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COMPARATIVE EVALUATION OF BLOOD COLLECTION TUBES AND EXTRACTION METHODS FOR CIRCULATING TUMOR DNA

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Abstract

Introduction. Circulating tumor DNA (ctDNA) has emerged as a valuable biomarker for non-invasive cancer diagnostics and treatment monitoring. However, pre-analytical variables, including blood collection and sample processing, significantly influence ctDNA yield and analytical reliability. Optimizing these conditions is crucial for ensuring reproducible and accurate ctDNA measurements.

Aim. To perform a comparative evaluation of blood collection tubes and DNA extraction methods for the isolation of circulating tumor DNA from the blood plasma of patients with oncological diseases.

Materials and Methods. Plasma samples were collected using two types of blood collection tubes: PaxGene and Streck. ctDNA was extracted using three different systems: Raissol, MagMax, and QiaAmp. Quantitative performance, reproducibility, and variability of ctDNA yield were assessed across all combinations of collection tubes and extraction methods. Statistical analysis was performed to evaluate differences among extraction systems.

Discussion. The results demonstrated that QiaAmp consistently provided higher ctDNA concentrations across both collection systems. Samples collected in PaxGene tubes exhibited lower variability and improved analytical stability compared with Streck tubes. Statistically significant differences among extraction methods were observed for PaxGene samples, while increased variability in Streck samples limited the ability to discriminate between methods. These findings emphasize the critical role of pre-analytical optimization in ctDNA workflows and support the implementation of standardized protocols to improve reliability in liquid biopsy analysis.

Conclusion. The results demonstrate that both blood collection tubes and the DNA extraction method significantly affect ctDNA recovery, highlighting the importance of optimizing and standardizing pre-analytical workflows for reliable liquid biopsy analysis.

Keywords. *circulating tumor DNA; liquid biopsy; DNA extraction; pre-analytical variables; blood collection tubes.*

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Резюме

СРАВНИТЕЛЬНАЯ ОЦЕНКА ПРОБИРОК ДЛЯ СБОРА КРОВИ И МЕТОДОВ ЭКСТРАКЦИИ ДЛЯ ЦИРКУЛИРУЮЩЕЙ ОПУХОЛЕВОЙ ДНК

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Введение. Циркулирующая опухолевая ДНК (ctDNA) стала ценным биомаркером для неинвазивной диагностики рака и мониторинга терапии. Однако преданалитические переменные, включая сбор крови и обработку образцов, существенно влияют на выход ctDNA и надежность анализа. Оптимизация этих условий необходима для обеспечения воспроизводимости и точности измерений ctDNA.

Цель. Целью данного исследования было проведение сравнительной оценки эффективности пробирок для сбора крови и методов экстракции ДНК при выделении циркулирующей опухолевой ДНК из плазмы крови пациентов с онкологическими заболеваниями.

Материалы и методы. Плазменные образцы были собраны с использованием двух типов пробирок: PaxGene и Streck. Экстракция ctDNA проводилась с использованием трех систем: Raissol, MagMax и QiaAmp. Оценивались количественные показатели, воспроизводимость и вариабельность выхода ctDNA для всех комбинаций пробирок и методов экстракции. Для оценки различий между методами экстракции проводился статистический анализ.

Обсуждение. Результаты показали, что система QiaAmp стабильно обеспечивала более высокие концентрации ctDNA при использовании обеих пробирок. Образцы, собранные в пробирки PaxGene, продемонстрировали меньшую вариабельность и улучшенную аналитическую стабильность по сравнению с пробирками Streck. Статистически значимые различия между методами экстракции наблюдались для образцов PaxGene, тогда как повышенная вариабельность в образцах Streck ограничивала возможность различия методов. Эти данные подчеркивают критическую роль оптимизации преданалитических условий и поддерживают внедрение стандартизированных протоколов для повышения надежности анализа жидкостной биопсии.

Заключение. Полученные результаты показывают, что как тип пробирок для сбора крови, так и используемые методы экстракции ДНК существенно влияют на выход циркулирующей опухолевой ДНК, что подчёркивает необходимость оптимизации и стандартизации преданалитических этапов для надёжного анализа жидкостной биопсии.

Ключевые слова. *циркулирующая опухолевая ДНК (ctDNA); жидкостная биопсия; экстракция ДНК; преданалитические переменные; пробирки для сбора крови.*

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Түйіндеме

ҚАН ЖИНАУ ТҮТІКТЕРІН ЖӘНЕ ҚАН АЙНАЛЫМДАҒЫ ҚАТЕРЛІ ІСІК ДНҚ-сын БӨЛУ ҮШІН ӘДІСТЕРІН САЛЫСТЫРМАЛЫ БАҚЫЛАУЫ

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Кіріспе. Циркуляциялық қатерлі ісік ДНҚ (ctDNA) ракты инвазивті емес диагностикалау және емдеу мониторингі үшін маңызды биомаркерге айналды. Алайда, қан жинау және үлгілерді өңдеу сияқты алдын ала аналитикалық факторлар ctDNA шығымына және талдау сенімділігіне елеулі әсер етеді. Бұл жағдайларды оңтайландыру ctDNA өлшеулерінің дәлдігі мен қайта өндірілетіндігін қамтамасыз ету үшін өте маңызды.

Мақсат. Зерттеудің мақсаты – Онкологиялық аурулары бар науқастардың қан плазмасынан қан айналымдағы ісік ДНҚ-сын бөліп алу үшін қолданылатын қан жинау пробиркалары мен ДНҚ экстракция әдістерінің тиімділігін салыстырмалы түрде бағалау.

Материалдар мен әдістер. Плазма үлгілері екі типтегі қан жинау түтіктерінде жиналды: PaxGene және Streck. ctDNA Raissol, MagMax және QiaAmp жүйелерін қолдану арқылы шығарылды. Барлық түтік пен экстракция әдістерінің комбинациялары бойынша ctDNA шығымы, қайта өндірілушілігі және вариабельдігі бағаланды. Экстракция әдістері арасындағы айырмашылықтарды бағалау үшін статистикалық талдау жүргізілді.

Талқылау. Нәтижелер QiaAmp жүйесінің екі түтік үшін де жоғары ctDNA концентрациясын тұрақты түрде қамтамасыз ететінін көрсетті. PaxGene түтіктерінде жиналған үлгілер Streck түтіктерімен салыстырғанда төмен вариабельдік пен жоғары аналитикалық тұрақтылық көрсетті. PaxGene үлгілерінде экстракция әдістері арасындағы статистикалық маңызды айырмашылықтар байқалды, ал Streck үлгілеріндегі жоғары вариабельдік әдістер арасындағы айырмашылықты анықтауды шектеді. Бұл нәтижелер алдын ала аналитикалық шарттарды оңтайландырудың маңызды рөлін көрсетеді және сенімді сұйықтық биопсиясы талдауын қамтамасыз ету үшін стандартталған протоколдарды енгізуді қолдайды.

Қорытынды. Алынған нәтижелер қан жинау пробиркаларының түрі мен ДНҚ экстракция әдістері қан айналымдағы ісік ДНҚ-сының шығымына елеулі әсер ететінін көрсетті, бұл сұйық биопсия талдауының сенімділігін арттыру үшін алдын ала аналитикалық кезеңдерді оңтайландыру мен стандарттаудың маңыздылығын көрсетеді.

Түйінді сөздер. *қан айналымдағы қатерлі ісік ДНҚ (ctDNA); сұйықтық биопсиясы; ДНҚ экстракциясы; алдын ала аналитикалық факторлар; қан жинау түтіктері.*

Дәйексөз үшін:

Айткулова А.М., Каденова Т.Б., Габдулкайюм А., Ережепов Д.А., Рахимова С.Е., Кожамкулов У.А., Каиров У.Е., Ермекбаева Б.А., Акильжанова А.Р., Сарбасов Д.Д. Қан жинау түтіктерін және қан айналымдағы қатерлі ісік ДНҚ-сын бөлу үшін әдістерін салыстырмалы бақылауы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 7-13. *doi 10.34689/SH.2025.27.6.001*

Introduction

Molecular genetic methods play a key role in modern oncology by enabling personalized treatment strategies, improving patient stratification, and allowing dynamic monitoring of therapeutic effectiveness. In recent years, liquid biopsy approaches based on the analysis of circulating tumor DNA (ctDNA) have gained increasing clinical and research relevance due to their minimally invasive nature and their ability to capture the molecular landscape of tumors in real time [2,14]. Unlike conventional tissue biopsies, liquid biopsy offers the possibility of repeated sampling, facilitating longitudinal assessment of tumor evolution and treatment response.

Circulating tumor DNA consists of short fragments of tumor-derived DNA released into various biological fluids, including blood, cerebrospinal fluid, urine, and pleural or ascitic effusions; however, blood plasma remains the most widely used and clinically relevant source for ctDNA analysis [8,15]. In patients with malignant neoplasms, ctDNA is released into the bloodstream primarily because of tumor cell apoptosis and necrosis, as well as active secretion mechanisms associated with tumor progression [9,16]. Due to its short half-life in circulation, estimated to range from several minutes to a few hours, ctDNA is highly susceptible to degradation and dilution by background genomic DNA released from lysed leukocytes, particularly under suboptimal pre-analytical conditions [1,13]. These characteristics necessitate careful control of sample handling to preserve ctDNA integrity and analytical sensitivity.

The low concentration and pronounced interindividual variability of ctDNA represent major methodological challenges that limit its broader implementation in routine clinical diagnostics. Even in patients with advanced-stage malignancies, ctDNA levels may fluctuate considerably depending on tumor burden, biological activity, and sample processing conditions. Accumulating evidence indicates that ctDNA yield is strongly influenced by pre-analytical variables, including the type of blood collection tubes used, time to plasma separation, stabilization chemistry, storage conditions, and DNA extraction methodology [4,12,17]. Variability introduced during these early stages can significantly affect downstream analytical performance, leading to reduced reproducibility and compromised quantitative accuracy.

Consequently, optimization and standardization of sample preparation workflows are considered essential prerequisites for reliable ctDNA analysis and for the successful translation of liquid biopsy technologies into routine clinical practice. Comparative evaluation of established blood collection systems and DNA extraction methods under standardized laboratory conditions may provide critical insights into sources of analytical variability and support the development of robust, reproducible protocols. Therefore, **the aim of the present study** was to optimize sample preparation conditions for ctDNA isolation from blood plasma by comparatively evaluating commonly used blood collection tubes and DNA extraction methods.

Materials and Methods

Venous blood samples were collected from 15 patients with confirmed malignant neoplasms at the Kazakh National Research Institute of Oncology and Radiology (KazIOR, Almaty, Kazakhstan) using standard venipuncture procedures in accordance with institutional protocols. All

enrolled patients met the inclusion criteria, which comprised metastatic involvement of regional lymph nodes or distant organ metastases corresponding to advanced disease stages (TNM stage III–IV), as well as ongoing targeted therapy for at least one week prior to blood collection. These criteria were selected to ensure a clinically relevant cohort with detectable levels of circulating tumor DNA.

Blood was drawn into two types of commercially available blood collection systems: PAXgene Blood DNA Tubes (Qiagen, Germany) and Cell-Free DNA BCTs (Streck, USA). For each patient, blood was collected in duplicate tubes of each type (9 mL per tube) to minimize sampling bias and to enable parallel processing. Following collection, blood tubes were stored at room temperature for up to 7 days prior to plasma separation, in accordance with manufacturers' recommendations and to simulate delayed sample processing conditions commonly encountered in clinical practice and multicenter studies.

Plasma separation was performed using a standardized two-step centrifugation protocol designed to minimize cellular contamination. Initially, whole blood samples were centrifuged at 1,600 × g for 30 min at room temperature to remove cellular components. The plasma supernatant was carefully transferred to sterile 2 mL polypropylene tubes without disturbing the buffy coat and subjected to a second high-speed centrifugation at 14,000 × g for 10 min at 4 °C to eliminate residual cellular debris. The resulting cell-free plasma was aliquoted and frozen using a gradual cooling procedure (−20 °C for 24 h followed by storage at −80 °C) until further analysis.

Circulating tumor DNA was isolated from 2 mL of plasma using one of three extraction methods: QIAamp MinElute ccfDNA Kit (Qiagen, Germany), MagMAX™ Cell-Free DNA Isolation Kit (Thermo Fisher Scientific, USA), or CF Extra Raissol™ Reagent Kit (Raissol Bio, Russia). All extractions were performed strictly according to the manufacturers' protocols by the same operator to reduce inter-operator variability. Eluted ctDNA samples were stored at −20 °C until downstream quantitative and qualitative analyses.

The quality and concentration of isolated ctDNA were assessed using complementary analytical approaches. DNA concentration was measured fluorometrically using a Qubit 2.0 fluorometer with the Qubit™ dsDNA High Sensitivity Assay Kit (Invitrogen, USA). Spectrophotometric assessment of nucleic acid purity was performed using a NanoDrop 2000 (Thermo Fisher Scientific, USA). Fragment size distribution and integrity of ctDNA were evaluated using an Agilent 2100 Bioanalyzer with High Sensitivity DNA reagents (Agilent Technologies, USA). DNA fragments within the size range of 120–250 bp were considered optimal and representative of circulating tumor-derived DNA.

Statistical analysis was performed using GraphPad Prism version 10. Prior to comparative analysis, data distribution was assessed for normality. Comparisons between two independent groups were conducted using the Student's t-test for normally distributed data. For small sample sizes (n = 5 per group) and non-normal distributions, non-parametric statistical methods were applied. Differences among DNA extraction methods within each blood collection system were evaluated using the Kruskal–Wallis test, followed by Dunn's multiple comparisons post-hoc test with Holm correction to account for multiple testing. Quantitative data are presented as mean ± standard deviation (SD), median, and range. A p-value of less than 0.05 was considered statistically significant.

Results

Between October 2024 and February 2025, venous blood samples were collected at the Kazakh National Research Institute of Oncology and Radiology (Almaty, Kazakhstan) from patients with various malignant neoplasms. All enrolled patients (100%) presented with advanced disease (clinical stages III–IV). A total of 30 plasma samples were obtained from 15 patients. The study cohort consisted of 9 females and 6 males, with a mean age of 56 years. These samples were used for subsequent comparative analyses of blood collection systems and ctDNA extraction methods.

Analysis of ctDNA concentration across individual patients revealed no statistically significant difference between PAXgene and Streck blood collection tubes (Mann–Whitney U test, p = 0.34). The median ctDNA concentration was 0.352 for PAXgene samples and 0.385 for Streck samples. In the PAXgene group, ctDNA values ranged from 0.128 to 1.230, whereas Streck samples demonstrated a wider range from 0.098 to 2.380. Accordingly, the interquartile range was narrower for PAXgene samples, reflecting a more compact distribution of individual measurements, while Streck samples exhibited a broader interquartile span and higher upper values (Figure 1). The increased dispersion in the Streck group was evident from the wider spread of individual data points and the presence of higher maximum concentrations, whereas ctDNA measurements obtained from PAXgene tubes clustered more closely around the median, indicating greater analytical consistency across the study cohort.

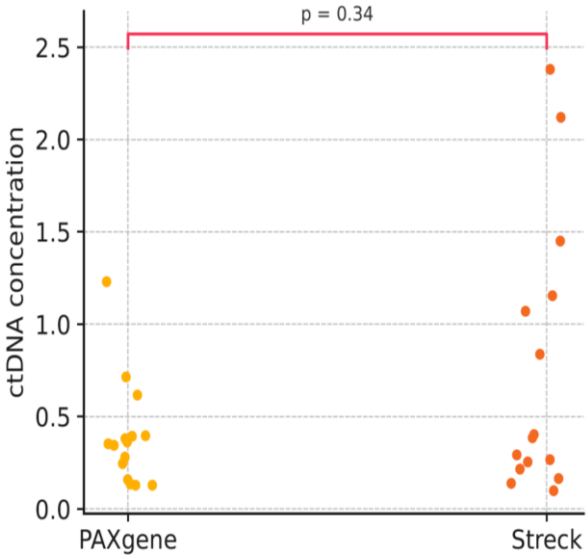


Figure 1. ctDNA concentration per patient in PAXgene and Streck tubes

Scatter plot showing individual ctDNA concentrations measured in plasma samples collected in PAXgene and Streck blood collection tubes. Each dot represents one patient. Statistical comparison was performed using the Mann–Whitney U test (p = 0.34).

Comparison of extraction methods revealed pronounced method-dependent differences in ctDNA recovery (Figure 2). In PAXgene samples, a statistically significant overall difference among extraction methods was detected (Kruskal–Wallis test, p = 0.029). Among the evaluated approaches, QIAamp consistently demonstrated higher ctDNA concentrations compared with both Raissol and MagMax. Post-hoc analysis using Dunn's multiple comparisons test confirmed a statistically significant difference between QIAamp and Raissol (p < 0.05), whereas differences between Raissol and MagMax as well as between MagMax and QIAamp did not reach statistical significance. In addition to higher absolute values, QIAamp in PAXgene samples showed a narrower dispersion, indicating more consistent analytical performance.

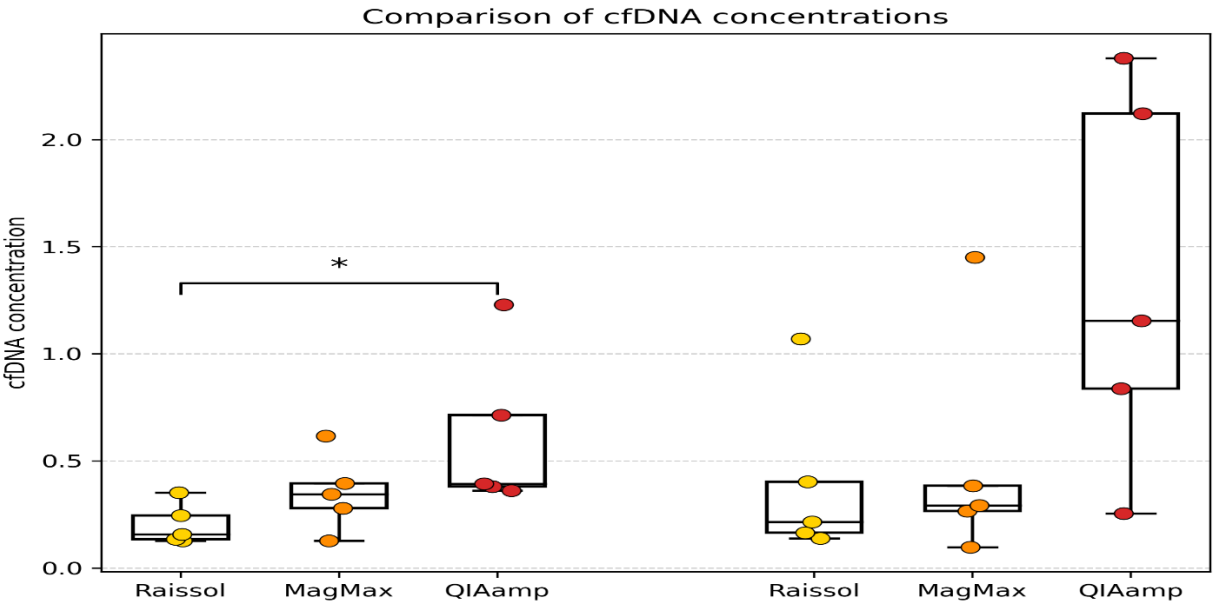


Figure 2 Comparison of ctDNA yield by extraction method

Box-and-whisker plots showing ctDNA yield obtained using Raissol, MagMax, and QIAamp extraction methods for PAXgene and Streck samples. Boxes represent the interquartile range with the median indicated by a horizontal line; whiskers show minimum and maximum values. Individual data points are displayed. Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's post-hoc test. *p < 0.05.

In Streck samples, QIAamp also yielded the highest absolute ctDNA concentrations across extraction methods (Figure 2); however, the overall comparison did not reach statistical significance (Kruskal–Wallis test, p = 0.134). This lack of significance was accompanied by substantially increased variability, particularly for Raissol and MagMax, as reflected by wider ranges and interquartile distributions (Table 1). Despite this variability, the consistent trend toward higher ctDNA recovery with QIAamp across both blood collection systems underscores its superior extraction efficiency.

Table 1.

ctDNA concentration according to blood collection tube and extraction method

Comparison	Median ctDNA	Range	Statistical test	p-value
PAXgene vs Streck	0.352 vs 0.385	0.128–1.230 vs 0.098–2.380	Mann–Whitney	0.34
PAXgene – Raissol	0.158	0.128–0.352	—	—
PAXgene – MagMax	0.344	0.128–0.616	—	—
PAXgene – QIAamp	**0.393**	**0.362–1.230**	**Kruskal–Wallis**	**0.029***
Streck – Raissol	0.215	0.138–1.070	—	—
Streck – MagMax	0.292	0.098–1.450	—	—
Streck – QIAamp	1.154	0.254–2.380	Kruskal–Wallis	0.134

* Post-hoc Dunn test (Holm-adjusted): QIAamp vs Raissol.

Overall, QIAamp consistently demonstrated superior ctDNA recovery across both blood collection systems, while PAXgene tubes provided improved analytical stability and reproducibility.

Discussion

The method-dependent differences in ctDNA recovery observed in the present study (Figure 2, Table 2) are consistent with a growing body of evidence highlighting the critical role of extraction chemistry in the efficient isolation of fragmented circulating DNA. Multiple comparative investigations have demonstrated that silica membrane–based extraction systems provide superior recovery of short DNA fragments characteristic of ctDNA compared with magnetic bead–based or precipitation-based approaches [3,5,6,9]. This advantage is particularly relevant for downstream applications requiring high analytical sensitivity, such as digital PCR or low-frequency variant detection.

In PAXgene samples, QIAamp yielded significantly higher ctDNA concentrations compared with Raissol, as confirmed by post-hoc statistical analysis. Similar results have been reported by El Messaoudi et al., who showed that silica-based extraction methods improve both yield and reproducibility of ctDNA in plasma samples from patients with solid tumors [6]. Devonshire et al. further demonstrated that differences in DNA extraction workflows can introduce substantial quantitative bias in digital PCR measurements, underscoring the importance of method standardization for reliable ctDNA analysis [3]. Comparable findings have been reported in more recent technical evaluations comparing commercial extraction platforms under controlled experimental conditions [5,7,10].

