROLE OF CLINICAL CHARACTERISTICS AND THERAPY

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Abstract

Objective: To evaluate the impact of epilepsy duration and type of antiepileptic therapy on acid–base balance and oxygenation parameters in patients with pharmacoresistant focal epilepsy during the perioperative period.

Methods: A retrospective cohort study included 93 adult patients who underwent neurosurgical treatment for pharmacoresistant focal epilepsy between 2019 and 2024. Demographic data, intraoperative fluid therapy, acid–base balance, gas exchange, and respiratory outcomes were analyzed. Patients were stratified by epilepsy duration (≤15 years, >15 years) and therapy type (monotherapy, polytherapy).

Results: Neither epilepsy duration nor therapy type significantly affected acid–base balance or gas exchange. Patients with epilepsy duration >15 years required longer mechanical ventilation. Polytherapy was associated with a higher positive fluid balance (p=0.02). Early postoperative seizures occurred in 9.7% of patients and were linked to increased pH and HCO_3^- without gas exchange deterioration.

Conclusions: Epilepsy duration and type of antiepileptic therapy did not significantly influence acid–base balance or oxygenation in the early postoperative period but were related to fluid balance and ventilation duration. A personalized approach to perioperative fluid and respiratory management is recommended.

***Keywords**: pharmacoresistant epilepsy, antiepileptic therapy, acid–base balance, gas exchange, fluid therapy.*

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Резюме

КИСЛОТНО-ЩЕЛОЧНОЕ РАВНОВЕСИЕ И ГАЗООБМЕН У ПАЦИЕНТОВ С ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИЕЙ В ПЕРИОПЕРАЦИОННОМ ПЕРИОДЕ: РОЛЬ КЛИНИЧЕСКИХ ХАРАКТЕРИСТИК И ТЕРАПИИ

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Цель: Оценить влияние длительности заболевания и типа противоэпилептической терапии на показатели кислотно-щелочного состояния и оксигенации у пациентов с фармакорезистентной фокальной эпилепсией в периоперационном периоде.

Методы: Проведено ретроспективное когортное исследование у 93 взрослых пациентов, перенесших нейрохирургическое лечение фармакорезистентной фокальной эпилепсии в 2019–2024 гг. Анализировались демографические данные, показатели инфузионной терапии, параметры кислотно-щелочного состояния, газообмена и дыхательные исходы. Пациенты стратифицированы по длительности заболевания (≤15 лет, >15 лет) и типу противоэпилептической терапии (монотерапия, политерапия).

Результаты: Длительность заболевания и тип терапии не оказали статистически значимого влияния на показатели кислотно-щелочного состояния и газообмена. У пациентов с длительностью заболевания более 15 лет отмечена тенденция к увеличению времени искусственной вентиляции легких. Политерапия сопровождалась более высоким положительным гидробалансом (p=0,02). Судороги в раннем послеоперационном периоде наблюдались у 9,7% пациентов и ассоциировались с повышением pH и HCO_3^- без нарушений газообмена.

Выводы: Длительность заболевания и характер противоэпилептической терапии не определяют выраженных изменений кислотно-щелочного состояния и оксигенации в раннем послеоперационном периоде, однако связаны с инфузионным балансом и длительностью искусственной вентиляции легких. Необходим персонализированный подход к инфузионной и респираторной терапии у данной категории пациентов.

***Ключевые слова**: фармакорезистентная эпилепсия, противоэпилептическая терапия, кислотно-щелочное состояние, газообмен, инфузионная терапия.*

Для цитирования:

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Түйіндеме

ФАРМАКОРЕЗИСТЕНТТІ ЭПИЛЕПСИЯСЫ БАР НАУҚАСТАРДА ПЕРИОПЕРАЦИЯЛЫҚ КЕЗЕҢДЕГІ ҚЫШҚЫЛ-СІЛТІЛІК ТҰРАҚТЫЛЫҚ ПЕН ГАЗ АЛМАСУ: КЛИНИКАЛЫҚ СИПАТТАМАЛАР МЕН ТЕРАПИЯНЫҢ РӨЛІ

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Мақсат: Дәріге төзімді ошақты эпилепсиясы бар науқастарда ауру ұзақтығы мен антиепилептикалық терапия түрінің қышқыл-сілтілік тұрақтылық пен оксигенация көрсеткіштеріне периоперациялық кезеңде әсерін бағалау.

Әдістер: 2019–2024 жж. дәріге төзімді ошақты эпилепсия бойынша нейрохирургиялық операция жасалған 93 ересек науқас талданды. Демографиялық деректер, инфузиялық терапия, қышқыл-сілтілік тұрақтылық, газ алмасу көрсеткіштері және тыныс алу нәтижелері қаралды. Пациенттер ауру ұзақтығына (≤15 жыл, >15 жыл) және терапия түріне (монотерапия, политерапия) бөлінді.

Нәтижелер: Ауру ұзақтығы мен терапия түрі қышқыл-сілтілік тұрақтылық пен газ алмасуға айтарлықтай әсер етпеді. >15 жылдық анамнезі бар науқастарда өкпенің жасанды желдету ұзақтығы ұзарды. Политерапия оң гидробаланс жоғарылауымен байланысты болды (p=0,02). Ерте операциядан кейінгі құрысу 9,7% науқаста байқалды, ол pH мен HCO_3^- жоғарылауымен, бірақ газ алмасу бұзылуымен сипатталмады.

Қорытындылар: Ауру ұзақтығы мен антиепилептикалық терапия түрі ерте операциядан кейінгі кезеңде қышқыл-сілтілік тұрақтылық пен оксигенацияға айқын әсер етпейді, бірақ инфузиялық баланс пен өкпені жасанды желдету ұзақтығымен байланысты. Бұл топтағы науқастарда инфузиялық және тыныс алу терапиясына жекеленген көзқарас қажет.

***Түйінді сөздер**: дәріге төзімді эпилепсия, антиепилептикалық терапия, қышқыл-сілтілік тұрақтылық, газ алмасу, инфузиялық терапия.*

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Introduction

Pharmacoresistant focal epilepsy (PRFE) represents a severe disease phenotype, as up to 30% of patients fail to achieve adequate seizure control with conventional therapy [1]. In this group, surgical treatment remains the most effective option, significantly reducing seizure frequency and improving quality of life [2]. However, prolonged disease duration, chronic antiepileptic drug (AED) exposure, and the complexity of surgical procedures create an unfavorable perioperative setting, often associated with respiratory complications and impaired gas exchange [3].

Epilepsy-related disturbances in central respiratory control, including apnea, hypoventilation, and oxygen desaturation, have been described even during focal

seizures [4,5]. The postictal state is marked by reduced sensitivity to hypercapnia, which compromises compensatory mechanisms and contributes to acute respiratory risk [6,7]. Respiratory dysfunction is also implicated in the pathogenesis of sudden unexpected death in epilepsy (SUDEP) [7]. Although the direct link between epilepsy duration and severity of respiratory impairment remains unclear, cumulative subclinical disturbances are likely to accrue over time [3,5].

AED therapy further complicates perioperative management by influencing central nervous system function, acid–base balance, and metabolic regulation [1,2]. While some drugs such as levetiracetam demonstrate favorable safety profiles [8], others, including valproate, carbamazepine, and topiramate, may induce adverse metabolic or respiratory effects [10–14]. Polytherapy and prolonged AED use can exacerbate these risks, particularly when combined with anesthetics and opioids, whereas drug withdrawal increases seizure likelihood [2,9,13]. Comorbidities such as obesity, OSA, and COPD further elevate the risk of perioperative hypoxemia and respiratory failure [9,14,15]. In selected cases, extended mechanical ventilation or ICU monitoring within the first 24 postoperative hours is required [9,13].

Neurosurgical procedures for PRFE are often prolonged, associated with blood loss, and necessitate high anesthetic doses. More than half of patients undergoing extensive resections require postoperative ventilatory support due to hypoxemia, aspiration, hypoventilation, or impaired consciousness, particularly in the context of polytherapy and metabolic imbalance [2,7,13].

Despite clinical experience, several gaps remain unresolved. Specifically, the effect of epilepsy duration on perioperative respiratory function, the cumulative impact of long-term AED exposure, and the interplay between therapy regimen (monotherapy vs. polytherapy) and postoperative outcomes are poorly characterized. Given the heterogeneity of PRFE patients—ranging from decades-long disease to adult-onset epilepsy—an individualized risk assessment approach is required to optimize anesthetic and perioperative strategies.

Purpose: To investigate the relationship between epilepsy tenure and antiepileptic drug regimen characteristics with regard to acid-base equilibrium and oxygenation parameters during the perioperative course among adult patients receiving neurosurgical management of pharmacoresistant focal epilepsy.

Materials and Methods

This retrospective cohort study was conducted at the Hospital of the Medical Center of the Administration of Affairs of the President of the Republic of Kazakhstan. We analyzed 93 adult patients who underwent surgery for pharmacoresistant focal epilepsy between 2019 and 2024.

Inclusion criteria: age ≥18 years, confirmed diagnosis of pharmacoresistant focal epilepsy, documented neurosurgical procedure with complete records, and perioperative observation up to 48 hours.

Exclusion criteria: generalized epilepsy, insufficient data, severe comorbidities (decompensated pulmonary disease, respiratory failure, end-stage cardiac insufficiency, neoplasia, stage IV hepatorenal dysfunction), major intraoperative hemorrhage, or reoperation.

Parameters recorded:

Demographics: age, sex, body mass index.

Surgical variables: anesthetic technique, duration.

Hemodynamics: arterial pressure, heart rate, oxygen saturation, fluid balance (administration, blood loss, urine output).

Respiratory and oxygenation: minute ventilation, fresh gas flow, ABG values (pH, pCO_2, pO_2, HCO_3^-, base excess, oxyhemoglobin, ctO_2, FiO_2, PaO_2/FiO_2, A–a gradient, a/A ratio) intraoperatively, at completion, on ICU admission, and 12 h post-op.

Clinical outcomes: duration of mechanical ventilation, RASS scores, ICU stay, need for non-invasive ventilation, postoperative seizures.

Perioperative fluid therapy targeted: MAP ≥70 mmHg, CVP 6–12 mmHg, urine output >0.5 mL/kg/h, lactate <2.0 mmol/L. Management used 0.9% saline, switching to Sterofundin (B.Braun, Switzerland) with high-volume needs or hyperchloremic acidosis; Gelofusine was applied as colloid support. Norepinephrine was administered if MAP <65 mmHg despite adequate volume expansion.

Ventilation and oxygenation strategies were titrated to arterial blood gases and acid-base status, with SpO_2 maintained ≥93% via continuous monitoring.

Stratification:

By disease duration: Group 1 (≤15 years) and Group 2 (>15 years).

By antiepileptic regimen: monotherapy vs. polytherapy.

Statistical Analysis: We analyzed data utilizing SPSS version 26.0 and JASP statistical software. Descriptive statistics for continuous variables included means with standard deviations, supplemented by medians and interquartile ranges where indicated. Categorical variables were expressed as absolute frequencies and proportions. We employed nonparametric Friedman and Wilcoxon tests for temporal comparisons of acid-base status parameters, given the non-normal distribution of quantitative data (Kolmogorov-Smirnov test, $p<0.05$). When statistical significance was established, we conducted post-hoc pairwise analyses via Wilcoxon signed-rank test.

Results

A total of 93 patients underwent neurosurgical treatment for pharmacoresistant focal epilepsy. The mean age was 33.2±8.2 years; 59.8% were male and 40.2% female. The mean body mass index (BMI) was 23.9 kg/m². Nutritional status assessment revealed malnutrition in 7.8%, overweight in 15.7% (16 patients), class I obesity in 10.8% (11 patients), and class II obesity in 0.98% (1 patient).

Antiepileptic therapy. Carbamazepine was the most frequently used agent, prescribed as monotherapy in 28 of 37 patients and incorporated as either primary or adjunctive therapy in polytherapy regimens. Levetiracetam was frequently administered in patients with longer disease duration (n=30), either as monotherapy (n=4) or adjunctive therapy (n=23). Lamotrigine, oxcarbazepine, and topiramate were exclusively prescribed in polytherapy. Valproic acid showed slightly greater prevalence in long-standing disease, always as part of polytherapy.

Stratification. Patients were grouped according to disease duration (≤15 vs. >15 years) and treatment regimen (monotherapy vs. polytherapy). Patients with epilepsy >15 years were older than those with shorter

disease duration (34.1 vs. 30.7 years, p<0.05). No significant differences were observed in BMI or sex distribution. Mean ages by treatment regimen were comparable (32.3 vs. 32.4 years), with male predominance in both groups.

Intraoperative course. Minute ventilation, fresh gas flow, and anesthetic exposure time did not differ between groups. Richmond Agitation-Sedation Scale (RASS) scores post-extubation clustered around –1 (drowsy but arousable), without group differences. All patients remained in ICU for >12 hours. Postoperative mechanical ventilation duration was significantly longer in patients with chronic epilepsy (>15 years, p<0.05), but did not differ between therapy regimens.

Table 1.

Clinical and demographic characteristics of patients depending on type of therapy and disease duration

Variables		Disease duration			Type of antiepileptic therapy		
		≤15 years (n=45)	>15 years (n=48)	p	Monotherapy (n=33)	Polytherapy (n=60)	p
Mean age (M, 95% CI)		30.7 (28.4-33.0)	34.1 (31.9-36.3)	0.01	32.3 (29.5-34.0)	32.4 (30.4-34.4)	0.51
Body mass index		24.92±4.02	23.31±4.69	0.85	24.11±4.8	23.68±4.2	0.97
Sex	Female	18 (40%)	20 (41.7%)		11 (33.3%)	26 (43.3%)	
	Male	27 (60%)	28 (58.3%)		22 (66.7%)	34 (56.7%)	
Minute ventilation during surgery, l/min.		6.73±0.79	7.0±0.89	0.1	6.81±0.90	6.89±0.81	0.5
Fresh gas flow during surgery l/min.		3.01±1.03	2.86±0.95	0.4	2.98±1.06	2,90±0.93	0.8
Anesthesia duration, min. (M ± SD)		552.29 ±120.9	559.8 ±112.3	0.16	536.3 ±116.6	579.59 ±109.9	0.07
Extubation time, min. (M ± SD)		81.66 ±44.16	111.93 ±70.5	0.03	93.45 ±58.30	97,76 ±61,35	0.38
RASS score (M ± SD)		-0.96±0.19	-0.93±0.24	0.57	-0.94±0.22	-0.95±0.21	0.59
ICU length of stay, h (M ± SD)		14.47±3.34	14.06±2.54	0.19	14.37±2.8	14.22±3.11	0.71
M ± SD – mean ± standard deviation; CI – confidence interval; RASS – Richmond Agitation-Sedation Scale; ICU – intensive care unit							

Hemodynamics. Systolic, diastolic, and mean arterial pressure, heart rate, and peripheral oxygen saturation remained stable and within reference ranges throughout the perioperative period. No intergroup differences were observed.

Infusion therapy. Analysis of infusion parameters (Table 2) revealed significantly higher intraoperative fluid administration and net fluid balance in the polytherapy cohort, with increased variability. Patients with epilepsy ≤15 years demonstrated a trend toward more favorable fluid balance, though not statistically significant. Blood loss was comparable between groups, and no transfusions were required. Urine output was slightly greater in polytherapy patients, without statistical significance.

Acid–base balance. Dynamic assessment (Table 3) demonstrated pH values within the physiological range, approaching significance (p=0.05). Arterial carbon dioxide tension remained stable with a trend toward normocapnia (p=0.06). Base excess and bicarbonate concentrations improved significantly from deficit to near-compensated values (p<0.001).

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	Disease duration			Type of antiepileptic therapy		
	≤15 years (n=45)	>15 years (n=48)	p	Monotherapy (n=33)	Polytherapy (n=60)	p
Total infusion volume, ml (Me, Q1–Q3)	2800.0 (2400.0–3000.0)	500.0 (2300.0–3400.0)	0.79	2500.0 (2200.0–2900.0)	2800.0 (2400.0–3400.0)	0.05
Urine output, ml (Me, Q1–Q3)	000.0 (650.0–1650.0)	900.0 (525.0–1250.0)	0.27	900.0 (550.0–1500.0)	1425.0 (650–2040.0)	0.89
Blood loss, ml (Me, Q1–Q3)	100.0 (100.0–200.0)	100.0 (100.0–200.0)	0.16	100.0 (100.0–200.0)	100.0 (100.0–200.0)	0.72
Fluid balance, ml (Me, Q1–Q3)	400.0 (960.0–1825.0)	600.0 (1100.0–2025.0)	0.11	1250.0 (950.0–1650.0)	1700.0 (1150.0–2000.0)	0.02
Norepinephrine dose, mcg/kg/min (Me, Q1–Q3)	0.040 (0.040–0.050)	0.050 (0.030–0.050)	0.60	0.050 (0.040–0.050)	0.040 (0.040–0.050)	0.69
Me – median; Q1–Q3 – interquartile range; p – Mann–Whitney test.						

Acid–base balance indicators over time.

Indicators	During surgery	At the end of surgery	On ICU admission	12 h post-op	p
pH (Me, Q1–Q3)	7.39 (7.35–7.42)	7.38 (7.35–7.41)	7.38 (7.35–7.41)	7.40 (7.37–7.42)	0.05
pO_2 (Me, Q1–Q3)	232.0 (183.5–261.0)	173.0 (147.0–236.0)	157.0 (122.0–212.0)	100.0 (89.0–138.0)	<0.001
pCO_2 (Me, Q1–Q3)	36.8 (32.7–40.1)	38.0 (34.7–41.0)	38.1 (34.5–38.9)	37.0 (34.3–40.3)	0.06
BE (Me, Q1–Q3)	3.20 (–4.85 – –1.50)	-2.80 (–4.60 – –1.00)	-2.50 (–4.30 – –0.80)	-1.40 (–2.95 – 0.35)	<0.001
HCO_3^- (Me, Q1–Q3)	22.3 (21.0–23.5)	22.1 (21.1–23.2)	22.5 (21.2–23.6)	23.4 (22.2–24.6)	<0.001
Hb (Me, Q1–Q3)	128.0 (110.0–139.5)	124.0 (109.0–138.0)	124.0 (110.0–138.0)	125.0 (108.0–136.5)	0.71
Ht (Me, Q1–Q3)	38.0 (32.0–41.0)	36.0 (32.0–41.0)	36.0 (32.0–41.0)	37.0 (32.0–40.0)	0.28
SO_2 (Me, Q1–Q3)	98.3 (97.7–98.8)	98.0 (97.3–98.4)	97.6 (96.1–98.2)	96.7 (94.1–97.6)	<0.001
PaO_2/FiO_2 (Me, Q1–Q3)	520 (460–596)	490 (397–570)	434 (367–537)	390 (314–470)	<0.001
A–a gradient (Me, Q1–Q3)	41.0 (23.9–71.0)	34.3 (22.8–44.9)	41.0 (25.2–55.6)	39.4 (32.0–56.2)	0.08
a/A ratio (Me, Q1–Q3)	84.0 (73.0–89.0)	74.0 (57.5–85.5)	72.0 (56.0–84.0)	73.0 (56.0–80.0)	<0.001
ctO_2 (Me, Q1–Q3)	18.5 (16.0–20.4)	17.4 (15.6–19.4)	17.1 (15.4–19.0)	16.2 (14.5–17.9)	<0.001
Lactate (Me, Q1–Q3)	1.02 (0.89–1.70)	1.25 (1.02–1.90)	1.30 (0.99–1.85)	1.06 (0.88–1.60)	0.004
FiO_2 (Me, Q1–Q3)	50.0 (50.0–50.0)	50.0 (45.0–50.0)	45.0 (40.0–45.0)	30.0 (30.0–31.0)	<0.001
Me – median; Q1–Q3 – interquartile range; p – Mann–Whitney test.					

Oxygenation. Oxygen tension (pO_2) declined significantly from intraoperative hyperoxia (232 mmHg) to physiological levels during recovery (p<0.001), paralleling FiO_2 reduction and restoration of spontaneous respiration. Hemoglobin oxygen saturation (SO_2) decreased modestly but remained within normal limits (p<0.001). The PaO_2/FiO_2 ratio declined significantly across the perioperative course (p<0.001). The alveolar–arterial (A–a) gradient trended toward higher values (p=0.08), whereas the arterial-to-alveolar ratio (a/A) and total oxygen content (ctO_2) decreased significantly (both p<0.001). Hemoglobin and hematocrit declined slightly but without significance (p=0.71 and p=0.28). Lactate rose mildly at the end of surgery and on ICU admission (1.25–1.30 mmol/L), with subsequent normalization (p=0.004).

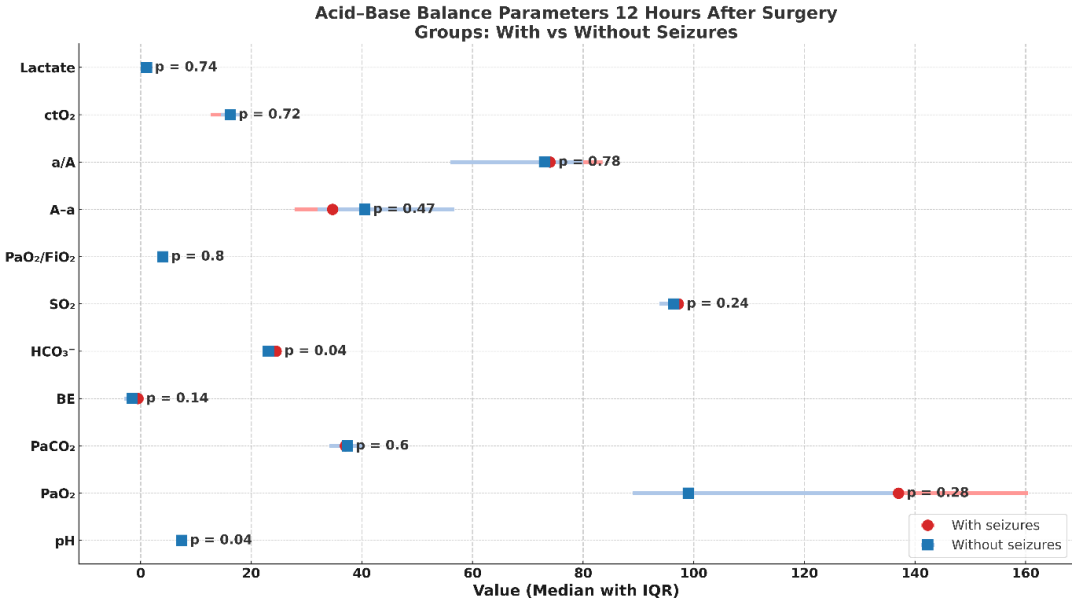
Stratified oxygenation analysis (Table 4).

Oxygenation parameters	Disease duration			Type of antiepileptic therapy		
	≤15 years (n=45)	>15 years (n=48)	p	Monotherapy (n=33)	Polytherapy (n=60)	p
SO_2 (Me, Q1–Q3)	96.8 (94.3–97.8)	96.2 (93.6–98.0)	0.8	96.3 (94.3–97.6)	96.8 (93.0-93.8)	0.7
A–a gradient (Me, Q1–Q3)	37.8 (30.1–50.4)	42.0 (32.4–58.4)	0.9	37.6 (28.4–53.5)	42.0 (32.0–56.8)	0.4
a/A ratio (Me, Q1–Q3)	74.0 (56.0–84.8)	71.0 (54.5–78.0)	0.3	73.0 (54.0–82.0)	74.0 (56.0–80.0)	0.4
ctO_2 (Me, Q1–Q3)	16.3 (14.1–18.3)	16.2 (14.6–17.8)	0.5	16.2 (14.6–18.2)	16.1 (14.4–17.7)	0.7
PaO_2/FiO_2 (Me, Q1–Q3)	4.01 (3.71–4.35)	3.85 (3.68–4.39)	0.9	4.07 (3.66–4.48)	3.85 (3.69–4.30)	0.6
Lactate (Me, Q1–Q3)	1.01 (0.83–1.26)	1.10 (0.90–1.60)	0.8	1.04 (0.89–1.60)	1.07 (0.87–1.59)	0.4
Mechanical ventilation duration, minute (Me, Q1–Q3)	70.0 (46.3–135.0)	100.0 (60.0–127.5)	0.7	90.0 (50.0–142.0)	77.5 (51.3–125.0)	0.3
Me – median; Q1–Q3 – interquartile range; p – Mann–Whitney test.						

By disease duration: SO_2 values were equivalent between ≤15 years and >15 years cohorts (p=0.8). The A–a gradient was higher in patients with epilepsy >15 years, but not significant (p=0.9). The reduced a/A ratio in chronic cases suggested modest impairment of gas exchange, though not clinically or statistically relevant. ctO_2 and lactate values were similar. Prolonged postoperative ventilation was more frequent in the >15 years cohort, without significance (p=0.7).

By treatment regimen: SO_2 values were comparable (p=0.7). The A–a gradient was slightly higher in polytherapy patients, without significance (p=0.4). The a/A ratio and ctO_2 did not differ. Lactate was similar between groups (p=0.4). Ventilation duration was longer in monotherapy patients (90 vs. 77.5 h), though not significant (p=0.3).

Seizure outcomes. Postoperative seizures occurred in 9 patients (9.7%) within 2–48 hours after surgery. Comparative analysis (Figure 1) demonstrated higher pH values in seizure patients (p=0.04), trending toward alkalosis. Bicarbonate concentrations were also higher (24.5 vs. 23.1 mmol/L, p=0.04). Base excess did not differ significantly (p=0.14). pO_2 and SO_2 were higher in seizure patients but without significance (p=0.28 and p=0.24). Neither the A–a gradient nor the a/A ratio differed (p=0.47 and p=0.78). Arterial oxygen content was identical in both groups (16.2, p=0.72). pCO_2 and lactate were essentially unchanged (p=0.60 and p=0.74).



Discussion

Pharmacotherapy patterns. This investigation evaluated the perioperative trajectory of acid–base equilibrium, oxygenation indices, and related clinical parameters, with particular emphasis on epilepsy chronicity and antiepileptic drug (AED) regimens. The findings are broadly consistent with existing literature [11,17], confirming carbamazepine and levetiracetam as the most frequently prescribed AEDs. Carbamazepine maintained its position as the predominant monotherapeutic agent, whereas levetiracetam and lamotrigine were preferentially administered within polytherapy regimens rather than as monotherapy. The use of polytherapy increased with disease duration, reflecting the necessity for comprehensive pharmacological strategies to manage pharmacoresistant epilepsy. The observed age differential is explained by the overrepresentation of older patients in the group with epilepsy exceeding 15 years in duration.

Fluid management implications. One of the most clinically relevant findings concerns fluid management. Patients on polytherapy exhibited greater positive fluid balance and higher intraoperative infusion volumes, despite comparable blood loss, urine output, and vasopressor use. Several explanations may account for this observation. First, polytherapy patients may have undergone technically complex or prolonged procedures, even though mean anesthesia duration was similar across groups. Second, confounders such as body composition, latent hypovolemia, or increased electrolyte requirements may have influenced perioperative fluid strategy. Third, cumulative metabolic disturbances associated with AEDs may alter water–electrolyte homeostasis and renal regulatory mechanisms, as previously suggested [18,19,25,28]. These findings highlight the need for cautious fluid administration, particularly in patients on polytherapy, where excessive positive balance may increase the risk of edema and pulmonary complications [20].

Respiratory and gas exchange dynamics. Intraoperative and postoperative courses demonstrated the expected transition from controlled surgical ventilation to spontaneous breathing under intensive care conditions. Stepwise FiO_2 reduction was associated with decreases in PaO_2 and SO_2, while pH remained within physiological limits, $PaCO_2$ trended toward normocapnia, and BE and HCO_3^- shifted toward compensated values, reflecting restoration of buffering capacity. Prior studies report that topiramate may contribute to perioperative metabolic acidosis [21], and *Türe H. et al.* recommend close acid–base monitoring in patients on long-term AED therapy [18].

The decline in PaO_2/FiO_2 ratio was primarily attributable to FiO_2 reduction and transition to spontaneous ventilation. Although values decreased significantly, median levels remained above 300 mmHg, excluding acute respiratory failure. No major intergroup differences were observed, suggesting preserved alveolar–capillary gas exchange. The alveolar–arterial gradient remained stable, while reductions in a/A ratio and ctO_2 at 12 hours reflected moderate impairment of oxygen transfer efficiency during oxygen weaning, likely due to decreased PaO_2 and hemoglobin concentration. Nevertheless, these changes did not compromise global oxygen delivery. Consistent with Kennedy J. and Seyal M., approximately one-third of epilepsy patients demonstrate respiratory disturbances and ventilation–perfusion mismatch [15,22]. Lactate normalization over time may indicate transient stress-induced hypermetabolism with subsequent recovery.

Impact of disease duration. Patients with epilepsy duration >15 years required longer postoperative mechanical ventilation. This finding is consistent with anticipated outcomes: age-related decline, cumulative sedative–hypnotic exposure, reduced pharyngeal muscle tone, occult sleep-disordered breathing, and altered central respiratory control may collectively hinder extubation and spontaneous breathing. Kanth K. et al. reported delayed recovery of respiratory function in patients with long-standing epilepsy [5]. However, the absence of differences in RASS scores (~−1), hemodynamic stability, and primary oxygenation parameters suggests that extended ventilation requirements were related to functional limitations (arousal, airway protection, reflex integrity) rather than overt respiratory failure. Previous investigations have

documented the potential for AEDs to impair brainstem respiratory centers [23], though no severe complications were observed in this cohort.

Although the >15-year group exhibited trends toward increased alveolar–arterial gradients, lower a/A ratios, and longer ventilatory support, no significant differences in core oxygenation or acid–base variables were demonstrated. Kouchi H. et al. described variable respiratory dysfunction in patients with pharmacoresistant epilepsy [3], supporting the plausibility of these findings as cumulative sequelae of chronic disease and comorbidities. Conversely, Kanth K. et al. reported no clear association between epilepsy duration and respiratory dysfunction severity [5]. Dereli A. et al. highlighted hypoventilation and respiratory instability as major determinants of postoperative complications [24]. Clinically, these results underscore the importance of enhanced respiratory monitoring in patients with prolonged disease, even though chronicity itself did not determine early postoperative gas exchange outcomes. Hampel et al. noted that hemodynamic and respiratory dysregulation during focal seizures is not directly correlated with oxygenation [25], while Blum A. et al. suggested that oxygenation status may serve as an adjunctive predictor of complications [26].

Seizures and acid–base balance. Postoperative seizures occurred in 9.7% of patients, consistent with prior reports documenting early seizures in >5% of cases [27]. Patients who experienced seizures exhibited modest but statistically significant increases in pH and HCO_3^- at 12 hours. This pattern likely reflects postictal hyperventilation combined with perioperative alkalosis induced by fluid administration and electrolyte correction. These findings are in line with Forsyth R., who postulated that seizures initiate under alkalotic conditions and terminate in acidic environments [28]. While other studies emphasize hypoxia and respiratory acidosis as seizure precipitants [29,30], neither hypoxemia nor acidosis was identified in our cohort. The lack of intergroup variation in PaO_2, $PaCO_2$, SO_2, A–a gradient, and lactate suggests that seizures primarily influenced acid–base balance without significant impact on tissue perfusion or ventilation.

Clinical implications. Taken together, the findings indicate no major association between disease chronicity or pharmacotherapy complexity and perioperative acid–base or oxygenation disturbances. Trends toward longer ventilation and positive fluid balance in certain subgroups highlight areas of potential vulnerability. Clinically, the immediate postoperative trajectory in patients with pharmacoresistant epilepsy appears more strongly determined by intraoperative management and intensive care interventions than by antecedent disease duration or AED regimen.

Study Limitations. Our investigation presents several limitations. First, the single-center retrospective design limits the generalizability of findings. Second, the relatively modest sample size constrains statistical power and increases the risk of type II error in intergroup comparisons. Third, heterogeneity of surgical interventions and antiepileptic therapy regimens precluded more detailed stratification by specific medications and dosages. Fourth, analysis was restricted to the early postoperative period, without assessment of long-term respiratory outcomes and complications. Finally, the potential influence of comorbid conditions (such as obesity, OSA, COPD) was not evaluated independently, which may constitute a confounding factor.

Conclusion. This study revealed that neither epilepsy chronicity nor antiepileptic pharmacotherapy complexity significantly impacts perioperative acid-base homeostasis or oxygenation indices following neurosurgical intervention for pharmacoresistant focal epilepsy. However, extended disease tenure correlated with prolonged ventilatory support duration and subtle oxygenation compromise, whereas polypharmaceutical regimens were characterized by excessive fluid accumulation. These observations emphasize the imperative for personalized perioperative protocols encompassing judicious volume management and vigilant respiratory surveillance. Convulsive episodes predominantly modulate acid-base parameters without inducing oxygen transport deficits or clinically relevant tissue hypoperfusion.

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COMPARATIVE ASSESSMENT OF CANDIDA SPP. SUSCEPTIBILITY AND RESISTANCE TO ANTIFUNGAL AGENTS BY BIOLOGICAL MATERIAL TYPE

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Abstract

Background: Invasive fungal infections caused by *Candida* species remain a significant global health concern, particularly in immunocompromised individuals. Effective treatment requires precise knowledge of antifungal susceptibility patterns, which may vary depending on the biological source of isolation.

Objective: This study aims to evaluate and compare the susceptibility and resistance profiles of *Candida* spp. to five major antifungal agents across different types of biological materials providing clinically relevant insights for antifungal stewardship and infectious disease management.

Materials and Methods: A retrospective, observational, and descriptive study was conducted using 1,220 clinical isolates of *Candida* spp., collected from sputum (n=893), ENT organs (n=277), and cerebrospinal canal (n=50). Identification was carried out using conventional culture and microscopy. Susceptibility to anidulafungin, micafungin, voriconazole, caspofungin, and fluconazole was assessed using the broth microdilution method according to CLSI M27 and EUCAST guidelines. Minimum inhibitory concentrations (MICs) were used to determine susceptibility and resistance. Data analysis was performed using Microsoft Excel and IBM SPSS Statistics.

Results: Fluconazole demonstrated the highest overall susceptibility across all specimen types, especially in cerebrospinal canal isolates (80.0%) and sputum (78.6%). Among echinocandins, anidulafungin and micafungin showed strong activity, particularly in CNS and respiratory isolates. Voriconazole consistently exhibited the lowest susceptibility and highest resistance, especially in ENT-derived samples. Caspofungin presented moderate efficacy with variable resistance patterns. Resistance was highest in voriconazole (up to 40.4% in ENT samples), followed by caspofungin and micafungin. Fluconazole had the lowest resistance across all groups.

Conclusion: The effectiveness of antifungal drugs varies by the source of Candida spp. Fluconazole was most effective, especially in CNS infections. Voriconazole showed lower efficacy and more resistance. Treatment should be based on infection source to improve outcomes and reduce resistance.

Keywords: Candida *spp., antifungal resistance, biological specimens, antifungal susceptibility, clinical isolates*

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Резюме

СРАВНИТЕЛЬНАЯ ОЦЕНКА ЧУВСТВИТЕЛЬНОСТИ И УСТОЙЧИВОСТИ CANDIDA SPP. К ПРОТИВОГРИБКОВЫМ ПРЕПАРАТАМ В ЗАВИСИМОСТИ ОТ ТИПА БИОЛОГИЧЕСКОГО МАТЕРИАЛА

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Введение: Инвазивные грибковые инфекции, вызываемые видами *Candida*, остаются серьёзной проблемой здравоохранения во всем мире, особенно среди пациентов с ослабленным иммунитетом. Эффективное лечение требует точного понимания профилей чувствительности к противогрибковым препаратам, которые могут варьироваться в зависимости от биологического материала, из которого выделен возбудитель.

Цель: Оценить и сравнить чувствительность и устойчивость *Candida* spp. к пяти основным противогрибковым препаратам в зависимости от типа клинического материала (мокрота, ЛОР-органы и ликвор), с целью предоставления клинически значимой информации для ведения инфекционных заболеваний и антимикотической стратегии.

Материалы и методы: Было проведено ретроспективное, описательное, наблюдательное исследование, включающее 1 220 клинических изолятов *Candida* spp., полученных из мокроты (n=893), ЛОР-органов (n=277) и цереброспинальной жидкости (n=50). Видовая идентификация проводилась с использованием стандартных микологических методов (посев, микроскопия). Тестирование чувствительности к анидулафунгину, микафунгину, вориконазолу, каспофунгину и флуконазолу проводилось методом микробульонного разведения в соответствии с рекомендациями CLSI M27 и EUCAST. Анализ данных выполнен с использованием Microsoft Excel и IBM SPSS Statistics.

Результаты: Флуконазол продемонстрировал наивысшую общую чувствительность по всем типам образцов, особенно в ликворе (80,0%) и мокроте (78,6%). Среди эхинокандинов наибольшую активность показали анидулафунгин и микафунгин, особенно в изолятах из ЦНС и дыхательных путей. Вориконазол продемонстрировал наименьшую чувствительность и наибольшую устойчивость, особенно в ЛОР-образцах. Каспофунгин показал умеренную активность и переменную устойчивость. Вориконазол продемонстрировал наибольшую устойчивость (до 40,4% в ЛОР-образцах), за ним следовали каспофунгин и микафунгин. Флуконазол имел наименьшие показатели устойчивости.

Вывод: Эффективность противогрибковых препаратов зависит от источника выделения Candida spp. Флуконазол был наиболее эффективен, особенно при инфекциях ЦНС. Вориконазол показал меньшую эффективность и большую устойчивость. Терапию следует подбирать с учётом источника инфекции для повышения эффективности и снижения резистентности.

Ключевые слова: *Candida spp., противогрибковая устойчивость, биологический материал, чувствительность, клинические изоляты*

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Түйіндеме

CANDIDA SPP. ЗЕҢДЕРІНЕ ҚАРСЫ ПРЕПАРАТТАРҒА СЕЗІМТАЛДЫҒЫ МЕН ТӨЗІМДІЛІГІНІҢ БИОЛОГИЯЛЫҚ МАТЕРИАЛ ТҮРІНЕ БАЙЛАНЫСТЫ САЛЫСТЫРМАЛЫ БАҒАЛАУ

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Кіріспе: Candida түрлерімен шақырылатын инвазивті зең инфекциялары, әсіресе иммунитеті төмен адамдар арасында, жаһандық денсаулық сақтау жүйесі үшін елеулі қауіп болып табылады. Тиімді ем жүргізу үшін зеңге қарсы дәрілерге сезімталдықтың биологиялық материалға байланысты ерекшеліктерін нақты білу қажет.

Мақсаты:Клиникалық маңызды ақпарат беру мақсатында, әртүрлі биологиялық материалдардан бөлінген Candida spp. изоляттарының бес негізгі зеңге қарсы препаратқа (анидулафунгин, микафунгин, вориконазол, каспофунгин және флуконазол) сезімталдық және төзімділік деңгейін бағалау және салыстыру.

Материалдар мен әдістер: Зерттеу сипаттамалы, ретроспективті және бақылаулық сипатта жүргізілді. Барлығы 1 220 *Candida* spp. клиникалық изоляттары зерттелді: қақырықтан (n=893), ЛОР-мүшелерінен (n=277), жұлын сұйықтығынан (n=50). Идентификация стандартты микологиялық әдістер арқылы жүргізілді. Зеңге қарсы препараттарға сезімталдық CLSI M27 және EUCAST ұсыныстарына сәйкес микробульонды сұйылту әдісімен анықталды. Мәліметтер Microsoft Excel және IBM SPSS Statistics бағдарламаларында өңделді.

Нәтижелер: Флуконазол барлық үлгілер арасында ең жоғары сезімталдықты көрсетті, әсіресе жұлын сұйықтығында (80,0%) және қақырықта (78,6%). Эхинокандиндер арасында анидулафунгин мен микафунгин жақсы белсенділік көрсетті. Вориконазол ең төмен сезімталдықты және жоғары төзімділікті көрсетті, әсіресе ЛОР-жинақтарында. Каспофунгин орташа тиімділікке ие болды. Вориконазолдың төзімділігі ең жоғары болды (ЛОР - 40,4%), флуконазол - ең төмен төзімді дәрі.

Қорытынды: Candida spp. түрлерінің антимикотикалық дәрі-дәрмектерге тиімділігі олардың алынған биологиялық материалына байланысты өзгереді. Флуконазол ең тиімді болып, әсіресе орталық жүйке жүйесінің инфекцияларында жақсы нәтиже көрсетті. Вориконазол тиімділігі төменірек және резистенттілік жоғары болды. Емдеуді инфекцияның көзіне байланысты таңдау науқастардың жағдайын жақсартуға және дәрі-дәрмекке төзімділікті азайтуға көмектеседі.

Түйінді сөздер: *Candida spp., зеңге қарсы төзімділік, биоматериал, сезімталдық, клиникалық изоляттар.*

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Introduction

Fungal infections, particularly those caused by Candida species, represent an escalating public health concern across both developed and developing regions. Each year, approximately 1,565,000 people worldwide develop invasive candidiasis. This condition primarily affects individuals with weakened immune systems, including critically ill patients in intensive care units, those undergoing prolonged treatment with broad-spectrum antibiotics, and more recently, people experiencing complications from post-COVID-19 syndrome (also known as long COVID). Invasive candidiasis is frequently misdiagnosed and is responsible for about 995,000 deaths annually, accounting for 63.6% of all cases [8].

Traditionally, Candida albicans has been considered the most prevalent species. However, recent studies reveal a marked epidemiological shift toward non-albicans Candida (NAC) species, including C. glabrata, C. parapsilosis, C.

tropicalis, and C. auris [19]. These species often exhibit intrinsic or acquired resistance to standard antifungal agents, posing challenges to effective treatment. In particular, Candida auris has gained global attention due to its multidrug resistance and capacity to cause nosocomial outbreaks [13].

A growing body of evidence indicates that addressing antifungal resistance requires consideration of site-specific factors, particularly the anatomical location from which Candida species are isolated. Clinical samples obtained from mucosal surfaces or catheterized areas frequently exhibit higher resistance levels, often due to biofilm formation and repeated exposure to antifungal agents. These findings highlight the importance of tailoring antifungal strategies based not only on species identification but also on the source of the clinical specimen [7].

Recent ICU-focused guidelines emphasize that the anatomical origin of Candida isolates plays a critical role in determining antifungal susceptibility. Isolates from sterile sites, such as blood or cerebrospinal fluid, tend to display higher susceptibility rates compared to those from non-sterile sites, including the urinary or respiratory tracts. This supports the integration of specimen-type considerations into both empirical antifungal therapy and local stewardship protocols [3].

Analysis of antifungal susceptibility in both environmental and clinical Candida isolates has revealed significant differences depending on the origin of the sample. Resistance to fluconazole was notably higher in isolates obtained from environments with strong anthropogenic influence. These observations support the concept that site-specific environmental pressures play a crucial role in shaping resistance patterns, even among clinically important yeast species [4].

Global surveillance data further highlight the growing concern of antifungal resistance in Candida species. Fluconazole-resistant C. parapsilosis has emerged as a serious clinical issue, particularly in intensive care settings, with resistance rates in certain regions exceeding 35%. This trend poses a direct threat to the efficacy of first-line antifungal treatments and underscores the urgent need for localized susceptibility testing and targeted antifungal stewardship strategies in high-risk hospital environments [6].

The compounding effects of co-infections and immunosuppressive therapies, particularly evident during the COVID-19 pandemic, have been associated with a marked increase in invasive fungal infections, including those caused by Candida spp. Delays in diagnosis and inappropriate use of azole antifungals have contributed to the emergence of resistant strains, especially in respiratory and urogenital samples. These observations highlight the importance of integrating clinical context, including the source of the isolate and the patient's background, into diagnostic and treatment strategies [10].

Aim to analyze the susceptibility profile of Candida spp. to five major antifungal agents according to biological specimen type, providing clinically relevant insights for infectious disease management and antifungal stewardship.

Materials and Methods

This study was designed as an observational, retrospective, and descriptive analysis. It included data on the susceptibility of 1,220 isolates of Candida spp., obtained from three types of clinical specimens: sputum (n = 893), ENT organs (n = 277), and cerebrospinal canal (n = 50). The analysis focused on five antifungal agents: anidulafungin, micafungin, voriconazole, caspofungin, and fluconazole.

Identification of Candida species was performed using standard mycological techniques, including culture-based methods and microscopic examination.

Antifungal susceptibility testing was conducted using the broth microdilution method, with determination of minimum inhibitory concentrations (MICs), in accordance with the CLSI M27 and EUCAST guidelines. Based on the MIC values obtained, isolates were classified as susceptible (S) or resistant (R).

Statistical Analysis

Data were entered into Microsoft Excel for preliminary sorting and calculation of susceptibility and resistance percentages. Statistical analysis was carried out using IBM SPSS Statistics, applying descriptive statistical methods.

To determine the rates of susceptibility and resistance for each biological specimen type, we calculated the percentage of susceptible and resistant *Candida* isolates relative to the total number of isolates from that material. The formulas used were:

- **Susceptibility (%)** = (Number of susceptible isolates / Total number of isolates per material) × 100
- **Resistance (%)** = (Number of resistant isolates / Total number of isolates per material) × 100

To assess overall trends, we also calculated the average susceptibility and resistance rates across all sample types using the following formulas:

- **Average susceptibility (%)** = (Total number of susceptible isolates from all materials / Total number of isolates) × 100
- **Average resistance (%)** = (Total number of resistant isolates from all materials / Total number of isolates) × 100

Results

Table 1 presents the susceptibility and resistance of *Candida* isolates to five antifungal agents across three types of clinical specimens: sputum, ENT organs, and cerebrospinal canal. The largest number of isolates was obtained from sputum (n=893), followed by ENT samples (n=277) and cerebrospinal canal specimens (n=50).

Table 1.

Antifungal Susceptibility and Resistance Patterns of Candida Isolates from Different Clinical Specimens.

Antifungal Agent	Sputum (n=893)		ENT Organs (n=277)		Cerebral Canal (n=50)	
	Sus	Res	Sus	Res	Sus	Res
Anidulafungin	647 (72.5%)	246 (27.5%)	174 (62.8%)	103 (37.2%)	38 (76.0%)	12 (24.0%)
Micafungin	649 (72.7%)	244 (27.3%)	170 (61.4%)	107 (38.6%)	35 (70.0%)	15 (30.0%)
Voriconazole	587 (65.7%)	306 (34.3%)	165 (59.6%)	112 (40.4%)	33 (66.0%)	17 (34.0%)
Caspofungin	640 (71.7%)	253 (28.3%)	167 (60.3%)	110 (39.7%)	32 (64.0%)	18 (36.0%)
Fluconazole	702 (78.6%)	191 (21.4%)	178 (64.3%)	99 (35.7%)	40 (80.0%)	10 (20.0%)

Fluconazole showed the highest overall susceptibility, particularly in isolates from sputum (78.6%) and cerebrospinal fluid (80.0%). Among the echinocandins, Anidulafungin and Micafungin demonstrated relatively high activity, especially in cerebrospinal isolates (76.0% and 70.0%, respectively). In contrast, susceptibility to Voriconazole and Caspofungin was moderate across all sample types, with lower rates observed in ENT isolates.

Table 2 offers a side-by-side comparison of the three most effective antifungal agents for each type of clinical specimen. Across all materials, fluconazole consistently emerged as the most active agent. In sputum samples, it reached a sensitivity of 78,6%, closely followed by micafungin (72,7%) and anidulafungin (72,5%). When considering ENT organ isolates, fluconazole again led with 64,3%, then anidulafungin (62,8%), and caspofungin (60,3%) not far behind. What's particularly noteworthy is that isolates from the cerebrospinal canal exhibited the highest overall antifungal susceptibility: fluconazole showed 80,0%, followed by anidulafungin (76,0%) and micafungin (70,0%).

Table 2.

Comparative Analysis of the Most Effective Antifungal Agents by Biological Source of Isolation.

Biological Material	1st Position	2nd Position	3rd Position
Sputum (n=893)	Fluconazole (78.6 %)	Micafungin (72.7 %)	Anidulafungin (72.5 %)
ENT Organs (n=277)	Fluconazole (64.3 %)	Anidulafungin (62.8 %)	Caspofungin (60.3 %)
Cerebral Canal (n=50)	Fluconazole (80.0 %)	Anidulafungin (76.0 %)	Micafungin (70.0 %)

Table 3 summarizes the three antifungal agents associated with the highest levels of resistance among fungal isolates from different biological materials. The results indicate a notable variability in resistance profiles depending on the source of isolation, although certain agents, particularly voriconazole and caspofungin, consistently demonstrated higher resistance rates across multiple specimen types. In respiratory samples (sputum), voriconazole showed the highest proportion of resistant isolates (34.3%), followed by caspofungin (28.3%) and anidulafungin (27.5%). Among isolates from ENT organs, voriconazole again ranked first (40.4%), with caspofungin (39.7%) and micafungin (38.6%) close behind highlighting a relatively high resistance burden in this localization. Isolates obtained from the cerebrospinal canal demonstrated a slightly different pattern: caspofungin exhibited the highest resistance (36.0%), followed by voriconazole (34.0%) and micafungin (30.0%).

Table 3.

Top Three Antifungal Agents with the Highest Resistance by Biological Source of Isolation.

Biological Material	1st Position	2nd Position	3rd Position
Sputum (n=893)	Voriconazole (34.3 %)	Caspofungin (28.3 %)	Anidulafungin (27.5 %)
ENT Organs (n=277)	Voriconazole (40.4 %)	Caspofungin (39.7 %)	Micafungin (38.6 %)
Cerebral Canal (n=50)	Caspofungin (36.0 %)	Voriconazole (34.0 %)	Micafungin (30.0 %)

Figure 1 presents a comparative analysis of Candida susceptibility to five antifungal agents across three biological sources: sputum, ENT organs, and cerebrospinal canal. Across all specimen types, fluconazole demonstrated the highest overall effectiveness, with sensitivity rates ranging from 64.3% (ENT) to 80.0% (cerebral canal). This confirms its broad-spectrum activity and continued relevance in empirical antifungal therapy. Among the echinocandins, anidulafungin and micafungin exhibited comparable efficacy. In particular, anidulafungin showed high activity in cerebrospinal isolates (76.0%) and sputum samples (72.5%), while micafungin showed slightly better performance in respiratory isolates (72.7%). Caspofungin displayed moderate activity across all materials, with sensitivity ranging from 60.3% to 71.7%. Voriconazole, though still active, consistently demonstrated the lowest susceptibility rates in all sample types, particularly in ENT-derived isolates (59.6%).

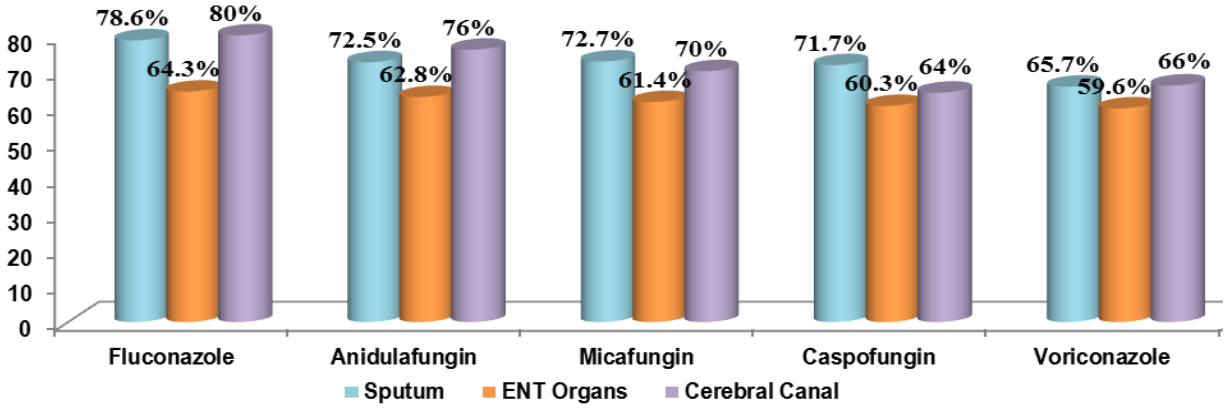

Figure 1. Comparative Susceptibility of Candida Isolates to Antifungal Agents Across Biological Materials.

Figure 2 presents the resistance percentages of five antifungal agents across three biological materials: sputum, ENT organs, and the cerebral canal. Voriconazole exhibits the highest resistance rates among the antifungals tested, with 34.3% resistance in sputum samples, 40.4% in ENT organ isolates, and 34% in the cerebral canal. Caspofungin follows closely, showing 28.3% resistance in sputum, 39.7% in ENT organs, and the highest resistance in the cerebral canal at 36%. Micafungin and anidulafungin demonstrate similar resistance profiles. Micafungin's resistance ranges

from 27.3% in sputum to 30% in the cerebral canal, while anidulafungin shows 27.5% resistance in sputum, increasing to 37.2% in ENT organs, but a lower 24% in the cerebral canal. Fluconazole has the lowest resistance rates across all sample types, with 21.4% in sputum, 35.7% in ENT organs, and 20% in the cerebral canal.

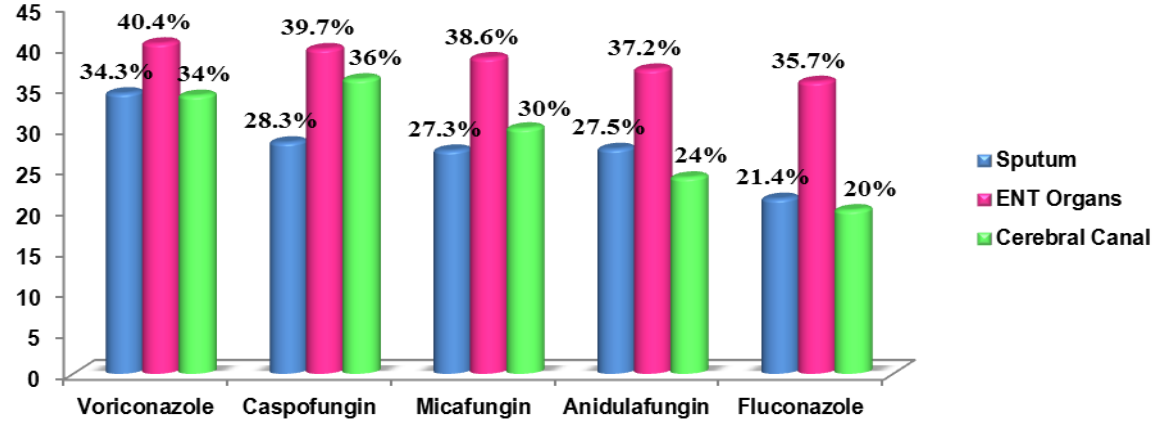

Figure 2. Antifungal Resistance Rates by Specimen Type.

Figure 3 shows the average susceptibility and resistance rates of five antifungal drugs based on data from various clinical samples. Fluconazole demonstrated the highest susceptibility at 75.4%, with the lowest resistance rate of 24.6%, indicating strong overall effectiveness. Anidulafungin and micafungin showed similar susceptibility rates of 70.4% and 70%, respectively, with corresponding resistance rates of 29.6% and 30%. Caspofungin had a slightly lower susceptibility at 68.8% and a resistance rate of 31.2%. Voriconazole showed the lowest susceptibility at 64.3% and the highest resistance rate of 35.7%, suggesting reduced effectiveness against Candida compared to the other antifungals.

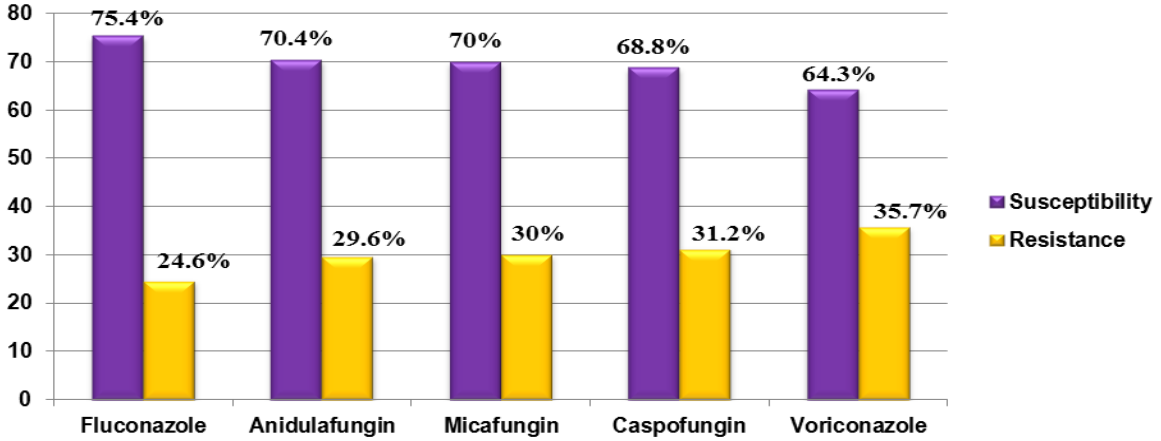

Figure 3. Average Susceptibility and Resistance Rates of Five Antifungal Agents.

Discussion

Our results confirm that Candida species show different antifungal susceptibility depending on the type of clinical sample. Isolates from cerebrospinal fluid had the highest susceptibility rates, especially to fluconazole (80.0%) and echinocandins like anidulafungin (76.0%) and micafungin (70.0%). On the other hand, samples from the ENT area and respiratory tract showed much higher resistance, particularly to voriconazole and caspofungin. This highlights the importance of considering the sample type when analyzing susceptibility results and choosing the right antifungal treatment.

Our results align with those presented by Parslow and Thornton (2022), who reported that Candida isolates from respiratory samples and non-sterile body sites showed higher resistance rates, especially among non-albicans Candida species [11]. Similarly, CDC surveillance data (*Toda et al.,* 2019) showed that bloodstream isolates were generally more susceptible to antifungals, whereas those from mucosal sites and devices exhibited reduced susceptibility consistent with our findings showing higher resistance in ENT and respiratory specimens [16].

Fisher et al. emphasized that antifungal resistance is shaped by site-specific factors such as prior drug exposure, local immune conditions, and the presence of biofilms. This is particularly relevant in ENT and respiratory tracts, where chronic colonization and topical azole use may promote the emergence of resistant strains [7]. Tellapragada et al. also demonstrated intra-species variability: C. albicans isolates from vaginal samples were significantly less susceptible to azoles than those from bloodstream infections [15].

Further evidence is provided by *Turan et al.* (2024), who found that C. albicans strains from the genitourinary tract had higher resistance to fluconazole and miconazole compared to blood-derived isolates [17]. El-Houssaini et al. (2019) reported similar trends in Egypt, where respiratory isolates displayed combined resistance to azoles and echinocandins [5]. These findings corroborate our observations that ENT-derived isolates exhibited the lowest susceptibility rates across all five antifungal agents tested.

Nett et al. (2015) provided mechanistic insight into this phenomenon, showing that Candida biofilms associated with catheters and mucosal surfaces confer significant resistance to echinocandins due to protective matrix formation [9]. *Berkow and Lockhart* (2017) further support this, noting that isolates from skin and mucosal tissues were more frequently resistant to fluconazole compared to those from sterile sites [2].

More recent studies continue to support these findings. *Shafiekhani et al.* observed that among solid organ transplant recipients, respiratory isolates contained the highest proportions of rare and multidrug-resistant Candida species [14]. Ashraf et al. showed that urinary catheter and respiratory isolates in India had higher resistance rates than those from CSF and blood, which were generally susceptible [1]. *Velmani et al.* also confirmed that C. auris exhibited the highest levels of resistance in respiratory and urogenital specimens, particularly to azoles. *Likewise [18]. Zhang et al.* found that C. parapsilosis strains from skin and catheter-associated sites were significantly more resistant than bloodstream isolates, which remained broadly susceptible [20].

The clinical source of Candida isolates has increasingly been recognized as a critical factor influencing antifungal susceptibility. Resistance patterns among Candida spp. are not only species-specific but also vary significantly depending on the site of isolation. Mucosal and respiratory tract isolates frequently exhibit higher resistance, while isolates from sterile sites such as bloodstream and cerebrospinal fluid tend to be more susceptible, particularly to echinocandins. These differences are often attributed to local drug exposure and biofilm formation at colonized sites [11].

Recent research on Candida auris has further demonstrated the complexity of antifungal resistance. This species displays clade-specific resistance traits, with less pronounced variation by body site, suggesting a primarily genetic basis for its multidrug-resistant phenotype [12]. Other studies have found that resistance to fluconazole and echinocandins can develop through both natural and acquired mechanisms. This is especially true for isolates from skin and mucous membranes, where biofilm formation creates a protective layer that greatly lowers the effectiveness of antifungal treatments [2].

Limitations

This study has several important limitations. First, because it was retrospective, we weren't able to include certain clinical details that could affect antifungal resistance — such as patients' prior use of antifungals, existing medical conditions, or full treatment histories. Second, we did not identify Candida isolates to the species level, which limited our ability to pinpoint species-specific resistance trends. Finally, since all the data were collected from one geographic region, the findings may not fully apply to other areas or diverse patient populations.

Recommendations

To better understand patterns of antifungal resistance, future research should use prospective designs and include species-level identification of Candida isolates, along with molecular testing methods. It's also important to track clinical outcomes, so we can link resistance patterns to actual treatment effectiveness. Exploring how infection site, resistance mechanisms, and drug activity interact will help refine treatment guidelines and improve patient care.

Conclusion

Our findings show a clear link between antifungal susceptibility and the site from which Candida isolates were obtained. Fluconazole showed the highest effectiveness overall, especially in samples from cerebrospinal fluid reinforcing its value in treating CNS infections. On the other hand, voriconazole had the lowest susceptibility and the highest resistance rates, particularly in ear, nose, and throat (ENT) samples. These results are in line with previous studies and emphasize the need to consider both the infection site and species type when selecting antifungal treatments. This approach can improve treatment accuracy and help reduce antifungal resistance in clinical practice.

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ASSESSMENT OF QUALITY OF LIFE IN HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY USING THE STANDARDIZED SF-36 INSTRUMENT

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Abstract

Background: With the advancement of antiretroviral therapy (ART), HIV infection has shifted from being a fatal disease to a chronic and manageable condition. In this context, not only the virological response but also the patients' quality of life becomes an important indicator of treatment effectiveness. Studying this aspect allows for a comprehensive assessment of the health status of people living with HIV and helps identify key areas that require additional medical and psychosocial support.

Objective: To assess the quality of life of HIV-positive patients receiving antiretroviral therapy, with an emphasis on physical, mental, and social well-being, and to identify factors limiting daily and professional activities.

Materials and Methods: The study included 70 patients with a confirmed diagnosis of HIV infection who had been on ART for at least 6 months. The standardized SF-36 questionnaire was used to assess eight key domains of quality of life. Data were analyzed using descriptive statistics with Microsoft Excel and SPSS. The study was approved by the Ethics Committee, and all participants signed informed consent forms.

Results: The analysis revealed that the overall quality of life of HIV-positive patients can be considered satisfactory. The highest average scores were observed in the domains of physical functioning (79.2 ± 20.9), role limitations due to physical health (79.7 ± 26.5), and emotional role functioning (79.5 ± 28.6), indicating relatively preserved physical and social activity. The lowest scores were recorded in general health perception (49.7 ± 11.3) and mental health (71.5 ± 16.3), suggesting psychological distress and emotional exhaustion. Moderate scores in vitality (63.9 ± 16.9) also indicate frequent fatigue. Emotional and physical challenges affected the performance of daily and work-related tasks for some participants, despite overall maintained social involvement.

Conclusion: The quality of life of HIV-positive patients on ART is generally satisfactory; however, the identified challenges in mental and general health emphasize the need for a comprehensive care approach. It is recommended to expand psychosocial support and physical rehabilitation programs to improve overall well-being and daily functioning.

Keywords: *HIV, antiretroviral therapy, quality of life, SF-36.*

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Резюме

ОЦЕНКА КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ С ВИЧ-ИНФЕКЦИЕЙ, НАХОДЯЩИХСЯ НА АНТИРЕТРОВИРУСНОЙ ТЕРАПИИ, С ИСПОЛЬЗОВАНИЕМ СТАНДАРТИЗИРОВАННОГО ИНСТРУМЕНТА SF-36

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Введение: С развитием антиретровирусной терапии (АРТ) ВИЧ-инфекция из фатального заболевания превратилась в хроническое, контролируемое состояние. При этом важным показателем эффективности лечения становится не только вирусологический ответ, но и качество жизни пациентов. Изучение этого аспекта позволяет комплексно оценить состояние здоровья ВИЧ-положительных лиц и выявить ключевые области, требующие дополнительной медицинской и психосоциальной поддержки.

Цель: Оценить качество жизни ВИЧ-положительных пациентов, находящихся на антиретровирусной терапии, с акцентом на физическое, психическое и социальное здоровье, а также определить факторы, ограничивающие повседневную и профессиональную активность.

Материалы и методы: В исследование включены 70 пациентов с подтвержденным диагнозом ВИЧ-инфекции, находящихся на АРТ не менее 6 месяцев. В качестве инструмента оценки использовался стандартизированный опросник SF-36, охватывающий восемь ключевых доменов качества жизни. Обработка данных проводилась с использованием описательной статистики в Microsoft Excel и SPSS. Исследование было одобрено этическим комитетом, все участники подписали информированное согласие.

Результаты: Анализ показал, что общее качество жизни ВИЧ-положительных пациентов можно охарактеризовать как удовлетворительное. Наивысшие средние баллы зафиксированы по шкале физического функционирования (79,2 ± 20,9), роли физического состояния (79,7 ± 26,5) и роли эмоционального состояния (79,5 ± 28,6), что свидетельствует о хорошей сохранности физической и социальной активности. Наименьшие средние значения были зафиксированы по шкале общего состояния здоровья (49,7 ± 11,3) и психического здоровья (71,5 ± 16,3), что может свидетельствовать о наличии эмоционального выгорания и психологического напряжения. Показатели жизнеспособности (63,9 ± 16,9) указывают на склонность к быстрой утомляемости. Несмотря на сохранение социальной активности у большинства участников, эмоциональные и физические трудности оказывали влияние на выполнение ими повседневных и профессиональных обязанностей.

Выводы: Качество жизни ВИЧ-положительных пациентов на АРТ в целом является удовлетворительным, однако выявленные проблемы в сфере психического и общего здоровья подчеркивают необходимость внедрения комплексного подхода к ведению таких пациентов. Рекомендуется расширить программы психосоциальной поддержки и физической реабилитации для повышения общего уровня здоровья и адаптации к повседневной жизни.

Ключевые слова: *ВИЧ, антиретровирусная терапия, качество жизни, SF-36.*

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Түйіндеме

АНТИРЕТРОВИРУСТЫҚ ТЕРАПИЯ ҚАБЫЛДАП ЖҮРГЕН ВИЧ-ИНФЕКЦИЯСЫ БАР ПАЦИЕНТТЕРДІҢ ӨМІР САПАСЫН SF-36 СТАНДАРТТАЛҒАН ҚҰРАЛЫН ҚОЛДАНА ОТЫРЫП БАҒАЛАУ

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Кіріспе: Антиретровирустық терапияның (АРТ) дамуы ВИЧ-инфекциясын өлімге әкелетін аурудан созылмалы және бақыланатын жағдайға айналдырды. Бұл жағдайда емнің тиімділігінің маңызды көрсеткіші ретінде тек вирологиялық жауап қана емес, сонымен қатар пациенттердің өмір сапасы да қарастырылады. Осы аспектіні зерттеу ВИЧ-пен өмір сүретін адамдардың денсаулық жағдайын кешенді бағалауға және қосымша медициналық әрі психоәлеуметтік қолдауды қажет ететін маңызды салаларды анықтауға мүмкіндік береді.

Мақсаты: Антиретровирустық терапия қабылдап жүрген ВИЧ-позитивті пациенттердің өмір сапасын физикалық, психикалық және әлеуметтік жағдайларына көңіл бөле отырып бағалау және олардың күнделікті және кәсіби қызметіне әсер ететін шектеуші факторларды анықтау.

Материалдар мен әдістер: Зерттеуге ВИЧ диагнозы расталған және АРТ қабылдап жүрген, кемінде 6 ай емделіп жатқан 70 пациент қатысты. Өмір сапасын бағалау үшін SF-36 стандартталған сауалнамасы қолданылды, ол сапаның сегіз негізгі саласын қамтиды. Мәліметтер Microsoft Excel және SPSS бағдарламалары арқылы сипаттамалық статистика әдістерімен өңделді. Зерттеу этикалық комитет тарапынан мақұлданып, барлық қатысушылар жазбаша түрде келісім берді.

Нәтижелер: Талдау нәтижелері бойынша ВИЧ-позитивті пациенттердің жалпы өмір сапасы қанағаттанарлық деп бағаланды. Ең жоғары орташа көрсеткіштер физикалық функция (79,2 ± 20,9), физикалық жағдай әсері (79,7 ± 26,5) және эмоционалдық жағдай әсері (79,5 ± 28,6) шкалаларында тіркелді, бұл физикалық және әлеуметтік белсенділіктің сақталғанын көрсетеді. Ал денсаулықты жалпы қабылдау (49,7 ± 11,3) және психикалық денсаулық (71,5 ± 16,3) шкалаларында ең төмен баллдар тіркелді, бұл психологиялық күйзеліс пен эмоционалдық шаршауды білдіреді. Тіршілік қабілетінің орташа көрсеткіші (63,9 ± 16,9) шаршағыштықтың жиі кездесетінін көрсетті. Кейбір пациенттерде эмоционалдық және физикалық қиындықтар күнделікті және кәсіби міндеттерді орындауға әсер етті, дегенмен әлеуметтік белсенділік негізінен сақталған.

Қорытынды: АРТ қабылдайтын ВИЧ-позитивті пациенттердің өмір сапасы жалпы алғанда қанағаттанарлық. Дегенмен психикалық және жалпы денсаулық салаларындағы анықталған мәселелер бұл пациенттерді кешенді түрде қолдау қажеттігін көрсетеді. Психоәлеуметтік көмек пен физикалық оңалту бағдарламаларын кеңейту ұсынылады, бұл пациенттердің жалпы жағдайын жақсартуға және күнделікті өмірге бейімделуіне мүмкіндік береді.

Кілт сөздер: *ВИЧ, антиретровирустық терапия, өмір сапасы, SF-36.*

Дәйексөз үшін:

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Introduction

Human immunodeficiency virus (HIV) remains one of the leading threats to global public health. Since the beginning of the epidemic, more than 42.3 million people have died from HIV-related illnesses, and transmission of the virus continues in many parts of the world [2, 21]. According to the World Health Organization (WHO), by the end of 2022, an estimated 39 million people were living with HIV globally, with 25.6 million of them residing in the African Region [2].

UNAIDS reports that in 2023 alone, 1.3 million new HIV infections were recorded, and 630,000 deaths were attributed to HIV/AIDS-related causes [21]. WHO notes that a significant proportion of new infections—approximately 65%—occurs among key populations and their sexual partners. The epidemic has a particularly severe impact on women and girls: in sub-Saharan Africa, young women aged 15–24 account for a quarter of all new infections, despite representing only 10% of the region's population [21].

According to UNAIDS, since the first detection of HIV, a total of 88.4 million infections have been reported worldwide, with 42.3 million deaths resulting from HIV-related diseases. As of 2023, approximately 39.9 million people globally are living with HIV, and 30.7 million of them are receiving antiretroviral therapy (ART). That same year, 1.3 million new infections and 630,000 AIDS-related deaths were recorded [22].

Thanks to the development and widespread use of ART, HIV infection has transitioned from a fatal disease to a manageable chronic condition. Effective ART significantly reduces viral load, increases CD4+ lymphocyte counts, and consequently improves clinical outcomes and patient survival [18, 5]. Today, the primary goal of treatment is not only to extend life expectancy but also to enhance quality of life.

However, the effectiveness of therapy is not limited to viral suppression alone. Modern treatment approaches also prioritize improving patients' quality of life (QoL), which has become a key component in the comprehensive assessment of the health status of people living with HIV [7, 11].

The quality of life of HIV-positive individuals is influenced by a variety of factors, including ART-related side effects, the level of social support, experiences of stigma, mental and emotional well-being, socioeconomic status, and adherence to therapy [17, 8].

The concept of quality of life reflects a patient's overall physical, psychological, and social well-being and serves as an important indicator of treatment success. Studies have shown that QoL among people living with HIV is affected by a wide range of factors, including adverse effects of ART, social support systems, psychological health, stigma, and economic conditions [7, 8].

The most reliable tools for assessing QoL are standardized questionnaires such as the WHOQOL-HIV BREF and SF-36. These instruments are widely used across countries and have demonstrated strong associations between clinical, behavioral, and social factors and the quality of life in people living with HIV [11].

Evaluating QoL is becoming increasingly important in the current epidemiological context, where HIV is increasingly regarded as a chronic condition requiring a systematic and integrated approach. As noted in the study by Zhuravlyova I.V. (2023), integrating QoL assessment into clinical practice enables a more comprehensive evaluation of treatment success and the quality of care provided [3].

In this context, the present study aims to assess the quality of life of HIV-positive patients receiving antiretroviral therapy, with particular attention to their physical, psychosocial, and social well-being.

Materials and Methods

The study included patients with a confirmed diagnosis of HIV infection who had been receiving antiretroviral therapy (ART) for at least six months. Inclusion criteria were age over 18 years and the provision of written informed consent to participate in the study.

Data collection was conducted using the standardized SF-36 (Short Form Health Survey), a 36-item questionnaire designed to assess eight key domains of quality of life: physical functioning, role limitations due to physical health, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. Each domain was scored on a scale from 0 to 100, with lower scores indicating poorer quality of life and higher scores reflecting better well-being.

The questionnaire was linguistically and methodologically adapted and validated for use in Russian by the Institute for Clinical and Pharmacological Research (St. Petersburg), ensuring its appropriateness in the Russian-speaking context. During the study, participants completed the survey, after which the responses were compiled, systematized, and prepared for statistical analysis.

Statistical Analysis

All data were presented as absolute numbers (n) and percentages (%). Descriptive statistics were used for data analysis. Proportions, category summaries, and result interpretation were presented in tabular form. Statistical analysis was conducted using Microsoft Excel and SPSS software.

Ethical Considerations

The study was approved by the Ethics Committee of the Semey Medical University (Protocol No. 1b, dated October 25, 2024) and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to completing the questionnaire. Anonymity and confidentiality of participant data were strictly maintained.

Results

The analysis of SF-36 scores indicated that the overall quality of life among HIV-positive patients can be considered generally satisfactory. The highest mean scores were observed in the domains of Physical Functioning (PF – 79.2 ± 20.9), Role Limitations due to Physical Health (RP – 79.7 ± 26.5), and Role Limitations due to Emotional Problems (RE – 79.5 ± 28.6), reflecting a relatively preserved level of physical activity and capacity for social engagement. However, lower scores were recorded in the domains of General Health Perception (GH – 49.7 ± 11.3) and Mental Health (MH – 71.5 ± 16.3), suggesting the presence of emotional strain, a reduced subjective perception of health, and possible psycho-emotional exhaustion. Moderate scores in the Vitality domain (VT – 63.9 ± 16.9) further indicate fatigue and diminished energy levels.The mean SF-36 domain scores are presented in Table 1.

Table 1.

Mean SF-36 Scores Among HIV-Positive Patients.

SF-36 Components	Mean Score (M ± SD)
Physical Functioning (PF)	79.2 ± 20.9
Role Limitations due to Physical Health (RP)	79.7 ± 26.5
Bodily Pain (BP)	76.0 ± 22.9
General Health (GH)	49.7 ± 11.3
Vitality (VT)	63.9 ± 16.9
Social Functioning (SF)	74.5 ± 20.5
Role Limitations due to Emotional Problems (RE)	79.5 ± 28.6
Mental Health (MH)	71.5 ± 16.3

Table 2 reflects the extent of physical activity limitations among the participants. Specifically, 44.3% reported that moderate physical tasks, such as house cleaning, cause only minor difficulties, while 17.1% experienced significant challenges when performing heavy physical activities. At the same time, the majority of respondents did not report limitations in performing everyday tasks: 68.6% were able to lift grocery bags without difficulty, 77.1% could climb one flight of stairs with ease, and 68.6% reported no issues with taking long walks. Most participants also indicated no difficulty with personal hygiene and dressing, with only 10% reporting significant limitations in these basic self-care activities.

Table 2.

Health Assessment and Physical Activity Limitations Among Study Participants.

Type of Physical Activity	Response Option	n	%
Heavy physical activities (e.g., running, lifting heavy objects)	Severely limited	12	17.1%
	Slightly limited	31	44.3%
	Not limited	27	38.6%
Moderate physical activities (e.g., moving furniture, vacuuming, berry picking)	Severely limited	5	7.1%
	Slightly limited	18	25.7%
	Not limited	47	67.1%
Lifting or carrying a grocery bag	Severely limited	6	8.6%
	Slightly limited	16	22.9%
	Not limited	48	68.6%
Climbing several flights of stairs	Severely limited	4	5.7%
	Slightly limited	22	31.4%
	Not limited	44	62.9%
Climbing one flight of stairs	Severely limited	6	8.6%
	Slightly limited	10	14.3%
	Not limited	54	77.1%
Bending, kneeling, or squatting	Severely limited	6	8.6%
	Slightly limited	10	14.3%
	Not limited	54	77.1%
Walking more than 1 kilometer	Severely limited	3	4.3%
	Slightly limited	19	27.1%
	Not limited	48	68.6%
Walking several blocks	Severely limited	8	11.4%
	Slightly limited	22	31.4%
	Not limited	40	57.1%
Walking one block	Severely limited	6	8.6%
	Slightly limited	18	25.7%
	Not limited	46	65.7%
Bathing or dressing yourself	Severely limited	7	10.0%
	Slightly limited	4	5.7%
	Not limited	59	84.3%

Table 3 illustrates the impact of participants' physical and emotional health on their ability to carry out daily activities and professional responsibilities over the past four weeks. Regarding physical health, 84.3% of respondents reported that it did not affect the amount of time they spent on work. However, 25.7% stated they accomplished less than they would have liked, and 18.6% reported being limited in the types of work they could perform. Emotional difficulties affected 20% of participants by reducing the amount of time they could dedicate to tasks, while 31.4% completed less than they intended. Nonetheless, 82.9% indicated that their emotional state did not affect the accuracy or quality of their work.

Table 3.

Impact of Physical and Emotional Health on Work and Daily Activities.

Question	Response Option	n	%
Had to reduce time spent on work or activities (physical condition)	Yes	11	15.7%
	No	59	84.3%
Did less than desired (physical condition)	Yes	18	25.7%
	No	52	74.3%
Were limited in the type of work or activities performed	Yes	13	18.6%
	No	57	81.4%
Had difficulties performing work or daily tasks (physical condition)	Yes	15	21.4%
	No	55	78.6%
Had to reduce time spent on work or activities (emotional condition)	Yes	14	20.0%
	No	56	80.0%
Did less than desired (emotional condition)	Yes	22	31.4%
	No	48	68.6%
Work or daily tasks were performed less carefully (emotional condition)	Yes	12	17.1%
	No	58	82.9%

Table 4 presents data on how frequently participants experienced feelings of vigor, nervousness, depression, calmness, energy, fatigue, discouragement, happiness, and tiredness over the past four weeks. According to the survey results, 40% of respondents reported feeling happy all the time, while 22.9% felt vigorous most of the time. Additionally, 42.9% indicated they had not experienced feelings of depression or sadness at all. Negative emotions were reported less frequently: 44.3% experienced nervousness only occasionally, and 24.3% reported episodic feelings of depression. Over the last four weeks, 24.3% of participants did not feel fatigued, and 35.7% did not experience feelings of discouragement. Moreover, 34.3% of respondents felt calm and at peace most of the time, while 21.4% experienced a surge of energy and strength.