Although QIAamp also produced higher absolute ctDNA values in Streck samples, the absence of significance in this group likely reflects increased pre-analytical variability. Blood stabilization systems are known to differ in their ability to prevent leukocyte lysis and subsequent release of background genomic DNA during storage and transport, which can dilute the ctDNA signal and increase variability [11,18,20]. Meddeb et al. emphasized that even minor deviations in pre-analytical handling may significantly affect ctDNA integrity and concentration, particularly in sample processed after prolonged storage [12]. This phenomenon becomes especially pronounced in studies involving heterogeneous clinical cohorts or delayed plasma separation [18,19].

Importantly, the integrated analysis of patient-level ctDNA variability (Figure 1), extraction-dependent performance (Figure 2), and summary statistics (Table 2) reinforces the concept that reliable ctDNA measurement depends on the combined optimization of blood collection systems and extraction methods. Even in cohorts dominated by advanced-stage malignancies, where ctDNA levels are generally elevated, methodological variability remains a major determinant of analytical robustness. These findings align with current recommendations advocating the implementation of standardized, validated workflows across all stages of liquid biopsy analysis to ensure reproducibility and facilitate clinical translation [16,17].

Study limitations

A limitation of this study is the relatively small sample size and the inclusion of patients exclusively with advanced-stage (III–IV) malignancies, which may limit the generalizability of the findings to earlier disease stages.

Conclusions

The findings of this study confirm that both blood collection systems and DNA extraction methods play a crucial role in determining the efficiency, variability, and reproducibility of circulating tumor DNA (ctDNA) isolation from blood plasma. Although no statistically significant differences in overall patient-level ctDNA concentrations were observed between PAXgene and Streck blood collection tubes, PAXgene samples exhibited lower variability and greater analytical stability, indicating more consistent preservation of ctDNA under the applied pre-analytical conditions.

Comparative evaluation of DNA extraction methods revealed method-dependent differences in ctDNA recovery. Among the tested approaches, the QIAamp extraction system consistently demonstrated higher ctDNA yields and significantly outperformed the Raissol method in PAXgene samples, highlighting the advantages of silica membrane–based extraction technologies for the isolation of fragmented circulating DNA. While QIAamp also produced higher absolute ctDNA concentrations in Streck samples, increased variability limited the statistical significance of these differences.

Overall, the combined assessment of blood collection tubes and extraction methods underscores the necessity of integrated optimization of pre-analytical and analytical workflows for ctDNA analysis. Implementation of standardized blood collection systems together with high-efficiency DNA extraction methods may substantially improve the robustness and reproducibility of ctDNA-based assays, thereby enhancing the clinical utility of liquid biopsy approaches in oncology.

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INFLUENCE OF SEX HORMONE-BINDING GLOBULIN (SHBG) ON THE LEVEL OF FREE TESTOSTERONE FRACTION IN OLDER OVERWEIGHT MEN

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Abstract

Relevance. Serum SHBG concentration varies across different stages of a man's life. In individuals with excess body weight and visceral obesity, SHBG levels may decrease, which in turn disrupts the balance between bound and free testosterone. This may lead to functional hypogonadism, particularly in middle-aged and older men. However, the mechanisms and the extent of SHBG influence on free testosterone levels in the context of excess body weight remain a subject of scientific debate.

Study objective. To assess the effect of sex hormone-binding globulin (SHBG) on the level of free testosterone fraction in men with excess body weight.

Materials and methods. The study involved 326 men living in Semey, Abay region. The subjects were stratified by body mass index (BMI) and divided into two groups: the study group (112 overweight men, BMI 25-29.9 kg/m²) and the control group (214 normal-weight men, BMI <25 kg/m²).

Results. Sex hormone-binding globulin (SHBG) levels were negatively correlated with body mass index, rs = -0.218. Free testosterone showed no differences between the normal-weight and overweight groups. A significant correlation was found between SHBG and free testosterone (rs = -0.422, $p < 0.01$). This confirms the role of SHBG in regulating free testosterone levels in the blood.

Discussion. With excess weight, SHBG levels in the blood decrease, which then has a cascading effect on the distribution of testosterone between its bound and free fractions. A significant correlation between SHBG and free testosterone has been proven. SHBG plays a key role in the binding and transport of sex hormones.

Conclusions. A significant correlation between SHBG and free testosterone has been demonstrated. In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation.

Keywords: *sex hormone-binding globulin (SHBG), free testosterone fraction, older men, overweight.*

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Резюме

ВЛИЯНИЕ ГЛОБУЛИНА, СВЯЗЫВАЮЩЕГО ПОЛОВЫЕ ГОРМОНЫ (ГСПГ), НА УРОВЕНЬ СВОБОДНОЙ ФРАКЦИИ ТЕСТОСТЕРОНА У МУЖЧИН СТАРШЕГО ВОЗРАСТА С ИЗБЫТОЧНЫМ ВЕСОМ

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Актуальность. Концентрация ГСПГ в сыворотке меняется в разные возрастные периоды жизни мужчины. При избыточной массе тела и висцеральном ожирении уровень ГСПГ может снижаться, что, в свою очередь, нарушает соотношение между связанным и свободным тестостероном. Это может приводить к состоянию функционального гипогонадизма, особенно у мужчин среднего и пожилого возраста. Однако механизмы и степень влияния ГСПГ на уровень свободного тестостерона при избыточной массе тела остаются предметом научной дискуссии.

Цель исследования. Влияние глобулина связывающего гормона (ГСПГ) на уровень свободной фракции тестостерона у мужчин на фоне избыточного веса.

Материалы и методы. В исследовании приняло участие 326 мужчин проживающие в городе Семей, области Абай. Обследованные стратифицированы по ИМТ и распределены на 2 группы: основная группа- с избыточной массой тела- 112 мужчин (ИМТ от 25- 29,9 кг/м^2) и контрольная группа с нормальным - 214 мужчин (ИМТ до 25 кг/м^2).

Результаты. Уровень глобулина, связывающего половые гормоны (ГСПГ), отрицательно коррелирует с индексом массы тела, r_s= -0,218. Свободный тестостерон не показал различий между группами с нормальным и избыточным весом. Установлено наличие значимой корреляционной связи между ГСПГ и свободным тестостероном (r_s = -0,422, p < 0,01). Это подтверждает роль ГСПГ в регулировании уровня свободного тестостерона в крови.

Обсуждение. При избыточном весе уровень ГСПГ в крови снижается. Это оказывает каскадное влияние на распределение тестостерона между его связанными и свободными фракциями. Доказана значимая корреляционная связь между ГСПГ и свободным тестостероном. ГСПГ играет ключевую роль в связывании и транспорте половых гормонов.

Выводы. Доказана значимая корреляционная связь между ГСПГ и свободным тестостероном. У мужчин старших возрастных групп эректильная функция определяется не только уровнем свободного тестостерона, но и состоянием сосудистой, эндотелиальной, нервной и метаболической регуляции.

Ключевые слова. *глобулин связывающий половые гормоны (ГСПГ), фракция свободного тестостерона, мужчины старшего возраста, избыточный вес.*

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Түйіндеме

АРТЫҚ ДЕНЕ САЛМАҒЫ БАР ЕГДЕ ЖАСТАҒЫ ЕР АДАМДАРДА ЖЫНЫС ГОРМОНДАРЫН БАЙЛАНЫСТЫРАТЫН ГЛОБУЛИННІҢ (ЖГБГ) ТЕСТОСТЕРОННЫҢ БОС ФРАКЦИЯСЫ ДЕҢГЕЙІНЕ ӘСЕРІ

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Өзектілігі. Ер адамдардың өмірінің әртүрлі жас кезеңдерінде қан сарысуындағы жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) концентрациясы өзгереді. Артық дене салмағы мен висцералды семіздік жағдайында ЖГБГ деңгейінің төмендеуі байқалуы мүмкін, бұл өз кезегінде байланысқан және бос тестостерон арасындағы арақатынастың бұзылуына әкеледі. Аталған өзгерістер, әсіресе орта және егде жастағы ер адамдарда, функционалдық гипогонадизмнің дамуына себеп болуы ықтимал. Алайда артық дене салмағы жағдайында ЖГБГ-ның бос тестостерон деңгейіне әсер ету механизмдері мен оның ықпал ету дәрежесі әлі күнге дейін ғылыми талқылау нысаны болып отыр.

Зерттеу мақсаты. Артық дене салмағы бар ер адамдарда жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) тестостеронның бос фракциясының деңгейіне әсерін бағалау.

Материалдар мен әдістер. Зерттеуге Абай облысы, Семей қаласында тұратын 326 ер адам қатысты. Зерттелушілер дене салмағының индексі (ДСИ) бойынша стратификацияланып, екі топқа бөлінді: негізгі топ —

артық дене салмағы бар 112 ер адам (ДСИ 25–29,9 кг/м²) және бақылау тобы — дене салмағы қалыпты 214 ер адам (ДСИ ≤25 кг/м²).

Нәтижелер. Жыныс гормондарын байланыстыратын глобулин (ЖГБГ) деңгейі дене салмағының индексімен теріс корреляция көрсетті (rs = −0,218). Қалыпты және артық салмақты топтар арасында бос тестостерон деңгейі бойынша айтарлықтай айырмашылық анықталған жоқ. Сонымен қатар ЖГБГ мен бос тестостерон арасында статистикалық мәнді корреляциялық байланыс анықталды (rs = −0,422, p < 0,01), бұл ЖГБГ-ның қандағы бос тестостерон деңгейін реттеудегі рөлін дәлелдейді.

Талқылау. Артық дене салмағы жағдайында қандағы ЖГБГ деңгейі төмендейді, бұл тестостеронның байланысқан және бос фракциялары арасындағы таралуына каскадты әсер етеді. ЖГБГ мен бос тестостерон арасында мәнді корреляциялық байланыс бар екені дәлелденді. ЖГБГ жыныс гормондарын байланыстыру мен тасымалдауда негізгі рөл атқарады.

Қорытындылар. ЖГБГ мен бос тестостерон арасында статистикалық мәнді корреляциялық байланыс анықталды. Егде жастағы ер адамдарда эректильді функция тек бос тестостерон деңгейімен ғана емес, сонымен қатар тамырлық, эндотелиалдық, жүйкелік және метаболикалық реттелу жағдайымен де анықталады.

Түйінді сөздер: *жыныс гормондарын байланыстыратын глобулин (ЖГБГ), бос тестостерон фракциясы, егде жастағы ер адамдар, артық дене салмағы.*

Дәйексөз үшін:

Аккалиев М.Н., Масабаева М.Р., Қазанғапов Р.С., Рахыжанова С.О., Апсаликов Б.А., Жунуспекова А., Базарбеков Р.Ж., Бухариева С.С. Артық дене салмағы бар егде жастағы ер адамдарда жыныс гормондарын байланыстыратын глобулиннің (ЖГБГ) тестостеронның бос фракциясы деңгейіне әсері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 14-20. *doi 10.34689/SH.2025.27.6.002*

Introduction

In recent decades, there has been a steady increase in the prevalence of overweight and obesity, which represents a serious medical and social problem worldwide. According to the World Health Organization (WHO), more than half of the adult male population in both developed and developing countries is overweight [1]. In the presence of excess body weight, a significant proportion of men experience hormonal imbalance and reduced androgen levels.

Androgen deficiency is determined by serum testosterone levels. In the circulation, testosterone exists in three fractions: free (approximately 2%), not bound to transport proteins; weakly bound (about 38%), reversibly associated with albumin; and bound (around 60%), tightly bound to sex hormone–binding globulin (SHBG) [2]. The free fraction of testosterone (approximately 1–3% of the total level) is considered biologically active and exerts a direct physiological effect on target tissues. The concentration of androgens in the blood depends not only on their rate of synthesis but also on the efficiency of their transport to target cells. The primary transport protein for androgens is SHBG [3]. SHBG is synthesized in the liver and serves as the primary transport protein for hydrophobic androgens in the bloodstream. It plays an important role in regulating the bioavailability of all androgen fractions [4].

The serum concentration of SHBG changes across different age periods in men. With increasing chronological age, SHBG levels rise while the total testosterone concentration remains within the normal range. This leads to a decrease in free testosterone. Changes in BMI and the accumulation of adipose tissue also alter SHBG concentrations [5]. There is substantial evidence indicating that excess body weight, particularly visceral obesity, is associated with reduced SHBG concentrations, leading to alterations in the equilibrium between bound and free testosterone [6]. This may lead to a state of functional hypogonadism, particularly in middle-aged and older men. However, the mechanisms and extent of SHBG's influence on free testosterone levels in individuals with excess body weight remain a subject of scientific debate.

In this context, studying the relationship between SHBG concentration and free testosterone levels in men with excess body weight is highly relevant. The results obtained may contribute to more accurate diagnosis of androgen deficiency and inform the selection of strategies for hormonal correction in this patient population.

Study Objective: To evaluate the influence of sex hormone-binding globulin (SHBG) on the level of free testosterone fraction in men with excess body weight.

2. Materials and Methods

The study included 326 men residing in the city of Semey, Abay region. Participants were randomly selected from patients who presented to a urologist, aged 45 to 65 years, and had excess body weight. All participants provided informed consent to take part in the study.

The subjects were stratified by BMI and divided into two groups: the main group—overweight men with a BMI of 25–29.9 kg/m² (n = 112), and the control group with normal BMI below 25 kg/m² (n = 214).

Inclusion criteria:

- Male sex only;
- Overweight status (BMI ranging from 25.0 to 29.9 kg/m²);
- Age between 45 and 65 years;
- Written informed consent to participate in the study.

Exclusion criteria:

- BMI < 24.9 kg/m²;
- Age younger than 45 years;
- Presence of acute psychiatric conditions;
- Presence of acute infectious diseases;
- Presence of decompensated somatic diseases;
- Withdrawal from the study before completion of statistical analysis.

Body mass index (BMI) was calculated as the ratio of body

weight in kilograms to the square of height in meters (BMI = weight [kg] / height² [m²]). Body weight was measured with participants wearing underwear only and without shoes. Waist circumference was measured in the standing position at the level of the umbilicus, directly on the skin.

Assessment and classification of erectile dysfunction were performed using a questionnaire based on the validated International Index of Erectile Function-5 (IIEF-5). The reference values for the IIEF-5 were as follows: no erectile dysfunction (normal, 21–25 points); mild erectile dysfunction (16–20 points); moderate erectile dysfunction (11–15 points); severe erectile dysfunction (5–10 points).

Ethical approval and informed consent.

Written informed consent was obtained from all participants in accordance with the Declaration of the World Medical Association (Declaration of Helsinki). Participants were provided with information regarding the purpose of the study and the procedures involved. The study protocol was approved by the Ethics Committee of the Semey Medical University (Protocol No. 11, June 23, 2020).

Laboratory assessments.

Biochemical parameters, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and albumin, were measured at the commercial laboratory INVIVO using a Cobas 8000 analyzer (Roche Diagnostics, Switzerland). Reference ranges were as follows: HDL- 0.78–2.20 mM/L; LDL- 2.33–5.31 mM/L; triglycerides- 1.70–2.25 mM/L; and albumin- 35–55 g/L.

Total testosterone, sex hormone–binding globulin (SHBG), and luteinizing hormone (LH) levels were also determined at the commercial laboratory INVIVO using an Architect i2000SR analyzer (Abbott Laboratories, IL, USA). Reference ranges were as follows: SHBG- 10–57 nM/L; LH- 1.14–8.75 mIU/mL; total testosterone- 5.41–19.54 nM/L.

Free and bioavailable testosterone fractions were calculated using an online calculator (https://www.issam.ch/freetesto.htm) based on total testosterone, SHBG, and albumin concentrations.

Statistical analysis.

Statistical analysis was performed using SPSS software (version 20.0). Both parametric and nonparametric statistical methods were applied. The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Quantitative variables with a normal distribution were expressed as mean ± standard deviation (M ± SD), whereas non-normally distributed variables were presented as median and interquartile range (Me [IQR]). For comparative analysis of quantitative variables, Student's t-test and the Mann–Whitney U- test for independent samples were used. Spearman's rank correlation coefficient (r_s) was applied to evaluate the association between two quantitative variables.

Results.

The average age of participants was 52(12) years in the study group and 58 (12) years in the control group, indicating a statistically relevant age difference, with younger individuals predominating in the study cohort.

Table 1.

Indicators of Androgen and Lipid Profiles.

Parameters	Main group (n=112) from 25–29.9 kg/m²	Control group (n=214) to ≤25 kg/m²	p
Body mass index (BMI)	29,3± 0,9	23,6±1,15	<0,001**
Age	46(12) (34-65)	53(12) (37-65)	<0,001*
Waist circumference	106 (11,50) 81-110	90 (7,0) 93-121	<0,001*
Hip circumference	56 (6,0) 47-61	50 (3,0) 42-56	<0,001*
Index of Erectile Function-5 (IIEF-5 score)	26,4± 2,5	22,7± 4,3	0.2**
sex hormone–binding globulin (SHBG)	23,0 (20,05) 10,80-43,20	34,1 (18,5) 10,80- 82,80	<0,001*
Albumin	43,2 (3,9) 28,70- 51,40	45,0 (4,98) 21,40- 52,40	<0,001*
luteinizing hormone LH	3,8 (1,94) 1,64- 12,03	4,09 (2,42) 1,64- 10,44	0,682*
Total testosterone	9,4 (2,14) 5,01- 12,75	12,5 (3,14) 8,42- 17,40	<0,001*
Bioavailable testosterone	4,99 5,3 (1,89)	5,14 5,3 (1,8)	0,361*
Free testosterone	0,213 0,2 (0,07)	0,210 0,2 (0,09)	0,032*
Triglycerides	2,5 (1,83) 0,53- 10,80	1,7 (1,22) 0,87- 7,44	<0,001*
low-density lipoprotein (LDL)	3,9 (+0,6) 2,0- 5,59	3,2 (+0,6) 2,79- 5,62	<0,001*
high-density lipoprotein (HDL)	1,0 (0,27) 0,62- 9,64	1,2 (0,63) 0,78- 9,05	0,384*

Notes:
1 * – Mann–Whitney U test, Me (IQR) (median (interquartile range)), min and max values;
2 ** – Student's t-test, M ± SD (mean ± standard deviation).

In this context, the higher BMI observed at a younger age may be attributed to the influence of hypogonadism. A consistent pattern was observed: as BMI increased, thigh circumference and body weight also increased. A negative correlation was noted between erectile dysfunction and BMI. An increase in BMI was significantly associated with

greater severity of erectile dysfunction (r_s = −0.560, p < 0.01). Additionally, sex hormone–binding globulin (SHBG) levels demonstrated a significant inverse correlation with BMI. The correlation coefficient (r_s) was –0.218, which, at p < 0.01, confirms the statistical significance of this association. As BMI increases, SHBG levels decrease, demonstrating the impact of obesity on the concentration of this protein. This observation directly affects circulating total testosterone concentrations, which are largely modulated by SHBG. A significant positive association was identified between SHBG and total testosterone levels (r_s = 0.266, p < 0.01). Moreover, decreases in serum total testosterone were proportional to SHBG concentrations, supporting the established role of SHBG as the principal carrier protein for sex steroids and a key regulator of their bioavailability and biological effects. These results confirm the importance of SHBG in regulating testosterone levels and underline its essential role in maintaining hormonal balance. In a comparative analysis with the normal-weight group, albumin levels were noticeably lower in the overweight group. However, no significant differences in albumin levels were observed when compared with other biochemical parameters between the groups. This may indicate that the decrease in albumin in the overweight group did not exert a meaningful influence on the other examined variables. Additionally, luteinizing hormone levels were lower in the overweight group, but still within the reference range. This suggests that excess body weight in this population does not lead to pronounced changes in LH secretion.

Free testosterone did not differ between the normal-weight and overweight groups. This phenomenon is likely associated with the compensatory decrease in total testosterone and SHBG levels in the overweight group, which may influence the balance between bound and free testosterone fractions. Nevertheless, a statistically significant inverse relationship was observed between SHBG and free testosterone (r_s = −0.422, p < 0.01), further substantiating the role of SHBG in the regulation of circulating free testosterone levels. Biologically active testosterone was also lower in the overweight group. This may be explained by the reduction in albumin levels in this group, which disrupts testosterone transport and leads to a decrease in the concentration of the active hormone fraction. The statistical significance of this association was r_s = 0.196 (p < 0.01), confirming the importance of albumin in maintaining biologically active testosterone levels.

Analysis of lipid metabolism revealed that overweight individuals exhibited elevated triglyceride and LDL concentrations, which were inversely related to reductions in SHBG levels. A statistically significant inverse correlation was observed between LDL cholesterol and SHBG (r_s = −0.197, p < 0.001). HDL levels decreased in parallel with SHBG in the overweight group, although this change did not reach statistical significance.

Discussion

The present study focuses on investigating the association between sex hormone–binding globulin (SHBG) levels and the concentration of free testosterone in overweight men. Free testosterone represents the biologically active component of circulating testosterone, existing independently of transport proteins and constituting approximately 1–3% of total serum testosterone [7]. Its concentration depends on the level of total testosterone as well as on the content of binding proteins, primarily sex hormone-binding globulin (SHBG) and, to a lesser extent, albumin. In the present study, a significant association was identified between SHBG levels and indicators of androgen status. Our findings demonstrated that SHBG levels negatively correlate with body mass index (BMI) (r_s = –0.218, p < 0.01). These findings suggest a trend toward reduced SHBG levels in men with excess body weight. The underlying mechanism of this association is likely related to metabolic alterations accompanying overweight, as increased visceral adiposity is associated with hyperinsulinemia due to insulin resistance, as well as elevated leptin concentrations. These inflammatory factors suppress the hepatic synthesis of SHBG[8]. As a result, the level of SHBG in the blood decreases, which produces a cascade effect on the distribution of testosterone between its bound and free fractions. Since SHBG plays a key role in the binding and transport of sex steroids, a reduction in its concentration may directly influence circulating total testosterone levels. In our study, a positive correlation between SHBG and total testosterone was observed (r_s = 0.266, p < 0.01). Men with lower SHBG levels demonstrated reduced total testosterone. This finding supports the assumption that SHBG serves as a major regulator of androgen bioavailability. A decrease in SHBG leads to a reduction in the proportion of testosterone in the bound state, which increases the relative amount of free testosterone. This explains why, in men with excess body weight, moderate reductions in total testosterone may still be accompanied by free testosterone levels within the normal range, owing to decreased SHBG binding. Thus, a compensatory redistribution of testosterone fractions occurs, allowing the biological activity of androgens to be maintained even when total testosterone levels decline.