Table 4.

Frequency of Various Emotional States and Moods in the Past 4 Weeks

Question	Most of the Time	All the Time	Sometimes	Rarely	Often	Never
Did you feel vigorous?	16 (22.9%)	13 (18.6%)	21 (30.0%)	2 (2.9%)	15 (21.4%)	3 (4.3%)
Did you feel very nervous?	3 (4.3%)	3 (4.3%)	31 (44.3%)	18 (25.7%)	6 (8.6%)	9 (12.9%)
Did you feel so depressed that nothing could cheer you up?	3 (4.3%)	3 (4.3%)	17 (24.3%)	20 (28.6%)	2 (2.9%)	25 (35.7%)
Did you feel calm and peaceful?	24 (34.3%)	12 (17.1%)	6 (8.6%)	8 (11.4%)	15 (21.4%)	5 (7.1%)
Did you feel full of energy and strength?	15 (21.4%)	15 (21.4%)	15 (21.4%)	8 (11.4%)	15 (21.4%)	2 (2.9%)
Did you feel worn out?	2 (2.9%)	3 (4.3%)	17 (24.3%)	17 (24.3%)	7 (10.0%)	24 (34.3%)
Did you feel downhearted and blue?	3 (4.3%)	1 (1.4%)	14 (20.0%)	22 (31.4%)	-	30 (42.9%)
Did you feel happy?	13 (18.6%)	28 (40.0%)	9 (12.9%)	5 (7.1%)	15 (21.4%)	-
Did you feel tired?	7 (10.0%)	3 (4.3%)	29 (41.4%)	14 (20.0%)	9 (12.9%)	8 (11.4%)

Table 5 describes how respondents assess various aspects of their health. The majority of participants (30%) reported that their physical or emotional condition never interfered with social interactions, while 27.1% experienced this sometimes, and 31.4% rarely. Only 8.6% of respondents stated that their condition interfered with socializing most of the time. Regarding health perception, 44.3% of participants believe they are definitely not prone to illness, whereas 31.4% mostly disagree with this statement. Meanwhile, 28.6% firmly believe their health is no worse than that of most acquaintances, while 21.4% consider this statement definitely untrue. At the same time, more than half of the participants (51.4%) do not expect their health to worsen in the future, and 41.4% consider their health to be excellent.

Table 5.

Impact of Physical or Emotional Health on Social Interaction and Health Perception.

Statement	Definitely True (%, n)	Mostly True (%, n)	Don't Know (%, n)	Mostly False (%, n)	Definitely False (%, n)
I feel that I am more prone to illness than others	2.9% (2)	4.3% (3)	17.1% (12)	31.4% (22)	44.3% (31)
My health is no worse than that of most of my acquaintances	28.6% (20)	18.6% (13)	20.0% (14)	11.4% (8)	21.4% (15)
I expect my health to get worse	1.4% (1)	5.7% (4)	24.3% (17)	17.1% (12)	51.4% (36)
I have excellent health	41.4% (29)	34.3% (24)	11.4% (8)	8.6% (6)	4.3% (3)

Discussion

Our analysis, conducted using the SF-36 questionnaire, showed that the overall quality of life (QoL) of HIV-positive patients receiving antiretroviral therapy (ART) is generally satisfactory, particularly in the domains of physical functioning and social activity. However, low scores in general health and mental health indicate the presence of psychological distress and chronic fatigue in some patients. Many participants experience limitations in performing physically demanding work, as well as emotional difficulties affecting their daily and professional activities.

The results of our study align with numerous scientific data indicating that initiation and continuation of ART lead to significant improvements in QoL across most SF-36 domains: physical health, general health, social and psychological functioning. The most pronounced positive changes are observed within 6–12 months after starting therapy [9,13].

For example, in a prospective study conducted in Brazil (2016–2018) using SF-36 and HAT-QoL scales, 91 patients (mean age 35.3 ± 10.7 years, 78% male) demonstrated significant improvement at 12 months after ART initiation in scales such as Physical Function, General Health, Social Functioning, and Mental Health (all $p < 0.001$), as well as Mental Component Summary ($p = 0.004$). Significant changes in HAT-QoL were observed in domains including Overall Function, Life Satisfaction, Sexual Function, and Provider Trust. Multiple regression analysis revealed that gender, age, income level, and presence of a partner influence physical and mental components of QoL [9].

Similar findings are supported by other studies, including work by Kariwala et al. (2022), which assessed QoL changes before and after therapy initiation using SF-36. Significant improvement across all scales was observed just 6 months after starting ART [13].

In two large international clinical trials involving more than 1,050 patients, it was found that mean QoL scores for physical and mental components improved within 1–4 months of therapy and remained stable over one year. Patients with high adherence (≥95%) demonstrated significantly better SF-36 domain scores compared to those with adherence below 80%, who instead showed worsening QoL [16].

The study by *Pimentel et al.* (2020) in Brazil also demonstrated substantial improvement in most QoL domains after 6 months of ART. Factors such as religious beliefs, cohabitation, and low levels of anxiety and depression positively influenced these outcomes. Conversely, the presence of therapy side effects was associated with worsened QoL, highlighting the need for a comprehensive approach in managing HIV patients, including psychological support and monitoring for adverse reactions [19].

A 2023 study published in *The Lancet HIV*, including a cohort of 206,891 patients receiving long-term ART in Europe and North America, showed that the expected life expectancy for women who started therapy after 2015 is 39 years, and 37 years for men (at age 40). For patients who began therapy before 2015, these figures were significantly lower. Moreover, patients with low CD4+ counts at therapy initiation had a reduced life expectancy, emphasizing the importance of early detection and treatment initiation [20].

The Strategic Timing of Antiretroviral Therapy (START) study demonstrated that immediate initiation of ART in patients with CD4+ counts above 500 cells/μL leads to more significant improvements in quality of life (QoL) compared to deferred therapy. Over an average follow-up period of three years, patients who started treatment immediately showed significant improvements in perceived general health as well as physical and mental QoL components compared to the deferred group. These improvements were consistent across all demographic and clinical subgroups, underscoring the robustness of the effect. Although patients experiencing primary adverse events had lower QoL scores, excluding such patients from the analysis did not change the overall positive trend favoring immediate treatment initiation [15].

In 2009, the New England Journal of Medicine published results of the CIPRAHT001 study conducted among 816 HIV-infected residents of Haiti. Patients were randomized into two groups: immediate therapy initiation and deferred therapy. Participants in the deferred group had twice the incidence of tuberculosis and four times higher mortality, confirming the importance of timely treatment initiation [12]. Additional large studies (SMART, NA-ACCORD) also demonstrated that delayed ART groups had a fivefold higher risk of mortality and AIDS-defining illnesses; in NA-ACCORD, mortality was 94% higher [10,14].

Adherence to therapy is emphasized as a key factor in successful disease control. According to a Russian study by *V.D. Vasilyev et al.* (2021), patients with high adherence show significantly better SF-36 scores, especially in physical and mental functioning domains [6].

Further data highlight the importance of gender and social factors. For example, T.I. Kolesnikova (2019) reported that HIV-positive women of reproductive age require additional support programs, including psychological and reproductive care, which contribute to improved quality of life and social adaptation [1].

A review by *R.A. Tursunov et al.* (2018) emphasizes that timely ART initiation within the “treatment as prevention” strategy effectively reduces infection spread, especially among key populations [4].

Based on the findings, the implementation of integrated psychological support programs for people living with HIV is recommended due to the identified pronounced emotional difficulties and signs of psycho-emotional burnout. Early diagnosis and immediate ART initiation are crucial as they help reduce the risk of physical limitations and improve quality of life. Physical rehabilitation programs are also beneficial for those experiencing mobility issues. Regular monitoring of patients’ psycho-emotional status will allow timely detection and management of deteriorations. Maintaining patients’ social activity is important, as it contributes to better mood and overall quality of life.

Limitations

While our study provides valuable insights into the quality of life of HIV-positive patients on antiretroviral therapy, there are a few limitations to keep in mind. First, the sample size was relatively small and drawn from a specific population, which might limit how well the results apply to other groups or regions. Also, since the data relied on self-reported questionnaires, there’s always the chance

of bias—people might overestimate or underestimate their symptoms or feelings. Another point is that the study was cross-sectional, so it gives a snapshot in time but doesn't capture changes over longer periods

Conclusion

The results of the present study indicate that the overall quality of life of HIV-infected patients receiving antiretroviral therapy can be considered satisfactory, with preservation of a significant portion of physical and social functions. At the same time, substantial psychological difficulties were revealed, including decreased general and mental health levels, as well as frequent complaints of fatigue and exhaustion. These data point to the need for a comprehensive approach to patient management that, alongside medication, should include psychotherapeutic support and interventions for physical rehabilitation. Such an approach may contribute not only to improved quality of life but also to better adaptation of patients to daily and professional activities.

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THE CURRENT STATE OF VIRTUAL AUTOPSY USING INTEGRATED VISUALIZATION TECHNOLOGIES

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Abstract

Relevance. Virtual autopsy is positioned as a non-invasive method of postmortal examination, which provides objectively verifiable forensic data without the need for a traditional autopsy.

The **aim** of this study was to evaluate the diagnostic value of virtual autopsy (virtopsy) as an alternative to traditional medical autopsy in patients undergoing intensive care in the anesthesiology intensive care unit (ICU).

Materials and methods: Study design: Prospective study. Multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), 3D image reconstruction, and histological assessment performed under the supervision of certified specialists. Diagnostic data from virtual autopsy were compared with clinical diagnoses and the results of traditional forensic examination, which allowed us to evaluate the accuracy and completeness of the identified pathologies.

Results: Virtual autopsy confirms 88% of clinical diagnoses and identifies additional pathologies, such as hemorrhages, strokes, and pneumothorax, including changes that could be missed during a traditional autopsy. These findings demonstrate the high diagnostic efficacy of the method, its practical value for improving the accuracy of postmortem diagnostics, and expanding capabilities in forensic and clinical fields. Overall, the study demonstrates the potential of virtual autopsy as a promising non-invasive tool in modern medicine.

Conclusions: The study confirmed the feasibility of using virtual autopsy as an effective complement to and temporary replacement for traditional autopsy, contributing to the development of modern postmortem diagnostic methods and improving the quality of medical examinations in both forensic and clinical fields.

Keywords: *virtual autopsy, virtopsy, forensic examination, imaging technologies, computed tomography, MRI, non-invasive autopsy.*

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Резюме

СОВРЕМЕННОЕ СОСТОЯНИЕ ВИРТУАЛЬНОЙ АУТОПСИИ С ИСПОЛЬЗОВАНИЕМ КОМПЛЕКСНЫХ ТЕХНОЛОГИЙ ВИЗУАЛИЗАЦИИ

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Актуальность: Виртуальная аутопсия позиционируется как неинвазивный метод постмортального исследования, обеспечивающий получение объективно верифицируемых судебно-медицинских данных без необходимости выполнения традиционного вскрытия.

Цель исследования: оценка диагностической ценности виртуальной аутопсии (виртопсии) как альтернативы традиционной медицинской аутопсии у пациентов, находящихся на интенсивной терапии в отделении анестезиологии и реанимации (ОРИТ).

Материалы и методы: Дизайн исследования: Проспективное исследование. Мультиспиральная компьютерная томография (МСКТ), магнитно-резонансная томография (МРТ), 3D-реконструкция изображений и гистологическое исследование, проведенные под наблюдением сертифицированных специалистов. Диагностические данные виртуальной аутопсии сопоставлялись с клиническими диагнозами и результатами традиционной судебно-медицинской экспертизы, что позволило оценить точность и полноту выявленных патологий.

Результаты: Виртуальная аутопсия подтверждает 88% клинических диагнозов и выявляет дополнительные патологии, такие как кровотечения, инсульты и пневмоторакс, включая изменения, которые могли быть пропущены при традиционной аутопсии. Полученные результаты демонстрируют высокую диагностическую эффективность метода, его практическую ценность для повышения точности посмертной диагностики и расширения возможностей судебно-медицинской и клинической практики. В целом, исследование демонстрирует потенциал виртуальной аутопсии как перспективного неинвазивного метода в современной медицине.

Выводы: Исследование подтвердило возможность использования виртуальной аутопсии в качестве эффективного дополнения и временной замены традиционной аутопсии, способствуя развитию современных методов посмертной диагностики и повышению качества медицинских экспертиз, как в судебно-медицинской, так и в клинической практике.

Ключевые слова: *виртуальная аутопсия, виртопсия, кожно-медицинская экспертиза, технологии визуализации, компьютерная томография, МРТ, неинвазивное вскрытие.*

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Мырзаханова М.Н., Рустемова К.Р., Абуталипова А.Д., Сыздыкбаев М.К., Тулеуов Б.М., Алимханова Г.Н. Современное состояние виртуальной аутопсии с использованием комплексных технологий визуализации. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (5), Б.112-119. *doi 10.34689/SH.2025.27.5.014*

Түйіндеме

КІРІКТІРІЛГЕН ВИЗУАЛИЗАЦИЯ ТЕХНОЛОГИЯЛАРЫН ПАЙДАЛАНҒАН ВИРТУАЛДЫ АВТОПСИЯНЫҢ ҚАЗІРГІ ЖАҒДАЙЫ.

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Өзектілігі. Виртуалды аутопсия дәстүрлі мәйітті ашусыз-ақ объективті түрде расталатын сот-медициналық деректерді алуға мүмкіндік беретін инвазивті емес постмортемдік зерттеу әдісі ретінде қарастырылады.

Зерттеудің мақсаты анестезиологиялық қарқынды терапия бөлімшесінде (ЖҚБ) қарқынды терапиядағы науқастарда дәстүрлі медициналық аутопсияға балама ретінде виртуалды аутопсияның (виртопсия) диагностикалық құндылығын бағалау болды.

Материалдар мен әдістер: Зерттеу дизайны: Перспективалық зерттеу. Сертификатталған мамандардың бақылауымен жүргізілген көп детекторлы компьютерлік томография (МДКТ), магнитті-резонанстық томография (МРТ), 3D кескінді қалпына келтіру және гистологиялық бағалау. Виртуалды аутопсиядан алынған диагностикалық деректер клиникалық диагноздармен және дәстүрлі сот-медициналық сараптама нәтижелерімен салыстырылды, бұл анықталған патологиялардың дәлдігі мен толықтығын бағалауға мүмкіндік берді.

Нәтижелері: Виртуалды аутопсия клиникалық диагноздардың 88%-ын растайды және дәстүрлі аутопсия кезінде байқалмайтын өзгерістерді қоса алғанда, қан кетулер, инсульттар және пневмоторакс сияқты қосымша патологияларды анықтайды. Бұл зерттеулер әдістің жоғары диагностикалық тиімділігін, өлімнен кейінгі диагностиканың дәлдігін арттырудағы практикалық құндылығын және сот-медициналық және клиникалық салалардағы мүмкіндіктерді кеңейтуді көрсетеді. Жалпы алғанда, зерттеу виртуалды мәйіт ашудың заманауи медицинадағы перспективалы инвазивті емес құрал ретіндегі әлеуетін көрсетеді.

Қорытынды: Зерттеу виртуалды мәйіт ашуды дәстүрлі мәйіт ашуды тиімді толықтыру және уақытша ауыстыру ретінде пайдаланудың орындылығын растады, бұл заманауи өлімнен кейінгі диагностикалық әдістердің

дамуына және сот-медициналық және клиникалық салалардағы медициналық тексерулердің сапасын жақсартуға ықпал етеді.

Түйінді сөздер: *виртуалды мәйіт ашу, виртопсия, сот-медициналық сараптама, бейнелеу технологиялары, компьютерлік томография, МРТ, инвазивті емес мәйіт ашу.*

Дәйексөз үшін:

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Introduction

Traditional medical autopsy has long served as the definitive benchmark in forensic medicine, having been relied upon for more than a century to yield precise information on the cause of death, validate clinical diagnoses, and enhance both diagnostic accuracy and the overall quality of patient care. [8]. The method retains substantial educational and epidemiological significance; nonetheless, in recent decades, a marked global reduction in autopsy rates has been observed. [21,10,11,4,12,16]. This decline is attributed to the requirement for obtaining consent from family members, the influence of religious and cultural constraints, prevailing societal reluctance toward the procedure, and various technical challenges that may lead to delays in burial. [4].

In response to these challenges, virtual autopsy, based on modern imaging technologies [12,16,1] such as multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and 3D imaging, is rapidly developing in forensic medicine. These methods allow obtaining detailed information about internal pathologies without the need for physical dissection, which is especially important for countries with a conservative attitude towards traditional autopsy [14,5].

Virtual autopsy has become widespread worldwide and is used to visualize complex injuries, evaluate foreign bodies, generate forensic reports, conduct telemedicine consultations, and conduct educational programs [20]. Research indicates that this approach offers substantial diagnostic precision, as reflected in its capacity to reliably identify pathological conditions-such as traumatic injuries, malpositioned medical devices, or foreign bodies—that may be challenging to detect through conventional autopsy techniques. [10,17,16].

In Kazakhstan, given traditional attitudes and limited experience implementing virtual autopsy technologies, this field is still in its infancy. Current scientific literature notes the need for further research and the implementation of virtual autopsy methods in Kazakhstani forensic practice to improve the efficiency and quality of examinations, as well as to ensure a more humane treatment of the deceased and their relatives.

Thus, despite the progress and existing advantages, there are gaps in knowledge regarding the full implementation and adaptation of virtual autopsy to national conditions, as well as the need to develop the technological base and professional training of specialists.

The **aim** of this study was to evaluate the diagnostic value of virtual autopsy (virtopsy) as an alternative to traditional medical autopsy in patients undergoing intensive care in the anesthesiology intensive care unit (ICU).

Materials and Methods

Study design: Prospective study. Multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), 3D image reconstruction, and histological evaluation performed under the supervision of certified specialists. Diagnostic data from the virtual autopsy were compared with clinical diagnoses and the results of traditional forensic examination, allowing for an assessment of the accuracy and completeness of the identified pathologies.

A Philips MX 8000 Quad 4 multidetector computed tomography scanner and the corresponding OsiriX V3.8.2 software were used for the virtual autopsy. All images and clinical data were collected during the study.

Hardware and Instruments

A Philips MX 8000 Quad 4 multislice CT scanner (Philips Healthcare, Best, Netherlands) with four slices, high resolution, and multislice reconstruction capabilities was used for the virtual autopsy. This provided detailed 3D images of the head, neck, chest, and abdomen [22].

Study Procedure

Prior to the study, all relatives provided written informed consent. Patients were examined virtually using MDCT, followed by a traditional medical autopsy. Results from both procedures were compared to determine the diagnostic value and accuracy of the virtual autopsy. The study was conducted in accordance with approved protocols and ethical standards.

Statistical Methods

Results were analyzed using methods to assess sensitivity, specificity, accuracy, and agreement coefficients. Data were processed using SPSS (version 25) or equivalent software. Appropriate statistical tests, including the κ -coefficient (kappa), were used to assess the significance of differences.

Ethical Considerations

All participants voluntarily consented to participate, and confidentiality of their personal data was guaranteed, with the exception of information provided with written consent.

Study Object

The study covered deaths of patients treated in intensive care units (ICUs) from November 1, 2024, to April 30, 2025.

We assessed the feasibility of performing virtual autopsies within the Department of Anesthesiology, Intensive Care, and Critical Care. For all patients who died in the department during the study period, we compared findings from virtual autopsies with those from conventional medical autopsies. Approval for the study was obtained from the local Forensic Center and the hospital's Institutional Review Board.

Results of the study

Study group. The study analyzed 285 cases of death among patients undergoing intensive care and critical care. Of these, 47 patients (16.5%) consented to both virtual and traditional autopsies, 115 patients (40.4%) consented to only virtual autopsy, and the remaining 123 (43.2%) were not included in the study for various reasons (see Figure 1).

Table 1 presents a summary indicator of diagnoses revealed by virtual and traditional medical autopsy, compared to clinical data recorded during life.

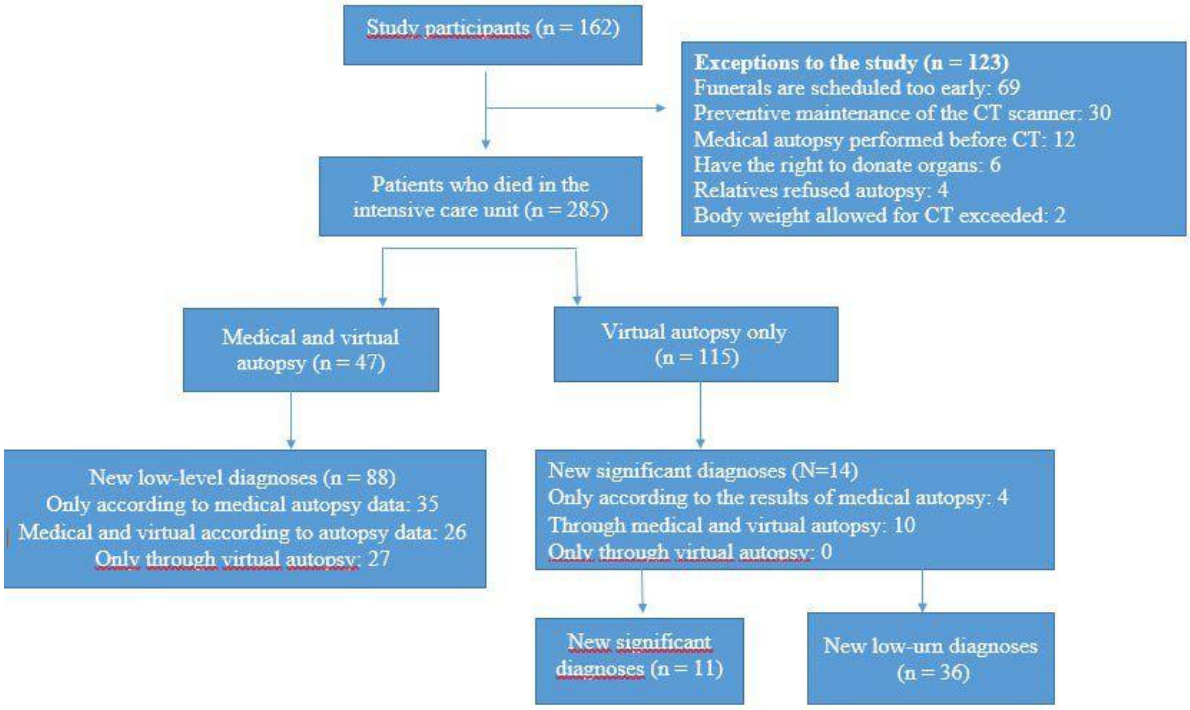

Figure 1. Research progress diagram.

Table 1.

Comparative table of diagnostic finds.

Category of diseases	Virtual autopsy (n, %)	Medical autopsy (n, %)	Joining (Virt. + med.) (n, %)	Total number of cases (n)
Cardiovascular diseases (e.g. myocardial infarction with ST lift, mesenteric)	58 (81%)	72 (100%)	63 (88%)	72
Respiratory system (e.g. pleural effusion, emphysema, pulmonary edema)	41 (71%)	55 (95%)	53 (91%)	58
Cerebrovascular diseases (e.g. ischemic stroke, intracerebral hemorrhage)	8 (73%)	11 (100%)	7 (64%)	11
Infectious diseases (e.g. pneumonia, cholecystitis, pancreatitis, endocarditis)	13 (68%)	19 (100%)	14 (74%)	19
Oncological diseases (cancer and metastases)	18 (60%)	27 (90%)	18 (60%)	30
Bleeding (not related to the brain)	11 (65%)	17 (100%)	15 (88%)	17
Miscellaneous (for example, traumatic brain injury, injuries after CPR, rib fractures, complications of procedures)	47 (52%)	57 (63%)	66 (73%)	91
Selection	196 (66%)	258 (87%)	236 (79%)	298

It was found that virtual autopsy confirmed clinical diagnoses in 88% of cases, while traditional medical autopsy confirmed them in 93%. Virtual autopsy identified 10 new primary diagnoses (5.8% of the total number of cases), while traditional medical autopsy identified 14 new primary diagnoses (7.7%).

The most frequently identified diagnoses were cardiovascular diseases (81% of virtual autopsy confirmations and 100% of medical autopsy confirmations), as well as respiratory diseases (71% and 95%, respectively (see Figure 1).

Table 2 shows the rates of identified diagnoses and why they were classified as primary diagnoses (see also Figures 2a and 2b for examples).

Rates of identified diagnoses:

• Cardiological diseases - identified in 81% (virtual autopsy) and 100% (medical autopsy) of confirmed cases;

• Respiratory diseases - in 71% and 95%;

• Cerebrovascular diseases - in 73% and 100%;

• Infectious diseases - in 68% and 100%;

• Oncological diseases - in 60% and 90%;

• Bleeding - in 65% and 100%;

• Various causes of death, including injuries and procedural complications, occurred in 52% and 63% of cases.

Table 2. **New important diagnoses were identified in patients who underwent medical and virtual autopsy.**

Situation №	Gender	Age	Duration of stay in the intensive care unit (days)	Clinical cause of death	New important diagnoses	Reason for classification as a new important diagnosis	Virtual autopsy	Virtual autopsy
1	M	61	57	Septic tank shock	a) Retroperitoneal blood loss b) Stroke with cerebral hemorrhage	a) Not determined during life b) No serious illness was identified during life	a) Retroperitoneal blood loss b) Stroke	a)Retroperitoneal blood loss b) Stroke
2	F	87	1	Right ventricular insufficiency	a) Pulmonary artery thromboembolism b) Stroke	a, b) Not determined during life	a) Жировая эмболия b) Stroke	a) Fat embolism b) Stroke
3	F	47	1	Septic tank shock	a) Central coccygeal catheter b) Improper placement of drainage	a and b) undiagnosed severe complications during life	a) central venous catheter installed b) The drainage is installed incorrectly	a) Venous catheter center b) Incorrect placement of drainage
4	F	47	1	Septic tank shock	a) Necrotic pancreatitis b) Retroperitoneal blood loss	a and b) severe concomitant pathology c) severe pathology	a) Pancreatitis b) bleeding	a) Pancreatitis b) bleeding c) arthritis
5	M	60	1	Septic tank shock, Severe melanoma	c) Septic joint arthritis d) Retroperitoneal blood loss	Not determined during life	bleeding	bleeding
6	F	81	5	Right ventricle inadequacy	Endocarditis	Not determined during life	—	Endocarditis
7	F	78	4	Pneumonia	—	Not determined during life	—	TEPA
8	F	53	36	Small cell of lung cancer	—	Not determined during life	—	Alveolar proteinosis
9	M	51	1	Ventricular arrhythmia	—	Not determined during life	—	TEPA

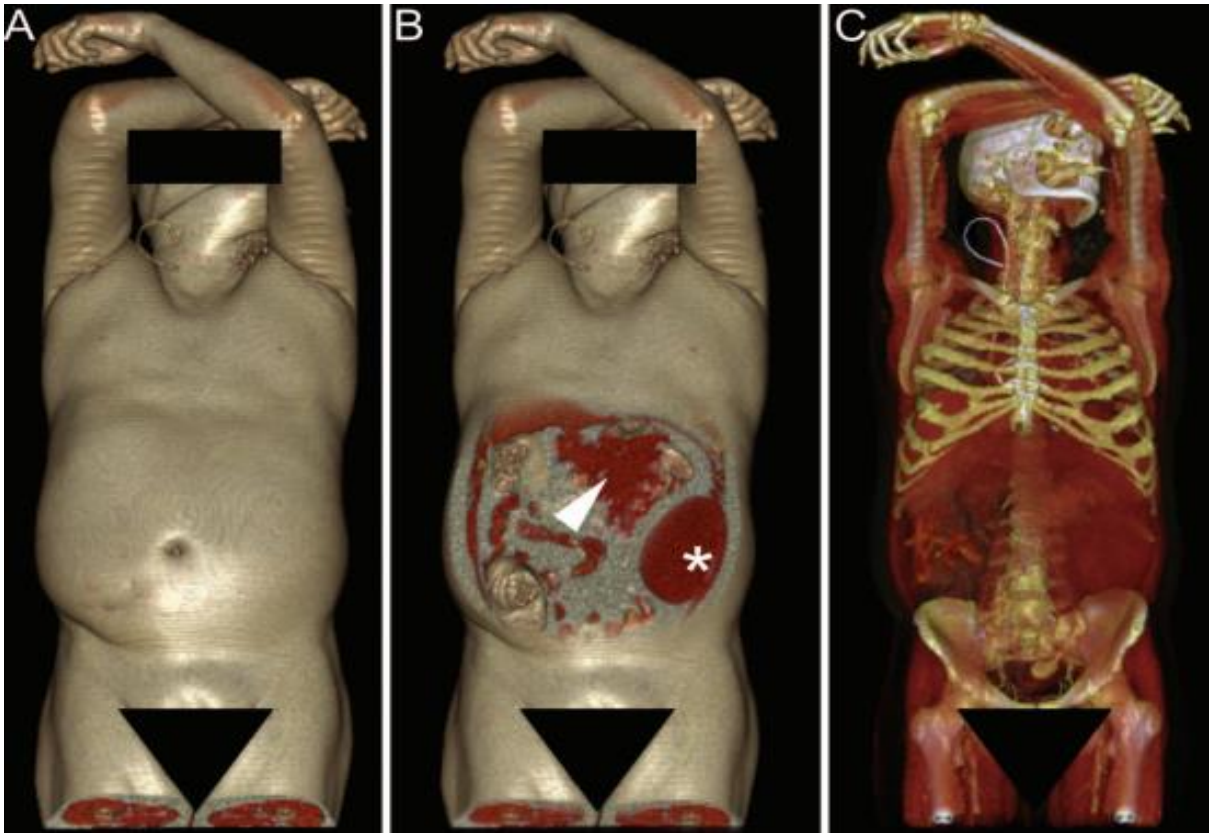

Figure 2a. Images of a virtual autopsy in occasion 1.
A. Three-dimensional reconstruction of the surface obtained using. Software for volumetric visualization.
B. Surface reconstruction with a partial overview of the abdominal cavity: a large zone of retroperitoneal hemorrhage (marked with an asterisk) is visualized, which caused detachment of the peritoneum from the left lateral wall, as well as hemorrhage in the pancreas area (indicated by an arrow).
C. Semiluminescent reconstruction - provides additional information about anatomical structures and spatial orientation.

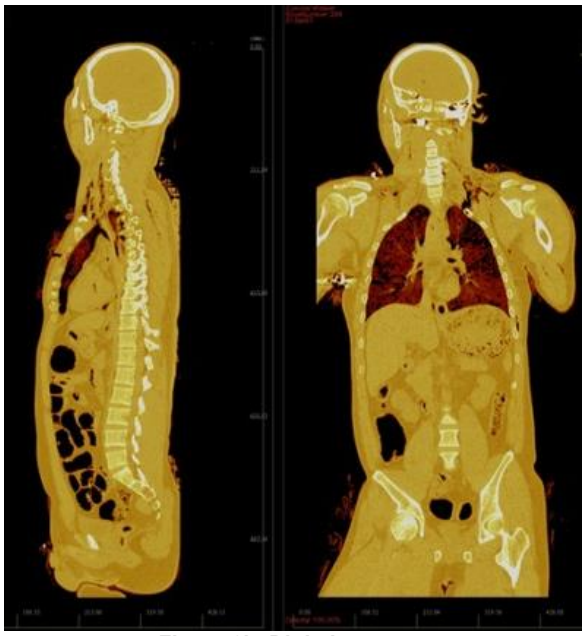

Figure 2b. Digital autopsy.

The overall diagnosis detection efficiency of virtual autopsy was 87%, demonstrating high agreement with traditional autopsy results.

After data analysis, it was found that virtual autopsy identified 10 additional new diseases, representing approximately 5.8% of all cases, while medical autopsy identified 14 new diagnoses, or approximately 7.7%. Overall, both methods identified additional diagnoses in 11 patients (approximately 4% of all studies).

Statistical Indicators

The diagnostic agreement rate between virtual and medical autopsies can be assessed using the κ-correlation index, which was high for confirmed diagnoses, indicating a significant statistical agreement ($P < 0.01$).

The probability of identifying new diagnoses using virtual autopsy is 5.8%, which compares to 7.7% for traditional autopsy.

The odds ratio for identifying new diagnoses using virtual autopsy compared to traditional autopsy is approximately 0.75 (95% confidence interval 0.50–1.12), indicating similar effectiveness of the two methods.

Discussion. This article provides compelling data on the high diagnostic accuracy of virtual autopsy (virtopsy) in identifying pathologies in deceased patients, particularly in intensive care settings. Key findings indicate that virtual autopsy confirms clinical diagnoses in 88% of cases and identifies additional pathologies, including intracerebral and intra-abdominal hemorrhages, strokes, and pneumothoraces, demonstrating its potential as a less invasive alternative to traditional autopsy [9,3,6,13].

These results support the study's hypothesis regarding the feasibility of implementing virtual autopsy as an effective diagnostic tool that expands the capabilities of forensic examination, particularly in situations where invasive procedures are not necessary. They support the hypothesis that virtual autopsy can not only confirm existing diagnoses but also identify additional ones missed during clinical examination, which is consistent with the study's objectives. Note the illustration in Figure 3, which depicts a Shaldon catheter (A) placed during resuscitation efforts. A virtual autopsy revealed malposition of this catheter, passing through the jugular foramen and penetrating the base of the skull - a fact highlighted by the arrow in the image. This example highlights the value of virtual visualization for identifying medical malpositions, which is important for assessing the causes of complications and errors, as well as for the correct interpretation of injuries and pathologies in deceased patients(B). In this case, 3D reconstruction allowed for the precise determination of the catheter's position and identification of a potential cause of complications that might have been diagnosed with less accuracy or missed entirely during a traditional autopsy

However, it is important to consider several limitations when interpreting the obtained data. First, the full range of pathologies identified by virtual autopsy depends on the quality of the images and available technologies, as well as on the interpretation of specialists, which can lead to subjectivity and errors. The article notes that some changes, such as electrolyte disturbances and arrhythmias, cannot be detected morphologically [24], which limits the completeness of the diagnostic picture [7,23,19]. Secondly, the majority of case studies are related to deaths in intensive care units, which may limit the generalization of the results to other areas of medicine and types of patients.

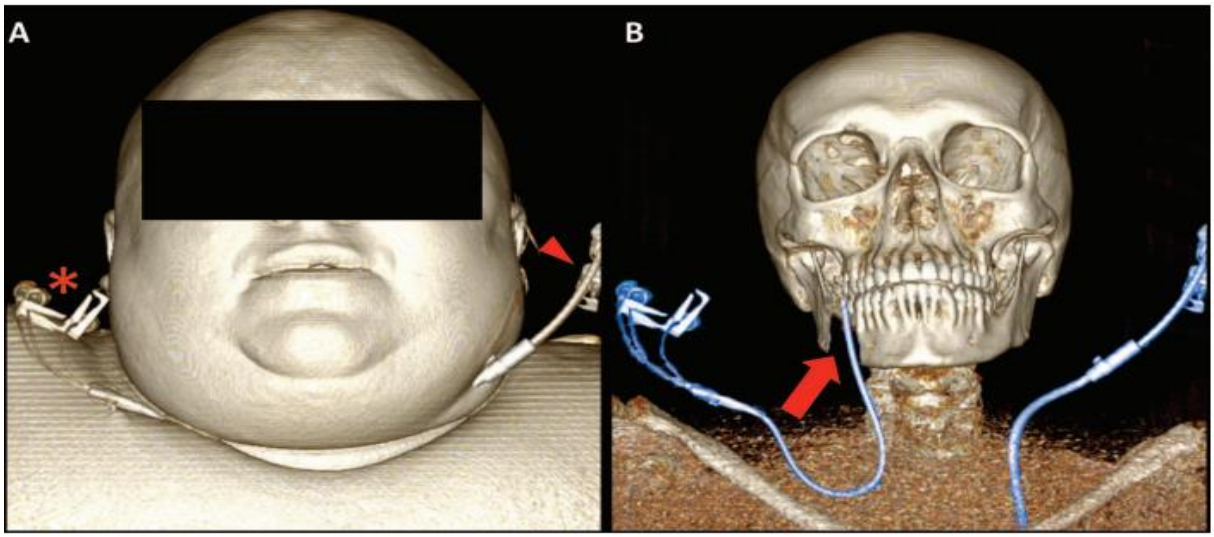

Figure 3. Images of a virtual autopsy, case 3.

A. Three-dimensional surface reconstruction obtained using software for volumetric visualization. The central venous catheter (marked with an asterisk) and the Shaldon catheter (indicated by an arrow) were installed during resuscitation. B. Soft tissues are digitally removed; catheters are rendered in blue. The incorrect position of the distal end of the central venous catheter was noted - after insertion through the right subclavian vein, it passed through the jugular opening and penetrated the base of the skull (indicated by the arrow). For comparison: the Shaldon catheter, installed through the left internal jugular vein, is located correctly.

In addition, the study is constrained by limitations associated with its sample size: of the original 285 investigations, only 47 incorporated both autopsy techniques. This restricts statistical power and may affect the precision of the resulting conclusions. Further limitations arise from variations in technological advancement across countries, which complicate direct comparisons with international research -particularly in Europe and the United States, where virtual autopsy has been implemented within more technologically advanced and administratively mature systems.

By comparing with international sources, for example, with studies [2,15], which note the high cost-effectiveness of virtual autopsy, our article confirms its potential value, especially in the context of limited access to traditional autopsy and the need for more ethical approaches. However, international practice emphasizes the need for further research aimed at standardizing methods, optimizing technologies, and developing automated image interpretation systems, which remains an unresolved issue in our article. Practical recommendations include the use of virtual autopsy as a complement to traditional autopsy, particularly for assessing internal hemorrhages, strokes, and respiratory and circulatory pathologies.

This could improve the accuracy of forensic examinations and reduce ethical conflicts. Future research should be expanded to include larger sample sizes, interdisciplinary approaches, and the implementation of automated diagnostic systems based on artificial intelligence.

Overall, the study results confirm the potential of virtual autopsy and justify its implementation in forensic practice in Kazakhstan. However, this requires overcoming current technological and methodological limitations, as well as conducting international comparative studies to confirm the universality of the data obtained.

Conclusion

According to the article, virtual autopsy exhibits substantial diagnostic superiority relative to conventional autopsy. The study reported that virtual autopsy verified 88% of initial clinical diagnoses and revealed additional comorbid conditions - including stroke, hemorrhage, and pneumothorax - thereby underscoring its promise as a valuable modality for postmortem assessment, particularly within intensive care environments. [22].

The significance of the study lies in demonstrating the feasibility of using virtual autopsy as a noninvasive and less costly alternative to traditional autopsy, which is particularly relevant for institutions where the decline in traditional autopsy rates is due to ethical, cultural, or organizational factors. It contributes to expanded capabilities for accurate diagnosis of the cause of death and also has educational value and the potential to establish new standards in postmortem medicine and forensic science [6].

For clinical practice, the results help improve the quality of postmortem diagnostics, identify hidden or missed conditions during life, and contribute to a better understanding of the pathogenesis of various diseases in the postmortem setting. From a scientific perspective, this study opens up prospects for the further implementation and development of virtual autopsy technologies, particularly given modern imaging technologies and their integration into forensic and clinical work, which generally contributes to progress in the field of non-invasive diagnostics and pathology [6].

Thus, the study's results confirm the potential for using virtual autopsy as an effective tool to complement and temporarily replace traditional autopsy, contributing to the development of modern postmortem diagnostic methods and improving the quality of medical examinations in both forensic and clinical settings.

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Contribution of the authors: *Conceptualization: Marzhan Myrzakhanova; methodology: Aibota Abutalipova; review: Kulsara Rustemova; formal analysis: Marat Syzdykbayev, Bazar Tuleuov, Gulshat Alimkhanova; writing manuscript: Marzhan Myrzakhanova, Aibota Abutalipova. Editing and approval of final draft: Kulsara Rustemova.*

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ASSESSMENT OF PUBLIC AWARENESS IN ABAI REGION REGARDING SPINAL MUSCULAR ATROPHY IN CHILDREN AND THE IMPORTANCE OF GENETIC COUNSELING IN FAMILY PLANNING

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Abstract

Introduction. Public awareness of spinal muscular atrophy (SMA) in children and the importance of genetic counseling during family planning represent key factors in the prevention and early diagnosis of this disease.

Objective. To assess the level of public awareness regarding spinal muscular atrophy in children and the significance of genetic counseling in family planning.

Materials and Methods. A cross-sectional study was conducted among 315 respondents**.** Statistical analysis was performed using SPSS software (version 26.0)**.** Histograms and the Kolmogorov–Smirnov test were applied to assess the normality of distribution for all variables. Given the non-normal distribution, non-parametric statistical methods were used. Quantitative continuous variables are presented as medians and percentiles**,** while dichotomous variables are presented as proportions (absolute numbers)**.** Results with $p \leq 0.05$ were considered statistically significant.

Results. According to the findings, only 47.6% of respondents had ever heard of spinal muscular atrophy (SMA). Among respondents, 64.1% indicated that in the future they plan to have children with their spouse or partner. A total of 58% expressed willingness to undergo genetic counseling, including genetic testing for SMA-related gene mutations.

However, only 35.6% of respondents were aware of the main clinical symptoms of SMA in children (such as muscle weakness, lethargy, weak sucking reflex, motor developmental delay, and breathing difficulties), which would enable timely suspicion of the disease and earlier referral to medical specialists.

Conclusion. Thus, the level of public awareness regarding spinal muscular atrophy remains low and requires educational efforts and broader dissemination of information about this disease.

Keywords: *spinal muscular atrophy, orphan diseases, genetic disorders, mutation.*

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Резюме

ОЦЕНКА УРОВНЯ ОСВЕДОМЛЕННОСТИ НАСЕЛЕНИЯ АБАЙСКОЙ ОБЛАСТИ О СПИНАЛЬНОЙ МЫШЕЧНОЙ АТРОФИИ У ДЕТЕЙ И ВАЖНОСТИ ГЕНЕТИЧЕСКОГО КОНСУЛЬТИРОВАНИЯ ПРИ ПЛАНИРОВАНИИ БЕРЕМЕННОСТИ

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Введение. Осведомленность населения о спинальной мышечной атрофии (СМА) у детей и важность генетического консультирования при планировании семьи являются ключевыми факторами профилактики и ранней диагностики этого заболевания.

Цель. Оценить уровень осведомленности населения о спинальной мышечной атрофии у детей и значение генетического консультирования при планировании семьи.

Материалы и методы. Было проведено поперечное исследование среди 315 респондентов. Статистический анализ проводился с использованием программы SPSS (версия 26.0). Для оценки нормальности распределения всех переменных использовались гистограммы и тест Колмогорова–Смирнова. Учитывая ненормальное распределение, были использованы непараметрические статистические методы. Количественные непрерывные переменные представлены в виде медиан и процентилей, а дихотомические переменные – в виде долей (абсолютных чисел). Результаты при $p \leq 0,05$ считались статистически значимыми.

Результаты. Согласно полученным данным, только 47,6% респондентов когда-либо слышали о спинальной мышечной атрофии (СМА). Среди респондентов 64,1% указали, что в будущем планируют иметь детей с супругом/партнером. 58% выразили готовность пройти генетическое консультирование, включая генетическое тестирование на наличие генных мутаций, связанных со СМА.

Однако только 35,6% респондентов были осведомлены об основных клинических симптомах СМА у детей (таких как мышечная слабость, вялость, ослабленный сосательный рефлекс, задержка моторного развития и затрудненное дыхание), что позволило бы своевременно заподозрить заболевание и направить пациента к врачу-специалисту.

Заключение. Таким образом, уровень осведомленности населения о спинальной мышечной атрофии остается низким и требует просветительской работы и более широкого распространения информации об этом заболевании.

Ключевые слова: *спинальная мышечная атрофия, орфанные заболевания, генетические нарушения, мутация.*

Для цитирования: *Курмашева А.Т., Хисметова З.А., Мукушева А.М., Сиязбекова З.С., Ахметова К.М.* Оценка уровня осведомленности населения Абайской области о спинальной мышечной атрофии у детей и важности генетического консультирования при планировании беременности .// Наука и Здравоохранение. 2025. Vol.27 (5), С.120-126. *doi 10.34689/SH.2025.27.5.015*

Түйіндеме

АБАЙ ОБЛЫСЫ ХАЛҚЫНЫҢ БАЛАЛАРДАҒЫ ЖҰЛЫН БҰЛШЫҚЕТ АТРОФИЯСЫ ТУРАЛЫ ЖӘНЕ ЖҮКТІЛІКТІ ЖОСПАРЛАУ КЕЗІНДЕГІ ГЕНЕТИКАЛЫҚ КЕҢЕС БЕРУДІҢ МАҢЫЗДЫЛЫҒЫ ЖӨНІНДЕГІ АҚПАРАТТАНУ ДЕҢГЕЙІН БАҒАЛАУ

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Кіріспе. Балалардағы жұлын бұлшықет атрофиясы туралы және жүктілікті жоспарлау кезіндегі генетикалық кеңес берудің маңыздылығы жөніндегі халықтың хабардар болуы аталған аурудың алдын алу мен ерте диагностикалау үшін негізгі факторлардың бірі болып табылады.

Зерттеудің мақсаты: Балалардағы жұлын бұлшықет атрофиясы туралы және жүктілікті жоспарлау кезінде генетикалық кеңес берудің маңыздылығы жөнінде халықтың хабардарлық деңгейіне баға беру.

Материалдар мен әдістер: 315 респонденттің қатысуымен бірмезеттік көлденең зерттеу жүргізілді. Статистикалық талдау SPSS бағдарламалық қамтамасыздандыруы (26.0 нұсқасы) арқылы орындалды. Барлық айнымалылардың таралуының қалыптылығын тексеру үшін гистограммалар және Колмогоров-Смирнов критерийі қолданылды. Таралудың қалыпты түрден ауытқығанын ескере отырып, параметрлік емес статистикалық әдістер пайдаланылды. Біздің нәтижелерде сандық үздіксіз айнымалылар медиана және процентильдер түрінде, ал дихотомиялық айнымалылар үлестер (абсолюттік саны) түрінде көрсетілді. $p=0,05$ мәні статистикалық тұрғыдан мәнді деп есептелді.

Нәтижелер: Алынған нәтижелерге сәйкес, респонденттердің тек 47,6%-ы жұлын бұлшықет атрофиясы туралы естіген. Респонденттердің 64,1%-ы болашақта жұбайымен немесе серіктесімен жүктілікті жоспарлауды көздейтінін атап өтті. 58% респондент генетикалық кеңес алуға және жұлын бұлшықет атрофиясын тудыратын мутациялық гендерді анықтауға арналған генетикалық тест тапсыруға дайын екенін білдірді. Респонденттердің тек 35,6%-ы балалардағы жұлын бұлшықет атрофиясының негізгі белгілерін білетінін көрсетті, бұл ауруды уақытылы күдіктенуге және дер кезінде дәрігерге жүгінуге көмектесер еді.

Қорытындылар: Осылайша, халықтың жұлын бұлшықет атрофиясы туралы хабардарлық деңгейі төмен болып табылады және бұл ауру туралы ақпараттандыру мен түсіндіру жұмыстарын күшейтуді талап етеді.

Түйінді сөздер: *жұлын бұлшықет атрофиясы, сирек кездесетін аурулар, генетикалық аурулар, мутация.*

Дәйексөз үшін: *Курмашева А.Т., Хисметова З.А., Мукушева А.М., Сиязбекова З.С., Ахметова К.М.* Абай облысы халқының балалардағы жұлын бұлшықет атрофиясы туралы және жүктілікті жоспарлау кезіндегі генетикалық кеңес берудің маңыздылығы жөніндегі ақпараттану деңгейін бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 120-126. *doi 10.34689/SH.2025.27.5.015*

Introduction

Spinal muscular atrophy (SMA) is a severe hereditary disease characterized by degeneration of motor neurons and progressive muscle weakness. With the growing availability of genetic testing, the level of public awareness of hereditary diseases and the possibilities for their early detection are becoming increasingly important. The present study is aimed at examining the awareness of SMA among different social groups as well as identifying the factors that influence the level of knowledge.

Spinal muscular atrophy (SMA) represents a group of genetic neuromuscular disorders that lead to progressive weakness, muscle atrophy, and paralysis due to the degeneration of motor neurons in the spinal cord [1]. In most cases, the cause of degeneration and death of alpha motor neurons in the spinal cord is a mutation in a specific region of chromosome 5 DNA, known as the SMN1 gene (survival motor neuron 1 gene), located at 5q11.2–q13.3 [1,2]. Under normal conditions, this gene regulates the synthesis of the SMN protein, which plays a critical role in the metabolism of motor neurons. Mutations in this gene result in insufficient SMN protein production, leading to progressive loss of spinal motor neurons and ultimately severe disability [3].

SMA is one of the most common conditions among so-called rare diseases, with a prevalence ranging from 1 in 6,000 to 1 in 10,000 live births worldwide [2]. Approximately 1 in 40 individuals is an asymptomatic carrier of the SMA mutation [2]. This inheritance pattern highlights the importance of genetic counseling as a preventive tool. As Alkuraya (2013) notes, *"genetics and genomic medicine represent essential components of preventive healthcare, and integrating genetic counseling into national health systems is critical, especially in regions with a high prevalence of recessive genetic diseases"* [5].

Moreover, the importance of timely identification is reinforced by clinical evidence. Dangouloff and Servais (2019) demonstrated that *"early treatment of patients with spinal muscular atrophy significantly improves outcomes when therapy is initiated prior to irreversible motor neuron loss"* [4]. This emphasizes the critical role of awareness and early diagnosis.

In addition, population-level approaches are becoming increasingly relevant. As *Nazareth, Lazarin, and Goldberg* (2015) highlight, *"carrier screening has undergone a paradigm shift in recent years, moving from ethnicity-based testing to expanded universal panels, reflecting the increasing need for population-level approaches to genetic disease prevention"* [6]. This perspective underscores the necessity of broad educational initiatives and carrier screening programs to reduce the risk of severe genetic diseases such as SMA.

Objective To assess the level of public awareness of spinal muscular atrophy (SMA) in children and the significance of genetic counseling in family planning.

Materials and Methods

A cross-sectional study was conducted using the online platform Google Forms. The study population consisted of residents of the Abai region. The survey was carried out from February 1, 2025, to March 25, 2025. The study was reviewed and approved by the Ethics Committee of Non-Commercial Joint Stock Company "Semey Medical University" (Protocol No. 2, dated December 12, 2023). All respondents were informed about the aim of the study. Participation was voluntary and anonymous.

The questionnaire consisted of 15 items, including: 6 sociodemographic questions (gender, age, marital status, education, presence and number of children), 4 questions on the importance of genetic counseling during pregnancy, 5 questions assessing awareness of SMA.

Inclusion criterion: residents of the Abai region aged 18 years and older.

Exclusion criterion: minors residing in the Abai region.

Quantitative data were tested for homogeneity of distribution using the Kolmogorov–Smirnov test. Based on the results, quantitative data are presented as medians. Qualitative data are described in absolute numbers and percentages.

For statistical analysis, descriptive statistics and the Pearson χ^2 test (table 3) were applied to examine associations between education and SMA awareness, as well as between gender and awareness. In addition, Cramer's V test (table 2) was used to assess the strength of associations between categorical variables. Data visualization was performed using distribution charts.

Results

A total of 315 respondents participated in the study, of whom 65 (20.6%) were men and 250 (79.4%) were women. The median age was 35–40 years, and the median number of children among respondents was 2. By educational level, 214 respondents (67.9%) reported having higher education. Regarding marital status, 195 (61.9%) were married. In addition, 232 respondents (73.7%) had children. When asked about family and pregnancy planning, 202 respondents (64.1%) stated that they intended to plan pregnancy with their spouse in the future (Table 1).

During family planning and pregnancy, 184 respondents (58.4%) expressed willingness to undergo genetic counseling, including genetic testing for mutations causing spinal muscular atrophy. However, awareness about SMA remained limited: 161 respondents (51.1%) did not know that spinal muscular atrophy is inherited. 182 respondents (57.8%) did not know that a person can be an asymptomatic carrier of the SMA mutation. 173 respondents (54.9%) were unaware of the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor developmental delay, and respiratory difficulties).

Thus, the table shows that none of the sociodemographic factors (gender, age, education, marital status, presence of children) had a statistically significant correlation with the level of awareness of SMA. Statistical analysis using the Pearson χ^2 test showed no significant association between the presence of children and willingness to undergo genetic counseling. This indicates that having children does not influence the decision to participate in genetic counseling.

Discussion

The present study revealed that awareness of spinal muscular atrophy (SMA) among the surveyed population is insufficient, and this lack of knowledge does not significantly depend on gender or education level. These findings highlight that informational gaps are widespread and not confined to any particular demographic or social group.

Table 1.

Knowledge of Spinal Muscular Atrophy and the Role of Genetic Counseling: Evidence from the Abay Region.

		n	%
1. Gender	Male	65	20,6
	Female	250	79,4
Total		**315**	**100,0**
2. Age	18-25 years	62	19,7
	25-30 years	39	12,4
	30-35 years	37	11,7
	35-40 years	45	14,3
	40-45 years	47	14,9
	50 and older	85	27,0
Total		**315**	**100,0**
3. Education	No education	4	1,3
	Higher	214	67,9
	Incomplete higher	31	9,8
	Secondary specialized	27	8,6
	Secondary	39	12,4
Total		**315**	**100,0**
4. Marital status	Marital status	7	2,2
	Married	195	61,9
	Single (never married)	84	26,7
	Divorced	21	6,7
	Widowed	8	2,5
Total		**315**	**100,0**
5. Do you have children?	Yes	232	73,7
	No	83	26,3
Total		**315**	**100,0**
6. If yes, how many children?	None	83	26,3
	One	44	14,0
	Two	79	25,1
	Three	65	20,6
	Four or more	44	14,0
Total		**315**	**100**
7. Do you know what "genetics" and "genetic diseases" are?			
Yes		278	88,3
No		20	6,3
Difficult to answer		17	5,4
Total		**315**	**100,0**
8. Do you think genetic counseling is important in family planning and pregnancy?			
Yes		84	26,7
No		13	4,1
Difficult to answer		218	69,2
Total		**315**	**100,0**

	n	%
9. If you do not yet have children, do you plan pregnancy with your spouse in the future?		
Yes	202	64,1
No	60	19,0
Difficult to answer	53	16,8
Total	**315**	**100**
10. If planning pregnancy, would you undergo genetic counseling, including SMA testing?		
Yes	184	**58,4**
No	63	**20,0**
Difficult to answer	68	**21,6**
Total	**315**	**100,0**
11. Have you ever heard of spinal muscular atrophy (SMA)?		
Yes	150	58,4
No	148	20,0
Difficult to answer	17	21,6
Total	**315**	**100,0**
12. Do you know that SMA is inherited?		
Yes	140	44,4
No	161	51,1
Difficult to answer	**14**	**4,4**
Total	**315**	**100.0**
13. Do you know that a person may be an asymptomatic carrier of the SMA mutation?		
Yes	106	33,7
No	182	57,8
Difficult to answer	27	8,6
Total	**315**	**100,0**
14. Do you know that SMA and carrier status can be diagnosed with a blood test?		
Yes	121	38,4
No	172	54,6
Difficult to answer	22	7,0
Total	**315**	**100,0**
15. Do you know the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor delay, tremor, respiratory problems)?		
Yes	112	35,6
No	173	54,9
Difficult to answer	30	9,5
Total	**315**	**100,0**

One of the key explanations for this outcome may be the limited dissemination of information about rare genetic diseases in public health campaigns, which predominantly focus on more common conditions. Furthermore, the absence of systematic premarital and preconception genetic counseling programs may contribute to low awareness levels, even among highly educated individuals. This underscores the need for nationwide initiatives aimed at increasing public understanding of hereditary disorders, particularly SMA, which is both life-limiting and preventable in terms of risk through carrier screening.

The findings of our study are consistent with international reports indicating insufficient knowledge of SMA and the benefits of genetic counseling in different countries. For example, studies by *Dangouloff and Servais* (2019) emphasize the critical role of early detection and treatment, while *Nazareth et al.* (2015) demonstrated that public awareness and trends in genetic carrier screening remain suboptimal despite technological progress. In contrast, in regions where genetic education and premarital screening are well-established, such as in *Saudi Arabia (Alkuraya, 2013),* awareness and participation in genetic counseling are significantly higher.

Table 2. **Assessment of public awareness in Abai region regarding spinal muscular atrophy in children and the importance of genetic counseling in family planning.**

	11.Have you ever heard of spinal muscular atrophy (SMA)?			
Gender	Yes	No	Difficult to answer	Total
Male	26	34	5	65
Female	124	114	12	250
Total	150	148	17	315
	12. Do you know that SMA is inherited?			
	Yes	No	Difficult to answer	Total
Male	25	37	3	65
Female	115	124	11	250
Total	140	161	14	315
	13. Do you know that a person may be an asymptomatic carrier of the SMA mutation?			
	Yes	No	Difficult to answer	Total
Male	16	42	7	65
Female	90	140	20	250
Total	106	182	27	315
	14. Do you know that SMA and carrier status can be diagnosed with a blood test?			
	Yes	No	Difficult to answer	Total
Male	19	41	5	65
Female	102	131	17	250
Total	121	172	22	315
	15. Do you know the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor delay, tremor, respiratory problems)?			
	Yes	No	Difficult to answer	Total
Male	17	42	6	65
Female	95	131	24	250
Total	112	173	30	315
	11. Have you ever heard of spinal muscular atrophy (SMA)?			
Education	Yes	No	Difficult to answer	Total
No education	3	1	0	4
Higher	104	98	12	214
Incomplete higher	21	9	1	31
Secondary specialized	9	16	2	27
Secondary	13	24	2	39
Total	150	148	17	315
	12. Do you know that SMA is inherited?			
	Yes	No	Difficult to answer	Total
No education	3	1	0	4
Higher	92	111	11	214
Incomplete higher	17	13	1	31
Secondary specialized	15	11	1	27
Secondary	13	25	1	39
Total	140	161	14	315
	13. Do you know that a person may be an asymptomatic carrier of the SMA mutation?			
	Yes	No	Difficult to answer	Total
No education	3	1	0	4
Higher	70	123	21	214
Incomplete higher	14	15	2	31
Secondary specialized	9	18	0	27
Secondary	10	25	4	39
Total	106	182	27	315
	14. Do you know that SMA and carrier status can be diagnosed with a blood test?			
	Yes	No	Difficult to answer	Total
No education	2	2	0	4
Higher	82	116	16	214
Incomplete higher	13	16	2	31
Secondary specialized	10	16	1	27
Secondary	14	22	3	39
Total	121	172	22	315

Continuation of Table 2.

	15. Do you know the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor delay, tremor, respiratory problems)?			
	Yes	No	Difficult to answer	Total
No education	3	1	0	4
Higher	69	122	23	214
Incomplete higher	18	11	2	31
Secondary specialized	11	15	1	27
Secondary	11	24	4	39
Total	112	173	30	315
	11. Have you ever heard of spinal muscular atrophy (SMA)?			
Marital status	Yes	No	Difficult to answer	Total
Marital status	4	2	1	7
Married	83	103	9	195
Single (never married)	50	29	5	84
Divorced	10	9	2	21
Widowed	3	5	0	8
Total	150	148	17	315
	12. Do you know that SMA is inherited?			
	Yes	No	Difficult to answer	Total
Marital status	5	1	1	7
Married	79	109	7	195
Single (never married)	44	37	3	84
Divorced	9	10	2	21
Widowed	3	4	1	8
Total	140	161	14	315
	13. Do you know that a person may be an asymptomatic carrier of the SMA mutation?			
	Yes	No	Difficult to answer	Total
Marital status	4	3	0	7
Married	60	123	12	195
Single (never married)	32	43	9	84
Divorced	8	9	4	21
Widowed	2	4	2	8
Total	106	182	27	315
	14. Do you know that SMA and carrier status can be diagnosed with a blood test?			
	Yes	No	Difficult to answer	Total
Marital status	2	3	2	7
Married	76	111	8	195
Single (never married)	34	41	9	84
Divorced	8	10	3	21
Widowed	1	7	0	8
Total	121	172	22	315
	15. Do you know the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor delay, tremor, respiratory problems)?			
	Yes	No	Difficult to answer	Total
Marital status	3	3	1	7
Married	60	120	15	195
Single (never married)	43	33	8	84
Divorced	4	11	6	21
Widowed	2	6	0	8
Total	112	173	30	315
	11. Have you ever heard of spinal muscular atrophy (SMA)?			
Presence of children	Yes	No	Difficult to answer	Total
Yes	103	120	9	232
No	47	28	8	83
Total	150	148	17	315
	12. Do you know that SMA is inherited?			
	Yes	No	Difficult to answer	Total
Yes	97	126	9	232
No	43	35	5	83
Total	140	161	14	315

Continuation of Table 2.

	13. Do you know that a person may be an asymptomatic carrier of the SMA mutation?			
	Yes	No	Difficult to answer	Total
Yes	74	141	17	232
No	32	41	10	83
Total	106	182	27	315
	14. Do you know that SMA and carrier status can be diagnosed with a blood test?			
	Yes	No	Difficult to answer	Total
Yes	86	132	14	232
No	35	40	8	83
Total	121	172	22	315
	15. Do you know the main symptoms of SMA in children (muscle weakness, lethargy, weak sucking reflex, motor delay, tremor, respiratory problems)?			
	Yes	No	Difficult to answer	Total
Yes	69	142	21	232
No	43	31	9	83
Total	112	173	30	315

Table 3.

Variable (independent)	Dependent variable	χ^2 (df)	p-value	Cramer's V	Interpretation
Gender	Awareness of SMA	2.27 (2)	0.318	0.085	No significant association
Education level	Awareness of SMA	4.81 (4)	0.307	0.092	No significant association
Marital status	Awareness of SMA	3.92 (3)	0.270	0.089	No significant association
Presence of children	Willingness for genetic counseling	2.56 (1)	0.112	0.070	No significant association

These differences suggest that structured national policies and cultural integration of genetic literacy can markedly influence public awareness.

The strengths of this study include its relatively large sample size (315 respondents), which exceeds the required minimum for statistical representativeness, and the inclusion of diverse demographic groups within the Abai region. However, several limitations should be acknowledged. First, the use of an online questionnaire may have introduced selection bias, favoring individuals with higher digital literacy. Second, awareness was measured through self-reported answers, which may not fully reflect objective knowledge. Finally, as this was a cross-sectional study, causal relationships between sociodemographic factors and awareness cannot be established.

Despite these limitations, the study provides important insights into the current state of genetic literacy regarding SMA in Kazakhstan. The results may serve as a basis for designing educational interventions, incorporating genetic counseling into routine reproductive health services, and promoting targeted information campaigns. Future research should explore the effectiveness of such interventions, assess the role of healthcare providers in improving genetic awareness, and examine attitudes toward genetic testing in different cultural and social contexts

Conclusion

The study revealed a low level of public awareness about SMA. Given the high importance of early diagnosis and the possibility of prevention through genetic counseling, government and public initiatives are needed to promote knowledge about hereditary diseases. The introduction of genetic education programs can help reduce the risk of children being born with severe genetic disorders.

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Contribution of the authors: *Each of the authors made an equal contribution.*

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INFLUENCE OF ASTHENIA ON THE PSYCHOLOGICAL WELL-BEING OF PATIENTS WITH TYPE 2 DIABETES IN AKTOBE

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Abstract

Abstract. Asthenia in patients with type 2 diabetes mellitus is a complex and multifaceted phenomenon that affects the physical and psycho-emotional state of patients. This condition of fatigue often arises against the background of chronic hyperglycemia, metabolic disorders, and complications of comorbid diseases.

The aim of our study was to examine the susceptibility to asthenia in patients with type 2 diabetes mellitus in the city of Aktobe.

Methods. The study design was a cross-sectional clinical study without a control group. The study population consisted of 1,500 patients with type 2 diabetes mellitus registered for follow-up care in state polyclinics of Aktobe, aged 18 to 70 years. To determine the degree of fatigue, the MFI–20 assessment scale was used.

Results. The findings indicate a tendency toward deterioration in each of the five indicators of psychophysical health in patients with type 2 diabetes mellitus. When comparing two independent groups, statistically significant differences were found in the indicators of general and physical asthenia ($p < 0.01$ for each indicator).

Conclusions. Patients with type 2 diabetes mellitus are susceptible to asthenia. The highest frequency of general asthenia was observed in patients with a diabetes duration of 5 to 10 years. A higher frequency of general asthenia was found among unemployed patients. Significant differences were established when comparing male and female patients with T2DM in terms of general and physical asthenia.

Keywords*: type 2 diabetes mellitus, asthenic syndrome, MFI–20 asthenia assessment scale, fatigue, psychological state.*

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Резюме

ВЛИЯНИЕ АСТЕНИИ НА ПСИХОЛОГИЧЕСКОЕ БЛАГОПОЛУЧИЕ ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА Г. АКТОБЕ

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Аннотация. Астения у больных сахарным диабетом 2 типа - сложное и многогранное явление, влияющее на физическое и психоэмоциональное состояние больных. Такое состояние утомления часто возникает на фоне хронической гипергликемии, нарушений обмена веществ и осложнений сопутствующих заболеваний.

Целью нашего исследования является изучение подверженности астении пациентов с сахарным диабетом 2 типа г. Актобе.

Методы исследования. Дизайн исследования - поперечное клиническое исследование без контрольной группы. Исследуемая популяция состояла из 1500 пациентов с сахарным диабетом 2 типа, находящихся на диспансерном учете в государственных поликлиниках города г. Актобе, в возрасте от 18 до 70 лет. Для определения степени усталости была использована шкала оценки MFI–20.

Результаты. Полученные результаты указывают на тенденцию ухудшения в каждом из пяти показателей психофизического состояния здоровья у пациентов с сахарным диабетом 2 типа. При сравнении двух независимых групп статистически значимые различия установлены по показателям общая и физическая астения ($p<0,01$ для каждого показателя).

Выводы. Пациенты с сахарным диабетом 2 типа подвержены астении. Наибольшая частота общей астении имеется у пациентов с длительностью диабета от 5 до 10 лет. Более высокая частота общей астении выявлена среди неработающих пациентов. Значимые различия установлены при сравнении по полу пациентов СД2 к общей и физической астении.

Ключевые слова: *сахарный диабет 2 типа, астенический синдром, шкала оценки астении MFI–20, усталость, психологическое состояние.*

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Түйіндеме

АҚТӨБЕ ҚАЛАСЫНДА 2 -ТИПТІ ҚАНТ ДИАБЕТІМЕН АУЫРАТЫН НАУҚАСТАРДЫҢ ПСИХОЛОГИЯЛЫҚ ӘЛ-АУҚАТЫНА АСТЕНИЯНЫҢ ӘСЕРІ

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Аннотация. 2 -типті қант диабетімен ауыратын науқастардағы астения - науқастың физикалық және психоэмоционалды жағдайына әсер ететін күрделі және көп қырлы құбылыс. Шаршау мен әлсіздіктің бұл күйі жиі созылмалы гипергликемия, метаболикалық бұзылулармен қатар жүретін аурулардың салдарында пайда болады.

Біздің зерттеуіміздің мақсаты Ақтөбе қаласындағы 2- типті қант диабетімен ауыратын науқастардың астенияға бейімділігін зерделеу болып табылады.

Зерттеу әдістері. Зерттеу дизайны бақылау тобынсыз көлденең қималық клиникалық зерттеу болды. Зерттелетін популяцияны Ақтөбе қаласының мемлекеттік емханаларында есепте тұрған 2 -типті қант диабетімен ауыратын 18 бен 70 жас аралығындағы 1500 пациент құрады. Сауалнама жүргізу үшін MFI-20 астенияны бағалау шкаласы қолданылды.

Нәтижелер. Алынған нәтижелер 2- типті қант диабетімен ауыратын науқастардың психофизикалық денсаулық жағдайының бес көрсеткішінің әрқайсысында нашарлау үрдісін көрсететті. Екі тәуелсіз топты салыстыру кезінде жалпы және физикалық астения көрсеткіштері бойынша статистикалық маңызды айырмашылықтар анықталды (әр көрсеткіш үшін $p<0,01$).

Қорытынды. 2- типті қант диабеті бар науқастар астенияға бейім. Жалпы астенияның ең жоғары жиілігі 5-тен 10 жылға дейінгі қант диабетімен ауыратын науқастарда кездеседі. Жұмыс істемейтін науқастарда жалпы астения жиілігі жоғары болды. 2- типті қант диабетіне шалдыққан науқастарды жынысы бойынша жалпы және физикалық астениямен салыстыру кезінде елеулі айырмашылықтар анықталды.

Түйінді сөздер: *2- типті қант диабеті, астениялық синдром, MFI-20 астенияны бағалау шкаласы, шаршау, психологиялық жағдай.*

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Introduction

Type 2 diabetes mellitus (T2DM) is currently recognized as a global medical and social problem. The prevalence of type 2 diabetes has reached 10% and is projected to increase to 12.2% of the world's population, which will amount to 783.2 million people. Diabetes ranks among the leading causes of mortality from all diseases [17]. Its complications negatively affect daily life, creating physical, psychosocial, and emotional burdens [12].

Asthenic disorders in the long course of T2DM are an integral part of the disease's manifestation. Asthenia in patients with type 2 diabetes is a complex and multifaceted phenomenon that affects both the physical and psycho-emotional state of the patient. This condition of fatigue and weakness often develops against the background of chronic hyperglycemia, metabolic disturbances, and the consequences of comorbid diseases. Patients report decreased work capacity, persistent fatigue, and a lack of energy, which can significantly impact their quality of life. Asthenia may be associated with sleep disturbances, depression, and anxiety, which further exacerbate the symptoms [4]. It has been established that the asthenic syndrome in T2DM often has a moderate character, and its severity increases in individuals with disease onset after the age of 30 and a disease duration of five years or more [2]. Anxiety-depressive disorders caused by hyperglycemia contribute to the progression of macroangiopathy and neuropathy, creating a vicious circle of complications [1].

One of the important characteristics of the patient profile with type 2 diabetes mellitus is low adherence to treatment. Most patients, due to insufficient knowledge, may skip medication doses, violate dietary recommendations, and limit physical activity. This leads to chronic hyperglycemia and predisposes patients to asthenia or fatigue. Fatigue, in turn, as a potentially exhausting and debilitating condition, represents a serious barrier to self-care [8].

A recent study found that patients with non-comorbid diabetes experience less fatigue compared to those with comorbid conditions [9].

The appearance of asthenic symptoms is considered a signal of self-intoxication by metabolic by-products and impaired regulation of the body's energy production and utilization [18].

Patients with diabetes were found to have higher fatigue scores using the Multidimensional Fatigue Inventory (MFI) compared to non-diabetic individuals, regardless of insulin treatment [16]. Moreover, when using various fatigue assessment scales, diabetic patients generally showed higher fatigue levels compared to non-diabetic subjects [17]. Type 2 diabetes mellitus is also associated with impaired cognitive function [5].

Kazakhstani researchers have established that poor psychological well-being negatively affects a person's ability to manage diabetes, reduces treatment adherence, and increases the risk of complications. However, asthenia among patients with diabetes mellitus in Kazakhstan remains an insufficiently studied issue.

Aim: to study the susceptibility to asthenia in patients with type 2 diabetes mellitus in Aktobe.

Materials and Methods

The study design was a cross-sectional clinical study without a control group. Inclusion criteria: the ability for autonomous behavior, provision of informed consent, and voluntary participation in the study. Exclusion criteria: type 1

diabetes, gestational diabetes, and other specific forms of diabetes; children and pregnant women; severe acute and chronic diseases; severe psychological impairment and absence of depression; respiratory failure; tumors and other severe conditions; participation in other studies.

The study population consisted of 1500 patients with type 2 diabetes mellitus registered for follow-up care in state polyclinics of the city of Aktobe, aged 18 to 70 years. A detailed characterization of the participants by age, education, and family income is presented in Table 1.

Table 1.

Quantitative sample of patients with type 2 diabetes mellitus in Aktobe.

Indicators	Age	18-44	8%
		45-59	34%
		60-70	58%
	Education	high	44%
		secondary specialized	33%
		secondary	23%
	Family income	up to 50 thousand per month	2%
		50–100 thousand per month	35%
		above 100 thousand	63%

Out of 1500 patients, there were 881 women and 619 men. The majority of respondents were aged 60-70 years (58% of the total), with the average age of participants being 62 years. By education level: higher education (33%), secondary specialized (43.56%), and secondary education (23.4%). Family income above 100 thousand was reported by 63% of respondents.

For self-assessment, the MFI–20 (The Multidimensional Fatigue Inventory) scale was used. The scale was developed by Dutch scientists *E. Smets, B. Garssen, B. Bonke, and J. Haes* and is a valid tool for measuring asthenia in the general population [15]. If the total score on one of the subscales is higher than 12, this may serve as a preliminary basis for diagnosing “asthenic syndrome.”

The survey was conducted by specially trained medical professionals. The results of the survey made it possible to combine the obtained data into homologous semantic groups - profiles reflecting various characteristics of the severity or absence of asthenia indicators. Below, in Table 1, the key and explanations of asthenia indicators are presented.

Table 2.

Key to the subjective asthenia assessment scale.

№	Indicators of asthenia	Question numbers of the scale	Scores
1	General asthenia	1, 5, 12, 16	
2	Reduced activity	3, 6, 10, 17	
3	Decreased motivation	4, 9, 15, 18	
4	Physical asthenia	2, 8, 14, 20	
5	Mental asthenia	7, 11, 13, 19	

The present work is part of the scientific research project of West Kazakhstan Marat Ospanov Medical University: “Personalized approach to diet therapy in patients with type 2 diabetes mellitus in the context of primary health care.” Approval was obtained from the Local Ethics Committee of West Kazakhstan Marat Ospanov Medical University on 19.11.2021, protocol №9.

Statistical processing was carried out using SPSS (Statistical Package for the Social Sciences) version 25 for Windows. Descriptive statistics, including medians, interquartile ranges (IQR), frequencies, and percentages, were used to characterize demographic and clinical variables. The normality of data distribution was tested using the Shapiro–Wilk test, and since most variables did not meet the criteria for normal distribution ($p < 0.05$), nonparametric methods were used for further analysis. The Pearson χ^2 test was applied to analyze differences in the frequency of categorical variables. The Mann–Whitney test was used to assess differences between men and women in various aspects of asthenia. Correlation analysis with Spearman’s coefficient was conducted to evaluate associations between age and different aspects of asthenia. All tests were two-tailed, and results were considered statistically significant at $p < 0.05$ and $p < 0.001$. Statistical analysis was performed using SPSS software version 25.0.

Results

Based on the results of our questionnaire, we obtained the following findings. Table 3 shows the differences between women and men across several parameters of asthenia (weakness and fatigue). The indicators of general asthenia were as follows: median in women - 11 (Q1-Q3: 8-12), in men - 10 (Q1-Q3: 8-12) ($p = 0.052$). The difference between women and men is insignificant, although close to the 0.05 threshold. For reduced activity, the median was the same (11) in both sexes ($p = 0.254$), indicating no significant differences. Decreased motivation showed the following results: median in women -10 (Q1-Q3: 8-12), in men - 10 (Q1-Q3: 7-12) ($p = 0.746$), no significant differences were found. Physical asthenia: in women the median was 11 (Q1-Q3: 9-13), in men - 11 (Q1-Q3: 9-12) ($p = 0.046$), which indicates a significant difference between sexes. Mental asthenia: median in women - 10 (Q1-Q3: 9-12), in men - 10 (Q1-Q3: 8-12) ($p = 0.351$), no significant differences were identified.

When analyzing the MFI–20 asthenia assessment scale in Table 3, it can be seen that the mean self-assessment value indicates a tendency toward deterioration in each of the five indicators of psychophysical health in patients with type 2 diabetes of both sexes, but higher scores were observed in women. It can also be concluded that the burden of the disease negatively affects the psychophysical state of the individual, contributing to the development of general asthenia and physical asthenia in both men and women. Thus, when comparing two independent groups (men and women) using the Mann–Whitney test, statistically significant differences were found for the indicators of general and physical asthenia ($p < 0.01$ for each indicator).

Table 3.

Quantitative analysis of self-assessment of patients with type 2 diabetes mellitus by gender using the MFI–20 scale.

Indicator	Gender of the participants				p value
	Female (n=881)		Male (n=619)		
	Me	Q_1-Q_3	Me	Q_1-Q_3	
General asthenia	11	8-12	10	8-12	0,052*
Reduced activity	11	9-13	11	9-13	0,254
Decreased motivation	10	8-12	10	7-12	0,746
Physical asthenia	11	9-13	11	9-12	0,046*
Mental asthenia	10	9-12	10	8-12	0,351

We analyzed (Table 4) the effect of diabetes duration on the manifestations of general asthenia. Only for the indicators of general asthenia, out of 1500 respondents, 1480 answered: among them, of 573 patients with diabetes lasting up to 5 years, 204 cases of general asthenia were identified; out of 681 patients with diabetes lasting 5-10 years, 296 cases; and among those with a disease duration of more than 10 years (233 patients), 87 cases of general asthenia were revealed. In all three surveyed groups, scores of ≤12 were obtained, reflecting the presence of asthenic syndrome.

Table 4.

Comparison of general asthenia in patients with type 2 diabetes mellitus with diabetes duration.

Duration of diabetes	number of general asthenia		p
	A6c. / n	%	
up to 5 years	204 / 573	35,6	0,014*
5–10 years	296 / 681	43,5	P_{1-2} = 0,014*
more than 10 years	87 / 233	37,3	

* - differences in indicators are statistically significant (p <0,05)

When comparing the frequency of general asthenia in the two groups with disease duration up to 5 years and from 5 to 10 years, statistically significant differences were found (p = 0.014). Patients with diabetes lasting 5 to 10 years had the highest frequency of general asthenia (43.5%), which was statistically significantly different from the group of patients with a diabetes duration of up to 5 years (35.6%). When assessing the relationship between the frequency of general asthenia and diabetes duration, an insignificant association was revealed (V = 0.076).

Analysis of employment status (Table 5) showed that employed individuals had a lower frequency of asthenia (32.7%) compared with the unemployed (44.5%) and pensioners (42.3%). The differences between employed and other groups (unemployed and pensioners) were statistically significant (p < 0.05). Employed people overall were less prone to general asthenia compared with the unemployed and pensioners.

Table 5.

Comparison of general asthenia with diabetes status.