In cases of pronounced obesity accompanied by a reduction in albumin levels, the concentration of biologically active testosterone (the sum of free and albumin-bound testosterone) may also decrease. This occurs because a portion of testosterone previously bound to albumin shifts into the free fraction. However, overall androgen activity may decline due to reduced total testosterone levels and gonadal dysfunction [9].

Excess body weight has a significant impact on lipid metabolism and hormonal status. In the presence of obesity, insulin resistance and inflammatory processes develop, adversely affecting lipid metabolism. This leads to an increase in triglyceride and LDL levels. The concentration of high-density lipoproteins (HDL) also decreases. These metabolic changes are associated with reduced hepatic synthesis of sex hormone–binding globulin (SHBG) [10].

Age-associated reductions in total testosterone activate compensatory feedback pathways, resulting in elevated luteinizing hormone (LH) secretion. Circulating LH levels may therefore serve as an indicator of gonadal functional integrity. Our findings demonstrate that this regulatory response is preserved in men with normal body mass. In contrast, individuals with excess body weight exhibit a decline in LH concentrations. This phenomenon is likely related to enhanced aromatase activity within adipose tissue, which promotes the conversion of testosterone to

estradiol. Increased estradiol levels exert negative feedback on LH secretion and inhibit the release of gonadotropin-releasing hormone (GnRH). [11]. As a result, circulating testosterone levels decline. In our study, the concentration of free testosterone was similar in both groups. However, despite the absence of significant differences in measured hormonal levels, the overweight group demonstrated a pronounced pattern of erectile dysfunction.

In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation [12]. In visceral obesity, a number of pathophysiological disturbances develop, which can lead to erectile dysfunction even if free testosterone levels remain within the normal range.

In the presence of excess adipose tissue, insulin resistance and elevated levels of free fatty acids are observed. These factors lead to a reduction in nitric oxide (NO) synthesis by the endothelium of penile vessels. NO deficiency impairs the relaxation of the corpora cavernosa and hinders adequate arterial blood inflow, which is the primary mechanism of erection. In older men, obesity accelerates atherogenesis. Narrowing of arterial lumens and decreased arterial elasticity reduce blood flow to the corpora cavernosa.

Since the penile vessels have a small diameter, erectile dysfunction often represents an early manifestation of systemic atherosclerosis. Insulin resistance also promotes the development of chronic subclinical inflammation, contributing to oxidative stress.

Even at normal levels of free testosterone, these mechanisms impair the hemodynamic phase of erection [13].

These factors lead to decreased libido, impaired psychosexual response, and exacerbation of erectile dysfunction, even though free testosterone levels formally remain within the normal range.

Moreover, reductions in SHBG and free testosterone in men with excess body weight may further exacerbate metabolic disturbances, creating a vicious cycle: hypogonadism increases insulin resistance and promotes fat accumulation, which in turn further decreases androgen levels. These interrelationships are particularly important for men over 40, who already experience a physiological decline in testosterone production.

The clinical relevance of the observed associations is that reliance solely on total testosterone measurements may not adequately reflect androgen status in men with excess body weight. In this population, evaluation of sex hormone–binding globulin (SHBG) concentrations and estimation of free testosterone using validated calculation methods (such as the Vermeulen equation) provide greater diagnostic value.

Accordingly, our findings highlight the importance of an integrated hormonal evaluation in overweight men and support the consideration of SHBG and free testosterone parameters in diagnostic and therapeutic algorithms for disorders of androgen homeostasis. Future prospective studies are needed to evaluate the impact of body weight normalization and metabolic parameter improvement on the dynamics of SHBG and free testosterone levels.

Conclusions

A correlation exists between SHBG and free testosterone. In older men, erectile function is determined not only by the level of free testosterone but also by the condition of vascular, endothelial, neural, and metabolic regulation.

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ASSESSMENT OF THE PROBABILITY OF DEVELOPING CARDIORENAL SYNDROME TYPE 2 DEPENDING ON POTENTIAL BIOMARKERS IN PEDIATRIC PATIENTS

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Abstract

Introduction. The investigation of cardiorenal syndrome holds significant clinical relevance, as both cardiovascular and renal diseases rank among the leading causes of mortality. Current research efforts are focused on identifying reliable biomarkers for the early detection of acute kidney injury (AKI), which may serve as a valuable predictor for improving prognosis and therapeutic strategies in patients with chronic heart failure.

The study aims to identify biomarkers associated with an increased risk of type 2 cardiorenal syndrome in children.

Materials and methods. We performed a retrospective analysis with a case-control design. From the medical records of the Scientific National Cardiac Surgery Center (NNCC), we identified all pediatric patients with CHF due to DCM who had an initial hospitalization in 2022 and a subsequent re-hospitalization in 2023. Based on their diagnosis at re-hospitalization, patients were classified into two groups: the case group (those with confirmed Type 2 CRS, n=18) and the control group (those with CHF but without CRS, n=21). We then extracted and compared laboratory data from both the 2022 (baseline) and 2023 (follow-up) hospitalizations for all participants.

Results. Reduced serum iron levels were observed at baseline and during follow-up in both the control and case groups (9 and 5.9 μmol/L, respectively). Elevated total bilirubin levels were also detected in both groups (0.41 μmol/L in controls and 0.55 μmol/L in cases). Notably, galectin-3 concentrations were elevated in the case group, showing a 13% increase compared to the control group. Markers of renal dysfunction, including the albumin-to-creatinine ratio (ACR) and the blood urea nitrogen-to-creatinine (BUN/Cr) ratio, were comparable between the two groups (ACR: 31 and 32 mg/g; BUN/Cr: 30 and 32, respectively). Statistically significant correlations were identified between kidney function (as measured by ACR) and levels of serum iron (p=0.05), hemoglobin (p=0.02), and galectin-3 (p=0.02). Galectin-3 was a significant predictor of renal dysfunction, with an 81% increase in the likelihood of renal dysfunction (OR = 1.81, 95% CI). Similarly, the BUN/Cr ratio was associated with a 70% increase in the likelihood of renal impairment (OR = 1.70, 95% CI).

Conclusion. The findings indicate that, despite similar baseline values of key renal markers across groups, galectin-3 levels were significantly elevated in cases and were strongly associated with renal dysfunction. Reduced serum iron and elevated bilirubin levels were observed in both groups, suggesting potential systemic involvement. However, the small sample size limits the statistical power and generalizability of these findings, warranting validation in larger, prospective cohorts.

Keywords: *cardiorenal syndrome type 2, galectin, troponin, potential biomarkers.*

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Резюме

ОЦЕНКА ВЕРОЯТНОСТИ РАЗВИТИЯ КАРДИОРЕНАЛЬНОГО СИНДРОМА 2 ТИПА В ЗАВИСИМОСТИ ОТ ПОТЕНЦИАЛЬНЫХ БИОМАРКЕРОВ У ДЕТЕЙ

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Введение. Исследование кардиоренального синдрома имеет важное клиническое значение, поскольку как сердечно-сосудистые, так и почечные заболевания входят в число основных причин смертности. Текущие исследовательские усилия сосредоточены на выявлении надежных биомаркеров для раннего выявления острого повреждения почек (ОПП), которые могут служить ценным предиктором для улучшения прогноза и терапевтических стратегий у пациентов с хронической сердечной недостаточностью.

Целью исследования является выявление биомаркеров, связанных с повышенным риском кардиоренального синдрома 2 типа.

Материалы и методы. Было проведено ретроспективное исследование типа «случай-контроль» с участием пациентов с подтвержденным диагнозом кардиоренального синдрома (КРС) 2-го типа (n=18) во время первичной госпитализации в 2022 г. и последующей повторной госпитализации в 2023 г., которые составили группу случая. Контрольная группа включала пациентов с хронической сердечной недостаточностью (ХСН), но без клинических или лабораторных признаков КРС 2-го типа (n=21).

Результаты. Снижение уровня сывороточного железа наблюдалось на исходном уровне и во время последующего наблюдения как в группе контроля, так и в группе случая (9 и 5,9) мкмоль/л соответственно). Повышенные уровни общего билирубина также были обнаружены в обеих группах (0,41 мкмоль/л в контрольной группе и 0,55 мкмоль/л в случаях). Примечательно, что концентрации галектина-3 были повышены в группе случая, показывая 13%-ное увеличение по сравнению с контрольной группой. Маркеры почечной дисфункции, включая соотношение альбумина к креатинину (ACR) и соотношение азота мочевины крови к креатинину (BUN/Cr), продемонстрировали сопоставимые значения в обеих группах (ACR: 31 и 32 мг/г; BUN/Cr: 30 и 32 соответственно). Статистически значимые корреляции были выявлены между функцией почек (измеренной по ACR) и уровнями сывороточного железа (p=0,05), гемоглобина (p=0,02) и галектина-3 (p=0,02). Было обнаружено, что галектин-3 является значимым предиктором почечной дисфункции, с 81%-ным увеличением вероятности (OR=1,81, 95% CI). Аналогичным образом, соотношение BUN/Cr продемонстрировало 70%-ную вероятность влияния на почечную недостаточность (OR=1,70, 95% CI).

Заключение. Результаты показывают, что, несмотря на схожие исходные значения ключевых почечных маркеров между группами, уровни галектина-3 были значительно повышены в случаях и продемонстрировали сильную связь с почечной дисфункцией. Снижение уровня сывороточного железа и повышение уровня билирубина наблюдались в обеих группах, что предполагает потенциальное системное вовлечение. Однако небольшой размер выборки ограничивает статистическую мощность и возможность обобщения этих результатов, что требует их подтверждения в более крупных проспективных когортах.

Ключевые слова: *кардиоренальный синдром II типа; галектин; тропонин; потенциальные биомаркеры.*

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Түйіндеме

БАЛАЛАРДА ПОТЕНЦИАЛДЫ БИОМАРКЕРЛЕРГЕ БАЙЛАНЫСТЫ КАРДИОРЕНАЛДЫ СИНДРОМНЫҢ 2-ТИПІНІҢ ДАМУ ЫҚТИМАЛДЫҒЫН БАҒАЛАУ

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Кіріспе. Кардиореналдық синдромды зерттеу клиникалық тұрғыдан маңызды, өйткені жүрек-қантамыр және бүйрек аурулары өлімнің негізгі себептерінің қатарына жатады. Қазіргі зерттеулер бүйректің жедел зақымдануын (БЖЗ) ерте анықтауға мүмкіндік беретін сенімді биомаркерлерді айқындауға бағытталған; олар созылмалы жүрек жеткіліксіздігі (СЖЖ) бар науқастарда болжамды жақсартуға және емдік тактиканы жетілдіруге құнды предиктор бола алады.

Мақсаты. Кардиореналдық синдромның (КРС) 2-типі даму қаупінің артуымен байланысты биомаркерлерді анықтау.

Материалдар және әдістер. 2022 жылы алғашқы, 2023 жылы қайталама госпитализация кезінде КРС-2 диагнозы расталған науқастар (n=18) “жағдай” тобына енгізілген, ал КРС-2-нің клиникалық не зертханалық белгілері жоқ СЖЖ-сы бар науқастар (n=21) бақылау тобын құрған, ретроспективті“жағдай–бақылау” типті зерттеу жүргізілген.

Нәтижелер. Сарысулық темір деңгейінің төмендеуі бастапқыда да, кейінгі бақылауда да әрі бақылау, әрі оқиға топтарында байқалды (тиісінше 9 және 5,9 мкмоль/л). Жалпы билирубин деңгейі де екі топта жоғары болды (бақылауда 0,41 мкмоль/л және оқиға тобында 0,55 мкмоль/л). Елеулі жайт - зерттеу тобында галектин-3 концентрациясы жоғарылап, бақылаумен салыстырғанда 13% өсім көрсетті. Бүйрек дисфункциясының маркерлері - альбумин/креатинин арақатынасы (ACR) және қан несепнәрі азоты/креатинин арақатынасы (BUN/Cr) - екі топта да ұқсас мәндер берді (ACR: 31 және 32 мг/г; BUN/Cr: сәйкесінше 30 және 32). Бүйрек қызметі (ACR бойынша) мен сарысулық темір (p=0,05), гемоглобин (p=0,02) және галектин-3 (p=0,02) деңгейлері арасында статистикалық мәнді өзара байланыстар анықталды. Галектин-3 бүйрек дисфункциясының мәнді предикторы болып табылды: бірлестік ықтималдығының 81% артуы байқалды (OR=1,81; 95% сенім аралығы). Сол сияқты BUN/Cr қатынасы да бүйрек жеткіліксіздігіне ықпал ету ықтималдығын 70% арттырды (OR=1,70; 95% сенім аралығы).

Қорытынды. Негізгі бүйрек маркерлерінің бастапқы мәндері топтар арасында ұқсас болғанына қарамастан, зеттелген топта галектин-3 деңгейі айқын жоғары болды және бүйрек дисфункциясымен күшті байланыс көрсетті. Сарысулық темірдің төмендеуі мен билирубиннің жоғарылауы, жүйелік сипаттағы өзгерісті көрсетеді. Дегенмен, іріктеменің шамалы көлемі бұл нәтижелердің статистикалық сенімділігі мен жалпыланған қорытындылар жасау мүмкіндігін шектейді, сондықтан оларды үлкенірек, перспективті когорттарда растау қажет.

Түйін сөздер: *II типті кардиореналды синдром; галектин; тропонин; потенциалды биомаркерлер.*

Дәйексөз үшін:

Байгалканова А.И., Абдрахманова С.Т., Месова А.М., Бесбаева Г.К., Тулеубаева А.А. Потенциалды биомаркерлерге байланысты кардиореналды синдромның 2-типінің даму ықтималдығын бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 21-29. *doi 10.34689/SH.2025.27.6.003*

Introduction

Cardiorenal syndrome (CRS) is characterized by acute or chronic dysfunction of the kidneys or heart, leading to secondary acute and/or chronic dysfunction of the other organ (Acute Dialysis Quality Initiative Group, 2008). The interaction between the heart and kidneys involves several complex cellular, subcellular, and molecular mechanisms. CRS often leads to dysfunction in both organs and is associated with adverse patient outcomes [18]. According to available data, in-hospital mortality among children with chronic heart failure (CHF) and comorbidities, particularly chronic kidney disease, can exceed 20%. Moreover, the risk of mortality remains high even after discharge from the hospital [10,18]. To improve treatment outcomes in CRS, a clear understanding of the pathophysiological interactions between the heart and kidneys, as well as the identification of reliable predictors, is essential [10,18].

Efforts are currently underway to identify biomarkers for the early detection of acute kidney injury (AKI), which could potentially serve as predictors to improve clinical outcomes in CRS [12]. Accordingly, recent research on the diagnosis of CRS has increasingly focused on biomarkers. Among the most commonly used biomarkers in clinical practice are cystatin C, galectin-3, N-acetyl-beta-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), fatty acid-binding proteins (FABPs), and neutrophil gelatinase-associated lipocalin (NGAL). However, their application remains restricted mainly to adult practice [7,22,26]. To date, there is limited evidence supporting the effectiveness of these biomarkers in pediatric CRS, and it remains challenging to classify them by CRS subtypes due to insufficient data [13].

Classical indicators of renal function, such as blood urea nitrogen (BUN) and serum creatinine, remain widely used. However, BUN is an unreliable indicator of renal function, as its levels can be influenced by high protein intake, dehydration, heart failure, increased catabolism, and diuretic use [14,15,24]. Similarly, creatinine is an inadequate early marker of renal dysfunction. Neither BUN nor creatinine alone is effective for the early detection of renal injury. However, the BUN-to-creatinine (BUN/Cr) ratio is a well-established marker of renal failure, and several studies have demonstrated its association with prognosis in heart failure and its role as an independent predictor of all-cause mortality [27].

New diagnostic modalities, such as strain echocardiography and cardiac MRI, offer distinct advantages, particularly for assessing ventricular size, function, and fibrosis. However, the complexity of these methods and their limited availability currently favor the use of traditional echocardiography and ultrasound. At the same time, advances in diagnostic techniques offer opportunities to optimize the algorithms for the timely diagnosis and treatment of CRS in pediatric patients. These topics, however, are insufficiently addressed in the available literature, and the existing data are often contradictory, with most studies originating from abroad. Notably, similar studies have not yet been conducted in Kazakhstan, highlighting the relevance and timeliness of the present research.

Aim: to identify predictors of the development of type 2 cardiorenal syndrome in children with chronic heart failure due to dilated cardiomyopathy (DCM).

Materials and Methods

A retrospective case-control analysis was conducted at the Scientific National Cardiac Surgery Center (hereinafter referred to as NNCC) during 2022-2023. The study design is a longitudinal, observational, case-control study, in which patients with a confirmed diagnosis of type 2 CRS (n=18) were selected. The "control" group included patients (n=21) with chronic heart failure without manifestations of type 2 CRS. Patients with confirmed diagnoses of CRS type 2 for the first time (2022 year) and repeated (2023 year) hospitalizations taken for the "case" group.

The study results were based on medical record extracts from pediatric patients who underwent repeated inpatient treatment at the NCCC in 2022 and 2023.

The study participants were pediatric patients (0-18 years old) with a confirmed diagnosis of cardiorenal

syndrome type 2. *The inclusion criteria were:*

1. Children's age participant (0-18 years);
2. Confirmed diagnosis—cardiorenal syndrome type 2;
3. The presence of cases of hospitalization in the 24-hour hospital of the NNCC in the period 2022 and 2023;
4. Availability of medical documentation indicators selected laboratory tests for each hospitalization.

Exclusion criteria were

1. Exceeding the age of children (older than 18 years);
2. Lack of medical records for laboratory tests. A longitudinal case-control study entails retrospective data collection; our study did not provide for patient contact. Coding is used to copy medical documentation data, thereby preventing loss of confidentiality. Informed agreement was not required.

Laboratory studies were divided into four groups according to the mechanisms of secondary kidney injury, according to international studies:

1. Hematological and biochemical indicators of anemia;
2. Biochemical indicators of kidney function;
3. Biochemical indicators of liver function.
4. Biochemical indicators of damage to cardiac muscles.

Descriptive and inductive statistics were used for qualitative and quantitative analyses, and diagrams and tables were used to visualize the results graphically.

Statistical analysis was used to assess the significance of differences in grouped results, to identify associations between variables, and to predict diagnostic test use at the 95% confidence level.

To determine the distribution of variables, histograms were constructed for each series. Parametric and nonparametric criteria were used to assess the statistical significance of differences, depending on the distribution's normality. The statistical significance of differences was determined using the Student criterion (with a normal distribution of variables) for dependent and independent samples, the Mann-Whitney criterion for independent samples, and the Kruskal-Wallis test for dependent samples (with a non-Gaussian distribution of variables), as well as multivariate analysis of variance (when comparing more than two groups of variables).

The presence of associations between variables was assessed using correlation and regression analyses, and odds ratios were computed when analyzing historical data. The coefficient was calculated using Pearson correlations.

To build a model for predicting the development of type 2 cardiorenal syndrome in pediatric patients with CHF in dilated cardiomyopathy using laboratory tests (serum iron, bilirubin, galectin-3, the ratio of albumin to creatinine in a single portion of urine, and the ratio of blood urea nitrogen to creatinine), ROC analysis (receiver operating characteristic) was used. ROC - the analysis is expressed graphically, where AUC (area under the ROC curve) - the area under the ROC curve characterizes the probability of success. Meanings are interpreted according to classification, where an AUC of 0.5 is considered equally likely for both groups; 0.5-0.75 is a sufficient level of success, and over 0.75 is a significant probability of success. To interpret the ROC, the analysis identified a cutoff threshold for each variable equal to its median value for each test.

Results

Comparative analysis of original and studied levels of potential biomarkers for the development of cardiorenal syndrome type 2 in pediatric patients with CHF in DCM. The study took place in the Department of Pediatric Cardiology at the National Scientific Cardiac Surgery Center. Clinical and laboratory data of 39 pediatric patients with chronic heart failure due to dilated cardiomyopathy, treated in the period from 2022 to 2023.

All study participants were diagnosed with chronic heart failure with dilated cardiomyopathy, with the presence of CRS confirmed in 18 children (46%), which comprised the group "case", and not confirmed in 21 (54%) children, which entered the group "control". In the case group, the distribution of boys and girls was 12 (66.7%) and 6 (33.3%), respectively; in the "control" group, 8 (38.1%) and 13 (61.9%).

We assessed laboratory indicators in both groups at the time of the first and subsequent hospitalizations to determine the initial and current levels of CRS type 2 markers. To conduct the analysis, we constructed histograms to assess the distribution of variables.

It was established that the distribution is non-Gaussian. To determine the presence of statistical significance of differences, we used a non-parametric criterion, the Mann-Whitney test, for comparisons between indicator groups "case" and "control", and the Kruskal-Wallis test for comparing indicators within each group according to the age and sex characteristics of the participants.

We examined indicators by participant gender in laboratory test groups that characterize the main pathogenetic mechanisms underlying the development of cardiorenal syndrome. It was found that the serum iron level in the "case" group was at the lower limit of the norm for both boys and girls. Comparison of indicators within the group was determined using the Kruskal-Wallis criterion. At the 95% confidence level, the indicators hemoglobin, platelets, and serum iron were not statistically significant ($p > 0.05$).

Next, we reviewed the laboratory test results for participants in the control group who were diagnosed with chronic heart failure in DCM but who did not have confirmation of the development of CRS 2nd type. The statistical significance of differences at the 95% confidence level has also not been established. It should be noted that the value of hematological parameters corresponds to the accepted normal values, and the level of serum iron is at the lower limit of the accepted norm.