Employment status	Frequency of General Asthenia		p
	Abs. / n	%	
employed	167 / 510	32,7	0,001*
unemployed	106 / 238	44,5	P_{1-2} = 0,003*
pensioner	302 / 713	42,3	P_{1-3} = 0,002*

* - differences in indicators are statistically significant (p <0,05)

When comparing the frequency of general asthenia depending on the employment status of the participants, statistically significant differences were found (p = 0.001). The identified differences were due to the higher frequency of general asthenia among the unemployed compared with the employed (p = 0.003) and between the unemployed and pensioners (p = 0.002). A weak association was noted between the compared characteristics (V = 0.1).

We conducted a Spearman correlation analysis between types of asthenia and the age of patients with type 2 diabetes mellitus. The graph shows the relationship between general asthenia (X-axis) and age (Y-axis) (Figure 1).

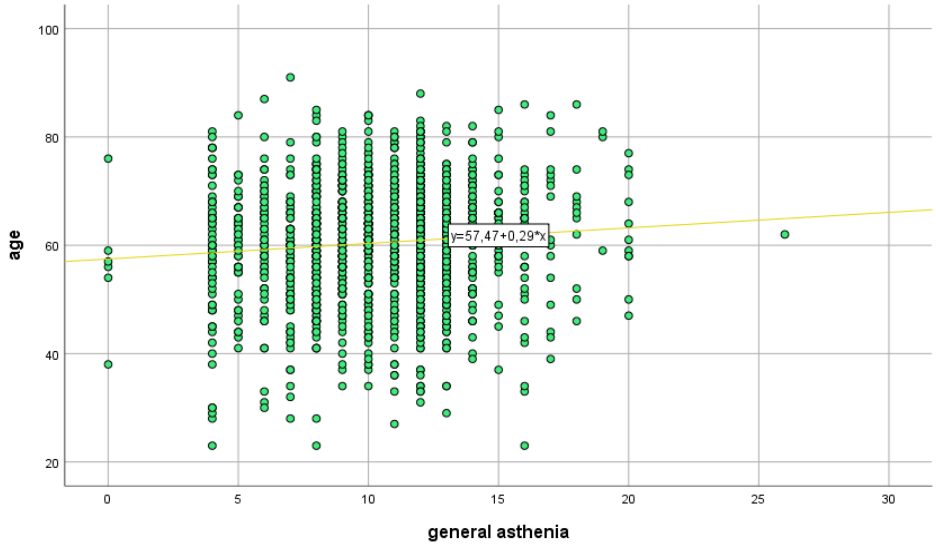

Figure 1. Correlation between general asthenia and age in patients with type 2 diabetes mellitus.

The dots represent individual observations, showing the level of general asthenia and the age of respondents. The trend line demonstrates the overall tendency of the relationship between age and the level of asthenia: as age increases, general asthenia rises. In our study results, general asthenia was weakly associated with age, which is evident from the slight slope of the trend line.

Figure 2 shows the relationship between the level of reduced activity and age. The trend line demonstrates the tendency of age dependence on reduced activity. The equation of the trend line indicates that reduced activity and age are weakly associated, since with an increase in the level of reduced activity, age increases only slightly.

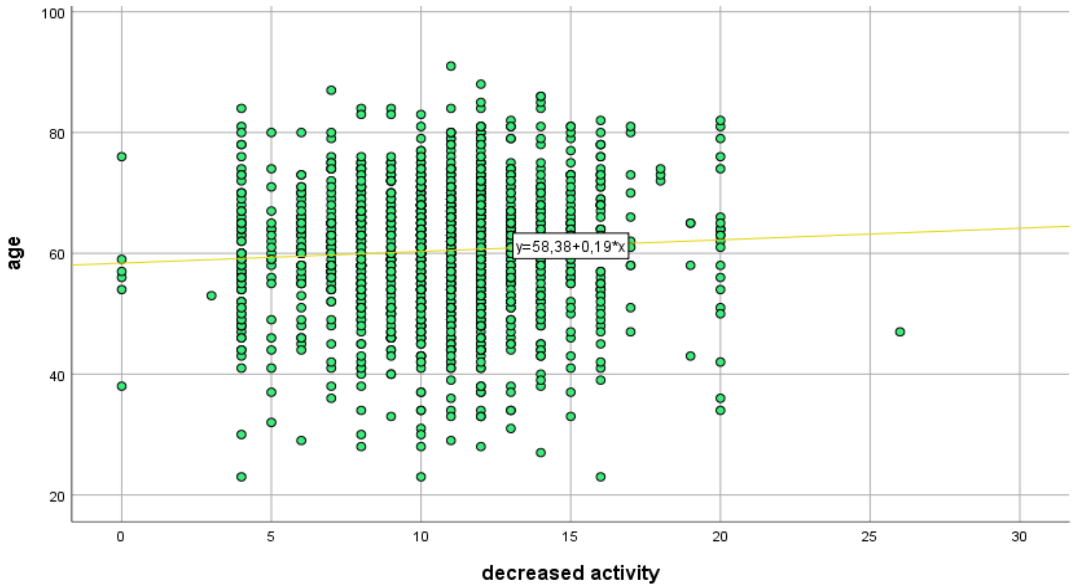

Figure 2. Correlation between decreased activity and age in patients with type 2 diabetes.

Figure 3 shows the relationship between the level of decreased motivation and age. An increase in the level of decreased motivation is associated with a slight increase in age, indicating a weak correlation.

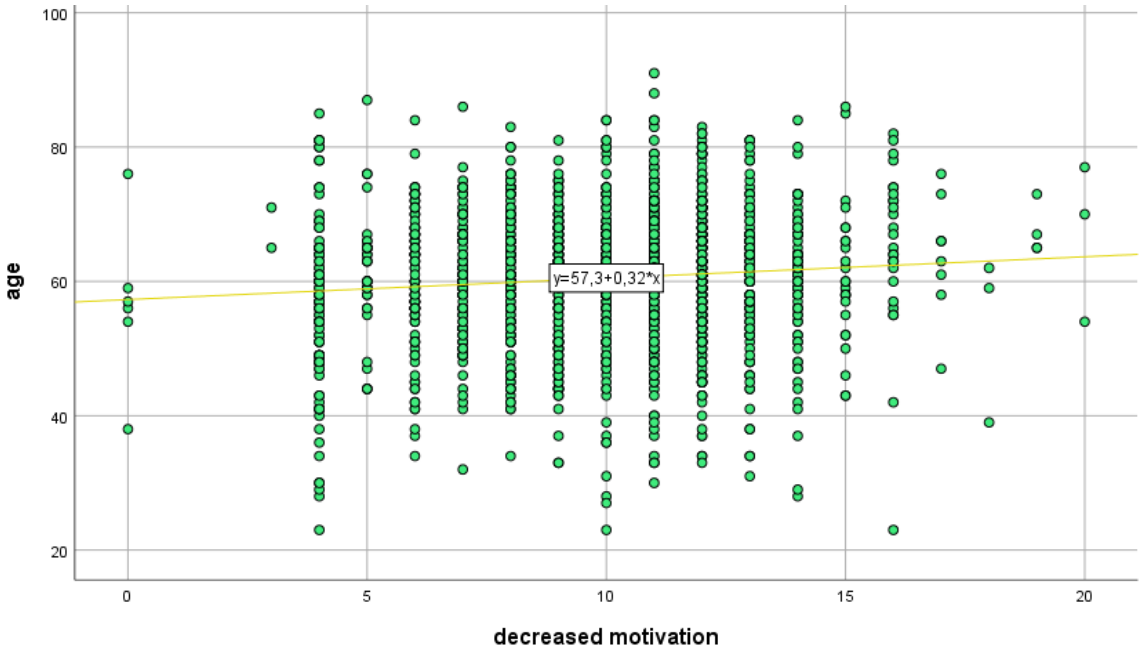

Figure 3. Correlation between decreased motivation and age in patients with type 2 diabetes.

Figure 4 shows the relationship between the level of physical asthenia and age. An increase in physical asthenia is associated with a slight increase in age; however, this relationship is rather weak.

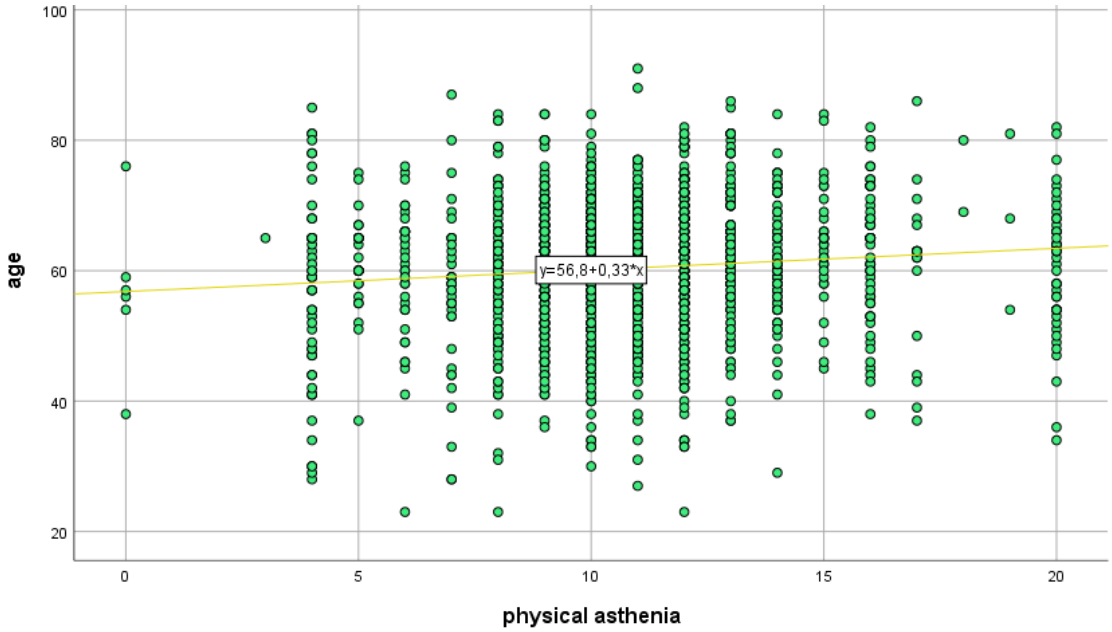

Figure 4. Correlation between physical asthenia and age in patients with type 2 diabetes mellitus.

Figure 5 shows the relationship between the level of mental asthenia and age. An increase in the level of mental asthenia is associated with a slight increase in age; however, this relationship is very weak and most likely insignificant for practical conclusions.

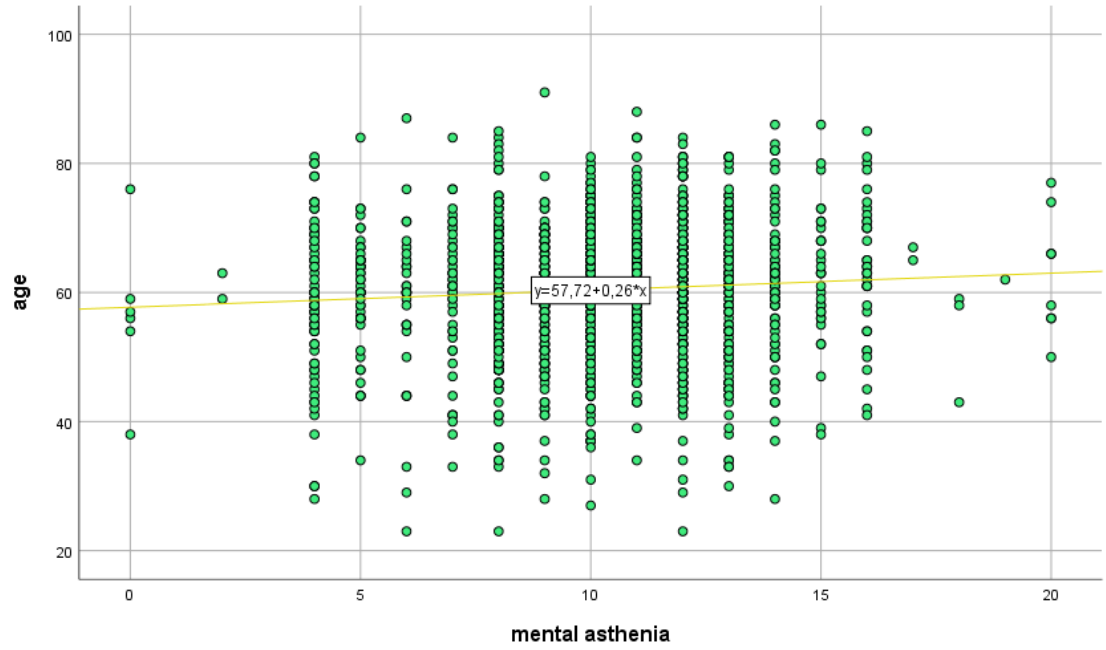

Figure 5. Correlation between mental asthenia and age in patients with type 2 diabetes mellitus.

Statistically significant direct correlations were also established between the age of patients with type 2 diabetes mellitus and types of asthenia: with general asthenia (rxy = 0.083; p = 0.001); reduced activity (rxy = 0.067; p = 0.010); decreased motivation (rxy = 0.089; p = 0.001); physical asthenia (rxy = 0.103; p = 0.000); mental asthenia (rxy = 0.067; p = 0.011).

Discussion

Based on the data analysis, we identified and described the psychological state of patients with type 2 diabetes mellitus. Each profile has its own characteristics that define susceptibility to asthenia. It is important to emphasize the significance of understanding asthenia, given its adverse consequences.

The duration and complications of type 2 diabetes are usually characterized by increased fatigue, impaired daily activities, and reduced productivity. Asthenia does not arise solely from physical fatigue or only from mental strain, etc. It may be caused by objective reasons, and most often they have a psychogenic nature. Asthenic disorders in the long course of T2DM are an integral part of the disease manifestation. With increasing duration of T2DM, cognitive

dysfunction progresses, while disease decompensation accelerates this process.

The symptoms of asthenia in T2DM mainly manifest in physical and psychological aspects. For example, patients experience weakness and low activity, cognitive impairments, and negative emotions, which seriously affect their daily lives and weaken normal functional activity [11]. Fatigue, including mental and physical exhaustion, is a common clinical symptom and is defined as a subjective perception of reduced ability to perform physical and intellectual tasks [6].

Chronic fatigue affects diabetes self-management, exerting a negative impact on daily functioning and well-being [2]. The prevalence of fatigue in patients with T2DM may be associated with various contributing factors, including socio-demographic aspects, clinical disease, inflammatory factors, psychological stress, as well as behavior and lifestyle [20].

With advancing age, the prevalence of type 2 diabetes increases significantly, also facilitated by the rising life expectancy of the population. In this regard, the management of patients with T2DM not only of elderly but also of senile age deserves special attention [13]. Patients with T2DM in older age groups much more frequently exhibit cognitive impairments than elderly individuals without this disease. These usually manifest as rapid fatigability, inadequate emotional reactions, impaired memory and attention, slower acquisition of new skills, etc. It has been established that further progression of cognitive dysfunction is influenced by the duration of T2DM, poor glycemic control, hypoglycemia, and social determinants of poor diabetes management [19]. Older patients significantly limit their activity, as they tire more quickly than younger patients, which causes distress, frustration, and ultimately depression.

In our study, although marital status was not examined, it is one of the predisposing factors of fatigue, which could influence its severity. Support provided by family members to patients with T2DM is very important due to the various limitations of the disease. Patients living in a family environment demonstrate significantly lower levels of fatigue, primarily thanks to the assistance they receive in daily life [3]. In contrast, patients living alone cannot share the burden of the disease or express their concerns to other family members. Thus, attempts to cope with the disease independently lead to increased levels of fatigue [7,14]. However, there are currently no unified recommendations for identifying and preventing fatigue or its clinical consequences in T2DM.

The prevalence of fatigue in patients with T2DM may be associated with various contributing factors, including socio-demographic aspects, clinical disease, inflammatory factors, psychological stress, as well as behavior and lifestyle. Considering these contributing factors, appropriate measures should be taken. For example, medical personnel should pay close attention to the patient's physical health, such as BMI, blood glucose levels, and other objective indicators, to monitor their condition.

One of the important components of therapy for patients with diabetes mellitus is adherence to treatment. It is known that most patients, due to insufficient knowledge, may skip medication doses, violate dietary recommendations, and avoid physical activity, which leads to chronic hyperglycemia and may predispose patients to asthenia [10].

Conclusions:

Patients with type 2 diabetes mellitus are susceptible to asthenia. The highest frequency of general asthenia is observed in patients with a diabetes duration of 5 to 10 years. A higher frequency of general asthenia was found among unemployed patients. Significant differences were established when comparing male and female patients with T2DM in terms of general and physical asthenia.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors:

Conceptualization: *Zinalieva A.N., Dilmagambetova G.S., Sartayeva A; methodology: Baspakova A.M;*

formal analysis: *Akhmetzhanova M.B., Tuleuova A.M; data processing: Moldasheva Z.B.;*

preparation of the original project: *Zinalieva A.N., Sartayeva A; review and editing: Dilmagambetova G.S.*

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EXPERIENCES OF PRIMARY CARE PSYCHOLOGISTS IN IDENTIFYING AND MANAGING GAMBLING DISORDER IN ALMATY AND ASTANA, KAZAKHSTAN: CHALLENGES AND IMPLICATIONS FOR PRACTICE

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Abstract

Background. Gambling addiction is becoming an increasingly common problem among adolescents and adults. Early diagnosis and prevention are key to avoid social and psychological consequences. As primary healthcare (PHC) serves as the first point of contact for patients, their families, and physicians, this study aims to examine the experiences of PHC psychologists in the detection, prevention, and management of gambling addiction across different age groups.

Materials and methods. We conducted a qualitative study with primary care psychologists to explore their experiences in identifying, preventing, and managing gambling disorder. Semi-structured interviews covered patient demographics, prevalence, diagnostic tools, prevention, support, and challenges. Data were analyzed using Dedoose software to identify themes, patterns, and barriers, providing insights for improving clinical practices, training, preventive programs, and policy interventions in gambling disorder care.

Results. Interviews with ten primary care psychologists (aged 25–45, 3 months–15 years' experience) revealed that gambling disorder is most prevalent among 18–24-year-olds, with adolescents 11–18 and adults 25–45 at moderate risk. Psychologists reported it often co-occurs with mental health issues such as depression, anxiety, and social isolation. Identification relies on interviews, standardized questionnaires, and observation, while prevention and intervention include education, therapy, family work, motivational interviewing, and collaboration with social and medical services. Specialists also noted a recent increase in female patients and emphasized that many individuals only seek help after family intervention. Loneliness and online engagement were identified as key vulnerability factors.

Conclusions. Gambling disorder is most prevalent among young adults and often co-occurs with mental health issues, highlighting the need for early identification and targeted interventions in primary care. Future efforts should focus on enhancing psychologist training, expanding preventive programs, and strengthening collaboration with social and medical services to improve detection, support, and treatment outcomes.

Key words: gambling addiction, population, primary health care, prevention, psychological assistance.

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Резюме

ОПЫТ ПСИХОЛОГОВ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ В ВЫЯВЛЕНИИ И ЛЕЧЕНИИ РАССТРОЙСТВ, СВЯЗАННЫХ С АЗАРТНЫМИ ИГРАМИ, В АЛМАТЫ И АСТАНЕ, КАЗАХСТАН: ПРОБЛЕМЫ И ПОСЛЕДСТВИЯ ДЛЯ ПРАКТИКИ

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Актуальность. Зависимость от азартных игр становится все более распространенной проблемой среди подростков и взрослых. Ранняя диагностика и профилактика являются ключом к предотвращению социальных и психологических последствий. Поскольку первичная медико-санитарная помощь (ПМСП) служит первым контактным лицом для пациентов, их семей и врачей, целью данного исследования является изучение опыта психологов ПМСП в выявлении, профилактике и лечении зависимости от азартных игр в разных возрастных группах.

Материалы и методы. Мы провели качественное исследование с участием психологов первичной медико-санитарной помощи, чтобы изучить их опыт выявления, профилактики и лечения расстройств, связанных с азартными играми. В ходе полуструктурированных интервью были представлены демографические данные пациентов, их распространенность, диагностические инструменты, профилактика, поддержка и проблемы. Данные были проанализированы с помощью программного обеспечения Dedoose для выявления тем, закономерностей и барьеров, что позволило улучшить клиническую практику, обучение, профилактические программы и политические вмешательства в лечение расстройств, связанных с азартными играми.

Результаты. Интервью с 10 психологами первичной медико–санитарной помощи (в возрасте 25-45 лет, опыт работы от 3 месяцев до 15 лет) показали, что расстройства, связанные с азартными играми, наиболее распространены среди 18-24-летних, при этом подростки 11-18 и взрослые 25-45 лет подвергаются умеренному риску. Психологи сообщили, что это часто сопровождается проблемами психического здоровья, такими как депрессия, тревожность и социальная изоляция. Выявление заболеваний основывается на опросах, стандартных анкетах и наблюдении, в то время как профилактика и вмешательство включают образование, терапию, семейную работу, мотивационные интервью и сотрудничество с социальными и медицинскими службами. Специалисты также отметили недавнее увеличение числа пациенток женского пола и подчеркнули, что многие люди обращаются за помощью только после вмешательства семьи. Одиночество и онлайн-активность были определены в качестве ключевых факторов уязвимости.

Выводы. Расстройство, связанное с азартными играми, наиболее распространено среди молодежи и часто сочетается с проблемами психического здоровья, что подчеркивает необходимость раннего выявления и целенаправленного вмешательства в рамках первичной медико-санитарной помощи. Будущие усилия должны быть направлены на повышение уровня подготовки психологов, расширение профилактических программ и укрепление сотрудничества с социальными и медицинскими службами для улучшения результатов выявления, поддержки и лечения.

Ключевые слова: *зависимость от азартных игр, население, первичная медико-санитарная помощь, профилактика, психологическая помощь.*

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Түйіндеме

ҚАЗАҚСТАН РЕСПУБЛИКАСЫНЫҢ АЛМАТЫ ЖӘНЕ АСТАНА ҚАЛАЛАРЫНДАҒЫ АЛҒАШҚЫ МЕДИЦИНАЛЫҚ-САНИТАРЛЫҚ ДЕҢГЕЙДЕГІ ПСИХОЛОГТАРДЫҢ ҚҰМАР ОЙЫНДАРҒА БАЙЛАНЫСТЫ БҰЗЫЛЫСТАРДЫ АНЫҚТАУ ЖӘНЕ КӨМЕК КӨРСЕТУДЕГІ ТӘЖІРИБЕСІ: ҚИЫНШЫЛЫҚТАР МЕН ПРАКТИКАҒА ӘСЕРЛЕРІ

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Кіріспе. Құмар ойындарға тәуелділік жасөспірімдер мен ересектер арасында жиі кездесетін проблемаға айналуда. Ерте диагностика және алдын-алу әлеуметтік және психологиялық зардаптарды болдырмаудың кілті болып табылады. Алғашқы медициналық-санитарлық көмек (МСАК) пациенттер, олардың отбасылары және дәрігерлер үшін бірінші байланыс нүктесі ретінде қызмет ететіндіктен, бұл зерттеу МСАК психологтарының әртүрлі жас топтарындағы құмар ойындарға тәуелділікті анықтау, алдын алу және басқарудағы тәжірибесін зерттеуге бағытталған.

Материалдар мен әдістер. Біз құмар ойындардың бұзылуын анықтау, алдын алу және басқару бойынша тәжірибелерін зерттеу үшін алғашқы медициналық-санитарлық көмек психологтарымен сапалы зерттеу жүргіздік. Жартылай құрылымдалған сұхбаттар пациенттердің демографиясын, таралуын, диагностикалық құралдарын, алдын алуды, қолдауды және проблемаларды қамтыды. Деректер тақырыптарды, үлгілерді және кедергілерді анықтау үшін Dedoose бағдарламалық құралын пайдалану арқылы талданды, бұл клиникалық тәжірибені, оқытуды, профилактикалық бағдарламаларды және құмар ойындардың бұзылуын емдеуге саяси араласуды жақсарту үшін түсінік береді.

Нәтижелер. Алғашқы медициналық–санитарлық көмек көрсететін 10 психологпен сұхбат (25-45 жас, 3 ай-15 жылдық жұмыс өтілі) құмар ойындардың бұзылуы 18-24 жас аралығындағы жасөспірімдер арасында жиі кездесетінін көрсетті, 11-18 жас аралығындағы жасөспірімдер мен 25-45 жас аралығындағы ересектер орташа тәуекелге ұшырайды. Психологтар бұл көбінесе депрессия, мазасыздық және әлеуметтік оқшаулану сияқты психикалық денсаулық мәселелерімен қатар жүретінін хабарлады. Сәйкестендіру сұхбатқа, стандартталған сауалнамаларға және бақылауға негізделген, ал алдын алу және араласу білім беруді, терапияны, отбасылық жұмысты, мотивациялық сұхбатты және әлеуметтік және медициналық қызметтермен ынтымақтастықты қамтиды. Мамандар сонымен қатар жақында әйел пациенттер санының артқанын атап өтті және көптеген адамдар отбасының араласуынан кейін ғана көмекке жүгінетінін атап өтті. Интернеттегі жалғыздық пен өзара әрекеттесу осалдықтың негізгі факторлары ретінде анықталды.

Қорытынды. Құмар ойындарға тәуелділік көбінесе жастар арасында жиі кездеседі және жиі психикалық денсаулық мәселелерімен қатар жүреді. Бұл алғашқы медициналық көмек көрсету деңгейінде ерте анықтау мен мақсатты араласудың қажеттілігін көрсетеді. Болашақтағы күш-жігер психологтарды даярлауды жетілдіруге, алдын алу бағдарламаларын кеңейтуге және анықтау, қолдау мен емдеу нәтижелерін жақсарту үшін әлеуметтік және медициналық қызметтермен өзара іс-қимылды күшейтуге бағытталуы тиіс.

Түйінді сөздер: *құмар ойындарға тәуелділік, халық, алғашқы медициналық-санитарлық көмек, профилактика, психологиялық көмек.*

Дәйексөз үшін:

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Introduction

Globally, gambling is highly prevalent, with approximately 1.4–1.9% of adults meeting criteria for problematic gambling, with the highest rates observed among online casino and slot players [18]. The prevalence is notably higher in North America (5.3%) compared to Europe (1.3%), and men are about 3.4 times more likely than women to develop gambling problems. Younger adults also show a greater risk than middle-aged or older individuals, reflecting clear regional and demographic variations [3,4]. Given its strong association with mental health and social harms, stricter regulation and public health monitoring of gambling are urgently needed worldwide.

Gambling addiction, classified as a behavioral (non-substance) addiction, involves persistent and recurrent maladaptive gambling behavior leading to significant distress or impairment. It closely resembles substance addictions in terms of neurobiology, comorbidity, and loss of control, and is currently the only behavioral addiction recognized in the DSM-5. While most individuals gamble recreationally, a small minority develop pathological patterns characterized by preoccupation, tolerance, withdrawal-like symptoms, and continued gambling despite adverse consequences [5, 15].

Gambling disorder is influenced by a combination of psychological, social, and behavioral risk factors. Key predictors include male gender, younger age, impulsivity, stress, cognitive distortions, and comorbid mental health disorders such as depression, anxiety, and substance use. Environmental and situational factors—like financial difficulties, family dysfunction, exposure to gambling advertising, and easy access to online gambling—further increase vulnerability. During the COVID-19 pandemic, isolation, boredom, and financial strain intensified online gambling behaviors, highlighting how stress and environmental changes can exacerbate gambling risk [12].

The study of 399 students in Kazakhstan found that 11% had some gambling problems and 5.76% were probable pathological gamblers, primarily males under 21 who frequently bet on sports. Problem gambling was associated with male gender, alcohol use, low family cohesion, depression, and suicidal thoughts, while higher paternal education and part-time employment appeared to

be protective factors. Despite certain limitations, the findings reveal an alarming prevalence of gambling among students and emphasize the need for increased awareness, preventive measures, and policy interventions in Kazakhstan [7]. Another study found that Russian students had higher gaming disorder scores than Kazakh students (14.2 vs. 12.9, $p<0.001$), males scored higher than females, and religiosity was associated with lower GD scores but was not a significant predictor, while significant predictors included eating behavior, weekly gaming hours, loneliness, male gender, country (Russia), and age [8].

Problem gambling affects a small but significant proportion of patients in healthcare settings, with rates of 0.9% for severe problems and 4.3% for low-to-moderate problems, and is more common among males, young adults, students, and those with depression or substance use [2]. Barriers to treatment include structural factors (availability, infrastructure, anonymity) and individual factors (guilt, awareness, motivation), while facilitators involve accessible and reputable services [20]. Mental health clinicians often encounter patients with gambling problems but lack consistent screening and training, with only a minority screening frequently or feeling confident to intervene. These findings underscore the need for enhanced clinician education, systematic screening, and integration of gambling services to improve identification and treatment [10].

In Kazakhstan, primary health care (PHC) is responsible for the health of the assigned population and includes psychologists on staff. Despite the existence of prevention programs and informational materials, early detection of gambling addiction remains challenging, as patients often conceal the problem and seek help only after family intervention or the development of comorbid mental disorders. Since PHC is the initial contact for patients, their families, and physicians, the aim of our study is to explore the experiences of PHC psychologists in identifying, preventing, and treating gambling addiction among various age groups.

Materials and methods

We conducted a qualitative study to explore the experiences and practices of psychologists working in primary care settings regarding the identification, prevention, and management of gambling disorder. Interview questions were carefully developed in collaboration with psychologists, public health specialists, and healthcare managers to ensure that they addressed the full scope of relevant clinical, preventive, and administrative aspects. Data were collected from primary care psychologists through semi-structured interviews, with each respondent asked 10 in-depth questions covering patient age groups, prevalence and severity of gambling addiction, diagnostic tools, prevention strategies, forms of psychological support, and the main challenges they face in practice. Interviews were conducted individually, both in person and online, depending on participant availability, and audio recordings were transcribed verbatim to maintain the accuracy of responses.

For data analysis, a qualitative approach was employed using Dedoose software, which allowed systematic organization and coding of responses, identification of recurring themes, patterns, and typical challenges, and comparative analysis across participants. This approach also enabled the researchers to capture nuanced insights into the strategies psychologists use, the obstacles they encounter in clinical practice, and the variations in approaches based on patient demographics or clinical context. In addition, the study explored structural, organizational, and contextual factors affecting psychologists' ability to detect and manage gambling disorder, including time constraints, patient disclosure issues, availability of resources, and collaboration with other healthcare and social services.

By combining detailed semi-structured interviews with rigorous qualitative analysis, this study provides a comprehensive understanding of the current practices, challenges, and needs of primary care psychologists in addressing gambling disorder, and offers valuable guidance for designing targeted training, preventive programs, and policy interventions to improve early identification and care.

Ethical Approval: The study was approved by the Local Ethics Committee of the West Kazakhstan Medical university (11-2025/128-МП), Aktobe, Kazakhstan

Results

Interviews were conducted with primary care psychologists (n=12) aged 25 to 40 years, with professional experience ranging from 3 months to 15 years.

Prevalence and Age Groups

According to the psychologists' experience, patients exhibiting signs of gambling disorder are encountered periodically. The most vulnerable groups are adolescents aged 11–24 and adults up to 40 years old, who often display impulsivity, emotional instability, and high engagement in online environments. Specialists also noted a recent increase in female patients, either seeking help for themselves or due to the gambling problems of close relatives.

Many do not openly admit to their addiction. Usually, it is noticed by parents or relatives, and only then is the patient referred for help," reported one participant.

Table 1 presents the frequency and characteristics of gambling disorder risk across different age groups, showing the highest risk among 19–24-year-olds, moderate risk in adolescents 11–18 and adults 25–40, and low risk in those over 40.

Table 1.

Age Groups and Gambling Disorder Risk.

Age Group	Frequency	Characteristics
11–18 years	Moderate	Transitional age, impulsivity, online involvement
19–24 years	High	Young adults, high emotional instability, online games
25–40 years	Moderate	Adult men and women, credit and financial risks
Over 40 years	Low	Rare, possible hereditary predisposition

Gambling Disorder as a Standalone or Secondary Condition

Specialists' opinions varied. 1 out of 10 psychologist views the gambling disorder as a standalone behavioral condition, while others note its strong association with psychological disorders as depression, anxiety, emotional burnout, and social maladaptation.

Gambling disorder can manifest as an independent condition, but it more often develops alongside other psychological problems," shared one clinician.

Individuals experiencing loneliness or social isolation were considered particularly vulnerable, as gambling is often used to relieve stress or distract from personal problems.

Prevention and Intervention Methods

A comprehensive approach is used for prevention and intervention. Identification is based on interviews, standardized questionnaires, and observation. Prevention strategies include individual psychological support through lectures, educational programs, and social media campaigns, while interventions involve cognitive-behavioral therapy, Gestalt therapy, family therapy, motivational interviewing, and, in some cases, hypnotherapy. Effectiveness is enhanced through collaboration with social and medical services. One psychologist expressed the concerns about the fragmented care for patients with gambling and missing time for timely interventions upon the patients' readiness. Table 2 summarizes the prevention methods, identification approaches, intervention strategies, and collaboration with other services used by psychologists to address gambling disorder.

Table 2.

Prevention, Identification, and Intervention Strategies.

	Prevention	Identification Methods	Intervention	Collaboration with Other Services
1.	Consultations, school lectures, brochures, social media	Clinical interview, questionnaires, observation	Individual counseling, motivational interviewing, group sessions, family work	Addiction services, social services, schools, adaptation centers
2.	Social media	Clinical interview	Group therapy	–
3.	Lectures	Interview, observation, comorbidity assessment	Individual counseling	–
4.	Not conducted	Individual interview	–	–
5.	Social media	Testing	Individual counseling	Social worker
6.	Lectures, informational materials	Interview, observation	Individual counseling, hypnotherapy, psychotherapy, family work	–
7.	Lectures, brochures, consultations, social media, financial literacy programs	Interview, testing	Individual and group counseling, Gestalt therapy	Addiction services, social workers

Discussion

Our study highlights multiple barriers to the identification, prevention, and treatment of gambling disorder (GD) in Kazakhstan. Primary care psychologists reported low public awareness of gambling addiction, denial by patients and their families, stigma associated with seeking psychological help, limited motivation to participate in treatment programs, and insufficient specialist training as the most salient challenges. These findings correspond closely with international research showing that GD is highly stigmatized compared to other mental health conditions [6,14]. Problem gambling is often associated with negative stereotypes such as irresponsibility, greed, and lack of self-control, which can lead to social distancing, perceived discrimination, and reduced opportunities in employment, education, and social functioning [11]. Our Table 2 results illustrate that psychologists perceive a need for active collaboration with social and medical services to overcome these barriers, reflecting the structural dimensions of stigma identified in the international literature [21].

Attribution theory provides a useful framework for interpreting our findings. Conditions perceived as controllable are more heavily stigmatized than those attributed to uncontrollable factors such as genetics or biology [19]. In line with this theory, our participants noted that patients and their families often view gambling disorder as a moral or character flaw rather than a medical or behavioral condition. This moralizing perspective contributes to concealment behaviors, consistent with international studies showing that individuals with GD frequently hide their gambling problems to avoid social judgment [16]. Our interviews indicated that concealment is often initiated by adolescents or young adults, or by family members of adult patients, and that problems are only addressed once comorbid psychological issues emerge. These findings align with research showing that secrecy and self-stigma exacerbate psychological distress and reduce help-seeking [17].

We revealed that adolescents aged 11–24 and adults up to 40 years old are the most vulnerable groups, often exhibiting impulsivity, emotional instability, and high engagement in online environments. This corresponds with international findings that younger individuals are particularly prone to problem gambling and stigma internalization [9]. Psychologists also reported a notable increase in female patients seeking help, either for themselves or due to the gambling problems of relatives. This observation aligns with prior studies indicating that women with gambling disorder may experience higher perceived and self-stigma, emphasizing the need for interventions specifically tailored to this demographic [16].

Structural and contextual factors further exacerbate the impact of stigma. Our participants emphasized limited training in gambling disorder and lack of standardized screening tools in primary care, which hinder early detection. International research shows that structural stigma—embedded in healthcare systems, societal norms, and institutional policies—can reinforce both public and self-stigma, negatively affecting mental health outcomes [1]. In Kazakhstan, collaborative approaches involving social services, schools, and healthcare providers, as described in Table 2, are essential to address these structural barriers and improve identification and intervention.

The international literature also underscores the importance of targeting both public and self-stigma. Public stigma in GD is driven by moralizing attributions, beliefs about dangerousness, and negative stereotypes, all of which our participants' experiences echo. While gambling disorder is generally perceived as less dangerous than alcohol use disorder or schizophrenia, it is still associated with disruptiveness and social consequences, which may reinforce concealment and internalized shame [6]. As our interviews reveal, patients' reluctance to openly disclose gambling behaviors can delay engagement in preventive or corrective interventions, a mechanism observed globally [13].

Limitations and Future Directions. This study has several limitations. First, the sample size was small (n=10) and limited to primary care psychologists aged 25–40, which may restrict the transferability of the findings to other regions, age groups, or professional categories. The study focused only on psychologists in primary care, excluding other healthcare providers (e.g., psychiatrists, social workers) and patients themselves, limiting perspectives on the broader system of care and lived experiences of gambling disorder. Finally, the study did not quantitatively assess the prevalence of stigma or evaluate the effectiveness of existing interventions, limiting its ability to provide causal or population-level conclusions.

Future research should expand to larger and more diverse samples, including different healthcare professionals, patients, and family members, to capture a more comprehensive view of gambling disorder management in Kazakhstan. Quantitative studies could measure the prevalence and impact of public, self-, and structural stigma, providing a stronger evidence base for targeted interventions. Longitudinal research is needed to evaluate the effectiveness and sustainability of stigma-reduction programs, including education, advocacy, and contact-based strategies. Additionally, culturally tailored interventions addressing gender-specific vulnerabilities, particularly among women and adolescents, should be developed and tested. Finally, exploring the structural stigma within healthcare, social services, and the gambling industry could inform policy and systemic approaches to reduce barriers to care and improve early detection and treatment outcomes.

Conclusions. Gambling disorder is most common among adolescents and young adults, with impulsivity, emotional instability, and social isolation increasing vulnerability. It often co-occurs with mental health issues such as depression and anxiety, and many patients seek help only after family intervention. Primary care psychologists use a combination of interviews, questionnaires, education, therapy, and collaboration with social services for prevention and intervention. Future efforts should focus on improving training, expanding preventive programs, and enhancing integrated care to support early identification and effective treatment.

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THE RESULTS OF PSYCHOMETRIC SCREENING TO STUDY THE PRESUICIDAL ATTITUDES OF YOUTH AND YOUNG ADULTS IN KAZAKHSTAN

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Abstract

Introduction: The relevance of the study is dictated by the need to develop a methodology for early recognition and study of suicide risk and its prevention. According to the World Health Organization (WHO), Kazakhstan is among the countries with the highest suicide rate in the world. The number of suicidal outcomes is not decreasing, bringing human grief to loved ones and putting a burden on the social and economic development of the country. It is believed that most of the suicides might not have happened if proper interventions had been taken.

The purpose of the study: To identify the underlying mechanisms of suicidal behavior and develop suicide prevention measures among young people in Kazakhstan (18-40 years old).

Methods. Clinical-psychopathological and clinical-dynamic methods; psychometric method - Depression, Anxiety, and Stress Scale and Paykel suicide risk questionnaire, as well as laboratory studies. The study included 100 patients with suicidal tendencies and 100 participants without mental pathology aged 18 to 40 years.

Results: The results obtained indicate that those at risk of suicide, that is, those who are depressed or anxious, as well as those who abuse psychoactive substances, deserve the most attention. In this group of examined individuals, the highest rates of psychometric research and laboratory markers of suicide were revealed.

Conclusions. The most significant is the conduct of screening studies using the DASS scale (Depression Anxiety Stress Scale) and the Paykel Questionnaire (Paykel Suicide Risk Questionnaire) in the future of the study, aimed at further work and offering simple ways to prevent suicide among the country's youth.

Keywords: *suicide, bio-psycho-social model, youth, depression, anxiety, stress, Depression Anxiety Stress Scale (DASS) and the Paykel Suicide Risk Questionnaire.*

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Резюме

РЕЗУЛЬТАТЫ БИОПСИХОМЕТРИЧЕСКОГО СКРИНИНГА ПО ИЗУЧЕНИЮ ПРЕСУИЦИДАЛЬНЫХ УСТАНОВОК ЮНОШЕСТВА И МОЛОДЫХ ВЗРОСЛЫХ В КАЗАХСТАНЕ

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Введение: Актуальность исследования диктуется необходимостью разработки методики раннего распознавания и изучения риска суицида и ее превенции. Согласно информации Всемирной организации здравоохранения (ВОЗ) Казахстан входит в число стран с самым высоким уровнем суицидов в мире. Количество суицидальных исходов не снижается, принося человеческое горе близким и накладывая бремя на социально-экономическое развитие страны. Считается, что большая часть самоубийств могла бы и не произойти, если бы были предприняты надлежащие вмешательства.

Цель исследования: Выявление глубинных механизмов суицидального поведения и выработка мер профилактики суицида среди молодежи Казахстана (18–40 лет).

Методы. Клинико-психопатологический и клинико-динамический методы; психометрический метод - Шкала депрессии, тревоги и стресса (Depression, Anxiety, and Stress Scale-21, DASS-21) и опросник суицидального риска Paykel, а также лабораторные исследования. Материалом исследования явились 100 пациентов с суицидальными тенденциями и 100 участников - без психической патологии в возрасте от 18 до 40 лет.

Результаты: Полученные результаты свидетельствуют о том, что наибольшего внимания заслуживают лица с риском суицида, то есть находящееся в состоянии депрессии либо тревоги, а также лица, злоупотребляющие психоактивными веществами. В данной группе исследованных выявлены наивысшие показатели психометрического исследования и лабораторных маркеров суицида.

Выводы. Наиболее значимыми является проведение скрининговых исследований с использованием шкалы DASS (Depression Anxiety Stress Scale) и Опросника Пайкеля (Опросник суицидального риска Paykel) в перспективе исследования, направленная для дальнейшей работы и предлагаются несложные пути профилактики суицидов среди молодежи страны.

Ключевые слова: *суициды, био-психо-социальная модель, молодежь, депрессия, тревога, стресс, шкала DASS (Depression Anxiety Stress Scale) и Опросник суицидального риска Paykel).*

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Түйіндеме

ҚАЗАҚСТАНДАҒЫ ЖАСӨСПІРІМДЕР МЕН ЖАС ЕРЕСЕКТЕРДІҢ ПРЕСУИЦИДТІК КӨЗҚАРАСТАРЫН ЗЕРДЕЛЕУ БОЙЫНША ПСИХОМЕТРИЯЛЫҚ СКРИНИНГТІҢ НӘТИЖЕЛЕРІ

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Кіріспе: Зерттеудің өзектілігі суицид пен оның алдын алу қаупін ерте тану және зерттеу әдістемесін әзірлеу қажеттілігінен туындайды. Дүниежүзілік денсаулық сақтау ұйымының (ДДҰ) ақпаратына сәйкес, Қазақстан әлемдегі суицид деңгейі ең жоғары елдердің қатарына кіреді. Өз-өзіне қол жұмсау нәтижелерінің саны азаймайды, бұл адамның қайғысын жақындарына әкеледі және елдің әлеуметтік-экономикалық дамуына ауыртпалық түсіреді. Егер тиісті араласулар жасалса, суицидтің көп бөлігі болмауы мүмкін деп саналады.

Зерттеу мақсаты: Суицидтік мінез-құлықтың терең тетіктерін анықтау және Қазақстан жастары (18-40 жас) арасында суицидтің алдын алу шараларын әзірлеу.

Әдістері. Клиникалық-психопатологиялық және клиникалық-динамикалық әдістер; психометриялық әдіс – депрессия, абыржу және стресс шкаласы (Depression, Anxiety, and Stress Scale-21, DASS-21) және Paykel суицид қаупінің сауалнамасы, сондай-ақ зертханалық зерттеулер. Зерттеу материалы суицид тенденциясы бар 100 пациент және 100 қатысушы болды - 18 бен 40 жас аралығындағы психикалық патологиясыз.

Нәтижелер: Нәтижелер өз-өзіне қол жұмсау қаупі бар, яғни депрессия немесе абыржу жағдайында, сондай-ақ нашақорлықпен ауыратын адамдарға көп көңіл бөлінетінін көрсетеді. Зерттелгендердің осы тобында психометриялық зерттеудің және суицидтің зертханалық маркерлерінің ең жоғары көрсеткіштері анықталды.

Қорытындылар. Одан әрі жұмыс істеуге бағытталған зерттеу перспективасында DASS (Depression Anxiety Stress Scale) шкаласын және Пайкель сауалнамасын (Paykel суицид қаупінің сауалнамасы) пайдалана отырып, скринингтік зерттеулер жүргізу аса маңызды болып табылады және ел жастары арасында суицидтің алдын алудың қарапайым жолдары ұсынылады.

Түйінді сөздер: *суицид, био-психо-әлеуметтік модель, жастар, депрессия, абыржу, стресс, DASS (Depression Anxiety Stress Scale) шкаласы, Пайкель сауалнамасы (Paykel).*

Дәйексөз үшін:

Есқалиева А.Т., Абетова А.А., Жамалиева Л.М., Есімов Н.Б., Музафаров Р.Х., Тілеубаева Ш.М., Абетова Д.Ә., Абенова Н.А., Жакиева Ш.С., Құдайбергенова С. К., Смолинов И.Ғ., Саттаров Г.Р., Султангереев Е.Б. Қолқамықын сегменті окклюзиясы бар науқастарды хирургиялық емдеудің асқынуларының алдын алу жөніндегі шаралардың тиімділігін бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 143-152. *doi 10.34689/SH.2025.27.5.018*

Introduction

The relevance of the study is dictated by the need to develop a methodology for early recognition and study of suicide risk and its prevention. According to the information of the World Health Organization (WHO), Kazakhstan is among the countries with the highest suicide rate in the world. The number of suicidal outcomes is not decreasing, bringing human grief to loved ones and putting a burden on the social and economic development of the country. It is believed that most of the suicides might not have happened if proper interventions had been taken [1, 2].

Suicide is formed by a number of interacting cultural, social, psychological, biological, and situational factors combined with mental disorders, which act as the main risk factor. National suicide studies show that suicidal behavior varies in different countries [3, 4].

Difficulties in regulating emotions are recognized as one of the reasons specific to adolescents and young people. Research focuses mainly on personality, while the theoretical foundations emphasize the role of emotions, relationships, community, and society [5]. In a systematic review, it was shown that difficulties in regulating emotions are associated with suicidal behavior (thoughts and attempts) in both adults and adolescents [6], however, other researchers report conflicting impact results on suicide attempts [7].

A large number of recent studies have revealed neurobiological mechanisms of suicide [8-10]. Important biomedical features identified by other authors also included malnutrition, alcohol consumption, smoking, sleep, exercise, markers of hypothalamic-pituitary-thyroid axis activity, and others [11, 4].

Scientific studies suggest a link between the intensity of suicidal behavior and changes in the concentration of certain biochemical parameters, including oxidative stress. The general oxidative status and the Index of oxidative stress can increase in parallel with the severity of suicidal behavior [12-16].

Patients with depressive disorders are particularly prone to suicide risk. Severe depression, severity of hopelessness, along with a history of suicide attempts, suicidal thoughts, and psychotic symptoms predicted subsequent suicide attempts and death by suicide [17-19].

Clinically significant symptoms of depression and anxiety are widespread among young people (according to various estimates, about 24% and 4-49%, respectively), suicidal thoughts from 2 to 12% [20-25], however, the review did not include people with medical problems.

Thus, numerous studies of the prevalence of suicidal outcomes and pre-suicidal states in many countries of the world and Kazakhstan have different limitations, either in terms of the characteristics of participants, or assessment tools, etc., therefore, they give contradictory results. Figures reflecting the number of suicides are usually underestimated due to the ineffectiveness of epidemiological surveillance systems, the misuse of suicide among accidental deaths, and the criminalization of suicide in some countries. In an effort to make suicide prevention strategies effective and culturally acceptable, it is important to study the underlying mechanisms, reliable indicators, and risk factors of suicidality in order to develop effective interventions, prevention, and rehabilitation programs.

Aim:

Identification of the underlying mechanisms of suicidal behavior and development of suicide prevention measures among the youth of Kazakhstan (18-40 years old).

Tasks:

1. Identification of new psychosocial suicide risk factors and their interrelationships.

2. Study of psychological suicide risk factors and their interrelationships.

3. Study of peripheral inflammatory markers of suicidal behavior and parameters of oxidative stress, with a focus on specific suicidal outcomes, their relationship with other clinical, demographic and psychosocial determinants for predicting suicide-related phenotypes.

Research design: A qualitative research was conducted using focus groups with 200 participants. The study was conducted in the period from January to June 2025 on the basis of the Republican State Enterprise on the right of economic management “Republican Scientific and Practical Center for Mental Health” of the Ministry of Health of the Republic of Kazakhstan and Municipal State Enterprise on the right of economic management “Mental Health Center” of the Almaty City Health Department.

Research materials

Inclusion and exclusion criteria: voluntary consent, age of participants from 18-40 years, absence of acute psychopathology.

1st group. With suicidal tendencies (with suicide attempt and/or suicidal thoughts) - 30 participants.

The 2nd group. People at risk group (stress, depression, anxiety, substance abuse and personality disorders) - 70 participants.

The 3rd group. Control group (without mental pathology) - 100 participants.

Research methods

I. Clinical and psychopathological method.

II. The clinical and dynamic method.

III. The psychrometric method.

b) Paykel Suicide Risk Questionnaire, which is a tool for assessing suicidal thoughts and behavior.

IV. Laboratory studies.

The results of the study:

An analysis of the social and demographic characteristics of the study participants showed that among the 30 surveyed individuals in the 1st group (n=14 female (43.8%) and n=18 (56.2% male), the ratio of female and male was presented in statistically comparable values. Among the 70 examined individuals in the 2nd group (n=51 females (2.9%) and n=19 (27.1%) males), the female sex ratio was significantly higher statistically ($p<0.005$) than the male sex. Among the 100 examined individuals in the 3rd group (n=61 females and n=39 males), the ratio of female participants was significantly higher statistically ($p<0.005$) than male.

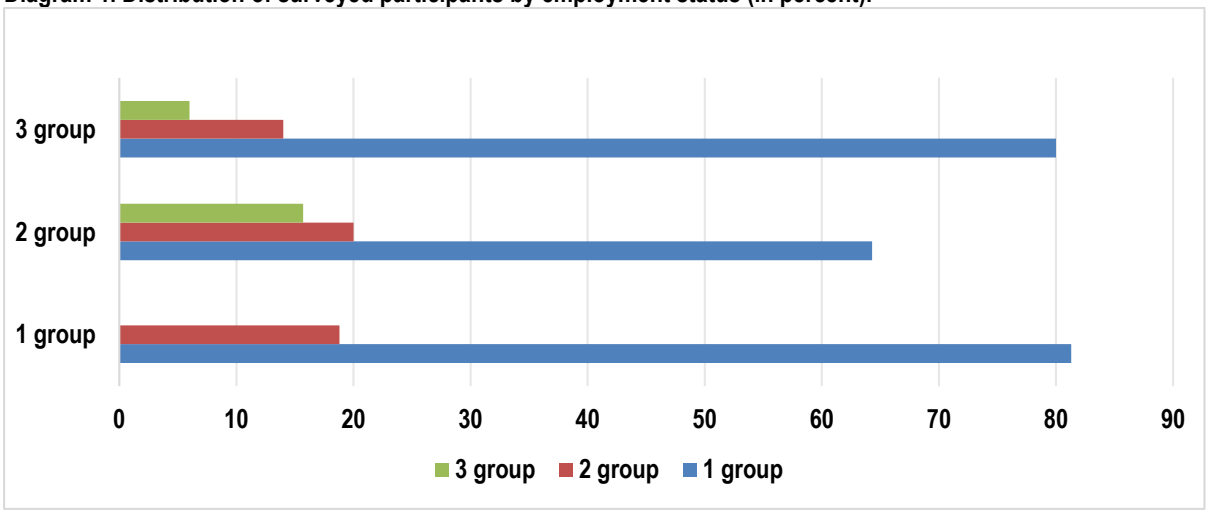
According to the data obtained, the average age of the surveyed in group 1 was 25.41 ±: from 16 to 18 years - 25%, n=8), from 19 to 25 years - 28.1%, n=9, and 46.9%, n=15 - were from 26 to 40 years old. The majority of the surveyed in the 2nd group were between the average age of 26 and 40 years (70%, n=49), from 19 to 25 years, 30%, n=21. The majority of the surveyed in the 3rd group were between the average age of 26 and 40 years (64%, n=64), from 19 to 25 years 35%, n = 35, only 1% - from 16 to 18

years. The Kruskal-Wallis criterion does not detect significant differences in all samples.

By the time of the survey, the majority of participants in group 1 had an average level of education: n=14 (43.8%), the rest n=7 (21.9%) had higher education and n=11 (34.4%) had incomplete secondary education. The majority of the participants in the 2nd group had a higher level of education: n=46 (65.7%), one third of the participants - n=24 (34.3%) - had secondary education. The vast majority of participants - n=90 (90%) of the control group had higher education, and only 10% (n=10) had secondary education. Pearson Chi-squared = 0.000 with a minimum estimated number of 1.74. The significance level of this relationship corresponds to $p<0.05$.

The distribution of the surveyed participants by education is shown in the diagram 1.

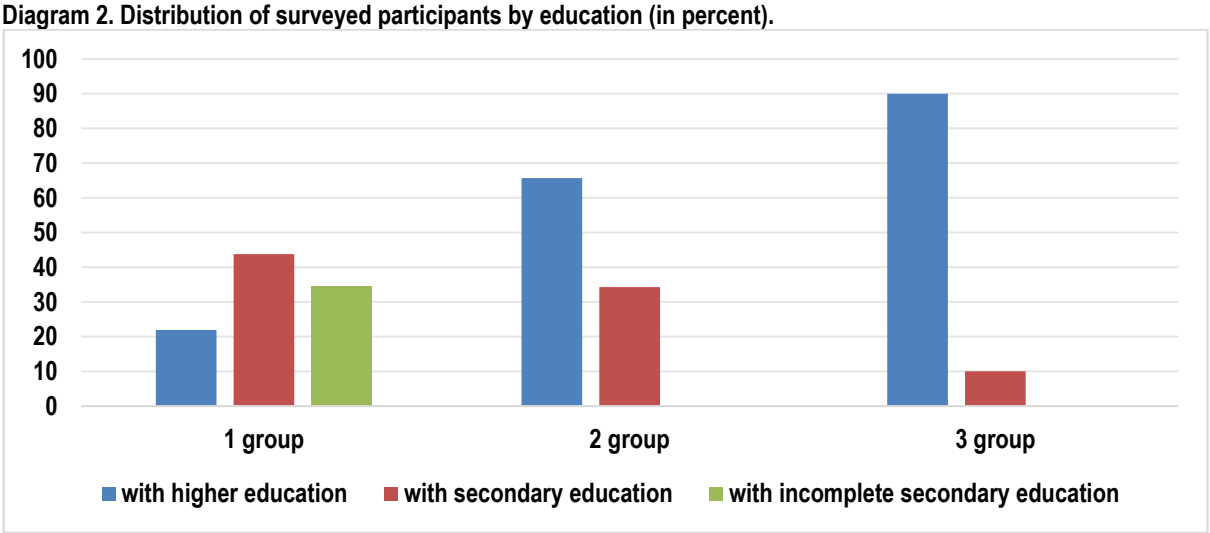
Diagram 1. Distribution of surveyed participants by employment status (in percent).



The analysis of the marital status of the surveyed persons showed that the majority of the participants from the 1st group were maladapted in family terms. Only 18.8% had their own family (were married), more than half of the surveyed persons (65.6%) did not marry (were single or unmarried), 15.6% were already divorced. The majority of the surveyed persons from the 2nd group were also maladapted in family terms. Only 27.1% had their own family (were married), and two thirds (72.7%) did not marry (were single or unmarried). Among the participants of the 3rd group, half (47%) had their own family (were married), and half of the surveyed persons (52%) were not married (were single or unmarried), only 1% were already divorced. Pearson Chi-squared = 0.000 with a minimum estimated number of 0.95. The significance level of this relationship corresponds to $p=0.05$.

The data on the marital status of the examined patients are shown on the diagram 2.

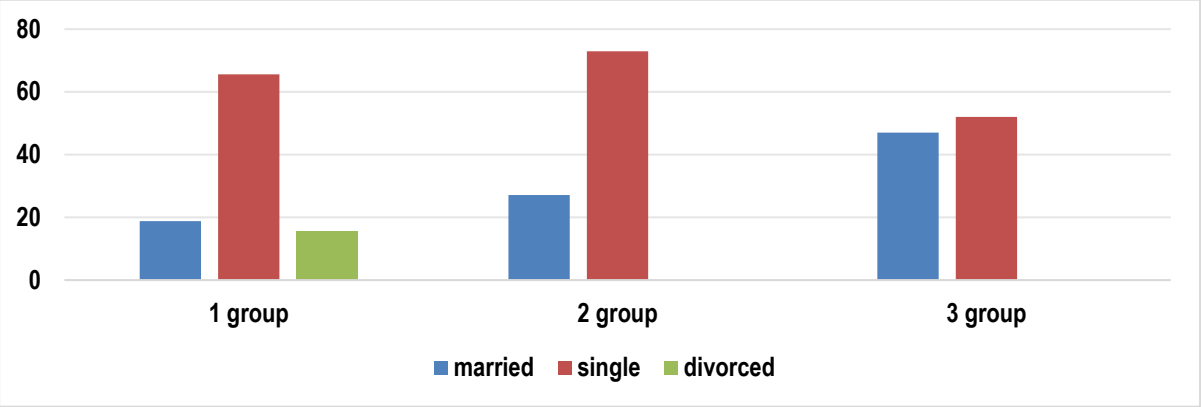
Diagram 2. Distribution of surveyed participants by education (in percent).



It was revealed that the majority of participants from the 1st group were employed: the main part of the surveyed people (n=26, 81.3%) were employed, and only n=6, 18.8% were students. The majority of the 2nd group were also employed: the main part of the surveyed people (n=45, 64.3%) were employed, n=14, 20% were students and 15.7% were unemployed. Among the participants of the 3rd group were employed: the main part of the surveyed people (n=80, 80%) were employed, n=14, 14% were students and n=6 - 6% were unemployed. Pearson chi-squared = 0.035 with a minimum estimated number of 2.69. The significance level of this relationship corresponds to $p<0.05$.

The data on the employment status of the surveyed persons are shown in the diagram 3. (Appendix 3).

Diagram 3. Distribution of surveyed participants by marital status (in percent).



Analysis of laboratory data showed that there was no significant difference in the indicators in all groups of some parameters. The difference was revealed in the study of cholesterol in venous blood (total). Thus, the majority (31.3% (n=10) of the surveyed people in the 1st group showed a decrease in cholesterol levels. In the examined patients of the 2nd group, an increase in the blood level was shown in almost a third (28.6%) of the examined people (n=20) and a decrease in the level in only a small number (8.6%) of the examined people (n=6). In the examined patients of the group 3, it showed an increase in the level of only 19 participants (19%) and a decrease in the level of only 12 (12%).

An insignificant difference in the study of platelets was found. Thus, a small number of the surveyed people in the 1st group showed changes: an increase in the level of only 9.4% (n=3) and 6.3% (n=2) of the surveyed persons showed a decrease in the level. In the surveyed people of the group 2, an increase in the level of almost a third of the surveyed persons (31.4%) and a decrease in the level of only a small number of the surveyed people (2.9%) was shown. In the examined patients of the group 3, it showed an increase in the level of only 24% and a decrease in the level of only 1%.

The difference in the study of hemoglobin was revealed. Thus, the examined patients of the group 1 showed an increase in the level of only 9.4% and 12.5% of the examined people showed a decrease in the level. In the examined patients of the group 2, it showed an increase in the level of almost a third of the surveyed persons (31.4%) and a decrease in the level of a small number of the surveyed people (15.7%). In the examined patients of the group 3, it showed an increase in the level of only 10% and a decrease in the level of only 14%.

Differences in the study of the color indicator were found. Thus, in the examined people of the group 1, it showed a decrease in the level of 34.4%. In the examined people of the group 2, it showed a decrease in the level of 28.6%. In the examined people of the group 3, it showed a decrease in the level of only 4%.

An insignificant difference was revealed in the study of HCT (hematocrit). Thus, in the examined people of the group 1, it showed an increase in the level of 21.9%. In the examined people of the group 2, it showed an increase in the level of 12.9%. In the examined patients of the group 3, it showed an increase in the level of only 4%.

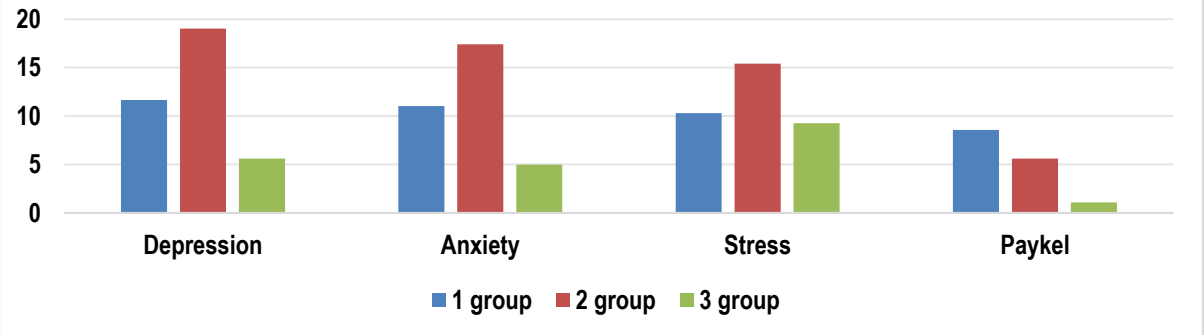
Analysis of the results of the psychometric study showed that in group 1 there was a significant correlation at 0.05 with moderate levels of depression, anxiety, stress on the DASS D scale (11.66 points)-Rs=0.479, DASS T (11.03 points) - Rs=0.599, DASS With (10.31 points)-Rs=0.428, which correlates with the result of the Pikel questionnaire (8.56 points)-Rs=1,000. The correlation is significant at 0.05 (two-way).

In group 2, there was a statistically significant association with high or moderate levels of depression, anxiety, and stress on the scale of DASS D (19.03 points) - Rs=0.610, DASS T (17.40 points)-Rs=0.231, DASS C (15.40 points)-Rs=0.430, which correlates with the result of the Pikel questionnaire (5.61 points). The correlation is significant at 0.05 (two-way).

In group 3, there was a statistically significant association with low or no depression, anxiety, or stress on the scale of DASS D (5.61 points) - Rs=0.454, DASS T (4.98 points)-Rs=0.335, DASS C (9.26 points) -Rs=0.419, which correlates with the result of the Pikel questionnaire (1.08 points). The correlation is significant at 0.05 (two-way).

The distribution of psychometric research data by group is shown on the diagram 4.

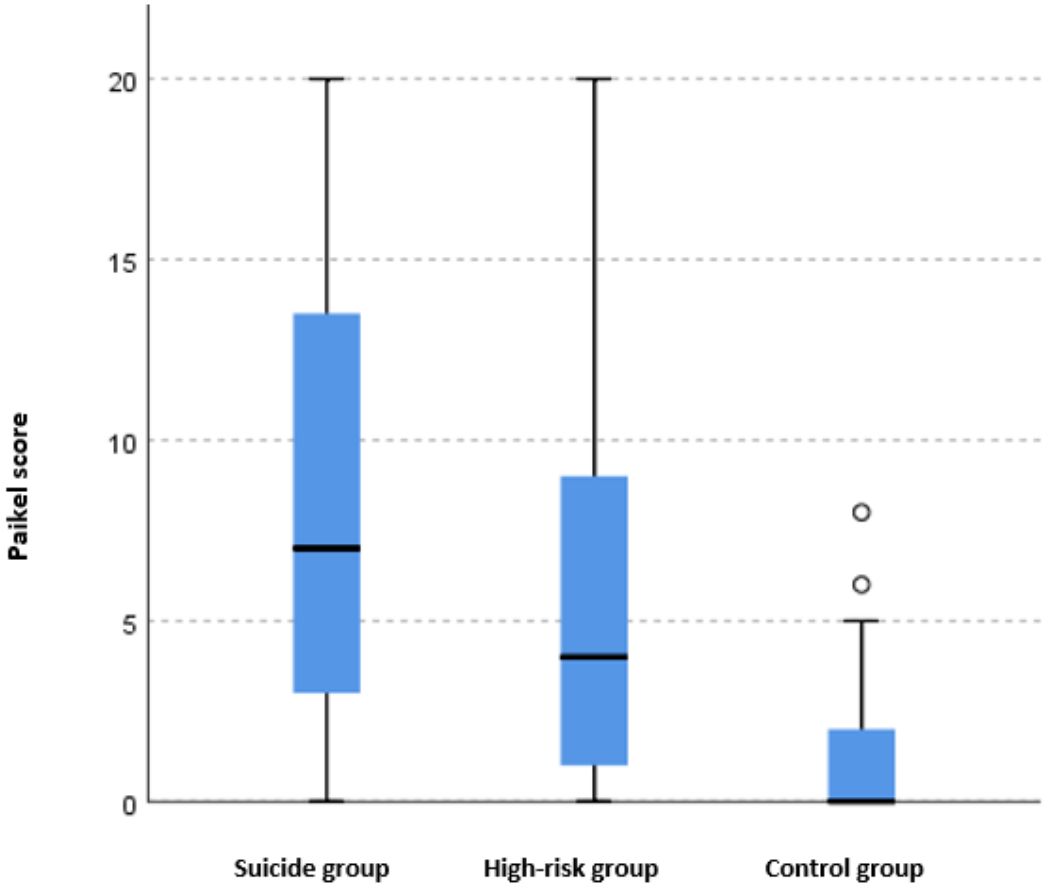
Diagram 4. Distribution of psychometric research data (in points).



When testing the null hypothesis in pairs with the Bonferroni correction for several trials, it was found that group 1 and group 2 have the same distributions. A comparison of group 1 with group 3 showed a score of 0.063 with a significance level of 0.05, which corresponds to $p<0.05$.

The Kraskell Wallis criteria for the results of a psychometric study is shown in the diagram 5.

Diagram 5. Kruskal-Wallis test for independent samples.



Discussion:

An analysis of the social and demographic characteristics of the participants showed that in all groups the ratio of female and male was represented in statistically comparable values. According to the data obtained, the average age of the surveyed people in all groups was in the statistically comparable values of -25.41 ±. The Kruskal-Wallis criterion does not detect significant differences in all samples.

There were differences in the level of education. So, if the majority of participants in the 1st group had an average level of education, the majority of participants in the 2nd and 3rd groups had a higher level of education. An analysis of the marital status of the surveyed persons showed that most of the participants from the 1st and 2nd groups were maladapted in family terms. Only a small part of the participants had their own family (were married), more than half of the surveyed people did not marry (were single or unmarried), while half of the participants in the 3rd group had their own family (were married). The study of labor adaptation showed that the majority of participants from groups 1 and 3 were employed: the majority of those surveyed people were employed, while two thirds of the participants in group 2 were employed.

Thus, the data obtained indicate that the group of surveyed people with suicide attempts is dominated by people aged 25.41 ±, with an average level of education, employed, maladapted in family terms, the sex ratio is equivalent.

The group of surveyed people at risk of suicide was dominated by individuals aged 28.51 ±, with a higher level of education, maladapted in labor and family terms - underemployed and unmarried, the sex ratio is equivalent.

The control group was also dominated by people aged 27.92 ±, had mostly a higher level of education, adapted to family and work status with an equal ratio of female and male sexes.

Analysis of laboratory data showed that there are some differences between the groups. Thus, in the examined people of the group 1, a decrease in the level of the color indicator was shown in 34.4%; a decrease in the level of cholesterol in the venous blood (total) in the majority (31.3%) of the examined people; a uniform platelet count; a decrease in the level of the color indicator in a third of the examined persons (34.4%).

In the examined individuals of the group 2, an increase in platelet levels was shown in almost a third of the examined people (31.4%); an increase in cholesterol levels in almost a third of the examined people (28.6%); a

decrease in the color index in 28.6% of the examined persons. The Kruskal-Wallis test does not detect significant differences in the first two samples.

In the examined patients of the group 3, a decrease in the level of the color indicator was shown in only 4%; an increase in cholesterol in 19%; an increase in platelet levels in 24% and a decrease in the level of the color indicator in only 4%. The Kraskal-Wallis criterion reveals significant differences when comparing the 3rd group with the 1st and 2nd groups.

An analysis of the results of the psychometric study showed that when testing the null hypothesis in pairs with the Bonferroni correction for several trials, it was found that group 1 and group 2 had the same distributions. A comparison of group 1 with group 3 showed a score of 0.063 with a significance level of 0.05, which corresponds to $p<0.05$.

Conclusions

1. The group of surveyed people with suicide attempts is dominated by people aged 25.41 ±, with an average level of education, employed, maladapted in family terms, the sex ratio is equivalent. The group of those surveyed at risk of suicide was also dominated by people aged 28.51 ±, with a higher level of education, maladapted in labor and family terms - underemployed and unmarried, the sex ratio is equivalent. The control group was also dominated by people aged 27.92 ±, had mostly a higher level of education, adapted to family and work status with an equal ratio of female and male sexes.

2. In group 1, a strong correlation was found with moderate levels of depression, anxiety, and stress on the DASS scale, which correlates with the results of the Pikel questionnaire. In group 2, there was a statistically significant association with high or moderate levels of depression, anxiety, and stress on the DASS scale, which correlates with the results of the Pikel questionnaire. In group 3, there was a statistically significant association with low or no depression, anxiety, or stress on the DASS scale, which correlates with the results of the Pikel questionnaire.

3. A significant difference in the study of laboratory parameters is revealed: in the examined individuals of the group 1, it showed a decrease in the level of the color indicator, a decrease in the level of cholesterol in the venous blood (total) and platelets in the majority of the examined people.

In the examined people of the group 2, an increase in platelet levels was shown in almost a third of the examined persons, an increase in cholesterol levels in almost a third of the examined individuals, and a decrease in platelet levels. In group 3, there was a statistically insignificant association with cholesterol levels and an increase in platelet levels, but a significant association with a decrease in the color index (only 4%).

Conclusion

The conducted research is evidence-based regarding the bio-psycho-social risk factor of suicide. The results obtained indicate that those at risk of suicide, i.e. those who are depressed or anxious, as well as those who abuse psychoactive substances, deserve the most attention. As in this group of the studied, the highest indicators of psychometric research and laboratory markers of suicide were revealed. In general, the result obtained correlates with the conclusions of other scientists. The most significant is the conduct of screening studies using the DASS and Pikel scale in the research perspective, aimed at further work and offering simple ways to prevent suicide among young people.

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Conflict of interest

The authors of this article confirmed the absence of a conflict of interest.

This material has not been published in other publications and is not under review by other publishers.

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EFFICACY AND SAFETY OF MOMETASONE FUROATE IN CHILDREN WITH ATOPIC DERMATITIS IN KAZAKHSTAN

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Abstract

Background. Atopic dermatitis is a serious chronic skin disease, often aggravated by the presence of microorganisms, which often responds well to strong corticosteroid therapy. However, long-term use of strong topical corticosteroids is associated with side effects such as skin atrophy. The current standard of local anti-inflammatory treatment is topical glucocorticosteroids and calcineurin inhibitors. Mometasone furoate 0.1 percent is a moderate efficacy corticosteroid, which is indicated for the treatment of atopic dermatitis in children. **This research aims** to evaluate the efficacy and safety of mometasone furoate in pediatric patients with atopic dermatitis.

Materials and methods. In this prospective trial, 60 pediatric patients diagnosed with mild to moderate AD were randomly assigned to two separate groups for comparison. The observation group (n=30) received treatment with 0.1% mometasone furoate, while the control group (n=30) underwent standard therapy without mometasone furoate. The study duration was 12 weeks and was conducted at San-Med Service Clinic in Shymkent, Kazakhstan, from December 1, 2024, to February 2025.

Results. Treatment with 0.1% mometasone furoate resulted in a more pronounced reduction in atopic dermatitis severity and greater improvement in quality of life (CDLQI) compared to standard therapy. The safety profile was favorable, with no significant adverse effects. Cortisol levels showed no statistically significant differences between the groups, confirming the absence of systemic effects.

Conclusions. Consistently using a 0.1% mometasone furoate topically to treat mild to moderate atopic dermatitis in children older than 2 years decreased the frequency of relapses and the quantity of mometasone furoate prescribed. It was also safe and well tolerated by patients.

Keywords: *atopic dermatitis, mometasone furoate 0.1%, topical corticosteroids, safety, quality of life, efficacy, pediatric patients*

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Резюме

ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ МОМЕТАЗОНА ФУРОАТА У ДЕТЕЙ С АТОПИЧЕСКИМ ДЕРМАТИТОМ В КАЗАХСТАНЕ

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Актуальность. Атопический дерматит - это тяжелое хроническое заболевание кожи, которое часто усугубляется присутствием микроорганизмов и часто хорошо поддается лечению сильнодействующими кортикостероидами. Однако длительное применение сильнодействующих местных кортикостероидов сопровождается побочными эффектами, такими как атрофия кожи. Топические глюкокортикостероиды и ингибиторы кальциневрина являются современным стандартом местной противовоспалительной терапии. Мометазон фуроат 0.1% - это кортикостероид средней эффективности, эффективный при лечении атопического дерматита у детей. **Целью данного**

исследования является оценка эффективности и безопасности мометазона фуроата у детей с атопическим дерматитом.

Материалы и методы. В проспективное исследование были включены 60 детей с атопическим дерматитом легкой и средней степени тяжести, которые были рандомизированы на две группы. Группа наблюдения (n=30) получала терапию мометазона фуроатом 0,1%, а контрольная группа (n=30) – стандартное лечение без применения мометазона фуроата. Продолжительность исследования составила 12 недель, и оно проводилось в клинике ТОО «Сан-Мед Сервис» в городе Шымкент, Казахстан, с 1 декабря 2024 года по февраль 2025 года.

Результаты. Терапия 0,1% мометазона фуроатом продемонстрировала более значительное снижение выраженности атопического дерматита и улучшение качества жизни (CDLQI) по сравнению со стандартным лечением. Профиль безопасности был благоприятным, без значимых побочных эффектов. Уровень кортизола оставался без статистически значимых изменений между группами, что подтверждает отсутствие системного воздействия.

Выводы. Лечение легкой и среднетяжелой формы атопического дерматита у детей старше 2 лет последовательным применением 0,1% раствора мометазона фуроата для местного применения значительно уменьшало количество рецидивов и количество назначаемого мометазона фуроата и было безопасным и хорошо переносилось пациентами.

Ключевые слова: *атопический дерматит, мометазон фуроат 0.1%, топический глюкокортикостероид, безопасность, качество жизни, эффективность, дети.*

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Түйіндеме

ҚАЗАҚСТАНДАҒЫ АТОПИЯЛЫҚ ДЕРМАТИТІ БАР БАЛАЛАРДАҒЫ МОМЕТАЗОН ФУРОАТЫНЫҢ ТИІМДІЛІГІ МЕН ҚАУІПСІЗДІГІ

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Кіріспе. Атопиялық дерматит- ол көбінесе микроорганизмдердің болуымен асқынатын және жиі күшті кортикостероидтармен емдеуге жақсы жауап беретін ауыр, созылмалы тері ауруы. Дегенмен, күшті жергілікті кортикостероидтарды ұзақ уақыт қолдану тері атрофиясы сияқты жанама әсерлермен бірге жүреді. Жергілікті глюкокортикостероидтар мен кальциневрин ингибиторлары жергілікті қабынуға қарсы терапияның заманауи стандарты болып табылады. Мометазон фуроаты 0.1% - бұл балалардағы атопиялық дерматитті емдеуде тиімді орташа күштілігі бар кортикостероид. **Бұл зерттеудің мақсаты** атопиялық дерматитпен ауыратын балалардағы мометазон фуроатының тиімділігі мен қауіпсіздігін бағалау болып табылады.

Материалдар мен әдістер. Перспективалық зерттеуге екі топқа рандомизацияланған жеңіл және орташа атопиялық дерматиті бар 60 бала қатысты. Бақылау тобы (n=30) мометазон фуроат терапиясын 0,1%, ал негізгі тобы (n=30) мометазон фуроатын қолданбай стандартты ем қабылдады. Зерттеудің ұзақтығы 12 аптаны құрады және ол 2024 жылғы 1 желтоқсаннан 2025 жылғы ақпанға дейін Шымкент қаласындағы "Сан-Мед Сервис" ЖШС клиникасында жүргізілді.

Нәтижесі. 0,1% мометазон фуроат терапиясы стандартты емдеумен салыстырғанда атопиялық дерматиттің ауырлығының айтарлықтай төмендеуін және өмір сапасының жақсаруын (CDLQI) көрсетті. Қауіпсіздік профилі маңызды жанама әсерлерсіз қолайлы болды. Кортизол деңгейі топтар арасында статистикалық маңызды өзгеріссіз қалды, бұл жүйелік әсердің жоқтығын растайды.

Қорытынды. 2 жастан асқан балалардағы атопиялық дерматиттің жеңіл және орташа түрін 0,1% жергілікті мометазон фуроат ерітіндісін қолдану арқылы қайталанатын және тағайындалған мометазон фуроатының көп мөлшерде қолдануын айтарлықтай азайтты және пациенттер үшін қауіпсіз, әрі жақсы төзімді болды.

Түйін сөздер: *атопиялық дерматит, мометазон фуроат 0.1%, жергілікті кортикостероид, қауіпсіздік, өмір сапасы, тиімділік, балалар.*

Дәйексөз үшін:

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease characterised by intense itching and distinctive inflammatory changes. AD has a pronounced negative impact on the patient's quality of life, as well as on the emotional and psychosocial state of his family [3]. Atopy is defined as a syndrome that can be described as a genetically determined disorder of the maturation of the immune system of unknown origin. It is characterised by an increased tendency to form IgE antibodies and is often associated with a personal or family history of atopic dermatitis, allergic rhinitis or asthma [5, 6, 14]. The first manifestation of the atopic march begins with AD. Atopic dermatitis is usually seen during the first 6 months of life and persists into adulthood in 25% of the population. The incidence of AD has increased significantly in recent decades, especially in high-income countries [9]. Thus, preventing even a small percentage of cases of AD can bring significant benefits to individual patients, the healthcare system, and socio-economic structures [4, 8, 21]. Traditionally, the early onset of AD compared to other allergic diseases, such as allergic rhinitis and asthma, has led to the assumption that AD progresses into allergic rhinitis and then into asthma in a linear sequence [1, 16]. Allergic asthma (AA) and allergic rhinitis (AR) represent the final stage of the atopic march.