Table 1 shows that overall hemoglobin levels in the control and case groups were comparable. Minor fluctuations were observed across individual age subgroups; however, no statistically significant differences between the Control and Case groups were identified.

Platelet counts varied across age groups but remained within physiological limits. In contrast, serum iron levels in the Case group were consistently lower than in the Control group. The median serum iron concentration in the Case group was approximately 5.9 μmol/L, compared with 9.0 μmol/L in the Control group, reflecting a nearly 40% reduction. This finding indicates a tendency toward iron-deficiency states in patients in the Case group, warranting further investigation and therapeutic correction.

Comparison of indicators by age groups was not conducted due to the small sample sizes for each age group. It is noteworthy that the serum iron level in the “case” group is 40% lower than that in the “control” group, based on the median value.

Next, we analyzed the liver function indicator, total bilirubin, in participants in the “control” and “case” groups.

High total bilirubin levels were observed in both boys and girls. Despite a three-fold increase in bilirubin levels in girls, by comparison with values in the boys group “case”, and on the contrary, in the “control” group, the statistical significance of differences was not established at a confidence level of 95% (p=0.38, p=0.6, respectively).

Table 1.

Iron metabolism parameters by age group at first hospitalization.

Age (years)	Hb (g/L) Control	Hb (g/L) Case	Platelets (*10⁹/L) Control	Platelets (*10⁹/L) Case	Serum iron (µmol/L) Control	Serum iron (µmol/L) Case
0–1	101.6	115.25	382	496	8.82	4.66
1–2	110	113	486	348	9.3	8.6
2–4	117	104	391	404	8.6	5.3
4–6	114	119	340	356	7.64	5.3
8–10	121	—	—	—	20.5	3.5
12–14	126	124	369	281	13.1	10
14–16	110	122	479	308	8.23	6.51
16–18	135	—	—	—	22.6	9.49

Bilirubin levels across different age groups demonstrate variable fluctuations in both study groups (Table 2). However, of particular note are the elevated bilirubin levels in the Case group with already established persistent renal pathology. Based on the median, bilirubin in the Case group was ~33% higher than in Controls (0.55 vs 0.41 µmol/L; unweighted medians across age groups, missing cells ignored).

Table 2.

Bilirubin levels by age group at first hospitalization.

Age group (years)	Control (µmol/L)	Case (µmol/L)
0–1	0.39	0.55
1–2	0.28	0.60
2–4	0.32	0.65
4–6	0.45	0.50
8–10	—	0.52
12–14	1.01	1.05
14–16	0.43	0.49
16–18	—	0.54

The next group of laboratory tests of interest in the study of type 2 CRS comprises troponin, a particular marker of myocardial injury, and galectin-3, a potential marker of fibrosis in parenchymatous organs [19]. Gal-3 was assessed clinically as a renal disease biomarker to monitor and guide therapeutic strategies [3].

In participants in the "control" group, the level of galectin-3 exceeded the normal value by 110.7% in boys and 47.3% in girls. It was found that troponin levels were within the reference range in participants in the "case" group, whereas galectin-3 levels exceeded reference values by 87.7% and 60.3% in boys and girls, respectively. In both groups, the statistical significance of gender differences was not established (p = 0.7 and p = 0.77 in the "control" and "case " groups, respectively).

The fourth group of laboratory parameters characterizing kidney function in the “control” group comprises urea and blood urea nitrogen levels. It has been established that urea and blood urea nitrogen levels exceed accepted reference values in both boys and girls. The albumin-to-creatinine ratio in a single urine sample is within the upper limits of the reference range. At the same time, the ratio of blood urea nitrogen to creatinine is high compared to normal. There are no statistically significant differences in kidney function indicators at the 95% confidence level across gender groups (p > 0.05).

Given the results indicating an excess of specific laboratory indicators, we conducted a comparative analysis of these indicators between the two groups. We assessed the statistical significance of differences using the nonparametric Mann-Whitney test (Table 3).

It was established that the parameters serum iron (p=0.02), total bilirubin (p=0.03), and galectin-3 (p=0.05) were statistically significant.

Given that galectin-3 levels exceeded normal values in both groups, we conducted correlation and regression analyses to assess associations with other laboratory parameters.

Table 3.

Laboratory test parameters (mean, median) “control” and “case” groups at the time of first hospitalization.

	Control		Case		p-value
	Mean	Median	Mean	Median	
Hemoglobin	112.1	114.0	110.5	111.8	0.41
Platelets	398.2	406.0	415.5	406.9	0.16
Creatinine	0.45	0.3	1.25	1.2	0.53
Urea	29.8	23.4	31.1	30.3	0.8
BUN	13.9	10.9	14.4	14.1	0.9
ACR	30.5	31	32.5	32.0	0.61
Serum iron	9.8	9.0	6.2	5.9	**0.02**
Total bilirubin	0.39	0.41	0.57	0.55	**0.03**
Troponin I	1.22	1	1.35	1.3	0.34
Galectin 3	34.0	19.8	38.5	22.4	**0.05**
BUN/creatinine	30.5	30.0	32.2	32	0.34

It was found that the studied laboratory parameters have very weak and weak associations with the level of galectin-3; the reverse association is with the bilirubin index (r =- 0.3). A linear regression corroborates the correlation analysis results. Regression analysis showed that the effects of the laboratory tests studied were not statistically significant (p > 0.05).

Next, we conducted correlational and regression analyses to assess the influence of the studied parameters on kidney function: the albumin-to-creatinine ratio in a single urine sample and the urea nitrogen-to-creatinine ratio in serum.

It was established that the inverse average correlation links for the increase in the blood serum ratio of urea nitrogen to creatinine in the "control" group are with hematological indicators (hemoglobin: 0.24; platelets: 0.35).

Regression analysis showed that hematological parameters and serum iron levels had a statistically significant effect on ACR and the urea nitrogen-to-creatinine ratio in the serum of the studied "control" group.

During rehospitalization after a 1-year interval, the participants in the case group were confirmed to have type 2 CRS. No statistically significant differences between the case and control groups were observed for any variable at the 95% confidence level (p> 0.05), confirming the diagnosis of type 2 CRS in the studied "case" group.

Our study has established that the development of persistent renal dysfunction in pediatric patients with chronic heart failure is influenced by iron metabolism indices, namely serum iron and hemoglobin (40% higher in the case group) and bilirubin (33% higher in the case group). This indicates more pronounced catabolic processes in the liver and greater iron consumption in the developed form of type 2 CRF. Regression analysis also showed the influence of these indices on renal function. Thus, a decrease in serum iron and elevated total bilirubin indices can be considered prognostic indicators of the development of persistent renal dysfunction.

Evaluation of probabilities for the development of cardiorenal syndrome Type 2, depending on potential biomarkers

To further elucidate the predictive relevance of these biomarkers, logistic regression modeling and receiver operating characteristic (ROC) curve analysis were performed, using the BUN/Cr ratio as the dependent variable. To clarify the effects of serum iron, total bilirubin, and galectin-3 levels on renal impairment, we constructed a logistic regression model and performed ROC analysis. The cutoff threshold was the parameter selected to calculate the odds ratio. The final parameter to which potential biomarkers were assigned was the blood urea nitrogen-to-creatinine ratio. STATA 16E software was used to construct the model.

The area under the curve of the serum iron model was 0.46, indicating insufficient sensitivity for predicting deterioration in the blood urea nitrogen-to-creatinine ratio and, consequently, deterioration in renal function.

For the total bilirubin parameter, the area under the curve was 0.41, indicating low sensitivity of this test as a prognostic indicator for renal dysfunction.

The area under the curve of the galectin-3 model was 0.9, indicating high accuracy in forecasting the increase in the blood urea nitrogen-to-creatinine ratio and supporting the diagnosis of type 2 CRS progression.

1.ROC Analysis of Biomarkers. The AUC for serum iron was 0.46, reflective of poor discriminative capability. The AUC for total bilirubin was 0.41, indicating low sensitivity and specificity. The galectin-3 model exhibited an AUC of 0.9, indicating high diagnostic accuracy and substantial predictive value for CRS2 development.

2. Supplementary ROC Analysis Using ACR as an Endpoint. The serum iron model demonstrated an AUC of 0.6, denoting moderate sensitivity. The total bilirubin model produced an AUC of 0.4, underscoring low sensitivity and specificity. The galectin-3 model achieved an AUC of 0.733, indicating moderate predictive utility for identifying CRS type 2.

3. ROC Analysis of the BUN/Cr Ratio. Subsequent ROC analysis for BUN/Cr produced an AUC of 0.65, indicative of moderate model performance in forecasting CRS type 2 development.

Our analysis establishes that, at the 95% confidence level, elevated galectin-3 levels precede the onset of CRS type 2 in 81% of cases (OR 1.81). While serum iron and total bilirubin showed potential associations with CRS type 2 risk (21% and 50%, respectively), their predictive values were not statistically significant (p > 0.05). The ROC analysis indicates that galectin-3 and the BUN/Cr ratio are promising biomarkers for early identification of declining renal function, with AUC values of 0.9 and 0.733, respectively (Figure 1).

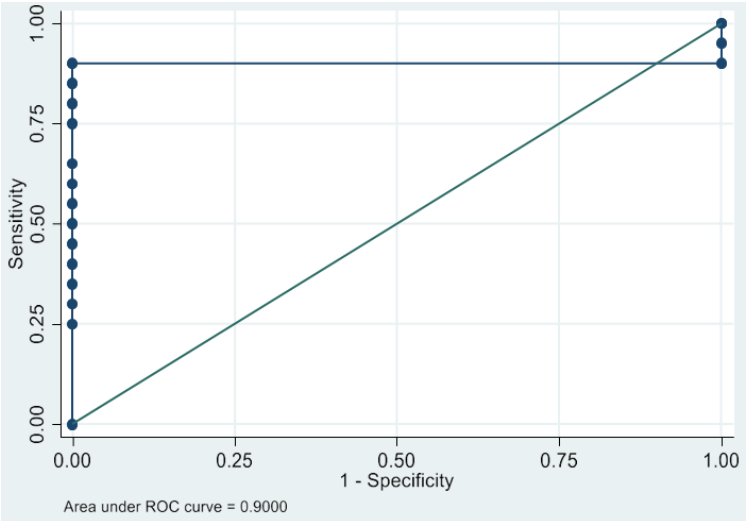


Figure 1. ROC curves for the blood urea nitrogen/creatinine (BUN/Cr) ratio stratified by galectin-3.

Discussion

In the statistical analysis of the data, accounting for the number of children examined, the distributions of the indicators were non-Gaussian. Therefore, to assess the statistical significance of differences, non-parametric methods were used: the Mann-Whitney U test was applied for comparisons between the case and control groups, while the Kruskal-Wallis test was used to analyze differences within each group according to age and gender.

We analyzed laboratory indicators that characterize the main pathogenetic mechanisms underlying the development of cardiorenal syndrome, while accounting for participants' gender.

Laboratory test results were analyzed for participants in the control group with an established diagnosis of chronic heart failure on the background of dilated cardiomyopathy but without confirmed type 2 cardiorenal syndrome. Notably, the serum iron level in the case group was 40% lower than that in the control group, as indicated by the median value.

It was found that the serum iron level in the case group was at the lower limit of normal in both boys and girls. Using the Kruskal-Wallis test for intragroup comparisons, no statistically significant differences were observed in hemoglobin, platelet count, and serum iron levels ($p > 0.05$).

We further analyzed liver function by assessing total bilirubin levels in the control and case groups. Elevated bilirubin levels were observed in both boys and girls. Despite a threefold increase in bilirubin levels in girls compared with boys in the case group, and, conversely, no differences in the case group, these differences were not statistically significant at the 95% confidence level ($p = 0.38$ and $p = 0.6$, respectively).

Of note was also the increased bilirubin level in the case group, in which persistent renal pathology had already developed. The median bilirubin level was 33% higher than in the control group.

The next group of laboratory tests relevant to the study of type 2 CRS included markers of myocardial injury: troponin, a particular marker of myocardial damage, and galectin-3, a potential marker of parenchymal organ fibrosis. It was found that troponin levels were within normal limits in the case group, while galectin-3 levels in both boys and girls exceeded normal values by 87.7% and 60.3%, respectively. In the control group, galectin-3 levels were also elevated above normal by 110.7% in boys and 47.3% in girls. No statistically significant differences by gender were observed within the case and control groups ($p = 0.7$ and $p = 0.77$, respectively).

In the fourth group of laboratory indicators reflecting kidney function in the case group, blood urea and blood urea nitrogen levels exceeded normal values in both boys and girls. The albumin/creatinine ratio in spot urine samples was at the upper limit of normal, while the blood urea nitrogen to creatinine ratio was significantly elevated. There were no statistically significant gender differences in these indicators within the group at the 95% confidence level ($p > 0.05$).

Given the identified excesses of specific laboratory parameters, a comparative analysis of the two groups was conducted, and the statistical significance of differences was assessed using the Mann-Whitney U test. The study revealed statistically significant differences in serum iron ($p = 0.02$), total bilirubin ($p = 0.03$), and galectin-3 ($p = 0.05$).

Upon rehospitalization after a one-year interval, participants in the case group were confirmed to have developed type 2 CRS.

Our study revealed that with the development of persistent renal dysfunction against the background of chronic heart failure in children with dilated cardiomyopathy, iron metabolism indicators such as serum iron and hemoglobin (40% higher in the case group) and bilirubin (33% higher in the case group) play a role. This suggests more pronounced catabolic processes in the liver and higher iron consumption in established type 2 CRS. Regression analysis also demonstrated the influence of these indicators on kidney function.

Thus, decreases in serum iron and an increase in total bilirubin levels may be considered prognostic markers for the development of persistent renal dysfunction. Although ACR is a recognized marker of current kidney function, our study did not establish its predictive value for the development of renal dysfunction, as ACR levels varied from normal to elevated in the case group during both initial and repeated hospitalizations.

Mechanisms of serum iron reduction in chronic heart failure and developed cardiorenal syndrome:

Chronic systemic inflammation increases the level of hepcidin, which suppresses the function of ferroprotein, resulting in decreased iron absorption in the intestine and impaired iron release from macrophage stores [8]; impaired iron absorption due to intestinal edema and hypoperfusion [16]; uremia causes disturbance of erythropoiesis and iron metabolism; activation of neurohormonal systems (renin-angiotensin-aldosterone and sympathetic nervous system) leads to a decrease in iron perfusion and activation of oxidative stress, which negatively affects iron hemostasis [25].

Increased bilirubin levels in patients with chronic heart failure in cardiorenal syndrome are associated with congestion in the inferior vena cava system (impaired liver drainage function, decreased hepatocyte function) [6]. Also, the development of cardiogenic hepatopathy leads to impaired bilirubin excretion [9]. Liver tissue ischemia increases oxidative stress, damages hepatocytes, and contributes to increased bilirubin [11]. Activation of neurohumoral systems exacerbates bilirubin synthesis and utilization [5].

Reduced cardiac output and venous congestion lead to decreased renal perfusion in patients with type 2 CRS and chronic heart failure. BUN/Cr increases as a result of neurohormonal system activation (RAAS, sympathetic nervous system), enhancing urea reabsorption without affecting creatinine. An elevated BUN/Cr ratio may serve as an early indicator of worsening renal function. Previous studies have shown that an elevated BUN/Cr ratio can identify a high-risk, potentially reversible form of renal dysfunction in patients with decompensated heart failure [4]. Another study demonstrated that the BUN/Cr ratio at admission predicts acute kidney injury in acute decompensated heart failure and aids risk stratification [23]. Furthermore, in patients with congestive heart failure, a high BUN/Cr ratio was associated with poor prognosis and predicted all-cause mortality [27]. Additionally, a higher and

more variable BUN/Cr ratio over time was independently associated with an increased risk of hospitalization for heart failure and all-cause mortality in patients with chronic heart failure with preserved ejection fraction [15].

ROC analysis confirmed galectin-3 as a potential biomarker of renal impairment, based on the blood urea nitrogen-to-creatinine ratio and ACR (AUCs of 0.9 and 0.733, respectively). Our results are consistent with previous studies indicating that galectin-3 may be a prognostic marker for the development of cardiorenal syndrome in patients with acute heart failure and reduced left ventricular ejection fraction. Galectin-3 levels were higher in patients who developed CRS compared to those who did not [25].

A meta-analysis of five studies involving 5,226 patients with chronic kidney disease found that elevated galectin-3 levels were associated with an increased risk of all-cause mortality and cardiovascular events. However, the association between galectin-3 and kidney disease progression was inconsistent [28]. Another systematic review failed to confirm a definitive role for serum galectin-3 in predicting the progression of cardiovascular or renal disease.

We acknowledge the small sample size as a limitation of our study, which is due to the severity of the pathology and the challenges associated with patient hospitalization in a single medical institution. Another limitation was the inability to examine other potential biomarkers of cardiorenal syndrome, such as cystatin C, KIM-1, and NGAL, owing to various factors. Nevertheless, our findings provide a foundation for further research and for improving early diagnostic approaches for CRS in children.

Conclusions

1. The laboratory studies conducted in our research, aimed at examining the pathogenetic mechanisms of chronic heart failure (CHF) and the development of type 2 cardiorenal syndrome (CRS), included four groups of indicators reflecting iron metabolism, liver function, myocardial injury, and kidney function.

2. Low serum iron levels were observed both initially and during follow-up in the control and case groups (9 and 5.9 μmol/L, respectively). Elevated bilirubin levels were also noted in both the control and case groups (0.41 and 0.54 μmol/L, respectively), along with increased galectin-3 levels in the case group (13% higher compared to controls). Additionally, markers of reduced kidney function were similar between the groups (ACR: 31 and 32 mg/g; blood urea nitrogen-to-creatinine ratio: 30 and 32, respectively). Statistically significant associations were established between serum iron ($p = 0.05$), hemoglobin ($p = 0.02$), and galectin-3 ($p = 0.02$) levels with markers of kidney function (ACR).

3. It was determined that galectin-3 has an 81% likelihood (OR = 1.81, 95% CI) of influencing the development of renal dysfunction, while the blood urea nitrogen to creatinine ratio has a 70% likelihood (OR = 1.70, 95% CI).

4. The use of the blood urea nitrogen to creatinine ratio and galectin-3 levels can serve as prognostic markers for the development of renal dysfunction in pediatric patients with CHF and dilated cardiomyopathy.

Practical Recommendation

1. Monitoring biomarkers of myocardial injury, particularly troponin and galectin-3, is recommended for the early detection and management of type 2 CRS in children.

2. Regular assessment of serum iron and bilirubin levels is advised to provide insight into systemic processes affecting multiple organs, including the kidneys. Tracking these parameters may also help evaluate the body's overall compensatory capacity during disease progression.

3. Given the limitations of the current study, particularly the inability to assess several potential biomarkers of cardiorenal syndrome (including cystatin C, NGAL, and KIM-1), further research is needed. Future studies should focus on a multimarker approach for the early diagnosis and stratification of CRS in pediatric patients.

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MORPHO-GENETIC VARIABILITY IN MYOCARDIAL TISSUE AFTER SEPTAL MYECTOMY IN PATIENTS WITH OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY: A FOUR-CASE SERIES STUDY

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Abstract

Background and Objective: Obstructive hypertrophic cardiomyopathy (OHCMP) is a heterogeneous disease with strong genetic determination.

The study aimed to identify myocardial morphological features in OHCMP patients depending on genetic status and to assess correlations between morphology and mutations in key genes.

Materials and methods. A descriptive study included 4 OHCMP patients undergoing septal myectomy. Myocardial morphology was assessed using hematoxylin-eosin, PAS, and Masson Trichrome staining. Genetic testing was performed by next-generation sequencing (NGS), including 17 genes: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Results. Genetically positive patients (MYH7, GLA, PRKAG2) demonstrated a chaotic arrangement of cardiomyocytes, marked nuclear polymorphism, and fine-fibrous perivascular and pericellular myocardial fibrosis. Genetically negative and control patients showed a more ordered arrangement of cardiomyocytes, focal coarse-fibrous fibrosis, and no nuclear polymorphism. Regardless of genetic status, all patients showed signs of cardiomyocyte hypertrophy and dystrophy, as well as a positive PAS reaction.

Conclusion. Myocardial morphological features differ significantly depending on genetic status, underscoring the importance of integrating histological and genetic analyses for risk stratification and personalized management of OHCMP patients. These findings provide a foundation for further research and development of clinical recommendations for cascade screening and prognosis.

Keywords: *obstructive hypertrophic cardiomyopathy, genetic status, myocardial morphology, nuclear polymorphism, PAS reaction, cardiac fibrosis, NGS, personalized medicine.*

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Резюме

МОРФОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ МИОКАРДА У ПАЦИЕНТОВ С ОБСТРУКТИВНОЙ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ ПОСЛЕ СЕПТАЛЬНОЙ МИЭКТОМИИ: АНАЛИЗ СЕРИИ ИЗ ЧЕТЫРЕХ СЛУЧАЕВ

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Предпосылки и цель: Обструктивная гипертрофическая кардиомиопатия (ОГКМП) является гетерогенным заболеванием с выраженной генетической детерминацией.

Цель исследования – выявить морфологические особенности миокарда у пациентов с ОГКМП в зависимости от генетического статуса и оценить корреляцию морфологии с мутациями ключевых генов.

Материалы и методы: Проведено описательное исследование с включением 4 пациентов с ОГКМП, подвергшихся септальной миоэктомии. Морфологический анализ миокарда включал окраски гематоксилином и эозином, PAS и Masson Trichrome. Генетическое тестирование осуществлялось методом секвенирования нового поколения (NGS), панель включала 17 генов: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Результаты: У генетически положительных пациентов (MYH7, GLA, PRKAG2) выявлено: хаотичное расположение кардиомиоцитов, выраженный полиморфизм ядер и тонковолокнистый периваскулярный и перицеллюлярный кардиосклероз. У генетически отрицательных и контрольных пациентов отмечалось более упорядоченное расположение кардиомиоцитов, грубоволокнистый очаговый фиброз и отсутствие полиморфизма ядер. Независимо от генетического статуса, у всех пациентов выявлялись признаки гипертрофии и дистрофии кардиомиоцитов, а также положительная PAS-реакция.

Выводы: Морфологические особенности миокарда существенно различаются в зависимости от генетического статуса, что подтверждает важность интеграции гистологического анализа и генетического тестирования для стратификации риска и персонализированного ведения пациентов с ОГКМП. Полученные данные могут служить основой для дальнейших исследований и разработки клинических рекомендаций по каскадному скринингу и прогнозированию течения заболевания.

***Ключевые слова**: гипертрофическая кардиомиопатия, обструктивная форма, генетические мутации, морфология миокарда, кардиомиоциты, кардиосклероз*

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Түйіндеме

ОБСТРУКТИВТІ ГИПЕРТРОФИЯЛЫҚ КАРДИОМИОПАТИЯСЫ БАР НАУҚАСТАРДА СЕПТАЛЬДЫ МИЭКТОМИЯДАН КЕЙІНГІ МИОКАРДТЫҢ МОРФОГЕНЕТИКАЛЫҚ ЕРЕКШЕЛІКТЕРІ: ТӨРТ ЖАҒДАЙДАН ТҰРАТЫН СЕРИЯНЫ ТАЛДАУ

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Кіріспе және мақсаты: Обструктивті гипертрофиялық кардиомиопатия (ОГКМП) – әртүрлі генетикалық детерминациясы бар ауру.

Зерттеудің мақсаты – ОГКМП науқастарында миокардтың морфологиялық ерекшеліктерін генетикалық статусқа байланысты анықтау және негізгі гендердің мутацияларымен корреляциясын бағалау.

Материалдар мен әдістер: Септальды миоэктомиядан өткен 4 науқасты қамтитын сипаттамалық зерттеу жүргізілді. Миокард морфологиясы гематоксилин-эозин, PAS және Masson Trichrome бояулары арқылы зерттелді. Генетикалық тестілеу жаңа буын секвенирлеу (NGS) әдісімен жасалды, панельге 17 ген кірді: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR.

Нәтижелері: Генетикалық жағынан оң науқастарда (MYH7, GLA, PRKAG2) кардиомиоциттердің хаотикалық орналасуы, ядрелердің айқын полиморфизмі және ұсақталымды периваскулярлық және перицеллюлярлық кардиосклероз анықталды. Генетикалық жағынан теріс және бақылау тобындағы науқастарда кардиомиоциттердің тәртіпті орналасуы, ұсақталмаған ошақты фиброз және ядро полиморфизмінің болмауы байқалды. Генетикалық статусқа қарамастан, барлық науқастарда кардиомиоциттердің гипертрофия және дистрофия белгілері, сондай-ақ оң PAS-реакция анықталды.

Қорытынды: Миокард морфологиясының ерекшеліктері генетикалық статусқа байланысты айтарлықтай өзгереді, бұл ОГКМП науқастарын басқаруда гистологиялық талдау мен генетикалық тестілеуді біріктірудің маңызды екенін растайды.

***Түйінді сөздер:** обструктивті гипертрофиялық кардиомиопатия, генетикалық статус, миокард морфологиясы, ядро полиморфизмі, PAS-реакция, кардиосклероз, NGS, персонализирленген медицина.*

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic myocardial disorder characterized by unexplained left ventricular hypertrophy, myocyte hypertrophy and dysfunction, interstitial fibrosis, and highly variable clinical manifestations ranging from an asymptomatic course to the development of heart failure or sudden cardiac death. According to current evidence, a prevalence of approximately 1:500 is considered the most accurate estimate for clinical assessment and management of HCM [12]. The main morphological substrate of HCM is left ventricular wall thickening in the absence of conditions associated with congenital or acquired heart defects, arterial hypertension (AH), coronary artery disease (CAD), or other diseases that can contribute to myocardial hypertrophy [10].

The obstructive form of HCM (oHCM) is the most common variant requiring surgical intervention. The principal treatment options include transaortic septal myectomy (the Morrow procedure), less invasive transapical septal myectomy, or alcohol septal ablation. The objective of surgical treatment is the resection of a portion of the hypertrophied interventricular septum that causes left ventricular outflow tract (LVOT) obstruction and impairs normal blood flow from the heart into the aorta.

The histological appearance of resected interventricular septal tissue in HCM is characterized by myofiber disarray with hypertrophic cardiomyocytes exhibiting nuclear polymorphism, including nuclei of diverse shapes. Typically, these nuclei are deformed and surrounded by a perinuclear halo with glycogen accumulation in these regions. Microscopic examination also reveals cardiomyocyte disarray, clustering of mitochondria, and scarring of nuclear membranes [14, 17]. In addition, changes involve the walls of intramural arterioles, which show medial hypertrophy and intimal hyperplasia, leading to luminal narrowing and, presumably, reduced overall coronary capacity, thereby contributing to dystrophic morphological alterations. Contemporary histological and electron microscopy studies examining myocardial biopsies in various heart diseases – congenital and acquired defects, AH, and CAD – describe similar morphological patterns. Thus, efforts to differentiate these conditions from HCM based solely on morphology have not yielded definitive criteria [1]. Therefore, the morphological changes described in the literature for HCM cannot be considered strictly specific.

Current international guidelines highlight the importance of a multimodal approach to diagnosis and management, including genetic testing [7]. Genetically, HCM is predominantly inherited in an autosomal dominant manner and results from mutations in genes encoding sarcomeric proteins responsible for myocardial contraction. The most frequently implicated genes include MYH7 (β-myosin heavy chain), MYBPC3 (cardiac myosin-binding protein C), TNNT2 (troponin T), TNNI3 (troponin I), TPM1 (tropomyosin), MYL2, MYL3, and ACTC1 [4, 16, 19].

Mutations in MYH7 and MYBPC3 account for up to 60-70% of all genetically confirmed HCM cases [16, 19]. They are typically associated with pronounced asymmetric septal hypertrophy and substantial cardiomyocyte disarray, reflecting profound disruption of myocardial architecture [18]. Despite known associations between individual genes and morphological phenotypes, the direct correlation between genotype and structural manifestations remains incomplete. Carriers of the same mutations often exhibit a wide range of morphological and clinical features, indicating the influence of gene expression modifiers, epigenetic mechanisms, and hemodynamic factors on the development of the pathological phenotype [9, 11].

One of the key challenges in contemporary HCM morphology is the absence of standardized morphometric criteria for assessing histological changes. Different studies employ varying quantitative parameters to evaluate cardiomyocyte disarray, fibrosis severity, and cellular hypertrophy, complicating cross-study comparisons and hindering the development of unified diagnostic scales [13]. Furthermore, many morphological studies rely on limited clinical samples and do not always include genetically confirmed diagnoses, reducing the reliability of conclusions regarding genotype–phenotype correlations [15].

This study aims to determine morphological patterns according to genetic status by performing histological examination of myocardial tissue obtained during septal myectomy in four patients with obstructive hypertrophic cardiomyopathy.

Materials and Methods

The study was conducted at the Research Institute of Cardiology and Internal Diseases between 2020 and 2021. Four consecutive patients undergoing surgery for obstructive hypertrophic cardiomyopathy with available myocardial tissue and genetic data were included. Resected myocardial tissue underwent morphological analysis, and molecular genetic testing for hypertrophic cardiomyopathy – associated mutations was performed. A descriptive comparative analysis was used to assess differences in morphological and genetic findings; no formal statistical analysis was conducted due to the small sample size.

Morphological analysis

Following surgical septal myectomy, the resected interventricular septal myocardium was fixed in 10% buffered formalin (pH 7.2-7.4) for 24 hours and subsequently processed manually in isopropyl alcohol through a series of six graded steps, each for 60 minutes. The tissue was then embedded in paraffin using a Leica EG 1150 H embedding station to create paraffin blocks. Sections of 5 μm thickness were cut using a Leica RM 2125 RT microtome.

For general morphological assessment, sections (4-5 μm) were stained manually with Mayer's hematoxylin and 1% aqueous eosin (H&E, hematoxylin and eosin staining) to evaluate nuclear and cytoplasmic changes in cardiomyocytes, tissue architecture, and cellular disorganization. A periodic acid-Schiff (PAS) reaction was performed to detect glycogen accumulation, including its perinuclear distribution. PAS-positive structures, indicative of carbohydrate degeneration and energy metabolism disorders, were observed as cytoplasmic regions or extracellular elements stained pink-purple with varying intensity. Staining intensity and distribution were assessed semi-quantitatively using light microscopy at ×10 and ×40 magnifications.

Masson's Trichrome staining was used to differentiate muscle and connective tissue and to assess perivascular and pericellular fibrosis (collagen fibers stained blue/green, muscle fibers stained red). After staining, sections were mounted under coverslips using Biomount medium to

ensure long-term preservation and prevent fading. Microscopy and photographic documentation were performed using a Leica DM 1000 microscope.

Histological analysis of all prepared slides was conducted in the pathomorphology laboratory of the Research Institute of Cardiology and Internal Disease.

Genetic Testing

Molecular genetic testing was performed at the DLE Laboratory (Genética Humana, Doenças Raras e Genômica, Brazil) (https://www.dle.com.br/). Mutation profiling was conducted using next-generation sequencing (NGS), which targets specific regions of isolated DNA followed by massively parallel sequencing. This method offers high sensitivity for detecting single-nucleotide variants and small insertion-deletion variants in genes associated with HCM. The genetic panel employed in this study included 17 key genes implicated in the development of HCM: ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, and TTR.

Prior to participation, all patients provided written informed consent, detailing the study objectives and procedural steps. Following consent, standard forms were completed, recording each patient's full name, date, and location of biopsy, and the attending physician's information (full name, phone number, and email address).

Biopsy samples were collected from all patients using the dried blood spot (DBS) method. Under sterile conditions, 1 ml of venous blood was drawn and evenly applied to diagnostic cards using a stencil, without exceeding the designated areas. The cards were left to dry at room temperature, protected from light, for three hours. Once dried, the diagnostic cards and signed consent forms were placed in specialized shipping envelopes and sent to the DLE Laboratory for NGS analysis.

For morphogenetic comparison, four patients were selected from those undergoing surgery for obstructive hypertrophic cardiomyopathy with known genetic testing results. The cohort included: one patient with a single identified mutation, one with three mutational variants, one with a negative test result, and one patient with unknown genetic status, used as a blinded control.

Ethics approval and consent to participate

This study was conducted in accordance with ethical standards and was approved by the Bioethical Commission of Kazakh National Medical University named after S.D. Asfendiyarov (Protocol #1071, dated March 31, 2021). Written informed consent was obtained from all participants.

Results

Histological analysis of myocardial tissue obtained after septal myectomy in four patients with OHCM revealed morphological differences that corresponded to the patients' genetic status (Fig. 1 - 4).

Morphological features of a MYH7 Gene-positive patient

Myocardial morphology of a MYH7 gene-positive patient (29 years old at the time of the study) is shown in Figures 1a–g.

H&E staining (Fig. 1a–b) demonstrated pronounced disruption of myocardial architecture, characterized by nuclear polymorphism, chaotic arrangement of muscle fibers with areas of side-to-side interweaving, the presence of multiple intermuscular bridges, end-to-side cardiomyocyte fusion, and longitudinally and transversely sheared muscle fiber bundles, resulting in a lobular myocardial structure (Fig. 1a, green arrow).

At ×40 magnification (Fig. 1b), marked multidirectionality of muscle fiber distribution was observed, including areas of interweaving, adhesion, and branching. Several cardiomyocytes appeared fragmented and dissociated, exhibiting nuclear polymorphism and uneven chromatin distribution (white arrows).

PAS staining (Fig. 1c) revealed enlarged, polymorphic nuclei with perinuclear glycogen accumulation (gray arrow). Masson's Trichrome staining (Fig. 1d) showed a fine, delicate network of perivascular and pericellular collagen fibers forming a "web-like" structure (black arrow) against a background of enlarged, randomly oriented cardiomyocytes (red arrow).

Morphological features in a gene-negative patient

A gene-negative patient (63 years old) (Fig. 2a-d) exhibited uneven hypertrophy of cardiomyocytes (Fig. 2a, green arrow), thickening of the arteriolar wall due to asymmetric hypertrophy of the muscular layer (Fig. 2a, blue arrow), and focal perivascular proliferation of course, mature connective tissue (Fig. 2a, black arrow). Some cardiomyocytes showed loss of transverse striations, foci of myocytolysis, and areas of cellular "melting".

At ×40 magnification (Fig. 2b), cardiomyocytes were arranged in a relatively orderly pattern, with no nuclear polymorphism observed (brown arrow). A few cardiomyocytes were fragmented and dissociated, but chromatin distribution remained uniform. Focal myocytolysis and small perivascular lymphocytic infiltrates were also noted (yellow arrow).

PAS staining (Fig. 2c) demonstrated enlarged nuclei with perinuclear glycogen accumulation (gray arrow). Masson's Trichrome staining (Fig. 2d) highlighted coarse fibrous connective tissue in perivascular foci (blue staining, black arrow) and red-stained, enlarged, orderly arranged cardiomyocytes (red arrow).

Morphological features in a MYH7, GLA, and PRKAG2 Gene-Positive Patient

A patient with positive molecular genetic testing for the MYH7, GLA, and PRKAG2 genes (female, 49 years old) exhibited the following myocardial morphological changes (Fig. 3a–d).

H&E staining (Fig. 3a) demonstrated markedly disorganized myocardial architecture, with chaotic muscle fiber distribution, areas of side-to-side interweaving, and multiple intermuscular bridges. Fibers were oriented in multiple directions, showing local adhesion, branching, and parquet-like interweaving. Cardiomyocytes were interconnected end-to-end, forming both longitudinally and transversely sheared muscle fiber bundles (Fig. 3a, green arrow).

An increased stromal component was observed due to the proliferation of mature connective tissue, predominantly perivascular and pericellular, forming a reticular network. Scattered lymphocytic infiltration was also noted in the stroma (Fig. 3a, yellow arrow). Some cardiomyocytes displayed uneven fragmentation, with foci of myocytolysis and areas of cellular "melting."

At higher magnification (×40, Fig. 3b), pronounced nuclear polymorphism was observed in cardiomyocytes, with uneven chromatin distribution and the appearance of characteristic “holey” nuclei (white arrows).

PAS staining (Fig. 3c) revealed enlarged and polymorphic nuclei with prominent perinuclear glycogen accumulation (gray arrow). Masson’s Trichrome staining (Fig. 3d) highlighted fine-fibrous collagen forming the perivascular and pericellular network (blue staining, black arrow) and intense red staining of enlarged, randomly arranged cardiomyocytes (red arrow).

Morphological features in a control patient with unknown genetic status

Histological examination of the surgical specimen from a patient with unknown genetic status (male, 33 years old) revealed the following myocardial changes (Fig. 4a-d).

Cardiomyocyte hypertrophy was unevenly expressed, but the myocardial fibers were generally arranged in an orderly fashion (Fig. 4a, green arrow). Perivascular and pericellular proliferation of coarse, mature connective tissue forming a reticular network was observed in the stroma (Fig. 4a, black arrow).

At higher magnification (×40, Fig. 4b), cardiomyocytes retained an organized architecture, and no nuclear polymorphism was detected. Some cells showed fragmentation and dissociation, but chromatin distribution remained uniform, and nuclear polymorphism was absent.

PAS staining (Fig. 4c) demonstrated enlarged nuclei with perinuclear glycogen accumulation (gray arrow). Masson’s Trichrome staining (Fig. 4d) highlighted blue-stained connective tissue forming a perivascular meshwork and red-stained, enlarged, orderly arranged cardiomyocytes (red arrow).

Comparative analysis of the histological specimens from four patients with a clinical diagnosis of OHCM revealed the following features (Table 1)

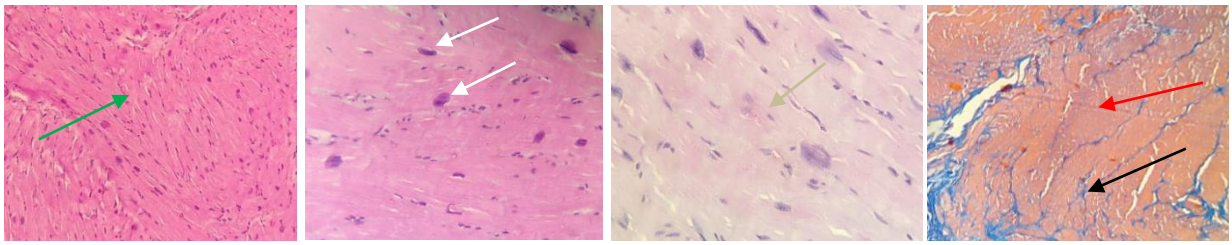


Figure 1a *Figure 1b* *Figure 1c* *Figure 1d*

Figure 1. Myocardial architectural abnormalities in a MYH7 gene-positive patient (male, 29 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

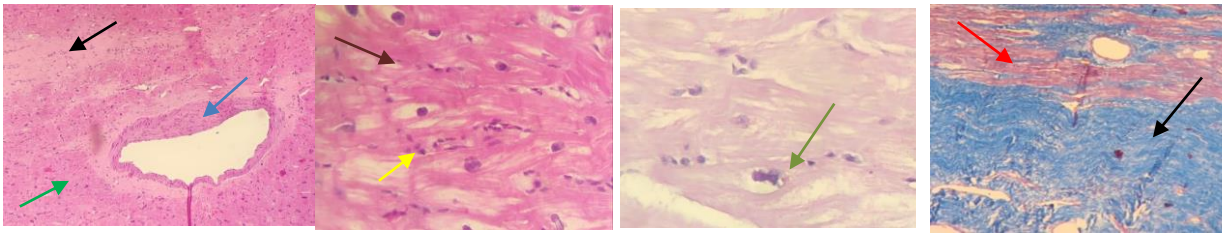


Figure 2a *Figure 2b* *Figure 2c* *Figure 2d*

Figure 2. Disruption of myocardial architecture in a gene-negative patient (male, 63 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

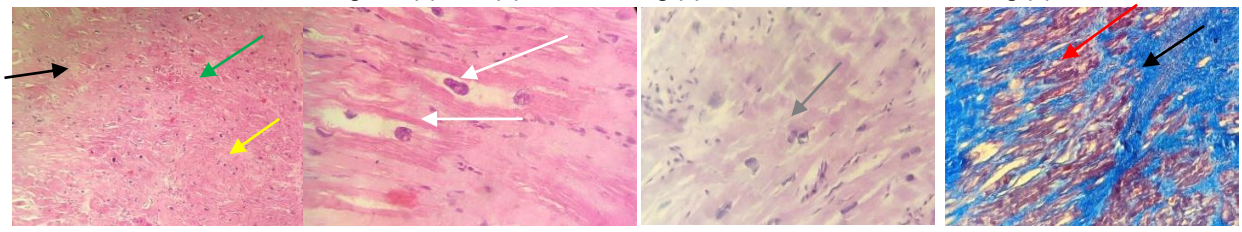


Figure 3a *Figure 3b* *Figure 3c* *Figure 3d*

Figure 3. Myocardial architectural abnormalities in a MYH7, GLA, and PRKAG2 gene-positive patient (female, 49 y): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

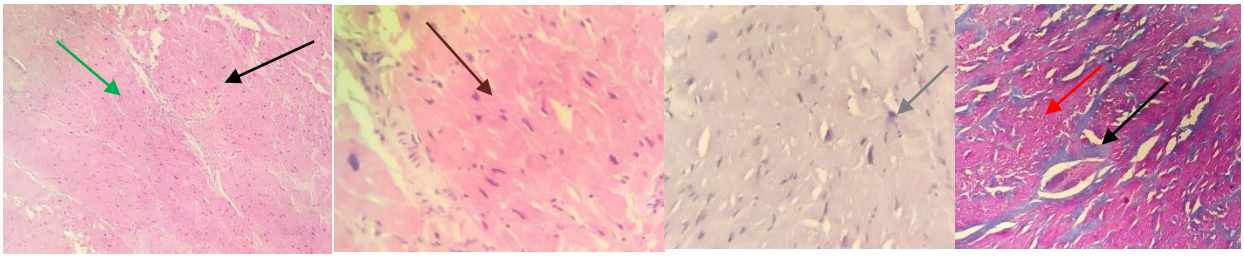


Figure 4a *Figure 4b* *Figure 4c* *Figure 4d*

Figure 4. Myocardial architectural changes in a control patient with unknown genetic status (male, 33 years old): H&E staining ×10 (a), ×40 (b); PAS staining (c); Masson’s Trichrome staining (d).

Table 1.

Comparative characteristics of myocardial morphological changes in patients with acute myocardial infarction depending on genetic status.

Genetic status Morphological features	MYH7 (+) (male, 29 y)	MYH7, GLA, PRKAG2 (+) (female, 49 y)	Unknown gene status - (male, 33 y)	Gene (-) (male, 68 y)
Cardiomyocyte hypertrophy with structural disorganization	+ Chaotic cardiomyocyte arrangement, “lobular” myocardium	+ Chaotic cardiomyocyte arrangement, “parquet-like” pattern	+ Ordered cardiomyocyte arrangement with uneven hypertrophy	+ Ordered cardiomyocyte arrangement with uneven hypertrophy
Nuclear polymorphism of cardiomyocytes	+	+ “holey” nuclei	-	-
Myocardial fibrosis	+ Fine-fibrous, delicate, perivascular, and pericellular, "web-like" type	+ Perivascular and pericellular, reticular	+ Perivascular and pericellular, reticular	+ Coarse fibrous, perivascular and focal
PAS staining	+	+	+ Mild	+
Vascular changes	-	-	-	+ Arteriolar wall hypertrophy
Pathological infiltration	-	+ Scattered, isolated lymphocytes	-	+ Focal lymphocytic infiltration
Cardiomyocyte dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Fine-droplet lipid and fine-granular dystrophy	+ Parenchymal fine-granular dystrophy

All patients demonstrated cardiomyocyte hypertrophy, parenchymal cardiomyocyte degeneration, positive PAS staining, and myocardial fibrosis. Patients with identified pathogenic mutations (MYH7; MYH7 + GLA + PRKAG2) exhibited more pronounced cardiomyocyte disorganization and nuclear polymorphism. Notably, the patient with three positive genetic mutations showed coarse-fibrous (dense) myocardial fibrosis, in contrast to the fine, delicate “web-like” fibrosis observed in the patient with a single genetic variant. Additionally, the patient with MYH7 + GLA + PRKAG2 exhibited the presence of “holey” nuclei in cardiomyocytes.