The pathophysiological mechanisms of atopic dermatitis (AD) remain to be fully elucidated. Numerous studies have confirmed that dysfunction of the skin barrier, in combination with impaired immune regulation, plays a key role in its pathogenesis [2, 13, 15]. According to an alternative hypothesis, AD is caused by dysregulation of the immune response, manifested by hyperactivation of Th2-mediated inflammation and overexpression of type II cytokines such as IL-4 and IL-13 [10]. In addition, there is preliminary evidence indicating the role of genetic factors in the pathogenesis of atopic dermatitis, in particular, that carriers of mutations in the filaggrin gene are highly susceptible to environmental influences, which contributes to the development of the disease [12].

Topical corticosteroids have been proven to be highly efficient in the treatment of atopic dermatitis; however, their frequent and prolonged utilisation, particularly in paediatric populations, is associated with numerous adverse effects. Mometasone furoate is a medium-efficacy corticosteroid that is indicated for the relief of inflammatory and pruritic manifestations of atopic dermatitis [17, 20]. Despite the existence of a significant number of international studies on the efficacy and safety of Mometasone furoate, information on its use in children with atopic dermatitis in Kazakhstan remains limited. **The objective** of the present study is to evaluate the efficacy and safety of Mometasone furoate in children with atopic dermatitis in Kazakhstan.

Materials and methods

Study design

The prospective study included 60 children with mild to moderate atopic dermatitis, divided into two groups: 30 patients in the observation group who received 0.1% Mometasone furoate therapy, and 30 patients in the control group who received standard treatment without Mometasone furoate. The study duration was 12 weeks and was conducted at the clinic of “San-Med Service” LLP in Shymkent, Kazakhstan, from December 1, 2024, to February 2025.

Study population

The study included children aged 2 to 18 years with a confirmed diagnosis of mild to moderate atopic dermatitis on the SCORAD scale (Scoring Atopic Dermatitis).

Inclusion criteria:

1. Demographic criteria:

- Age: 2-18 years’ old
- Gender: girls and boys

2. Diagnostic criteria:

- Confirmed diagnosis of atopic dermatitis following the Hanifin and Rajka criteria and international guidelines (EAACI, AAD).
- Mild and moderate degree of atopic dermatitis according to SCORAD (15-45 points).
- Complete blood count test (eosinophilia)
- Total IgE
- With diagnosed rhinitis, a nasal cytology

3. Informed consent:

Signed informed consent of the parents/guardians for the child's participation in the study.

Treatment methods: patients were randomized into two groups:

1. Observation group: topical application of mometasone furoate 0.1% 1 time per day on the affected skin areas.
2. Control group: the use of antihistamines. Both groups also used emollients at least twice a day.

Exclusion criteria:

1. Diseases and conditions affecting the results of the study:

- Severe form of atopic dermatitis (SCORAD >50).
- Presence of secondary skin infection (bacterial, fungal, viral, including herpes, molluscum contagiosum).
- The presence of other chronic skin diseases such as psoriasis, ichthyosis, and contact dermatitis.
- Severe immunodeficiency (primary and secondary immunodeficiencies).

2. The use of other treatment methods:

- Systemic therapy (glucocorticosteroids, immunosuppressant, biologics) 4 weeks before the start of the study.
- Topical corticosteroids or calcineurin inhibitors 7 days before the start of the study.

3. Allergic reactions and individual intolerance:

- Allergy or hypersensitivity to the components of the drug mometasone furoate.

4. Other medical and social factors:

• Decompensated chronic diseases (for example, severe bronchial asthma, uncontrolled diabetes mellitus).

• Parents/guardians' refusal to participate in the study.

Effectiveness assessment:

The effectiveness of therapy was evaluated at weeks 2, 4, 8, and 12 according to the following criteria:

- Dynamics of the SCORAD index;
- Assessment of the severity of itching on a Visual Analog Scale (VAS) (0-10 points);
- Improving the quality of life according to the CDLQI (Children's Dermatology Life Quality Index) questionnaire;
- The level of cortisol in the blood.

Safety assessment: Side effects were recorded at each visit, including:

- Development of skin atrophy (assessment by dermatoscopy);
- The appearance of telangiectasia;
- The development of hypopigmentation;
- Systemic side effects (analysis of blood cortisol levels in patients using the drug for more than 4 weeks).

Statistical analysis

The data was analyzed using Excel 2013. The Student's t-test (for parametric data) and the Mann-Whitney U Test (for nonparametric data) were used to assess the differences between the groups. The significance of the differences was considered significant at $p<0.05$.

Ethical aspects

The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committee. All parents signed an informed consent for their children to participate in the study.

Results

A total of 60 children with mild and moderate atopic dermatitis were included in the study, which were divided into two groups. In the observation group (group A, n=30), patients received 0.1% Mometasone furoate therapy, and in the control group (group B, n=30), standard treatment with antihistamines and emollients was performed without the use of Mometasone furoate. In the group receiving Mometasone furoate, there were 12 boys (40%) and 18 girls (60%), while in the control group not receiving Mometasone furoate, there were 17 boys (56.67%) and 13 girls (43.33%).

The mean age of patient's in-group A was 10.27±6.61 years, and in group B was 4.77±4.55 years. 46.67% of patients in group A and 86.67% of patients in group B were in the age group from 1 to 10 years, and 53.33% and 13.33%, respectively, were in the age group over 10 years (see Table 1).

Table 1.

Distribution of patients by age and mean age.

Age in years	Group A (n=30)	Group B (n=30)
from 1 to 10	14 (46,67)	26 (86.67)
> 10	16 (53.33)	4 (13.33)
Total	30 (100.00)	30 (100.00)
Mean± SD	10.27±6.61	4.77± 4.55

A complete blood count test was performed to assess the level of eosinophils. In the group receiving Mometasone furoate, the average level of eosinophils was 5.26±3.35%, while in the control group, this indicator was 5.13±3.12%. There were no significant differences between the control and observation groups. The data obtained indicate that there is no significant effect of Mometasone furoate on eosinophilia.

At baseline, the average overall severity score of atopic dermatitis was 31.00 ± 7.40 in group A and 26.33 ± 9.14 in group B.

• At the first control examination, the indicators decreased to 25.00 ± 8.23 in group A and 23.54 ± 8.86 in group B.

• At the second control examination, the indicators were 16.23 ± 12.74 in group A and 20.62 ± 8.06 in group B.

• At the final control examination, the scores decreased to 11.87 ± 8.04 in group A and 18.83 ± 7.05 in group B ($p>0.05$, statistically insignificant).

The total percentage of reduction in the severity of the disease from baseline to final examination:

• Group A: 61.71%

• Group B: 28.49% (see Table 2).

Table 2.

Average SCORAD (general assessment of the severity of atopic dermatitis) at different stages of follow-up.

	Group A	Group B	p value
Initial	31.00 ± 7.40	26.33 ± 9.14	0.05
1st examination	25,00 ± 8,23	23.54 ± 8.86	<0.05
2nd examination	16,23 ± 12,74	20.62 ± 8,06	<0.05
Last checkup	11,87 ± 8,04	18.83 ± 7.05	<0.05
Percentage decrease from baseline to last examination	61.71%	28.49%	

The study analyzed cortisol levels in patients of both groups. In the group receiving Mometasone furoate, the average cortisol level was 287.59±110.11 nmol/l, while in the control group this indicator was 205.33±98.22 nmol/L. Statistical analysis did not reveal significant differences between groups A and B, which indicates that there was no significant effect of Mometasone furoate on cortisol levels in this study.

According to the diagnostic criteria of Hanifin and Rajka criteria, all study participants were evaluated for itching. In our study, 22 patients (73.3%) in the momatesone furoate group and 21 patients (70.0%) in the control group had localized itching, while 8 patients (26.7%) and 9 patients (30.0%), respectively, experienced generalized itching.

According to the severity of itching, the acute form was recorded in 15 patients (50.0%) in the Mometasone furoate group and in 14 patients (46.7%) in the control group, while the chronic form was observed in 15 patients (50.0%) and 16 patients (53.3%), respectively. Other common symptoms were dry skin, observed in 22 patients (73.3%), and inflamed skin, detected in 4 patients (13.3%) at the initial examination.

After a 12-week treatment period, 26 patients (86.67%) in the Mometasone furoate group achieved good control of atopic dermatitis symptoms compared to 18 patients (60.0%) in the control group. At the same time, 4 patients (13.33%) in the Mometasone furoate group and 12 patients (40.0%) in the control group continued to experience uncontrolled symptoms, which indicates a higher effectiveness of treatment in the Mometasone furoate group.

The mean (± SD) CDLQI score in the study population was 8.42 (± 3.57) out of 30. In the observation group, the average CDLQI score was 7.90 (± 3.42), while in the

control group it was 9.14 (± 3.69), which indicates a tendency towards a better quality of life in children receiving Mometasone furoate. Among all participants, 18 children (60.0%) in the observation group and 16 children (53.3%) in the control group experienced a moderate effect of AD on their quality of life. Only 1 child (3.3%) in the observation group and 1 child (3.3%) in the control group noted that the disease had an extremely strong impact on their daily lives. The analysis of individual CDLQI domains showed that Q1 (itching, burning, painful sensations on the skin) had the greatest impact on the quality of life, with an average (± SD) score of 1.83 (± 0.78) out of 3. In the follow-up group, 43.3% of children reported that itching and burning significantly worsened their quality of life, while in the control group this figure was 36.7%. Q6 (avoiding swimming or playing sports) had the least impact on quality of life, with an average score of 0.27 (± 0.48). The majority of participants (76.7% in the observation group and 71.7% in the control group) noted that atopic dermatitis did not affect their participation in sports. Similarly, the effect of atopic dermatitis on Q8 (name-calling) was low, with an average score of 0.35 (± 0.50) out of 3, while 66.7% of children in the observation group and 64.3% in the control group reported that this factor did not affect their quality of life. Regarding Q4 (influence on clothing/shoe choice), 40.0% of children in the observation group and 34.3% in the control group noted that atopic dermatitis had a slight effect on their clothing choice, with an average (± SD) score of 1.76 (± 0.92). A similar trend was observed concerning sleep disorders (domain Q9). 53.3% of children in the observation group and 50.0% in the control group noted that sleep disorders slightly worsened their quality of life, with an average score of 1.47 (± 0.84) (see Diagram 1).

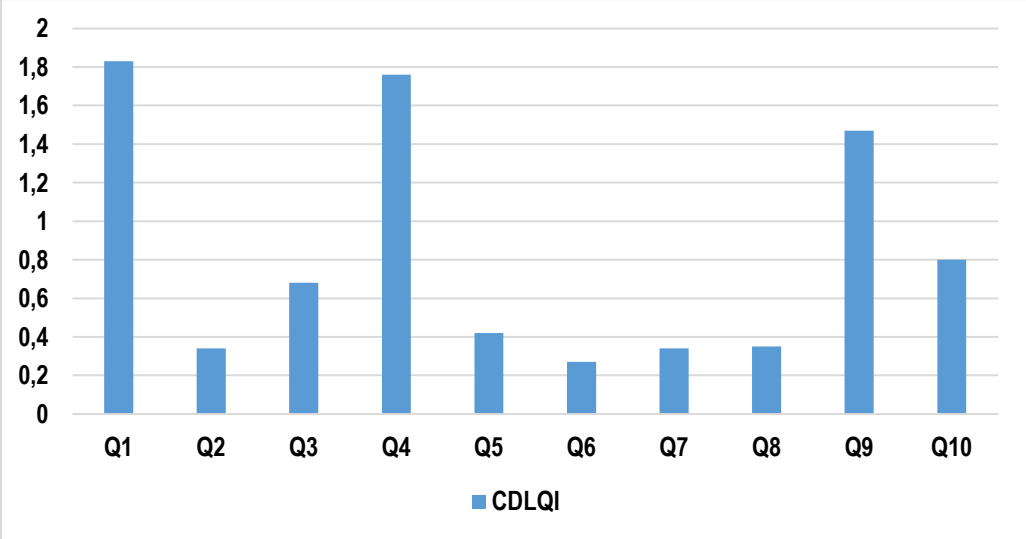

Diagram 1. Distribution of symptoms/effects on quality of life by CDLQI.

Discussion

This prospective study evaluated the efficacy and safety of Mometasone furoate in children with atopic dermatitis in Kazakhstan. The results of the study showed a significant clinical improvement in most patients treated with Mometasone furoate, as well as a high safety profile and good tolerability of this drug. These data emphasize the importance of using Mometasone furoate as the main element of therapy for atopic dermatitis in children, especially in regions with a high incidence rate.

Clinical improvements in patients were manifested in a significant reduction in the severity of the main symptoms of atopic dermatitis, including itching, erythema, skin infiltration and the presence of scratching. Most of the children showed a reduction in the area of the affected skin and an improvement in the quality of life, which corresponds to the results of international studies. Similar studies by *Yang et al.* It has been shown that the consistent use of Mometasone and Crisaborol significantly reduces the frequency of relapses in children with mild and moderate forms of AD [22]. In group B, who received standard therapy using antihistamines and emollients without the use of Mometasone furoate, there was also a decrease in SCORAD scores. This indicates the importance of basic treatment in the complex therapy of atopic dermatitis. However, the degree of reduction in the severity of skin manifestations was less significant compared to group A, where Mometasone furoate was used. These differences highlight the key role of topical corticosteroids in controlling inflammation in atopic dermatitis. In other similar studies, Mometasone has demonstrated significant efficacy in reducing the severity of atopic dermatitis, as evidenced by improved SCORAD scores in clinical trials [18,11]. The data obtained from our study indicate that there is no significant effect of Mometasone furoate on eosinophilia. However, a study by *Kato et al.,* [7], *Tsuda et al.,* [19] shows that Mometasone furoate, a local corticosteroid, significantly affects the level of eosinophils and reduces the severity of the clinical picture and associated eosinophilic activity, as evidenced by a decrease in serum levels of eosinophilic cationic protein (ECP), markers of eosinophil activation and inflammation in patients with atopic dermatitis. The Quality of Life Index for Children with Dermatological Diseases (CDLQI) is an essential tool for assessing the quality of life of children with atopic dermatitis (AD), especially when evaluating the effectiveness of treatments such as mometasone. Studies show that AD significantly affects the quality of life of children, with varying degrees of severity

correlating with CDLQI indicators. In our study, the average CDLQI score in the observation group was 7.90 (± 3.42), while in the control group it was 9.14 (± 3.69), which indicates a tendency towards a better quality of life in children receiving Mometasone furoate. It should be noted that there are very few studies in the literature evaluating the effect of Mometasone furoate using the Quality of Life Index of Pediatric Dermatology (CDLQI), which underlines the importance of further observations and research in this area.

The statistical analysis did not reveal significant differences between the control and the main group in terms of cortisol levels, which indicates that there is no significant effect of Mometasone furoate on adrenal function in children with atopic dermatitis in this study. This corresponds to the available literature data, although there is little information about the effect of Mometasone on cortisol levels in children, and further study of this issue is required.

Limitations

Due to the fact that our study is the first phase of the work, it has a number of limitations that should be taken into account when interpreting the results. First, the relatively small number of patients in each group limits the statistical power of the analysis and may prevent the identification of significant differences between the groups. Secondly, the duration of follow-up was only 12 weeks. This period may not be sufficient to identify possible long-term effects of therapy, such as persistent changes in cortisol levels or the development of chronic adverse reactions. Thirdly, this study did not include a direct comparison of Mometasone furoate with other topical corticosteroids. Consequently, we cannot draw conclusions about its relative advantage or comparability with alternative medications

These limitations emphasize the need for additional, larger, and longer-term studies to confirm and refine our findings.

Further studies are planned to involve a greater number of patients and a longer follow-up period. This will facilitate not only the confirmation of the current results but also the detailed analysis of mometasone furoate therapy's effect on the prevention of subsequent allergic diseases in children with atopic dermatitis. Furthermore, future research should incorporate direct comparive testing of Mometasone furoate against other topical corticosteroids to definitively establish its clinical advantages over alternative drugs.

Conclusion

Based on the data obtained, it is concluded that Mometasone furoate 0.1% therapy is effective and safe in the treatment of atopic dermatitis in children. In the observation group administered Mometasone furoate, there was a significant decrease in the severity of clinical manifestations of the disease, which was comparable to the dynamics in the control group. However, the efficacy of treatment with Mometasone furoate was superior to that observed in the control group, as evidenced by a more pronounced decrease in the SCORAD index and an enhancement in the quality of life of patients, as assessed by the CDLQI (Children's Dermatology Life Quality Index). The safety profile of Mometasone furoate was satisfactory, with no significant side effects. Furthermore, no statistically significant difference in cortisol levels was observed between the groups, thereby confirming the absence of a systemic effect of therapy. Further studies involving a large number of patients and a longer follow-up period are needed to confirm the results obtained and to evaluate in more detail the long-term efficacy and safety of treatment.

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RECTAL CANCER IN KAZAKHSTAN, 2005–2024: COMPONENT ANALYSIS OF INCIDENCE TRENDS IN THE CONTEXT OF SCREENING AND COVID-19

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Abstract

Introduction. Rectal cancer constitutes a sizable share of the oncology workload. Reliable interpretation of long‑term trends requires disentangling demographic forces from genuine changes in age‑specific risk, particularly during program roll‑out and the service disruptions associated with COVID‑19.

The aim of the study is to quantify the separate contributions of population size, age structure, and age‑specific risk to rectal cancer incidence in Kazakhstan, 2005–2024, partitioned into five phases: pre‑screening (2005–2010), early roll‑out (2011–2013), program stabilization (2014–2019), pandemic impact (2020–2021), and post‑pandemic recovery (2022–2024).

Material and research methods. A population‑based retrospective study using the Ministry of Health Form No. 7 (ICD‑10: C19–C21). We applied a seven‑term decomposition with demographic components and risk‑related terms; here, "risk" denotes residual change in age‑specific incidence after removing demographic effects.

Results. Over 2005–2024, 28,368 new cases were registered. The crude incidence rate (CR) increased from 7.80 to 9.13 per 100,000 (+1.34). Decomposition of CR yielded: $\sum\Delta_A$=+1.42, $\sum\Delta_R$=−0.05, $\sum\Delta_{RA}$=−0.03 (per 100,000), indicating a rise driven by population ageing with stable or slightly declining age-specific risks. By phase: 2005–2010 – declines in CR and ASR due to $\Delta R<0$; 2011–2013 – screening-related "peak" ($\Delta_R>0$); 2014–2019 – CR rises while ASR falls, increase fully demographic; 2020–2021 – compensatory increase versus 2020, yet 2021 below 2019; 2022–2024 – CR rises with a "flat" ASR, contribution almost exclusively demographic. Age profile stable: ages 50–79 ≈80.7% of registrations.

Conclusions. The upward drift in crude incidence is primarily demographic, while true risk variation is phase‑bound and program‑linked. Policy should prioritize resilient early‑detection pathways, surge capacity for endoscopy, and routine component‑based surveillance focused on ages 50–79.

Key words: *rectal cancer, incidence, trends, component analysis.*

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Резюме

РАК ПРЯМОЙ КИШКИ В КАЗАХСТАНЕ, 2005–2024 ГГ.: КОМПОНЕНТНЫЙ АНАЛИЗ ТРЕНДОВ ЗАБОЛЕВАЕМОСТИ НА ФОНЕ СКРИНИНГА И COVID-19

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Введение. Рак прямой кишки вносит существенный вклад в суммарную нагрузку онкологических заболеваний. Корректная интерпретация временных рядов требует раздельной оценки демографических эффектов и подлинной динамики возраст‑специфического риска, особенно при развёртывании организованного скрининга и структурных ограничениях периода COVID‑19.

Цель исследования: количественно разложить вклад демографических факторов (численность населения и возрастная структура) и возраст‑специфического риска в изменение заболеваемости раком прямой кишки в Казахстане в 2005-2024 гг., с анализом пяти фаз: доскрининговый этап (2005-2010), раннее развёртывание (2011-2013), стабилизация программы (2014-2019), пандемическое воздействие (2020-2021) и постпандемическое восстановление (2022-2024).

Материалы и методы. Популяционное ретроспективное исследование на основе официальной отчётной формы № 7 Минздрава РК (МКБ‑10: C19–C21). Для оценки динамики числа случаев применено компонентное разложение с выделением семи факторов.

Результаты. За 2005–2024 гг. зарегистрировано 28 368 первичных случаев. Грубый показатель заболеваемости (ГП) вырос с 7,80 до 9,13 на 100 000 (+1,34). Декомпозиция ГП: суммарно $\sum\Delta_A$=+1,42, $\sum\Delta_R$=−0,05, $\sum\Delta_{RA}$=−0,03 (на 100 000) – прирост обусловлен старением населения при стабильных/слегка снижающихся возрастных рисках. По этапам: 2005–2010 – снижение ГП и ВСП за счёт Δ_R<0; 2011–2013 – скрининговый «пик» (Δ_R>0); 2014–2019 – рост ГП при снижении ВСП, прирост полностью демографический; 2020–2021 – компенсаторный рост относительно 2020 г., но уровень 2021 г. ниже 2019 г.; 2022–2024 – рост ГП при «плоском» ВСП, вклад почти исключительно демографический. Возрастной вклад устойчив: 50–79 лет ≈80,7% всех регистраций.

Выводы. Долгосрочный рост заболеваемости определяется главным образом старением и увеличением численности населения; изменения «истинного» риска носят кратковременный характер и совпадают с программными и организационными сдвигами. Рекомендуется внедрять устойчивое компонентное наблюдение, планировать резерв мощности эндоскопии и фокусировать профилактику на когортах 50–79 лет.

Ключевые слова: *рак прямой кишки, заболеваемость, тренды, компонентный анализ.*

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Түйіндеме

ҚАЗАҚСТАНДАҒЫ ТІК ІШЕКТІҢ ҚАТЕРЛІ ІСІГІ, 2005–2024 ЖЖ.: СКРИНИНГ ПЕН COVID-19 АЯСЫНДА АУРУШАҢДЫҚ ҮРДІСТЕРІНІҢ КОМПОНЕНТТІК ТАЛДАУЫ

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Кіріспе. Тік ішек қатерлі ісігі онкологиялық қызметтің елеулі бөлігін құрайды. Ұзақ мерзімді динамиканы дұрыс түсіндіру үшін демографиялық әсерлерді жас‑ерекшелік қауіптің нақты өзгерісінен ажырату қажет, әсіресе скринингті енгізу және COVID‑19 кезіндегі қызметтің шектелуі жағдайында.

Зерттеу мақсаты: 2005–2024 жж. Қазақстандағы тік ішек қатерлі ісігінің аурушаңдығына халық саны, жас құрылымы және жас‑ерекшелік қауіптің үлесін бөлек‑бөлек сандық бағалау; кезеңдік талдау: скринингке дейінгі (2005–2010), бастапқы енгізу (2011–2013), бағдарламаның тұрақтануы (2014–2019), пандемиялық әсер (2020–2021) және постпандемиялық қалпына келу (2022–2024).

Зерттеу материалдары мен әдістері. ҚР ДСМ № 7 нысанының (МКБ‑10: C19–C21) деректеріне негізделген ретроспективті популяциялық зерттеу. Жеті компоненттен тұратын компоненттік декомпозиция қолданылды: демографиялық және ауру даумуы қауіпіне байланысты.

Нәтижелері. 2005–2024 жж. аралығында 28 368 жаңа жағдай тіркелді. Қатаң аурушаңдық (ҚА) көрсеткіші 7,80-ден 9,13-ке дейін (100 000 тұрғынға; +1,34) өсті. Декомпозиция: $\sum\Delta_A$=+1,42, $\sum\Delta_R$=−0,05, $\sum\Delta_{RA}$=−0,03 (100 000 тұрғынға) – өсу халықтың қартаюымен түсіндіріледі, ал жас-ерекшелік тәуекел тұрақты немесе сәл төмендеуде. Кезеңдер бойынша: 2005–2010 – ҚА және жасқа стандартталған аурушаңдық (ЖСА) төмендеуі, Δ_R<0; 2011–2013 – скринингке байланысты «шақпақ» (Δ_R>0); 2014–2019 – ҚА өсіп, ЖСА төмендейді, өсім толықтай демографиялық; 2020–2021 – 2020 жылмен салыстырғанда өтемдік өсу, бірақ 2021 деңгейі 2019-дан төмен; 2022–2024 – «тегіс» ЖСА аясында ҚА-ның өсуі, үлес дерлік тек демографиямен анықталады. Жас құрылымы тұрақты: 50–79 жас ≈80,7% тіркелімдер.

Тұжырымдар. Жалпы аурушаңдықтағы өсімнің басым бөлігі демографиялық факторлармен түсіндіріледі; нақты қауіптің өзгерісі қысқа мерзімді және бағдарламалық өзгерістермен байланысты. Эндоскопиялық қызметтің өткізу қабілетін күшейту және 50–79 жас топтарына бағытталған компоненттік мониторингті жүйелі жүргізу қажет.

Түйін сөздер: *тік ішектің қатерлі ісігі, аурушаңдық, трендтер, компоненттік талдау.*

Дәйексөз үшін:

Игісін Н.С., Тельманова Ж.Б., Мурзагулов Н.А., Игисинова Г.С., Туребаев Д.К., Дьяков С.С., Молдағали Р.С., Шишкин И.Ю., Билялов А.Р., Маматов Н.Н., Билялова З.А. Қазақстандағы тік ішектің қатерлі ісігі, 2005–2024 жж.: Скрининг пен COVID-19 аясында аурушаңдық үрдістерінің компоненттік талдауы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), С. 160-168. *doi 10.34689/SH.2025.27.5.020*

Introduction

Colorectal malignancies – especially tumors of the rectum—continue to account for a large share of the global oncologic workload [12]. In 2020, international compilations indicated that colorectal cancer occupied the top tier of cancers by occurrence and was among the leading causes of cancer death [2]. The steady accumulation of prevalent cases reflects both longer survival and an ongoing inflow of newly diagnosed patients [5]. Against this backdrop, population ageing and lifestyle-related exposures (dietary patterns, excess weight, insufficient physical activity) interact with unequal access to prevention and early detection, shaping country-specific burdens [9]. Looking ahead, modelling exercises consistently anticipate further growth in case counts, which highlights the practical need to enhance screening pathways, streamline patient flows, and maintain fit-for-purpose epidemiologic surveillance systems [19].

Patterns remain highly uneven across settings: age-standardized incidence tends to be greatest in high-income health systems and lower in parts of Asia, yet secular changes in lifestyle and expanding diagnostic capacity are narrowing these gaps [8, 15]. Importantly, summary metrics alone cannot distinguish how much of the observed change comes from shifting demographics versus true alterations in age-specific risk or screening effects. Accordingly, methods that separate demographic components from risk dynamics are essential for credible trend interpretation.

In Kazakhstan, CRC and rectal cancer in particular – represents a public health priority: thousands of new cases are registered annually, and the disease contributes substantially to the national cancer burden [5]. Growth in the absolute number of recorded cases coexists with improvements in quality indicators of oncologic care, partially attributed to the development of organized screening and strengthening of oncology services [1, 20]. At the same time, structural demographic transformation (increasing share of older adults) and regional disparities in diagnostic access call for analyses that disentangle the demographic backdrop from changes in the underlying risk of disease. A prior nationwide component analysis of CRC incidence documented upward trends across all regions, with increases explained predominantly by demographic factors – population growth and shifts in the age structure [10].

Kazakhstan's organized CRC screening began in 2011 with a two-step pathway (iFOBT followed by diagnostic colonoscopy for positives) and later expanded age eligibility. As documented internationally, program initiation often produces a short-term rise in detected disease due to lead-time and depletion of the preclinical reservoir, which then stabilizes. Service reconfiguration during COVID-19 likely influenced endoscopy capacity and screening coverage, complicating interpretation of routine metrics [13]. In this study, we conduct a component analysis of long-term rectal cancer incidence dynamics in Kazakhstan to quantify the respective contributions of demography and disease risk across program phases and within the context of pandemic constraints – pre-screening (2005–2010), early rollout (2011–2013), program stabilization (2014–2019), pandemic impact (2020–2021), and post-pandemic recovery (2022–2024). This design enables (i) separation of demographic drivers from the true dynamics of risk, (ii) quantitative assessment of phase-specific screening effects, and (iii) characterization of the magnitude of pandemic-related underdiagnosis and subsequent compensation.

Materials and Methods

Cancer registration and case ascertainment

We ascertained incident rectal cancer from the Ministry of Health reporting system (Form No. 7), which consolidates the population-based registry. Eligible records were first primary tumors registered between 2005 and 2024 and coded as C19–C21 (ICD-10).

Population denominators

Population denominators used for rate calculations were sourced from the Bureau of National Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan. We used mid‑year totals for each calendar year; all figures are publicly accessible [3].

Study design and setting

This was a registry-based, retrospective ecological analysis at the national level. We applied a repeated cross-sectional time-trend framework with a seven-term component decomposition across pre-specified program phases and the COVID-19 interval. Reporting followed STROBE principles for observational studies using routinely collected data.

Statistical analysis

We calculated ASR using eighteen five-year age strata (0–4 through ≥85) and the 2013 WHO world standard population. Alongside ASR, we tabulated crude and extensive rates, annual means with standard errors and 95% confidence intervals, and the average annual percent change (T, %) [6, 11].

Long‑term temporal dynamics were described using ordinary‑least‑squares models applied to annual indicators. To attribute changes in the number of cases, we used a seven‑term decomposition separating demographic drivers from residual risk components, with the latter reflecting shifts in age‑specific incidence that may arise from etiologic change or ascertainment intensity [4].

We express the net change in case numbers as the sum of seven terms. Three capture purely demographic forces: (i) the shift in total population size (Δ_P); (ii) the shift in age composition (Δ_A); and (iii) their joint interaction ($\Delta_{P\times A}$). A fourth term isolates the contribution of altered disease risk, independent of demography (Δ_R). The remaining three terms quantify how changes in risk combine with population growth and ageing—namely the interactions of ΔR with ΔP, with ΔA, and with both simultaneously. In this framework, "risk of disease" is defined as the residual change in age-specific incidence after removing demographic effects, and may reflect etiologic influences as well as diagnostic and ascertainment intensity.

Symbols and abbreviations used: AC – absolute count; Δ_A (ASP) – age structure of the population; Δ_P (PS) – population size; Δ_R (RD) – risk of disease.

Ethics approval

We analyzed only de-identified, publicly available administrative data and did not contact individuals. The study protocol was reviewed and approved by the local ethics committee of the Central Asian Institute for Medical Research.

Results

Overall picture (2005–2024). Over the 20-year period, 28,368 new rectal cancer cases were registered. The annual case count increased from 1,181 in 2005 to 1,830 in 2024 (minimum – 1,132 in 2008; maximum – 1,893 in 2023; median – 1,434 per year).

The age profile was strongly right-skewed: individuals aged 50–79 accounted for ~80.7% of registrations (50–54: 9.0%; 55–59: 13.3%; 60–64: 16.2%; 65–69: 17.0%; 70–74: 14.7%; 75–79: 10.4%).

The crude incidence rate increased from 7.8 to 9.13 per 100,000 (+1.34 per 100,000; Fig. 1).

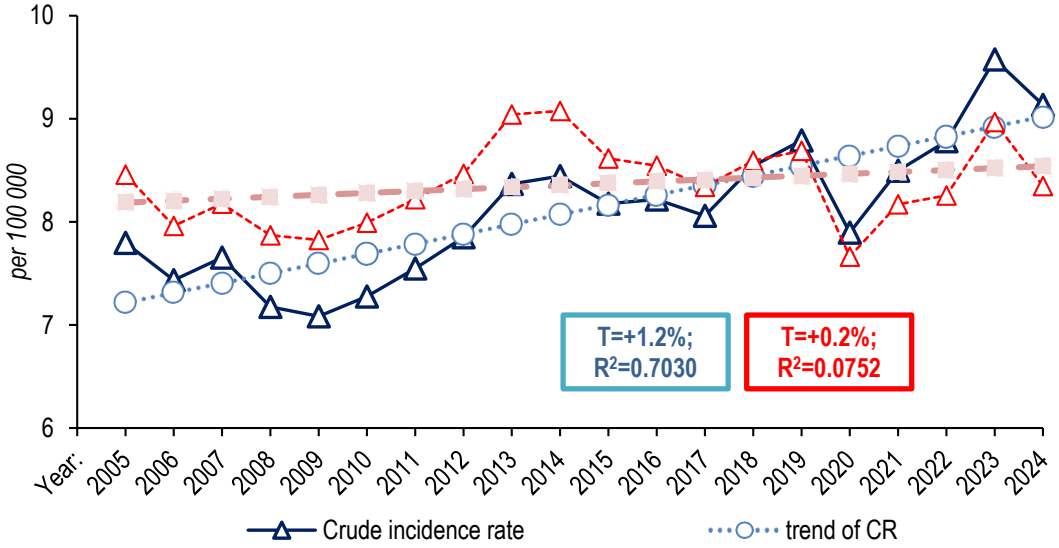

Figure 1. Long-term rectal cancer incidence in Kazakhstan, 2005–2024.

Component decomposition of the CR increase indicated a dominant demographic contribution: the age-structure term ($\sum\Delta_A$) was +1.42 per 100,000, whereas risk of disease term ($\sum\Delta_R$) was −0.05 per 100,000, and the joint age structure × risk term ($\sum\Delta_{R+A}$) was −0.03 per 100,000.

In counts, the total increase was +649 cases (1,181 → 1,830). Decomposition of ΔN:

- **Population growth (Δ_P): +381** cases (**+32.3%**);
- **Shift in age structure of the population (Δ_A): +215** (**+18.2%**);
- **Joint** effect **Δ_{P+A}: +69** (**+5.9%**);
- **Change in** risk of developing disease **(Δ_R): −7** (**−0.6%**);
- **Interactions:** $\Delta_R \times \Delta_P$ **−2** (**−0.2%**), $\Delta_R \times \Delta_A$ **−5** (**−0.4%**), $\Delta_R \times \Delta_P \times \Delta_A$ **−2** (**−0.2%**).

Taken together, these findings confirm that the **primary driver of the increased burden is demographic (population growth and ageing)**, whereas the "pure" risk component shows **no sustained long-term increase**.

Periods. Pre-screening period (2005–2010). The CR declined from 7.80 to 7.28 per 100,000 (−0.52 per 100,000, −6.7%), and the ASR decreased from 7.80 to 7.31 per 100,000 (−6.2%). The total number of cases was virtually unchanged: 1181 → 1179 (ΔN=−2). The overall reduction in the CR (−0.52) was driven primarily by the risk component (Δ_R=−0.48), with a small negative contribution from age structure (Δ_A=−0.07); their interaction term was mildly compensatory (Δ_{R+A}=+0.04) (Table 1). Thus, the observed decline reflects a true decrease in age-specific incidence, rather than demographic shifts. Although population growth generated a potential increase of +82 cases, this was fully offset by a decrease in risk (−73 cases) and an unfavorable redistribution by age (−11 cases), with minimal cross-effects overall (≈ 0) (Tables 2, 3).

Table 1.

Decomposition of changes in rectal cancer incidence (rates per 100,000), 2005–2024.

Periods	Incidence rate, ‰		Changes in incidence, ‰			
			Total	Including due to		
	P_1	P_2	(P_1-P_2)	Δ_A	Δ_R	Δ_{RA}
2005–2010	*P*=7.8	*P*=7.3	−0.52	−0.07	−0.48	+0.04
2011–2013	*P*=7.55	*P*=8.37	+0.82	+0.15	+0.60	+0.08
2014–2019	*P*=8.44	*P*=8.79	+0.35	+0.70	−0.36	+0.003
2020–2021	*P*=7.90	*P*=8.50	+0.60	+0.12	+0.50	−0.02
2022–2024	*P*=8.78	*P*=9.13	+0.35	+0.32	+0.01	+0.02

Δ_A – age structure of the population. Δ_R – risk of disease.
Δ_{RA} – combined effect of disease risk and population age structure.

Early rollout of screening (2011–2013). During 2011–2013, concurrent with the rollout of screening, a clear increase in incidence was observed: the crude rate rose from 7.55 to 8.37 per 100,000 (total increase +0.82 per 100,000), which cannot be attributed to demography alone (Table 1). The component decomposition confirms dominance of the risk component (+0.60) with a moderate accompanying contribution of age structure (+0.15) and a

small positive interaction (+0.08). The rise from 1,241 to 1,415 cases (+174) decomposed into +98 due to change in risk (56.6% of the increase), +35 due to population growth (20.4%), and +24 due to population ageing (13.7%) (Tables 2,3). Taken together, this reflects the typical early-screening phenomenon of depleting the preclinical pool (lead time), yielding a short-term rise in incidence indicators.

2014–2019 (program stabilization). In 2014–2019, a "stabilization" phase was observed: with a modest rise in the crude rate from 8.44 to 8.79 per 100,000 (+0.35 per 100,000), the age-standardized rate decreased from 8.44 to 8.08 per 100,000, while case counts increased from 1,449 to 1,617 (+168) (Tables 1,2). The component decomposition indicates a demographic pattern: the rise in the crude rate was generated by age structure (+0.70), whereas the risk component was negative (−0.36). In counts, demography almost entirely explains the increase: +104 from population growth, +120 from ageing, and +9 from their joint effect; change in risk contributed a dampening effect (−62; interactions involving risk were slightly negative overall) (Table 3). In other words, after the initial screening-related uptick, the depletion effect waned and demographic drivers predominated, alongside a tendency toward declining age-specific incidence.

*Pandemic impact (2020–2021).*Amid partial restoration of diagnostic activity after the 2020 downturn, the crude rate increased from 7.90 to 8.50 per 100,000 (+0.60 per 100,000) (Table 1). The period was characterized by dominance of the risk component (+0.50), with a moderate contribution from age structure (+0.12) and a small negative interaction (−0.02). Case counts rose from 1,471 to 1,604 (+133), 69.4% of which is attributable to change in risk (+92), while population growth (+20) and ageing (+23) contributed 32% in total; cross-effects were minimal. Thus, within 2020–2021, a compensatory ("catch-up") effect in detection predominated; nevertheless, the 2021 level remained below the pre-pandemic 2019 level (8.50 vs 8.79) (Table 2).

Table 2.

Component analysis of rectal cancer incidence in Kazakhstan, 2005–2024.

Indicators	Registered cases (n_{ij})		Population size (N_{ij})		Crude incidence rate (P_{ij})		Age-standardized incidence rate (P^c_{ij})		Expected number of cases
2005-2010									
Total	n_{2005}=1181	n_{2010}=1179	N_{2005}=15147029	N_{2010}=16203274	P_{2005}=7.80	P_{2010}=7.28	P^c_{2005} = 7.80	P^c_{2010} = 7.31	$E(n_{2010})$=1252
Change	$\frac{n_{2005}-n_{2010}}{n_{2005}}100 = -0.2\%$		$\frac{N_{2005}-N_{2010}}{N_{2005}}100 = +7.0\%$		$\frac{P_{2005}-P_{2010}}{P_{2005}}100 = -6.7\%$		$\frac{P^c_{2005}-P^c_{2010}}{P^c_{2005}}100 = -6.2\%$		
2011-2013									
Total	n_{2011}=1241	n_{2013}=1415	N_{2011}=16440470	N_{2013}=16910246	P_{2011}=7.55	P_{2013}=8.37	P^c_{2011} = 7.55	P^c_{2013} = 8.15	$E(n_{2013})$=1301
Change	$\frac{n_{2011}-n_{2013}}{n_{2011}}100 = +14.0\%$		$\frac{N_{2011}-N_{2013}}{N_{2011}}100 = +2.9\%$		$\frac{P_{2011}-P_{2013}}{P_{2011}}100 = +10.9\%$		$\frac{P^c_{2011}-P^c_{2013}}{P^c_{2011}}100 = +7.9\%$		
2014-2019									
Total	n_{2014}=1449	n_{2019}=1617	N_{2014}=17160855	N_{2019}=18395567	P_{2014}=8.44	P_{2019}=8.79	P^c_{2014} = 8.44	P^c_{2019} = 8.08	$E(n_{2019})$=1682
Change	$\frac{n_{2014}-n_{2019}}{n_{2014}}100 = +11.6\%$		$\frac{N_{2014}-N_{2019}}{N_{2014}}100 = +7.2\%$		$\frac{P_{2014}-P_{2019}}{P_{2014}}100 = +4.1\%$		$\frac{P^c_{2014}-P^c_{2019}}{P^c_{2014}}100 = -4.3\%$		
2020-2021									
Total	n_{2020}=1471	n_{2021}=1604	N_{2020}=18631779	N_{2021}=18878966	P_{2020}=7.90	P_{2021}=8.50	P^c_{2020} = 7.90	P^c_{2021} = 8.39	$E(n_{2021})$=1514
Change	$\frac{n_{2020}-n_{2021}}{n_{2020}}100 = +9.0\%$		$\frac{N_{2020}-N_{2021}}{N_{2020}}100 = +1.3\%$		$\frac{P_{2020}-P_{2021}}{P_{2020}}100 = +7.6\%$		$\frac{P^c_{2020}-P^c_{2021}}{P^c_{2020}}100 = +6.3\%$		
2022-2024									
Total	n_{2022}=1713	n_{2024}=1830	N_{2022}=19503159	N_{2024}=20033842	P_{2022}=8.78	P_{2024}=9.13	P^c_{2022} = 8.78	P^c_{2024} = 8.79	$E(n_{2024})$=1825
Change	$\frac{n_{2022}-n_{2024}}{n_{2022}}100 = +6.8\%$		$\frac{N_{2022}-N_{2024}}{N_{2022}}100 = +2.7\%$		$\frac{P_{2022}-P_{2024}}{P_{2022}}100 = +4.0\%$		$\frac{P^c_{2022}-P^c_{2024}}{P^c_{2022}}100 = +0.1\%$		

Post-pandemic recovery (2022–2024)

In 2022–2024, a post-pandemic consolidation was observed: the crude rate rose from 8.78 to 9.13 per 100,000 (+0.35 per 100,000) alongside an essentially flat age-standardized rate (8.78 → 8.79, +0.1%), i.e., without a substantive increase in risk of disease. Component decomposition confirms the demographic nature of the crude-rate increase: age structure +0.32, risk +0.01, interaction +0.02. Case counts increased 1,713 → 1,830 (+117), 96% of which is explained by demography (+47 from population growth and +63 from ageing; joint effect +2), while change in risk contributed only +2 cases (≈1.7% of the increase). Overall, this indicates a return to a stable level of detectability, with demographic drivers predominating and the prior catch-up effect largely exhausted.

Table 3.

Contributions of demographic and risk components to case counts (%), Kazakhstan, 2005–2024.

Компоненты прироста числа заболевших за счет:	Change, %				
	2005-2010	2011-2013	2014-2019	2020-2021	2022-2024
1. Growth PS $\Delta_P = \frac{N_1 - N_2}{N_1} n_1$	+7.0	+2.9	+7.2	+1.3	±2.7
2. Changes ASP $\Delta_A = \frac{N_1}{N_2}(E(n_2) - n_2 - \Delta_H$	−0.9	+1.9	+8.3	+1.5	+3.7
3. Combined effect of changes in PS+ASP $\Delta_{PA} = \frac{N_2 - N_1}{N_1}\Delta_A$	−0.1	+0.1	+0.6	+0.02	+0.1
	$\sum_{1-3}$=+6.0	$\sum_{1-3}$=+4.8	$\sum_{1-3}$=+16.1	$\sum_{1-3}$=+2.9	$\sum_{1-3}$=+6.5
4. Change in risk of disease (RD) $\Delta_R = N_1(P_2^c - P_1^c) \times 10^{-5}$	−6.2	+7.9	−4.3	+6.3	+0.1
5. Combined effect of changes of RD+PS $\Delta_{RP} = \frac{N_2 - N_1}{N_1}\Delta_R$	−0.4	+0.2	−0.3	+0.1	0.00
6. Combined effect of changes of RD+ASP $\Delta_{RA} = \frac{N_2 - N_1}{N_1}\Delta_R$	+0.5	+1.0	+0.04	−0.2	+0.2
7. Combined effect of the changes RD+PS+ASP $\Delta_{RAP} = \frac{N_1}{N_2}\left(n_2 - n_1 - \sum_{x=1}^{5}\right)$	+0.03	+0.03	0.00	0.00	+0.01
	$\sum_{4-7}$=−6.1	$\sum_{4-7}$=+9.2	$\sum_{4-7}$=−4.5	$\sum_{4-7}$=+6.1	$\sum_{4-7}$=+0.3
Total $\sum_{1-7}$	−0.2	+14.0	+11.6	+9.0	+6.8

Discussion

Our 20-year analysis shows that the increase in rectal cancer incidence in Kazakhstan (2005-2024) was driven predominantly by demographic forces (population ageing and growth), whereas risk component overall remained stable or slightly declined. Two short-lived positive “risk” peaks were observed – at screening rollout (2011–2013) and during the pandemic window (2020–2021). This phased profile aligns with the expected dynamics following implementation of organized screening (lead-time and depletion of the preclinical pool with subsequent stabilization) [18].

Stage-specific interpretation in context of the literature.

1. Pre-screening (2005–2010). Concurrent declines in CR and ASR with an almost unchanged case count indicate a moderate reduction in age-specific incidence in the absence of external interventions – a typical “pre-reform” background in which behavioral and clinical-diagnostic factors shape risk while demography exerts a weak countertrend. Globally, this matches evidence that CRC variation is strongly tied to age structure and exposure to risk factors [17].

2. Early rollout (2011–2013). We observe a classic screening-related surge: ASR increases and the risk component dominates against a moderate contribution of age structure – an established pattern at the start of organized CRC screening (heightened detectability and a shift in time-to-diagnosis). International reviews and network meta-analyses document short-term increases in detection after adoption of organized programs, particularly with FIT/iFOBT and expanded colonoscopy capacity [14, 18].

3. Program stabilization (2014–2019). Declining ASR alongside a modest rise in CR and a negative risk component indicates attenuation of the initial screening effect and demographic predominance. Similar profiles are reported in settings with mature programs, where further increases in crude incidence are largely demographic while the risk component stabilizes or declines. For Kazakhstan, earlier studies documented upward trends in recorded cases across all regions with substantial roles for demography and risk, consistent with our component decomposition [10].

4. Pandemic impact (2020–2021). The 2020 drop and partial recovery in 2021 feature a positive risk component over 2020–2021, yet levels remained below pre-pandemic benchmarks; this mirrors international series showing sharp reductions in screening/endoscopy in 2020, diagnostic delays, and a partial rebound in 2021 based on systematic reviews, SEER-based analyses, and multi-site studies [7].

5. Post-pandemic recovery (2022–2024). A flat ASR with a modest rise in CR and near-exclusive demographic contributions indicates exhaustion of the catch-up effect and return to baseline detectability; analogous plateaus after 2021–2022 are reported in large health systems as screening coverage stabilizes [16].

Implications for policy and practice.

(1) **Sustaining screening resilience.** Ensure reserve endoscopy capacity and flexible pathways (broader use of home-based iFOBT) to buffer shocks during crises.

(2) **Focus on ages 50–79.** These cohorts account for the bulk of cases; resource allocation should follow the region-specific demographic profile.

(3) **Component-based monitoring.** Routine decomposition into **size/structure/risk** should become a KPI for oncology services, allowing separation of true risk changes from demographic artifacts and correct interpretation of rising CR with stable/declining ASR.

(4) **Population communication.** Post-COVID compensation does not warrant over-diagnosis; stable coverage and targeted outreach to groups who missed screening in 2020–2021 are key.

Strengths and novelty. (i) Nationwide scope and a long observation window (2005–2024); (ii) a formal **component (decomposition) analysis** with phase-specific periodization, enabling quantitative separation of demography from risk; and (iii) explicit positioning against international screening trends and COVID-related disruptions. Unlike aggregate trend summaries, our approach elucidates the **mechanisms** and **temporal structure** of change.

Limitations. Potential variation in registration completeness across country/years and heterogeneity in screening quality metrics (coverage, FIT positivity, colonoscopy completion, stage distribution), as well as lack of individual-level risk factors. The COVID period may have involved patient selection and stage delays, potentially biasing short-term estimates. These limitations are typical for national registries and are discussed in the international literature on pandemic effects on oncology indicators.

Conclusions. In Kazakhstan's rectal cancer incidence dynamics, **demography** is the principal determinant of the increase in crude rates, while **risk changes** manifest in phases—at screening initiation and during compensatory recovery after the pandemic. This configuration is consistent with global evidence and underscores the need for robust early-detection programs, contingency-ready capacity, and routine **component-based surveillance** to correctly interpret incidence trends.

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MAPPING THE RESEARCH LANDSCAPE: IONIZING RADIATION-INDUCED OXIDATIVE STRESS AND INFLAMMATION IN THE BRAIN – A BIBLIOMETRIC ANALYSIS

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Abstract

Introduction: Ionizing radiation (IR) - induced oxidative stress and inflammation in the brain represent a significant global challenge, contributing to the molecular mechanisms underlying brain tissue damage and neurovascular disruption.

Objective: This bibliometric analysis aims to evaluate the findings of studies investigating IR-induced oxidative stress and inflammation in the brain.

Search Strategy: Utilizing the Scopus and Web of Science (WOS) databases, we analyzed 524 articles, including 404 research articles and 120 review articles.

Results: Our results reveal a notable rise in research activity, reflecting increased awareness of this critical issue. The "International Journal of Radiation Biology" and the "International Journal of Molecular Sciences" emerged as the most prolific journals, playing pivotal roles in disseminating relevant findings. The United States, China, Egypt and India were identified as leading contributors, with institutions in Egypt and United States making significant impacts through high publication volumes. Kim J. and Tang F. emerged as notable authors in the field. **Conclusions:** Insights from this work are essential for shaping future research directions and enhancing our understanding of the underlying mechanisms, which are vital for developing protective and therapeutic strategies to mitigate radiation exposure's effects.

Keywords: *ionizing radiation; brain; oxidative stress; inflammation.*

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Резюме

КАРТИРОВАНИЕ ИССЛЕДОВАТЕЛЬСКОГО ЛАНДШАФТА: ОКИСЛИТЕЛЬНЫЙ СТРЕСС И ВОСПАЛЕНИЕ В ГОЛОВНОМ МОЗГЕ, ВЫЗВАННЫЕ ИОНИЗИРУЮЩИМ ИЗЛУЧЕНИЕМ – БИБЛИОМЕТРИЧЕСКИЙ АНАЛИЗ

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Введение: Ионизирующее излучение (ИИ), индуцирующее окислительный стресс и воспаление в головном мозге, представляет собой значительную глобальную проблему, способствующую молекулярным механизмам повреждения мозговой ткани и нарушению нейроваскулярной функции.

Цель: Данный библиометрический анализ направлен на оценку результатов исследований, посвящённых влиянию ИИ на развитие окислительного стресса и воспаления в мозге.

Стратегия поиска: С использованием баз данных Scopus и Web of Science (WOS) было проанализировано 524 статьи, включая 404 оригинальных исследования и 120 обзорных статей.

Результаты: Наши результаты выявили заметный рост исследовательской активности, что отражает возрастающее внимание к данной проблеме. Журналы International Journal of Radiation Biology и International Journal of Molecular Sciences оказались наиболее продуктивными и играют ключевую роль в распространении соответствующих научных данных. Соединённые Штаты, Китай, Египет и Индия определены как ведущие страны-участники, при этом учреждения Египта и США внесли значительный вклад благодаря высокому количеству публикаций. Среди авторов выделяются Kim J. и Tang F.

Выводы: Полученные выводы имеют важное значение для формирования будущих направлений исследований и углубления понимания основных механизмов, что критически важно для разработки защитных и терапевтических стратегий по снижению последствий воздействия радиации.

Ключевые слова: *ионизирующее излучение; мозг; окислительный стресс; воспаление.*

Для цитирования:

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Түйіндеме

ЗЕРТТЕУ ЛАНДШАФТЫНЫҢ КАРТАСЫ: ИОНДАУШЫ СӘУЛЕЛЕНУДІҢ МИДАҒЫ ТОТЫҒУ КҮЙЗЕЛІСІ МЕН ҚАБЫНУҒА ӘСЕРІ – БИБЛИОМЕТРИЯЛЫҚ ТАЛДАУ

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Кіріспе: Иондаушы сәулелену (ИС) - мида тотығу күйзелісі мен қабынуды тудырады, ми тінінің зақымдануы мен нейроваскулярлық бұзылыстардың молекулалық механизмдеріне ықпал ететін елеулі жаһандық мәселе болып табылады.

Зерттеу мақсаты: Бұл библиометриялық талдау мида сәулеленудің әсерінен дамитын тотығу күйзелісі мен қабыну туралы зерттеген жұмыстардың нәтижелерін бағалауға бағытталған.

Зерттеу әдістері: Scopus және Web of Science (WOS) деректер қорларын пайдалана отырып, барлығы 524 мақала талданды, оның ішінде 404 түпнұсқа зерттеу және 120 шолу мақалалары.

Нәтижелері: Нәтижелер зерттеулер белсенділігінің айтарлықтай өскенін көрсетті, бұл мәселенің маңыздылығына деген назардың артқанын білдіреді. *International Journal of Radiation Biology* және *International Journal of Molecular Sciences* журналдары ең өнімді басылымдар ретінде анықталды және маңызды ғылыми деректерді таратуда жетекші рөл атқарады. АҚШ, Қытай, Египет және Үндістан жетекші елдер ретінде ерекшеленді, олардың ішінде Египет пен АҚШ мекемелері жоғары жарияланымдарымен айтарлықтай үлес қосты. Авторлар арасында Kim J. және Tang F. ең белсенді зерттеушілер ретінде аталды.

Қорытынды: Бұл жұмыстың нәтижелері болашақ зерттеу бағыттарын айқындау және негізгі механизмдерді тереңірек түсінуді қамтамасыз ету үшін маңызды, ал бұл радиация әсерін азайтуға арналған қорғаныш және терапиялық стратегияларды әзірлеуде шешуші мәнге ие.

Түйінді сөздер: *иондаушы сәулелену; ми; оксидативті стресс; қабыну.*

Дәйексөз үшін:

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Introduction

Ionizing radiation (IR) is a type of radiation with energy sufficient to overcome the bonding forces holding tightly bound electrons in their respective orbitals around the nuclei of atoms and molecules, causing the atoms to lose or gain electrons, thus becoming charged ions or free radicals. In biological organisms, ionization exerts its effects through two primary mechanisms: direct and indirect [44]. Direct ionization damages cellular molecules by breaking chemical bonds, leading to DNA strand breaks [5]. Indirect effects arise when radiation interacts with water molecules within cells, producing reactive oxygen species (ROS) via water radiolysis, which can damage DNA, proteins, and lipids [67], ultimately leading to cellular dysfunction, DNA mutations, and cell death [36]. The biological consequences of radiation exposure depend on several factors, including radiation type, dose rate, exposure duration, and tissue radiosensitivity [28].

The discovery of X-rays by Wilhelm Conrad Röntgen (November 8, 1895), radioactivity by Antoine Henri Becquerel (1896) and the free electron by Joseph John Thomson (1897) were pivotal events that revolutionized science at the end 19th century, profoundly influencing the development of physics, chemistry and medicine, while laying the groundwork for future scientific discoveries and advances. These breakthroughs significantly expanded scientific and medical knowledge, marking a milestone in the progress of their respective fields [45]. However, the advent of nuclear technology has also been associated with catastrophic events, including the bombings of Hiroshima and Nagasaki (Japan, 1945), accidents at Kyshtym (Russia, then USSR, 1957), Windscale Piles (United Kingdom, 1957), Three Mile Island (USA, 1979), Chernobyl (Ukraine, then USSR, 1986), and Fukushima (Japan, 2011) [23].In Kazakhstan, the Semipalatinsk nuclear test site saw 456 nuclear explosions, including 111 atmospheric tests (86 in the air and 25 on the surface), between 1949 and 1962 [6]. These events have had profound consequences, including genomic instability, increased incidence of cancers and non-cancerous diseases, and population decline [35, 24, 22]. Currently, there are 411 nuclear power plants operating worldwide to meet growing energy demands, which does not exclude the possibility of future nuclear incidents [30].

The use of IR in industry (sterilization, materials testing), medical procedures (X-rays, computed tomography), and oncology (radiation therapy) has expanded significantly over the last decade [21, 55]. The International Commission on Radiological Protection (ICRP) has established a threshold dose of 0,5 Gy for cardiovascular and cerebrovascular diseases. However, clinical studies in neuroradiology and radiotherapy indicate that this threshold is frequently exceeded during medical interventions, Highlighting the need for research on the cumulative effects of repeated radiation exposure on patients and healthcare workers [52]. Research indicates that radiation doses exceeding > 0.5 Gy cause brain damage, while doses between 0 and 0.5 Gy do not exclude the possibility of developing neurocognitive and neurodegenerative diseases [48], necessitating further detailed investigation.

Under normal physiological conditions, ROS are primarily generated in cells by the mitochondrial electron transport chain and NADPH oxidases, playing critical roles in energy metabolism and immune defense, maintaining vital cellular functions [7]. Cells have endogenous antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which effectively neutralize ROS, maintaining their levels within physiological norms and preventing cellular and tissue damage [31]. In pathological conditions, oxidative stress is defined as an imbalance between the excessive production of ROS and the cell's ability to neutralize them through its antioxidant defense mechanisms. As a result, oxidative stress disrupts redox signaling processes [9], which contributes to the development of diseases such as atherosclerosis [66] and neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease [33]. Oxidative stress also triggers lipid peroxidation, damaging polyunsaturated fatty acids (PUFAs) in cell membranes, leading to compromised cellular integrity and function [69].

The body’s protection is supported not only by endogenous antioxidants but also by the inflammatory response. Inflammation is a defensive reaction of the immune system aimed at eliminating the cause of damage, clearing away damaged cells, and initiating the healing process. However, an excessive inflammatory response, despite its protective and beneficial role, can lead to increased ROS production, tissue damage, and the progression of disease. Oxidative stress, lipid peroxidation, and neuroinflammation are central to the development of neurodegenerative diseases. Globally, the incidence of neurological disorders ranges from 10 to 15 cases per 100,000 people annually [53]. Furthermore, oxidative stress stimulates the production of pro-inflammatory cytokines, such as interleukins, interferons, and growth factors [1].

The brain, in turn, consumes 20% of the body's total oxygen and 25% of its glucose supply [19], while PUFAs account for approximately 35% of the brain's total lipids [49]. Compared to other organs, the brain is unique due to its high PUFA content, low levels of endogenous antioxidants, and increased sensitivity to oxygen deprivation, making it particularly vulnerable to oxidative stress [50]. Modern radiology does not plase sufficient emphasis on the cerebrovascular network, despite its crucial role in oxygen transport and brain metabolism. Secondary damage caused by oxidative stress is directly linked to the inflammatory process, which leads to neurovascular network. [4]. Radiation induces neuropathological changes in the brain [26], leading to subsequent neurological and neuropsychological disorders [8], including neuroinflammation [59], neurovascular dysfunction, blood-brain barrier (BBB) disruption, synaptic impairment, neuronal death [43], and impaired neurogenesis. These effects ultimately contribute to cognitive decline [61] and neurodegenerative diseases [56].

In academic literature, numerous bibliometric analyses cover various aspects, including radiotherapy, diagnostics, treatment methods, primary and metastatic brain cancer, and radionecrosis [65]; studies examining the relationship between oxidative stress and cognitive impairments (chemobrain) associated with cancer treatment, particularly chemotherapy [40]; and the biological effects of radiation exposure below 100 mSv [46]. Unlike previous bibliometric analyses, which primarily focus on cancer treatment and cognitive impairments, our study provides a more targeted and in-depth investigation of specific processes. Specifically, our analysis examines publications

from various countries and journals, exploring how IR induces oxidative stress and subsequent neuroinflammation, while detailing the molecular and cellular mechanisms involved. Additionally, we evaluate global publication trends, collaboration networks, and influential contributors in this field.

The aim of our analysis is to comprehensive assess the impact of IR on oxidative stress and inflammation in the brain, exploring their roles in cognitive and cerebrovascular impairments and neurodegenerative diseases. By identifying current trends and knowledge gaps, this study seeks to guide future research and advance understanding of these critical processes.

Search Strategy. On December 30, 2024, we conducted a bibliometric analysis examining the effects of IR on oxidative processes and neuroinflammation in the brain. This analysis involved a comprehensive search of the Scopus and Web of Science (WOS) databases. Inclusion criteria were restricted to original and review articles primarily available in English, while proceeding papers, book chapters, and editorial materials were excluded. Using advanced search parameters, we conducted an exhaustive query of both databases and downloaded all relevant bibliographic metadata in BibTeX and text formats. The collected data were then exported into RStudio as an Excel file. Figure 1 presents a flowchart depicting the complete search strategy employed for data collection. Articles deemed irrelevant based on their titles, abstracts, and full-text content were systematically excluded.

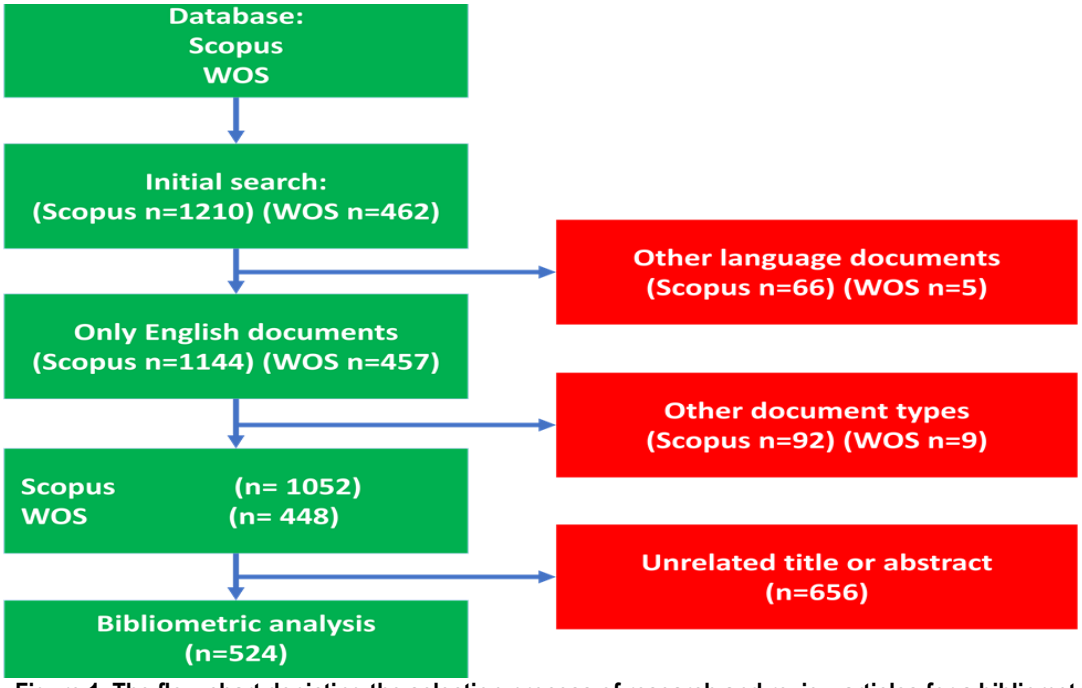

Figure 1. The flow chart depicting the selection process of research and review articles for a bibliometric analysis on the effects of IR on oxidative stress and neuroinflammation in the brain.

Bibliometric Analyses

In this investigation, we conducted performance analysis and science mapping utilizing the bibliometric package (version 4.1.3) and Biblioshiny web applications within RStudio (RStudio 2023.09.1+494, PBC, Boston, MA). The analysis covered a period of 58 years for English-language research articles and 43 years for English-language review articles, focusing on key bibliometric indicators such as citation and publication counts, prolific institutions and authors, and international collaborations.

Results

Search results

Initially, 1210 papers from Scopus and 462 from WOS were collected for a comprehensive examination of the impact of IR on oxidative stress and neuroinflammation in the brain. After applying eligibility criteria and excluding 656 unsuitable studies, a total of 524 papers were deemed suitable for this bibliometric analysis (Figure 1).

Key attributes of the encompassed studies

This bibliometric analysis aims to examine global research findings on IR-induced oxidative stress and neuroinflammation in the brain. In total, 524 research and review articles were identified and analyzed. The dataset included 404 research articles, involving 2008 authors, sourced from 246 documents. Similarly, the 120 review articles featured contributions from 536 authors, originating from 94 sources. On average, these research articles received 31.32 citations per document, while the review articles had a higher citation impact, averaging 81.5 citations per document. Table 1, "Most Globally Cited Documents," presents the 10 most frequently cited research and review articles. The publication growth rate over the study period was calculated using the annual growth rate. In this research domain, the growth rate for research articles was determined to be 6.04%, while review articles exhibited a notably lower growth rate of 3.28%. Additionally, an analysis of research articles revealed a total of 10617 references and 956 author keywords. In contrast, review articles contained 6062 references and 386 author keywords.

Trend of publication and citation

Interest in studying IR, oxidative stress, and neuroinflammation in the brain emerged at the end of the 20th century. Between 1966 and 1986, the number of English language research publications on this topic was at its lowest, with only 8 studies conducted. However, with the advancement of innovative technologies in the 21st century, the demand for research on the effects of IR has increased

Table 1. **Ranking of the Top 10 most cited research and review publications worldwide on the effects of IR on oxidative processes and neuroinflammation in the brain.**

Ranking	Study references	Title of the document	Journal name	DOI	Total citations
Research articles					
1	Monje M.L. et al. (2003) [42]	Inflammatory blockade restores adult hippocampal neurogenesis	Science	10.1126/science.1088417	2081
2	Hong J.H. et al. (1995) [29]	Induction of acute phase gene expression by brain irradiation	International Journal of Radiation Oncology*	10.1016/0360-3016(95)00279-8	317
3	Cronk J.C. et al. (2018) [12]	Peripherally derived macrophages can engraft the brain independent of irradiation and maintain an identity distinct from microglia	Journal of Experimental Medicine	10.1084/jem.20180247 10.1038/srep42928	275
4	Wood K.A. et al. (1995) [64]	The role of free radicals and p53 in neuron apoptosis in vivo	Journal of Neuroscience	10.1523/JNEUROSCI.15-08-05851.1995	218
5	Clark P.J. et al. (2008) [11]	Intact neurogenesis is required for benefits of exercise on spatial memory but not motor performance or contextual fear conditioning in C57BL/6J mice	Neuroscience	10.1016/j.neuroscience.2008.06.051	202
6	Hwang S.Y. et al. (2006) [32]	Ionizing radiation induces astrocyte gliosis through microglia activation	Neurobiology of disease	10.1016/j.nbd.2005.08.006	186
7	Lee W.H., Wood K.A. et al. (2010) [39]	Irradiation induces regionally specific alterations in pro-inflammatory environments in rat brain	International journal of radiation biology	10.3109/09553000903419346	153
8	Kyrkanides S. et al. (1999) [37]	TNFα and IL-1β mediate intercellular adhesion molecule-1 induction via microglia–astrocyte interaction in CNS radiation injury	Journal of neuroimmunology	10.1016/S0165-5728(98)00270-7	142
9	Kyrkanides S. et al. (2002) [38]	Cyclooxygenase-2 modulates brain inflammation-related gene expression in central nervous system radiation injury	Molecular Brain Research	10.1016/S0169-328X(02)00353-4	140
10	Daroczi, B. et al. (2006) [13]	In vivo radioprotection by the fullerene nanoparticle DF-1 as assessed in a zebrafish model	Clinical Cancer Research	10.1158/1078-0432.CCR-06-0514	135
Review articles					
1	Galano A. et al. (2011) [17]	Melatonin as a natural ally against oxidative stress: a physicochemical examination	Journal of pineal research	10.1111/j.1600-079X.2011.00916.x	1040
2	Stewart F.A. et al. (2012) [58]	ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs–threshold doses for tissue reactions in a radiation protection context	Annals of the ICRP	10.1016/j.icrp.2012.02.001	1025
3	Chen X. et al. (2012) [10]	Oxidative stress in neurodegenerative diseases	Neural regeneration research	10.3969/j.issn.1673-5374.2012.05.009	515
4	Tofilon P.J. et al. (2000) [60]	The radioresponse of the central nervous system: a dynamic process	Radiation research	10.1667/0033-7587(2000)153[0357:TROTCN]2.0.CO;2	459
5	García J.J. et al. (2014) [18]	Protective effects of melatonin in reducing oxidative stress and in preserving the fluidity of biological membranes: a review	Journal of pineal research	10.1111/jpi.12128	424
6	Shiloh Y. et al. (1997) [54]	Ataxia-telangiectasia and the Nijmegen breakage syndrome: related disorders but genes apart	Annual review of genetics	10.1146/annurev.genet.31.1.635	409
7	Wells P.G. et al. (2009) [63]	Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer	Toxicological sciences	10.1093/toxsci/kfn263	363
8	Hajam Y.A. et al. (2022) [20]	Oxidative stress in human pathology and aging: molecular mechanisms and perspectives	Cells	10.3390/cells11030552	351
9	McKinnon P.J. et al. (2009) [41]	DNA repair deficiency and neurological disease Johnson K. J. et al. (2014)	Nature Reviews Neuroscience	10.1038/nrn2559	248
10	Holley A.K. et al. (2011) [27]	Manganese superoxide dismutase: guardian of the powerhouse	International journal of molecular sciences	10.3390/ijms12107114	240

significantly. Notably, the highest number of publications was recorded in 2024 (n = 30) and in 2020 (n = 28) (Figure 2A). When examining the trend in average annual citations, a significant increase in total citations per article was observed in 2003, peaking at 10.17 citations per study (Figure 2B).

From 1981 to 2024, there was a steady increase in the number of review articles exploring the effects of IR on oxidative stress and neuroinflammation in the brain. The period between 1981 and 2001 had the lowest rate of scientific publications, with only 5 studies released. Conversely, the highest number of publications was observed in 2022 (n=15) and 2021 (n=14), as depicted in Figure 2C. When analyzing trends in average annual citations within the same timeframe, the total number of citations peaked in 2012 at 24.66 and has since declined (Figure 2D).

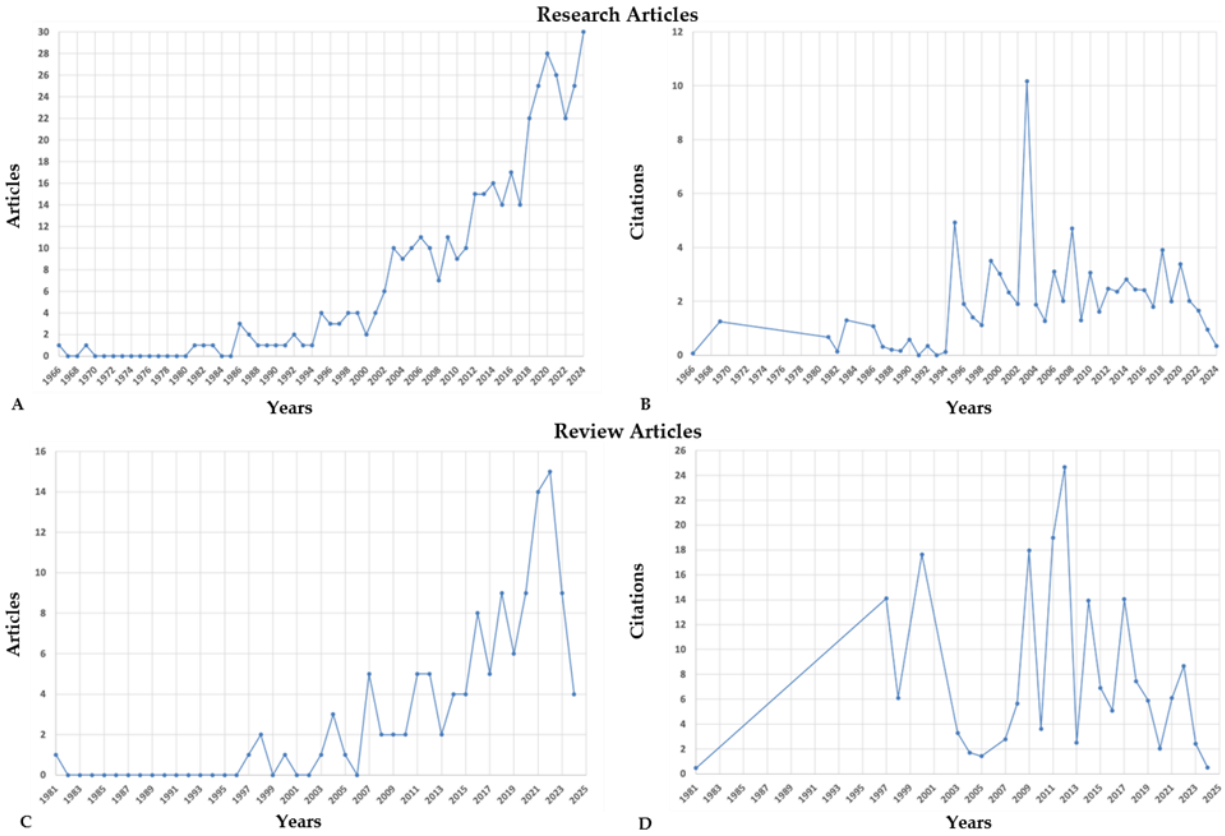

Figure 2. Global annual trends in (A) research article publications and (B) citations, as well as (C) review article publications and (D) citations, in the field of IR's impact on oxidative processes and neuroinflammation in the brain.

Most relevant affiliations

The Egyptian Atomic Energy Authority (EAEA) and the National Center for Radiation Research and Technology secured the top position among the leading ten institutions publishing the highest number of research articles on the effects of IR on oxidative stress and neuroinflammation in the brain, each contributing 33 articles. Closely following are the Egyptian Atomic Energy Authority (EAEA) and University of California System, ranking second and third, with 24 and 19 articles, respectively.

In our examination of review articles within this research domain, University of California System stands out as the most prolific institution, contributing 9 articles. Additionally, National University of Singapore and Stanford University each contributed significantly, publishing five articles respectively, demonstrating notable research productivity.

Most Productive Authors and Their Collaboration Network

During our examination of the effects of IR on oxidative stress and neuroinflammation in the brain, we analyzed the number of publications authored by various researchers.

Among the top contributing researchers in terms of published research articles, *Kim J., Li Y., Limoli C. and Zhang Y.* rank as the most prolific authors, each demonstrating a stable research trajectory with eight articles published consistently from 2004 to 2024. Similarly, *Deng Y., Fike J., Kim S., Ma H., and Wang X.* have each published seven articles, sustaining high productivity. *Tang F.* ranks first among the most influential authors of review articles, having published five articles between 2017 and 2022. Following closely behind, Marazziti D. has authored four review articles from 2012 to 2020, placing them in second place in terms of publication volume. *Baroni S., Costes S., Fike J., Loganovsky K., and Ren B.* have each published three articles, placing them third among the leading authors. The ongoing contributions of these authors highlight their significant impact and continued engagement in advancing research within their respective fields.

Most Productive Journals

Among the leading journals contributing a significant portion of the total publications in this research domain, the "International Journal of Radiation Biology" has the highest

number of research articles, with 22 publications. It is followed by "Radiation Research" and "International Journal of Molecular sciences", which have published 15 and 14 research articles.

Regarding review articles, the "International Journal of Molecular Sciences" is the most prolific journal, with seven published review articles. Following this, "Cells", “Frontiers in Oncology”, “International Journal of Radiation Biology”, “Medical Hypotheses”, “Neuroscience and Biobehavioral Reviews” and “Radiation Research” are the second most productive journals, each with three review articles. Additionally, “Cancers”, “Clinical Neuropsychiatry” and “CNS and Neurological Disorders – Drug Targets” have each published two review articles, making them the third most productive journals.

World Research Production and Collaborations

Figure 3A illustrates the most significant scholarly contributions from 76 known international collaborations, focusing on published research articles examining the impact of IR on oxidative processes and neuroinflammation in the brain. In terms of international cooperation and leading contributions, the United States (n=29), China (n=13), and Germany (n=9) rank first, second, and third among the top 10 countries. Figure 6A also presents that collaborative efforts between China and United States, as well as between Canada and United States, each occurred five times. In contrast, the highest collaboration was observed between the China and Singapore, as well as between the Egypt and Saudi Arabia, with three instances in each case.

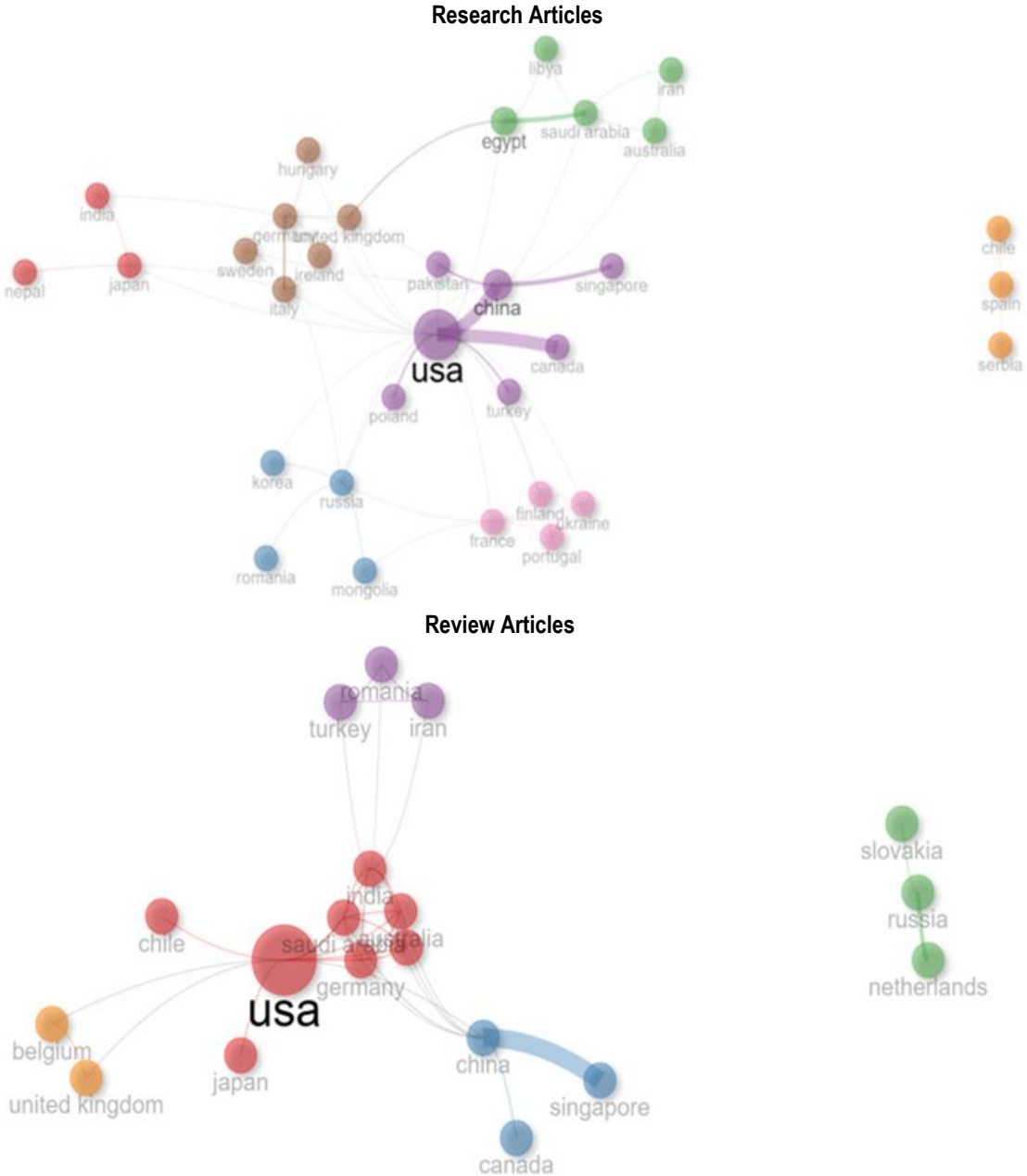

Figure 3. (A) World collaboration map provides a visual representation of international collaborations in publishing research articles, highlighting the global scope of studies on the effects of IR on oxidative stress and neuroinflammation in the brain. Figure 3. (B) World collaboration map illustrates collaboration networks between countries in publishing review articles, summarizing research on the same topic. The thickness of the connecting arrows indicates the strength of collaboration between countries.

Figure 3B highlights 39 notable international collaborations related to review articles on the influence of IR on oxidative stress and neuroinflammation in the brain. Our analysis identified USA (n=10), China (n=10) and India (n=9) as the leading contributors in terms of scholarly output. Figure 6B emphasizes that the strongest collaboration occurred between China and Singapore, with 4 instances of joint publications.

Upon analyzing the most cited countries in research and review articles, our findings indicate that the United States holds the top position, with articles authored by US-based researchers receiving the highest average citation counts - 6318 citations for research articles and 2521 citations for review articles. Furthermore, China ranks second, with 829 citations for research articles, followed by India with 726 citations. For review articles, Mexico and Canada are among the most highly cited, with 1040 and 974 citations, respectively, highlighting their significant contributions to the academic discourse on the effects of IR on oxidative processes and neuroinflammation. These results underscore extensive global collaboration and notable expertise, fostering a deeper understanding of the interplay between IR, oxidative stress and neuroinflammation.

A bibliometric analysis further reveals the scientific productivity of various countries. The USA leads in both research and review articles, with 233 and 68 publications, respectively, demonstrating its significant contributions to the field. It is followed by China, which has published 130 research articles and 25 review articles, indicating its active research engagement. Egypt ranks third with 90 research articles, while India has published 16 review articles, showcasing strong academic performance. These findings highlight the prominence of these countries in scientific research on IR-related oxidative stress and neuroinflammation.

TreeMap

Figure 4A presents a TreeMap visualization depiction the top 20 author keywords most frequently used in research articles on IR-induced oxidative stress and neuroinflammation in the brain. The analysis revealed that the keywords “ionizing radiation” (30%) and “oxidative stress” (13%) were the most commonly applied in this research domain.

Similarly, Figure 4B provides a TreeMap visualization illustrating the top 20 author keywords frequently encountered in review articles within this field. The most recurrent keywords were “ionizing radiation” (21%) and “neuroinflammation” (13%).

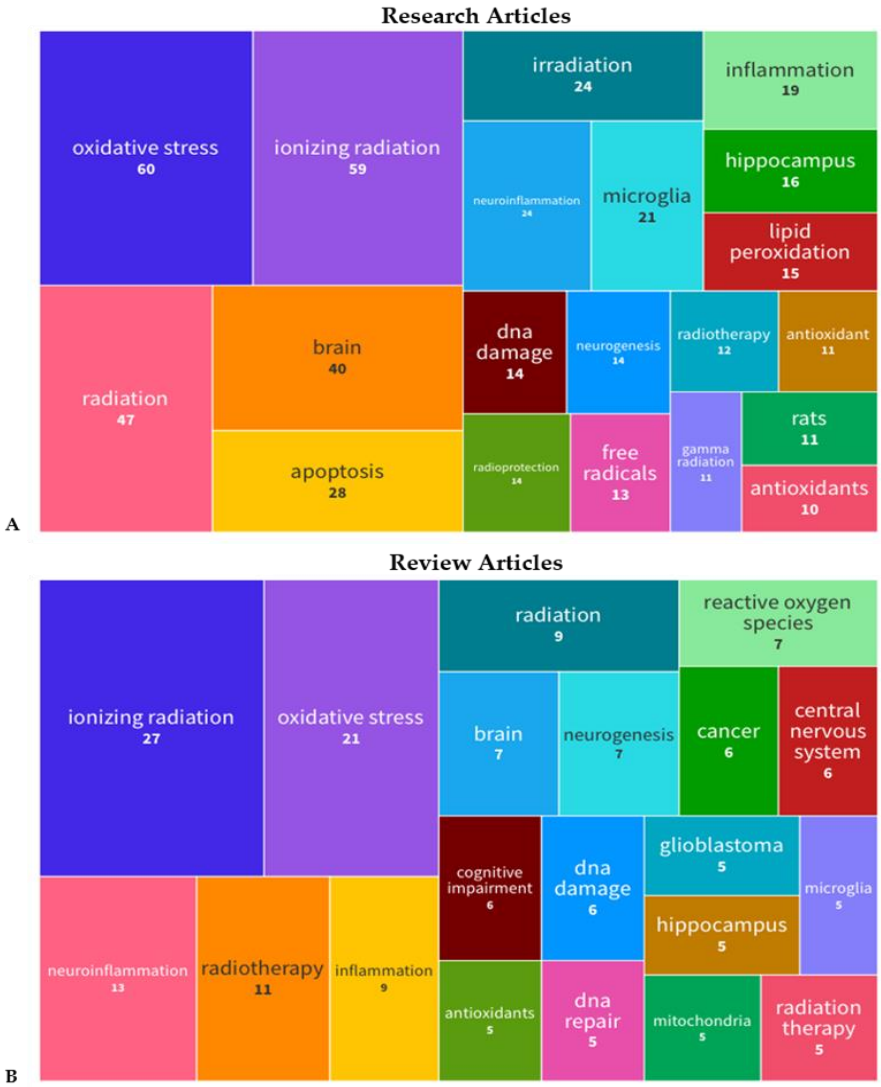

Figure 4. TreeMap representing the top twenty authors' keywords commonly found in research (A) and review articles (B) related to the influence of IR on oxidative stress and neuroinflammation in the brain.

Discussion

Given the growing publication trend on the effects of IR in inducing oxidative stress and neuroinflammation in the brain since 1966, it is evident that this topic remains a critical issue in scientific research, yet to be fully resolved. Of the total 524 review and research articles analyzed, 239 research papers and 87 review articles were published in the last decade, accounting for 62,2% of all publications. This trend suggests that the effects of IR on oxidative stress and neuroinflammation in the brain will remain a subject of interest, with the number of related studies likely to increase in the coming years.

Among the contributing countries, the United States holds the leading position, having published 301 articles in this field. These findings highlight the significant scientific contribution of American researchers, reaffirming the country's role as a major source of scientific literature, particularly in peer-reviewed scientific journals. China follows with 155 articles, demonstrating its active participation in this area of study. This surge in radiology-related publications reflects the country's growing investment in nuclear energy for peaceful purposes.

Egypt ranks third, contributing 90 research articles. Notably, institutions such as the Egyptian Atomic Energy Authority (EAEA), the National Center for Radiation Research and Technology and the Egyptian Knowledge Bank (EKB) have collectively published 90 research papers, securing the first, second and third positions in terms of institutional contributions. This highlights Egypt's significant commitment to scientific progress in this field.

Based on the publications included in the bibliometric analysis, a positive correlation has been identified between exposure to IR at various doses and the risk of developing neurological disorders. Despite extensive research efforts, the molecular mechanisms underlying this association remain insufficiently understood. The INWORKS study demonstrated a increased risk of mortality from "mental disorders" following radiation exposure, while data from Mayak workers indicated a statistically significant elevation in the risk of Parkinson's disease. Additionally, there is a documented link between low to moderate doses of chronic radiation exposure and an elevated risk of dementia, Alzheimer's disease, and Parkinson's disease. Alzheimer's disease is characterized by intracellular accumulation of beta-amyloid and neurofibrillary tangles, accompanied by oxidative stress, inflammation, apoptosis and neuronal necrosis. In contrast, the pathogenesis of Parkinson's disease involves the degeneration of dopaminergic neurons in the substantia nigra and other neuronal structures, as well as the formation of cytoplasmic inclusions containing ubiquitinated proteins (Lewy bodies) within neurons [57]. A synthesis of study results, based on 13 relevant studies involving over 276 000 participants, has provided limited evidence of a decline in overall cognitive functions worldwide after exposure to low to moderate doses of IR [47]. Ahmad's studies indicate that radiation-exposed workers exhibited elevated levels of superoxide ($O_2\bullet^-$), IL-6, interleukin-1a (IL-1a) and macrophage inflammatory protein 1α (MIP-1α) in the moderate and high dose groups (as classified by ICRP data) compared to both the control group and low dose group. The biological effects of IR are induced either directly through DNA damage or indirectly through the generation of ROS, which account for approximately 70% of all radiation-induced biological effects. Based on the assessment of ROS levels in the blood under conditions of increased $O_2\bullet^-$, it was hypothesized that lymphocytes and erythrocytes could be the primary sources of the elevated superoxide levels [2]. The meta-analysis results emphasize the significant impact of low doses of IR on the dynamics of antioxidant-oxidative stress, particularly on catalase (CAT) and superoxide dismutase (SOD), which account for 55% of all assessed markers. This highlights the need for continued research to elucidate the underlying mechanisms and to inform targeted interventions aimed at mitigating the adverse effects of low-dose IR exposure on human health [14]. Despite credible causal interpretations and evidence of potential dose-response relationships suggesting the occurrence of neurological changes after radiation exposure, uncertainty remains regarding random or confounding factors.

Our bibliometric study analyzes research on alterations in particularly vulnerable regions of the brain following radiation exposure. Exposure to IR has been shown to induce the generation of reactive oxygen and nitrogen species (ROS/RNS), leading to a decreased in Na, K-ATPase activity in the cerebral cortex, while the cerebellum demonstrates relative resistance to radiation-induced alterations in this enzyme. Consequently, the radiation-induced reduction in a2 and a3 isoforms results in the relative predominance of the a1 isoform, enhancing Na^+ binding efficiency by the enzyme. Contemporary theories of primary brain dysfunction suggest that the impaired functionality of a2 and a3 Na, K-ATPase subunits may increase susceptibility to neurodegenerative disorders following radiation exposure [34]. Studies on animal models have demonstrated that exposure to a 9 Gy dose significantly decreased the activities of SOD, CAT, and glutathione reductase, and also increased the levels of malondialdehyde (MDA) and carbonyl proteins in the tissues of the cerebellum and cerebral cortex, indicating pronounced oxidative stress. Additionally, changes in neurotransmitter levels, enhanced inflammatory and apoptotic responses, accumulation of amyloid plaques, and reduced brain electrical activity were observed [3].

The keyword "hippocampus" appears multiple times, highlighting its relevance as a key area for further research. The study demonstrated that the hippocampal response to IR suggests a neuroprotective effect at the lowest whole-body exposure dose (0.063 Gy), as it activated the CREB pathway and exhibited anti-inflammatory properties by reducing the number of activated microglia. In contrast, after two years, exposure to 0.5 Gy led to an increase in inflammation and oxidative stress markers, along with CREB deactivation, indicating a shift toward neurodegeneration [25]. Radiation-induced oxidative stress, inflammation and apoptosis in the brain are hypothesized to be associated with the dysregulation of the Nrf2/HO-1/NF-κB signaling pathway. As evidence of oxidative and inflammatory damage, results of study demonstrated that post-irradiation, the activity of key antioxidant enzymes, including CAT, SOD, glutathione peroxidase (GSH-Px), glutathione (GSH), and glutathione reductase (GSR), as well as the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), were significantly reduced and levels of MDA, nitric

oxide (NO), interleukin-1β (IL-1β), IL-6, transforming growth factor-β1 (TGF-β1), and nuclear factor-kB (NF-kB) protein were markedly elevated. Furthermore, B-cell lymphoma 2 (Bcl-2) expression was downregulated, while Bcl-2-associated X protein (Bax) and tumor necrosis factor-alpha (TNF-α) expression were significantly upregulated, along with an increase in caspase-3-positive cells in the hippocampus, confirming the activation of apoptotic pathways. These findings suggest that radiation disrupts the Nrf2/HO-1/NF-kB axis, leading to impaired antioxidant defense, sustained neuroinflammation, and apoptotic neuronal loss, highlighting the potential of targeting this pathway for neuroprotection in radiation-induced brain injury [70]. Studies have also shown that excessive oxidative stress activates NF-κB, a key regulator of inflammatory and immune responses, as well as the Nrf2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway, which plays a crucial role as an endogenous antioxidant defense mechanism. These pathways play a crucial role in modulating inflammatory, antioxidant, and anti-apoptotic processes, making them potential therapeutic targets for diseases associated with oxidative stress and inflammation. In response to γ-radiation exposure, the study results demonstrated a significant increase in the levels of neuroinflammatory mediators IL-6, NF-κB, and GFAP ($p \leq 0.001$), along with a marked reduction in the anti-inflammatory marker IL-10. Radiation exposure inhibited the expression of Nrf2 and HO-1 proteins and genes by promoting ROS activation—key mediators of radiation-induced damage—thereby inducing apoptosis and triggering multiple inflammatory factors. Apoptosis is regulated by the caspase signaling cascade, and this study revealed a significant upregulation of caspase-3 expression, whereas the expression of the anti-apoptotic marker Bcl-2 was markedly decreased in the IR group compared to the control group. Histological analysis confirmed these findings: γ-radiation exposure in rats led to severe degeneration of cortical neurons, neuronal apoptosis, pronounced perivascular edema, and vascular congestion in the brain. Additionally, the hippocampus exhibited signs of cellular disorganization, shrinkage of large pyramidal neurons with hyperchromatic nuclei, and prominent vacuolation in the granular cell layers [15].

The results also show that both single (5 Gy) and fractionated (10 Gy) exposure to ionizing radiation lead to impairments in spatial memory, reduced motor activity, and cognitive dysfunction. It is suggested that radiation-induced damage, manifested as edema and necrosis of the dentate gyrus (DG) in the hippocampus, may contribute to cognitive decline. Post-irradiation, a significant decrease in BDNF and Tau gene expression was observed, potentially promoting neurodegenerative processes. Under normal conditions, Tau protein plays a crucial role in the formation and stabilization of microtubules; however, its abnormal phosphorylation disrupts tubulin binding, leading to cognitive impairment. The results demonstrated a substantial downregulation of genes associated with neuronal function, including calcium ion transport regulation, neurotransmitter secretion, and neuronal differentiation, which may further exacerbate cognitive deficits. Concurrently, an upregulation of genes involved in inflammatory and immune responses, such as monocyte and lymphocyte chemotaxis, angiogenesis, and chemokine-mediated signaling pathways, highlights the pivotal role of neuroinflammation in the pathogenesis of radiation-induced cognitive dysfunction. Furthermore, the results of the study confirms that ionizing radiation-induced brain damage is driven by oxidative stress, DNA strand breaks, and apoptosis, as evidenced by the downregulation of key antioxidant genes (Nrf2, HO-1, Keap1) and the upregulation of p21. The regulation of genes associated with p53-dependent apoptosis (bax, bcl2, caspase3) underscores the critical role of programmed cell death in radiation-induced neurotoxicity [51].

Exposure to 7 Gy of brain irradiation resulted in significant cognitive and emotional dysfunctions, including impaired contextual fear memory and depression-like behavior in mice. A reduction in the number of immature neurons, indicating impaired proliferation of neural stem cells and adult hippocampal neurogenesis, may contribute to the cognitive and emotional disturbances observed after irradiation. Further analysis revealed that cranial irradiation disrupted the hippocampal neurogenic microenvironment, characterized by increased oxidative stress and neuroinflammation. Antioxidant defense markers, including SOD, GSH-Px and CAT, were significantly decreased, while GSH levels declined and MDA levels increased, indicating oxidative damage. Additionally, hippocampal levels of pro-inflammatory cytokines IL-6, TNF-α, and IL-17A were significantly elevated, whereas the anti-inflammatory cytokine IL-4 was markedly reduced. These findings suggest that radiation-induced cognitive and emotional dysfunctions may be linked to disruptions in hippocampal neurogenesis and a pro-inflammatory shift in the neurogenic microenvironment [62]. There is also evidence suggesting that whole-body irradiation of rats at a dose of 4 Gy induces oxidative stress, inflammation, and apoptosis. This is demonstrated by a significant increase in pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and C-reactive protein, accompanied by a concurrent decrease in IL-10 levels. Additionally, elevated MDA levels, along with reduced activity of SOD, CAT, GSH-Px and GSH, indicate impaired antioxidant defense mechanisms. Immunohistochemical analysis further revealed a marked upregulation of caspase-3 and p53, highlighting enhanced apoptotic activity in the brains of irradiated rats [16].

In rats exposed to 15 Gy of radiation, the expression levels of NOX2, NOX4, and caspase-3 were significantly increased compared to the control group ($p < 0.001$). The key mediators of the oxidative system include NADPH oxidases (NOX), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), mitochondria, and antioxidant defense enzymes. Among the NADPH oxidase subgroups, NOX2 and NOX4 play a critical role in radiation-induced oxidative stress. Ionizing radiation-induced oxidative stress, DNA damage, and genomic instability trigger the activation and upregulation of these enzymes. The release of pro-inflammatory and pro-fibrotic cytokines, along with the activation of endothelial cells, fibroblasts, macrophages, neutrophils, and lymphocytes, can enhance the expression and activity of NOX2 and NOX4, leading to excessive ROS production and the development of oxidative stress. Excessive ROS production can suppress antioxidant defense enzymes, compromise vascular integrity, and disrupt the cerebral microcirculation, leading to hypoxia and necrosis of normal brain tissue. MDA and NO levels were significantly increased in the brains of rats exposed to

radiation compared to the control ($p < 0.001$), whereas CAT, SOD, and GSH-Px levels were markedly reduced in the irradiated group ($p < 0.01$). These findings highlight the role of NOX-mediated oxidative stress in radiation-induced brain damage and emphasize the need for further investigation into potential neuroprotective strategies [68].

In our bibliometric study, we explored various aspects of radiology, oxidative stress and neuroinflammation of the brain. Our analysis covered topics such as radiation-induced brain damage across different dose levels, alterations in neurogenesis due to prenatal and postnatal radiation exposure, oxidative stress mechanisms in the brain and the roles of pro-inflammatory and anti-inflammatory cytokines. All data were sourced from the WOS and Scopus databases. Despite our comprehensive analysis, several unresolved challenges persist in this field. One of the primary obstacles is the transition from experimental studies to clinical applications, which is complicated by factors such as environmental influences, dietary habits and physical and psychological conditions. These variables can lead to inconsistencies and hinder the accuracy of research findings. Our bibliometric approach, based on empirical data from published articles, focused on metadata analysis, including information about authors, institutions and countries, to evaluate research productivity and collaboration. However, we did not perform a textual content analysis. Additionally, only full-text articles in English were included in our study, while publications with abstracts in English and those published in other languages were excluded.

Conclusions

International collaboration in research on the effects of IR on oxidative stress and neuroinflammation in the brain is essential for develop advanced strategies to prevent and treat radiation-induced health complications. This bibliometric analysis offers comprehensive qualitative and quantitative insights into key contributing countries, leading authors, institutions, scientific journals and global collaboration trends in radiology. Our results highlight the substantial contributions of the United States, Egypt, China and India, underscoring their leading roles in this research field. Furthermore, the involvement of regions with prior radiation exposure further emphasizes the global significance of this issue.

Over the past decade, there has been a notable surge in research on IR-induced oxidative stress and neuroinflammation, reflecting its growing importance in understanding the broader implications of radiation exposure. Despite persistent knowledge gaps regarding the effects of IR, our analysis provides valuable insights that can help shape future research directions. Given the increasing evidence of IR's detrimental impact on brain health, it is crucial for future studies to adopts a multidisciplinary approach, integrating radiology, neuroscience and molecular biology. This integration will be key to developing targeted therapeutic strategies and protective measures. This comprehensive review serves as a foundation for advancing our understanding of IR's effects on brain health, guiding future research priorities and informing clinical practice to mitigate radiation-induced neurotoxicity.

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ASSOCIATION BETWEEN EXPOSURE TO IONIZING RADIATION AND THE DEVELOPMENT OF CARDIOVASCULAR DISEASES: A LITERATURE REVIEW

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Abstract

Introduction. Pathology of the cardiovascular system is the leading cause in the structure of the causes of death in all countries of the world in recent decades. The impact of ionizing radiation on the cardiovascular system is a complex process that includes various molecular and cellular mechanisms that lead to tissue damage and disruption of their functions. The aim of our research was the analysis and evaluation of modern literature data on the possible association between exposure to ionizing radiation and the development of diseases of cardiovascular system.

Search strategy. For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and eLIBRARY. 124 literary sources were identified, of which 48 publications were the basis of the analytical material for this article.

Results. The development of circulatory diseases due to radiation exposure is based on damage to the vascular intima, primarily in the coronary arteries, changes in the endothelium associated with the accumulation of reactive oxygen species, and low-intensity inflammation leading to the development of atherosclerosis. Acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis. High doses of radiation to the cardiovascular system are typically associated with radiation therapy for cancers such as breast or lung cancer. Low doses of radiation are typical for radiation situations associated with occupational exposure to ionizing radiation, as well as for residents of radiation-contaminated, environmentally unfavorable areas due to nuclear weapons testing or radiation accidents.

Conclusion. The results of the literature review demonstrate a clear link between radiation exposure over a wide range of doses and excess risks of circulatory diseases, primarily coronary heart disease, stroke, myocardial infarction, and hypertension.

Key words*: ionizing radiation, circulatory system diseases, radiation doses, mortality, morbidity.*

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Резюме

СВЯЗЬ МЕЖДУ ВОЗДЕЙСТВИЕМ ИОНИЗИРУЮЩЕГО ИЗЛУЧЕНИЯ И РАЗВИТИЕМ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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Введение. Патология сердечно-сосудистой системы является лидирующей причиной в структуре причин смерти во всех странах мира в последние десятилетия. Воздействие ионизирующего излучения на сердечно-сосудистую систему является сложным процессом, включающим разнообразные молекулярные и клеточные механизмы, приводящие к повреждению тканей и нарушению их функций. Целью исследования явился анализ и оценка современных литературных данных о возможной связи между воздействием ионизирующей радиации и развитием патологии сердечно-сосудистой системы.

Стратегия поиска. Для поиска и анализа научных данных использовались базы данных и веб-ресурсы: MEDLINE, Pubmed, Google Scholar, Cyberleninka, eLIBRARY. Было выявлено 124 литературных источника, из которых 48 публикаций легли в основу аналитического материала данной статьи.

Результаты. В основе развития болезней системы кровообращения при радиационном воздействии лежат повреждение интимы сосудов, в первую очередь, коронарных артерий, изменения в эндотелии, связанные с накоплением активных форм кислорода, а также малоинтенсивное воспаление, ведущее к развитию атеросклероза. Острое лучевое повреждение сердца связано с воспалением и митохондриальной дисфункцией, а хроническое с фиброзом миокарда. Высокие дозы облучения сердечно-сосудистой системы связаны, как правило, с лучевой терапией онкологических заболеваний, таких как рак молочной железы или рак легкого. Низкие дозы облучения характерны для радиационных ситуаций, связанных с профессиональным воздействием ионизирующей радиации, а также для жителей радиационно-загрязненных экологически неблагоприятных территорий вследствие испытаний ядерного оружия либо радиационных аварий.

Заключение. Результаты обзора литературных источников свидетельствуют о связи между радиационным воздействием в широком диапазоне доз и избыточными рисками болезней системы кровообращения, в первую очередь, ишемической болезни сердца, инсультами, инфарктом миокарда и артериальной гипертензией.

***Ключевые слова**: ионизирующая радиация, болезни системы кровообращения, дозы облучения, смертность, заболеваемость.*

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Түйіндеме

ИОНДАУШЫ РАДИАЦИЯНЫҢ ӘСЕРІ МЕН ЖҮРЕК-ҚАНТАМЫР АУРУЛАРЫНЫҢ ДАМУЫ АРАСЫНДАҒЫ БАЙЛАНЫС: ӘДЕБИ ШОЛУ

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Кіріспе. Соңғы онжылдықтарда жүрек-қантамыр жүйесі патологиясы әлемнің барлық елдерінде өлім себептері құрылымында жетекші орын алады. Иондаушы сәулеленудің жүрек-қантамыр жүйесіне әсері — ұлпалардың зақымдануы мен олардың қызметінің бұзылуына әкелетін алуан түрлі молекулалық және жасушалық механизмдерді қамтитын күрделі үдеріс. Зерттеудің мақсаты – иондаушы радиацияның әсері мен жүрек-қантамыр жүйесі патологиясының дамуы арасындағы мүмкін байланысты сипаттайтын қазіргі заманғы әдеби деректерді талдау және бағалау.

Іздеу стратегиясы. Ғылыми деректерді іздеу және талдау үшін MEDLINE, PubMed, Google Scholar, Cyberleninka, eLIBRARY деректер базалары мен веб-ресурстары пайдаланылды. 124 әдеби дерек анықталып, олардың ішінде 48 жарияланым осы мақаланың талдамалық материалының негізіне алынды.

Нәтижелер. Радициялық әсер кезінде қанайналым жүйесі ауруларының дамуында ең алдымен коронарлық артериялар интима қабатының зақымдануы, белсенді оттегі түрлерінің жиналуымен байланысты эндотелий өзгерістері,

сондай-ақ атеросклероздың дамуына алып келетін төмен қарқынды қабыну үрдістері маңызды рөл атқарады. Жедел радиациялық жүрек зақымдануы қабынумен және митохондриялық дисфункциямен байланысты болса, созылмалы зақымдану миокард фиброзына әкеледі. Жүрек-қантамыр жүйесінің жоғары дозада сәулеленуі көбінесе сүт безі обыры немесе өкпе обыры сияқты онкологиялық ауруларды сәулелік терапиямен емдеуге тән. Төмен дозалар, әдетте, иондаушы радиацияның кәсіптік әсерімен немесе ядролық қару сынақтары мен радиациялық апаттар салдарынан экологиялық қолайсыз, радиациялық ластанған аймақтарда тұратын халыққа тән.

Қорытынды. Әдеби деректерге жасалған шолу радиациялық әсердің кең дозалық ауқымында жүрек-қантамыр жүйесі ауруларының, ең алдымен ишемиялық жүрек ауруы, инсульт, миокард инфарктісі және артериялық гипертензияның артық қаупімен сөзсіз байланысты екенін көрсетеді.

Түйінді сөздер: *иондаушы радиация, қанайналым жүйесі аурулары, сәулелену дозалары, өлім-жітім, сырқаттанушылық.*

Дәйексөз үшін:

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Introduction

The effect of ionizing radiation on the human body in most cases is manifested by an increased risk of developing malignant neoplasms [13]. This effect has been demonstrated in a number of studies, most notably in the Life Span Study (LSS) cohort study of the health status of survivors of the bombing in Japan [29]. A series of reports found that there was a 17% excess risk of cancer among the affected population. Furthermore, it was demonstrated that the excess relative risk (ERR) per Gy was 0.42 Gy-1 (95% CI 0.32–0.53) for all solid cancers among the affected population of Japan.

One area of interest has been determining the radiation dose that is a factor in adverse prognosis [31]. In the aforementioned LSS study, the minimum dose range associated with an increased risk of ERR was 0–0.2 Gy for malignant tumors. For a long time, possible non-oncologic effects of ionizing radiation were virtually excluded. However, modern epidemiological data, particularly studies among atomic bomb survivors, indicate an increased risk of cardiovascular diseases CVD [6,21].

It is well known that cardiovascular pathology has been the leading cause of death worldwide in recent decades [45]. The main known modifiable risk factors for circulatory system diseases include nicotine addiction, diabetes mellitus, arterial hypertension, excess weight, hypercholesterolemia, and elevated levels of low-density lipoproteins [43]. The risks of developing CVD when exposed to ionizing radiation have not been sufficiently studied. They are primarily associated with diagnostic procedures and radiation treatment of oncological diseases, since in these cases the radiation doses are clearly defined and belong to the high-dose range (> 5 Gy) [40]. Exposure to such radiation doses causes damage to the structures of the heart, as well as the coronary, carotid, and other large arteries [3]. The effects of ionizing radiation on the cardiovascular system are complex, involving a variety of molecular and cellular mechanisms that lead to tissue damage and dysfunction. Key mechanisms include endothelial cell damage, accelerated atherosclerosis, inflammation, oxidative stress, fibrosis, and alterations in metabolic pathways [38, 7].

The aim of our research was the analysis and evaluation of modern literature data on the possible association between exposure to ionizing radiation and the development of diseases of cardiovascular system.

Search strategy

For the search and analysis of scientific data, we used databases and web resources: MEDLINE, Pubmed, Google Scholar, Cyberleninka, and e-LIBRARY. For the literature review, we used sources published from 1998 to 2025. Scientific articles were used that correspond to the topic and the basic context of the study. During the selection of literature for writing an article, preference was given to publications in peer-reviewed publications. During the primary analysis, a general array of articles was selected, which was filtered for compliance with keywords and context. As a result of the primary selection, 124 literary sources were identified, of which 45 publications were the basis of the analytical material for this article.

Inclusion criteria: reports of randomized and cohort studies, systematic reviews and meta-analyses, diagnostic and treatment protocols, and articles in English. Exclusion criteria: personal communications, newspaper publications, abstracts, and articles with fuzzy conclusions.

Results and discussion

Pathogenetic mechanisms of cardiovascular pathology development under the influence of ionizing radiation

Radiation-induced circulatory pathology, according to many studies, is associated with acute exposure to high doses of radiation [21, 26]. The effect of high doses of ionizing radiation on blood vessels is well illustrated by the example of radiation therapy for cancer, which is accompanied by damage to the vascular intima. At the level of large vessels, such damage is similar to atherosclerotic lesions. Similar changes are observed, for example, in the coronary arteries during the treatment of lung or mediastinal cancer, as well as in peripheral arteries during the treatment of corresponding cancer sites. At the microvascular level, endothelial damage is observed, leading to damage to internal organs such as the kidneys, skin, and brain [1].

The early development and progression of atherosclerotic cardiovascular diseases is primarily based on the development of endothelial dysfunction with the accumulation of reactive oxygen species in endothelial cells, as well as chronic low-intensity inflammation, which plays a key role in atherogenesis [38]. Thus, a number of studies, including experimental ones, have shown that exposure to high radiation doses can lead to

an increase in the levels of adhesion molecules, such as intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), E-selectin, and platelet endothelial adhesion molecule (PECAM-1) [5, 44]. In addition, another probable mechanism of dysfunction has been shown: a decrease in the activity of thrombomodulin and an increased formation of von Willebrand factor, one of the key factors of endothelial dysfunction [41].

In recent years, the concept of radiation-induced heart disease, which occurs as a result of radiation therapy, has emerged. In an experimental study on mice irradiated with a dose of 30 Gy of 60Co γ-rays, a significant number of inflammatory cells was detected, and after one and a half months, an increase in hypertrophied cardiomyocytes and increased myocardial fibrosis. Furthermore, radiation-induced heart disease was associated with the expression of the Cmpk2, Ifit3, Dhx58, Slc2a1, and Thbs1 genes. The results of the study allowed the authors to conclude that acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis [23, 32]. Diffuse fibrosis, following high-dose exposure, affects not only the myocardium but also the pericardium, causing pericardial adhesions, microvascular damage, damage to the intracardiac conduction system, and valvular stenosis, as well as stenosis of the coronary, carotid, and other major arteries. These effects can occur both in humans receiving radiation therapy and in experimental animals [2].

Effects of high doses of ionizing radiation on the cardiovascular system

High risks of radiation-induced cardiac pathology are associated with postoperative radiation therapy for malignant breast neoplasms. Doses to individual parts of the heart muscle during this type of treatment can exceed 40 Gy with fractionated double irradiation of 20 Gy. When calculated for the entire heart muscle, this dose corresponds to 1-2 Gy [32]. Mortality rates from circulatory diseases in women who underwent surgery and radiation exposure were almost 30% higher than in women who received surgery alone [8]. Adverse effects on the heart are observed more often with left-sided neoplasms than with right-sided cancers. Radiation doses to the heart in patients with left-sided tumors undergoing radiation therapy are higher than in patients with right-sided tumors undergoing radiation therapy [10]. This is confirmed by the results of a large-scale epidemiological study of 72,000 breast cancer patients with a 30-year follow-up period. In this cohort, women with left-sided cancers (average radiation dose greater than 6 Gy) had an increased risk of coronary heart disease, pericarditis, and valvular defects compared to patients with tumors located on the right (average radiation dose to the heart of approximately Gy) [26].

Some studies have reported involvement of the immune system in response to exposure to ionizing radiation. In particular, variations in T-cell and B-cell populations depending on radiation doses were found in Japanese atomic bomb survivors [16]. This relationship is especially pronounced with irradiation of the bone marrow or the whole body. It is assumed that radiation exposure causes death of monocytes in the arterial intima, which is associated with the development of atherosclerosis [19]. Monocyte adhesion is associated with radiation-induced aging of the vascular endothelium [24]. With regard to arterial hypertension, the kidneys are considered to be the main target organ for radiation exposure, which is confirmed both by experimental studies and in a study conducted in a cohort of atomic bomb survivors in Japan [12, 17].

Effects of low doses of ionizing radiation on the cardiovascular system

There is evidence that cardiovascular diseases may also be associated with lower levels of radiation exposure, particularly occupational exposure [18, 20, 11]. Some studies conducted in the last decade suggest an excess radiation-related risk at doses received in occupational settings or in unfavorable environmental conditions (<0.5 Gy/L) [20, 21, 22], but the existence of such risks and their magnitude remain unclear. The primary cause of damage to the vascular network is systemic hypoxia, which affects the function of many organs, primarily the myocardium and brain. At moderate radiation doses averaging approximately 50 cGy, the cardiovascular risks for exposed individuals were comparable to those associated with cancer [22].

Cohorts of atomic bomb survivors in Japan

Ecological studies examining the relationship between morbidity and mortality from cardiovascular disease and radiation exposure primarily include studies on cohorts of individuals who survived the atomic bombing in Japan and who received relatively high doses of external gamma radiation in a single instance. For example, the Life Span Study (LSS) cohort study revealed an excess of mortality associated with cardiovascular disease and stroke [35]. These studies have reliably established a link between ionizing radiation from nuclear testing and mortality from the main circulatory diseases – stroke and coronary heart disease (CHD). Thus, the ERR for ischemic stroke was 0.04 Gy-1 (95% CI -0.1, 0.2), for hemorrhagic stroke 0.05 Gy-1 (95% CI -0.06-0.17), while this indicator was 0.58 (95% CI 0.45-0.72) for all cases of CVD [36].

Another study conducted in the same cohort found increased risks of LSS, arterial hypertension, and acute coronary syndrome, but these indicators were not statistically significant [47]. These risks were significantly increased among cohort members exposed in early childhood, but among individuals exposed in utero, the risks of CVS were significantly lower. It should be noted that cohort members exposed in utero had lower doses than those exposed in childhood [39].

According to the study by Preston D.L. et al. (2003), in the LSS cohort, the excess relative risk (ERR) estimates were 0.17 with 90% CI (0.08–0.26) for all circulatory diseases and 0.12 (90% CI, 0.02–0.22) for stroke for the period from 1968 to 1997 [31]. In the study by Takahashi et al., who also studied this population, an increased risk of developing valvular heart disease, more often of rheumatic genesis, was established. Thus, the ERR/Gy for rheumatic heart diseases was 0.96 Gy-1 (95% CI 0.28–1.92), while for coronary heart disease only a slight increase was observed - 0.03 Gy-1 (95% CI -0.08–0.15) [37].

It should be noted that the unique situation of the atomic bomb survivors in Japan was that ionizing radiation was not the only factor. The victims also suffered burns, multiple injuries to various organs and bones, and severe stress, which could have affected their health and led to the development of cardiovascular diseases in subsequent years.

Persons exposed to occupational radiation

Adverse effects of radiation exposure have been identified not only among those affected by nuclear weapons testing, but also among occupational groups. For example, the International Nuclear Worker study (INWORKS) found a significant increase in the risk of cardiovascular diseases (CVD), including coronary heart disease (ERR 0.18; 95% CI 0.004–0.36), acute myocardial infarction (ERR 0.26; 95% CI 0.003–0.51), and chronic cerebrovascular diseases (ERR 0.5; 95% CI 0.12–0.94) [11].

In 2007, the International Agency for Research on Cancer (IARC) conducted a large-scale study examining the risk of various diseases among nuclear energy workers in fifteen countries. The study's results suggested increased risks of mortality from CVD in general, cerebrovascular diseases, and certain circulatory diseases, but not from heart failure or deep vein thrombosis; however, the results were not statistically significant [42].

Another significant group of professionals exposed to single-dose radiation is the Chernobyl disaster liquidators. The dose range was very wide. In this group, the risks of not only mortality but also cardiovascular disease (CVD) incidence related to radiation exposure were studied. This cohort exhibited an excess incidence of coronary heart disease and stroke, and a link was established between these and exposure to ionizing radiation. However, no such link was found for arterial hypertension [17].

The effects of ionizing radiation on circulatory diseases have been studied in considerable detail using workers at the Mayak Production Association in the Chelyabinsk Region, who produce nuclear weapons components and isotopes, as well as store and recycle spent nuclear fuel. A distinctive feature of radiation exposure for this group is the relatively high average whole-body dose (approximately 0.5–0.6 Gy) that accumulated over a long period of time. Furthermore, the majority of this dose was delivered via α-emitting plutonium radioisotopes, representing internal doses, primarily to the liver. In this cohort of professionals, trends toward increased coronary heart disease and cerebral vascular pathology, both for morbidity and mortality, were also identified [4]. A study including representatives of the Mayak cohort of workers demonstrated dose-dependent trends for CHD (ERR 0.06 Gy-1; 95% CI 0.001–0.13) and cerebrovascular disease (ERR 0.00 Gy-1; 95% CI -0.06–0.08) [4]. An excess relative risk of cardiovascular mortality per Sievert was also found in a group of UK radiation industry workers (ERR 0.25 Sv−1), but this figure was of borderline significance [28].

In a cohort study conducted in China, it was found that long-term exposure to low doses of ionizing radiation is also a risk factor for the development of hypertension (RR = 2.09; 95% CI: 1.40–3.06). The fundamental fact is the establishment of a linear increase in risk depending on the dose. Thus, the average dose (5.17–20.00 mSv) caused an increase in RR of 2.70 (95% CI: 1.39–4.99); a high dose (48.33–110.84 mSv) was characterized by the maximum RR, amounting to 3.05 (95% CI: 1.46–5.96) [46].

Population of radioecologically unfavorable territories

The least accurate determination of radiation doses is characteristic of cohorts of residents of areas exposed to radiation from nuclear weapons testing or radioecological disasters. This is due to significant uncertainties associated with population migration, different dietary habits and lifestyles, and the need to calculate doses retrospectively using a survey of exposed individuals, which is associated with memory errors. For example, in a cohort of individuals exposed to radiation in the Southern Urals (the Techa River cohort), significantly elevated excess relative risks of mortality from all circulatory diseases (ERR 0.24 Gy−1) and, in particular, coronary heart disease (ERR 0.40 Gy−1) were found. However, when calculating the indicator for the entire population (exposed + unexposed), it increased significantly – up to 3.15 Gy−1 for diseases of the circulatory system, 3.22 Gy−1 for cardiac pathology and 2.96 Gy−1 for stroke [15].

Results of studies published in recent decades assessing the health status of the population living in the Semipalatinsk Nuclear Test Site (SNTS) also demonstrate a clear link between radiation exposure and the risk of developing CVD. A cohort study that included residents of Kazakhstan exposed to radiation as a result of nuclear weapons tests at the Semipalatinsk nuclear test site compared with unexposed residents from 1960 to 1999 found that radiation doses ranged up to 0.63 Gy to the whole body. Overall, the exposed population showed high mortality from cardiovascular diseases, significantly exceeding that in the unexposed cohort. However, no clear dose-response relationship was found for all cardiovascular diseases, heart disease, and stroke [14]. Long-term exposure to low and medium doses of ionizing radiation was shown to result in an increased ERR among the general population living in the area of 3.15 Gy-1 (95% CI 2.48–3.81). This study also found an increased relative risk of stroke among the affected population.

This relationship was confirmed in another study that included patients injured in ground-level explosions and their descendants [34]. The authors found that patients exposed to radiation were younger than those not exposed (mean age 63 years versus 64 years, $p < 0.001$) and had a higher prevalence of almost all comorbidities. Furthermore, exposed patients had a higher risk of stroke mortality than non-exposed patients.

Of particular interest are studies assessing the role of radiation exposure and the risk of developing arterial hypertension (AH). Currently, there is no doubt that AH is one of the main risk factors for the development of the most significant CVDs, as well as mortality due to CVDs in the world. Thus, a series of LSS studies determined the association of radiation exposure not only with the risk of developing AH (ERR was 0.07 Gy-1 with 95% CI -0.22, 0.55) [36], but also with the progression of organ damage mediated by AH (ERR 0.360 Gy-1; 95% CI 0.1-0.68) [37]. An increased risk of developing AH was also established among residents affected by the activities of the STNPS; thus, the study by *Markabayeva A. et al.* also established an excess relative risk of developing AH [25].

Conclusion

Our literature review demonstrates a clear link between radiation exposure over a wide range of doses and increased risks of circulatory diseases, primarily coronary heart disease, stroke, myocardial infarction, and hypertension. The development of circulatory diseases due to radiation exposure is primarily due to damage to the

vascular intima, primarily in the coronary arteries, changes in the endothelium associated with the accumulation of reactive oxygen species, and low-grade inflammation leading to the development of atherosclerosis. Acute radiation injury to the heart is associated with inflammation and mitochondrial dysfunction, while chronic radiation injury is associated with myocardial fibrosis. High doses of cardiovascular radiation are typically associated with radiation therapy for cancers such as breast or lung cancer. Low doses of radiation are typical for radiation situations associated with occupational exposure to ionizing radiation, as well as for residents of radiation-contaminated ecologically unfavorable areas due to nuclear weapons testing or radiation accidents.

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ADVANCES IN POTENTIAL BIOMARKERS FOR RHEUMATOID ARTHRITIS: SYSTEMATIC REVIEW

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Abstract

Introduction. Rheumatoid arthritis (RA) is a chronic autoimmune condition marked by continuous inflammation of the synovial membrane, gradual joint damage and involvement of internal organs. Its relapsing-remitting course leads to joint deformation, disability and impaired quality of life. The Institute for Health Metrics and Evaluation estimated the global prevalence of RA to exceed 18 million cases in 2019. Given the multifactorial nature of RA, increasing attention is being directed to the role of genetic predisposition, autoantibody formation and cytokine dysregulation in disease onset and progression. Understanding these elements is essential for developing tools for early diagnosis and therapy.

Objective. To analyze current achievements in genetic mutations, autoantibodies, and cytokine profiles involved in RA pathogenesis and assess their potential for early diagnosis of this disease.

Search Strategy. A systematic review was conducted using PubMed and Google Scholar databases. The search included full text articles in English, prioritizing peer-reviewed research, systematic review and meta-analysis. Search terms included “rheumatoid arthritis”, “genetic mutations”, “autoantibodies”, “cytokine production”. *Inclusion criteria:* studies focusing on human subjects, evaluating the role of genetic variants, cytokines or autoantibodies in RA pathogenesis. *Exclusion criteria:* abstracts without full text, animal studies.

Results. From 1990 to 2024, 33,908 publications on RA were identified, with 4,080 meeting the criteria. The findings highlight that RA has a multifactorial pathogenesis with a complex genetic background involving both HLA and non-HLA genes such as HLA-DRB1, STAT4, PADI4 and PTPN22. These gene alterations contribute to T-cell activation, increased cytokine production, including IL-6, TNF-α and IL-17, and subsequent osteoclast–mediated joint destruction. Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies are considered as key diagnostic biomarkers, often detectable years before the clinical onset of symptoms. Environmental triggers like smoking induce the formation of autoantibodies, activation of the complement system and sustained synovial inflammation. Together, these mechanisms underline the diagnostic and prognostic relevance of genetic, cytokine and autoantibody profiling in RA and support the development of diagnostic and therapeutic approaches.

Conclusion. Genetic susceptibility, cytokine dysregulation and autoantibody production act synergistically in rheumatoid arthritis, causing joint damage and systemic complications. Emerging biomarkers for RA show considerable promise in improving early diagnosis, prognosis, and personalized treatment approaches. While several candidates demonstrate strong potential, further validation and standardization are necessary before widespread clinical implementation. Continued research will be essential to translate these findings into routine practice.

Keywords: *rheumatoid arthritis, genes, antibodies, cytokines*.

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Резюме

ДОСТИЖЕНИЯ В ОБЛАСТИ ИССЛЕДОВАНИЯ ПОТЕНЦИАЛЬНЫХ БИОМАРКЕРОВ РЕВМАТОИДНОГО АРТРИТА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Введение. Ревматоидный артрит (РА) — это хроническое аутоиммунное состояние, характеризующееся продолжительным воспалением синовиальной мембраны, постепенным разрушением суставов с вовлечением в процесс внутренних органов. Рецедивирующий характер течения приводит к деформации суставов, с последующей инвалидизацией и снижением качества жизни пациентов. На 2019 год, согласно отчету Института измерения показателей и оценки состояния здоровья, распространенность РА превышает более 18 миллонов зарегестрированных случаев по миру. Учитывая мультифакториальную природу РА, все больше внимания уделяется роли генетической предрасположенности, образованию аутоантител и нарушению регуляции цитокинов в возникновении и прорессировании заболевания. Понимание этих факторов необходимо для разработки инструментов ранней диагностики и последующего лечения.

Цель исследования. Проанализировать современные достижения в области изучения генетических мутаций, аутоантител и цитокинов, участвующих в патогенезе РА и оценить их потенциал для ранней диагностики заболевания.

Стратегия поиска. Систематический обзор литературы был проведен с использованием баз данных PubMed и Google Scholar. Поиск включал полнотекстовые публикации на английском, в первую очередь исследования, опубликованные в рецензируемых журналах, систематические обзоры и мета-анализы. В поиск были включены термины «ревматоидный артрит», «генетические мутации», «аутоантитела», «продукция цитокинов». *Критерии включения* составляли исследования с участием людей, оценивающие роль вариантов генетических мутаций, цитокинов и спектр аутоантител при ревматоидном артрите. *Критерии исключения:* тезисы без полного текста, исследования на животных.

Результаты. С 1990 по 2024 год было выявлено 33 908 публикаций о РА, из которых 4080 соответствовали критериям. Исследования подчёркиваю, что РА имеет мультифакториальный патогенез со сложным генетическим фоном, включающим как HLA, так и не-HLA гены, такие как HLA-DRB1, STAT4, PADI4 и PTPN22. Эти генетические изменения способствуют активации Т-клеток, повышенной выработке цитокинов, включая IL-6, TNF-α и IL-17, и последующему разрушению суставов остеокластами. Аутоантитела, такие как ревматоидный фактор (РФ) и антитела к цитруллинированным белкам (АЦЦП) считаются ключевыми диагностическими биомаркерами, которые часто обнаруживаются за несколько лет до появления клинических симптомов. Факторы окружающей среды, такие как курение, вызывают цитруллинирование, способствуя образования аутоантител, активации системы комплимента и устойчивому воспалению синовиальной оболочки. В совокупности эти механизмы подчеркивают диагностическую и прогностическую значимость определения генов, цитокинов и аутоантител при РА и способствуют разработке диагностических и терапевтических подходов.

Заключение. Генетическая предрасположенность, дисрегуляция цитокинов и продукция аутоантител действуют синергетически при ревматоидном артрите, вызывая повреждение суставов и системные осложнения. Новые биомаркеры ревматоидного артрита демонстрируют значительный потенциал в улучшении ранней диагностики, прогноза и персонализированных подходов к лечению. Несмотря на высокую перспективность ряда кандидатов, необходима дальнейшая валидация и стандартизация перед их широким клиническим применением. Продолжение исследований имеет ключевое значение для внедрения этих находок в клиническую практику.

Ключевые слова: *ревматоидный артрит, гены, антитела, цитокины*

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Түйіндеме

РЕВМАТОИДТЫ АРТРИТ ҮШІН ЫҚТИМАЛ БИОМАРКЕРЛЕРДІ ЗЕРТТЕУДЕГІ ЖЕТІСТІКТЕР: ЖҮЙЕЛІ ШОЛУ

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Кіріспе. Ревматоидты артрит (РА) — бұл буындардың синовиальды мембранасының ұзақ мерзімді қабынуымен, ішкі ағзалардың бұзылысының біртіндеп қосылуымен сипатталатын ұзақ мерзімді аутоиммунды ауру. Ағымның қайталанатын сипаты буындардың деформациясына, кейін мүгедектікке және өмір сапасының төмендеуіне әкеледі. Денсаулық көрсеткіштерін өлшеу және бағалау институтының есебі бойынша 2019 жылы РА-тың таралуы бүкіл әлем бойынша 18 миллионнан асады. РА-тың мультифакторлық сипатын ескере отырып, аурудың пайда болуы мен дамуындағы генетикалық бейімділіктің, аутоантиденелердің және цитокиндердің реттелуінің бұзылуына көбірек көңіл бөлінеді. Бұл факторларды түсіну ерте диагностика және кейінгі емдеу құралдарын жасау үшін өте маңызды.

Зерттеудің мақсаты: РА патогенезіне қатысатын генетикалық мутацияларды, аутоантиденелерді және цитокиндерді зерттеудің заманауи жетістіктерін талдап, олардың ауруды ерте диагностикалаудағы әлеуетін бағалау.

Әдістер. Әдебиеттерге жүйелі шолу PubMed және Google Scholar дерекқорларының көмегімен жүргізілді. Іздеу ағылшын тіліндегі толық мәтінді басылымдарды, ең алдымен рецензияланған зерттеулерді, жүйелі шолуларды және мета-талдауларды қамтыды. Іздеуге "ревматоидты артрит", "генетикалық мутациялар", "аутоантиденелер", "цитокин өндірісі" терминдері қолданылды. *Іріктеу талаптары* ревматоидты артриттегі мутациялардың, цитокиндердің және аутоантиденелердің генетикалық нұсқаларының рөлін бағалайтын адамдарға қатысты зерттеулерді құрады. *Ескерілмейтін талаптар:* толық мәтінсіз тезистер, жануарларда жүргізілген зерттеулер.

Нәтижелер. 1990 жылдан 2024 жылға дейін РА туралы 33 908 басылым анықталды, оның 4080-і адам зерттеулері немесе жүйелі шолулар талаптарына сәйкес келді. Зерттеулер РА-тың HLA және HLA емес гендер HLA-DRB1, STAT4, PADI4, PTPN22 сияқты күрделі генетикалық фоны бар, көп факторлы патогенезі бар екенін атап көрсетеді. Бұл генетикалық өзгерістер Т-жасушаларды белсендіріп, IL-6, TNF-α және IL-17 цитокиндерін көбейтіп, нәтижесінде остеокласттар буындардың бұзылуына ықпал етеді. Ревматоидты фактор (РФ) және цитруллинденген ақуызға қарсы антиденелер (АЦЦП) клиникалық белгілер пайда болмай, бірнеше жыл бұрын кездесетін негізгі диагностикалық биомаркерлер болып саналады. Темекі шегу сияқты қоршаған орта факторлары цитруллинацияны тудырады, аутоантиденелердің пайда болуына, комплимент жүйесінің белсендірілуіне және синовиальды қабықтың тұрақты қабынуына ықпал етеді. Бұл механизмдердің бірігуі РА-те гендерді, цитокиндерді және аутоантиденелерді анықтаудың диагностикалық және болжамды маңыздылығын көрсетеді, диагностикалық және емдік тәсілдерді дамытуға ықпал етеді.

Қорытынды. Генетикалық бейімділік, цитокиндердің реттелуінің бұзылысы және аутоантиденелердің өндірісі ревматоидты артрит кезінде бірлесіп әсер етіп, буындардың зақымдалуына және жүйелік асқынуларға әкеледі. Ревматоидты артриттің жаңа биомаркерлері ерте диагностика, болжам жасау және жеке бағытталған ем тәсілдерін жетілдіруде үлкен әлеуетке ие. Генетикалық бейімділік, цитокиндердің реттелуінің бұзылысы және аутоантиденелердің өндірісі ревматоидты артрит кезінде бірлесіп әсер етіп, буындардың зақымдалуына және жүйелік асқынуларға әкеледі. Ревматоидты артриттің жаңа биомаркерлері ерте диагностиканы, болжамды және емдеудің жекелендірілген тәсілдерін жақсартуда айтарлықтай әлеуетті көрсетеді. Бірқатар кандидаттар жоғары перспективалы болғанымен, оларды клиникалық тәжірибеде кеңінен қолданбас бұрын, одан әрі валидациялау және стандарттау қажет. Зерттеулерді жалғастыру нәтижелерді клиникалық тәжірибеге енгізудің кілті болып табылады.

Түйінді сөздер: *ревматоидты артрит, гендер, антиденелер, цитокиндер*

Дәйексөз үшін:
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Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disease characterized by the gradual development of inflammation in the joints, which can lead to cartilage degradation, bone erosion, and reduced mobility. Initially, only a few joints may be affected, usually small joints of the hand and wrist, but over time, the chronic inflammatory process causes the formation of rheumatoid nodules, vasculitis, and various other conditions, including cardiovascular, pulmonary, neurological, gastrointestinal, renal, and hematological problems [15]. Although the cause of RA is still unknown, research has shown that both genetic and environmental factors play a role in its occurrence.

The prevalence of RA differs depending on gender, ranging from 0.4% to 1.3% of the population. At the same time, the incidence is higher in women compared to men, and there is a growing trend among individuals over the age of 60. RA is a highly prevalent chronic inflammatory disease that affects millions worldwide, leading to joint pain, stiffness, and disability [56].

Like other autoimmune disorders, RAA is likely to be the result of a complex interplay between genetic and environmental factors. To begin with, individuals with genetic predisposition develop self-reactive T and B cells. Then, an initial event such as a viral or bacterial infection or tissue damage triggers the activation of antigen-presenting cells (APCs), which in turn activates these self-reactive lymphocytes. This process disrupts immune tolerance and leads to tissue and organ damage. Therefore, RA develops in individuals with a genetic predisposition due to a combination of genetic, epigenetic, and environmental factors, with an initial event playing a crucial role [38]. Due to remarkable advances in the pharmaceutical industry, innovative therapeutic approaches are becoming increasingly available. However, the challenge of discovering curative treatments persists, largely due to a limited understanding of the molecular mechanisms that regulate the behavior of antibodies, genes, and cytokines. The cornerstone of effective therapy is early diagnosis and the implementation of optimized pharmacological and non-pharmacological treatments, combined with regular assessment of therapeutic efficacy and safety. This necessitates a comprehensive diagnostic approach at the earliest stage, including not only immunological evaluation but also genetic analyses. Early and accurate diagnosis coupled with timely intervention, significantly improves disease outcomes and minimizes the risk of complications.

Aim. To analyze current achievements in genetic mutations, autoantibodies and cytokine profiles involved in RA pathogenesis and assess their potential for early diagnosis of this disease.

Search Strategy. Potential genetic mutations, autoantibodies, and cytokines implicated in autoimmune aggression during RA were identified through a systematic review of biomedical literature and comparison with genetic panels offered by leading global manufacturers. The literature search was conducted using the PubMed and Google Scholar platforms, employing a combination of targeted keywords, including “rheumatoid arthritis”, “genetic mutations”, “autoantibodies”, “cytokine production”, “sequencing”, “NGS” and “exome.” The review included full-text English publications that focused on the prevalence of genetic variations, autoantibodies, and cytokine profiles associated with autoimmune diseases. Articles were screened for relevance, and studies providing detailed information on these parameters were prioritized. Exclusion criteria included literature reviews, abstracts, and other forms of limited publications. Peer-reviewed studies, systematic reviews, and meta-analyses were prioritized for inclusion. Additionally, the Ion AmpliSeq™ Designer gene repository was used to identify disease-associated genes relevant to RA pathogenesis. This approach ensured a comprehensive and evidence-based selection of molecular targets for further analysis. A schematic search strategy is shown in Figure 1.

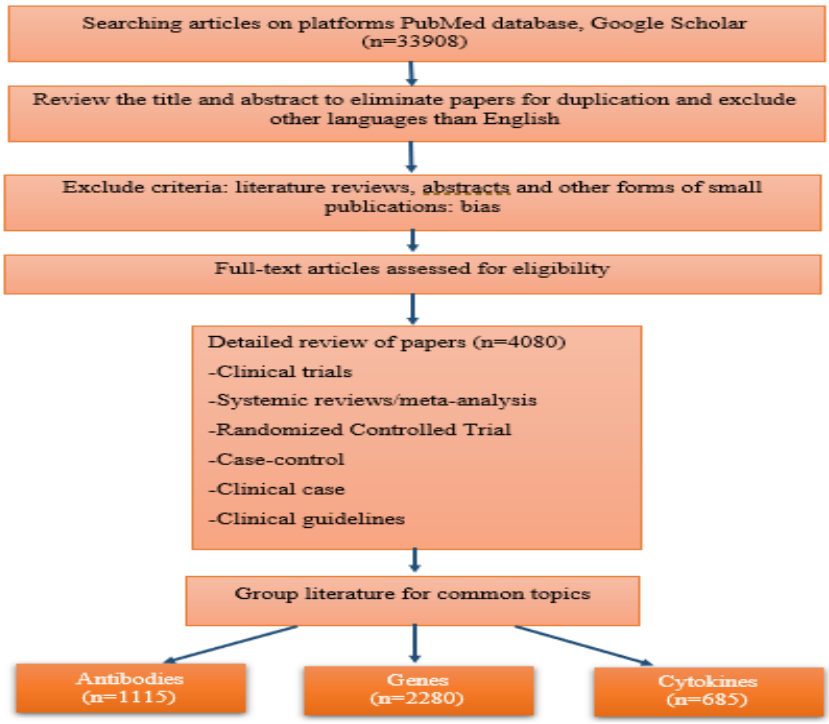

Figure 1. Search strategy (n – number of articles).

Results

The literature search covering the years 1990–2024 yielded 33,908 publications. After applying predefined inclusion criteria - human studies, original investigations, and systematic reviews - a total of 4,080 articles were included in the final analysis.

The importance of antibodies in RA

In contemporary diagnostic procedures, the presence of antibodies such as rheumatoid factor (RF) and antibodies to anticitrullinated proteins (ACPA) serves as a diagnostic tool for rheumatoid arthritis [28]. Novel autoantibodies targeting post-translationally modified proteins—such as carbamylated or acetylated epitopes—are increasingly used to improve diagnostic sensitivity and specificity. Anti-carbamylated protein antibodies (anti-CarP) can also serve as biomarkers, helping stratify patients based on serological profile. This enables the prediction of the disease progression and the selection of the most suitable treatment approach [57].

Additional autoantibodies reported in RA include anti–acetylated vimentin, anti-PAD4, anti-PTX3, and antibodies to DUSP11, although their clinical utility requires further validation [5, 30, 31, 57]. These autoantibodies can be identified primarily in the blood and synovial fluid of individuals with RA years before symptom onset [20]. Upon clinical manifestation of the disease, a broad spectrum of autoantibody isotypes is typically detected. This suggests that, in individuals genetically or environmentally predisposed to RA, specific immunological processes are initiated well in advance of symptom onset, leading to the early production of autoantibodies. The detection of these autoantibodies may serve as a valuable predictive tool for identifying individuals at elevated risk of developing RA.

The key serological markers in RA are RF and ACPA. Beyond their diagnostic utility, these autoantibodies are also instrumental in predicting disease progression and therapeutic outcomes. ACPAs and RF contribute to pathogenesis by forming immune complexes with citrullinated proteins, which subsequently activate macrophages and stimulate the release of pro-inflammatory cytokines. This cytokine-driven inflammatory cascade plays a central role in the initiation and progression of RA.

The cytokines signature

The role of cytokines in the development of RA has been actively studied for many years. Scientific research has confirmed their significant involvement in both the pathogenesis of the disease and its relationship with other systemic disorders.

In the affected joint, infiltrating immune cells in the synovium produce a range of pro-inflammatory cytokines, which are key mediators of cellular differentiation, inflammation, immune pathology, and immune response [32]. Tumor necrosis factor-alpha (TNF-α), mainly secreted by synovial macrophages, B-cells, and NK-cells, is a key driver of inflammatory process [38]. The significance of IL-17A produced by Th17 cells is also emphasized, as it promotes secretion of pro-inflammatory cytokines such as IL-6, IL-8, and GM-CSF, contributing to bone erosion, cartilage damage, and the neoangiogenesis in patients with RA [33]. Additionally, Interleukin 1 has been linked to interstitial lung damage [41], while interleukin 17 has been associated with atherosclerosis [61].

Cytokines could be effective targets for early diagnosis and treatment of RA with targeted biologic therapies. Biologic agents that inhibit TNF-α or block the IL-6 receptor have substantially improved clinical outcomes in RA. Detailed cytokine characteristics are summarized in Table 1.

Table 1.

Cytokines involved in the development of rheumatoid arthritis.

N	Cytokine abbreviation	Cytokine name	Summary (role, mechanism of working, findings)	Reference
1	2	3	4	5
1	TNF-α	tumor necrosis factor alpha	TNF-α is involved in the development and advancement of rheumatoid arthritis (RA) by controlling the growth and development of lymphocytes, promoting the growth of synovial cells, releasing metalloproteinases and cytokines, and inhibiting the function of regulatory T cells.	[1, 27]
2	IL-6	interleukin-6	A distinctive feature of IL-6 is its dual signaling process, known as classical and trans-signaling. In classical IL-6 signaling, IL-6 binds to the membrane-bound form of the IL-6-specific receptor α subunit (IL-6Rα), causing it to interact with the signal-transducing gp130 receptor subunit through the membrane-bound IL-6 receptor. Trans-signaling occurs through the soluble IL-6 receptor. In this case, IL-6 binds to the soluble form of the receptor, which then interacts with the gp130 subunit through the membrane.	[54]
3	IL-7	interleukin-7	IL-7 enhances the differentiation of Th1 cells in RA and increases the secretion of interferon gamma (IFNγ). This process can directly stimulate the expression of the myeloid interleukin-7 receptor (IL-7R), which can exacerbate the inflammatory and erosive effects of IL-7 on joints. Additionally, IL-7 promotes angiogenesis in joints by increasing the production of pro-angiogenic factors by macrophages and endothelial cells in RA.	[45]
4	IL-17	interleukin-17	IL-17 includes several subtypes, such as IL-17A, IL-17B, IL-17C, IL-17D, IL-25, and IL-17F. Patients with RA often have an increased level of IL-17 in their synovial tissues, which suggests that this cytokine may play a role in the inflammatory processes that occur in the joints.	[61]

Continuation of Table 1.

1	2	3	4	5
5	IL-21	interleukin-21	IL-21 has a complex impact on the immune system and plays a crucial role in B-cell function, including responsiveness, proliferation, plasma differentiation, and antibody production. As a result, the effects of IL-21 on B cells may contribute to the development of autoimmune diseases.	[8]
6	IL-1α	interleukin-1 α	The production of IL-1α results in the immune and inflammatory response. Elevated IL-1α correlated with extra-articular manifestations - particularly - interstitial lung disease (ILD) associated with RA.	[41, 48]
7	IL-23	interleukin-23	IL-23 is predominantly produced by macrophages and dendritic cells that are activated and located in peripheral tissues, including skin, intestinal mucosa, joints, and lungs.	[51]
8	IL-1β	interleukin-1β	The level of IL-1β was substantially elevated in individuals with rheumatoid arthritis.	[37]
9	IL-18	interleukin-18	The levels of IL-18 and TNF-α in individuals with RA can be used as reliable indicators of disease progression. IL-18 plays a crucial role in the development and maintenance of inflammatory joint conditions.	[49, 60]
10	IL-33	interleukin-33	In RA IL-33 plays a critical role in the development of the disease. It influences the behavior of several types of immune cells, such as circulating monocytes, tissue macrophages, synovial fibroblasts, mast cells, dendritic cells, neutrophils, T cells, B cells, and endothelial cells.	[39]
11	GM-CSF	Granulocyte-macrophage colony-stimulating factor	GM-CSF is a small cytokine that plays a crucial role in stimulating the growth and development of myeloid cells derived from bone marrow stem cells.	[3]
12	IL-2	interleukin-2	IL-2 plays a fundamental role in maintaining cartilage damage and severe joint destruction by unregulated activation of the immune system.	[35]
13	IL-12p40	Interleukin-12 subunit beta	The Bulgarian RA patients had a significant increase in the blood levels of both IL-12p40 and IL-23 in patients with RA.	[42]
14	IL-17A	Interleukin-17A	They stimulate movement, activation of the gene responsible to produce chemokines, and the ability of synovial membrane cells to penetrate into other tissues. These processes contribute to the transition of the disease into a chronic form, preventing death of synovial cells and increasing production of enzymes that destroy cartilage tissue.	[22]
15	IL-17F	Interleukin-17F		
16	IL-3	Interleukin-3	IL-3 controls growth of Th17 cells by inhibiting the activation of STAT3.	[50]
17	IL-4	Interleukin-4	The research revealed that the IL-4-590 T gene variant is linked to an increased risk of developing RA in individuals of Spanish and Chinese descent.	[26]
18	IL-1	Interleukin-1	It plays a role in the development of RA. IL-1, primarily produced by activated macrophages, is one of the earliest cytokines involved in the inflammatory cascade of RA. Beyond promoting synovial inflammation, IL-1 enhances the expression of adhesion molecules, facilitates leukocyte recruitment, and stimulates fibroblast-like synoviocytes to produce matrix metalloproteinases, thereby accelerating cartilage degradation. IL-1 also drives osteoclast differentiation through RANKL-mediated pathways, contributing directly to bone erosion. Elevated IL-1 levels correlate with disease activity, radiographic progression, and extra-articular manifestations - particularly ILD.	[6]
19	IL-10	Interleukin-10	IL-10 is a versatile anti-inflammatory cytokine produced by various types of immune cells, including macrophages, regulatory T cells, B cells, and mast cells. Decrease in IL-10 levels triggers a severe inflammation response in RA greatly accelerating the progression of the disease.	[10]
20	IL-8	interleukin-8	IL-8 is a powerful chemoattractant that plays a central role in attracting neutrophils to the synovial fluid. IL-8 is activated by TNF-α, IL-1β, and IL-6 and binds to the CXCR1 and CXCR2 receptors on neutrophils, causing their migration and activation. IL-8 is also involved in angiogenesis by promoting the formation of new blood vessels in the synovial membrane, which supports chronic inflammation. Additionally, it stimulates the release of TNF-α and IL-6 creating a vicious cycle of inflammation	[17]

The relevance of genes in RA

Numerous epidemiological investigations have been carried out to identify the elements that make individuals more susceptible to RA, with a particular emphasis on genetic factors. In 2007, the first genomic association studies (GWAS) initiated the investigation of genetic variants in RA [46] . Herein, we analyzed 2,280 articles and identified 32 genes that may predispose to the disease and 12 associated with RA activity. A crucial genetic link in RA is the major histocompatibility complex, particularly the HLA-DR molecule. Variations in the HLA-DRB1 gene containing the shared epitope sequence are linked to an increased likelihood of developing RA and its severe manifestations [16]. In addition to HLA genes, attention has also been focused on non-HLA gene variations like STAT4, PADI4, and TRAF6 that influence the risk of developing rheumatoid arthritis [18, 21, 44]. The genetic profile of the patient can also determine the clinical manifestation of RA, including the presence of rheumatoid factor and antibody-mediated cellular cytotoxicity, as well as the speed at which erosive changes occurs in the joints [32, 46].

Active RA is marked by a distinct molecular profile characterized by upregulation of genes involved in inflammation and immune regulation. During disease flares, genes encoding pro-inflammatory mediators show increased expression, reflecting heightened immune activation. Genes participating in intracellular signaling cascades, particularly those associated with the JAK-STAT pathway (STAT1), are also elevated, underscoring their role in perpetuating cytokine-driven inflammation. The immune response is further intensified by enhanced expression of co-stimulatory molecules such as CD40, indicating active antigen presentation. Collectively, these genetic signatures mirror the pathological mechanisms underlying active RA and may aid in identifying disease activity and guiding targeted therapeutic approaches. Table 2 provides complete information about the genes involved in RA including genes increased during active disease.

Table 2.

The genetic factors involved in the development of rheumatoid arthritis: a review of recent findings.

N	Gene abbreviation	Gene name	Summary (role, mechanism of working, findings)	Reference
1	2	3	4	5
Significant genes associated with susceptibility to the development of RA				
1	AFF3	ALF Transcription Elongation Factor 3	The AFF3 gene is located at 2q11.2 locus and encodes a protein consisting of 1,227 amino acids. This gene is predominantly expressed in lymphoid tissues and is linked to their development. However, low levels of expression have also been observed in other tissues such as the brain and lungs.	[2]
2	FCGR2A	Fc Gamma Receptor IIa	The FCGR2A and FCGR3A genes variations have been discovered to be associated with RA in individuals of European descent, but not in those of Asian ancestry.	[36]
3	IL2 / IL21	Interleukin 2 / Interleukin 21	The IL2/IL21 genes are potential contributors to the development of RA.	[40]
4	IRAK1	Interleukin 1 Receptor Associated Kinase 1	IRAK1 serves as a pivotal controller of the inflammatory environment in joints which depends on IL-1β and represents a promising therapeutic target for inflammatory arthritis.	[23]
5	PIP4K2C	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Gamma	These are hereditary features that increase the likelihood of developing rheumatoid arthritis.	[58]
6	SPRED2	Sprouty Related EVH1 Domain Containing 2	The SPRED2 gene plays a role in controlling the inflammatory process, white blood cells infiltration, and local chemokines synthesis.	[47]
7	IL2RA	Interleukin 2 Receptor Subunit Alpha	The IL2RA gene is located on the shorter segment of chromosome 10 (10q15-q14), also known as CD25. This gene is highly expressed in CD4+CD25+ regulatory T cells and plays a critical role in maintaining immune balance and suppressing autoimmune responses.	[64]
8	ARID5B	AT-Rich Interaction Domain 5B	The variant in the intron of the ARID5B gene, which is associated with an increased risk of RA, may lead to elevated levels of IL-6 production.	[53]
9	TRAF6	TNF Receptor Associated Factor 6	The study revealed a link between a specific TRAF6 gene variant and low bone mineral density in patients with RA.	[21]
10	CD28	CD28 Molecule	CD28 and CTLA-4 are crucial in controlling the stimulatory and inhibitory signals in T cells.	[19]
11	GATA3	GATA Binding Protein 3	GATA3 is directly involved in the process of differentiation and work of Th17 cells.	[59]
12	IL2RB	Interleukin 2 Receptor Subunit Beta	As is known, variations in the IL-2RA and IL-2RB genes can affect the predisposition to RA among Europeans.	66]

Continuation of Table 2.

1	2	3	4	5
13	IRF8	Interferon Regulatory Factor 8	IRF8, a member of the IRF family, is produced by various cells, such as B cells, dendritic cells, macrophages, and activated T cells. Its role in regulating innate and adaptive immune responses has been demonstrated.	[59]
14	RBPJ	Recombination Signal Binding Protein for Immunoglobulin Kappa J Region	RBPJ may play a role in controlling the activation of T cells, the differentiation of lymphocytes and mononuclear cells, and regulating cell-to-cell adhesion.	[11]
15	PRKCQ	Protein Kinase C Theta	They are directly involved in the process of differentiation and the work of Th17 cells.	[59]
16	CCL21	C-C Motif Chemokine Ligand 21	The monokines activated by CCL21 can transform naive T cells into Th17, which contributes to the development of osteoclasts in RA.	[55]
17	IL6ST	Interleukin 6 Cytokine Family Signal Transducer	The IL6/IL6ST signaling pathway is a crucial factor in the development of RA.	[4]
19	NFKBIL1	NFKB Inhibitor Like 1	NFKBIL1 contributes to the development of RA, at least in part, by influencing the activity of dendritic cells.	[12]
20	IKZF3	IKAROS Family Zinc Finger 3	Engaged in the process of differentiation and operation of Th17 cells.	[59]
21	PTPRC	Protein Tyrosine Phosphatase Receptor Type C	The existence of LGALS9, PTPRC, and CD44 in platelets could potentially serve as a diagnostic marker for RA.	[65]
22	RUNX1	RUNX Family Transcription Factor 1	Engaged in the process of differentiation and operations of Th17 cells.	[59]
23	TNFRSF14	TNF Receptor Superfamily Member 14	TNFSF14 is part of the tumor necrosis factor family and serves as messenger for TR2 and lymphotoxin (LT)-β.	[29]
24	CCR5	C-C Motif Chemokine Receptor 5	The CCR5 receptor and its ligands play a crucial role in the development of RA and systemic lupus erythematosus.	[43]
25	ARG1	Arginase 1	ARG1 produces enzyme arginase, which is a key component of the urea cycle in liver cells. Arginine metabolism has been shown to play a critical role in both innate and adaptive immune responses.	[62]
26	TYMS	Thymidylate Synthetase	TYMS is a gene that encodes thymidylate synthase, an enzyme that catalyzes the methylation of deoxyuridine monophosphate to form thymidine monophosphate (dTMP). dTMP is crucial for DNA repair and replication and its deficiency leads to damage to DNA. Therefore, TYMS is targeted by some medications, such as methotrexate used to treat RA to inhibit cell proliferation.	[62]
27	SORT1	Sortilin 1	SORT1 is a gene producing the protein sortilin involved in intracellular transport processes.	[62]
28	OLFM4	Olfactomedin 4	The gene OLFM4 produces olfactomedin 4, which has been demonstrated to play a role in various cellular processes, including the innate immune system and the inflammatory response.	[62]
29	BIRC5	Baculoviral Inhibitor of Apoptosis Repeat Containing 5	BIRC5 plays a key role in pulmonary fibrosis.	[62]
30	MS4A4A	Membrane Spanning 4-Domains A4A	MS4A4A is a gene that produces a tetraspan surface protein, which is primarily expressed in white blood cells, particularly macrophages. This protein is essential for activating the immune system's inflammatory response when it detects an infection.	[62]
31	CLEC12A	C-type Lectin Domain Family 12 Member A	CLEC12A is a gene that codes for a member of the C-type lectin domain family 12. In addition to its functions in cell adhesion and intercellular communication, CLEC12A is expressed in alveolar macrophages. It has been implicated in the development of fibrotic lung diseases.	[62]
32	STAT4	Signal Transducer and Activator of Transcription 4	STAT4 is a regulatory protein that participates in the signaling cascades of cytokines and T-cell subsets development. Numerous investigations have shown a correlation between variations in STAT4 and autoimmune disorders.	[18]

Continuation of Table 2.

1	2	3	4	5
33	STAT3	Signal Transducer and Activator of Transcription 3	STAT3 is involved in a pathway that regulates Th17 cell differentiation. Increased activity of STAT3 in T-cells leads to suppression of Treg cells and stimulation of inflammation. STAT3 also affects the inhibition of the expression of FOXP3, which is main transcription factor for Treg cells. Recent studies have shown that suppression of FOX3 in RA disrupts the function of Treg cell, contributing to autoimmune responses.	[26]
34	STAT 6	Signal Transducer and Activator of Transcription 6	STAT6 is a dominant transcription factor for Th2 cell differentiation, activated when IL-4 binds to its receptor. It promotes the expression of genes associated with Th2 differentiation. Disruption of the STAT6 pathway in RA can impair Th2 cell function and result in expand inflammation through Th1 and Th17 cells. Recent research confirms that disturbances in STAT6 lead to decreased Th2 activation and worsening inflammatory responses.	[34]
Genes increased during active disease				
1	CD2	CD2 Molecule	The synovial area of joints in individuals with RA exhibits an elevated level of co-stimulatory molecules.	[14]
2	TRAF1	TNF Receptor Associated Factor 1	TRAF1 is a member of the TRAF protein family that can transmit a signal by interacting with various protein kinases and adapter proteins for different receptors in the TNF superfamily, including TNF-α.	[25]
3	TAGAP	T Cell Activation RhoGTPase Activating Protein	The TAGAP protein activates Rho GTPases in T cells, is involved in various autoimmune diseases, including RA, and is closely linked to the development of Th17 cells.	[52]
4	CD40	CD40 Molecule	CD40 is a marker of stimulatory activation that plays a role in driving pathogenic processes through the CD40/CD40L pathway, contributing to the persistence of chronic inflammation in RA.	[29]
5	PADI4	Peptidyl Arginine Deiminase 4	The process of citrullination is facilitated by the enzyme peptidyl arginine deiminase 4 (PAD4), which is encoded by the PADI4 gene. Elevated PAD4 activity contributes to RA development and progression.	[44]
6	HLA-DR15 (DRB1 / DRB5)	Major Histocompatibility Complex, Class II, DR Beta 1/ Major Histocompatibility Complex, Class II, DR Beta 5	The HLA-DR15 haplotype (DRB1/DRB5) is associated with a higher likelihood of developing active disease in ACPA-positive RA patients in a large sample of untreated individuals.	[63]
7	STAT1	Signal Transducer and Activator of Transcription 1	They control the inflammatory process in the synovial membrane mainly by acting on cytokines.	[9]
8	miR-146	MicroRNA 146	In the blood of patients with RA, the levels of miR-146, miR-155, and miR-16 are elevated, particularly during active disease periods.	[7]
9	miR-155	MicroRNA 155		[7]
10	miR-16	MicroRNA 16		[7]
11	miR-346	MicroRNA 346	miR-346 inhibits the IL-18 response in RA fibroblasts.	[7]
12	CTLA4	Cytotoxic T-lymphocyte-associated Protein 4	The CTLA4 gene contributes to the progression of RA in patients with ACPA compared to those without ACPA.	[13]

Discussion

The results underscore the intricate and multifaceted nature of RA, emphasizing the interdependent roles of genetic susceptibility, autoantibody production, and cytokine-driven inflammation. Autoantibodies such as RF and ACPA, have emerged as crucial serological markers for RA [28]. Their presence, often detectable years before the onset of clinical symptoms, emphasizes their significance in early diagnosis and assessment of disease risk. They are important early markers of rheumatoid arthritis in the pre-RA stage. The production of anti-CarP and anti-PAD4 autoantibodies provides additional diagnostic and prognostic value, as well as sheds light on the molecular mechanisms driving the transition from asymptomatic autoimmunity to clinically manifest RA [5, 30, 31, 57]. These findings support the idea that immune dysregulation precedes the development of symptomatic RA, opening a window for early intervention therapy.

The synovial tissue and immune cells in the bloodstream of individuals with RA produce pro-inflammatory cytokines, which contribute to the development of systemic inflammation. The study supports the importance of cytokines, such as TNF-α, IL-6, and IL-17, in maintaining joint inflammation and causing systemic complications [1, 22, 27, 38, 54]. It confirms their involvement in both synovial inflammation and systemic manifestations, such as interstitial lung disease and atherosclerosis [22, 54]. A higher level of IL-4 has been found in the synovial fluid of early-stage RA

compared to established RA. This suggests that IL-4 could be a useful diagnostic biomarker for early RA patients [24]. This finding emphasizes the dual role of cytokines as potential targets for controlling disease and preventing comorbidities. Development of cytokine-blocking therapies leads to more personalized approaches for managing the various clinical manifestations of rheumatoid arthritis.