In contrast, the gene-negative patient and the control patient displayed a more orderly myocardial architecture, with uneven cardiomyocyte hypertrophy. In the control patient (male, 63 y), coarse-fibrous focal fibrosis was observed alongside focal lymphocytic infiltration and hypertrophy of the arteriolar muscular layer, which may reflect ischemic cardiomyopathy.

The primary distinction between genetically positive and negative patients was reflected in myocardial morphology: genetically positive patients exhibited pronounced chaotic cardiomyocyte arrangement, nuclear polymorphism, and fine-fibrous perivascular and pericellular fibrosis, whereas genetically negative patients showed orderly cardiomyocyte arrangement, absence of nuclear polymorphism, and coarse-fibrous, perivascular, and focal myocardial fibrosis.

Discussion

This descriptive study aimed to identify myocardial morphological features in four patients with obstructive hypertrophic cardiomyopathy undergoing septal myectomy, with consideration of their genetic profiles for key HCM-associated genes.

Morphological Characteristics and Relationship with Genotype

The observed morphological changes demonstrate a clear dependence of myocardial structure on the presence of pathogenic mutations in the MYH7, GLA, and PRKAG2 genes. Patients with genetically confirmed mutations exhibited pronounced alterations in myocardial architecture, including chaotic cardiomyocyte arrangement, nuclear polymorphism, intermuscular bridge formation, and parquet-like fiber disorganization. These features reflect the structural disorientation of myocardial fibers characteristic of hereditary HCM and are recognized morphological markers of sarcomeric mutations [6].

Furthermore, gene-positive patients demonstrated “holey” cardiomyocyte nuclei and perinuclear glycogen accumulation on PAS staining, indicative of disrupted carbohydrate metabolism and cellular energy degeneration, which is particularly characteristic of metabolic HCM variants, such as PRKAG2 [3]. Perivascular and pericellular fine-fibrous “spiderweb” fibrosis in these patients may represent compensatory myocardial remodeling in response to chronic metabolic stress.

In contrast, patients without identified mutations displayed relatively ordered myocardial architecture, moderate cardiomyocyte hypertrophy, and focal coarse-

fibrous fibrosis, likely secondary to ischemic or hemodynamic factors, including age-related changes. The absence of pronounced nuclear polymorphism and metabolic alterations supports the predominantly secondary nature of these morphological changes.

Data Integration and Clinical Significance

These findings are consistent with previous studies demonstrating disrupted fiber organization, interstitial fibrotic replacement, and nuclear polymorphism as hallmarks of genetically determined HCM [20]. Fine-fibrous reticular fibrosis and metabolic markers (glycogen accumulation, "holey" nuclei) are characteristic of metabolic/genetic subtypes, whereas coarse focal fibrosis and preserved cardiomyocyte architecture are more typical of non-genetic secondary forms.

From a clinical perspective, such morphological patterns hold diagnostic and prognostic significance. Their presence may serve as an indirect indicator of a hereditary form of HCM, which is particularly valuable in settings with limited access to molecular genetic testing. These patterns aid in distinguishing primary (hereditary) from secondary (hemodynamic or ischemic) forms of HCM and may indicate an increased risk of disease progression and adverse outcomes. Early identification of at-risk asymptomatic individuals via molecular and clinical cascade screening, along with optimal risk stratification for sudden cardiac death, can facilitate timely preventive interventions to mitigate irreversible myocardial remodeling [5, 8, 16].

Integrating morphological analysis with genetic and clinical assessments enables more accurate individualized risk stratification and management of HCM patients and their relatives. This approach underscores the importance of combining histopathological, genetic, and clinical data when interpreting identified variants. Thus, the observed differences reinforce the notion that myocardial morphological features can serve as indirect markers of genetically determined forms of hypertrophic cardiomyopathy, particularly in the absence of molecular genetic testing.

Strengths and Limitations

This study provides valuable insights into the relationship between myocardial morphological changes and genetic variants in patients with obstructive hypertrophic cardiomyopathy in Kazakhstan. Analysis of these well-characterized cases highlights genotype–phenotype correlations, demonstrating how particular genetic variants manifest as distinct structural myocardial patterns. These observations enhance understanding of disease heterogeneity, support the identification of patients likely to harbor pathogenic mutations, and may inform risk stratification and management of both patients and their first-degree relatives.

However, several limitations should be acknowledged. The descriptive nature of the study and the small sample size (four patients) limit the generalizability of the findings, reflecting the high costs and logistical challenges of combined morphological and genetic testing. Additionally, the interpretation of results may be affected by the routine collection and storage of biopsy material prior to analysis. Finally, morphological data were obtained exclusively from myectomy specimens, without longitudinal or dynamic clinical follow-up. Further studies with larger cohorts and integrated clinical, genetic, and morphological analyses are warranted to validate these patterns and clarify their prognostic significance.

Future directions

Future research should expand the patient cohort, implement quantitative fibrosis assessment, and investigate correlations between genotype and phenotype. Enlarging the sample size and applying advanced sequencing technologies may reveal novel disease markers. Integrating morphological, genetic, and clinical data will provide a foundation for developing personalized diagnostic and therapeutic strategies for HCM patients and their families.

Conclusion

Overall, the morphological data indicate that myocardial structure in OHCM patients varies according to genetic status. Distinct patterns – disrupted myocardial architecture, nuclear alterations, metabolic markers, and fibrosis characteristics – can complement clinical and genetic diagnostics. These findings underscore the importance of integrating histopathology, genetics, and clinical information to guide individualized management of HCM. Further studies with larger cohorts and high-sensitivity genetic analyses are needed to validate these patterns and deepen understanding of HCM pathogenesis.

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Declaration of conflicting interests: *The authors declare that there is no conflict of interest in the present study.*

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CLINICAL EFFICACY OF SELECTIVE PLASMA FILTRATION (EVACLIO) IN CARDIOVASCULAR COMPLICATIONS: A CASE SERIES FROM THE HEART CENTER KAZAKHSTAN

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Abstract

Background: Cardiovascular surgical patients with sepsis and hepatic dysfunction present significant perioperative management challenges. Selective plasma filtration using the Evaclio system has emerged as a novel extracorporeal therapy for the removal of inflammatory mediators and bilirubin. This is the first case series from Kazakhstan reporting the use of Evaclio in a cardiothoracic setting.

Materials and methods: This retrospective case series describes 15 patients (mean age: 56±3,65 years) who underwent open-heart surgery at the CF UMC "Heart Center" between 2023 and 2024 and subsequently developed sepsis and/or hyperbilirubinemia indicative of acute hepatic dysfunction. All patients received selective plasma filtration using the Evaclio system as part of their post-operative critical care. Statistical data processing was performed using IBM SPSS 29.0. Descriptive statistics, Wilcoxon test and Spearman correlation test were used. Values of $p < 0.05$ were considered statistically significant.

Results: This retrospective cohort study was conducted at the CF UMC "Heart Center" in Astana, Kazakhstan, from January 2023 to December 2024. The study included 15 patients who underwent heart defect correction with cardiopulmonary bypass (CPB). The use of the Evaclio filter was associated with a significant reduction in ALT, AST levels ($p < 0.01$), and platelets ($p < 0.05$), reflecting a decrease in inflammatory response and cytolysis. A positive trend in bilirubin and uremic markers was observed, and in some patients (up to 40%), a reduction in bilirubin of ≥ 30% was achieved, indicating the potential effectiveness of the method as part of comprehensive sepsis therapy.

Conclusion: Evaclio selective plasma filtration demonstrated promising results in managing postoperative sepsis and hepatic dysfunction in pediatric cardiac surgery patients. Its use may offer an effective adjunct to conventional intensive care in similar settings. Further prospective studies are needed to validate these findings.

Keywords: *cardiac surgery, postoperative period, MODS, SIRS.*

For citation:

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Резюме

КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ СЕЛЕКТИВНОЙ ПЛАЗМОФИЛЬТРАЦИИ (EVACLIO) ПРИ СЕРДЕЧНО-СОСУДИСТЫХ ОСЛОЖНЕНИЯХ: СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ ИЗ ЦЕНТРА СЕРДЦА, КАЗАХСТАН

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Введение: Пациенты, перенесшие кардиохирургические операции и страдающие сепсисом и печёночной дисфункцией, представляют собой серьёзную проблему для периоперационного ведения. Селективная плазмофильтрация с использованием системы Evaclio представляет собой новую экстракорпоральную терапию, направленную на удаление воспалительных медиаторов и билирубина. Настоящая работа представляет собой первый в Казахстане клинический случайный ряд, описывающий применение Evaclio в кардиохирургической практике.

Материалы и методы: В данном ретроспективном исследовании описаны 15 пациентов (средний возраст: 56 ± 3,65 лет), перенесших операции на открытом сердце на базе КФ UMC «Центр сердца» в период с 2023 по 2024 год и у которых впоследствии развился сепсис и/или гипербилирубинемия, указывающая на острую печёночную дисфункцию. Все пациенты получили сеансы селективной плазмофильтрации с использованием системы Evaclio в рамках послеоперационного интенсивного лечения. Статистическая обработка данных проводилась с использованием IBM SPSS 29.0. Применялись описательная статистика, критерий Вилкоксона и корреляционный анализ Спирмена. Значения $p < 0,05$ считались статистически значимыми.

Результаты: Исследование проводилось на базе КФ UMC «Центр сердца» в г. Астана, Казахстан, в период с января 2023 по декабрь 2024 года. В него были включены 15 пациентов, которым была выполнена коррекция пороков сердца с использованием искусственного кровообращения. Применение фильтра Evaclio ассоциировалось с достоверным снижением уровней АЛТ, АСТ ($p < 0,01$), а также количества тромбоцитов ($p < 0,05$), что отражает уменьшение воспалительной реакции и цитолиза. Отмечалась положительная динамика по билирубину и уремическим маркёрам, причём у части пациентов (до 40 %) наблюдалось снижение билирубина на ≥ 30 %, что свидетельствует о потенциальной эффективности метода в составе комплексной терапии сепсиса.

Заключение: Селективная плазмофильтрация Evaclio продемонстрировала обнадеживающие результаты в лечении послеоперационного сепсиса и печёночной дисфункции у пациентов, перенесших кардиохирургические вмешательства. Её применение может служить эффективным дополнением к стандартной интенсивной терапии в аналогичных клинических ситуациях. Необходимы дальнейшие проспективные исследования для подтверждения полученных данных.

Ключевые слова: *кардиохирургическая операция, послеоперационный период, синдром полиорганной недостаточности (СПОН), синдром системной воспалительной реакции (ССВР).*

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Түйіндеме

EVACLIO СЕЛЕКТИВТІ ПЛАЗМОФИЛЬТРАЦИЯСЫНЫҢ ЖҮРЕК-ҚАНТАМЫР АСҚЫНУЛАРЫНДАҒЫ КЛИНИКАЛЫҚ ТИІМДІЛІГІ: ҚАЗАҚСТАН ЖҮРЕК ОРТАЛЫҒЫНАН КЛИНИКАЛЫҚ ЖАҒДАЙЛАР ТОПТАМАСЫ

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Кіріспе: Кардиохирургиялық операциялардан кейінгі сепсис және бауыр дисфункциясы бар науқастар периоперациялық кезеңде айтарлықтай қиындық тудырады. Evaclio жүйесін қолданатын селективті плазмофильтрация — қабыну медиаторлары мен билирубинді жоюға бағытталған жаңа экстракорпоральды

терапия әдісі. Бұл жұмыс — Қазақстанда алғаш рет кардиохирургиялық тәжірибеде Evaclio жүйесін қолдану туралы клиникалық жағдайлар топтамасын сипаттайтын зерттеу.

Әдістер: Бұл ретроспективті зерттеуде 2023–2024 жылдар аралығында Қазақстан Республикасы, Астана қаласындағы Ұлттық ғылыми кардиохирургия орталығында ашық жүрекке операция жасалған және кейіннен сепсис пен/немесе жедел бауыр жеткіліксіздігімен (гипербилирубинемия) асқынған 15 науқас (орташа жас: 56 ± 3,65 жас) қамтылды. Барлық науқастарға отадан кейінгі қарқынды терапия аясында Evaclio жүйесін қолдана отырып, селективті плазмофильтрация сеанстары жүргізілді. Деректердің статистикалық өңделуі IBM SPSS 29.0 бағдарламасы арқылы жүзеге асырылды. Сипаттамалық статистика, Вилкоксон критерийі және Спирменнің корреляциялық анализі қолданылды. $p < 0,05$ мәні статистикалық тұрғыдан маңыздылығы ретінде қабылданды.

Нәтижелер: Зерттеу 2023 жылдың қаңтарынан 2024 жылдың желтоқсанына дейінгі аралықта Астана қаласындағы «Ұлттық ғылыми кардиохирургия орталығы» корпоративтік қорында жүргізілді. Жасанды қан айналымын пайдалана отырып жүрек ақауларын түзету операциясы жасалған 15 науқас зерттеуге енгізілді. Evaclio сүзгісін қолдану АЛТ, АСТ деңгейлерінің ($p < 0,01$), сондай-ақ тромбоциттер санының ($p < 0,05$) сенімді төмендеуімен байланысты болды, бұл қабыну реакциясы мен цитолиздің азаюын көрсетеді. Билирубин және уремиялық маркерлер бойынша оң динамика байқалды, кейбір науқастарда (40 %-ға дейін) билирубин деңгейінің ≥ 30 % төмендеуі тіркелді, бұл әдістің сепсисті кешенді емдеудегі әлеуетті тиімділігін көрсетеді.

Қорытынды: Evaclio селективті плазмофильтрациясы жүрекке жасалған операциялардан кейін дамитын сепсис және бауыр дисфункциясын емдеуде үміт күттіретін нәтижелер көрсетті. Бұл әдіс ұқсас клиникалық жағдайларда стандартты қарқынды терапияға тиімді қосымша бола алады. Алынған мәліметтерді растау үшін болашақта проспективті зерттеулер қажет.

Түйінді сөздер: *кардиохирургиялық операция, операциядан кейінгі кезең, көпмүшелі жетіспеушілік синдромы (КМЖС), жүйелі қабыну реакциясы синдромы (ЖҚРС)*

Дәйексөз үшін:

Аманжолова А.К., Койчубаева Д.К., Зупаров Е.Н., Серикова А.А., Абильбаева А.А., Бекишев Б.Е. Evaclio селективті плазмофильтрациясының жүрек-қантамыр асқынуларындағы клиникалық тиімділігі: Қазақстан кардиологиялық орталығынан клиникалық жағдайлар топтамасы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 38-45. *doi 10.34689/SH.2025.27.6.005*

Introduction

Postoperative sepsis and liver dysfunction are among the most common and serious complications following open-heart surgery, significantly contributing to both short- and long-term morbidity and mortality. These adverse outcomes are often the result of a complex interplay between systemic inflammatory response, ischemia-reperfusion injury, and the effects of cardiopulmonary bypass, all of which can precipitate multiorgan dysfunction, particularly hepatic impairment characterized by elevated serum bilirubin levels.

Evaclio, a novel selective plasma filtration technology developed in Japan, offers an extracorporeal method for the removal of medium-molecular-weight substances, including pro-inflammatory cytokines and albumin-bound bilirubin. Although Evaclio has demonstrated effectiveness in treating adult patients with septic shock and liver failure, there is currently limited evidence regarding its application in cardiac surgery patients, particularly in settings with complex postoperative comorbidities.

This study presents the first case series from Kazakhstan describing the use of Evaclio therapy in 15 adult patients who underwent open-heart surgery and subsequently developed postoperative sepsis and hepatic dysfunction. The study aims to address a critical gap in clinical practice by evaluating the therapeutic potential of selective plasma filtration in complex postoperative scenarios.

The relevance of this research lies in the high incidence of postoperative complications, the serious impact of multiple organ dysfunction syndrome (MODS) on patient outcomes, and the current lack of standardized protocols for early diagnosis and management in such cases. Improved understanding of associated risk factors may enhance preventive strategies and reduce morbidity and mortality in adult patients undergoing cardiac surgery.

Study Objectives

The primary aim of this study is to evaluate the clinical efficacy of Evaclio selective plasma filtration in managing sepsis and hepatic dysfunction in adult patients after cardiac surgery. The specific objectives are as follows:

1. **To compare key laboratory and clinical parameters before and after Evaclio therapy**, including serum bilirubin levels, inflammatory markers (CRP, procalcitonin), and hemodynamic status.
2. **To analyze the distribution of patients** by age, sex, and intensive care unit (ICU) location.
3. **To assess the relationship between surgical characteristics** (e.g., duration of cardiopulmonary bypass, total operation time) and treatment outcomes.
4. **To classify the success rate of therapy**, with a reduction of ≥30% in total bilirubin considered a marker of therapeutic efficacy.

The findings of this study are expected to contribute to the development of unified clinical protocols for early recognition and intervention in postoperative complications following cardiac surgery.

Methods

Study Design and Setting:

This retrospective case series was conducted at the CF UMC “Heart Center” between January 2023 and February 2024.

Ethical Considerations

Ethical approval was obtained, and informed consent was waived due to the retrospective nature of the study.

The study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Local Committee on Bioethics of the Corporate Fund "University Medical Center" (Protocol No. 4/2024/PE dated April 15, 2024. Assigned number 2024/02-008). Compliance with international Good Clinical Practice (GCP) standards, Joint Commission International (JCI) requirements, and Order No. 248 of the Ministry of Health of the Republic of Kazakhstan (dated December 11, 2020) was ensured. All participants' legal representatives provided informed consent.

Patient selection:

Fifteen adult patients who underwent open-heart surgery and developed clinical signs of sepsis and/or hepatic dysfunction were included. All patients received Evaclio therapy postoperatively.

Inclusion Criteria:

1. Adult patients (≥18 years) who underwent open-heart surgery with cardiopulmonary bypass.
2. Development of clinical signs of hepatic dysfunction (e.g., hyperbilirubinemia) and/or sepsis within the early postoperative period (≤7 days post-surgery).
3. Written informed consent obtained from the patient or their legal representative.

Exclusion Criteria:

1. Pre-existing end-stage renal disease requiring dialysis.
2. Diagnosed chronic liver failure or cirrhosis prior to surgery.
3. Hemodynamic instability incompatible with extracorporeal therapy.
4. Refusal to participate in the study.
5. Inability to perform cardiac surgery due to absolute medical contraindications.

Evaclio Procedure:

The Evaclio system was applied according to clinical indications. Each session lasted approximately 6 hours. Depending on the clinical response, each patient received between 1 to 3 sessions.

Priming and rinsing of circuits were performed using 0.9% sodium chloride solution, 500 mL × 3.

The procedure was conducted using a Dialog+ machine with a plasma fractionator Evaclio EC–2C20 (1 unit).

Sodium profile: 14.5–14.0

Blood flow rate: stepwise progression from 50 → 100 → 150 → 180 → 200 mL/min

Replacement solutions included:

- Duasol, 5000 mL (1 unit)
- Sterofundin, 1000 mL (1 unit)

Substitution flow rate: 666 mL/hour

An additional replacement fluid was ABO-compatible fresh frozen plasma (FFP) — 3000 mL, with a flow rate of 333 mL/hour.

Total substitution volume: 6000 + 3000 mL

Anticoagulation was achieved with Arixtra 2.5 μg / 0.5 mL (1 dose).

Activated clotting time (ACT) values during the procedure ranged between: 172 – 158 – 150 – 152 – 144 – 142 seconds.

Vascular access was provided via ECMO circuit and double-lumen central venous catheter.

Data Collection:

Laboratory parameters, including serum bilirubin (direct and total), ALT, AST, albumin, creatinine, urea, hemoglobin, hematocrit, platelet count, as well as systolic and diastolic blood pressure, were measured before and after each Evaclio session. To assess and classify acute kidney injury (AKI) in this patient population, several scoring systems were employed, including the adapted KDIGO (Kidney Disease: Improving Global Outcomes) criteria.

The diagnosis of AKI was primarily based on serial measurements of serum creatinine and urine output over time, allowing for accurate staging of AKI severity. This dual-parameter approach enabled timely identification and stratification of renal dysfunction, which is critical in the context of postoperative care following cardiac surgery.

The prevention and management of AKI focused on several intraoperative and postoperative strategies. These included careful optimization of hemodynamics during cardiopulmonary bypass, maintenance of appropriate fluid balance, judicious use of nephrotoxic medications, and continuous monitoring of renal function during the postoperative period.

To evaluate hepatic dysfunction, standard laboratory parameters were used, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin levels. Elevations in these markers—particularly in conjunction with clinical features—were considered indicative of hepatic impairment, commonly observed in the setting of low cardiac output or systemic inflammatory response.

The diagnosis of sepsis and systemic inflammatory response syndrome (SIRS) was established using established clinical and laboratory criteria. These included abnormal core temperature, leukocytosis or leukopenia, elevated C-reactive protein (CRP) and procalcitonin (PCT) levels, as well as hemodynamic instability requiring vasopressor support. Blood culture results and clinical course were used to further substantiate sepsis diagnosis when applicable.

Patient Demographics and Clinical Characteristics

The study cohort was characterized by a range of demographic and clinical variables. Key demographic parameters included age, sex, weight and height. Clinical metrics comprised duration of hospitalization, total ICU stay (in days), preoperative diagnosis, type of cardiac defect, and the complexity of the surgical procedure performed.

Statistical analysis

The collected data were processed using the IBM SPSS 29.0 statistical program. The study used descriptive statistics methods, including calculation of percentages, determination of medians and percentiles. Since the data were not normally distributed, the Wilcoxon signed-rank test was employed to assess the dynamics of the parameters before and after therapy using the Evaclio system. Values of $p < 0.05$ were considered statistically significant. Spearman's correlation coefficient was used to determine the correlation between the duration of surgical intervention and laboratory parameters.