The analysis of genetic data has revealed significant correlations between certain HLA and non-HLA genes and susceptibility to rheumatoid arthritis. Variations in the HLA-DRB1 gene, particularly those encoding the shared epitope sequence, are strongly associated with an increased risk and severity of the disease [63]. In addition to HLA, other genes such as STAT4, PADI4, and TRAF6 have been linked to immune dysfunction, inflammation, and joint damage [18, 21, 44].

There is a lot of evidence in scientific papers that autoantibodies, genetic changes, and cytokines play a vital role in the development of RA. The incorporation of immunological indicators into diagnostic and prognostic frameworks offers great potential for enhancing early identification, and prevention of RA. This study highlights the potential of these molecular and immunological markers as valuable diagnostic tools and reliable predictors of disease severity and outcome. By elucidating these interconnected pathways, this research opens up opportunities for more accurate diagnostic approaches and personalized treatment plans, ultimately improving the management of RA. These findings highlight the importance of incorporating genetic profiling into the diagnosis and prognosis of RA, thereby paving the way for identifying vital selections of autoantibodies and immune biomarkers that can be used in an immunogenic panel for RA, representing a promising approach to early diagnosis and personalized treatment strategies. Ongoing research continues to validate and expand these panels through multi-omics approaches and cohort studies.

Conclusion

Genetic factors, cytokines, and autoantibodies play a vital role in the development of rheumatoid arthritis. Studies have shown that specific genetic variations can disrupt the regulation of the immune system, leading to the formation of various autoantibodies, which serve as important biomarkers for the disease. Increased cytokines involved in inflammatory processes indicate the activity of the immune response. A deeper understanding of these interactions offers new perspectives for personalized early detection and timely management of RA, helping to prevent the progression of this chronic condition, which can result in significant disability.

Prospects for further research

The future endeavors should thoroughly examine the complex interplay between genetic mutations, cytokine-mediated processes, and the formation of autoantibodies in the development of RA, encompassing the exploration of distinctive genetic and immunological characteristics of autoimmune diseases in the local Kazakh population. Ongoing research will verify the effectiveness of the immunogenic panel in a clinical context and evaluate its usefulness for patient classification, prognostic assessment, and as a means of uncovering genetic profiles for autoimmune diseases.

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RISK FACTORS AND PREVALENCE OF URINARY INCONTINENCE AMONG WOMEN IN FOREIGN COUNTRIES. LITERATURE REVIEW

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Abstract

Introduction: Urinary incontinence in women is a common medical and social problem affecting the quality of life and increasing with age, especially after menopause. The main risk factors include age, obesity, childbirth, decreased estrogen levels, chronic diseases, and social and behavioral conditions. Despite its high prevalence, the topic remains insufficiently discussed, which leads to a delay in diagnosis and therapy and an aggravation of psychoemotional consequences [8].

Objective: to analyze the literature on the prevalence and risk factors of urinary incontinence in women in foreign countries, as well as to assess the impact of this condition on the quality of life of women.

Search strategy: scientific publications from the past 10 years were reviewed through databases such as Scopus, PubMed, Web of Science, CyberLeninka, among others.

Research results: the analysis showed that urinary incontinence in women occurs in 20-30% of the general population and in more than 35% over the age of 55, with age, hormonal changes, multiple births, obesity and a sedentary lifestyle being the most significant risk factors. A comparative analysis of international data revealed significant differences in prevalence and access to treatment between high- and low-income countries, as well as the impact of cultural and social barriers on access to care. It has been found that urgent and mixed forms of urinary incontinence worsen the quality of life the most, causing anxiety, depression and decreased social activity. The identified gaps — a lack of longitudinal research, poor adaptation of programs to the cultural context, and limited representation of vulnerable groups — highlight the need to create sustainable, culturally sensitive models of women's care.

Conclusions: urinary incontinence in women is a global public health problem that requires an integrated approach. The existing differences in epidemiology, access to diagnosis and treatment, as well as the lack of data on cultural and age characteristics emphasize the need for interdisciplinary and cross-country research. The development of culturally sensitive and evidence-based programs will increase access to care, improve women's quality of life, and reduce the global burden of this condition.

Key words: *women, urinary incontinence in women, risk factors, prevalence; stress urinary incontinence, quality of life.*

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Резюме

ФАКТОРЫ РИСКА И РАСПРОСТРАНЕННОСТЬ НЕДЕРЖАНИЯ МОЧИ СРЕДИ ЖЕНЩИН В ЗАРУБЕЖНЫХ СТРАНАХ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Недержание мочи у женщин - распространённая медицинская и социальная проблема, затрагивающая качество жизни и усиливающаяся с возрастом, особенно после менопаузы. Основные факторы риска включают возраст, ожирение, роды, снижение уровня эстрогена, хронические заболевания и социально-поведенческие условия. Несмотря на высокую распространённость, тема остаётся недостаточно обсуждаемой, что приводит к задержке диагностики и терапии и усугублению психоэмоциональных последствий [8].

Цель исследования: анализ литературы о распространенности и факторах риска недержания мочи у женщин в зарубежных странах, а также оценить влияние этого состояния на качество жизни женщин.

Стратегия поиска: поиск научной литературы в базах данных Scopus, PubMed, Web of Science, CyberLeninka и др., глубиной поиска в 10 лет.

Результаты исследования: анализ показал, что недержание мочи у женщин встречается у 20–30 % в общей популяции и более чем у 35 % старше 55 лет, причём наиболее значимыми факторами риска являются возраст, гормональные изменения, многократные роды, ожирение и малоподвижный образ жизни. Сравнительный анализ международных данных выявил существенные различия в распространённости и доступе к лечению между странами с высоким и низким уровнем дохода, а также влияние культурных и социальных барьеров на обращаемость за помощью. Установлено, что ургентная и смешанная формы недержания мочи сильнее всего ухудшают качество жизни, вызывая тревожность, депрессию и снижение социальной активности. Выявленные пробелы — нехватка лонгитюдных исследований, слабая адаптация программ к культурному контексту и ограниченное представительство уязвимых групп — подчёркивают необходимость создания устойчивых, культурно-чувствительных моделей помощи женщинам.

Выводы: недержание мочи у женщин является глобальной проблемой общественного здоровья, требующей комплексного подхода. Существующие различия в эпидемиологии, доступе к диагностике и лечению, а также недостаток данных о культурных и возрастных особенностях подчеркивают необходимость проведения междисциплинарных и межстрановых исследований. Разработка культурно чувствительных и научно обоснованных программ позволит повысить доступность помощи, улучшить качество жизни женщин и снизить глобальное бремя этого состояния.

Ключевые слова: *женщины, недержание мочи у женщин, факторы риска, распространённость; стрессовое недержание мочи, качество жизни.*

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Түйіндеме

ШЕТ ЕЛДЕРДЕГІ ӘЙЕЛДЕР АРАСЫНДА ЗӘР ШЫҒАРУДЫ ҰСТАМАУДЫҢ ҚАУІП-ҚАТЕР ФАКТОРЛАРЫ МЕН ТАРАЛУЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Әйелдердегі зәрді ұстамау- өмір сапасына әсер ететін және қартайған сайын, әсіресе менопаузадан кейін күшейетін жалпы медициналық және әлеуметтік мәселе. Негізгі қауіп факторларына жас, семіздік, босану, эстроген деңгейінің төмендеуі, созылмалы аурулар және әлеуметтік-мінез-құлық жағдайлары жатады. Жоғары таралуына қарамастан, тақырып жеткілікті түрде талқыланбайды, бұл диагностика мен терапияның кешігуіне және психоэмоционалды салдардың нашарлауына әкеледі [8].

Зерттеудің мақсаты: шет елдердегі әйелдердің зәр шығаруды ұстамаудың таралуы мен қауіп факторлары туралы әдебиеттерді талдау, бұл жағдайдың әйелдердің өмір сапасына әсерін бағалау.

Іздеу стратегиясы: соңғы 10 жыл ішінде жарық көрген ғылыми әдебиеттер Scopus, PubMed, Web of Science, CyberLeninka және басқа да мәліметтер базаларында ізделді.

Зерттеу нәтижелері: талдау көрсеткендей, әйелдерде зәрді ұстамау жалпы халықтың 20-30% - кездеседі, 55 жастан асқан 35% - дан астамында кездеседі, ең маңызды қауіп факторлары жас, гормоналды өзгерістер, бірнеше рет босану, семіздік және отырықшы өмір салты болып табылады. Халықаралық деректерді салыстырмалы талдау табысы жоғары және төмен елдер арасындағы таралу мен емдеуге қол жеткізудегі айтарлықтай айырмашылықтарды, сондай-ақ мәдени және әлеуметтік кедергілердің көмекке жүгінуге әсерін анықтады. Зәрді ұстамаудың ургентті және аралас түрлері өмір сүру сапасын нашарлатып, мазасыздықты, депрессияны және әлеуметтік белсенділіктің төмендеуін тудыратыны анықталды. Анықталған олқылықтар- ұзақ зерттеулердің жетіспеушілігі, бағдарламалардың мәдени контекстке нашар бейімделуі және осал топтардың шектеулі өкілдігі әйелдерге көмектесудің тұрақты, мәдени-сезімтал модельдерін құру қажеттілігін көрсетеді.

Қорытынды: әйелдердегі зәрді ұстамау-бұл кешенді тәсілді қажет ететін жаһандық денсаулық мәселесі. Эпидемиологиядағы, диагностика мен емдеуге қол жеткізудегі бар айырмашылықтар, сондай-ақ мәдени және жас ерекшеліктері туралы деректердің болмауы пәнаралық және еларалық зерттеулерді жүргізу қажеттілігін көрсетеді. Мәдени сезімтал және ғылыми негізделген бағдарламаларды әзірлеу көмектің қолжетімділігін арттыруға, әйелдердің өмір сүру сапасын жақсартуға және осы жағдайдың жаһандық ауыртпалығын азайтуға мүмкіндік береді.

Түйінді сөздер: *әйелдер, әйелдерде зәрді ұстамау, қауіп факторлары, таралуы; стрессті ұстамау, өмір сапасы.*

Дәйексөз үшін:

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Introduction

Urinary incontinence (UI) in women is a significant medical and social problem that affects both the physical and psychoemotional state of women in different age groups. According to the definition of the International Continence Society (ICS), UI is an involuntary leakage of urine, which can be either a minor inconvenience or a serious disorder that significantly worsens the quality of life. In the context of rapidly aging population, an increase in chronic diseases and lifestyle changes, the relevance of studying the prevalence and risk factors of UI increases, especially in the international context, where rates may vary depending on cultural, medical and socioeconomic conditions [8, 11].

According to numerous studies, the prevalence of UI among women varies widely, from 5% to 70%, depending on age, country, diagnostic methods, and study design [9]. The most common forms are stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed urinary incontinence (MUI), each with unique causes, clinical manifestations, and consequences for the patient [6]. The prevalence of UI increases significantly with age, especially after menopause, with women over 60 years of age at much greater risk [3].

Risk factors for urinary incontinence in women are multifaceted and include physiological, behavioral, and social aspects. The most well-known predictors are age, obesity, multiple births, mode of delivery (vaginal birth), decreased estrogen levels in the postmenopausal period, surgical interventions (e.g., hysterectomy), and the presence of chronic diseases such as diabetes or chronic cough [10, 12]. At the same time, increasing attention in recent years has been paid to social determinants of health - level of education, physical activity, smoking, and even access to sanitary conditions [2; 7].

At the same time, despite its high prevalence and serious consequences, urinary incontinence remains an under-discussed topic in society. Women often do not seek medical help due to a sense of shame, fear of being misunderstood, or the belief that it is a natural consequence of aging that nothing can be done about [5]. This leads to delays in diagnosis and treatment, as well as to a significant decrease in quality of life. Women with UI may experience difficulties in social, professional, and intimate spheres, suffer from anxiety and depression, limit their activity, which in turn aggravates the severity of the condition [1, 4].

Modern research emphasizes the importance of a comprehensive approach to assessing not only physiological symptoms, but also subjective experiences and patient perceptions of their condition. The purpose of this literature review is to comprehensively analyze scientific data from the last 10 years (2015–2025) on risk factors and prevalence of urinary incontinence among women in foreign countries, as well as to consider the impact of this condition on quality of life. The review focuses on systematization of available epidemiological data, classification of risk factors by their nature and modifiability, analysis of differences in prevalence by regions and cultures, and identification of research gaps that require further scientific attention.

The review will cover the following key areas: definition and classification of urinary incontinence types, biomedical and social risk factors, statistical data on prevalence in different countries and regions, as well as psychosocial aspects and the impact of UI on the quality of life of women. Academic sources were used in preparing the review: peer-reviewed articles, meta-analyses, systematic reviews, international reports and clinical guidelines published no earlier than 2015. Thus, the presented review is aimed at forming a holistic and evidence-based understanding of urinary incontinence in women, its main predictors, epidemiology and consequences, which is important for both clinicians and researchers, as well as for public health specialists, policy makers and women's health programs.

Definition and classification

According to the International Continence Society (ICS), urinary incontinence (UI) is "a complaint of any involuntary leakage of urine" [15]—that is, a symptom that may occur without necessarily being associated with a social or hygienic problem [22]. This interpretation ensures diagnostic sensitivity, but at the same time raises debate about its effectiveness in linguistic and sociomedical research [13].

The classification of UI includes three main types: stress urinary incontinence (SUI), urge urinary incontinence (UUI) and mixed urinary incontinence (MUI). These categories are based on differences in clinical manifestations, pathophysiological mechanisms and treatment approaches. This typology is recognized by leading international organizations and is widely used in clinical and epidemiological studies [10, 17].

Stress urinary incontinence (SUI) is defined as involuntary leakage of urine during physical effort, coughing, sneezing or other stress accompanied by an increase in intra-abdominal pressure (ICS, 2018). The most common cause of SUI is urethral hypermobility associated with weakening of the muscles and connective tissue of the pelvic floor, especially after vaginal childbirth and in the postmenopausal period. The second pathogenetic mechanism is considered to be intrinsic sphincter deficiency, in which the pressure in the urethra decreases, and it is unable to hold urine even in a normal position [17,19]. SUI is the most common form of UI in young and middle-aged women, accounting for up to 40% of all cases of urinary incontinence [10].

Urge urinary incontinence (UUI) is characterized by a sudden and strong urge to urinate, accompanied by urine leakage. It is associated with overactivity of the detrusor, a muscle layer of the bladder that contracts involuntarily before the required volume is reached (American Urological Association [AUA], 2019). UUI can have both idiopathic mechanisms and organic causes, including neurological diseases (Parkinson's disease, multiple sclerosis, consequences of stroke), as well as urinary tract infections and innervation disorders [19]. UUI is more common in older women and can significantly reduce quality of life, especially when accompanied by social anxiety.

Mixed urinary incontinence (MUI) combines symptoms of both stress and urge incontinence, i.e. leakage can occur both during physical activity and during strong urges. MUI is often diagnosed in older women and requires an individualized approach to treatment, with an emphasis on the dominant type of symptomatology (AUA, 2019; 18]. Differential diagnosis and accurate determination of the predominant form are especially important for choosing effective therapy.

In addition to the three main types, ICS also distinguishes additional clinical forms: postpartum incontinence, nocturnal enuresis, coital incontinence, and functional incontinence [38]. Postpartum incontinence occurs during the first 12 months after childbirth and may be due to damage to the pelvic floor. Coital urinary incontinence occurs during or after sexual intercourse and is often associated with the presence of pelvic organ prolapse. Nocturnal enuresis in adult women is rare, but may accompany neurogenic diseases. Functional incontinence is associated with cognitive or physical limitations, in which the patient does not have time to get to the toilet in time, despite the preserved ability to control urination [19].

A clear classification of urinary incontinence is necessary not only for correct diagnosis, but also for choosing the optimal treatment strategy. Thus, in case of stress incontinence, the first line of therapy is considered to be exercises for the pelvic floor muscles, while urgent incontinence often requires drug intervention aimed at reducing the activity of the detrusor. In case of the mixed form, a combined approach is used. Thus, the typology of UI has important practical significance and directly affects the quality of medical care for women suffering from this disorder.

The use of international definitions and typologies developed by the ICS and endorsed in clinical guidelines helps standardise approaches to the diagnosis, treatment and investigation of urinary incontinence. This consistency allows for cross-national comparisons, adaptation of treatment protocols and development of effective prevention and intervention programmes, particularly in the context of the increasing prevalence of this condition among women worldwide.

Risk factors

Urinary incontinence (UI) in women is a multifactorial condition, the development of which is caused by the interaction of physiological, medical, behavioral and socioeconomic factors. Scientific research in recent years confirms that the risk of UI increases under the influence of both unchangeable factors, such as age, and modifiable factors, including lifestyle, body weight, reproductive history and the presence of chronic diseases. A comprehensive assessment of these factors allows not only to clarify the prognosis, but also to develop personalized prevention strategies.

One of the most significant risk factors is age. Modern studies show a clear relationship between the aging of the body and the increased prevalence of urinary incontinence, especially after 50 years. The postmenopausal period is accompanied by a decrease in estrogen levels, which leads to atrophic changes in the genitourinary system: tissue elasticity deteriorates, urethral pressure decreases, and pelvic floor muscles weaken. These changes contribute to the development of stress incontinence and other forms of urinary retention disorders [18, 24].

Reproductive factors play an equally important role. Scientific data demonstrate that with an increase in the number of births, especially vaginal, the likelihood of developing UI increases significantly. Parity is an independent predictor of stress incontinence, since each subsequent vaginal birth increases the risk of damage to the supporting structures of the pelvic floor, in particular the fascia and muscles responsible for urinary continence. In addition, surgical interventions in gynecological practice, including hysterectomy, are also associated with an increased likelihood of UI, especially in cases where the anatomical integrity of the pelvic floor is disrupted [17, 19].

Overweight and obesity are among the most studied and clinically significant modifiable risk factors. Meta-analyses confirm that body mass index (BMI) is closely associated with the likelihood of developing both stress and

urge incontinence. Increased intra-abdominal pressure in obese women contributes to deterioration of urethral sphincter function and weakening of pelvic support, which makes urinary continence less effective. In addition, obesity is often accompanied by metabolic syndrome, insulin resistance, and type 2 diabetes, conditions that also increase the risk of UI [18, 23].

Behavioral factors and lifestyle also play a significant role. Low physical activity and prolonged sitting (more than 7 hours per day) have been shown to correlate with an increased prevalence of both stress and urge incontinence. The mechanisms include deterioration of blood circulation in the pelvic area, decreased muscle tone, and general physical inactivity. Studies based on NHANES (2007–2018) demonstrated a significant association between a sedentary lifestyle and an increased risk of UI in women [25]. Smoking, as another lifestyle factor, can increase UI symptoms through the development of chronic cough and increased intra-abdominal pressure, as well as due to vascular damage and ischemia of the pelvic floor muscles [23].

A recently published study from Hungary found that the risk of sarcopenia (reduced muscle mass and function) is a significant independent factor for the development of urinary incontinence in women over 50 years of age. In addition to age factors and complications of childbirth, the SARC-F score was significantly associated with the presence of UI (turn0search5) - women with a high risk of sarcopenia had a significantly higher probability of incontinence [69]. This highlights the need to include biomuscular parameters in multivariate risk models.

In recent years, there has been growing interest in the use of machine learning methods to predict the risk of developing UI. One such study by Benítez-Andrades et al [20] found that the most significant variables associated with postpartum incontinence were body weight, physical activity, lifestyle, age, and voiding habits. This opens up prospects for early intervention and prevention, especially in high-risk groups.

It is important to note that systematic differences in the level and structure of risk between regions and countries require further study. International reviews indicate that risk factors are similar in developing countries, but the prevalence of UI may be higher due to limited access to treatment, higher birth rates, and lack of prevention programs [21, 26]. In addition, cultural differences in the perception of women's health and the taboo nature of the topic of incontinence may reduce the likelihood of seeking help, and, as a result, increase the burden of the disease.

hus, risk factors for urinary incontinence in women are multicomponent and interrelated. They include age, hormonal changes, obstetric and gynecological history, body weight, chronic diseases, lifestyle characteristics and social determinants. Given the high prevalence of UI and its negative impact on quality of life, timely identification and control of modifiable risk factors, as well as the development of individualized prevention and treatment strategies, are of particular importance.

Prevalence and statistics

Urinary incontinence (UI) among women is a global problem, and its prevalence varies significantly depending on the region, age structure of the population, study methodology, and diagnostic tools used. Recent meta-analyses cover dozens of countries and show that in developing countries, the global prevalence is approximately 31.2% (95% CI: 29.0–33.4), with stress UI recorded in 20.7%, urgency UI in 13.1%, and mixed UI in 17.8% of women [27, 33]. In countries with higher incomes and developed health care systems, overall UI rates are about 25.7% (95% CI: 22.3–29.5) [27].

In older women, the prevalence of UI is even higher: according to a meta-analysis of 29 population-based studies involving 518,465 women aged 55 to 106 years, the rate was 37.1% (95% CI: 29.6–45.4), with maximum values of up to 45.1% in Asian countries and minimum values of up to 9.5% in Mexico [28, 31]. There is also a tendency for the prevalence of UI to increase in studies of a later period, which is recorded by meta-regressions over time [28]. A global prevalence analysis of overactive bladder (OAB) as a syndrome closely associated with urgency incontinence showed that it occurs in 21.9% of women (95% CI: 20–24%), with a higher risk in women over 60 years of age (OR ≈ 28.3) and in obese individuals (OR ≈ 18.6) [29]. Since OAB is often associated with UUI, these data indirectly confirm the increased prevalence of the urgency form in the elderly and women with high BMI. Data from the United States, obtained using representative samples and standardized questionnaires, show that approximately 61.8% of the adult female population in the United States has ever experienced UI, and 32.4% of women experience symptoms monthly. Among women with UI, 37.5% suffer from the stress form, 22.0% from the urgent form, 31.3% from the mixed form, and approximately 9% from the indeterminate form (Sandvik Severity Index ≥ moderate) [30].

A review of sexual and professional behavior in women in the Persian Gulf revealed unique regional characteristics: in the Gulf countries (Saudi Arabia, UAE, Kuwait, etc.), the prevalence of UI varied from 10% to 50%, while a significant proportion of women were embarrassed to discuss the problem with health professionals, which could lead to underestimation of the actual rates [32].

In Africa, based on the results of 22 studies covering different regions of the continent, the pooled prevalence of UI was about 24% (95% CI: 17–33), with variability from 2% to 80%. SUI was observed in 35% of women, UUI in 28%, and MUI in 31% [62]. In North Africa and the Maghreb, the overall rates were up to 41%, with some studies reporting 80% UI in women in Egypt [35].

In a large-scale population-based study in southern China (n=9584) conducted in 2022–2023, the prevalence of UI among women was 24.8%. The stress form was observed in 12.7%, mixed form in 8.0%, and urgent form in 4.1% [70]. Key risk factors included urban lifestyle, postmenopause, multiple vaginal births, fetal macrosomia, and previous pelvic floor surgeries. Despite the significant negative impact on quality of life, only 20.6% of women with UI sought medical help.

Regional reviews of Europe and Asia also show a range of prevalence, from 5% in individual countries to 57.7% in Iran, with an overall mean of about 25.7%. In these countries, the most common forms are SUI (~12.6%), followed by MUI (~9.1%) and UUI (~5.3%) [27].

Contemporary reviews of SUI in Saudi Arabia found a mean prevalence of stress incontinence of 26% (95% CI:

approximately 14–41), with a wide range from 3.3% to 50% depending on the population and methodology. In women postpartum or with underlying chronic conditions, the prevalence was as high as 33%, and in the general population, approximately 17% [34].

Thus, despite methodological differences, it can be stated that the prevalence of UI among women ranges from 20% to 30% in the general population and exceeds 35% in age groups over 55 years or in the presence of risk factors such as obesity, high reproductive load and metabolic diseases [42]. The stress form remains dominant in young and middle age, while the urgent and mixed forms increase with age, obesity and chronic pathology. This policy of epidemiological trends emphasizes the need to adapt national screening strategies, prevention programs and information campaigns to raise awareness among women and health professionals.

The Impact of Urinary Incontinence on Women's Quality of Life

Urinary incontinence (UI) has a significant negative impact on women's quality of life, affecting both physical and emotional and social well-being. A meta-analysis of over 24,000 participants found that UI was significantly associated with poorer health outcomes as measured by the SF-36 scale, with a strong effect size, especially for the general mental and physical health scale [27]. This is supported by local studies, in which women with UI symptoms demonstrated significantly lower quality of life scores on the IIQ-7, UDI-6 and ICIQ-LUTSqol scales.

In a population-based study conducted in India, nearly 35% of women of reproductive age reported symptoms of UI. More than 95% of them said that UI interfered with their daily activities, limited their mobility, public places, and family life. Women reported anxiety, decreased self-esteem, and social isolation. This indicates that the impact of UI goes far beyond a medical problem, becoming a barrier to a fulfilling social life.

Similar results were obtained in Saudi Arabia. A study involving over 1,700 women aged 30 to 75 years established a high prevalence of all forms of UI. Moreover, the most pronounced deterioration in quality of life was recorded in women with urgent and mixed forms. The use of validated questionnaires showed that women with severe symptoms of UI significantly more often experience depressive disorders, psychological exhaustion, decreased sexual satisfaction and social anxiety [36]. Similar data are coming from Jordan: there, a pronounced link was also found between the presence of UI and decreased self-esteem, social involvement and overall psychoemotional well-being [37].

A UK study has shown that even in countries with high levels of healthcare development, urinary incontinence remains a stigmatised issue. Although around 40% of women report symptoms, only 17% seek help, citing shame and the belief that urinary incontinence is a natural part of ageing. This highlights the global nature of the problem and the importance of social support and awareness raising.

Asian data also confirm the global nature of the problem. According to the large-scale LUTS Asia study conducted in China, South Korea, and Taiwan, women with SUI symptoms were 1.6 times more likely to suffer from anxiety disorders and also reported decreased work and home productivity [41]. In South Korea and Japan, even mild UI was found to impact self-esteem and confidence, while severe forms significantly increased the risk of social isolation.

Of interest are studies conducted among physically active women. In a sample of female athletes and participants in CrossFit programs, 36% reported symptoms of UI. This was accompanied by decreased confidence, limited training, and avoidance of social events [71]. The data indicate that UI is not only a problem for older or multiparous women, but also for younger, athletic, and socially active groups.

An integrative review of Brazilian studies from 2015 to 2019 confirmed the widespread use of instruments such as the I-QOL, ICIQ-SF, and KHQ. The authors identified four key categories: women's perception of UI, impact on daily life, association with depressive and anxiety symptoms, and the need for a multidisciplinary approach [39]. UI was viewed not only as a physical problem but also as a factor undermining women's identity and dignity.

In summary, the impact of UI on women's quality of life is universal but varies across cultural, economic and health contexts. Key impacts include physical limitation of activity, sleep deterioration, anxiety, depression, and decreased sexual and social activity. Urgent and mixed incontinence, as well as severe symptoms, are the most predictive factors for decreased quality of life. Current approaches require a comprehensive assessment of patients with UI, including not only physiological but also psychological and social aspects. Providing access to treatment, reducing stigma and raising awareness are key steps to improving the overall health of women with UI.

International approaches to screening, prevention and treatment of urinary incontinence in women

Many countries around the world implement strategies for screening and prevention of female urinary incontinence (UI), but approaches vary significantly in effectiveness, coverage, and cultural context. In the United States, the Women's Preventive Services Initiative (WPSI) recommends annual screening of all women for UI, including assessment of the impact of symptoms on daily life and quality of life, and referral for further evaluation and treatment when indicated [48]. This strategy is designed to identify complaints that often go unreported by the woman herself.

In the UK and Europe, the 2021 NICE Guidelines recommend the implementation of screening and prevention programmes, including monitoring of women in age groups from pregnancy to menopause. NICE emphasises the importance of women learning correct pelvic floor exercise techniques under the supervision of qualified professionals, ideally starting before birth and continuing into the postnatal period [47]. The UK model also includes assessment of family history and calculation of individual risk using the UR-CHOICE algorithm, allowing for proactive provision of PFMT to high-risk groups [47].

In the European Union, the European Association of Urology (EAU) guidelines for non-mechanical LUTS (including UI) also support pelvic floor exercises (PFMT), particularly to reduce symptoms of urge incontinence and overactive bladder (OAB). PFMT has shown statistically significant reductions in urge frequency and leakage

episodes in most RCTs, although some studies note heterogeneity of protocols and inconsistent results [50].

In Asian countries such as South Korea, Taiwan, and China, digital technologies have been developed to complement traditional methods. A review included 89 studies from 14 countries and found that mobile apps, web-based programs, and telemedicine support women in completing PFMT, increasing adherence to therapy and making the intervention more convenient. However, these technologies are often not adapted to cultural contexts and the changing needs of women at different stages of life [44].

In Canada and Australia, national campaigns, World Continence Week, have been organized under the auspices of the International Continence Society (ICS), with educational events, hotlines, media, and public campaigns aimed at reducing stigma and raising awareness. These efforts encourage women to seek help earlier and to participate more actively in prevention programs [51].

Conservative prevention and treatment measures in many countries are based on PFMT. Meta-analyses and systematic reviews confirm that pelvic floor exercises are effective for stress and mixed incontinence, being superior to placebo or no treatment. The combination of PFMT with biofeedback may improve muscle strength, but the overall effect on reducing leakage episodes remains controversial [45, 52]. Supervised PFMT during pregnancy reduces the risk of developing PFD and is cost-effective in high-risk groups [47].

In addition to PFMT, physiotherapeutic methods have become widespread: biofeedback, electrical stimulation, magnetic stimulation, vibration training. They are especially in demand in contexts where women are unable to independently initiate pelvic floor contractions, or with a combination of OAB and UUI [49]. At the same time, innovative methods such as laser therapy, plasma injections, stem cells and radiofrequency exposure are still at the stage of clinical research and require standardization of procedures and long-term evaluation of effectiveness [46].

The transition to drug regimens for UUI is based on the recommendations of the American Urological Association (AUA) - treatment includes anticholinergic drugs and beta-3 agonists, but the AUA emphasizes that drug intervention should be accompanied by behavioral therapy and PFMT [43].

Surgical methods remain the last line of treatment for SUI: the most commonly used are slang procedures, colposupsions, injections of bulking agents (e.g. Macroplastique). Recent studies confirm the effectiveness under strict patient selection, but require long-term follow-up due to possible complications and variability of results [46].

Barriers to the implementation of screening and treatment programmes include lack of trained staff, cultural stigma, low adherence to exercise among women, financial constraints and low access to telemedicine platforms, particularly in low-income countries. Research has highlighted the need to tailor programmes to local realities, taking into account linguistic, cultural and socio-economic factors [44].

Thus, international models of UI prevention and treatment demonstrate a diversity of strategies: from standardized screening recommendations, national promotional campaigns and PFMT to the introduction of digital technologies and complex conservative and surgical methods. Early diagnosis, multidisciplinary approaches and adaptation according to the culture and resources of the country are always prioritized. The effectiveness of further measures depends on strengthening the evaluation of the real results of interventions, scaling up successful programs and removing structural barriers to women's access to adequate care.

Research gaps and directions for future research on urinary incontinence in women

The international scientific literature has seen many advances in understanding the risk factors, prevalence, and impact of urinary incontinence (UI) on women's quality of life. However, there are still a number of significant gaps that need to be addressed to improve data accuracy and the effectiveness of prevention and treatment. First, despite the existence of screening recommendations, there are no randomized controlled trials (RCTs) demonstrating that mass screening improves clinical outcomes and women's quality of life. Existing assessment tools—the Michigan Incontinence Symptom Index, Bladder Control Self-Assessment, Overactive Bladder Awareness Tool—show good sensitivity and specificity, but their impact on symptom reduction requires confirmation by large multicenter studies [55].

Second, most studies have focused on PFMT and basic cognitive-behavioural interventions; but only recently have the range moved from physical exercise to innovative e-health tools. Despite the positive results of digital therapies, there is little long-term data on the sustainability of effects 1–2 years after programme completion [54]. Furthermore, current RKIs on the use of telemedicine are often limited by small sample sizes, short follow-up periods, and are conducted in high-income countries, limiting their applicability to developing regions [61].

The third important area is surgical methods: there are many types of interventions, including minimally invasive slang procedures, colpospuspension, injections of bulking agents. However, comparative studies of the effectiveness and safety of different techniques in women of different ethnic groups and ages are rare. Possible complications (erosions, dysfunctions, recurrences) require long-term (>5 years) observation, which is often not carried out [53].

The fourth gap concerns cultural and socioeconomic aspects. In most countries in Africa, Asia and Latin America, data on perceptions of TM, willingness to seek care and stigma barriers are extremely limited. There is a particularly limited amount of research comparing successful awareness-raising strategies across different cultural contexts [56]. Without this, it is difficult to tailor interventions and educational campaigns to local needs.

The fifth gap concerns age groups. Most studies focus on either older women or women of reproductive age, while pre- and perimenopausal women have received less attention. Pilot studies suggest that menopause is a time when unique hormonal and psychological triggers for UI occur [59], but this has not been confirmed in larger samples.

The sixth aspect is the lack of studies on comorbidity and multi-syndrome interactions: diabetes, asthma, obesity, depression, pelvic organ prolapses. Most studies consider factors in isolation, rather than in combination, while clinical practice often encounters complex cases [57].

The seventh gap concerns diagnostic methods: most studies use self-report scales, while uroflowmetry, voiding diaries, and bioimpedance measurements are rarely integrated into epidemiological studies. Such biometric data could improve risk stratification and diagnostic accuracy [58]. The eighth gap is the lack of comparisons between low-, middle-, and high-income countries regarding treatment access, cost of PFMT, telemedicine, and surgery. Economic barriers are often overlooked by researchers, although they are critical for scaling up programs [60].

Future research perspectives include: conducting multicenter RCTs of mass screening, including monitoring of impact on quality of life and reimbursement of costs; long-term follow-up of the effectiveness of digital and physical therapy regimens; comparative studies of surgical procedures taking into account ethnic and age differences; culturally contextual studies in low-income countries to develop adaptive educational programs; focused studies on the transition of women from premenopause to menopause; and integration of biometric data into the epidemiology of UI.

Global differences, migration and age-related challenges in the context of female urinary incontinence

This meta-analysis demonstrates differences in access to and choice of surgical treatment for stress urinary incontinence in women according to geographic region, age and level of health infrastructure, highlighting that countries with limited resources and migration barriers experience less access to modern surgical options [38]. This highlights global inequalities and the need to adapt interventions to demographic realities.

Urinary incontinence in women is not only a clinical problem, but also a phenomenon deeply rooted in the social, cultural and economic context. Differences in access to treatment, awareness, perception of symptoms and willingness to seek help are influenced by many factors, from geography and income level to migration status and age [40]. This requires taking into account cross-cultural and age-specific features in the development of care programmes and research.

In low-income countries such as Nigeria, awareness programmes on UI have only recently been implemented at the health care level. A cluster randomized trial found that women's education campaigns increased health care utilization, improved knowledge about the causes and prevention of UI, and increased women's self-efficacy in urinary control [62]. However, stigma and lack of trained personnel remain major barriers to the sustainability of such programmes.

The lack of long-term longitudinal studies is another systemic gap in understanding the dynamics and development of urinary incontinence. A systematic review found a lack of data on how the disease progresses over time and the effectiveness of different prevention strategies over decades [63]. Without reliable long-term data, it is impossible to develop sustainable interventions and evidence-based national policies.

Comparative analyses of invasive and non-invasive treatments for UI have shown that many studies are limited to comparing individual methods within narrow populations, without taking into account the social and cultural context [64]. For example, women of migrant background or ethnic minorities are often excluded from clinical trials, despite the fact that they may face higher barriers to treatment.

A study in Bangladesh found that awareness of symptoms and access to diagnosis remain very low among older women. Even when symptoms are present, most women do not seek medical care, citing the "naturalness" of symptoms in old age, shame, and lack of time [65]. These findings support the need for culturally sensitive programs that address stigma and educate both women and health care providers.

In the context of migration and cultural adaptation, particularly in Western Europe and North America, migrant women face particular barriers. A study of women of South Asian descent living in the UK found that even when symptomatic, they were unaware of the benefits of pelvic floor exercise (PFMT), distrusted doctors, and had cultural discomfort discussing intimate topics [66]. These barriers highlight the need to tailor treatment programs to cultural norms, language, and health literacy.

A comparative analysis of access to UI care in Hong Kong found that even in urbanised societies there are significant gender and class differences in access to diagnosis, particularly in public facilities. Women with low incomes or without regular health insurance were less likely to receive adequate diagnosis and PFMT [67]. This suggests structural barriers in health systems that require policy intervention.

Finally, postmenopausal UI requires special attention. In Asian countries, despite the high prevalence of urogenital symptoms, there is an extremely low proportion of clinical visits. In particular, a study in South Korea and China demonstrated that a decrease in estrogen levels is often interpreted as a normal sign of aging, and UI is not considered a pathological condition requiring treatment [68]. This limits the possibilities for early intervention and prevention of complications.

Thus, global challenges in the context of female urinary incontinence go beyond clinical diagnosis. Inequalities in access to information, treatment and prevention are caused not only by economic resources, but also by cultural, migration and age barriers. Promising areas for future research and interventions should include: longitudinal studies in different populations, adaptation of PFMT and screening programs to the cultural context, gender-sensitive training of professionals, and reducing systemic barriers in health care systems. Addressing these disparities will improve the quality of life of millions of women worldwide and ensure equitable access to health care.

Conclusion

Urinary incontinence in women is a significant global public health problem with complex impacts on physical, psychological and social well-being. The literature review demonstrated that despite a wide range of studies on the definition, classification and risk factors of incontinence, there are still significant gaps in the scientific literature, particularly regarding age and cultural differences, long-term effectiveness of interventions and equitable access to treatment.

A comparative analysis of international data revealed not only the epidemiological features of UI in different countries, but also significant diversity in approaches to screening, prevention and treatment. It was found that high-

income countries have a more developed infrastructure for diagnosis and intervention, while in low- and middle-income countries, barriers include stigma and lack of resources, as well as a lack of adapted programs.

Particular attention should be paid to the need for culturally sensitive, accessible, and evidence-based programs to help women, adapted to different age, ethnic, and social groups. Challenges related to the lack of longitudinal studies, the lack of biometric data in epidemiological models, and the limited representation of vulnerable groups in scientific papers remain relevant.

Addressing these gaps requires interdisciplinary and cross-country collaboration, strengthening research in diverse populations, and integrating innovative, sustainable models of diagnosis and treatment. Only through such an approach can equitable access to care be achieved and the global burden of female urinary incontinence be substantially reduced.

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THE IMPACT OF SCREEN TIME ON THE HEALTH OF THE MUSCULOSKELETAL SYSTEM IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW

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Abstract

Introduction. Modern children and teenagers are increasingly spending a significant amount of time in front of digital device screens, which is associated with lifestyle changes, the introduction of distance learning and digital entertainment. In recent decades, there has been a significant increase in the time spent by children and adolescents behind the screens of digital devices. This trend is accompanied by a decrease in physical activity and an increase in sedentary behavior, which raises concerns about the impact of such changes on the physical and mental health of the younger generation.

The purpose of this review article is to analyze current scientific evidence on the impact of sedentary behavior, in particular screen time, on various aspects of the health of children and adolescents.

Search strategy. The review of domestic and foreign publications, including systematic reviews, meta-analyses and cross-sectional studies published in the international databases PubMed and Scispace in the period from 2015 to 2024, is carried out. The selection includes studies examining associations between the length of screen time and the health parameters of children and adolescents.

The results show that excessive sedentary behavior is associated with an increased risk of neck and back pain, decreased bone density, impaired development of cognitive and social skills, and impaired psycho-emotional well-being. The analysis revealed a stable relationship between an increase in screen time and an increase in the frequency of neck and back pain, a decrease in bone density, the development of musculoskeletal disorders and cognitive and social impairments. Children of preschool and primary school age were particularly vulnerable. Regular use of digital devices for more than 2-3 hours a day was accompanied by statistically significant health impairments. The need to develop and implement preventive measures aimed at limiting screen time, increasing physical activity and developing healthy behavioral habits in children and adolescents is emphasized.

Conclusions. Sedentary behavior and excessive screen time have multifactorial negative effects on the health of children and adolescents. To minimize risks, it is necessary to implement preventive strategies, including limiting screen time, increasing physical activity, educating parents and teachers, and creating an ergonomically safe educational environment.

Keywords: *screen time, children, teenagers, posture, back pain, sedentary behavior, health.*

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Резюме

ВЛИЯНИЕ ЭКРАННОГО ВРЕМЕНИ НА ЗДОРОВЬЕ ОПОРНО-ДВИГАТЕЛЬНОЙ СИСТЕМЫ У ДЕТЕЙ И ПОДРОСТКОВ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Введение. Современные дети и подростки все чаще проводят значительное количество времени перед экранами цифровых устройств, что связано с изменением образа жизни, внедрением дистанционного обучения и цифровых развлечений. В последние десятилетия наблюдается значительное увеличение времени, проводимого детьми и подростками за экранами цифровых устройств [2]. Эта тенденция сопровождается снижением уровня физической активности и увеличением доли сидячего поведения, что вызывает обеспокоенность в отношении влияния таких изменений на физическое и психическое здоровье молодого поколения.

Целью. Изучить влияние экранного времени на состояние здоровья опорно-двигательной системы у детей и подростков на основе анализа современных научных исследований

Стратегия поиска. Проведен обзор отечественных и зарубежных публикаций, включающих систематические обзоры, метаанализы и поперечные исследования, опубликованные в международных базах данных PubMed и Scispace в период с 2015 по 2024 гг. В отбор включены исследования, изучающие ассоциации между продолжительностью экранного времени и параметрами здоровья детей и подростков.

Результаты показывают, что чрезмерное сидячее поведение ассоциировано с увеличением риска развития болей в шее и спине, снижением плотности костной ткани, нарушением развития когнитивных и социальных навыков, а также ухудшением психоэмоционального благополучия. Анализ выявил устойчивую связь между увеличением экранного времени и ростом частоты болей в шее и спине, снижением плотности костной ткани, развитием мышечно-скелетных расстройств и нарушениями в когнитивной и социальной сферах. Особенно уязвимыми оказались дети дошкольного и младшего школьного возраста. Регулярное использование цифровых устройств в течение более 2–3 часов в день сопровождалось статистически значимыми ухудшениями состояния здоровья. Подчеркивается необходимость разработки и внедрения профилактических мер, направленных на ограничение экранного времени, повышение физической активности и формирование здоровых поведенческих привычек у детей и подростков.

Выводы. Сидячее поведение и чрезмерное экранное время оказывают многофакторное негативное воздействие на здоровье детей и подростков. Для минимизации рисков необходимо внедрение превентивных стратегий, включая ограничение экранного времени, повышение двигательной активности, просветительскую работу среди родителей и педагогов, а также создание эргономически безопасной образовательной среды.

***Ключевые слова**: экранное время, дети, подростки, осанка, боль в спине, сидячее поведение, здоровье ОДА*

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Түйіндеме

БАЛАЛАР МЕН ЖАСӨСПІРІМДЕРДІҢ ТІРЕК-ҚИМЫЛ ЖҮЙЕСІ МЕН ДЕНСАУЛЫҒЫНА ЦИФРЛЫҚ ҚҰРЫЛҒЫ ЭКРАН УАҚЫТЫНЫҢ ӘСЕРІ: ЖҮЙЕЛІК ШОЛУ

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Кіріспе. Қазіргі балалар мен жасөспірімдер цифрлық құрылғылар экрандары алдында көп уақыт өткізетін болды. Бұл өмір сүру салтының өзгеруімен, қашықтықтан оқытудың енгізілуімен және цифрлық ойын-сауықтың кең таралуымен байланысты. Соңғы онжылдықтарда балалар мен жасөспірімдердің экран алдында өткізетін уақыты айтарлықтай арта түсті. Бұл үрдіс физикалық белсенділіктің төмендеуімен және отырықшы өмір сүру салтының артуымен қатар жүруде, бұл жас ұрпақтың дене және психикалық денсаулығына әсер етуі мүмкін деген алаңдаушылық тудыруда.

Шолудың мақсаты. Заманауи ғылыми зерттеулерді талдау негізінде балалар мен жасөспірімдердің тірек-қимыл аппаратының денсаулығына экран алдындағы уақыттың әсерін зерттеу

Материалдар мен әдістері. 2015–2024 жылдар аралығында PubMed және Scispace халықаралық дерекқорларында жарияланған жүйелі шолуларды, метасараптамалар және көлденең зерттеулерді қамтитын отандық және шетелдік жарияланымдарға шолу жасалды. Сұрыптауға экран алдында өткізілетін уақыттың ұзақтығы мен балалар мен жасөспірімдердің денсаулық көрсеткіштері арасындағы байланыстарды зерттеген ғылыми еңбектер енгізілді.

Нәтижелері. Шамадан тыс отырықшы өмірсүру салты мойын мен арқа ауруларының даму қаупінің жоғарылауымен, сүйек тінінің тығыздығының төмендеуімен, когнитивтік және әлеуметтік дағдылардың дамуының бұзылуымен, сондай-ақ психоэмоционалдық әл-ауқаттың нашарлауымен байланысты екені анықталды. Талдау барысында балалардың экран алдында отыру уақытының артуы мен мойын-арқа ауруларының жиілеуі, сүйек тінінің тығыздығының төмендеуі, тірек-қимыл жүйесінің бұзылыстары, когнитивтік және әлеуметтік салалардағы бұзылыстар арасындағы тұрақты байланысты көрсетті. Ең осал топ ретінде мектепке дейінгі және бастауыш мектеп жасындағы балалар анықталды. Цифрлық құрылғыларды тәулігіне 2–3 сағаттан артық пайдалану денсаулық жағдайының статистикалық тұрғыда айтарлықтай нашарлауымен қатар жүрді. Экран алдында отыру уақытын шектеуге, физикалық белсенділікті арттыруға және балалар мен жасөспірімдерде салауатты мінез-құлық әдеттерін қалыптастыруға бағытталған алдын алу шараларын әзірлеу мен енгізудің маңыздылығы атап өтілді.

Қорытынды. Отырықшы өмір сүру салты мен шамадан тыс экран уақыты балалар мен жасөспірімдердің денсаулығына көп факторлы теріс әсер етеді. Қауіп-қатерлерді азайту үшін алдын алу стратегияларын енгізу қажет. Оған балалар үшін экран уақытын шектеу, қимыл-қозғалыс белсенділігін арттыру, ата-аналар мен педагогтер арасында түсіндіру жұмыстарын жүргізу, сондай-ақ эргономикалық тұрғыдан қауіпсіз білім беру ортасын қалыптастыру кіреді.

Түйінді сөздер: *экран уақыты, балалар, жасөспірімдер, дене бітімі, арқа ауруы, отырықшы өмір салты, тірек-қимыл жүйесінің денсаулығы*

Дәйексөз үшін:
Туйебахов М.Д., Текманова А.К., Кусайынова Э.И., Бейсенбинова Ж.Б., Нурбақыт А.Н., Маратбекова А., Хайруллаева Н.З., Апбасова С.А., Маукаева С.Б. Балалар мен жасөспірімдердің тірек-қимыл жүйесі мен денсаулығына цифрлық құрылғы экран уақытының әсері: жүйелік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 214-222 *doi 10.34689/SH.2025.27.5.025*

Introduction

Over the past few decades, the use of screen-based devices such as smartphones, tablets, computers, and televisions among children and adolescents has increased dramatically. Today's children are exposed to digital technologies from a very early age, and the total amount of time they spend in front of screens far exceeds the limits recommended by organizations such as the World Health Organization (WHO) [1]. and the American Academy of Pediatrics (AAP). This trend raises growing concerns regarding the potential impact of screen exposure on the physical health of developing bodies. Particularly alarming is the influence of prolonged and excessive screen time on the condition of the musculoskeletal system. Numerous studies have reported a rise in complaints of neck, back, shoulder, and joint pain among children and adolescents. These issues are often associated with extended periods of static posture, poor ergonomics, and reduced levels of physical activity. Given the sensitivity of the developing musculoskeletal system to such stressors, these factors may contribute to chronic postural disorders, scoliosis, pain syndromes, and other related conditions. Despite the abundance of research on this topic, comprehensive data that systematically examine the relationship between various characteristics of screen time (such as device type, duration of use, and content nature) and musculoskeletal health risks remain limited**.**

Aim. To study the impact of screen time on the health of the musculoskeletal system in children and adolescents based on an analysis of modern scientific research

Research Tasks

1. To systematically review existing studies investigating the effects of screen time on the musculoskeletal system in children and adolescents.

2. To analyze the correlation between the duration of exposure to various screen types (computer, smartphone, television) and the occurrence of musculoskeletal problems.

3. To examine the influence of screen time on physical activity and sedentary behavior among children and adolescents, and to evaluate these factors as potential risk determinants for musculoskeletal disorders.

Search for a strategy. This study was conducted as a systematic literature review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The aim of the review was to summarize current evidence regarding the impact of screen time on the musculoskeletal health of children and adolescents.

A comprehensive search for scientific publications was performed across multiple electronic databases, including PubMed, Embase, Web of Science, Scopus, Cochrane Library, as well as regional sources such as eLIBRARY, CyberLeninka, and official information resources of the Ministry of Health of the Republic of Kazakhstan. The review covered studies published between 2010 and 2024.

The following key terms and their combinations using Boolean operators (AND/OR) were employed: *screen time*, *musculoskeletal system*, *children*, *adolescents*, *postural disorders*, *neck pain*, *hypodynamia*.

Inclusion Criteria. Studies meeting the following criteria were included in the review: articles published in peer-reviewed journals; availability of quantitative or qualitative data linking screen time to musculoskeletal health parameters; participants aged 6–18 years; clearly described study design (cross-sectional, cohort, case-control, meta-analysis, etc.); full-text availability of the article. The initial selection was performed at the title and abstract level, followed by full-text analysis. Data were extracted and evaluated according to the following parameters: author(s), year of publication, country, study design, participant age range, type of screen exposure, duration of device use, main findings, and methods for diagnosing musculoskeletal disorders. Where a sufficient number of homogeneous and comparable studies were identified, a meta-analysis was performed using RevMan and Stata 16 software. Depending on the degree of heterogeneity (assessed using the I^2 *statistic*), either fixed-effect or random-effects models were applied. The effects were expressed as odds ratios (ORs) or standardized mean differences (SMDs) with corresponding 95% confidence intervals (CIs).

In addition, the review incorporated official data published by the Ministry of Health of the Republic of Kazakhstan [3], the Committee on Statistics of the Ministry of National Economy, and the National Center of Public Health. Special attention was given to national data on the prevalence of postural abnormalities and pain syndromes among school-aged children, as well as findings from national monitoring studies assessing risk factors related to the use of digital technologies among children and adolescents in Kazakhstan.

Results and Discussion

This systematic review included findings from 65 studies conducted in various countries, including Kazakhstan, China, the United States, Germany, Japan, and others. The studies predominantly involved children and adolescents aged 6 to 18 years. The most commonly applied study designs were cross-sectional, cohort, case-control, and meta-analytic approaches. Both observational and analytical methods were used to explore the relationship between screen time and musculoskeletal (MSK) health. Various types of screen-based devices were examined as exposure factors - smartphones, tablets, personal computers, televisions, and gaming consoles. The reported daily screen time ranged from less than one hour to six hours per day. Most studies identified a significant increase in the risk of musculoskeletal disorders when screen time exceeded two hours per day. The most frequently assessed MSK health parameters included: the presence of neck, lower back, or general back pain; postural deviations, including the development of kyphosis and scoliosis; restricted mobility and a decline in physical activity levels.

For instance, *Priftis and Panagiotakos* (2023), in their systematic review comprising 43 original studies, confirmed a broad range of adverse health outcomes associated with excessive screen time (ST) in children and adolescents. In particular, prolonged screen exposure was strongly correlated with postural disorders, as well as pain in the neck, back, and shoulder regions. These results are consistent with findings from other studies included in the present review. Children who used mobile devices for extended periods in fixed or ergonomically poor positions were found to be especially vulnerable. Beyond musculoskeletal outcomes, the review also revealed associations between screen exposure and a range of somatic and psychological conditions, including obesity,

metabolic disturbances, reduced physical activity, impaired sleep and cognitive function, and increased anxiety and stress levels. According to pooled data, each additional hour of daily screen time was associated with a 13% increase in obesity risk, as well as a significantly higher likelihood of depressive symptoms, particularly among adolescent girls. The type of screen activity was also found to influence health outcomes differently. Passive screen time (e.g., video viewing) exerted the most substantial impact on the musculoskeletal system, especially when mobile devices were used in static postures. Among younger children, prolonged screen exposure was linked to delays in speech, motor, and social development, and in some cases, symptoms resembling autism spectrum disorders [11].

A systematic review and meta-analysis conducted by *Zhang C., Li Q., Yue Y., et al.* (2022) [2] included 252 articles encompassing 268 unique studies that examined the effects of screen time on the health of Chinese schoolchildren and adolescents aged 6 to 18 years, further reinforcing these global patterns. Based on the analysis results, exceeding two hours of daily screen time was found to significantly increase the risk of various health disorders, including obesity, psycho-emotional disturbances, myopia, reduced physical fitness, and sleep disorders. The pooled adjusted odds ratio (OR) was 1.40 with a 95% confidence interval (CI) of 1.31–1.50, indicating a 40% higher risk of adverse health outcomes associated with screen exposure exceeding two hours per day.

A particular focus of the review was on musculoskeletal disorders. All included studies consistently demonstrated a positive association between prolonged use of screen devices and the occurrence of neck, shoulder, wrist, and lower back pain [2]. A direct correlation between screen time and neck pain among children and adolescents was highlighted in a systematic review by *Rampurawala S. & Rampurawala S.* (2024) [3], which analyzed 13 studies involving 14,353 participants aged 6 to 25 years. The study population included school and university students from Brazil, Portugal, Thailand, Iran, China, Kuwait, Turkey, Lebanon, and Taiwan, and the results were published on the medRxiv platform. The review found a significant inverse correlation between reduced screen time and lower prevalence of neck pain. The highest rates of neck pain were observed among adolescents and young adults aged 10–25 years, emphasizing the need for age-specific recommendations to limit screen exposure. Moreover, the review revealed that improper posture, particularly when using screen devices while lying down, posed a significant risk factor for developing neck pain [12]. Another notable study examined the relationship between screen time and lower back pain in children and adolescents [15]. According to *Yue Y., Li Q., Zhang C., et al.* (2023) [7], prolonged screen use was significantly associated with the development of low back pain among young individuals, further confirming the detrimental impact of excessive screen exposure on musculoskeletal health [7].

The presented data form a dose-dependent relationship between screen time and the risk of low back pain for different types of screen devices (computer, mobile phone, TV) based on data from the study by Yue et al. (2023) (Table 1). In the systematic review and meta-analysis conducted by "The Role of Sedentary Behavior and Neck Pain in Children and Adolescents" (2023) [15], valuable insights were provided regarding the relationship between prolonged sedentary behavior and the development of neck pain among youth.

Table 1.

Association of screen time with low back pain in children and adolescents according to Yue et al. (2023).

Parameter	Result / Value
Study type	Systematic review and meta-analysis
Sample size	57 831 participants
Age of participants	6–18 years
Number of studies included	2023 (16 included studies)
Main conclusion	Direct dose-dependent association between screen time and low back pain among children and adolescents
Computer use	OR = 1.08 (95% CI: 1.05–1.11) per additional hour of screen time
Mobile phone use	OR = 1.32 (95% CI: 1.00–1.64)
Television viewing	OR = 1,07 (95% CI: 1,04–1,09)
Dose–response relationship model	The risk of developing low back pain increases by approximately 8–10% for each additional hour of daily screen activity.

Baradaran Mahdavi et al. (2022) included 15 cross-sectional studies with a total of 15,512 participants aged 8 to 19 years, of which seven studies were incorporated into the meta-analysis. The primary findings indicated a significant increase in the risk of neck pain associated with prolonged mobile phone use (OR = 1.36; 95% CI: 1.001–1.85; I^2 = 40.8%; p = 0.119) [13]. Initially, the association between extended screen time and neck pain appeared minimal (OR = 1.13; 95% CI: 0.98–1.30; I^2 = 60.3%; p = 0.01); however, after sensitivity analysis and the exclusion of a single study, the association became statistically significant (OR = 1.30; 95% CI: 1.03–1.64) [5]. Two articles included in the review demonstrated a notable link between prolonged sitting and neck pain. The review encompassed data from both cohort and experimental studies, enabling the identification of important trends. The evidence suggests that sedentary behavior, including time spent in front of screens and maintaining static postures, is associated with a higher risk of developing neck pain in children and adolescents. These findings support the hypothesis that prolonged sitting, particularly during mobile device use, may negatively affect posture and neck musculature. The study emphasized the mechanisms by which sedentary behavior impacts health. Mechanistically, extended periods of static postures typical of sedentary activity can lead to excessive tension in neck muscles and

impaired circulation, potentially contributing to the development of chronic pain and muscle spasms. Although a relationship between sedentary behavior and neck pain has been established, the meta-analysis results highlight the need for further research. In particular, future studies should explore potential risk factors more deeply, including age-specific effects, sex differences, and other physical determinants.

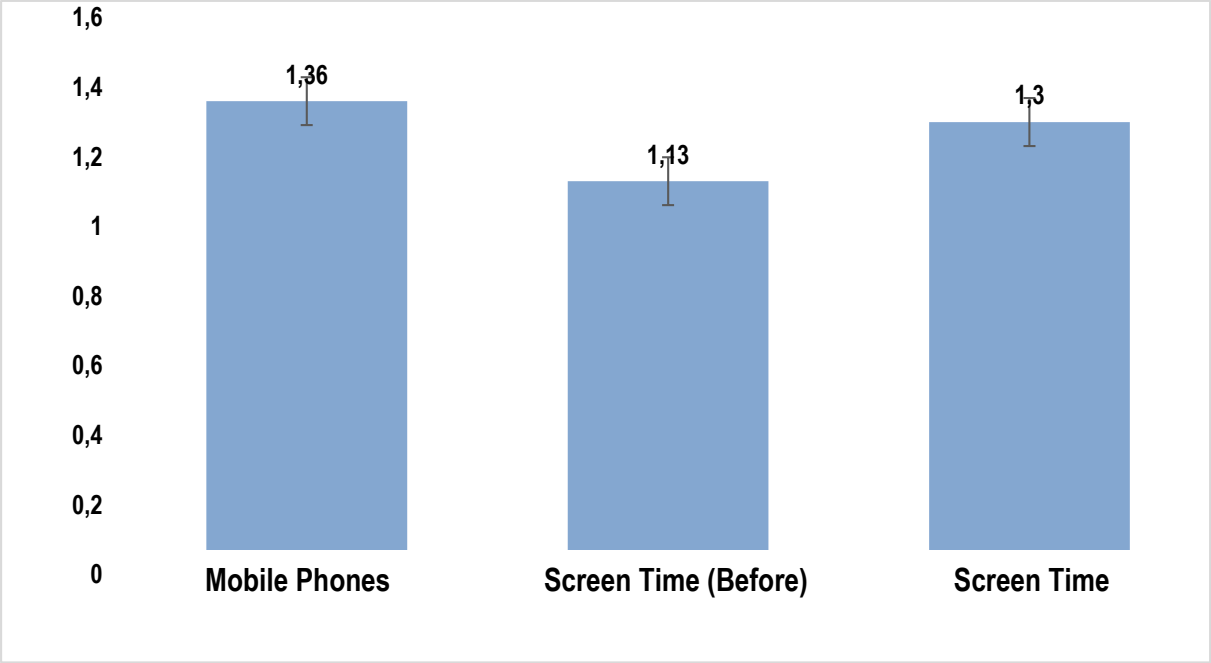

Figure 1. Potential associations between different forms of sedentary behavior and the risk of developing neck pain in children and adolescents (OR).

The graph presents the results of a meta-analysis showing the potential associations between different forms of sedentary behavior and the risk of developing neck pain in children and adolescents (OR). The red dotted line represents no effect (OR = 1). As observed, mobile phone use is significantly and directly associated with an increased risk. Screen time emerges as a statistically significant risk factor following sensitivity analysis[9]..

The study “Screen Time and Developmental Health” (2023) examined the effects of preschool-aged children’s screen exposure on their cognitive, social, and physical development. The findings indicated that excessive screen time was associated with delays in cognitive and language development, as well as a higher risk of behavioral problems [10]. According to the meta-analysis data, children who spent more than 2–3 hours per day in front of screens demonstrated impairments in attention and memory skills, alongside reduced social skills such as peer interaction. These changes were particularly pronounced in children aged 3–5 years, a period of active social and cognitive development.

The effects were more noticeable in children who consumed content passively (e.g., watching television), whereas active use (e.g., educational games or interactive apps) had a weaker impact. Additionally, the study reported negative effects of prolonged screen time on children’s physical health. Increased screen time was linked to reduced physical activity, which may, in turn, increase the likelihood of abnormal body posture and overweight issues. Reduced overall physical activity can also have long-term adverse health consequences. However, the authors noted that limited, educational use of screens can be beneficial, emphasizing that the quality of content and duration of exposure may differentially affect child development.

The cross-sectional study “Cumulative Musculoskeletal Disorders Related to Computer Use” (2023) investigated the cumulative impact of computer use on the development of musculoskeletal disorders. The study findings indicate that prolonged computer use is directly associated with an increased risk of musculoskeletal disorders, including pain in the neck, back, forearms, and shoulders. These effects are particularly pronounced among office workers and students who spend more than four hours per day at a computer. The data support the hypothesis that extended periods of sitting in a fixed posture during computer use can lead to muscle tension, poor posture, and the development of chronic pain.

The condition, often referred to as “computer-related musculoskeletal syndrome,” is associated with poor workplace ergonomics, improper posture, and insufficiently organized breaks. Furthermore, the study showed that the greatest strain occurs in the neck and back regions. Over the long term, this can contribute to the development of chronic conditions such as osteochondrosis and scoliosis. Participants who used computers in uncomfortable postures or with inadequately equipped setups (e.g., chairs without back support or improperly positioned monitors) were particularly susceptible to these disorders [9].

The systematic review “Screen Time and Bone Health in Children and Adolescents” (2022) examined the relationship between screen time and spinal development in children and adolescents. The review of various studies indicated that excessive screen time, particularly when combined with low levels of physical activity, may negatively

affect bone mass development in youth, thereby increasing the risk of osteoporosis and other bone-related disorders. The main conclusion of the review was that children and adolescents who spend more than two hours per day in front of screens tend to have lower bone density, whereas those with limited screen time exhibit higher bone density. Prolonged sedentary behavior in front of screens is often associated with reduced physical activity, which is a crucial factor for strengthening bone tissue and promoting its proper development. Additionally, studies suggest that excessive screen time may also reduce the amount of time children spend outdoors, limiting exposure to sunlight. Sunlight is necessary for vitamin D synthesis, and vitamin D deficiency adversely affects bone health because of its essential role in calcium metabolism and the maintenance of bone density [6].

According to data from the Malaysian Communications and Multimedia Commission, approximately 83.2% of internet users in the country are children aged 5–17 years [8], indicating a high level of digital engagement among minors. A similar trend is observed in the Republic of Kazakhstan. According to the National Bureau of Statistics [4], between 2013 and 2021, the proportion of children aged 6–15 using computers increased from 50% to 89.5%, while internet access rose from 42.5% to 91.5%. The youngest age group (6–10 years) were the most active users of digital devices. In 2021, 37.3% of them used computers regularly, 39% accessed the internet, and 40.2% used mobile phones. Among regular mobile phone users, the proportion was 91.4% in rural areas and 94.1% in urban areas.

Furthermore, patterns of internet use indicate frequent online interaction among children. Among children aged 6–15, 77% go online daily. Official statistics from Kazakhstan confirm an epidemiological association between increased screen time and musculoskeletal disorders, which is observed at a moderate level (*Table 2)*. In this context, school programs in Kazakhstan, such as "Health Preservation and Digital Hygiene", demonstrate promising preventive potential and may serve as a model for other countries in Central Asia.

Table 2.

Key data from official statistics of the Republic of Kazakhstan on screen time and musculoskeletal disorders in children and adolescents.

Primary Data Sources	Data Utilized	Key Indicators
National Bureau of Statistics of the Republic of Kazakhstan (NSB) ASPiR – "Women and Men of Kazakhstan, 2019–2023"	Tables 5.17–5.18: "Results of Preventive Examinations of Children Aged 0–14"	Scoliosis: 1.9 → 1.6 per 1,000 children (2019–2023). Postural disorders: 2.4 → 2.3 per 1,000 children. Regional increases in 2023: Pavlodar Region - 4.5 / 6.9 (scoliosis / spine disorders); Karaganda Region - 4.3 / 6.7 (scoliosis / spine disorders). Statistics of the Republic of Kazakhstan
National Bureau of Statistics – "Children of Kazakhstan, 2018–2022"	Section2: "Healthcare"	The decrease in the proportion of children with musculoskeletal disorders for 2018–2022 was confirmed, consistent with data from annual medical examinations. Statistics of the Republic of Kazakhstan
National Center for Public Health, Ministry of Health of the Republic of Kazakhstan – HBSC 2023 Report	Section: "Lifestyle Factors of Schoolchildren"	> 60% of adolescents spend more than 2 hours per day in front of screens; 1 in 4 girls and 1 in 3 boys report "persistent" back or neck pain (occurring ≥ once per week) among those aged 11, 13, and 15 years). HBSC
"Children's Safety in the Digital Environment" Methodological Guide (Ministry of Culture of the Republic of Kazakhstan – MPMRM, 2024)	Section 1.2: "ICT Use"	-91.3% of children aged 6–15 use ICT devices, representing an increase of 14.4 percentage points since 2019. 26% of children have fallen victim to phishing, and 35% experience phishing at least once a month. -55% of children share their personal information on social media api.kipd.kzapi.kipd.kz
2024 Data Report / Kepios	Summary of «Digital 2024: Kazakhstan»	Internet penetration stands at 92.3%, with over 71% of the population actively using social media. This indirectly reflects the screen time of schoolchildren. DataReportal – Global Digital Insights

To estimate the regional effect in Central Asia, national coefficients for scoliosis and postural disorders were combined with international coefficients. Within the framework of a random-effects model, Kazakhstan was analyzed as a separate entity. This approach allowed for the assessment of global trends (screen time > 2 hours/day ↔ risk of musculoskeletal disorders) under conditions of high internet use, while accounting for countries with a moderate prevalence of musculoskeletal disorders. The proportion of children spending more than two hours daily in front of screens, along with their digital literacy, was compared to peak regional scoliosis rates, revealing a significant correlation ($r = 0.41$; $p < 0.05$).

Within the framework of the official program of the Ministry of Health of the Republic of Kazakhstan for 2024, the projects "Children's Proper Posture" and "Children's Safety in the Digital Space" have been widely used as examples of integrating ergonomics and digital hygiene into school curricula.

Conclusion

Analysis of the selected studies demonstrated a consistent association between prolonged screen time and musculoskeletal disorders in children and adolescents. Most of the publications included in the systematic review reported adverse outcomes such as poor posture, neck, back, and shoulder pain, as well as an increased risk of developing chronic musculoskeletal conditions. These

effects were particularly pronounced when daily screen time exceeded 2–3 hours, aligning with thresholds recommended in international guidelines. The application of meta-analytic methods (using comparative data from sufficiently large studies, n ≥ specified minimum) allowed for the identification of a statistically significant increase in the risk of musculoskeletal disorders associated with prolonged use of screen devices (expressed as odds ratios [OR] or standardized mean differences [SMD], with 95% confidence intervals). The largest effects were observed with low-activity forms of screen use (e.g., passive video viewing) and when smartphones or tablets were used in ergonomically unfavorable postures or without posture variation. Analysis of international guidelines, including documents from the World Health Organization (WHO), the American Academy of Pediatrics (AAP), and the Canadian Pediatric Society, confirmed that specific limits for screen time exist for different age groups. In particular, WHO recommends no screen time for children under 2 years and limiting screen use to 1 hour per day for children aged 2–4 years. Despite variations in specific recommendations, all guidelines emphasize the importance of physical activity, breaks during device use, and adherence to ergonomic standards. Overall, the systematic review of the literature confirmed that excessive screen use can act as a significant risk factor for musculoskeletal disorders in children and adolescents. Given the increasing prevalence of digital technologies, these findings highlight the need for preventive strategies aimed at regulating screen activity and promoting healthy behavioral habits among the younger generation.

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REPRODUCTIVE HEALTH ISSUES AMONG ADOLESCENT AND YOUNG MALE POPULATIONS. PART II

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Abstract

Introduction: The reproductive health of adolescents and young men is a crucial component of overall health and well-being. Despite increasing attention to this issue, there remains a lack of information and awareness in society regarding male reproductive health, which leads to the neglect of important aspects of prevention and treatment. In particular, young men are exposed to numerous risk factors, including behavioral, socioeconomic, and environmental ones, which can negatively affect their future reproductive potential. The timely identification and elimination of these factors are essential for preserving the health of future generations.

Objective: To conduct a comprehensive analysis of the key risk factors affecting the reproductive health of adolescents and young men.

Search Strategy: After systematizing keywords and their synonyms, a comprehensive bibliographic search was carried out. Data was collected from leading international (PubMed, Google Scholar, Embase) and Russian-language (Cyberleninka, eLibrary) scientific databases, focusing on publications from the last ten years. The source selection process included an analysis of abstracts for relevance and an assessment based on citation frequency. Only full-text works were subjected to an in-depth analytical review. The main inclusion criteria were: relevance to the research topic, publication language (English or Russian), full text availability, and a variety of study types. The final selection included original and review articles, systematic reviews, meta-analyses, clinical guidelines, scientific monographs, and collections of abstracts, which ensured a comprehensive coverage of the research problem.

Results and Conclusion: Age is a key factor in the deterioration of reproductive health: men over 45 show a statistically significant decline in sperm quality. Sociocultural aspects, such as distorted family and religious norms, as well as media influence, can contribute to an early onset of sexual activity and neglect of contraception methods, increasing the risk of STIs. Behavioral factors, including smoking, alcohol abuse, and being overweight, have a direct negative impact on spermatogenesis and erectile function. To preserve men's reproductive health, it is necessary to carry out comprehensive preventive measures aimed at increasing awareness of the risks associated with lifestyle and behavior, as well as removing sociocultural barriers to open discussion of sexual health. Special attention should be paid to programs for adolescents and young men to foster a responsible attitude towards their own health. Early diagnosis and timely treatment of congenital and acquired diseases of the reproductive system are also critically important for preventing infertility.

Keywords: *reproductive health, risk factors, adolescents, male fertility.*

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Резюме

ВОПРОСЫ РЕПРОДУКТИВНОГО ЗДОРОВЬЯ СРЕДИ ПОДРОСТКОВ И МОЛОДЫХ МУЖЧИН. ЧАСТЬ II

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Введение: Репродуктивное здоровье подростков и молодых мужчин является важным компонентом общего здоровья и благополучия. Несмотря на растущее внимание к этой проблеме, в обществе сохраняется недостаток информации и осведомленности о репродуктивном здоровье мужчин, что приводит к упущению важных аспектов профилактики и лечения. В особенности, молодые мужчины подвержены влиянию множества факторов риска, включая поведенческие, социально-экономические и экологические, которые могут негативно сказаться на их будущем репродуктивном потенциале. Своевременное выявление и устранение этих факторов имеет решающее значение для сохранения здоровья будущих поколений.

Цель: провести комплексный анализ ключевых факторов риска, влияющих на репродуктивное здоровье подростков и молодых мужчин.

Стратегия поиска: После систематизации ключевых слов и их синонимов был проведён комплексный библиографический поиск. Сбор данных осуществлялся в ведущих международных (PubMed, Google Scholar, Embase) и русскоязычных (Cyberleninka, eLibrary) научных базах, с фокусом на публикации за последние десять лет. Процесс отбора источников включал анализ аннотаций на предмет их релевантности и оценку по частоте цитирования. Лишь полнотекстовые работы были подвергнуты углубленному аналитическому обзору. Основными критериями включения стали: соответствие тематике исследования, язык публикации (английский или русский), полный текст статей и разнообразие типов исследований. В итоговую выборку вошли оригинальные и обзорные статьи, систематические обзоры, метаанализы, клинические рекомендации, научные монографии и сборники тезисов, что обеспечило всесторонний охват исследуемой проблемы.

Результаты и Заключение: Возраст является ключевым фактором ухудшения репродуктивного здоровья: у мужчин старше 45 лет наблюдается статистически значимое ухудшение качества спермы. Социально-культурные аспекты, такие как искаженные семейные и религиозные нормы, а также влияние медиа, могут способствовать раннему началу половой жизни и пренебрежению методами контрацепции, что повышает риск ИППП. Поведенческие факторы, включая курение, злоупотребление алкоголем и избыточный вес, имеют прямое негативное воздействие на сперматогенез и эректильную функцию. Для сохранения репродуктивного здоровья мужчин необходимо проводить комплексные профилактические мероприятия, направленные на повышение осведомлённости о рисках, связанных с образом жизни и поведением, а также на устранение социально-культурных барьеров для открытого обсуждения сексуального здоровья. Особое внимание следует уделять программам, ориентированным на подростков и молодых мужчин, с целью формирования ответственного отношения к собственному здоровью. Ранняя диагностика и своевременное лечение врождённых и приобретённых заболеваний репродуктивной системы также являются критически важными для предотвращения бесплодия.

Ключевые слова: *репродуктивное здоровье, факторы риска, мужская фертильность*

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Түйіндеме

ЖАСӨСПІРІМДЕР МЕН ЖАС ЕРЛЕР АРАСЫНДА РЕПРОДУКТИВТІК ДЕНСАУЛЫҚ МӘСЕЛЕЛЕРІ. II БӨЛІМ

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Кіріспе: Жасөспірімдер мен жас ерлердің репродуктивті денсаулығы — жалпы денсаулық пен әл-ауқаттың маңызды құрамдас бөлігі. Бұл мәселеге деген қызығушылықтың артуына қарамастан, қоғамда ерлердің репродуктивті денсаулығы туралы ақпарат пен хабардарлық жетіспейді, бұл алдын алу мен емдеудің маңызды аспектілерін назардан тыс қалдырады. Әсіресе, жас ерлердің репродуктивті денсаулығына мінез-құлықтық, әлеуметтік-экономикалық және экологиялық сияқты көптеген қауіп факторлары әсер етеді, бұл олардың болашақ репродуктивті әлеуетіне кері әсерін тигізуі мүмкін. Осы факторларды уақтылы анықтау және жою болашақ ұрпақтың денсаулығын сақтау үшін шешуші маңызға ие.

Мақсаты: Жасөспірімдер мен жас ерлердің репродуктивті денсаулығына әсер ететін негізгі қауіп факторларына кешенді талдау жүргізу.

Іздеу стратегиясы: Негізгі сөздер мен олардың синонимдерін жүйелегеннен кейін кешенді библиографиялық іздеу жүргізілді. Деректерді жинау соңғы он жылдағы жарияланымдарға бағытталған жетекші халықаралық (PubMed, Google Scholar, Embase) және орыс тіліндегі (Cyberleninka, eLibrary) ғылыми базаларда жүзеге асырылды.

Дереккөздерді іріктеу процесі олардың өзектілігін анықтау үшін аннотацияларды талдауды және дәйексөз жиілігі бойынша бағалауды қамтыды. Тек толық мәтінді жұмыстар ғана тереңдетілген талдауға алынды. Зерттеу тақырыбына сәйкестік, жарияланым тілі (ағылшын немесе орыс), толық текст және зерттеу түрлерінің әртүрлілігі негізгі іріктеу критерийлері болды. Қорытынды іріктеуге зерттеліп отырған мәселені жан-жақты қамтуды қамтамасыз ететін түпнұсқа және шолу мақалалары, жүйелі шолулар, мета-анализдер, клиникалық нұсқаулар, ғылыми монографиялар және тезистер жинақтары енді.

Нәтижелер мен қорытынды: Жас репродуктивті денсаулықтың нашарлауының негізгі факторы болып табылады: 45 жастан асқан ерлерде сперма сапасының статистикалық тұрғыдан маңызды түрде нашарлауы байқалады. Бұрмаланған отбасылық және діни нормалар сияқты әлеуметтік-мәдени аспектілер, сондай-ақ медианың ықпалы жыныстық өмірді ерте бастауға және контрацепция әдістерін елемеуге ықпал етуі мүмкін, бұл ЖЖБИ қаупін арттырады. Шылым шегу, алкогольді шамадан тыс пайдалану және артық салмақ сияқты мінез-құлықтық факторлар сперматогенез бен эректильді функцияға тікелей теріс әсер етеді. Ерлердің репродуктивті денсаулығын сақтау үшін өмір салты мен мінез-құлыққа байланысты қауіптер туралы хабардарлықты арттыруға, сондай-ақ жыныстық денсаулықты ашық талқылау үшін әлеуметтік-мәдени кедергілерді жоюға бағытталған кешенді профилактикалық іс-шараларды жүргізу қажет. Жасөспірімдер мен жас ерлерге бағытталған бағдарламаларға ерекше назар аудару қажет, бұл олардың өз денсаулығына жауапкершілікпен қарауын қалыптастыруға көмектеседі. Туа біткен және жүре пайда болған репродуктивті жүйе ауруларын ерте диагностикалау және уақтылы емдеу де бедеуліктің алдын алу үшін өте маңызды.

Түйін сөздер: *репродуктивті денсаулық, қауіп факторлары, ерлер фертильдігі.*

Дәйексөз үшін:

Мухамеджан М.Б., Алчинбаев М.К., Табынбаев Н.Б., Кусаинова А.А., Касым Л.Т. Жасөспірімдер мен жас ерлер арасында репродуктивтік денсаулық мәселелері. II бөлім // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 223-232. *doi 10.34689/SH.2025.27.5.026*

Background

Investigation into the reproductive health of adolescents and young men is a critical and burgeoning field of modern medicine, foundational to both individual well-being and global public health. Male infertility and other reproductive disorders are no longer considered marginal issues but have emerged as a significant and growing concern worldwide, impacting demographic trends and quality of life for millions of people [68, 98]. Data from a vast body of literature consistently indicate a worrying global decline in key male reproductive parameters, including sperm count and semen quality, over the past several decades [61, 74]. This trend has been documented across various populations and geographical regions, prompting an urgent need to identify its underlying causes [51]. The etiology of these disorders is highly complex and multifactorial, involving a dynamic interplay of demographic, genetic, behavioral, medical, and environmental factors [8]. Each of these domains contributes uniquely to the overall risk profile, with their combined effects often leading to more severe outcomes [10].

Objective: To identify key factors influencing the reproductive health of adolescent and young males, with a focus on prevention and early correction of disorders.

Search strategy. The methodological approach began with the systematic identification of primary search terms and their synonymous expressions. A subsequent comprehensive literature search was conducted across major international databases, including PubMed, Google Scholar, and Embase, as well as regional Russian-language academic platforms such as Cyberleninka and e-Library. Selected articles underwent an initial screening of their abstracts to determine thematic relevance. This was followed by a process of bibliographic cross-referencing, which involved analyzing both the cited references and subsequent works that had cited the selected articles. The remaining literature was then categorized according to predefined eligibility criteria, and full-text versions were retrieved for a detailed analytical review. Only methodologically sound and validated studies that met all inclusion criteria were ultimately integrated into the final synthesis. Finally, 101 references were included in this part of the review.

Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (a) thematic relevance to the study's scope; (b) availability in either English or Russian; (c) full text is available. Conversely, publications that did not satisfy these predefined standards were consequently excluded from the review.

The main part

In contemporary scientific literature, the causes and risk factors influencing men's reproductive health are systematically categorized into four key areas: biological and physiological determinants, behavioral and lifestyle factors, environmental exposures, and socio-demographic characteristics [78]. This multifaceted approach provides a more complete understanding of fertility disorders and helps identify the most significant links in the pathogenesis of male infertility (see Figure 1).

Demographic Factors

To date, it has been well established that age, ethnicity, and level of education/living standards represent significant demographic indicators that may exert a substantial impact on male reproductive health [20, 66].

A meta-analysis covering data from 1965 to 2015 identified age as one of the major risk factors for reduced sperm concentration in 13 out of 14 analyzed studies [91]. Research demonstrates that with advancing age, men experience deterioration in key semen parameters — including sperm count, motility, and morphological integrity [49, 54]. For example, *Lee T. et al.* (2023) reported statistically significant alterations in semen quality among

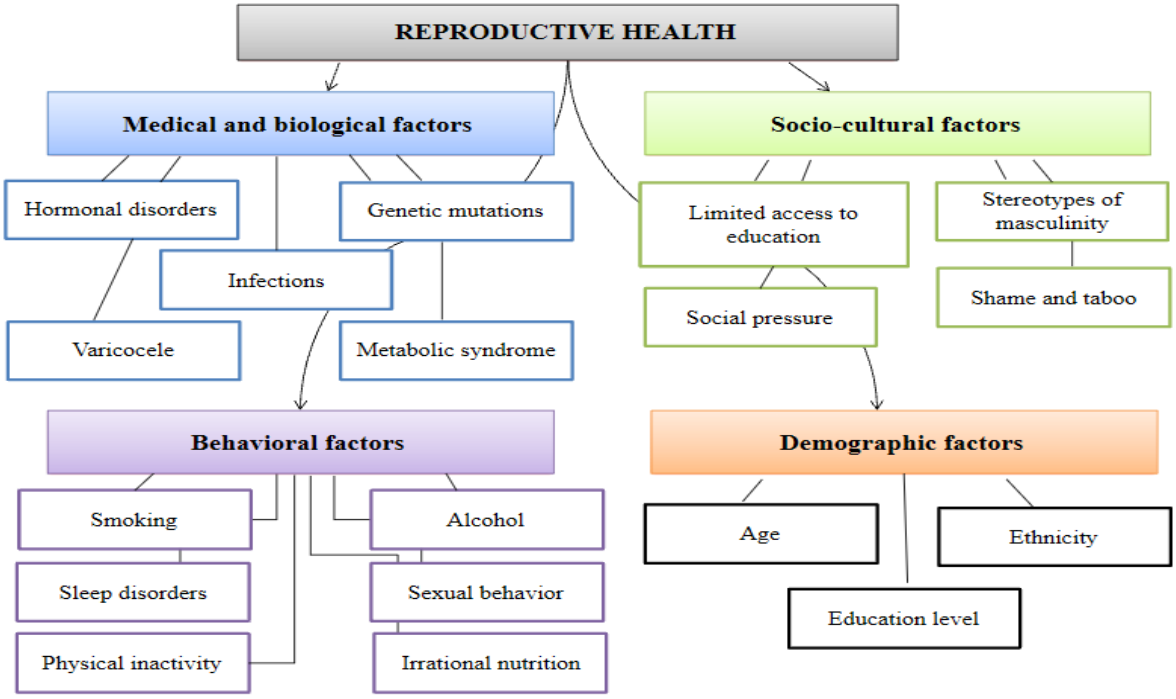

Figure 1. The spectrum of risk factors influencing male reproductive health

men aged 45 years and older compared to those younger than 35. Specifically, reductions were observed in ejaculate volume (2.5 ml vs. 3.2 ml; $p < 0.001$), total sperm motility (31.2% vs. 42.3%; $p < 0.001$), and progressive motility (28.4% vs. 39.2%; $p < 0.001$). The authors associated these changes with age-related dysfunction of Sertoli cells — somatic elements providing structural and metabolic support to spermatogenesis — which in turn may contribute to reduced fertility in middle-aged men [58]. In another study, researchers suggested that ejaculate volume progressively decreases after the age of 45 due to the functional decline of accessory glands in the male reproductive system [37]. Age-related changes also occur in the hormonal profile and functional state of the testes, including reduced Leydig cell numbers and progressive decline in testosterone production [71]. These tendencies are of particular concern given that paternal age is steadily increasing worldwide, largely due to delayed marriage and childbearing for socio-economic reasons [53].

At the same time, a number of studies demonstrate a strong association between early sexual initiation (before the age of 16) and increased risks of adverse outcomes in reproductive and sexual health. Such consequences include a higher likelihood of multiple sexual partners, sexual encounters under the influence of alcohol or drugs, elevated risk of unintended pregnancy, and sexually transmitted infections (STIs) [39]. Data from the Youth Risk Behavior Surveillance System (YRBSS, 2017) revealed that 4.8% of male high school students in the United States had initiated sexual activity before the age of 13 — more than double the prevalence among their female peers (2%) [50].

Furthermore, *Lindberg L. et al.* (2019), in a study among U.S. high school students, documented pronounced ethnocultural differences in the timing of sexual initiation. The highest proportion of very early debut (before 13 years) was observed among African American adolescent males, ranging from 12% to 29% depending on the region. Among Latino adolescents, prevalence varied between 6% and 17%, while among white males it ranged from 2% to 10% [62]. An analysis of demographic data from the Nigerian Department of Health (2003, 2008, 2013) showed that among the 374 ethnic groups in the country, Yoruba males aged 15–19 years exhibited the highest likelihood of early sexual initiation [75]. According to *Burns J. et al.* (2021), young Black men aged 18–24 are at greater risk of STIs, including HIV/AIDS, and demonstrate greater unmet needs in sexual and reproductive health services compared to other ethnic groups [16]. These findings are consistent with earlier evidence (2011) showing that the prevalence of ED among Asian men aged 40–49 years (7–15%) was considerably higher than rates observed in Australia (5–6%) and Europe (3–5%) [59]. Interestingly, within the Asian population, the lowest rates of ED were recorded among certain ethnoreligious minorities, such as Muslims and Zhuangs [106]. In larger ethnic groups, prevalence values of ED were reported as 0.767 among Malays, 0.705 among Chinese, 0.793 among Indians, and 0.667 among other groups [55].

The influence of education level on sexual dysfunction remains a subject of ongoing debate. Several studies, including *Johannes C. et al.* (2000), reported that men with lower educational attainment were at greater risk of developing ED [48]. These findings are supported by other research demonstrating a positive correlation between the severity of erectile and orgasmic dysfunctions and low educational levels [30]. However, contradictory results also exist. For instance, a study involving 1000 men aged 45–70 years in two Finnish cities revealed that higher-educated men more frequently reported ED (OR: 0.52; 95% CI: 0.33–0.83; P = 0.013). Moreover, *Hwang T.* (2010) observed that continuing education up to university level was associated with increased ED prevalence [42]. Finally, several investigations have reported no statistically significant association between educational attainment and the

prevalence of ED, anorgasmia, or disorders related to sexual satisfaction [56, 88].

Some studies highlight an association between men's occupational activity and reproductive health. For example, civil servants more frequently present with abnormal semen parameters, which may be explained by the higher prevalence of risk factors such as smoking and excessive alcohol consumption that negatively affect fertility [99]. An Iranian study revealed that men engaged in manual labor were more prone to infertility compared with office workers. They more frequently exhibited conditions such as varicocele and inguinal hernia (2.4 and 1.6 times higher, respectively), likely due to sustained physical strain and mechanical stress on the reproductive organs, resulting in reduced sperm quality [64].

Social and Cultural Factors

In addition to demographic determinants, social and cultural aspects play an equally important role in shaping male reproductive health. Family attitudes, community norms, religious values, and media influence directly affect sexual behavior, reproductive awareness, and access to medical services. For example, several studies have demonstrated that insufficient communication between parents and adolescents on topics of sexual and reproductive health contributes to higher levels of risk-taking behavior, including early sexual debut and low contraceptive use [82, 89]. Conversely, open dialogue with parents has been associated with delayed initiation of sexual activity and increased adherence to safe sexual practices [96].

Religious beliefs and traditions also exert a considerable influence. In a systematic review by *Kiani Z. et al.* (2021), a strong correlation was found between religious affiliation and sexual activity among adolescents. Boys and young men who were regularly involved in religious practices reported later initiation of sexual activity, fewer partners, and reduced risk of STIs compared with their non-religious peers [84].

Socioeconomic inequality is another critical determinant. In regions with low income and limited access to education, men demonstrate poorer knowledge of reproductive health issues and more often encounter problems in receiving timely medical care. For example, a study in sub-Saharan Africa revealed that young men from lower socioeconomic groups were significantly less likely to use modern contraceptives and more likely to be exposed to sexual risk factors [47]. At the same time, cultural attitudes toward masculinity and sexuality can increase the prevalence of risk-taking behaviors. In many societies, sexual activity at an early age and having multiple partners are perceived as indicators of male "status" and "strength." However, this significantly increases the risks of unprotected sexual activity, infertility, and STIs, including HIV [79, 2].

Finally, mass media and social networks also play a growing role in shaping reproductive attitudes. On the one hand, they serve as a source of information on safe sexual practices; on the other hand, the spread of pornography and sexualized content has been associated with distorted perceptions of sexuality, leading to unrealistic expectations, increased anxiety, and in some cases, erectile dysfunction [65].

Lifestyle Factors

Lifestyle is one of the key determinants of male reproductive health, with particular emphasis on nutrition, physical activity, alcohol consumption, smoking, and psycho-emotional stress. Numerous studies have shown that overweight and obesity are associated with impaired spermatogenesis and an increased risk of erectile dysfunction (ED) [35, 40]. According to a meta-analysis by *Sermondade N. et al.* (2013), men with a body mass index (BMI) above 30 kg/m² had a 21% higher likelihood of oligozoospermia or azoospermia compared with men of normal weight [57]. Excess adipose tissue contributes to increased aromatization of androgens into estrogens, which negatively affects hormonal balance and reduces testosterone levels [1, [63]. Weight reduction may be recommended for infertile patients to enhance their fertility potential [6, 38].

Nutrition plays a crucial role in reproductive health. Diets rich in saturated fats and processed foods are associated with decreased sperm motility and abnormal morphology [3]. In contrast, a Mediterranean-style diet, rich in antioxidants, polyunsaturated fatty acids, and vitamins (C, E, folate), has been shown to improve sperm quality [95, 15]. Micronutrient deficiencies - particularly of zinc, selenium, and folate - are strongly associated with impaired spermatogenesis and reduced fertility [93].

Alcohol consumption negatively affects both spermatogenesis and erectile function. Chronic alcohol intake reduces testosterone synthesis, impairs Leydig cell function, and increases the risk of hypogonadism [100]. Studies have also demonstrated that men who consume more than 20 alcoholic drinks per week have a higher prevalence of ED compared with moderate drinkers [21].

Smoking remains a significant risk factor for reproductive dysfunction. Tobacco smoke contains more than 4000 toxic compounds, including cadmium, lead, and polycyclic aromatic hydrocarbons, which lead to oxidative stress, DNA damage in spermatozoa, and reduced sperm motility [86, 105]. A meta-analysis by *Sharma R. et al.* (2016) confirmed that smokers have significantly lower sperm concentration and motility compared with non-smokers [67].

Psychological stress and chronic fatigue also play a major role. Stress activates the hypothalamic-pituitary-adrenal axis, increases cortisol production, and suppresses the hypothalamic-pituitary-gonadal axis, which leads to reduced testosterone secretion and disruption of spermatogenesis [36]. In addition, stress is considered a significant predictor of ED and decreased sexual satisfaction [18].

Insufficient or excessive physical activity can also negatively influence reproductive health. A sedentary lifestyle leads to obesity, hormonal imbalance, and reduced sperm quality, while excessive endurance exercise (e.g., marathon training) is associated with oxidative stress, hypogonadotropic hypogonadism, and reduced testosterone levels [83, 60].

Environmental Factors

Alongside demographic, social, and lifestyle determinants, environmental conditions play an increasingly important role in male reproductive health [92]. Anthropogenic pollution, exposure to endocrine-disrupting chemicals, radiation, and occupational hazards have been identified as risk factors for infertility and sexual dysfunction. A decline in semen quality has been reported worldwide over the past decades. For instance, *Levine H. et al.* (2017)

demonstrated in a large-scale meta-analysis that sperm concentration in men from North America, Europe, Australia, and New Zealand declined by 52.4% between 1973 and 2011 [103]. The authors attributed this trend to environmental pollution, unhealthy lifestyles, and occupational exposures.

Endocrine-disrupting chemicals (EDCs) - such as bisphenol A (BPA), phthalates, pesticides, and heavy metals - interfere with hormonal regulation of spermatogenesis and reduce testosterone levels [7]. For example, BPA exposure has been linked to decreased sperm count, reduced motility, and increased DNA fragmentation [94]. Air pollution, particularly fine particulate matter (PM2.5), has also been associated with impaired sperm quality. A Chinese cohort study found that long-term exposure to high PM2.5 concentrations was associated with decreased semen volume and abnormal sperm morphology [69]. Similarly, exposure to high concentrations of nitrogen oxides and sulfur dioxide has been correlated with reduced sperm motility [24]. Occupational hazards, especially in industries involving heat exposure, ionizing radiation, solvents, or pesticides, significantly contribute to reproductive disorders [73]. For example, men working in agriculture and pesticide production are at higher risk of infertility due to chronic exposure to organophosphates [26]. Workers exposed to high temperatures (e.g., welders, bakers, drivers) frequently present with impaired spermatogenesis due to scrotal hyperthermia [76].

Finally, climate change and rising global temperatures may also have an indirect negative impact on male reproductive health. Recent studies suggest that prolonged heat exposure may reduce sperm quality and contribute to seasonal fluctuations in semen parameters [12].

Conclusion

A comprehensive understanding of these diverse risk factors is essential for developing effective prevention and intervention strategies [80, 819(105-]. While numerous studies have individually explored the impact of specific factors such as age, smoking, obesity, and exposure to endocrine-disrupting chemicals, the current scientific landscape often lacks a cohesive, synthesized analysis that integrates these disparate findings. The fragmentation of knowledge across multiple specialties and research areas creates a significant gap in the ability of healthcare professionals to provide holistic, evidence-based guidance to young men. Without a clear framework that outlines the relative importance and synergistic effects of these factors, public health initiatives may prove less effective. Furthermore, a deeper understanding of these risks is necessary to distinguish between modifiable and non-modifiable factors, allowing for targeted campaigns that promote healthier lifestyles and responsible reproductive choices.

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PERCUTANEOUS ENDOSCOPIC GASTROSTOMY IN PEDIATRICS. LITERATURE REVIEW

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Abstract

Introduction: Percutaneous endoscopic gastrostomy (PEG) is a common procedure performed worldwide in patients with a variety of comorbidities, with multiple indications. Although the procedure is considered generally safe, life-threatening complications can sometimes occur. The purpose of this review is to analyze endoscopic percutaneous access techniques and determine the frequency of associated complications.

Methods: analytical review of the literature on main complications associated with PEG in children. A literature search was conducted in PubMed, CyberLeninck, and Elibrary databases using the keywords “percutaneous endoscopic gastrostomy,” “complications,” and “children.” The depth of the search was 10 years.

Results: Thirteen articles with 2009 pediatric patients were analyzed. The most common PEG methods are Pull and Push. Pull method was performed in 29.9% of patients and Push method in 48.7%. In 21.4% of patients, the method of PEG was not specified in the publications. Dysphagia of neurologic origin was the main indication followed by the need for nutritional support in different diseases. A total of 1505 complications were reported, of which 1370 (91.0%) were minor complications and 135 (9.0%) were major complications. Hypergranulation was the most frequent minor complication, followed by leakage of gastric contents through the gastrostomy site, peristomal infections, dislocation and early exit of the gastrostomy tube. Among the serious complications, gastric heterotopia was the most frequent in one-stage Button PEG. Peritonitis, gastrointestinal bleeding, hidden bumper syndrome, gastrointestinal fistula and bowel obstruction were next in frequency. Perforation of esophagus, stomach and intestine occurred in 2 cases each. Fatal outcome was reported in 2 patients, the cause of death was sepsis after perforation of the esophagus and gastrointestinal fistula formation.

Conclusion: Children undergoing percutaneous endoscopic gastrostomy often have minor complications. PEG has a low incidence of major complications and mortality.

Keywords: *children; complications; percutaneous endoscopic gastrostomy.*

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Резюме

ЧРЕСКОЖНАЯ ЭНДОСКОПИЧЕСКАЯ ГАСТРОСТОМИЯ В ПЕДИАТРИИ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Чрескожная эндоскопическая гастростомия (ЧЭГ) - распространенная процедура, проводимая во всем мире у пациентов с различными сопутствующими заболеваниями, с множеством показаний. Хотя процедура считается в целом безопасной, иногда могут возникнуть опасные для жизни осложнения. Целью данного обзора является анализ эндоскопических методов чрескожного доступа и определение частоты связанных с ними осложнений.

Стратегия поиска: аналитический обзор литературы по основным осложнениям, связанным с ЧЭГ у детей. Поиск литературы проведен в базах данных PubMed, КиберЛенинка и Elibrary с использованием ключевых слов «чрескожная/перкутанная эндоскопическая гастростомия», «осложнения» и «дети». Глубина поиска – 10 лет.

Результаты: Анализ охватил тринадцать научных работ, в которых участвовало 2009 детей. Самыми распространенными методами ЧЭГ являются Pull и Push. Метод вытягивани (Pull) выполнялся у 29,9% пациентов, метод проталкивания (Push) у 48,7%. У 21,4% пациентов метод ЧЭГ не указан в публикациях. Дисфагия неврологического происхождения была основным показанием, за которым следовала потребность в нутритивной поддержке при разных заболеваниях. Всего сообщено о 1505 осложнениях, из них 1370 (91,0%) – незначительные осложнения 135 (9,0%) – серьезные осложнения. Гипергрануляция была наиболее часто встречающимся незначительным осложнением, за ними следовали утечка желудочного содержимого через место наложения гастростомы, перистомальные инфекции, смещение и ранний выход гастростомической трубки. Среди серьезных осложнений гетеротопия желудка оказалась самым частым при проведении одноэтапной Button ЧЭГ. Далее по частоте распределились перитонит, кровотечения из ЖКТ, синдром скрытого бампера, гастрокишечнокожные свищи и непроходимость кишечника. Перфорация пищевода, желудка и кишечника встречались по 2 случая каждый. О летальном исходе сообщено у 2 пациентов, причина смерти была связана с сепсисом после перфорации пищевода и сформирования гастрокишечного свища.

Заключение: У детей, перенесших чрескожную эндоскопическую гастростому, часто возникают незначительные осложнения. ЧЭГ имеет низкую частоту серьезных осложнений и смертности.

Ключевые слова: *дети; осложнения; чрескожная/перкутанная эндоскопическая гастростомия.*

Для цитирования:

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Түйіндеме

ПЕДИАТРИЯДАҒЫ ПЕРКУТАНДЫ ЭНДОСКОПИЯЛЫҚ ГАСТРОСТОМИЯ. ӘДЕБИЕТТІК ШОЛУ

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Кіріспе: Перкутанды эндоскопиялық гастростомия (ПЭГ) - әртүрлі сырқаты бар науқастарға, әртүрлі көрсеткіштерге байланысты әлемде кеңінен орындалатын процедура. Процедура жалпы қауіпсіз деп саналғанымен, кейде өмірге қауіп төндіретін асқынуларға әкелуі мүмкін. Бұл шолудың мақсаты тері арқылы эндоскопиялық гастростомия әдістерін талдау және онымен байланысты асқынулардың жиілігін анықтау болып табылады.

Әдістер: Бұл зерттеуде балалардағы теріарқылы эндоскопиялық ассистенция арқылы гастростома орнатумен байланысты асқынулар бойынша әдебиет талданды. Әдебиет іздеуі PubMed, КиберЛенинка және Elibrary дерекқорларында жүргізілді, іздеу сөздері ретінде «теріарқылы/перкутанды эндоскопиялық гастростомия», «асқынулар» және «балалар» қолданылды. Іздеу тереңдігі – 10 жыл.

Нәтижелер: ізденіске сай 13 мақала таңдалып алынып, 2009 науқас бала мәліметтері талданды. Теріарқылы эндоскопиялық ассистенция арқылы гастростомия әдістерінің ең кең таралғандары Pull және Push болып табылады. Pull әдісі 29,9%, Push әдісі 48,7% науқаста қолданылды. 21,4% науқаста ПЭГ әдісі мақалаларда көрсетілмеген. Неврологиялық себептерге байланысты дисфагия, одан кейін әртүрлі сырқаттарға байланысты нутритивтік қолдау ПЭГ орнатудың негізгі көрсеткіштері болды. Мақалаларда 1505 асқыну туралы хабарланған, оның ішінде 1370 (91,0%) – жеңіл асқынулар, 135 (9,0%) – ауыр асқынулар. Гипергрануляция ең жиі кездескен жеңіл асқыну болды, одан кейін гастротүтікше орнатылған жерден асқазан ішіндегі сұйықтықтың ағуы, перистомалық инфекциялар, гастротүтікшенің орнынан ығысуы немесе ерте шығып кетуі байқалған. Ауыр асқынулардың арасында асқазан гетеротопиясы бірқадамды Button ПЭГ әдісінің ең жиі асқынуы болған. Одан кейінгі орындарда перитонит пен асқазан-ішек жолдарынан қан кетулері, жасырын бампер синдромы, асқазан-ішек-тері жыланкөздері және ішек өтпеушілігі орналасқан. Өңеш, асқазан және ішек перфорациясы әрқайсысы 2 науқаста кездескен. 2 науқаста өлім жағдайы хабарланған, өлім себебі өңеш перфорациясынан кейінгі сепсис пен гастроинтестинальды жыланкөздің қалыптасуы болған.

Қорытынды: Перкутанды эндоскопиялық гастростомия жасалған балаларда жеңіл асқынулар жиі кездеседі. Теріастылық эндоскопиялық ассистенция арқылы гастростомия ауыр асқынулар мен өлімнің төмен деңгейімен сипатталады.

Түйінді сөздер: *балалар; асқынулар; теріарқылы эндоскопиялық ассистенция арқылы гастростомия.*

Дәйексөз үшін:

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Introduction

Nutritional deficiency in children associated with various diseases is a pressing problem in childhood and has been the subject of numerous foreign studies. The importance of this problem is due to its widespread prevalence, confirmed negative impact on the course of the underlying disease and the immune system, as well as the risk of developing infectious complications, prolonged hospital stays, and increased treatment costs [45,46]. Providing nutritional support plays a key role in the treatment of this category of patients. Temporary enteral nutrition can be provided via a nasogastric tube, but it needs to be replaced every four to six weeks. It is also important to note that nasogastric tubes can cause complications such as aspiration pneumonia, gastric ulcers, and bleeding [25,26]. If long-term enteral feeding is necessary, gastrostomy may be considered instead of a nasogastric tube [8,33]. Experts from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) indicate that it is advisable to perform a gastrostomy if enteral feeding is expected to be necessary for more than three to six weeks [24].

According to ESPGHAN recommendations, gastrostomy is usually indicated for children with concomitant chronic nutritional needs, in whom oral intake is insufficient to maintain growth. Although the specific indications for gastrostomy are numerous and varied, the most common indications are related to insufficient oral fluid and nutrient intake and/or swallowing disorders in central nervous system disorders, either as the primary cause or in combination with chromosomal or metabolic disorders. In addition, renal disorders, congenital heart disease, cancer, chronic respiratory diseases such as cystic fibrosis, and gastrointestinal disorders such as Crohn's disease and intestinal failure may require feeding through a gastrostomy to correct nutritional deficiencies. Gastrostomy tubes are also placed for congenital or acquired conditions such as esophageal atresia and craniofacial surgery, when eating through the mouth may be anatomically difficult. Furthermore, they may be necessary for children who require nutritional restoration to achieve a recommended weight that is appropriate for certain surgical procedures, such as infants with congenital heart defects [22,24].

Gastrostomy is also sometimes indicated for children with unsafe swallowing, at risk of recurrent aspiration during oral feeding, and when gastric drainage and decompression are required in cases of anterior intestinal motility disorders. Another rare but recognized indication is the delivery of therapeutic formulas to patients with certain metabolic disorders, which are usually unpleasant to taste. It can also be offered to patients who require multiple medications due to diseases of other organs, to improve compliance and medication effectiveness [8,14,23,24].

The decision to perform a gastrostomy should be made on a case-by-case basis, taking into account the patient's needs, primary diagnosis, and life expectancy. The first gastrostomy was used to feed an adult with obstruction in the cardia or above. It was first proposed by Egeberg in 1837, but after numerous attempts and failures, it was only successfully performed in 1876 by Verneuil [12] using an open surgical method [40]. In pediatrics, this procedure was the main treatment for early-stage esophageal atresia, and the first successful results of treating these patients were reported in the works of Leven [32] and Ladd [31] in the early 1940s. In subsequent years, researchers expanded the surgical conditions for which open gastrostomy was performed.

Less invasive percutaneous endoscopic gastrostomy (PEG) was introduced in 1980 by *M.W. Gauderer et al.* [18]. The inspiration for the development of this procedure came from the glow in the stomach of a newborn baby undergoing endoscopy. The first PEG was performed in a pediatric operating room on June 12, 1979, at Cleveland University Hospital (USA) on a four-month-old child with insufficient oral intake of neurological etiology under sedation. During and after the operation, no complications were noted in the early period, but after three weeks, migration of the probe from the stomach was observed, associated with the use of a thin probe with a distal end in the form of a mushroom, as well as, most likely, the use of excessive force when pulling the anterior wall of the stomach to the anterior abdominal wall. The author subsequently improved the probe by adding an internal limiter and avoiding excessive pressure on the tissue between the internal and external limiters, using thicker probes [19]. In subsequent years, PEG became a popular method of enteral nutrition among adults as well. In 2001, 20 years after its invention, more than 216,000 operations were performed annually in the United States [20]. Later, gastrostomy began to be used for non-surgical indications, for example, to meet the nutritional needs of patients with severe neurological disorders and developmental delays.

PEG has become widely used by both adult and pediatric physicians to provide enteral nutritional support to patients who, despite maintaining gastrointestinal absorption and motility functions, are unable to consume solid or liquid food due to various diseases. Due to its effectiveness, safety, ease of use, and relatively low cost, PEG has become an increasingly popular method. Compared to open gastrostomy, PEG is easily performed by experienced endoscopists. The success rate of tube placement is 99.5%, with a mortality rate of 0.5% to 2% [27,39]. A PEG tube can remain in place for at least six months.

Although the placement of a percutaneous endoscopic gastrostomy (PEG) tube is a minimally invasive procedure, like any surgical intervention, it carries a risk of complications [34]. ESPGHAN suggests classifying complications by severity (minor and major complications) or by time of occurrence (early or late postoperative). Early complications include bleeding associated with endoscopy, damage to internal organs (colon and small intestine, in rare cases - liver and spleen damage), pneumoperitoneum, cellulitis, and minor wound infections.

Late complications include: impaired wound healing (granulation, peristomal infection, edge separation), intraperitoneal leakage of gastric contents, gastric perforation, transhepatic and transpancreatic placement, incorrect placement of the gastrostomy tube in the abdominal wall, aspiration pneumonia, exacerbation of GERD, postpyloric migration with possible dumping syndrome, mucosal damage, ulceration, luminal obstruction, pancreatitis, hidden bumper syndrome, mechanical problems with the tube: displacement, clogging, porosity, kinking or fracture, gastric paresis [24].

The aim is to analyze endoscopic methods of percutaneous access and determine the frequency of associated complications.

Search strategy

For the literature review, the first step was to select keywords: "percutaneous endoscopic gastrostomy," "children," "complications." Based on the keywords, a literature search was conducted to identify articles published in the PubMed, CyberLeninka, and Elibrary databases. The search covered a period of 10 years.

Only original full-text articles reporting the results of observational studies involving children under the age of 18 were included. Reviews, meta-analyses, systematic reviews, editorial articles, letters, lecture notes, and clinical case reports were excluded. In the first stage of the literature search, articles were selected based on their titles and abstracts. The full texts were then analyzed to select articles for inclusion. In accordance with our objective, a total of 13 publications were selected for analysis, containing data on 2,009 patients.

Search results

Methods of performing the PEG procedure:

In the PEG surgical technique, there are two fundamentally different ways of performing the procedure: "pull" and "push."

The pull technique according to Gauderer–Ponsky is the most commonly used in modern practice. The site for gastrostomy insertion is determined using a transabdominal impulse/finger pressure and transillumination on the anterior abdominal wall. Local anesthesia is administered into the abdominal wall and skin.

The puncture cannula is inserted through the anterior abdominal wall into the stomach cavity under endoscopic guidance, while the stomach is distended to ensure that the stomach wall is opposed to the abdominal wall. The needle is removed from the cannula and an introducer containing a double thread is inserted through the cannula. The thread is pushed through the cannula until it is visible endoscopically in the stomach cavity. The thread is then grasped and secured through the endoscope using forceps. The endoscope with biopsy forceps/clips and the attached thread is pulled out through the mouth as a single unit. The thread is then connected to the PEG, the PEG is lubricated, and the guide thread, which has been brought out through the abdominal wall, is pulled through the cannula while the PEG is pulled through the mouth, esophagus, and into the stomach. The PEG tube is pulled through the abdominal wall, with the inner disc fitting snugly against the stomach lining. Finally, the PEG is secured to the anterior abdominal wall by adjusting the external bumpers that come with the gastrostomy device used [10].

The "from oneself" or push technique according to the Sacks–Vine method was proposed in 1983 by V.A. Sacks and others [13]. Under endoscopic control, gastropexy is performed using a one-step fixator with three fixators. The puncture site is determined in the center of the gastropexy, and a trocar is inserted into the stomach lumen under the direct supervision of an endoscopist. A guidewire is passed through the trocar, which is then used to insert the dilator. After sequential dilation of the future gastrostomy, a feeding tube is inserted into the stomach and the dilator is removed. The balloon is inflated [29].

The introducer insertion technique is a modified push technique using an introducer, proposed in 1984 by T.R. Russell and co-authors, developed on the basis of the Seldinger technique used to insert a subclavian catheter into the central vein [38]. The technique is performed by inserting a gastric tube through a transcutaneous puncture to avoid passing it through the mouth. Long curved needles are used to place two parallel sutures during gastropexy under gastroscopic control.

These sutures secure the front wall of the stomach. A metal trocar designed for PEG is inserted through a percutaneous incision. The membrane is removed and the balloon with the gastric tube is inflated. This method prevents peristomal infections and implantation of tumors in the pharynx and esophagus [9,11,15].

Image-guided technique – PEG is performed under visual control using fluoroscopy in two projections. It was first described in 1981 by R.V. Preshaw [37]. An oral suspension of barium sulfate is administered to the patient on the eve of the procedure to localize the colon. Ultrasound is used to visualize the liver. The loop is inserted through the mouth, and the guidewire is inserted into the stomach under fluoroscopic guidance and removed through the mouth. The mesh catheter is pulled retrograde from the abdominal wall to the mouth, and then the PEG is pulled through the esophagus [9,35]. Similar methods have been described using computed tomography, but these techniques have not found widespread use in practice [6].

Laparoscopically assisted CHG insertion – this procedure requires both endoscopic and laparoscopic techniques, so both an endoscopist and a pediatric surgeon are needed. A 5-millimeter optical tube for the laparoscope is inserted through the navel. The procedure requires both endoscopic and laparoscopic techniques, so both an endoscopist and a pediatric surgeon are needed. A 5-millimeter optical tube for the laparoscope is inserted through the navel. A pneumoperitoneum at a pressure of 8-12 mmHg is recommended. At the same time, gastroscopy and visualization of the stomach lumen are performed. After purging the stomach, the optimal location for the gastrostomy is selected by external finger pressure and direct visualization. Gastropexy is performed using 3 fixators, a needle is inserted into the stomach lumen, through which a guide wire is passed, which is then used to guide the dilator. After sequential expansion of the canal, the GT is inserted, the balloon is inflated, and the tube is fixed to the skin at the appropriate length. The gastrostomy is performed under direct laparoscopic and endoscopic visualization [9,10,44,47].

Researchers continued to work on improving techniques, and in 1984, *M.W. Gauderer and J.L. Ponsky* proposed a device to prevent gastric contents from leaking during the pull method, which was called the "gastric button" [19]. In 1993*, D.R. Ferguson et al.* reported on the use of the "one-step button" device, which is a "gastric button" and is initially installed during PEG [6,16]. A modification of this device is the low-profile gastrostomy tube, which is used in practice.

There are two main types of gastrostomy tubes: standard gastrostomy tubes and low-profile gastrostomy tubes. A standard gastrostomy tube is a long silicone tube.

The distal end of the gastrostomy tube, located in the lumen of the stomach after insertion, has a wide disc-shaped funnel-shaped extension called an internal bumper. When traction is applied, it ensures close contact between the stomach wall and the peritoneum of the anterior abdominal wall. To ensure constant tight contact between the bumper and the outer part of the abdominal wall, a disc-shaped device similar in structure, called an anti-bumper, is mounted on the gastrostomy. The stable position of the gastrostomy is ensured by compression of the tissues in the area where the gastrostomy tube passes through the thickness of the anterior abdominal wall using an anti-bumper, which is fixed with removable plastic clips [3].

Low-profile gastrostomy tubes are individually selected in size depending on the thickness of the anterior abdominal wall. The gastrostomy tube is fixed by carefully selecting its length during installation and inflating the internal balloon, which resembles a Foley catheter device. The outer part of the tube is equipped with a lock, which allows for the airtight connection of standard enteral feeding systems during feeding.

Between feedings, the external opening in the gastrostomy tube is closed [3]. A low-profile gastrostomy has a number of advantages. Due to its small size, the external part of the gastrostomy practically does not protrude above the surface of the body and is invisible under clothing, thereby improving the quality of life for pediatric and adult patients who lead an active lifestyle.

Results

Table 1 lists the publications included in this literature review. The most common methods are Pull and Push. The Pull method was performed in 587 (32.9%) patients, and the Push method in 908 (45.2%). In 441 (21.9%) patients, the PEG method was not specified in the publications.

Table 1.

Publications analyzed in this literature review / Table 1. Publications analyzed in this literature review.

№	Authors, year of publication, reference to literature	Period analyzed	Number of patients	Technique TEG
1	Franco Neto J.A. et al .(2021) [17]	2003-2018	152	Pull – 140 Push - 12
2	Szlagatys-Sidorkiewicz A. et al. (2015) [41]	2000-2009	350	PEG
3	Takalo M. et al. (2024) [43]	2002-2020	217	Push – 138 Pull - 79
4	Gothberg G. et al. (2015) [21]	2005-2012	168	Pull
5	Jacob A., et al. (2015) [29]	2007-2010	128	Button peg - 73 Pull - 55
6	Karaseva O.V. et al. (2016) [1]	2010-2015	45	Push
7	Shamanskaya T.V. et al. (2014) [7]	2012-2014	9	Push
8	Rachkov V.E. et al. (2015) [4]	2014	20	Push
9	Ryzhov E.A. et al. (2014) [5]	2012013	7	Pull
10	Lozovaya V.V. et al. (2024) [2]	2022	13	Pull – 8 Push - 5
11	Özçelik Z. et al (2023) [36]	2013-2020	130	Pull
12	Jean-Bart C. (2022) [30]	2009-2020	679	Push
13	Işık I. et al. (2021) [28]	2014-2019	91	PEG

In Table 2, patients are grouped according to the reasons for gastrostomy placement. We divided the reasons into four groups: neurological dysphagia, mechanical dysphagia, nutritional support, and gastric decompression.

Table 2.

Distribution of patients by reasons for gastrostomy [1,2,4,5,7,17,21,28-30,36,41,43].

№	Causes	Numbers	%
1	Neurological dysphagia	1264	62.9
2	Need for nutritional supplements	664	33.1
3	Mechanical dysphagia	79	3,9
4	Gastric decompression	2	0,1

The group with neurological dysphagia included patients with cerebral palsy, neuromuscular and genetic diseases, central nervous system disorders, and chronic neurological diseases. The group of patients requiring nutritional supplements consisted of patients with cancer, cystic fibrosis, chronic diseases of the gastrointestinal tract, heart, lungs, kidneys, immunodeficiency conditions, metabolic disorders, and palliative patients with various nosologies. The group with mechanical dysphagia included patients with neck lymphangioma, esophageal stricture, stomach and neck tumors, adenobuccal dystrophy, and ENT diseases. Patients with visceral myopathy formed a group with gastric decompression. In Table 3, we have grouped the complications mentioned in the publications under review that are associated with the placement of a pacemaker.

Table 3.

Distribution of complications following CHD implantation [1,2,4,5,7,17,21,28-30,36,41,43].

Types of complications	Absolute quantity	%
Minor complications		
Hypergranulation	479	23,8
Local peristomal infection	220	10,9
Leakage	229	11.4
Premature tube exit	120	5,9
Tube migration	176	8,7
Tube clogging and obstruction	23	1,1
Tube degradation	28	1,2
Pneumoperitoneum	39	1,9
Subcutaneous emphysema	10	0,5
Esophagitis	4	0,2
Ulcer	7	0,4
Others	35	1,7
Serious complications		
Abdominal abscess	4	0,2
Hidden bumper syndrome	9	0,5
Peristomal cellulitis	4	0,2
Gastrointestinal fistula	11	0,5
Intestinal obstruction	10	0,5
Peritonitis	16	0,8
Bleeding associated with endoscopy (bleeding from the upper gastrointestinal tract)	16	0,8
Gastric atony	5	0,2
Esophageal perforation	2	0,1
Small bowel perforation	2	0,1
Gastric perforation	2	0.1
Gastric heterotopia	44	2.2
Pulmonary aspiration, pneumonia	4	0,2
Sepsis	8	0,4

Discussion

This review analyzes endoscopic methods of percutaneous gastrostomy and determines the frequency and types of complications associated with gastrostomy tube placement. Percutaneous endoscopic gastrostomy is considered the method of choice when long-term enteral feeding is necessary in children with malnutrition due to various diseases, even in low-weight and premature infants. In this review, the youngest patient who had a PEG tube placed was 1 month old (body weight 2800 g), and the oldest patient was 17 years and 7 months old.

We divided the reasons for the need for a gastrostomy tube into four groups. The most common reason for PEG placement was neurological dysphagia, with a predominance of patients with cerebral palsy. The second most common reason for PEG placement was nutritional support for patients due to catabolic conditions associated with various pathologies. Cancer patients accounted for 9.3% (188) of all patients included in the second group. Patients with chronic heart, kidney, and lung diseases, cystic fibrosis, and metabolic disorders were also more likely to undergo gastrostomy. The proportion of patients with mechanical dysphagia was 4%; PEG was performed on 2 patients (0.1%) due to gastric decompression.

When analyzing the techniques used to perform PEG, it was found that in 21.9% (441) of patients included in the analysis, the method of surgical intervention was not specified. The traction technique was used in 32.9% (587) of cases (including 73 patients who underwent button PEG), and the pushing technique was used in 45.2% (908) of cases. We intended to evaluate the frequency of complications for each EGS method. However, not all publications covering both methods separately describe complications. Therefore, we were unable to achieve this goal. However, previous studies indicate that each method has its own advantages and disadvantages.

The pull method is relatively simple for the endoscopist to perform. The doctor can directly visualize the stomach and surrounding structures, which reduces the risk of displacement. The number of immediate complications, such as bleeding and perforation, is relatively low. However, the disadvantage is that the pull method is more invasive, as the endoscope must pass through the abdominal wall, creating a risk of infection around it. Patients may experience greater discomfort during the procedure due to tissue manipulation. This method is not suitable for all patients, especially if there are certain anatomical abnormalities or previous surgeries that make access difficult. The Pull method allows large-diameter PEG tubes to be inserted. However, two stages of endoscopy are required to remove the guide wire and insert the PEG tube [6,42].

The push method may cause less trauma to surrounding tissues, which may lead to faster recovery. However, there is a high risk of incorrect tube insertion, which can lead to complications such as aspiration or

perforation. The Push method requires a single endoscope insertion and has a low risk of infection. However, due to the small diameter of PEG tubes, they can easily become clogged. In addition, damage to the fixing balloon can cause displacement of the PEG tube [42].

M. Takalo and co-authors described the advantages of the Russell modification of the Push balloon technique. Thus, the installed gastrostomy slightly rises above the skin surface and has a valve that prevents the release of gastric contents into the external environment, it is much more convenient to care for and does not require specialized medical involvement when replacing it.

Replacement of a gastrostomy tube inserted using the Russell method can even be performed at home, whereas the Pull method requires hospitalization of the child [42]. However, the initial insertion of a low-profile gastrostomy tube is technically more difficult with the Push method and is contraindicated in a number of cases in patients with anatomical features. One of the reasons that may contribute to complications with the Push method is the method of gastropexy. To date, none of the existing methods of fixing the gastrostomy tube allows for the achievement of tightness of the external gastric anastomosis, accompanied by leakage of stomach contents to the outside.

The choice between these two methods often depends on the specific condition of the patient, the qualifications of the endoscopist, and clinical conditions. Proper assessment and consideration of the potential risks and benefits are crucial in determining the most appropriate approach for each individual patient.

Despite the minimally invasive nature of PEG, complications associated with PEG tube placement remain common. In our analysis of 13 publications, there were 1,505 complications, of which 1,370 (91.0%) were minor complications and 135 (9.0%) were serious complications. Hypergranulation (n = 479; 23.8%) was the most common minor complication. In 229 (21.4%) patients, gastric contents leaked through the gastrostomy site. Peristomal infections were reported in 220 (10.9%) patients, gastrostomy tube displacement in 176 (8.3%) patients, and early tube exit in 120 (5.9%) patients. Serious complications developed in 135 (9.0%) patients. As for the distribution of serious complications, 44 (2.2%) patients developed gastric heterotopia during a single-stage Button PEG.

Next in frequency were peritonitis (0.8%) and gastrointestinal bleeding (0.8%). Hidden bumper syndrome, gastrointestinal-skin fistulas, and intestinal obstruction occurred in 0.5% of patients each. In our review, perforation of the esophagus, stomach, and intestines occurred in 2 cases each (0.1%). Fatal outcomes from the procedure were reported in 2 patients (0.1%), with the cause of death related to sepsis following esophageal rupture and the formation of a gastrointestinal fistula [40]. Repeat surgery was performed in 1.2% (24) of patients.

The work of *Balogh et al.,* published in 2018, is one of the largest meta-analyses, which reviewed 18 articles with a total of 4,631 patients who underwent gastrostomy between 1994 and 2017. The incidence of serious complications was 10%, and minor complications were 33%.

However, it should be noted that in 5.8% of cases, image-guided techniques and laparoscopically assisted CHG administration were used, which were not applied in the publications we analyzed. In their meta-analysis, serious complications were mainly represented by cellulitis (1.5%), peritonitis (1.5%), sepsis or surgical wound dehiscence (1.5%), hidden bumper syndrome (1.0%), severe pneumoperitoneum (0.7%), and gastrointestinal fistula (0.45%) [9].

The frequency of complications is related to the duration of patient follow-up. Due to the retrospective nature of the publications included in this analysis, it was not possible to establish the median follow-up time, as it was not reported by all authors. To reduce complications and mortality, ESPGHAN recommends individualizing the indications for PEG and making the decision to insert a PEG by a multidisciplinary team, taking into account all relevant circumstances in children. Adequate planning and preparation before the procedure, follow-up observation of patients, treatment of any complications, and optimal timing for PEG removal are important.

Conclusion

Summarizing the analysis of the literature, it can be stated that percutaneous endoscopic gastrostomy is a practical and safe method of nutritional support for children with various health problems, regardless of the child's weight. Children who have undergone percutaneous endoscopic gastrostomy often experience minor complications. Percutaneous endoscopic gastrostomy has a low incidence of serious complications and mortality.

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THE IMPACT OF ANTIEPILEPTIC DRUGS ON COGNITIVE FUNCTIONS IN EPILEPSY. LITERATURE REVIEW

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Abstract

Background: Epilepsy affects more than 70 million people worldwide. Antiepileptic drugs (AEDs) represent the basis of treatment; however, 30-40% of patients develop drug resistance. In addition, cognitive impairments are frequently observed in the context of polytherapy.

Objective: To analyze the literature on the effects of antiepileptic drugs on cognitive functions assessed using EpiTrack tool in patients with epilepsy.

Materials and methods: A literature search was performed in PubMed, Scopus, and Google Scholar databases. Eligible studies included full-text publications in English and Russian over the past 15 years that investigated the effect of antiepileptic drugs on cognitive functions.

Results: A total of 1,066 records were identified in the PubMed, Scopus, and Google Scholar databases. After screening, 5 full-text articles met the inclusion criteria and were analyzed.

Conclusions: The review highlights that the cognitive impact of AEDs depends on both the quantity and the pharmacological profile of the drugs used.

Keywords: *epilepsy, antiepileptic drugs, cognitive functions, neuropsychological testing, EpiTrack.*

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Резюме

ВЛИЯНИЕ ПРОТИВОЭПИЛЕПТИЧЕСКИХ ПРЕПАРАТОВ НА КОГНИТИВНЫЕ ФУНКЦИИ ПРИ ЭПИЛЕПСИИ. ОБЗОР ЛИТЕРАТУРЫ

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Во всем мире эпилепсией страдают более 70 миллионов человек. Как известно, основой лечения являются противоэпилептические препараты (ПЭП), однако при применении ПЭП у 30-40% пациентов развивается лекарственная устойчивость. И на фоне политерапии часто развиваются когнитивные нарушения.

Цель: анализ литературных источников, в которых изучалось влияние противоэпилептических препаратов на когнитивные функции, оцененные с помощью EpiTrack у пациентов с эпилепсией.

Материалы и методы. Поиск литературных источников проводился в базах данных PubMed, Scopus, Google Scholar. В исследование были включены полнотекстовые публикации на английском и русском языках за последние 15 лет, в которых изучены влияние противоэпилептических препаратов на когнитивные функции.

Результаты. В результате поиска было идентифицировано 1066 источников в базах данных PubMed, Scopus, Google Scholar. После проведения скрининга было отобрано и включено в исследование 5 полнотекстовых статей.

Выводы. Таким образом, анализ литературных источников показал, что влияние антиэпилептических препаратов на когнитивные функции может быть обусловлено количеством применяемых препаратов, видом и механизмом действия препарата.

Ключевые слова: *эпилепсия, противоэпилептические препараты, когнитивные функции, нейропсихологическое тестирование, EpiTrack.*

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Түйіндеме

ЭПИЛЕПСИЯ КЕЗІНДЕГІ КОГНИТИВТІК ФУНКЦИЯЛАРҒА ЭПИЛЕПСИЯҒА ҚАРСЫ ДӘРІЛЕРДІҢ ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Дүниежүзінде 70 миллионнан астам адам эпилепсиямен ауырады. Білетініміздей, емдеудің негізі - эпилепсияға қарсы препараттар (ЭП) болып табылады, алайда ЭП қолданған кезде 30-40% пациенттерде дәріге төзімділік дамиды. Политерапия фонында когнитивті бұзылулар жиі дамиды.

Мақсат. Эпилепсияға қарсы препараттардың эпилепсиямен ауыратын пациенттерде EpiTrack көмегімен бағаланған когнитивті функцияларға әсерін зерттейтін әдебиеттерді талдау.

Материалдар мен әдістер. Әдеби дереккөздерді іздеу PubMed, Scopus, Google Scholar дерекқорларында жүргізілді. Зерттеуге эпилепсияға қарсы препараттардың когнитивті функцияларға әсерін зерттеген соңғы 15 жылдағы ағылшын және орыс тілдеріндегі толық мәтінді жарияланымдар енгізілді.

Нәтижелер. Іздеу нәтижесінде PubMed, Scopus, Google Scholar дерекқорларында 1066 дереккөз анықталды. Скринингтен кейін 5 толық мәтінді мақала іріктеліп, зерттеуге енгізілді.

Қорытынды. Сонымен, әдеби дереккөздерді талдау - эпилепсияға қарсы препараттардың когнитивті функцияларға әсері қолданылатын препараттардың санына, препараттың түрі мен әсер ету механизміне байланысты болуы мүмкін екенін көрсетті.

Түйін сөздер: *эпилепсия, эпилепсияға қарсы препараттар, когнитивті функциялар, нейропсихологиялық тестілеу, EpiTrack.*

Дәйексөз үшін:

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Introduction

Epilepsy is characterized by a persistent predisposition to the occurrence of epileptic seizures [4] and at least two unprovoked seizures with an interval of more than 24 hours [13].

According to the literature, more than 70 million people worldwide suffer from epilepsy [23]. Currently, the treatment of epilepsy includes both drug therapy and surgical treatment. As a rule, the choice of method depends on the type and form of the disease, as well as on the individual characteristics of the organism. Antiepileptic drugs are the basis of treatment, however 30-40% of patients develop drug resistance when treated with antiepileptic drugs (AEDs) [10]. It is known that drug-resistant epilepsy (DRE) is defined as the lack of control over seizures after using two or more adequately selected antiepileptic drugs at sufficient doses and for sufficient duration [5]. Pharmacoresistance is an indication for surgical treatment.

Nevertheless, cognitive impairment is not excluded in both drug-based and surgical treatment. Long-term follow-up of more than 5 years showed that, with complete control of seizures, the risk of verbal memory decline after left-sided resection decreases to 3–17%, whereas with ongoing seizures – 37% on the left side and 20% on the right [7]. However, the nature and severity of memory impairments vary depending on a number of epilepsy-related factors, such as the side of the seizure focus, the duration of the disease, and other specific characteristics.

In the treatment with antiepileptic drugs, regardless of the number of medications prescribed, achieving a favorable profile requires doctors not only to be aware of the potential side effects of antiepileptic drugs, but also to carefully monitor cognitive changes in their patients. Relying solely on patient complaints is often insufficient, as patients may not realize the presence of impairments or cognitive alterations, or may mistakenly attribute their difficulties to epilepsy or normal aging. In addition, patients, like healthcare professionals, may have different perceptions about cognitive functions, which can easily lead to misunderstanding [5,6,9]. In this regard, an adequate neuropsychological assessment is an essential prerequisite for the correct identification of cognitive changes.

Several instruments are available for the assessment of cognitive functions in epilepsy. The Montreal Cognitive Assessment (MoCA) can be considered a simple and reliable test, recommended for screening cognitive impairments in patients with epilepsy in outpatient settings. Research findings on the assessment of cognitive functions in patients with epilepsy using MoCA have shown that their total MOCA scores were significantly lower compared with the control group (23.3, SD 4.5 vs. 27.5, SD 1.9; $p < 0.001$). However, it should be noted that this assessment tool has been validated primarily for cognitive screening in Alzheimer's disease and vascular dementia [21].

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a concise neuropsychological battery validated for the evaluation of patients with dementia and epilepsy. Some researchers have reported that RBANS is useful for assessing cognitive functions in patients with epilepsy and allows for differentiation between patients with temporal lobe epilepsy (TLE) and those without it. In addition, the authors found that the number of antiepileptic drugs (AEDs) is associated with general cognitive functions in adults with epilepsy [17].

Considering that all these tools are widely used, Helmstaedter and Lutz developed in 2005 a screening tool called EpiTrack [16], which is specifically designed for use epilepsy. EpiTrack is a 12-15-minute test for monitoring cognitive side effects. It consists of six subtests (verbal fluency, reaction inhibition, working memory, anticipation, speed, and flexibility) which are aimed at checking attention and executive functions. The maximum score that patients can receive is 49 (after age correction). A total score from 29 to 31 indicates mild impairment, while the threshold for a significant impairment is <28 points. A significant change is defined as a gain of >3 points or a loss of >2 points. [19].

The purpose of this review is to analyze publications that have investigated the effects of antiepileptic drugs on cognitive functions, assessed using EpiTrack, in patients with epilepsy.

Materials and Methods

This systematic review included studies aimed at investigating cognitive functions in patients with epilepsy receiving antiepileptic drugs, evaluated using EpiTrack. Literature searches were conducted in PubMed, Scopus, and Google Scholar databases. The following keywords were applied when searching in English-language databases: 'The EpiTrack Cognitive Assessment' OR/AND 'EPITRACK' OR/AND 'Cognition' OR 'Memory' OR/AND 'Executive function' OR/AND 'Attention' AND 'Pharmacoresistant epilepsy' OR/AND 'Epilepsy' OR/AND 'Seizures' AND 'Medical treatment' OR/AND 'Anti-epileptic drugs'. For the Russian-language search in the Google Scholar, the following keywords were used: 'Epilepsy, antiepileptic drugs, cognitive functions', 'Epilepsy, the effect of drugs on cognitive functions, EpiTrack'.

This review was in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. A comprehensive search strategy was developed in collaboration with a medical specialist.

Exclusion criteria were as follows: conference materials, abstracts, short reports, clinical case description, reviews; studies including participants younger than 16 years; animal studies; publications whose titles referred to other neurological disorders; recurring publications; as well as meta-analyses, systematic or literary reviews. Publications with titles indicating only "assessment of cognitive functions" were selected only after reviewing the abstract.

Subsequently, screening was performed based on the content of the abstracts. In several studies, cognitive functions were assessed using methods other than EpiTrack. These articles were not included in the review, as our analysis focused on data obtained with EpiTrack.

Ethical aspects

Ethical approval was not required for this study, as it involved the analysis of previously published data and did not include any new data collection on humans or animals.

Results

A total of 1,066 publications were identified, of which 28 full-text articles were selected as a result of screening. In addition, 2 publications were identified from the reference list and included in the review.

Following further screening based on abstract review, 18 publications were excluded from the study for the following reasons:

Studies that investigated disorders other than epilepsy -4;

Studies in which the participants were children- 10;

Studies that applied other cognitive function assessment tools (not EpiTrack) -3;

Non-full-text article - 1.

Further, after reviewing the full-text publications, five articles were excluded as they assessed cognitive functions in the context of other types of treatment (non-pharmacological) -5. Thus, the final number of publications after screening was five, all of which focused on investigating cognitive functions in relation to antiepileptic drug use.

As a result, five articles were included in the review. The main drugs studied for their effect on cognitive functions were Topiramate, Lacosamide, Perampanel, Zonisamed, and Lamotrigine. The largest number of study

participants in publications was 834 people, while the smallest number was 70 people (Table 1). In one of the studies, neither the names nor the number of drugs were specified. The analysis of the included publications is presented below depending on the effect of drugs that researchers have identified on cognitive functions: positive effect, adverse effect, or no effect.

Table 1.

Publications included in the review.

Authors, year, country	Research design	Number of patients	The purpose of the study
Niina Lähde et al [12]	A retrospective cross-sectional study	94	The aim of this study was to use EpiTrack to evaluate cognitive functions, particularly attention and executive functions in patients with refractory epilepsy, taking into account therapeutic interventions such as antiepileptic drug (AED) modification and/or neuromodulation therapy.
Carolin Meschede, Juri-Alexander Witt et al [19]	A retrospective cohort study	94	The aim of this study was to compare the long-term cognitive and behavioral side effects of adjunctive antiepileptic therapy with perampanel (PER) and lacosamide (LCM), two third-generation antiepileptic drugs with presumed favorable cognitive profiles.
Dominika Jarcuskova et al [9]	A cross-sectional study	206	The aim of the study was to evaluate the impact of demographic and clinical characteristics of epilepsy, anxiety, depressed mood, sleep, and quality of life on predicting cognitive decline in patients with epilepsy.
Helmstaedter C. et al [8]	A retrospective controlled study	70	In this retrospective controlled study, the effect of adjunctive therapy with lacosamide (LCM) on cognitive function in patients with epilepsy was evaluated and compared with that of topiramate (TPM) and lamotrigine (LTG) under natural outpatient conditions.
Juri-Alexander Witt et al [23]	A retrospective cross-sectional study	834	The study was conducted to evaluate the impact of the overall drug load of antiepileptic pharmacotherapy on cognitive functions.

For the study groups that demonstrated a positive or negative effects of antiepileptic drugs, results with $p < 0.05$ were considered. In contrast, for the groups of studies that did not reveal any effect of drugs on cognitive functions, the results with $p > 0.05$ were also analyzed, since in this context a statistically insignificant p-value reflects 'the absence of drug effects'.

Drugs with a positive effect on cognitive functions

Among the analyzed publications, two publications reported the positive effects of drugs. Assessment of cognitive functions using EpiTrack in the study by Niina Lähde showed that EpiTrack scores were higher in patients treated with two drugs (32 points), excluding Topiramate or Zonisamide, compared with patients treated with 3-4 drugs (28 points) that included Topiramate or Zonisamide.

A second study related to the positive effects of antiepileptic drugs on cognitive function revealed the beneficial effects of Lacosamide in the form of significant improvements in EpiTrack and memory performance. Similarly, Helmstaedter C. et al. confirmed the positive cognitive profile of Lacosamide, noting that its cognitive side-effect profile is comparable to LTG and superior to TPM (Table 2).

Drugs with adverse effects on cognitive functions

In the analyzed publications, two studies similarly reported adverse effects of antiepileptic drugs on cognitive functions. According to *Helmstaedter C. et al.,* Topiramate treatment was associated with impaired executive functions and a significant decline in EpiTrack scores. Another study investigating the impact of more than 20 different drugs on cognitive functions, with the primary aim of evaluating the effect of the overall antiepileptic drug burden. The authors reported that a lower number of medications was associated with better cognitive performance, whereas the addition of each new drug resulted in a significant reduction in EpiTrack scores. However, they also noted that patients treated with Levetiracetam (LEV) and Lamotrigine (LTG) demonstrated better executive function outcomes compared to those who did not receive these two drugs. The data is presented in Table 2.

Drugs with no effect on cognitive functions

As can be seen from Table 2, analysis of the literature revealed that three publications did not establish an association between antiepileptic drugs and cognitive functions. According to Niina Lahde, Clobazam does not affect the average EpiTrack scores. Studies investigating Lacosamide and Perampanel demonstrated that Perampanel does not improve cognitive function. According to other authors, there is no relationship between the amount of drugs administered and cognitive functions

Discussion

Thus, the analysis of literature has demonstrated that the number of drugs administered, their type, and mechanism of action may determine the impact of antiepileptic drugs on cognitive functions. Despite the fact that the use of no more than two drugs is mainly associated with more favorable cognitive effect compared to polytherapy involving 3-4 drugs, this effect largely depends on the type of drug itself. Thus, the use of Topiramate or Zonisamide, as one of the two drugs in the treatment, may exert an adverse effect on cognitive functions. It should also be noted that the mechanism of action of drugs does not necessarily explain whether a drug exerts beneficial or adverse cognitive effects.

Table 2.

The impact of different antiepileptic drugs on cognitive funtions.

Authors	Number of patients	The investigated drugs	Positive effect	Adverse effect	No effect
EpiTrack is a feasible tool for assessing attention and executive functions in patients with refractory epilepsy *Niina Lähde et al.*	94	Topiramate (TPM) Zonisamide (ZNS) Clobazam (CLB) Lacosamide (LCM) Lamotrigine (LTG) Levetiracetam (LEV) Oxcarbazepine (OXC) Valproic Acid (VPA) Pregabalin (PGB) Carbamazepine (CBZ) Clonazepam (CZP)	EpiTrack scores were significantly higher in the group of patients treated with 2 AEDs excluding TPM or ZNS compared with the group with 3-4 AEDS, which included either TPM or ZNS, p=0.023		There were no significant differences in mean EpiTrack scores between patients receiving Clobazam (CLB) and those not treated with it.
Evaluating the longer-term cognitive effects of adjunctive perampanel compared to lacosamide in a naturalistic outpatient setting *Carolin Meschede et al.*	94	Lacosamide (LCM) Perampanel (PER)	A significant improvement in EpiTrack scores (p = 0.009) and memory performance (p = 0.02) was observed in the Lacosamide (LCM) treatment group.		No improvement in EpiTrack scores or memory performance was observed during treatment with Perampanel (PER) p=0.89.
Which clinical and neuropsychological factors are responsible for cognitive impairment in patients with epilepsy? *Dominika Jarc˘us˘kova´et al.*	206	The names of the drugs are not specified.			No association was found between the number or type of drugs and cognitive functions (p=0.19).
The longer-term cognitive effects of adjunctive antiepileptic treatment with lacosamide in comparison with lamotrigine and topiramate in a naturalistic outpatient setting *Helmstaedter C. et al.*	70	Zonisamide (ZNS) Lacosamide (LCM) Topiramate (TPM) Lamotrigine (LTG)	The results of this study demonstrate for the first time that the profile of cognitive side effects of LCM is comparable to that of LTG and surpasses that of TPM.	Subjective cognitive complaints increased in 5 out of 9 patients whose seizures were treated with Topiramate (TPM) p<0.01, with executive functions worsening under TPM treatment (p = 0.001). Patients whose seizures were treated with TPM showed a significant decrease in EpiTrack scores.	
Adverse cognitive effects of antiepileptic pharmacotherapy: each additional drug matters *Juri-Alexander Witt et al.*	834	More than 20 drugs		With each additional drug, a significant decrease in EpiTrack scores was observed. Considering the EpiTrack threshold values, untreated patients and patients receiving two drugs demonstrated mild impairment, whereas patients with three or more concomitant drugs demonstrated severe impairment.	

According to the analysis, it was revealed that among the sodium channel blockers there are drugs that have both beneficial (Lacosamide) and adverse effects (Topiramate, Zonisamide, Lamotrigine), while stimulants of the GABA-ergic system had no effect on cognitive functions.

Regarding the effect of Topiramate on cognitive functions, some experimental studies have revealed that Topiramate does not affect cognitive performance [7], while others, on the contrary, have demonstrated a moderate beneficial effect on cognitive functions, which was further confirmed histologically. Although these studies have been conducted in animal models, the observed patterns may nevertheless indicate a link between specific antiepileptic mechanisms of action and the occurrence of cognitive side effects. [1,22]

Consistent with the findings of the present analysis, Thompson et al. reported that Topiramate administration was associated with a significant cognitive impairment, particularly in tests of verbal fluency and verbal learning ($p<0.001$) [24].

Regarding the effect of Lacosamide on cognitive functions, most studies are consistent with our findings and indicate that it carries a low risk of adverse events in relation to cognitive functions, both in monotherapy and in polytherapy [3,8,14].

It is known that cognitive status in epilepsy is recommended to be assessed as early as possible. However, the quality of the neuropsychological profile is of great importance and can have a significant impact on the subsequent treatment of patients with epilepsy. Effective anticonvulsant medications may be unreasonably reduced or discontinued, and the possibility of surgical intervention may be mistakenly excluded if patterns of widespread cognitive impairment are incorrectly identified [25]. This highlights the crucial role of timely and accurate cognitive assessment in the clinical practice of an epileptologists, not only for diagnosis, but also for selecting the most appropriate treatment strategy.

Taking into account the above, we recommend readers to interpret the conclusions of our analysis with caution, as the following limitations should be acknowledged: a small number of publications included in the analysis; difficulties in summarizing the results of studies carried out at different times, in different cohorts, and using non-identical methodologies; a systematic error in selecting only published works (some relevant work may not be represented in the analyzed databases). Although it was not within the scope of this review, it should be noted that not all analyzed studies specified clear inclusion and exclusion criteria. As is known, poor test performance and the risk of false neuropsychological test results may be associated with such factors as advanced age [15], impaired intelligence and memory [11,25] and the use of liberal thresholds [2,25]. Moreover, the sample sizes in the analyzed publications are relatively small and geographically limited, which restricts the generalizability of the findings to patients from other regions with different demographic or clinical characteristics.

Conclusion.

Despite its limitations, our study has its potential strengths. This review represents one of the few attempts to systematize and analyze publications investigating cognitive functions in the context of different treatment approaches for epilepsy over time, with the application of the EpiTrack tool. Although the analysis of 5 publications can hardly be regarded as a full-scale systematization. it nevertheless provides a general overview in which a certain trend can be observed. It should also be emphasized that there was no bias in defining the study objective; we did not focus solely on a specific type or group of drugs, nor did we seek to demonstrate the advantages of particular drugs. The data obtained may contribute to further refinement of approaches to neuropsychological testing, particularly through using the EpiTrack tool.

It is necessary to develop specific recommendations for reporting results in a standardized and unified format that takes into account sample-specific characteristics. Furthermore, the establishment of clearly developed inclusion and exclusion criteria should be considered essential in order to minimize the risk of false positive and false negative results.

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Author contribution

Conceptualization: Nazira Bekenova (NB) and Balzhan Kassiyeva (BK); methodology: NB, Alisher Aitkaliyev (AA), Guldana Zhumabayeva (GZh); investigation: NB, BK, Akmaral B. Suleimenova (AS), Tamara A. Vochshenkova (TV), Mukhit A. Dossov (MD), (GZh); writing-original draft preparation: NB, BK, AS, GZh; writing-review and editing: NB, BK, AA, TV, GZh. All authors have read and agreed to the published version of the manuscript.

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ASSESSMENT OF THE POPULATION'S HEALTH LITERACY AND THE CULTURE OF NUTRACEUTICAL CONSUMPTION. LITERATURE REVIEW

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Abstract

Background: In the current healthcare context, the level of health literacy and the culture of nutraceutical consumption among the population acquire particular importance. The widespread use of nutraceuticals such as vitamins, minerals, amino acids, and plant-based components contributes to the formation of public perceptions regarding their safety and universality. However, in practice, there is a tendency toward uncontrolled and unjustified use of nutraceuticals without considering individual needs and without prior medical diagnosis. This situation is further complicated by a low level of health literacy, which hampers critical evaluation of health information and increases the risks of self-medication.

Objective: To assess the level of health literacy of the population in the use of nutraceuticals.

Methods: Relevant literature was identified through searches in the PubMed, Scopus, Web of Science, CyberLeninka, and Google Scholar databases. The search covered publications up to January 2025 using the keywords: "health literacy," "nutraceuticals," "population health," and "consumption culture." A total of 263 sources in both English and Russian were found. Eighty publications were selected for analysis.

Results: The article addresses the issue of low health literacy and the uncontrolled consumption of nutraceuticals, particularly among at-risk groups, alongside the high level of adherence to nutraceutical use in European and Asian countries. People with higher education tend to have a greater demand for nutraceuticals compared to those with lower educational levels. A high level of education is also associated with higher health literacy. However, as noted by several researchers, the widespread availability of information and high trust in online sources often lead to the uncontrolled intake of dietary supplements and other nutraceutical products without consulting healthcare professionals. This approach may have potentially negative consequences for public health, including risks of overdose, adverse interactions with medications, and the development of side effects. Thus, a high level of literacy and public awareness does not always correlate with a rational approach to nutraceutical use, which requires additional attention from healthcare systems and regulatory bodies. It is necessary to promote increased interest in healthy lifestyles, disease prevention, and well-being maintenance through the rational consumption of nutraceuticals.

Conclusions: This review emphasizes that the low level of health literacy, particularly concerning the uncontrolled consumption of nutraceuticals, represents a significant risk factor for public health. The findings confirm the need to improve public awareness and promote educational programs, which are considered effective strategies to reduce self-medication, strengthen health, and, in the long term, reduce the burden on healthcare systems and improve quality of life indicators.

Keywords: *health literacy, nutraceuticals, population health, consumption culture.*

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Резюме

ОЦЕНКА УРОВНЯ ГРАМОТНОСТИ НАСЕЛЕНИЯ В ВОПРОСАХ ЗДОРОВЬЯ И КУЛЬТУРА ПОТРЕБЛЕНИЯ НУТРИЦЕВТИКОВ. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. В современных условиях здравоохранения уровень грамотности населения в вопросах здоровья и культуры потребления нутрицевтиков приобретает особую значимость. Широкое распространение нутрицевтиков, таких как витамины, минералы, аминокислоты и растительные компоненты, сопровождается формированием у населения представлений об их безопасности и универсальности. Однако на практике наблюдается тенденция к бесконтрольному и необоснованному применению нутрицевтиков без учёта индивидуальных потребностей и без предварительной медицинской диагностики. Ситуация осложняется низким уровнем медицинской грамотности, что затрудняет критическую оценку информации о здоровье и повышает риски самолечения.

Цель исследования: Оценить уровень грамотности населения в вопросах здоровья в применении нутрицевтиков.

Стратегия поиска: Актуальная литература была найдена посредством поиска в базах данных PubMed, Scopus, Web of Science, CyberLeninka и Google Scholar. Поиск охватывал публикации до января 2025 года с использованием ключевых слов: «*медицинская грамотность, нутрицевтики, здоровье населения, культура потребления.* Всего было найдено 263 источника на английском и русском языках. Для анализа были отобраны 80 публикаций

Результаты: В статье рассматривается проблема низкого уровня грамотности в вопросах здоровья и неконтролируемого потребления нутрицевтиков с одной стороны, особенно в группах риска и высокий уровень приверженности к потреблению нутрицевтиков в европейских и азиатских странах. Люди, имеющие высшее образование более склонны к повышенному спросу на нутрицевтики, по сравнению с населением, с более низким уровнем образования. Высокий уровень образования также связан с высоким уровнем грамотности населения. Также, широкая доступность информации и высокая доверчивость к источникам из интернета, нередко, приводят к бесконтрольному приёму биологически активных добавок (БАД) и других нутрицевтических средств без консультации специалистов. Такой подход может иметь потенциально негативные последствия для здоровья населения, включая риск передозировок, неблагоприятных взаимодействий с лекарственными препаратами и развитие побочных эффектов. Таким образом, высокий уровень грамотности и самосознания общества не всегда коррелирует с рациональным подходом к применению нутрицевтиков, что требует дополнительного внимания со стороны системы здравоохранения и регуляторных органов. Необходимо способствовать росту интереса к вопросам здорового образа жизни, профилактики заболеваний и поддержания благополучия с помощью рационального потребления нутрицевтиков.

Выводы: Настоящий обзор подчеркивает, что низкий уровень грамотности населения в вопросах здоровья, в частности в отношении неконтролируемого потребления нутрицевтиков, представляет собой значимый фактор риска для общественного здоровья. Полученные данные подтверждают необходимость повышения информированности населения и развития просветительских программ, что рассматривается как эффективное направление для снижения случаев самолечения, укрепления здоровья и, в долгосрочной перспективе, снижения нагрузки на систему здравоохранения и улучшению показателей качества жизни.

Ключевые слова: *медицинская грамотность, нутрицевтики, здоровье населения, культура потребления.*

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Түйіндеме

ДЕНСАУЛЫҚ МӘСЕЛЕЛЕРІНДЕГІ ХАЛЫҚТЫҢ САУАТТЫЛЫҚ ДЕҢГЕЙІН БАҒАЛАУ ЖӘНЕ НУТРАЦЕВТИКТЕРДІ ТҰТЫНУ МӘДЕНИЕТІ. ӘДЕБИЕТТІК ШОЛУ.

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Өзектілігі. Қазіргі денсаулық сақтау жағдайында халықтың денсаулық мәселелері және нутрицевтиктерді тұтыну мәдениеті бойынша сауаттылық деңгейі ерекше маңызға ие болуда. Витаминдер, минералдар, аминқышқылдары және өсімдік компоненттері сияқты нутрицевтиктердің кең таралуы бұл заттардың қауіпсіздігі мен әмбебаптығы туралы халық арасында белгілі бір көзқарастың қалыптасуына алып келді. Алайда, тәжірибеде нутрицевтиктерді алдын ала медициналық диагностикасыз және жеке қажеттіліктерді ескерместен бақылаусыз әрі негізсіз қолдану үрдісі байқалады. Бұл жағдай медициналық сауаттылық деңгейінің төмендігімен күрделене түседі, ол денсаулық туралы ақпаратты сыни тұрғыдан бағалауды қиындатып, өз бетінше емделу қаупін арттырады.

Зерттеу мақсаты: Халықтың денсаулық мәселелері жөніндегі сауаттылық деңгейін және нутрицевтиктерді қолданудағы көзқарасын бағалау.

Әдістер: Ғылыми әдебиеттер PubMed, Scopus, Web of Science, CyberLeninka және Google Scholar дерекқорларынан ізделді. Іздеу 2025 жылдың қаңтарына дейінгі жарияланымдарды қамтыды және келесі кілт сөздер қолданылды: «медициналық сауаттылық, нутрицевтиктер, халық денсаулығы, тұтыну мәдениеті». Іздеу нәтижесінде ағылшын және орыс тілдеріндегі 263 дереккөз табылды, олардың ішінен 80 мақала талдау үшін іріктелді.

Нәтижелер: Мақалада денсаулық сауаттылығының төмен деңгейі мен нутрицевтикаларды бақылаусыз қолдану мәселесі қарастырылады, әсіресе тәуекел тобына жататын адамдар арасында. Сонымен қатар, Еуропа және Азия елдерінде нутрицевтикаларды қолдануға жоғары деңгейдегі ұстаным байқалады. Жоғары білім деңгейі бар адамдар нутрицевтикаларға төмен білім деңгейіндегі халыққа қарағанда көбірек сұраныс көрсетеді. Жоғары білім деңгейі денсаулық сауаттылығының жоғары болуымен де байланысты. Дегенмен, бірнеше зерттеушілердің атап өткеніндей, ақпараттың кең қолжетімділігі және интернеттегі дереккөздерге жоғары сенім нутрицевтикалар мен биологиялық белсенді қоспаларды мамандарға кеңес алмай бақылаусыз қабылдауға әкеледі. Мұндай тәсіл денсаулыққа теріс әсер етуі мүмкін, оның ішінде дозаны асырып алу қаупі, дәрі-дәрмектермен жағымсыз өзара әрекеттесулер және жанама әсерлердің даму қаупі бар. Сондықтан, жоғары сауаттылық пен қоғамдық сананың болуы әрдайым нутрицевтикаларды рационалды пайдалануымен сәйкес келмейді, бұл денсаулық сақтау жүйесі мен реттеуші органдардың қосымша назарын талап етеді. Денсаулығы жақсы өмір салтына, аурулардың алдын алуға және әл-ауқатты сақтауға деген қызығушылықты арттыру үшін нутрицевтикаларды ұтымды пайдалану қажет.

Қорытындылар: Бұл шолу халықтың денсаулық мәселелері бойынша, әсіресе нутрицевтиктерді бақылаусыз қолдануға қатысты сауаттылық деңгейінің төмендігі қоғамдық денсаулық үшін маңызды қауіп факторы екенін көрсетеді. Алынған деректер халықтың хабардарлығын арттыру және ағартушылық бағдарламаларды дамыту қажеттілігін дәлелдейді, бұл өздігінен емделу жағдайларын азайтуға, денсаулықты нығайтуға және ұзақ мерзімді перспективада денсаулық сақтау жүйесіне түсетін жүктемені төмендетуге, сондай-ақ өмір сүру сапасын арттыруға ықпал етеді.

Түйінді сөздер: *медициналық сауаттылық, нутрицевтиктер, халық денсаулығы, тұтыну мәдениеті.*

Дәйексөз үшін:

Ордабаева И.Н., Шалтынов А.Т., Абенова М.Б., Қайратова А.К., Байбусинова А.Ж. Халықтың денсаулық мәселелері жөніндегі сауаттылық деңгейін бағалау және нутрицевтиктерді тұтыну мәдениеті. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 251-260. *doi 10.34689/SH.2025.27.5.029.*

Introduction

In the current healthcare landscape, the level of health literacy and the culture of nutraceutical consumption among the population have acquired particular importance. Nutraceuticals—biologically active compounds such as vitamins, minerals, amino acids, and herbal ingredients—are now widely used both in everyday life and in clinical settings. However, the widespread perception of their safety and universality has led to a growing trend of uncontrolled and unjustified consumption. This issue is especially pronounced in the context of insufficient public awareness about health matters, lack of preliminary medical diagnostics, and the absence of professional consultations. A low level of health literacy hinders the ability to critically evaluate health-related information and increases the risks of self-medication, which can have adverse health consequences, particularly for individuals with chronic conditions or those taking pharmacological treatments.

Literacy is a fundamental human right and a crucial aspect that influences a person's ability to express themselves and actively participate in society. It forms the basis for continuous learning, personal growth, and involvement in social and economic processes. A high level of literacy not only improves the quality of life but also contributes to solving global challenges such as stabilizing demographic trends and maintaining sustainable development. Moreover, literacy is a vital condition for ensuring peace, social justice, and strengthening democratic institutions [5]. Health literacy, as a specific subset of general literacy, encompasses the intellectual and interpersonal abilities that empower individuals to seek out, comprehend, and utilize health information effectively. These skills contribute to both the desire and the capacity to make informed decisions regarding one's well-being and to actively engage in behaviors that support and sustain good health [5].

Objective of the study: To assess the level of health literacy of the population in the use of nutraceuticals

Search strategy and Source Selection Algorithm:

A comprehensive search of relevant scientific literature was conducted using the databases in PubMed, Scopus, Web of Science, CyberLeninka, and Google Scholar databases publications available up to January 2025 using the keywords *"health literacy," "nutraceuticals," "population health,"* and *"consumption culture"*.Both English- and Russian-language sources were considered in order to ensure a broad and inclusive analysis ofthe topic;

The initial search yielded a total of 263 publications. Following a thorough review, 80 publications were selected for detailed analysis based on their relevance, scientific quality, and alignment with the research objective;

The inclusion criteria focused on studies that addressed the relationship between health literacy and the use of nutraceuticals, as well as the sociocultural and behavioral aspects influencing patterns of consumption. Studies lacking empirical data or those focusing solely on the biochemical properties of nutraceuticals without reference to health literacy or consumer behavior were excluded from the final selection.

Results and Discussion:

Global and local aspects of public health literacy.

Inadequate health literacy presents a significant global challenge, impacting both developing and developed nations.

Many studies have found a clear link between insufficient medical literacy and poor health. People who do not have comprehensive knowledge about healthcare often face numerous problems. These include difficulties understanding medical information, interpreting doctors' instructions, and following prescribed treatment plans. Consequently, they face difficulties in promptly detecting diseases, effectively implementing preventive measures, and making informed decisions about their well-being. This leads to a higher prevalence of chronic diseases, a delay in seeking medical help, and an increased likelihood of hospitalization due to preventable complications. The consequences are not limited to the quality of life of individuals, which leads to a significant increase in health care costs and puts a strain on the health care system as a whole [3, 21, 34].

Despite this, some population groups continue to demonstrate significantly lower levels of health literacy compared to the general population in Europe. These include individuals with low levels of social protection, limited education, chronic illnesses, those living in socioeconomically disadvantaged conditions, as well as older adults [68, 64, 77]. Such groups often face numerous overlapping barriers, including financial instability, limited access to healthcare services, language difficulties, and a lack of access to reliable health information — all of which reduce their ability to understand and engage with health-related content.