Results

Patients who received therapy using the Evaclio system were included in the study. The mean age of the patients

was 56 ± 3.65 years. Distribution across hospital departments showed a predominance of patients from cardiac surgery and intensive care units (Table 1).

A comparative analysis of laboratory parameters before and after therapy revealed a statistically significant decrease in liver enzyme levels (ALT and AST) as well as platelet count:

- ALT: p = 0.003
- AST: p = 0.003
- Platelets: p = 0.031

A marked reduction in transaminases during therapy suggests a decrease in hepatocellular injury and indicates a potential anti-inflammatory effect of the filtration procedure.

The observed decline in platelet count (p = 0.031) may also reflect a reduction in systemic inflammatory response.

Table 1.

Descriptive statistics.

Indicators	Before treatment			After treatment		
	Me	25th percentile	75th percentile	Me	25th percentile	75th percentile
Systolic blood pressure	113	100	122	115	98	125
Diastolic blood pressure	62	42	68	61	45	66
Total bilirubin	3,63	3	5,41	2,65	1,267	4,68
Direct bilirubin	2,36	1,48	4,63	1,77	0,87	3,39
ALT	47,5	15,78	717,85	32,4	15,3	188,3
AST	84,7	30,35	1375,5	41,3	30,8	345,2
Platelets	107	72,25	166,75	92	59	129
Creatinine	1,63	1,07	2,65	1,06	0,77	2,25
Urea	72,8	33,7	105,3	31,2	20,5	83,02
Hemoglobin	90	83,75	97	90	80	93
Hematocrit	26,7	24,78	29,75	26,6	23,9	28
Albumin	3,18	2,99	3,77	3,08	2,81	3,6

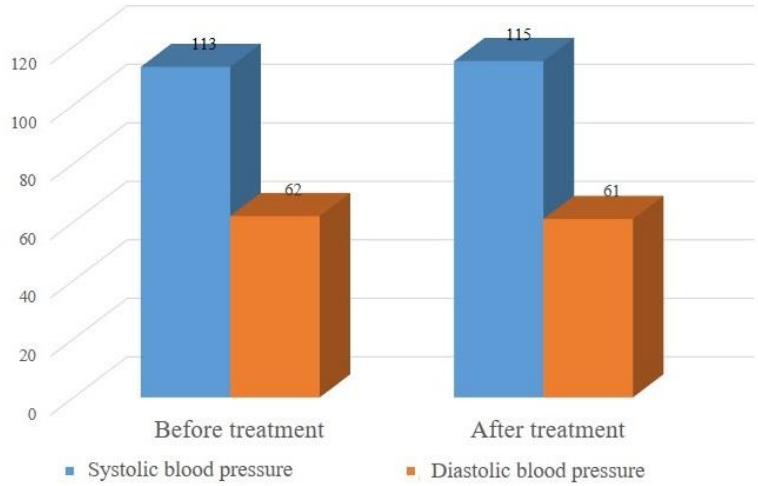


Figure 1. Changes in systolic and diastolic blood pressure before and after therapy

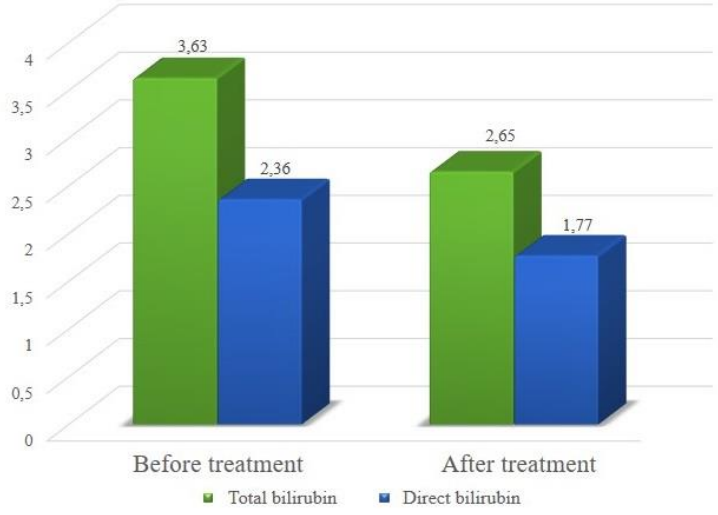


Figure 2. Changes in total and direct bilirubin levels before and after therapy.

Changes in other parameters — including bilirubin, creatinine, urea, hemoglobin, hematocrit, albumin, and blood pressure — did not reach statistical significance ($p > 0.05$) (Figure 1, 2), although a trend toward reduction in total and direct bilirubin levels was observed.

Correlation analysis did not reveal any statistically significant associations between surgery duration and the main laboratory parameters. A comparative analysis of clinical and laboratory parameters before and after therapy is presented in Table 2. The strongest, though not statistically significant, correlations were observed between:

Duration of surgery and diastolic blood pressure ($r = 0.327$; $p = 0.217$)

Duration and AST levels ($r = 0.264$; $p = 0.342$)

Duration and hemoglobin levels ($r = 0.263$; $p = 0.344$)

The criterion for treatment success was defined as a ≥ 30% reduction in total or direct bilirubin levels from baseline.

According to this criterion, the success rate of therapy was: 27% for total bilirubin (4 out of 15 patients); 40% for direct bilirubin (6 out of 15 patients).

Table 2.

Comparative analysis of indicators before and after Evaclio therapy.

Indicators	T	Z	p
Systolic blood pressure	46	-0,796	0,426
Diastolic blood pressure	37,5	-0,560	0,575
Total bilirubin	36	-1,363	0,173
Direct bilirubin	39	-1,193	0,233
ALT	8,5	-2,926	0,003
AST	7	-3,010	0,003
Platelets	22	-2,159	0,031
Creatinine	38	-1,250	0,211
Urea	26	-1,931	0,053
Hemoglobin	28	-1,822	0,068
Hematocrit	34,5	-1,449	0,147
Albumin	41,5	-1,051	0,293

Despite the lack of statistical significance in several parameters, Evaclio-based therapy demonstrated a consistent downward trend in total and direct bilirubin, urea, and creatinine levels, indicating a clinically relevant detoxification effect.

The study also analyzed the relationship between the duration of extracorporeal hemocorrection procedures and various clinical and laboratory parameters, as well as the success of therapy, defined as a ≥ 30% reduction in total bilirubin (Table 3).

Correlation analysis between the duration of the procedure and various clinical and laboratory parameters revealed no statistically significant associations ($p > 0.05$ for all variables). The strongest, though still non-significant, positive correlations were observed between procedure duration and diastolic blood pressure ($r = 0.327$, $p = 0.217$), as well as with aspartate aminotransferase (AST) levels ($r = 0.264$, $p = 0.342$). A negative correlation with systolic blood pressure (SBP) was also noted ($r = –0.32$, $p = 0.907$), but did not reach statistical significance.

Table 3.

Classification of therapy success

Indicator	Success of therapy (bilirubin reduction ≥ 30%)	
	Success	Failure
Total bilirubin	4 (27%)	11 (73%)
Direct bilirubin	6 (40%)	9 (60%)

To assess the clinical effectiveness of the therapy, a ≥ 30% reduction in total bilirubin level was used as the primary criterion. Based on this criterion, a successful therapeutic response was observed in 4 patients (27%), while 11 patients (73%) were classified as having an unsuccessful response. When analyzing direct bilirubin reduction, a favorable response was noted in 6 patients (40%), whereas in 9 patients (60%), the effect was considered insufficient.

Discussion

To our knowledge, this study represents the first reported clinical experience with selective plasma filtration using the Evaclio system in Kazakhstan and Central Asia, and the first application in postoperative cardiac surgery patients with sepsis and hepatic dysfunction. The findings suggest that Evaclio may serve as a valuable adjunctive extracorporeal therapy in critically ill cardiovascular patients, particularly in the context of systemic inflammation and hyperbilirubinemia liver injury following cardiopulmonary bypass (CPB).

Cardiac surgery with CPB is well known to trigger a systemic inflammatory response syndrome (SIRS) due to blood-surface interaction, ischemia-reperfusion injury, endotoxemia, and cytokine activation. This inflammatory cascade plays a central role in the development of sepsis-associated liver dysfunction, hyperbilirubinemia, and multiorgan failure [1-3]. Elevated levels of bilirubin and transaminases after cardiac surgery are independently associated with increased mortality and prolonged ICU stay [4].

Selective plasma filtration using Evaclio is designed to remove middle-to-large molecular weight substances, including bilirubin bound to albumin, inflammatory cytokines (IL-6, TNF-α), and other hepatotoxic mediators, while preserving essential plasma proteins, coagulation factors, and immunoglobulins [5, 6]. This selective mechanism differentiates Evaclio from conventional plasma exchange, which is associated with higher risks of bleeding, immunosuppression, and volume shifts.

In the present series, Evaclio therapy was associated with a statistically significant reduction in ALT and AST levels, reflecting attenuation of hepatocellular injury and cytolysis. Similar reductions in transaminases and bilirubin have been reported in patients with acute liver dysfunction treated with selective plasma filtration or albumin-permeable membranes [7–9]. Although a decrease in platelet count was observed, this finding is consistent with prior reports on extracorporeal blood purification techniques and may reflect platelet activation and adsorption on the membrane surface rather than clinically significant thrombocytopenia [10]. Importantly, no major bleeding events or therapy-limiting complications were observed in our cohort, supporting the acceptable safety profile of Evaclio in a postoperative cardiac population.

Up to 40% of patients achieved a ≥30% reduction in bilirubin levels, which is clinically meaningful, as early bilirubin clearance has been associated with improved

outcomes in septic patients with liver dysfunction [11]. The observed positive trends in uremic markers further suggest a multiorgan modulatory effect, likely mediated by systemic inflammation reduction.

Previous studies investigating extracorporeal liver support systems such as Molecular Adsorbent Recirculating System (MARS) or Coupled Plasma Filtration and Adsorption (CPFA) have demonstrated mixed results, often limited by complexity, cost, and hemodynamic instability [12, 13]. In contrast, Evaclio offers a technically simpler and more hemodynamically tolerable approach, making it particularly attractive for use in cardiac ICUs, where patients frequently require combined renal and hepatic support.

The introduction of Evaclio therapy at the CF University Medical Center “Heart Center” reflects the growing integration of advanced extracorporeal blood purification technologies into critical care practice in Kazakhstan. This experience may serve as a foundation for regional protocols, multicenter collaborations, and future prospective studies evaluating standardized indications, timing, and treatment intensity.

In addition, increasing evidence supports the role of extracorporeal blood purification as an immunomodulatory rather than purely detoxifying strategy in critically ill patients with sepsis and postoperative systemic inflammation. Excessive cytokine release, endothelial dysfunction, and dysregulated host response have been identified as key drivers of organ failure following CPB and septic shock, providing a mechanistic rationale for early extracorporeal intervention [14–16]. Selective plasma filtration may contribute to restoration of immune homeostasis by reducing circulating inflammatory mediators while preserving protective plasma components, thereby potentially avoiding the immune paralysis associated with non-selective plasma exchange [17].

Furthermore, integration of selective plasma filtration into multimodal extracorporeal support strategies, including continuous renal replacement therapy and mechanical circulatory support, has been increasingly reported in contemporary critical care practice [18, 19]. Such combined approaches may be particularly relevant in cardiac ICUs, where patients frequently present with overlapping cardiac, renal, and hepatic dysfunction. Although current evidence remains largely observational, expert consensus and international guidelines acknowledge extracorporeal blood purification as a promising adjunctive therapy in selected septic patients with organ failure, warranting further prospective evaluation [20, 21].

Limitations of the Study

One of the main limitations of this study is the small sample size, which may affect the generalizability of the findings to broader patient populations. Additionally, long-term outcomes related to the development of acute kidney injury (AKI) were not assessed, and the influence of other potential factors, such as genetic predisposition or comorbid conditions, was not considered.

Another limitation is the lack of control over other concurrent interventions and pharmacological treatments, which may have influenced the progression of multiple organ dysfunction syndrome (MODS). The inability to obtain data on certain variables, such as individual drug responses, may also limit the completeness of the conclusions.

Conclusion

As a result of therapy using the Evaclio filter, a marked improvement in cytolysis markers (ALT, AST; $p < 0.01$) was observed, along with a consistent trend toward reduction in bilirubin, creatinine, and urea levels. In several patients, bilirubin levels decreased by more than 30%, which is considered a clinically meaningful effect.

These findings suggest that the use of Evaclio may have a beneficial impact on markers of systemic inflammatory response and liver function, particularly in the context of severe septic conditions.

Authors' Contributions:

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Methodology – Amanzholova A.; Bekishev B.

Verification – Zuparov Y.

Formal analysis – Koichubayeva D.; Serikova A.

Writing (original draft preparation) – Amanzholova A.; Koichubayeva D.

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All authors have read and agreed to the published version of the manuscript.

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CHEMOTHERAPY-INDUCED ECHOCARDIOGRAPHY CHANGES IN HEPATOCELLULAR CARCINOMA PATIENTS

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Abstract

Introduction. Cardiovascular diseases (CVD) still remain a major health problem, occupying a leading position in the structure of morbidity and mortality. The incidence of comorbidities increases with age and when CVD is added to cancer, it becomes a major healthcare problem.

The aim. To identify earlier echocardiographic changes in myocardial dysfunction in patients with hepatocellular carcinoma without cardiovascular disease receiving targeted therapy along or in combination with transcatheter arterial embolization (TACE).

Materials and methods. In this prospective study, 73 patients undergoing targeted therapy by sorafenib and targeted therapy by sorafenib + TACE (doxorubicin) for hepatocellular carcinoma, underwent serial echocardiograms pre- and 6 months during therapy. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) and global longitudinal strain (GLS) of the left ventricle. The mean values of the listed echocardiography parameters were assessed both within groups over time and between groups of patients receiving different treatment protocols. The nonparametric method U Mann-Whitney (between groups) and Wilcoxon criterion (within group) were used for samples with irregular distribution. Student's t-test was used for parameters with normal distribution. Statistically significant differences were considered at $p<0.05$.

Results. Baseline left ventricular ejection fraction (LVEF) before targeted therapy along and targeted therapy + TACE was 61,6±4,4% vs 58,2±3,9% respectively. LVEF, LVEDV and LVESV there were no statistically significant changes in ejection fraction within 6 months from the start of therapy. However, we found a statistically significant decrease in GLS: -14,2±2,9 and -14,8±2,2, p=0,044 in both groups after 6 months targeted therapy; -20,1±2,6 and -14,2±2,9, p=0,029 in target therapy along group in dynamics after 6 months of therapy; -20,4±2,0 and -14,8±2,2, p=0,036 in target therapy + TACE group in dynamics after 6 months of therapy.

Conclusion. GLS can be used to determine preclinical myocardial systolic dysfunction in patients undergoing anticancer therapy.

Keywords: *hepatocellular carcinoma, cardiotoxicity, echocardiography, myocardium.*

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Резюме

ЭХОКАРДИОГРАФИЧЕСКИЕ ИЗМЕНЕНИЯ, ВЫЗВАННЫЕ ХИМИОТЕРАПИЕЙ, У ПАЦИЕНТОВ С ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМОЙ

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Введение. Сердечно-сосудистые заболевания (ССЗ) остаются одной из главных проблем здравоохранения, занимая ведущее место в структуре заболеваемости и смертности. Частота сопутствующих заболеваний увеличивается с возрастом, и когда ССЗ сочетаются с раковыми заболеваниями, это создает серьезные проблемы для здравоохранения.

Цель. Целью данного исследования было выявление ранних эхокардиографических изменений миокардиальной дисфункции у пациентов с гепатоцеллюлярной карциномой (ГЦК), не имеющих предшествующих сердечно-сосудистых заболеваний, которые получали таргетную терапию как в монотерапии, так и в комбинации с трансартериальной химиоэмболизацией (ТАХЭ).

Материалы и методы. В данном проспективном исследовании участвовали 73 пациента с ГЦК, которые получали таргетную терапию сорафенибом или комбинацию сорафениба и ТАХЭ (доксорубицин). Пациентам выполняли серию эхокардиографического исследования до начала лечения и через 6 месяцев после старта лечения. Оценивались параметры: фракция выброса левого желудочка (ФВЛЖ), конечный диастолический объем левого желудочка (КДО ЛЖ), конечный систолический объем левого желудочка (КСО ЛЖ) и глобальную продольную деформацию левого желудочка (GLS). Для статистической обработки использовались непараметрический критерий Манна-Уитни (для сравнения групп), критерий Уилкоксона (для анализа внутри групп) и t-тест Стьюдента для параметров с нормальным распределением, при этом статистически значимыми считались различия при $p<0,05$.

Результаты. Исходная ФВЛЖ до начала лечения сорафенибом составила 61,6 ± 4,4% в группе сорафениба и 58,2 ± 3,9% в группе сорафениб + ТАХЭ. Через 6 месяцев не было статистически значимых изменений ФВЛЖ, КДО ЛЖ и КСО ЛЖ в обеих группах. Однако было выявлено статистически значимое снижение (GLS): -14,2 ± 2,9 и -14,8 ± 2,2 в группе комбинированной терапии ($p=0,044$); -20,1 ± 2,6 и -14,2 ± 2,9 в группе сорафениб ($p=0,029$); -20,4 ± 2,0 и -14,8 ± 2,2 в группе сорафениб + ТАХЭ ($p=0,036$).

Вывод. Глобальная продольная деформация может быть использована для выявлени доклинической миокардиальной систолической дисфункции у пациентов, проходящих противоопухолевую терапию.

Ключевые слова: *гепатоцеллюлярная карцинома, кардиотоксичность, эхокардиография, миокард.*

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Түйіндеме

ГЕПАТОЦЕЛЛЮЛЯРЛЫ КАРЦИНОМАСЫ БАР НАУҚАСТАРДАҒЫ ХИМИОТЕРАПИЯ ӘСЕРІНЕН ТУЫНДАҒАН ЭХОКАРДИОГРАФИЯЛЫҚ ӨЗГЕРІСТЕР

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Кіріспе. Жүрек-қан тамырлары аурулары (ЖҚА) денсаулық сақтаудың негізгі мәселерлерінің бірі бола отырып, ауру мен өлім құрылымында жетекші орын алады. Қосымша жүретін аурулардың жиілігі жас ұлғайған сайын артады және ЖҚА қатерлі ісікпен біріктірілгенде, бұл денсаулық сақтау үшін елеулі мәселелер қаупін тудырады.

Мақсаты. Бұл зерттеудің мақсаты монотерапияда да, трансартериялық химиоэмболизациямен (ТАХЭ) біріктірілуде де мақсатты терапия алған алдыңғы жүрек-қан тамырлары аурулары жоқ гепатоцеллюлярлық карциномасы (ГЦК) бар емделушілерде миокард дисфункциясының ерте эхокардиографиялық өзгерістерін анықтау болды.

Материалдар мен әдістер. Осы проспективті зерттеуге сорафенибпен мақсатты терапия немесе сорафениб пен ТАХЕ (доксорубицин) комбинациясын алған 73 ГЦК бар пациенттер қатысты. Пациенттерге емдеу басталғанға дейін және емдеу басталғаннан кейін 6 айдан кейін бірқатар эхокардиографиялық зерттеулер жүргізілді. Келесі параметрлер: сол қарыншаның шығарылу (аластау) фракциясы (LVEF), сол қарыншаның соңғы диастолалық көлемі (LVEDV), сол қарыншаның соңғы систолалық көлемі (LVESV) және сол қарыншаның глобалды бойлық деформациясы (GLS) бағаланды. Статистикалық өңдеу үшін Манна-Уитнидің параметрлік емес критерийі (топтарды салыстыру үшін), Уилкоксон критерийі (топтар ішіндегі талдау үшін) және Стьюденттің қалыпты үлестірім параметрлері үшін t тесті қолданылды, $p<0,05$-тегі айырмашылықтар статистикалық маңызды болып саналды.

Нәтижелер. Бастапқы сол қарыншаның шығарылу (аластау) фракциясы (LVEF) сорафенибпен емдеуді бастамас бұрын сорафениб тобында 61,6 ± 4,4% және сорафениб + TAXE тобында 58,2 ± 3,9% құрады. 6 айдан кейін екі топта да LVEF, LVEDV, және LVESV статистикалық маңызды өзгерістер болған жоқ. Алайда, статистикалық маңызды төмендеу (GLS) анықталды: аралас терапия тобында -14,2 ± 2,9 және -14,8 ± 2,2 (p=0,044); сорафениб тобында -20,1 ± 2,6 және -14,2 ± 2,9 (p=0,029); сорафениб + TAXE тобында -20,4 ± 2,0 және -14,8 ± 2,2 (p=0,036).

Қорытынды. Ісікке қарсы терапияны қабылдап жатқан науқастарда клиникаға дейінгі миокардтың систолалық дисфункциясын анықтау үшін глобалды бойлық деформацияны қолдануға болады.

Түйінді сөздер: *гепатоцеллюлярлық карцинома, кардиоуыттылық, эхокардиография, миокард.*

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Introduction

Despite the rapid development of cardiology and cardiac surgery, cardiovascular diseases remain a major problem, causing significant harm to the health of the global population [7, 10]. Kazakhstan is no exception, and cardiovascular diseases occupy a leading position in the structure of morbidity and mortality. Despite of the measures on prevention and treatment the general cardiovascular morbidity (CVD) for the expired years of the XXI century in the Republic of Kazakhstan has increased by 2,5 times, from 6775,6 on 100 thousand population in 2001 up to 16982,9 in 2022 [26]. The first registered CVD in adults (18 years and older) during these years has increased from 1841,3 (2001) to 4378,6 (2020) per 100 thousand population, including arterial hypertension (AH) from 614,0 to 2138,9, ischemic heart disease (IHD) from 321,5 to 604,2 and cerebrovascular disease (CVD) from 210,3 to 433,7 respectively. The growth of CVDs, along with other factors, to some extent is due to the increase in life expectancy. The vast majority of CVDs are in the elderly and old age, and they are more likely to have comorbid diseases. Approximately 80% of elderly people have three or more diseases [2, 13, 27], which significantly increases mortality, so with two or more diseases it reaches 82% [15, 21].