Numerous studies have shown how health literacy varies across different segments of the population. For example, research has analyzed differences across age groups [39, 71], revealing that younger people generally possess higher levels of functional health literacy compared to older adults. Similarly, studies on various social groups [35, 37] indicate that individuals with lower income or educational attainment often face greater difficulties in understanding medical instructions or navigating healthcare systems. Gender differences in health literacy have also been examined, with some studies showing that women may be more proactive in seeking health information, while others reveal different patterns depending on cultural or regional contexts [32, 39, 79].

The situation of older adults is particularly critical, as their health literacy levels are consistently among the lowest [1, 44]. This can be explained by several age-related factors, including cognitive decline, memory impairments, reduced vision or hearing, and limited digital literacy — especially as more and more health information becomes available primarily through online platforms.

In 2013, the Asian Health Literacy Association (based in Taiwan) spearheaded a multinational research project examining health literacy levels across Asia. This initiative, known as the Health Literacy Survey - Asia, encompassed six participating nations: Indonesia, Kazakhstan, Malaysia, Myanmar, Taiwan, and Vietnam. Kazakhstan's involvement marked its contribution to this comprehensive assessment of health literacy within the region [23, 24].

The issue of health literacy in the Republic of Kazakhstan was first studied by *A.M. Aringazina.* The level of literacy is determined by factors such as age, marital status, religious affiliation, education level, average income, and social status of the respondents [2, 9, 47].

A study assessing health literacy in five cities of Kazakhstan revealed the following key findings: two-thirds of respondents confidently use health information, while one-third of respondents experienced difficulties in obtaining, interpreting, evaluating, and applying this information, indicating health literacy issues among this group [10].

According to researchers, the health literacy level of the adult population in Kazakhstan in 2022 was 45.8%, which is a low indicator. The authors attribute this to differences in the population size living in urban or rural areas and the level of socio-economic development [4].

Health literacy and modern nutraceutical consumption.

According to health information, people with low literacy levels are generally more susceptible to persuasion [73], and there is a correlation between health literacy and socio-economic status [12]. *Kerdsri K. and Lerkiatbundit S.* found that people with high literacy levels positively correlate their ability to self-protect with healthy food products [43]. Over the past few decades, the consumption of nutraceuticals, dietary supplements, and biological supplements has significantly increased across all age groups, including the younger generation. Awareness of supplements refers to a person's ability to rationally analyze advertising messages to use them correctly, including their intentions for future use [49]. Television and social media actively promote the use of nutraceuticals and various supplements to improve health, balanced nutrition, physical performance, and longevity, but the importance of preliminary deficiency control is often omitted [13, 56, 63].

Maintaining a stable balance of essential nutrients is crucial for human health and proper bodily function. While dietary supplements and nutraceuticals can aid in achieving this balance, their unregulated and widespread use over the past decade raises concerns [28, 53]. This trend indicates a lack of health literacy among the population, as many individuals consume supplements without adequate knowledge about appropriate dosage, potential interactions with other substances, or intended benefits. Such uninformed consumption not only diminishes the potential health advantages but can also pose risks to overall well-being. Therefore, there is an urgent need to prioritize education and awareness campaigns that promote responsible supplement use and empower individuals to make informed decisions regarding their health.

In the context of modern healthcare management, nutraceuticals are becoming increasingly important as an effective tool for maintaining health and preventing chronic diseases. This group of biologically active substances, including vitamins, minerals, probiotics, amino acids, fatty acids, and phytonutrients, affects key physiological processes such as modulating the immune system, reducing inflammatory reactions, and optimizing metabolism. The increasing attention to preventive medicine and personalized treatment approaches is contributing to the integration of nutraceuticals into comprehensive wellness programs. It should be noted that the use of nutraceuticals requires a competent and responsible approach to maximize benefits and minimize potential risks [38, 60, 66].

The term "nutraceuticals" was introduced in 1989 by Stephen DeFelice. They are substances that provide both nutrition and therapeutic effects to the body. Sources of nutraceuticals range from natural products to synthetic forms [27].

Research confirms that nutraceuticals play an important role in preventing diseases such as cardiovascular diseases. Omega-3 fatty acids found in fish and supplements reduce triglyceride levels and the risk of heart attacks. Clinical studies show the effectiveness of nutraceuticals in combination with pharmacotherapy. For example, the combination of curcumin and standard anti-inflammatory drugs demonstrates a synergistic effect in treating chronic inflammation. Although nutraceuticals have significant potential, their uncontrolled use may be associated with risks. Excess vitamins (e.g., vitamin A) can lead to toxic effects. Therefore, standardization and control of their use are important [15, 29, 33, 57, 62].

The global healthcare landscape is witnessing a significant rise in the utilization of nutraceuticals, encompassing substances like vitamins, antioxidants, fiber, trace elements, and amino acids [14, 48, 51, 61]. This trend is driven by an increasing emphasis on preventative health measures, healthy aging practices, and performance enhancement across diverse demographics. Nutraceuticals and vitamins are readily available for purchase in pharmacies [19], facilitating widespread accessibility. However, this ease of access can sometimes lead to unregulated consumption patterns [75, 76]. The perception of these products as "natural" and safe, coupled with aggressive marketing strategies, often encourages self-medication practices without seeking professional medical advice.

The role of nutraceuticals in the prevention of diseases and the problems of their uncontrolled use"

Statistics compiled by the National Center for Health Statistics reveal that a substantial portion, approximately 33.2%, of American youth utilize nutraceuticals. These products encompass a wide range, predominantly comprising multivitamins, dietary supplements such as iron, calcium, and vitamin D, as well as alternative medicines including bodybuilding supplements, melatonin, and omega-3 fatty acids. Notably, the prevalence of nutraceutical consumption varies significantly across different countries. For instance, while only 16% of children in Slovenia use these products, the figure rises to 45% for adolescents in Finland [70]. The utilization of nutraceuticals among younger demographics is notable in several countries. Research indicates substantial usage rates: 21% in Germany, 68% in Serbia, and 43% in Malaysia [69]. Furthermore, studies conducted in Japan reveal that 20.4% of individuals under the age of 18 have consumed supplements either currently or within the preceding year [20]. According to the study, it was found that the consumption of nutraceuticals among Australian youth is quite common: approximately 20.1% of teenagers and 23.5% of children regularly use these products [54]. The varying rates of dietary supplement usage across diverse populations highlight the significant impact of cultural and environmental influences. For instance, the observed differences in iron and folic acid supplement consumption among women in developing nations suggest that cultural

norms and beliefs may be key drivers in shaping these health practices [6, 42].

Prior research indicated a lack of awareness among individuals regarding the potential adverse effects linked to herbal remedies and dietary supplements. Consumption of these products often stemmed from informal recommendations within social circles, bypassing consultation with qualified healthcare providers [54, 58].

Health literacy refers to an individual's ability to successfully access, understand, critically evaluate, and apply health information. This proficiency enables them to make knowledgeable decisions concerning their overall health, encompassing aspects such as disease prevention, health enhancement, and effective healthcare utilization. Consequently, robust health literacy is a significant determinant of enhanced quality of life throughout one's lifetime [17, 18].

A study conducted in Thailand demonstrated that individuals' ability to effectively access, understand, and critically evaluate health information is closely linked to their rational use of dietary supplements [59]. Participants who possessed higher skills in navigating health-related content were more likely to make informed decisions about supplement intake, avoiding unnecessary or excessive consumption. Conversely, limited health literacy in this area often led to misuse or overreliance on dietary supplements without proper guidance.

Individuals possessing robust health literacy skills demonstrate a greater propensity for making well-informed decisions concerning dietary supplement consumption. Their ability to locate, comprehend, and critically evaluate health information enables them to utilize supplements responsibly and minimize the risk of unnecessary or excessive intake. Conversely, those with limited health literacy are more susceptible to inappropriate use or overreliance on supplements, frequently without seeking guidance from healthcare providers or contemplating potential adverse effects. This highlights the paramount importance of adequate health literacy in ensuring the safe and efficacious utilization of dietary supplements [59].

A 2017 survey of Thai individuals aged 15 and above revealed a significant prevalence of the belief that dietary supplements are essential for health. Among the 512 participants, 70% expressed this sentiment. Notably, individuals with greater financial resources and those who engaged in healthier lifestyles were more inclined to consume nutraceuticals. However, this group tended to overlook the importance of seeking medical advice regarding supplement use. The belief in the necessity of dietary supplements was most pronounced among respondents aged 21-30 (74%), followed closely by those aged 31-40 (72%). Furthermore, a correlation was observed between educational attainment and this belief, with a higher percentage of individuals holding bachelor's degrees or higher subscribing to the view that supplements are necessary. [22, 45]. Furthermore, the study found a positive correlation between healthy lifestyle choices and nutraceutical consumption. Students who abstained from smoking, engaged in regular physical activity, and actively monitored their health exhibited a higher propensity to incorporate nutraceuticals into their diets. Other sources also emphasize that students and medical professionals, particularly those studying healthcare and other population groups [7, 20], are more likely to consume nutraceuticals compared to students of other specialties and fields [65]. All of the above highlights that a high level of health literacy increases the likelihood of uncontrolled nutraceutical consumption. In developed countries, micronutrient deficiencies in the diet are becoming rarer, and most nutraceutical consumers actually receive excessive amounts of vitamins and minerals [26, 30, 75]. This may also be related to insufficient diagnosis of primary micronutrient levels in the body and the preventive prescription of nutraceuticals by modern doctors [16].

Some studies suggest the role of nutraceuticals in preventing or progressing chronic and non-communicable diseases [40, 72], while others have found no positive link between supplement intake and the progression of chronic diseases. The term "nutraceuticals" is widely used to denote the use and effectiveness of various plant products, "nutrient elements"—herbs, vitamins, proteins, minerals, fats, fibers, and amino acids. Nutraceuticals are purported to enhance physical well-being and offer substantial health advantages. Their claimed benefits include mitigating the risk of both acute and chronic illnesses, improving overall fitness levels, and potentially slowing down the aging process, thereby extending lifespan [25, 55].

The perceived health benefits associated with nutraceuticals may be partially attributable to the placebo effect, wherein individuals experience improvements due to their belief in the product's efficacy. Many nutraceuticals enter the market without undergoing thorough scientific scrutiny, gaining consumer trust through aggressive marketing strategies and anecdotal testimonials. This premature acceptance can lead to inappropriate usage, as consumers may rely on these products without a complete understanding of their potential benefits or risks. The lack of comprehensive scientific evidence and well-designed clinical trials underscores the need for further research to establish the safety and effectiveness of nutraceuticals [19].

While certain nutraceutical products demonstrate favorable safety records, a considerable number have been documented to engage in unfavorable interactions with conventionally prescribed medications [8, 41, 67, 78]. Their potential benefits are publicly promoted, but their possible harmful effects are less obvious, and their therapeutic efficacy is not fully established [11, 27]. Sometimes they can alter the effectiveness of medications and lead to side effects or dangerous conditions. This issue requires healthcare professionals to counsel on their use [80]. Over-the-counter supplements can increase health risks if consumed beyond recommended amounts [31, 74].

Unfortunately, as researchers have noted, the widespread practice of using nutraceuticals without a proper prescription and in the absence of thorough scientific research often leads to unjustifiably high financial costs for the general population [50, 52]. This trend is exacerbated by the easy accessibility of dietary supplements, aggressive marketing strategies, and a lack of adequate public awareness regarding their appropriate use. While dietary supplements may appear beneficial and are often perceived as a means to enhance health or prevent disease, their use is generally not recommended except in specific medical circumstances where a clear clinical need has been

established. For example, pregnant and breastfeeding women may require supplementation with essential nutrients such as folate, iodine, or iron to meet the increased physiological demands during these periods. However, even in such cases, it is crucial to consult a qualified healthcare professional to assess individual nutritional status and determine the appropriate dosages and forms of supplementation. The use of dietary supplements should be carefully reserved for instances of documented nutritional deficiencies, such as iron-deficiency anemia, folic acid deficiency, or iodine deficiency, and must always be undertaken under the guidance and supervision of medical practitioners to avoid potential adverse effects or interactions with other medications [46]. This cautious and evidence-based approach is essential to maximize the benefits of supplementation while minimizing risks and unnecessary expenditures.

Conclusions

Thus, increasing the level of public health literacy and conscious consumption of nutraceuticals is a key direction for strengthening public health and reducing the risks associated with the uncontrolled use of nutraceuticals. Despite the growing interest in nutraceuticals, supplements and their potential role in the prevention of chronic diseases, the lack of scientific evidence, lack of proper monitoring and awareness lead to health risks and significant financial costs among the population. It is especially important to pay attention to vulnerable groups, including children, the elderly and socially vulnerable segments of the population, for whom the level of health literacy remains low. An integrated approach, including education, expert advice and regulatory measures, will ensure the rational and safe use of nutraceuticals. Improving public literacy and awareness of health issues and rational consumption of nutraceuticals is one of the priorities of public health in the near future.

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STEATOTIC LIVER DISEASE: THE IMPACT OF TEA AND COFFEE CONSUMPTION. LITERATURE REVIEW

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Abstract

Background. Globally, nonalcoholic fatty liver disease (NAFLD) affects more than one quarter of the adult population. It is characterized by excessive hepatic fat accumulation, associated with insulin resistance and defined as the histological presence of steatosis in >5% hepatocytes.

Objective. The purpose of this review is to study the influence of tea and coffee consumption on liver function in NAFLD.

Search Strategy. The following databases were used: Google Scholar, PubMed, and Scopus. We included articles written in English. The search keywords in PubMed are liver, coffee/tea, NAFLD. We included articles in the review published between 2017 and 2025, mostly at evidence levels A and B.

Research Results. According to numerous studies, regular coffee drinkers are far less likely to develop NAFLD, and those who have already been diagnosed with NAFLD are much less likely to develop liver fibrosis. Coffee drinkers who consume ≥3 cups/day of coffee are significantly associated with a reduced risk of liver-related hospitalizations. Moderate coffee consumption (three to five cups per day) is acceptable as part of a healthy diet.

Studies show that various types of tea protect hepatocytes from lipid toxicity by effectively improving the imbalanced lipid metabolism in the serum and liver tissue. The studies were conducted primarily in mice and showed some benefits related to liver function.

Conclusion. Moderate coffee consumption (3 cups per day) is recommended for patients with NAFLD to prevent the development of liver fibrosis. More research needs to be conducted to evaluate the effects of tea on people soon.

Keywords. *liver, coffee/tea, nonalcoholic fatty liver disease, Liver steatosis/fibrosis*

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Резюме

СТЕАТОТИЧЕСКАЯ БОЛЕЗНЬ ПЕЧЕНИ: ВЛИЯНИЕ ПОТРЕБЛЕНИЯ ЧАЯ И КОФЕ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Во всем мире неалкогольная жировая болезнь печени (НАЖБП) поражает более четверти взрослого населения. Она характеризуется избыточным накоплением жира в печени, связанным с инсулинорезистентностью и определяемым как гистологическое наличие стеатоза более чем в 5% гепатоцитов.

Целью данного обзора является изучение влияния потребления чая и кофе на функции печени при НАЖБП.

Стратегия поиска. При поиске статей на английском языке использовались следующие базы данных: Google Scholar, PubMed и Scopus. Ключевые слова для поиска в PubMed: печень кофе/чай, НАЖБП. В обзор мы включили статьи, опубликованные с 2017 по 2025 год, в основном с уровнем доказательности A,B.

Результаты исследований. Согласно многочисленным исследованиям, у потребителей, регулярно употребляющих кофе, гораздо меньше шансов заболеть НАЖБП, а у тех, кому уже поставили диагноз НАЖБП, гораздо меньше шансов заболеть фиброзом печени. У потребителей кофе, которые употребляют ≥3 чашек кофе в день, значительно снижен риск госпитализаций, связанных с заболеваниями печени. Умеренное потребление кофе (от трех до пяти чашек в день) приемлемо как часть здоровой диеты.

Исследования показывают, что различные виды чая защищают гепатоциты от липидной токсичности, эффективно улучшая несбалансированный липидный обмен веществ в сыворотке и тканях печени. Исследования проводились в основном на мышах и показали некоторые преимущества, связанные с функциями печени.

Заключение. Пациентам с НАЖБП рекомендуется умеренное потребление кофе (3 чашки в день) для предотвращения развития фиброза печени. Для оценки влияния чая на функцию печени необходимо проводить исследования среди людей в ближайшем будущем.

Ключевые слова. *печень, кофе/чай, неалкогольная жировая болезнь печени, стеатоз/фиброз печени.*

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Түйіндеме

БАУЫРДЫҢ СТЕАТОЗДЫҚ АУРУЫ: ШАЙ МЕН КОФЕ ТҰТЫНУДЫҢ ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Бүкіл әлемде алкогольды емес майлы бауыр ауруы (АЕМБА) ересек тұрғындардың төрттен бірінен астамына әсер етеді. Ол инсулинге төзімділікпен байланысты бауыр майының шамадан тыс жиналуымен сипатталады және гепатоциттердің >5%-да стеатоздың гистологиялық болуы ретінде анықталады.

Мақсаты. Бұл шолудың мақсаты шай мен кофені тұтынудың АЕМБА бауыр функциясына әсерін зерттеу.

Іздеу стратегиясы. Біз ағылшын тіліндегі жазылған мақалаларды іздеген кезде келесі дерекқорларды қолдандық: Google Scholar, PubMed және Scopus. PubMed-те іздеу кілт сөздері - бауыр, кофе/шай, АЕМБА. Біз 2017 жылдан 2025 жылға дейінгі жарияланған мақалаларды шолуға қостық, көбінесе А, В дәлелдер деңгейінде.

Зерттеу нәтижелері. Көптеген зерттеулерге сәйкес, тұрақты кофе ішетіндердің АЕМБА-ын дамыту ықтималдығы әлдеқайда төмен, ал АЕМБА диагнозы қойылған адамдарда бауыр фиброзының даму ықтималдығы әлдеқайда аз. Күніне ≥3 шыныаяқ кофе тұтынатын кофе ішетін адамдар бауырға байланысты ауруханаға жатқызу қаупінің төмендеуімен айтарлықтай байланысты. Кофенің қалыпты тұтынуы (тәулігіне үш-бес кесе) дұрыс тамақтану диетаның бөлігі ретінде қабылданады.

Көптеген зерттеулер көрсеткендей, шайдың әртүрлі түрлері сарысу мен бауыр тініндегі теңгерімсіз липидтер алмасуын тиімді жақсарту арқылы гепатоциттерді липидтердің уыттылығынан қорғайды. Зерттеулер негізінен тышқандар арасында жүргізілді және бауыр функциясына қатысты кейбір артықшылықтарды көрсетті.

Қорытынды. Бауыр фиброзының дамуын болдырмау үшін АЕМБА бар науқастарға кофені қалыпты тұтыну (тәулігіне 3 кесе) ұсынылады. Жақын болашақта шайдың адамдарға әсерін бағалау үшін зерттеулер жүргізу қажет.

Түйінді сөздер. *бауыр, кофе/шай, алкогольды емес майлы бауыр ауруы, бауыр стеатозы/фиброз.*

Дәйексөз үшін:

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Introduction

Annually, 2 million people die from liver disease, with 1 million due to complications of cirrhosis [1] caused mostly by excessive alcohol consumption. However, cirrhosis could induced by the absence of excessive alcohol consumption in case of nonalcoholic fatty liver disease (NAFLD) [37].

Globally, NAFLD affects more than one quarter of the adult population [52]. It is characterized by excessive hepatic fat accumulation, associated with insulin resistance and defined as the histological presence of steatosis in >5% hepatocytes [17].

The annual incidence of NAFLD is approximately two new cases/100 patients per year [47]. This hazard rises mostly due to the obesity and diabetes epidemics, which lead to a heavy clinical and economic burden on society [70]. The global prevalence of NAFLD is approximately 25%, ranging from 13% in Africa to 42% in Southeast Asia [20]. Asia is a growing epicentre for industrialisation, and changing lifestyles and diet that have contributed to the obesity and NAFLD epidemic in Asia [28]. NAFLD severity correlated with obesity, but interestingly, non-obese persons can also have NAFLD, particularly in certain Asian countries [50]. The incidence of NAFLD was higher in males vs. females (P<0.0001) in Asia [58]. Women exhibit a reduced susceptibility to NAFLD compared to men, at least until menopause, after which the prevalence of NAFLD becomes comparable across the sexes, indicating the protective influence of estrogens [4].

Patients with NAFLD face an elevated risk of all-cause and liver-related mortality, with this risk escalating exponentially as the fibrosis stage progresses from stage 0 to stage 4 [7].

In the US, the prevalence of NAFLD was about 30% among the population aged ≥15 years in 2015 [11]. Annual direct medical costs for NAFLD are estimated at $101 billion in the United States €35 billion in Europe [25].

It has been demonstrated that coffee consumption improves liver health, including hepatitis B and C, NAFLD, and alcoholic liver disease [5] slowing the progression of fibrosis. Moreover, coffee consumption could be a protective factor against NAFLD and liver fibrosis [23]. Tea intake is causally associated with a decreased risk of NAFLD [32].

Objective. The purpose of this review is to study the influence of tea and coffee consumption on liver function in NAFLD.

Search Strategy. The following databases were used: Google Scholar, PubMed, and Scopus. We included articles written in English. The search keywords in PubMed are liver, coffee/tea, and NAFLD/ MAFLD.

Inclusion criteria. We included articles in the review published between 2017 and 2025, mostly at evidence levels A and B. We evaluated the effects of coffee and tea consumption on the progression of NAFLD/MAFLD. We paid attention to the following issues with the PICOS model: number of patients, cups per day, many comparisons, and effects on liver functions.

Exclusion criteria. We excluded articles published before 2016. In addition, we excluded expert opinion in the form of short communications, promotional articles.

Research Study.

Redefining NAFLD to MAFLD. NAFLD is a major public health crisis [49] of the 21st century [41] and one of the main reasons for liver transplantation [3]. It is currently estimated that 25% of people worldwide suffer from NAFLD [66] up to one billion people worldwide [34].

NAFLD refers to a clinicopathological syndrome characterized by hepatic steatosis [41] via triglyceride accumulation in hepatocytes [29], with a condition of fatty infiltration in the liver [27] in the absence of excessive alcohol consumption [40]. NAFLD is generally associated with an unhealthy lifestyle, which may progress to fibrosis and cirrhosis [45]. Optimizing lifestyle through a rational diet, exercise, and a combination of drugs that effectively regulate glucose and lipid metabolism is a proven intervention for NAFLD treatment [48]. The Mediterranean diet is a good choice for NAFLD treatment because it offers numerous health benefits, including weight loss, reduced total cholesterol, antioxidant, and anti-inflammatory effects [46]. Moreover, Genetic and lifestyle factors play an important role in the pathogenesis of NAFLD [8]. That is why public health initiatives that support nutrition and exercise, raise awareness, and improve diagnosis can help manage the growth in future disease burden.

To understand the global burden of NAFLD, it is important to consider a global health problem requiring the attention of the World Health Organization (WHO) to address this growing health problem across the globe [67].

Since its first description as the "unnamed disease" in 1980 [42], the term “non-alcoholic” was first used to describe the liver histology associated with excess liver fat in the absence of significant alcohol consumption [16]. In 1986, Schaffner first introduced the term NAFLD [33]. After 3 decades in 2019, NAFLD redefined to MAFLD. It was the resolution of a group of experts who offered redefining NAFLD to an alternative terminology, metabolic dysfunction-associated fatty liver disease (MAFLD) [10]. MAFLD suggested as a more suitable term, since it more accurately represents the disease's pathogenetic basis and facilitates a more thorough and consistent patient management strategy [13]. The term also highlights the complex and diverse characteristics of this disease and prevents overgeneralization as fatty liver disease in the absence of excess alcohol intake [2]. The etiology of MAFLD is multifactorial, involving the following factors: lifestyles, dietary factors, individual inheritance, and so on [60].

To acknowledge the role of dysmetabolism in liver disease in at-risk individuals who may also display hepatic comorbidities like viral hepatitis or behaviors like moderate alcohol intake, a new nomenclature must be adopted promptly. Additionally, they stress that a generic word will actively recognize disease heterogeneity, such as among people who may be obese or thin [34]. Substantial momentum will be necessary to adopt the suggested transition from NAFLD to MAFLD completely, and there are valid concerns that redefining and renaming the illness may confuse patients and professionals alike [59].

NAFLD is a complex metabolic disorder strongly associated with obesity, diabetes, dyslipidemia, and cardiovascular disease [38]. Moreover, NAFLD is associated with aging, too [14]. The high prevalence of NAFLD is linked to overnutrition and intake of highly processed foods [9].

The diagnostic criteria for metabolic dysfunction are straightforward and include the presence of Type 2 diabetes mellitus, overweight or obesity, or clinical markers of metabolic dysfunction such as increased waist circumference or abnormal glycemia or lipid profiles [44].

Scientists predict a slight increase in NAFLD cases (0-30%) between 2016 and 2030. China will see the largest increase in NAFLD due to urbanization, while Japan will experience the lowest growth due to population decline. However, both conditions are becoming increasingly prevalent as the epidemics of obesity and diabetes continue to increase [7]. It is important to manage blood glucose and lipids in obesity in NAFLD prevention due to the mediation effects of type 2 diabetes and dyslipidemia in the association between BMI and NAFLD [68].

Coffee and tea consumption in NAFLD

Coffee and tea are the two most commonly consumed beverages globally [56]. Caffeine, one of the world's most widely consumed pharmacologically active ingredients, is the main component of coffee and tea [55]. Nevertheless, coffee generally divided into regular coffee and decaffeinated coffee [63]. Approximately 80% of people worldwide use caffeine because it is a socially acceptable drug and a widely accessible psychostimulant [15]. Over 100 compounds have been identified in coffee extracts, many of several compounds have hepatoprotective health benefits [51].

Unfortunately, no recommendations were given for coffee consumption by the associations EASL-EASD–EASO, APASL. ESPEN just mentioned that coffee is more likely to benefit health than harm [53]. *Patress Ann Persons* reviewed that regular coffee consumption has a favorable effect on NAFLD [43]. Newer evidence supports the role of coffee as a therapeutic agent in metabolic liver disease, especially in lower aminotransferase levels, slower fibrosis progression, and less frequent decompensation of cirrhosis [6].

Many diseases like Kidney Stones [69], type 2 diabetes [39], and stroke [57] have been associated with coffee and tea consumption. On the other hand, the positive effects of coffee and tea on liver functions have been well-documented over the past three decades [3].

Results of the National Health and Nutrition Examination Survey (1999-2014) showed that moderate caffeine intake is associated with a lower risk of all-cause mortality in a large study of U.S. adults, especially among those who are overweight. It means that overweight individuals have benefited from moderate caffeine intake. [30]. However, the use of ‘cups per day’ as a form of measurement, as cup size can vary significantly, and this will have a notable impact on the exact amount of coffee that is consumed [54]. Compared to non-coffee drinkers, frequent coffee drinking, particularly 2–3 cups per day, was linked to a lower risk of hepatocellular carcinoma (and chronic liver disease mortality, and the benefits were higher for those who drank ≥4 cups per day [35], the risk was halved with consumption of 5 cups per day [24] A meta-analysis of 11 epidemiological studies confirmed that regular coffee consumption is significantly associated with a reduced risk of NAFLD [18].

In Table 1, we demonstrate some results of studies about the positive effects of coffee consumption, demonstrating the PICO model.

In 2016, there were 5.53 million tonnes of tea consumed worldwide, with a 4.5% annual increase from 2007 to 2016. Tea consumption is significantly lower in

high-income countries, often one-fifth that of low- and middle-income countries [8].

Historically, tea has been claimed to have various health benefits and is used for medical purposes like cancer prevention [22], reduction of the risk of dementia [21], and preventive effects against influenza infection [61].

In Table 2, we show some research results about the effects of tea consumption mostly among mice.

Table 1.

Effects of coffee consumption on liver function.

Research	PICOS	Effects
Coffee consumption is associated with lower liver stiffness: a nationally representative study [12]	P - 4,510 participants/ ≥20 years' old I – Coffee C- Coffee, decaffeinated coffee, tea O – decreasing liver stiffness S- Cross-sectional study	Subjects who drank more than three cups of coffee had significantly lower liver stiffness measurements (LSM). In contrast, there was no significant relationship between LSM and either decaffeinated coffee or tea. In this logistic regression analysis, only >3 cups of coffee remained significantly associated with LSM (OR 0.5, 95%CI 0.2–0.9, p=0.03).
Exploring the impact of coffee consumption on liver health: A comprehensive bibliometric analysis [29]	S – Review using bibliometric analysis	The research primarily revolves around the preventive effects of coffee on various liver diseases and its hepatoprotective properties, including HBV and HCV infections, ALD, NAFLD, cirrhosis, liver failure, and HCC.
Coffee consumption and liver-related hospitalizations and deaths in the ARIC study [19]	P- 14,208 participants aged 45–64 years I - Coffee consumption (cups/day) C- coffee drinkers ≥3 cups/day of coffee / never-drinkers O- liver-related hospitalization S - Prospective analysis	Consuming ≥3, cups/day of coffee was significantly associated with a reduced risk of liver-related hospitalizations compared with never-drinkers (hazard ratio: 0.79, 95% CI: 0.63–0.99). Coffee consumers may be at lower risk for liver-related hospitalizations. A healthy diet can include moderate amounts of coffee (3–5 cups daily).

Table 2.

Effects of different types of tea on liver functions.

Name of tea	Effects on liver functions	
	Studies showed mostly positive effects among mice	Registered a limited number of publications related to studies among people in PubMed
Bowl Tea (Tuocha)	Raw Bowl Tea polyphenols effectively improved the imbalanced lipid metabolism in the serum and liver tissue; furthermore, it reduced the mice's hepatic inflammatory response in NAFLD [31]	No publications
Kombucha Tea	Through the regulation of lipid metabolism, Kombucha Tea protects hepatocytes from lipid toxicity. Additionally, it reduces inflammation and fibrosis, which leads to liver repair in mice with NAFLD [26]. This probiotic drink has a beneficial effect in reducing the metabolic alterations associated with diet-induced obesity in mice [36].	No publications
Three Flower Tea	Three Flower Tea could prevent and treat NAFLD by reducing lipid levels, enhancing insulin sensitivity, decreasing inflammation, and lowering oxidative stress in mice [65].	No publications
Green tea	Green tea combined with exercise can relieve hepatic steatosis and obesity complications in mice fed a high-fat diet by reducing inflammation, lipid production, and improving glucose transport and metabolism [62]. CGT could make the abnormal metabolic state return to normal by intervening in different metabolic pathways to partially reverse the lipid metabolism disorder, and reduce the risk of atherosclerosis and non-alcoholic fatty liver caused by high-fat diet feeding, which may be ascribed to the anti-HLP, anti-oxidant and anti-inflammatory effects of its ingredients [71].	
Citrus maxima and tea	The anatomical and pathological results showed that CMT relieved fatty liver in mice and reduced excessive lipid deposition and inflammatory infiltration. Active ingredients of CMT might be beneficial in NAFLD therapy [64].	No publications

Conclusion. Moderate coffee consumption (3 cups per day) is recommended for patients with NAFLD to prevent the development of liver fibrosis. More research needs to be conducted to evaluate the effects of tea on people soon. Clinical protocol on MAFLD is in the process of development in Kazakhstan.

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LOW KLOTHO LEVELS AND HIGH PLATELET REACTIVITY AS PREDICTORS OF ADVERSE OUTCOMES IN MYOCARDIAL INFARCTION: A CASE-BASED INSIGHT. CLINICAL CASE

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Abstract

We describe a case of ST-elevation myocardial infarction in a 74-year-old patient with peripheral artery disease. Despite dual antiplatelet therapy with high-dose clopidogrel, stent thrombosis and recurrent infarction occurred, requiring escalation to ticagrelor. Additionally, a low level of Klotho protein was detected, associated with increased risk of complications. This case highlights the importance of platelet function testing and emerging biomarkers for individualized therapy.

Keywords: *Klotho protein, ST-segment elevation myocardial infarction, renal dysfunction, aggregometry, residual platelet reactivity*

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Резюме

НИЗКИЙ УРОВЕНЬ KLOTHO И ВЫСОКАЯ РЕАКТИВНОСТЬ ТРОМБОЦИТОВ КАК ПРЕДИКТОРЫ НЕБЛАГОПРИЯТНЫХ ИСХОДОВ ПРИ ИНФАРКТЕ МИОКАРДА: АНАЛИЗ НА ОСНОВЕ КОНКРЕТНОГО СЛУЧАЯ

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Описан случай инфаркта миокарда с подъёмом ST у 74-летнего пациента с поражением периферических артерий. На фоне резистентности к клопидогрелю развился тромбоз стента и повторный инфаркт, что потребовало эскалации терапии до тикагрелора. Дополнительно выявлен низкий уровень белка Klotho, ассоциированный с высоким риском осложнений. Случай подчёркивает значимость тестирования функции тромбоцитов и поиска новых биомаркеров для индивидуализации терапии.

Ключевые слова: *белок Klotho, инфаркт миокарда с подъемом сегмента ST, почечная дисфункция, агрегометрия, остаточная реактивность тромбоцитов.*

Для цитирования:

Жунуспекова А.С., Аккалиев М.Н., Аширов Б.А, Мансурова Д.А., Токбулатова М.О., Капакова М.А., Токтарова Ж.Ж., Нургалиева Д.Т. Низкий уровень klotho и высокая реактивность тромбоцитов как предикторы неблагоприятных исходов при инфаркте миокарда: анализ на основе конкретного случая. Клинический случай // Наука и Здравоохранение. 2025. Vol.27 (5), С.267-273. *doi 10.34689/SH.2025.27.5.031*

Түйіндеме

KLOTHO АҚУЫЗЫНЫҢ ТӨМЕН ДЕҢГЕЙІ МЕН ТРОМБОЦИТТЕРДІҢ ЖОҒАРЫ РЕАКТИВТІЛІГІ МИОКАРД ИНФАРКТІСІНДЕ ҚОЛАЙСЫЗ НӘТИЖЕЛЕРДІҢ ПРЕДИКТОРЛАРЫ РЕТІНДЕ: НАҚТЫ ЖАҒДАЙҒА НЕГІЗДЕЛГЕН ТАЛДАУ

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74 жастағы перифериялық артерия ауруы бар науқаста ST сегментінің көтерілуімен миокард инфарктісі жағдайы сипатталған. Жоғары дозадағы клопидогрелмен қос антитромбоцитарлық терапияға қарамастан, стент тромбозы және қайталама инфаркт дамыды, бұл тикагрелорға эскалацияны қажет етті. Сонымен қатар, асқыну қаупінің жоғарылауымен байланысты төмен Klotho ақуызының деңгейі анықталды. Бұл жағдай тромбоциттердің функциясын тестілеудің және жаңа биомаркерлерді қолданудың терапияны жекелендіру үшін маңыздылығын көрсетеді.

Түйінді сөздер: *Klotho ақуызы, ST сегментінің жоғарылауымен жүретін миокард инфарктісі, бүйрек қызметінің бұзылысы, агрегометрия, тромбоциттердің қалдық реактивтілігі.*

Дәйексөз үшін:

Для цитирования:

Жунуспекова А.С., Аккалиев М.Н., Аширов Б.А, Мансурова Д.А., Токбулатова М.О., Капакова М.А., Токтарова Ж.Ж., Нургалиева Д.Т. Klotho ақуызының төмен деңгейі мен тромбоциттердің жоғары реактивтілігі миокард инфарктісінде қолайсыз нәтижелердің предикторлары ретінде: нақты жағдайға негізделген талдау. Клиникалық жағдай // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 267-273. *doi 10.34689/SH.2025.27.5.031*

Introduction:

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor remains the cornerstone of treatment in patients with acute coronary syndrome (ACS), particularly those undergoing percutaneous coronary intervention (PCI). However, a significant proportion of patients experience high on-treatment platelet reactivity (HTPR), which is associated with an increased risk of stent thrombosis and adverse cardiovascular events [1,2].

Clopidogrel, the most widely used P2Y12 inhibitor, exhibits substantial interindividual variability in its antiplatelet effect, influenced by factors such as genetic polymorphisms, drug interactions, and comorbidities [3]. In patients with peripheral artery disease (PAD), who often have diffuse atherosclerosis and heightened thrombotic risk, optimal platelet inhibition is critical for improving outcomes [4].

Recent studies have highlighted the potential role of morphogenetic protein Klotho as a biomarker of vascular aging, atherosclerosis, and cardiovascular risk. Low serum

Klotho levels have been linked to increased vascular calcification, endothelial dysfunction, and poor prognosis in patients with coronary artery disease [5,6].

This case report presents a patient with ST-elevation myocardial infarction (STEMI) and PAD who developed stent thrombosis despite intensified clopidogrel therapy. We discuss the utility of platelet function testing in guiding antiplatelet therapy, the role of genetic resistance, and the prognostic significance of Klotho levels in such high-risk patients.

Clinical case:

Patient: B., male, 74 years old. Medical Record No.: 13002

On October 8, 2024, the patient was urgently transported by the Emergency Medical Services (EMS) team to the Emergency Cardiology Department of the City Hospital with a diagnosis of: Coronary Artery Disease (CAD). Acute Coronary Syndrome (ACS) with ST-segment elevation (STEMI).

Complaints:

Pressing chest pain radiating to the lower jaw and left arm, pain duration >20 minutes, unrelieved by nitroglycerin, general weakness, shortness of breath.

Medical History: Atherosclerosis, Leriche syndrome, Bifurcation aorto-femoral bypass (2008), Left femoral-popliteal bypass (2008), Right lumbar sympathectomy (2009), Arterial hypertension (20 years), Obesity (BMI 30.1 kg/m²)

Pre-hospital Emergency Care (by EMS): Morphine 1.0 ml + 0.9% NaCl 10.0 ml, Isoket (isosorbide dinitrate) — 2 sprays sublingually, Aspirin 325 mg (chewed), Clopidogrel 300 mg orally.

Physical Examination on Admission: General condition: serious. Conscious and responsive. Hypersthenic body type. Pale skin and mucous membranes. Auscultation: harsh breathing sounds, diminished in lower lung fields. Respiratory rate: 18 breaths/min.Percussion: heart borders shifted to the left. Auscultation: muffled heart sounds, no murmurs, regular rhythm. Heart rate: 110 bpm, blood pressure: 180/100 mmHg, Moist tongue, not coated. Abdomen: normal shape, non-tender. Normal bowel and bladder function. No peripheral edema.

Electrocardiogram (ECG): Sinus tachycardia (HR 111 bpm). Left ventricular hypertrophy (LVH). Transmural myocardial infarction of the anterior, anteroseptal, and lateral walls of the left ventricle (Figure 1).

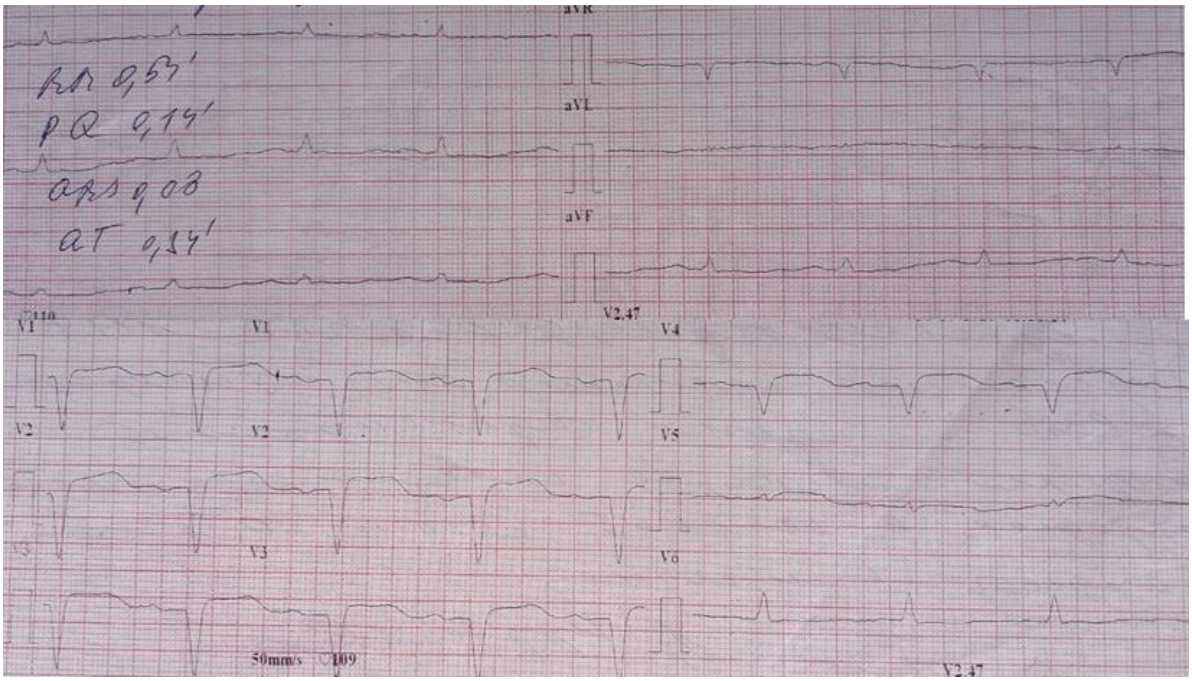

Figure 1. ECG on admission.

Laboratory Findings:

Complete Blood Count (CBC): Hemoglobin: 113 g/L, RBC: 4.1 x 10^9 /L, WBC: 8.2 x 10^9 /L, Platelets: 342 x 10^9 /L. Biochemistry: Total protein: 75 g/L, LDL: 3.86 mmol/L, HDL: 1.42 mmol/L, ALT: 13 U/L, AST: 23 U/L, CK-MB: 4 U/L, Total CK: 76 U/L, Total cholesterol: 7.0 mmol/L, Triglycerides: 2.32 mmol/L, Blood glucose: 4.8 mmol/L, Creatinine: 106 µmol/L, CRP: 4.0 mg/L, eGFR (CKD-EPI): 49 ml/min/1.73 m², Troponin I: 0.10 ng/ml, Klotho protein level: 42.9 ng/ml.

The patient was urgently transferred to the endovascular radiology laboratory for coronary angiography. Findings on Coronary Angiography: Left-dominant coronary circulation. Left Main Coronary Artery (LMCA): Smooth contours, patent. Left Anterior Descending artery (LAD): 70% stenosis in the proximal segment. Left Circumflex artery (LCx): Smooth contours, patent. Right Coronary Artery (RCA): Occlusion at the origin; distal segments are filled via intersystem collateral circulation (Figure 2).

Simultaneously, transluminal coronary angioplasty was performed with stent implantation in the proximal segment of the left anterior descending (LAD) artery. A drug-eluting stent measuring 3.5 x 24.0 mm was implanted. The result after (Figure 3).

After the endovascular intervention, a follow-up ECG was performed: Sinus rhythm with a heart rate of 70 bpm. Horizontal position of the electrical axis (EAX). Mild R-wave progression in leads V1–V3. Following revascularization, standard therapy was initiated, including dual antiplatelet therapy (DAPT) with aspirin in combination with clopidogrel at a maintenance dose of 75 mg/day.

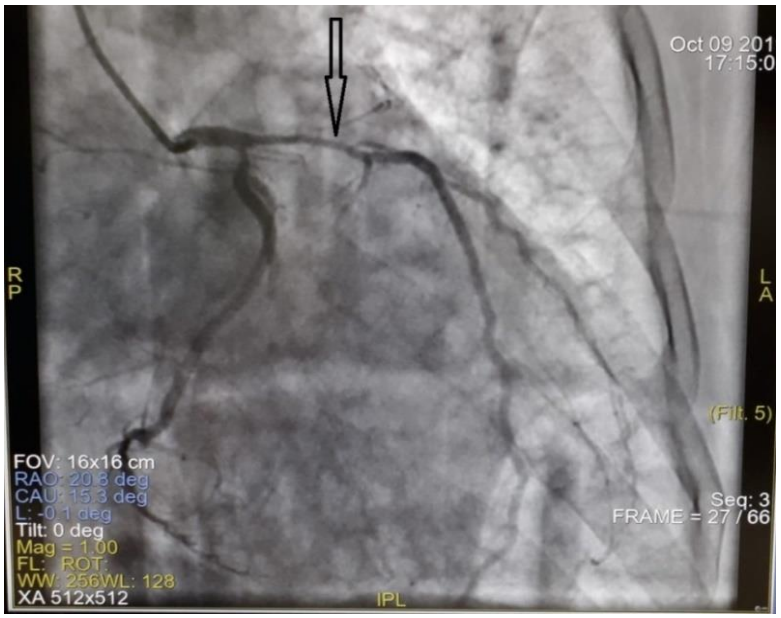

Figure 2. Coronary angiogram of the LAD basin before stenting.

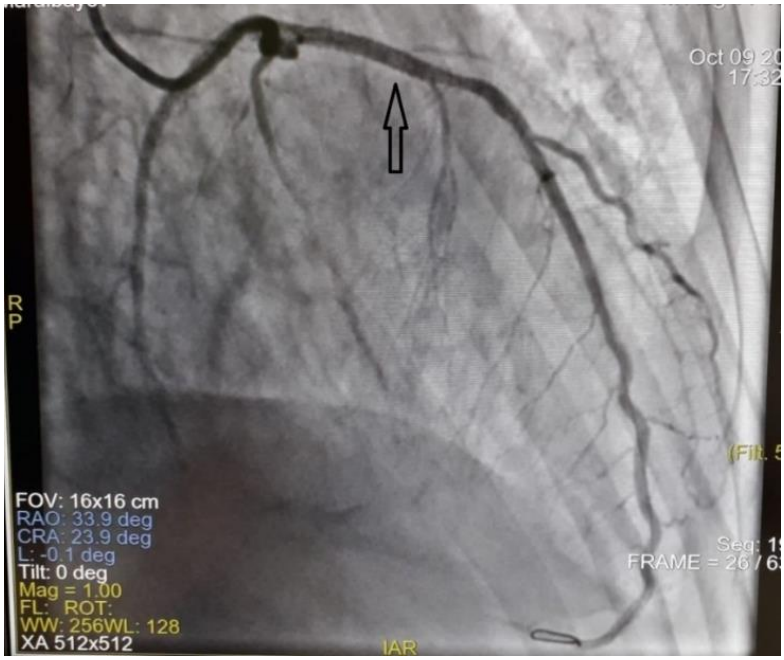

Figure 3. Coronary angiogram of the LAD territory after stenting.

On the morning of the following day, platelet aggregation activity was assessed. The VerifyNow P2Y12 Reaction Test (PRT) under dual antiplatelet therapy showed 82.5% inhibition and an area under the curve (AUC) of 75.1% (Figure 4). Given the high aggregation values, indicating inadequate platelet inhibition, the clopidogrel dose was increased to 150 mg/day to prevent stent thrombosis.

After 24 hours of hospitalization, the patient's condition showed negative dynamics, with new complaints of dizziness, speech disturbance, visual impairment, and nausea.

An emergency consultation with a neurologist was conducted, and cranial computed tomography (CT) was recommended. CT findings: CT signs of acute ischemic stroke in the left occipital lobe and cerebellum. Chronic cerebral microangiopathy. Mild external and internal non-occlusive hydrocephalus.

The patient was re-evaluated by a neurologist, and the following diagnosis was established: Acute Cerebrovascular Accident (CVA), ischemic stroke in the vertebrobasilar circulation, involving the left occipital lobe and cerebellar region (*atherothrombotic type*). Vestibuloatactic syndrome. Cerebral atherosclerosis. Arterial hypertension, grade III, risk category IV. Recommendations were provided.

On the eighth day of hospitalization, the patient's condition suddenly deteriorated. He began experiencing anginal chest pain, general weakness, and sweating. ECG findings: Sinus tachycardia with a heart rate of 115 bpm. Increased ST-segment elevation in leads V1–V4 (Figure 5).

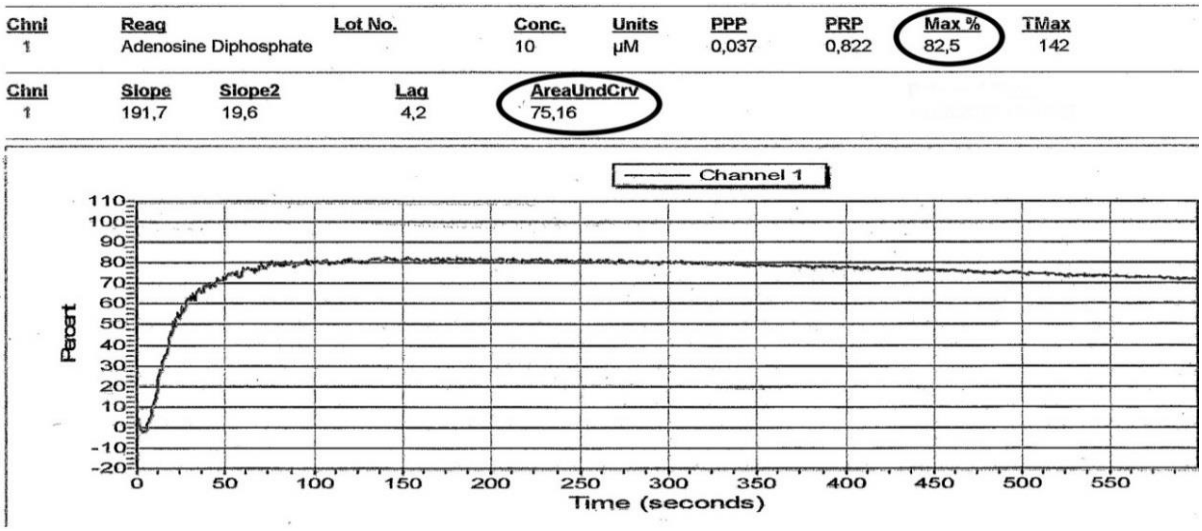

Figure 4. Aggregatogram.

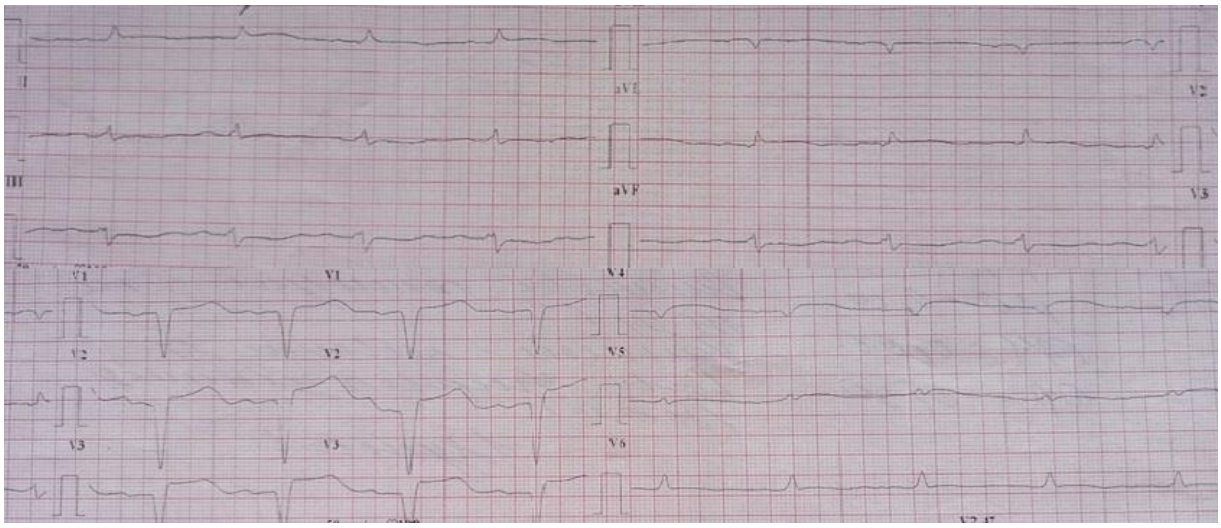

Figure 5. ECG in case of repeated angina.

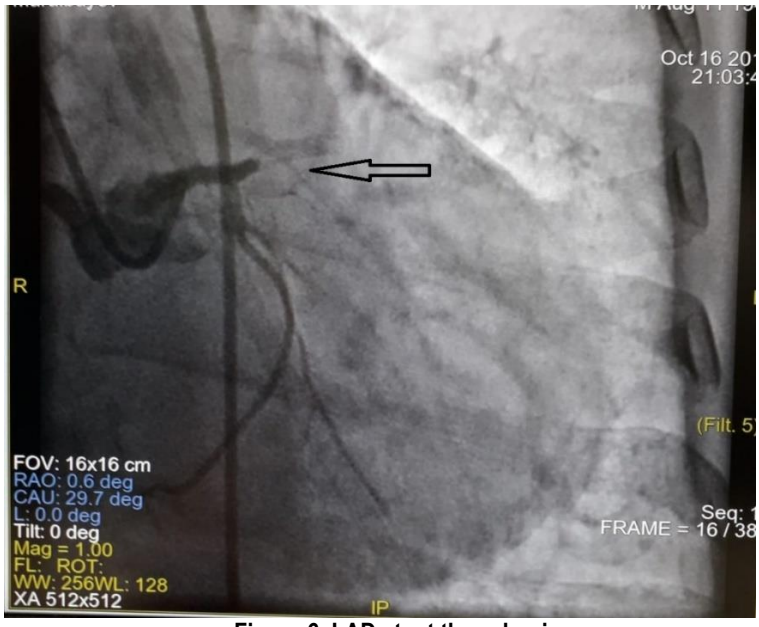

Figure 6. LAD stent thrombosis.

Laboratory findings: Troponin level increased to 4.67 ng/mL. Blood was simultaneously drawn to assess platelet reactivity (PRT).

Due to emergency indications, the patient was taken for repeat percutaneous coronary intervention (PCI). Coronary angiography (CAG) findings: Left main coronary artery (LMCA): patent. Left anterior descending artery (LAD): stent thrombosis in the proximal segment; distal flow not visualized. Left circumflex artery (LCx): 50% stenosis at the ostium (Figure 6). Procedure performed: repeat stenting of the LAD with a drug-eluting stent measuring 3.5 × 18.0 mm.

Platelet aggregation testing revealed high on-treatment platelet reactivity (HTPR).

Under the doubled dose of clopidogrel, the P2Y12 Reaction Test (PRT) showed:82.5% platelet reactivity. Area under the curve (AUC): 75.1% (Figure 7).

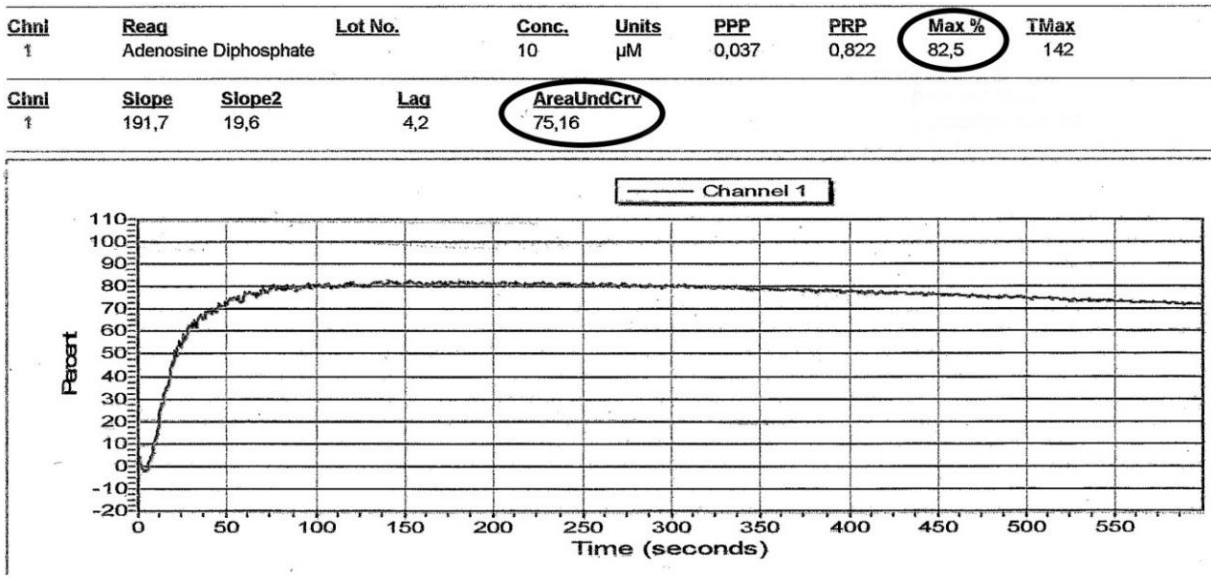

Figure 7. Aggregatogram. ORT against the background of a double dose of clopidogrel 150 mg.

The patient's results were comparable to the reference values of platelet aggregation in healthy volunteers not taking antiplatelet agents (82.1% vs. reference interval 76.8–97.2%, and AUC 75.1% vs. reference interval 68.8–90.4%). The presence of high on-treatment platelet reactivity (HTPR) despite antiplatelet therapy indicates the ineffectiveness of the current antiplatelet agent.

As a result, antiplatelet therapy was escalated, and the patient was switched to ticagrelor 90 mg twice daily. Follow-up platelet function testing was performed 3 days later, showing: Platelet reactivity of 51.1%, AUC:31.6% (Figure 8).

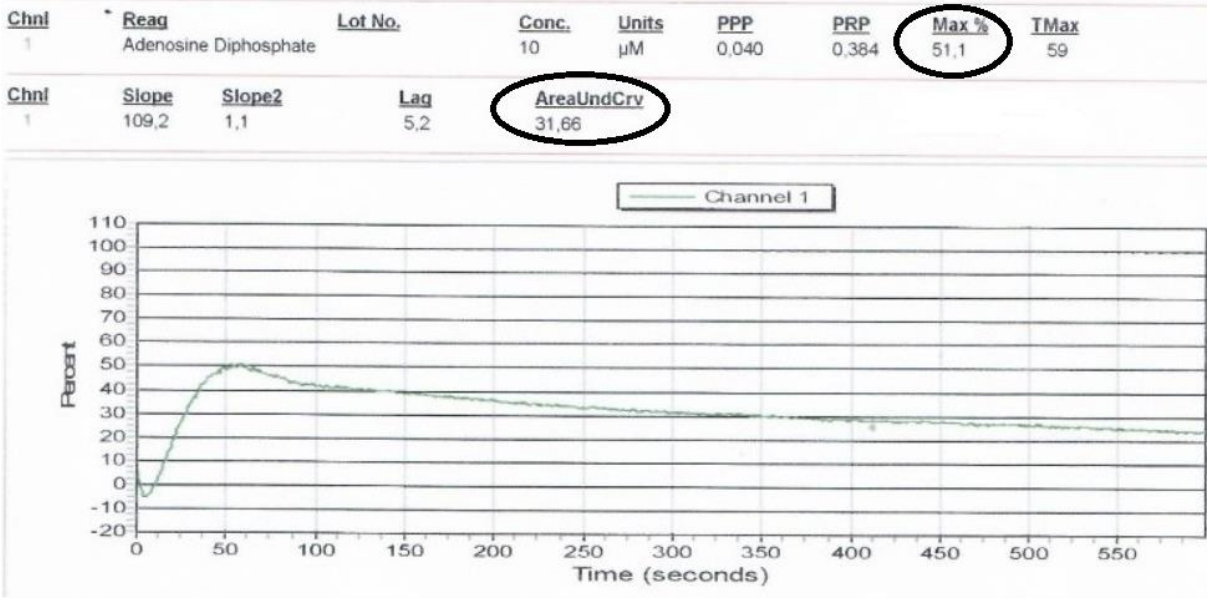

Figure 8. Aggregatogram. Platelet reactivity after escalation therapy.

Thus, in our patient with coronary artery disease involving not only the coronary vessels but also the lower limb arteries, and with clinical presentation of STEMI, stent implantation in the LAD while on a double dose of clopidogrel was complicated by the development of a recurrent type IVb myocardial infarction due to stent thrombosis.

Following antiplatelet therapy escalation, platelet reactivity significantly decreased, indicating the effectiveness of the new therapy.

The low level of the morphogenetic protein Klotho is consistent with findings from other authors, who have demonstrated that reduced Klotho levels are directly associated with the severity of atherosclerosis and calcification of the heart and vessels.

Discussion

This clinical case highlights several crucial considerations in the management of high-risk patients with ST-elevation myocardial infarction (STEMI) and concomitant peripheral artery disease (PAD), particularly regarding personalized antiplatelet therapy and emerging biomarkers such as Klotho.

The patient underwent primary percutaneous coronary intervention (PCI) with stent implantation in the left anterior descending artery (LAD). Despite receiving a double maintenance dose of clopidogrel (150 mg/day), he experienced subacute stent thrombosis and recurrent type IVb myocardial infarction. High on-treatment platelet reactivity (HTPR) was confirmed by platelet function testing, a finding that has been repeatedly associated with increased risk of stent thrombosis and adverse cardiovascular outcomes [7,8].

HTPR in this context likely reflects clopidogrel resistance, which may be mediated by genetic polymorphisms in the CYP2C19 gene, particularly the *CYP2C19* *2/*2 and *2/*3 loss-of-function alleles [9]. Although genotyping was not performed in this case, the platelet function assay (VerifyNow) showed clear evidence of pharmacological ineffectiveness, justifying the escalation of antiplatelet therapy. Switching to ticagrelor, a direct-acting reversible P2Y12 inhibitor, significantly reduced platelet reactivity and area under the curve (AUC), confirming its efficacy in overcoming clopidogrel resistance [10].

The patient's low level of circulating Klotho protein is also of particular interest. Klotho is an anti-aging and vasculoprotective protein involved in regulation of endothelial function, calcium-phosphate metabolism, and inhibition of vascular calcification. Low Klotho levels have been shown to correlate with increased arterial stiffness, atherosclerotic plaque burden, and adverse cardiovascular outcomes in both the general and chronic kidney disease populations [11,12]. In a study by Semba et al., lower serum Klotho levels were associated with higher risk of cardiovascular events and mortality in older adults [13]. These findings support the hypothesis that Klotho may serve not only as a marker of vascular aging, but also as a predictive biomarker in acute coronary syndromes.

Furthermore, the occurrence of an acute ischemic stroke in the vertebrobasilar territory during hospitalization highlights the patient's diffuse atherosclerotic burden and vulnerable vascular state. This underscores the need for comprehensive secondary prevention strategies in patients with polyvascular disease, including more intensive antiplatelet regimens, lipid-lowering therapy, and possibly adjunctive approaches targeting vascular inflammation and calcification.

This case underscores the clinical value of platelet function testing in tailoring antiplatelet therapy, especially in high-risk individuals with evidence of inadequate

pharmacological response. It also brings attention to Klotho as a potential prognostic marker of cardiovascular vulnerability and as a possible future therapeutic target.

Conclusions

This clinical case:

- Demonstrates the importance of assessing platelet function in myocardial infarction, which allows for the personalization of antiplatelet therapy in patients with MI and peripheral artery disease (PAD);

- Indicates the need for genetic testing to identify clopidogrel resistance-related gene polymorphisms, as high platelet reactivity despite a double dose of clopidogrel may have contributed to stent thrombosis;

- Confirms that a low level of the morphogenetic protein Klotho serves as a predictor of cardiovascular complications and adverse events in patients with myocardial infarction and PAD.

Author Contributions: *All authors contributed equally to the preparation and writing of the manuscript.*

Conflict of Interest: *The authors declare no conflict of interest. We confirm that the materials presented in this article have not been published in any other printed publication.*

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A CASE REPORT OF MYOCARDIAL INFARCT PROCESSED ON POLYMORBID BACKGROUND

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Introduction. Polymorbidity in the form of uncontrolled arterial hypertension, heart failure, severe out-of-hospital polisegmental pneumonia complicated by pleurisy and respiratory failure significantly affects the tactics of myocardial infarction management in polypragmatic conditions and worsen prognosis. Additional difficulties in myocardial infarction management are: Dressler syndrome, recurrent course of infarction and ventricular fibrillation, repeated interventions (coronarography and stenting), contrast induced nephropathy on the background of chronic heart failure with low ejection fraction and pulmonary hypertension. **Material and methods.** Analysis of the medical record data of patient B, 58 years old. **Results and discussion:** This case highlights the challenges faced by physicians in the management of patients with myocardial infarction on polymorbid background, requiring simultaneous intensive treatment of myocardial infarction and combined diseases, which increases the risk of circulatory instability in conditions of forced polypragmasy. **Conclusion:** This case demonstrates the need for active identification of patients with CHD at the outpatient stage and interdisciplinary approach including general practitioners, internists, cardiologists, cardiac surgeons, pulmonologists, intensive care specialists and nephrologists.

Key words: *myocardial infarction, polymorbidity, polypragmasy.*

For citation:

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Резюме

КЛИНИЧЕСКИЙ СЛУЧАЙ ИНФАРКТА МИОКАРДА, ПРОТЕКАЮЩЕГО НА ПОЛИМОРБИДНОМ ФОНЕ

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Введение. Полиморбидность в виде неконтролируемой артериальной гипертензии, сердечной недостаточности, тяжелой внебольничной полисегментарной пневмонией, осложненной плевритом и дыхательной недостаточностью существенно влияет на тактику ведения инфаркта миокарда в условиях полипрагмазии и ухудшают прогноз. Дополнительные сложности в управлении инфарктом миокарда представляют: синдром Дресслера, рецидивирующее течение инфаркта и фибрилляции желудочков, повторные вмешательства (коронарографии и стентирования), контраст индуцированная нефропатия на фоне хронической сердечной недостаточности с низкой фракцией выброса и легочной гипертензии. **Материал и методы.** Анализ данных медицинской карты пациента В, 58 лет. **Результаты и обсуждение**: Данный случай подчеркивает вызовы, с которыми сталкиваются врачи при ведении пациентов с инфарктом миокарда на полиморбидном фоне, требующих одновременного интенсивного лечения инфаркта миокарда и сочетанных заболеваний, что повышает риск нестабильности кровообращения в условиях вынужденной полипрагмазии. **Вывод:** Этот случай демонстрирует необходимость активного выявления пациентов с ИБС на амбулаторном этапе и междисциплинарного подхода, включающего врачей общей практики, терапевтов, кардиологов, кардиохирургов, пульмонологов, реаниматологов и нефрологов.

Ключевые слова: *инфаркт миокарда, полиморбидность, полипрагмазия.*

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Түйіндеме

ПОЛИМОРБИДТІ ФОНДА ӨТЕТІН МИОКАРД ИНФАРКТІНІҢ КЛИНИКАЛЫҚ ЖАҒДАЙЫ

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Кіріспе. Бақыланбайтын артериялық гипертензия, жүрек жеткіліксіздігі, плевритпен және тыныс алу жеткіліксіздігімен асқынған ауруханадан тыс полисегментарлық пневмония түріндегі полиморбидтілік полипрагмазия жағдайларында миокард инфарктісін жүргізу тактикасына елеулі әсер етеді және болжамды нашарлатады. Миокард инфарктін басқарудағы қосымша қиындықтар: Дресслер синдромы, инфаркттің және қарыншалардың фибрилляциясының қайталанатын ағымы, қайталама араласулар (коронарография және стенттеу), төмен шығарынды фракциясы мен өкпе гипертензиясы бар созылмалы жүрек функциясының жеткіліксіздігі фонындағы индукцияланған нефропатияның контрастысы. **Материал және әдістер.** В, 58 жастағы пациенттің медициналық картасының деректерін талдау. **Нәтижелері және талқылауы:** Бұл жағдай мәжбүрлі полипрагмазия жағдайларында қан айналымының тұрақсыздығы қаупін арттыратын миокард инфарктін және аралас ауруларды бір мезгілде қарқынды емдеуді талап ететін полиморбидті фонда миокард инфарктімен ауыратын пациенттерді емдеу кезінде дәрігерлер кездесетін сын-қатерлерді баса көрсетеді. **Қорытынды:** Бұл жағдай жалпы практика дәрігерлерін, терапевтерді, кардиологтарды, кардиохирургтарды, пульмонологтарды, реаниматологтарды және нефрологтарды қамтитын амбулаториялық кезеңде және пәнаралық тәсілмен ЖИА бар пациенттерді белсенді анықтау қажеттілігін көрсетеді.

Түйінді сөздер: миокард инфарктісі, полиморбидтілік, полипрагмазия.

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Introduction

In recent decades, the proportion of individuals of working age with cardiovascular pathology has been steadily increasing, presenting a significant socio-economic challenge [1,2,3].

The purpose of this clinical report description is to draw attention to the complexity of managing a multimorbid working-age patient with early-onset cardiovascular disease, which presented with recurrent myocardial infarction and severe community-acquired pneumonia. This case is intended to raise clinicians' awareness of the risks of forced polypharmacy and the importance of timely identification and structured outpatient management.

Materials and Methods:

The material is based on the medical records of patient B., 58 years old, who underwent inpatient treatment at the City Cardiology Center in Almaty. Research method: clinical case description.

Research Results:

The patient presented with complaints of episodes of pressing chest pain, dyspnea at rest, and weakness.

Medical history revealed arterial hypertension for several years, with a maximum recorded blood pressure of 160/90 mmHg and an adapted blood pressure of 120/80 mmHg. The patient was not under regular medical follow-up. Worsening of symptoms was noted over the previous two weeks: recurrent pressing chest pain, fever up to 38°C, and dyspnea on minimal physical exertion. The patient had not received any treatment prior to admission.

On June 18, 2024 (date changed for confidentiality), the patient independently sought medical attention at the emergency department of the cardiology center and was urgently hospitalized in the intensive care unit.

Past medical history: No family history of cardiovascular disease. The patient denies any chronic conditions or unhealthy behaviors (e.g., smoking, alcohol use). No history of allergic reactions.

Physical examination: General condition: severe. Position: orthopnea. BMI: 29.1 kg/m² (overweight). Consciousness clear, patient is adequate. Body temperature: 36.5°C. SpO_2: 96%. Respiratory rate: 18/min. Vesicular breath sounds, weakened in the lower lung fields, with fine moist rales bilaterally. Heart sounds muffled, first sound diminished, regular rhythm. Blood pressure: 130/80 mmHg. Heart rate: 88 bpm. No peripheral edema.

Based on the complaints, history, and objective, laboratory, and instrumental findings, the following were noted:

- History of uncontrolled arterial hypertension;
- Delayed presentation: for two weeks the patient had experienced recurrent chest pain and progressive weakness;
- Fever up to 38°C;
- Clinical signs of myocardial infarction lasting more than two weeks, with elevated troponin I at admission: 2.51 ng/ml and 2.66 ng/ml after 3 hours. The positive result without dynamic increase/decrease supports a diagnosis of myocardial infarction that occurred at least a week prior;
- ECG on 18.06.2024: sinus rhythm, HR 80 bpm. ST-segment depression in leads I, II, III, aVL, aVF, V3–V6. No R wave progression in V1–V4;
- Echocardiography: conducted during arrhythmia. Aortic wall and valve leaflets thickened. Dilation of the left heart chambers. Left ventricular (LV) myocardial hypertrophy. Hypo- and akinesis of the LV apex. Diffuse hypokinesis of other LV walls. LV systolic function reduced (Simpson's EF 32%), right ventricular function preserved. Pericardial effusion: ~100 ml. Mild pulmonary hypertension: systolic pulmonary artery pressure 26 mmHg. Pleural effusion: right side 460 ml, left side 660 ml;
- Dyslipidemia on admission: Total cholesterol – 5.12 mmol/L; HDL – 0.91 mmol/L; LDL – 3.92 mmol/L; Triglycerides – 1.46 mmol/L;
- Pneumonia symptoms: febrile syndrome, progressive inflammatory markers (Table 1), elevated procalcitonin – 2.43 ng/ml; D-dimer – 1600 ng/ml; fibrinogen – 7.44 g/L. Chest X-ray: multisegmental pneumonia (50% lung involvement). Positive dynamics with combined parenteral antibiotic therapy (ceftriaxone 2 g/day IV and levofloxacin 500 mg/day IV), as shown by decreased CRP and a slight reduction in band neutrophils (Table 1);
- Pleural effusion findings: moderate bilateral effusion on ultrasound (19.06.2024, 12:22) – ~400 ml on the right, ~380 ml on the left;
- Elevated creatinine and reduced GFR – indicating contrast-induced nephropathy following coronary angiography.

Table 1.

Dynamics of Laboratory Parameters Over Time.

Parameter	18.06.2024	19.06.2024	28.06.2024	30.06.2024	02.07.2024
Leukocytes	11,19 x10^9/л	16,70 x10^9/л	13,35 x10^9/л	12,04 x10^9/л	13,68 x10^9/л
Band neutrophils (%)	10	23	14	14	12
Eosinophils (%)	8	6	6	5	4
ESR (mm/hour)	36,06	31,65	57,79	71,46	53,50
Creatinine (μmol/L)	84	84	260	107	84
GFR(CKD-EPI) (mL/min/1.73 m²)	88	88	22	66	88
Potassium (mmol/L)	2,8	4,2	3,2	3,6	3,6
hs-CRP (mg/L)	70,70	80,86	87,39	114,05	70,70

- Persistent hypokalemia (Table 1);

- Ultrasound Doppler (03.07.2024): Echo signs of atherosclerotic lesions in the brachiocephalic arteries and lower extremity arteries, with atherosclerotic plaques causing up to 37% luminal stenosis.

Final Diagnosis:

Primary diagnosis: Ischemic heart disease. Primary anterior extensive non-ST elevation myocardial infarction (NSTEMI) dated 12.06.2024, recurrent course (date changed for confidentiality, likely occurred one week prior to admission). Type 1.

Procedure: Myocardial revascularization via stenting of the left anterior descending (LAD) and circumflex artery (LCx) on 18.06.2024 (day of admission).

Concurrent disease: Community-acquired bilateral multisegmental pneumonia of mixed etiology (hemodynamic and inflammatory), severe course.

Complications: Acute heart failure, type 1 (ESC);

Moderate pulmonary hypertension;

Dressler's syndrome;

Pericarditis with mild effusion;

HFrEF (LVEF by Simpson's method 32–39%), NYHA functional class III, ACC/AHA Stage C;

Recurrent myocardial infarction as of 24.06.2024;

Hypokalemia;

Recurrent ventricular fibrillation;

Bilateral exudative pleuritis;

Respiratory failure grade II–III;

Contrast-induced nephropathy.

Procedure on 24.06.2024: Coronary angiography and stenting of the right coronary artery (RCA). Temporary pacemaker implantation.

Procedure on 03.07.2024: Implantation of automatic implantable cardioverter-defibrillator (AICD) Biotronik Rivacor 5 DR-T.

Comorbidity:

Grade I arterial hypertension, very high cardiovascular risk;

Secondary dyslipidemia;

Metabolic syndrome;

Ischemic heart disease: multivessel obstructive coronary artery disease;

Multifocal atherosclerosis.

On this multimorbid background, despite potassium supplementation, persistent hypokalemia led to multiple (8 total) episodes of ventricular fibrillation. Rapid normalization of glomerular filtration rate and creatinine levels during therapy confirmed the diagnosis of contrast-induced nephropathy. Sepsis and pulmonary embolism were excluded based on the diagnostic data and clinical dynamics.

Coronary angiography revealed chronic occlusions in four vessels; infarct-related arteries—the LAD and LCx—were stented on 18.06.2024.

On the morning of 24.06.2024, the patient experienced cardiac arrest due to ventricular fibrillation in the cardiology department. After successful resuscitation, he was transferred to the ICU, where a second episode of ventricular fibrillation occurred. Emergency coronary angiography was repeated for life-saving indications. During the procedure, another episode of VF occurred, requiring defibrillation by the resuscitation team. Sinus rhythm was restored and the patient regained consciousness. Given repeated VF episodes and new ST elevation in leads II, III, and aVF, stenting of the chronically occluded RCA was performed. Control angiography showed good angiographic results with full restoration of the vessel lumen and satisfactory TIMI III blood flow.

Due to recurrent episodes of VF, temporary pacemaker implantation was performed on 24.06.2024. A multidisciplinary team decided to implant an AICD (Biotronik Rivacor 5 DR-T) on 03.07.2024 due to:

- Persistent hypokalemia;
- Prolonged QT interval;
- Eight episodes of ventricular fibrillation during hospitalization;
- Reduced left ventricular ejection fraction.

Polypharmacy:

According to the medication chart, the 58-year-old patient received 13–15 drugs per day, including:

- Four medications for heart failure;
- Diuretic;
- Two antibiotics;
- Ibuprofen (later switched to colchicine);
- Intravenous fluid therapy with potassium and magnesium supplementation;
- Proton pump inhibitors;
- Two antiplatelet agents;
- Anticoagulant;
- Statin;
- Nitrates.

Discussion:

This clinical report highlights the complexity of managing a patient with uncontrolled arterial hypertension and a very high cardiovascular risk. Notably, the presence of prolonged chest pain and worsening symptoms over two weeks points to the possibility of a "silent" myocardial infarction, which is commonly seen in patients with hypertension. Upon admission, Dressler's syndrome was diagnosed.

The patient's extremely serious condition was exacerbated by pneumonia and persistent hypokalemia, which led to eight episodes of ventricular fibrillation, despite stenting of three coronary arteries. Coronary angiography confirmed multivessel coronary disease with chronic occlusions, indicating long-standing ischemic heart disease.

Doppler ultrasound of the neck and lower extremity vessels also revealed atherosclerotic plaques. Decreased ejection fraction and left ventricular hypertrophy may have resulted from both ischemic heart disease and long-standing hypertension.

Pneumonia and pleuritis: Laboratory findings (elevated CRP and procalcitonin) and imaging confirmed bilateral multisegmental pneumonia. The etiology is likely mixed—infection and hemodynamic changes—supporting the hypothesis of a combined origin. Pleural effusion could be caused by inflammation, Dressler's syndrome, or heart failure, requiring a comprehensive treatment strategy.

Contrast-induced nephropathy: A sharp rise in creatinine and decline in GFR are consistent with contrast-induced nephropathy, which may also be linked to polypharmacy [4].

In summary, this 58-year-old patient residing in a metropolitan area with access to routine screening for coronary artery disease and hypertension experienced delayed diagnosis of multifocal atherosclerosis during inpatient care.

A key concern often raised by clinical pharmacologists and medical chart reviewers is the presence of

polypharmacy, where patients receive five or more drugs per day. Future research should focus on improving diagnostic and treatment protocols to enhance care for multimorbid patients and to explore new definitions and evaluation standards for justifiable polypharmacy in modern clinical medicine [5,6].

Conclusion:

This clinical report describes a 58-year-old working-age patient with early-onset cardiovascular and multimorbid pathology who required extensive pharmacotherapy. The case emphasizes the importance of interdisciplinary collaboration in managing multimorbid patients, necessitating individualized treatment strategies and continuous monitoring. This approach optimizes therapy and improves prognosis and quality of life in the context of inevitable polypharmacy. It also highlights the need to redefine polypharmacy in the context of contemporary clinical practice.

Prognosis: Extremely serious; scheduled cardiac rehabilitation by a multidisciplinary team is necessary. Further evaluation is required to identify the cause of treatment-resistant hypokalemia.

Informed Consent: *Informed consent was obtained for the publication of this clinical case and use of medical data for scientific purposes.*

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