The above-mentioned circumstances become especially relevant when CVD is combined with oncopathology [4, 5, 8, 28]. The analysis by K.C. Stoltzfu et al.[8] of 7529481 lethal outcomes of cancer patients showed that in 5,24 % of the causes were the heart diseases and mortality rate from CVD made 10,61/10000 man-years, and the standardized coefficient was 2,24 (95% CI: 2,23-2,25). The authors noted that the risk of CVD mortality increases with age and increases in cancer survivors over time. Here, it should be noted that first-diagnosed cancer morbidity in Kazakhstan, over the past 20 years has decreased from 195.9 (2001) per 100,000 population to 94.2 (2020), also significantly decreased mortality from 134.4 to 75.0 respectively.

Every year, the oncology field is developing more and more, with minimally invasive surgery using targeted chemotherapy drugs, such as hepatic artery chemoembolization (TACE), and new classes of pharmaceutical groups appearing for the treatment of cancer patients. Unfortunately, the use of antitumor drugs leads to the development of cardiotoxicity, worsening the quality of life of patients and the survival prognosis [14].

Echocardiography is a key noninvasive method for the early detection of cardiotoxicity in patients receiving potentially cardiac-damaging therapies. This method allows for the assessment of structural and functional changes in the myocardium, which can appear long before the development of clinical symptoms. Determining the ejection fraction and global longitudinal strain (GLS) helps detect subclinical reductions in cardiac contractility. Regular echocardiographic monitoring allows for timely treatment adjustments, reducing the risk of heart failure progression.

Due to its high availability and safety, echocardiography remains the primary tool for monitoring cardiac function during chemotherapy and other potentially cardiotoxic treatments.

For two years we have providing a project of identification early potential CVD complications in patient with HCC. The main **aim** is to identify earlier echocardiographic changes of myocardial dysfunction in patients with liver cancer without concomitant cardiovascular diseases that developed during chemotherapy and chemotherapy in combination with transcatheter arterial embolization (TACE).

Materials and methods. The result of the article is a subanalysis in a prospective study performed under grant from the Ministry of Education and Science of the Republic of Kazakhstan (Individual Registration Number AP19176025). The study was approved by the Ethical Commission of NJSC Astana Medical University (No. 21 from 09/2023). This subanalysis included 73 patients over 18 years of age with hepatocellular carcinoma who were followed from October 2023 to November 2024 at the clinical site of Astana Medical University. Patient selection was carried out using a continuous method, including patients with histologically verified hepatocellular carcinoma without cardiovascular diseases. Before inclusion in the study, all patients signed informed consent. They were divided into two groups depending on the chemotherapy method: targeted therapy with sorafenib (Nexavar, Bayer, Germany) at a dose of 800 mg per day (n=29) or targeted therapy with TACE doxorubicin (Zuvidox, OncoAce, India) at a dose of 50 mg (n=44). We monitored the echocardiographic parameters of patients before the start of therapy and 6 months after the start of therapy.

Exclusion criteria included patients under 18 years of age, those with metastatic liver cancer, cardiovascular diseases, other types of malignancies, any intraventricular conduction abnormalities, heart rhythm disturbances, ejection fraction less than 50% and a glomerular filtration rate (GFR) less than 30 mL/min.

All patients underwent serial 2DE studies (GE Ultrasound System, Vivid E95, GE Healthcare, Milwaukee, WI) before and 6 months after initiation of chemotherapy. Dedicated apical 2- and 4-chamber images were obtained for measurement of bi-plane left ventricular ejection fraction (Simpson method). For measurement of GLS apical 4-, 3-, and 2-chamber images of the LV were obtained for 3 cardiac cycles at high frame rates (40 to 80 frames/s) Peak systolic GLS was measured using EchoPAC version 202 (AFI, GE). The following measurements were taken: left ventricular ejection fraction (LV EF,%), left ventricular end-diastolic volume (LVEDV, ml/m²) and left ventricular end-systolic volume (LVESV, ml/m²) corrected for body surface area and global longitudinal strain (GLS) of the left ventricle [16, 24].

Statistical analysis was performed using the statistical package SPSS, version 26 (IBM, USA). The nonparametric method U Mann-Whitney (between groups) and Wilcoxon criterion (within group) were used for samples with irregular distribution. Student's t-test was used for parameters with normal distribution. Statistically significant differences were considered at $p<0.05$. Data are presented as median, 25th and 75th percentiles, mean and standard deviation; binary variables are presented as frequencies in absolute values and percentages.

Results

Table 1 shows the characteristics of patients suffering from hepatocellular carcinoma. In the targeted therapy group, 38% were women, in the targeted therapy with TACE group, 47%. The average age was 58±10.7 and 60±8.2, respectively. There were no differences in general clinical laboratory parameters between the two subgroups and the data did not go beyond the reference values; the ejection fraction parameters were also within the normal range. Surgical treatment was low in both subgroups and amounted to 27% and 32%. There was no difference in blood pressure between the groups, while heart rate was slightly higher in the group of patients receiving targeted therapy with TACE - 69 bpm vs 73 bpm in targeted therapy with TACE (Table 1).

Table 1.

Characteristics of patients on targeted and targeted therapy with TACE.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
Female gender, people (%)	11 (38%)	21 (47%)	0,467
Age, years old	58±10,7	60±8,2	0,782
Duration of disease, months	12,6±4,6	7,6±3,3	0,037
Hemoglobin, g/l	122,4±20,6	118,3±13,4	0,487
Potassium, μmol/L	4,16±1,1	3,89±0,82	0,140
Glucose, mmol/L	5,4±1,8	5,2±2,4	0,422
Creatinine, μmol/L	76,4±17,4	88,9±13,9	0,067
Systolic blood pressure, mm Hg	128±13	130±12	0,251
Diastolic blood pressure, mm Hg	84±10	79±12	0,540
Rest heart rate, beats per min	69±8	73±8	0.049
Operative treatment, people (%)	8 (27%)	14 (32%)	0,019

Echocardiographic parameters showed no differences between the two groups and were within normal range before starting therapy. Echocardiographic parameters of the targeted therapy and targeted therapy with TACE are summarized in Table 2.

Table 2.

Echocardiographic parameters of patients in both groups before starting therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
LV EF, %	61,6±4,4	58,2±3,9	0,299
LVEDV, ml/m2	56,5±7,4	55,7±8,0	0,058
LVESV, ml/m2	22,9 ±3.2	23,1±3,1	0,082
GLS, %	-20,1±2,6	-20,4±2,0	0,199

After 6 months, we performed a follow-up Echocardiogram. LV EF, as well as end-diastolic and LVEDV and LVESV values, were within normal ranges, while the GLS index began to statistically significantly decrease in both groups, decrease to -14,2±2,9 in targeted therapy group and -14,8±2,2 in targeted therapy with TACE (p=0.044) (Table 3).

Table 3.

Echocardiographic parameters of patients in both groups after 6 months targeted therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy + TACE (n=44)	p
LV EF, %	60,1±4,4	59,4±4,1	0,061
LVEDV, ml/m2	56,2±7,1	56,7±7,8	0,091
LVESV, ml/m2	22,6 ±3.5	21,9±3,7	0,086
GLS, %	-14,2±2,9	-14,8±2,2	0,044

We also compared echocardiographic parameters within groups using different treatment protocols. A statistically significant reduction in GLS was observed in the targeted therapy along group 6 months after the start of therapy (-20,1±2,6 vs -14,2±2,9, p=0,029) (Table 4).

Table 4.

Echocardiographic parameters of patients in the targeted therapy group along in dynamics after 6 months of therapy.

Indicator	Targeted therapy along (n =29)	Targeted therapy along after 6 months (n=29)	p
LV EF, %	61,6±4,4	60,1±4,4	0,312
LVEDV, ml/m2	56,5±7,4	56,2±7,1	0,074
LVESV, ml/m2	22,9 ±3.2	22,6 ±3.5	0,09
GLS, %	-20,1±2,6	-14,2±2,9	0,029

In patients of the target group + TACE, a statistically significant decrease in GLS was also observed, amounting to -20,4±2,0 before the start of therapy and -14,8±2,2 (p=0,036) after 6 months from the start of therapy (Table 5).

Table 5.

Echocardiographic parameters of patients in the target therapy + TACE group in dynamics after 6 months of therapy.

Indicator	Targeted therapy + TACE (n=44)	Targeted therapy + TACE after 6 months (n=44)	p
LV EF, %	58,2±3,9	59,4±4,1	0,061
LVEDV, ml/m2	55,7±8,0	56,7±7,8	0,095
LVESV, ml/m2	23,1±3,1	21,9±3,7	0,084
GLS, %	-20,4±2,0	-14,8±2,2	0,036

Discussion

The problem of cardiotoxicity in cancer patients is increasingly attracting the attention of the medical community. Cardiovascular disease plays a significant role in the administration of cardiotoxic antitumor therapy. In cardiac patients receiving chemotherapy, the risk of developing complications increases severalfold [17,18]. According to *Morris P.G. et al*. [22], the presence of arterial hypertension in patients receiving trastuzumab was 1.89 times higher than in those receiving trastuzumab. There is accumulated experience and data of long-term observation of cancer survivors, which shows various complications - from myocardial dysfunction, myocardial remodelling and reduced contractility to potentiation of arrhythmogenesis with influence on all types of cells of the cardiac conduction system. The cardiotoxic effect of chemotherapy can be manifested by a wide range of Echocardiography changes, including reduction of left ventricular ejection fraction, increase LVEDV, LVESV and GLS reduction. [1, 12, 26].

Baseline LVEF and GLS levels are recommended for all patients undergoing TTE before initiating cardiotoxic anticancer therapy to stratify the risk of anticancer drugs and identify significant changes during treatment. Most often, left ventricular injury is a consequence of cardiotoxicity in patients undergoing anticancer therapy. Changes in loading conditions frequently occur during chemotherapy (eg, volume gain due to intravenous fluid administration, volume loss due to vomiting or diarrhea, changes in blood pressure and heart rate due to pain or stress) and can affect cardiac volume, LVEF, and GLS quantification. Echocardiography is undoubtedly the primary noninvasive and reproducible method. However, visible changes, such as increased LVEDV and LVESV, which characterize a decrease in left ventricular ejection fraction, are usually irreversible.

It's important to remember that a normal left ventricular ejection fraction does not rule out damage and decreases as heart failure progresses. However, the left ventricular ejection fraction is a reliable test for the early detection of left ventricular systolic dysfunction. But it is important to remember that strain measurements may vary between different equipment, so it is recommended to perform serial GLS measurements for each patient using the same device/software.

The most important in identifying cardiotoxicity is its early, reversible detection [27]. Undoubtedly, GLS determination is the primary noninvasive method for the early detection of left ventricular systolic myocardial dysfunction [25, 29]. Yes, GLS has some limitations: high software requirements, an experienced physician, a normal heart rate, and sinus rhythm. However, these should not be a limitation in identifying myocardial dysfunction in cancer patients [28].

Bellinger A. M. et al. reported that anthracyclines cause cardiomyocyte death, leading to irreversible myocardial damage [3]. The extent of this damage depends on the total dose of the anticancer drug. Additionally, anthracyclines can cause cardiac rhythm and conduction disorders in 16-36% of cancer patients. While our study did not detect reduced ejection fraction, we observed differences in GLS after 6 months of therapy.

Our results are supported by studies conducted in cancer patients. A study by *Gonzalez-Manzanares et al.* identified of patients on antitumor therapy in patients with acute leukemia subclinical decrease in GLS before changes in left ventricular ejection fraction [9]. Another study by *Niemelä J. et al.* demonstrated that patients with different malignancies had abnormal LV longitudinal strain and 70% of patients had normal LV ejection fraction [23].

Our subanalysis demonstrated a stable decrease in the GLS level, both within the group of patients with target therapy along (-20.1±2.6 vs. -14.2±2.9, p=0.029) and with target therapy + TACE (-20.4±2.0 vs. -14.8±2.2, p=0.036), as well as with the appointment of group therapy under different treatment protocols (-14.2±2.9, -14.8±2.2, p=0.044).

Unfortunately, our study has several limitations. The quality of documentation remains inconsistent. Some

missing data regarding the frequency of therapy and periods when the patient was off treatment may introduce some errors. Although echocardiography in our study was performed directly by the researchers, extrapolating these results to all patients likely has some limitations. All cases for both medical examination and medical history collection were intentionally selected, which may have introduced some bias.

Conclusion

According to *Felker G.M.* (2000), fibrotic focal changes dominated in myocardial histopreparations in patients receiving traditional chemotherapy with taxanes and anthracyclines, possibly as a consequence of cardiomyocyte apoptosis during therapy with these chemotherapy drugs [6]. The appearance of clinical symptoms such as chronic Heart Failure requires a long period of time and irreversible changes on echocardiography, such as a decrease in the LV EF. Thus, the inclusion of GLS in diagnostic and treatment protocols for patients with oncological diseases helps to identify cardiotoxicity at early stages and prevent the development of left ventricular systolic dysfunction [11, 24].

In patients with HCC without cardiovascular pathology, comparison between the groups of targeted therapy along and targeted therapy + TACE, as well as observation within the groups in dynamics for 6 months after the start of therapy showed a decrease in GLS. The GLS has proven to be a valuable diagnostic parameter for predicting subclinical cardiac dysfunction and predicting future significant decline in LVEF in cancer patients. The results highlight the importance of careful monitoring of Echocardiographic characteristics during targeted chemotherapy without or with TACE, especially given the potential risk of adverse cardiovascular events. Our findings significantly contribute to the accumulating evidence on chemotherapy-induced Echo changes in HCC patients. This necessitates comprehensive cardiac monitoring and personalized treatment strategies for this vulnerable population.

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EVALUATION OF THE SATISFACTION AND SUCCESS LEVELS OF BASIC LIFE SUPPORT, ADVANCED CARDIAC LIFE SUPPORT, AND TRAUMA TRAININGS PROVIDED TO SIXTH-YEAR STUDENTS OF MEDICAL FACULTY KARADENIZ TECHNICAL UNIVERSITY

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Abstract

Aim. To evaluate the success and satisfaction levels of sixth-year medical students who received Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and Advanced Trauma Life Support (ATLS) training during their emergency medicine internship.

Materials and Methods. This descriptive retrospective study included sixth-year medical students who completed their emergency medicine internship at the Karadeniz Technical University (KTU) Faculty of Medicine between 2019 and 2020. A total of 120 students were included in the study. Questionnaire forms containing socio-demographic characteristics were prepared. Before and after the trainings, assessment tests were administered to measure students' knowledge levels. Following the trainings, satisfaction questionnaires were conducted. Data were analyzed using the IBM SPSS 23 statistical package program.

Results. The mean pre-test and post-test scores of those who received BLS and ACLS training were 60.44 ± 11.84 and 87.93 ± 10.57, respectively ($p < 0.05$). Similarly, the mean pre-test and post-test scores of participants who received trauma training were 62.35 ± 13.73 and 78.41 ± 9.38, respectively ($p < 0.05$). There was no statistically significant difference between the pre-test and post-test scores of students who had previously received BLS or ACLS training and those who had not such training. Likewise, there was no significant difference between students who aimed to specialize in emergency medicine and those who did not ($p > 0.05$). Interestingly, students who were satisfied with studying at the Faculty of Medicine had significantly higher pre-test scores in trauma training compared to those who were dissatisfied ($p < 0.05$).

Conclusion. Basic, advanced cardiac, and trauma life support represent some of the most critical and essential medical interventions. In our study, it was demonstrated that these simulation-based trainings significantly improved the knowledge and skills of pre-graduation medical students and had a positive impact on their satisfaction levels.

***Key words**: Basic Life Support, Advanced Cardiac Life Support, Advanced Trauma Life Support, training, internship, satisfaction.*

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Резюме

ОЦЕНКА УРОВНЯ УДОВЛЕТВОРЕННОСТИ И УСПЕШНОСТИ ПРОВЕДЕНИЯ ОБУЧЕНИЯ ПО БАЗОВОЙ И РАСШИРЕННОЙ СЕРДЕЧНО-ЛЕГОЧНОЙ РЕАНИМАЦИИ И РАСШИРЕННОЙ ТРАВМАТОЛОГИЧЕСКОЙ РЕАНИМАЦИИ ДЛЯ СТУДЕНТОВ ШЕСТОГО КУРСА МЕДИЦИНСКОГО ФАКУЛЬТЕТА ТЕХНИЧЕСКОГО УНИВЕРСИТЕТА КАРАДЕНИЗ

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Цель. Оценка уровня успешности и удовлетворенности студентов шестого курса медицинского факультета, прошедших обучение по базовой сердечно-легочной реанимации (БСЛР), расширенной сердечно-легочной реанимации (РСЛР) и расширенной травматологической реанимации (РСТЛР) во время интернатуры по неотложной медицине.

Материалы и методы. В это описательное ретроспективное исследование были включены студенты шестого курса медицинского факультета, завершившие интернатуру по неотложной медицине на медицинском факультете Караденизского технического университета (КТУ) в период с 2019 по 2020 год. В исследование было включено 120 студентов. Были подготовлены анкеты, содержащие социально-демографические характеристики. До и после обучения проводились оценочные тесты для измерения уровня знаний студентов. После обучения проводились анкеты для оценки удовлетворенности. Данные были проанализированы с помощью статистического пакета IBM SPSS 23.

Результаты. Средние баллы до и после тестирования у тех, кто прошел обучение по базовой и расширенной сердечно-легочной реанимации, составили 60,44 ± 11,84 и 87,93 ± 10,57 соответственно ($p < 0,05$). Аналогично, средние баллы до и после тестирования у участников, прошедших обучение по оказанию травматологической помощи, составили 62,35 ± 13,73 и 78,41 ± 9,38 соответственно ($p < 0,05$). Статистически значимой разницы между баллами до и после тестирования у студентов, ранее прошедших обучение по базовой или расширенной сердечно-легочной реанимации, и у тех, кто такого обучения не проходил, не было. Также не было значимой разницы между студентами, стремящимися специализироваться в неотложной медицине, и теми, кто этого не делает ($p > 0,05$). Интересно, что студенты, удовлетворенные обучением на медицинском факультете, показали значительно более высокие баллы до тестирования по травматологической помощи по сравнению с теми, кто был недоволен ($p < 0,05$).

Заключение. Базовая, расширенная сердечно-легочная реанимация и реанимация при травмах представляют собой одни из наиболее важных и необходимых медицинских вмешательств. В нашем исследовании было показано, что эти тренировки на основе симуляции значительно улучшили знания и навыки студентов-медиков, готовящихся к завершению обучения в медицинском вузе, и оказали положительное влияние на уровень их удовлетворенности.

***Ключевые слова**: базовая сердечно-легочная реанимация, расширенная сердечно-легочная реанимация, расширенная реанимация при травмах, обучение, удовлетворенность.*

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Түйіндеме

МЕДИЦИНА ФАКУЛЬТЕТІНІҢ АЛТЫНШЫ КУРС СТУДЕНТТЕРІ ҮШІН НЕГІЗГІ ЖӘНЕ КЕҢЕЙТІЛГЕН ЖҮРЕК-ӨКПЕ РЕАНИМАЦИЯСЫ ЖӘНЕ КЕҢЕЙТІЛГЕН ТРАВМАТОЛОГИЯЛЫҚ РЕАНИМАЦИЯ БОЙЫНША ОҚЫТУДЫ ӨТКІЗУДІҢ ҚАНАҒАТТАНУ ДЕҢГЕЙІ МЕН ТИІМДІЛІГІН БАҒАЛАУ КАРАДЕНИЗ ТЕХНИКАЛЫҚ УНИВЕРСИТЕТІ

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Мақсат. Шұғыл медицина интернатурасы кезінде негізгі жүрек-өкпе реанимациясы (БСДР), кеңейтілген жүрек-өкпе реанимациясы (РСДР) және кеңейтілген травматологиялық реанимация (рстдр) бойынша оқудан өткен медицина факультетінің алтыншы курс студенттерінің табыстылығы мен қанағаттану деңгейін бағалау.

Материалдар мен әдістер. Бұл сипаттамалық ретроспективті зерттеуге 2019-2020 жылдар аралығында Караденiз техникалық университетінің (КТУ) медицина факультетінде шұғыл медицина бойынша интернатураны аяқтаған медицина факультетінің алтыншы курс студенттері енгізілді. Зерттеуге 120 студент қатысты. Әлеуметтік-

демографиялық сипаттамалары бар сауалнамалар дайындалды. Оқудың алдында және одан кейін студенттердің білім деңгейін өлшеу үшін бағалау тестілері өткізілді. Оқудан кейін қанағаттанушылықты бағалау үшін сауалнамалар жүргізілді. Деректер IBM SPSS 23 статистикалық пакеті арқылы талданды.

Нәтижелер. Негізгі және кеңейтілген жүрек-өкпе реанимациясы бойынша оқығандардың тестілеуге дейінгі және кейінгі орташа ұпайлары сәйкесінше 60,44 ± 11,84 және 87,93 ± 10,57 құрады ($p < 0,05$). Сол сияқты, травматологиялық көмек көрсету бойынша оқудан өткен қатысушылардың тестілеуге дейінгі және кейінгі орташа балдары тиісінше 62,35 ± 13,73 және 78,41 ± 9,38 ($p < 0,05$) құрады. Бұрын негізгі немесе кеңейтілген жүрек-өкпе реанимациясы бойынша оқыған студенттерде тестілеуге дейінгі және кейінгі ұпайлар арасында статистикалық маңызды айырмашылық болған жоқ. Сондай-ақ, жедел медициналық көмекке мамандағысы келетін студенттер мен оны жасамайтындар арасында айтарлықтай айырмашылық болған жоқ ($p > 0,05$). Бір қызығы, медицина факультетінде оқуға қанағаттанған студенттер қанағаттанбағандармен салыстырғанда травматологиялық көмекке тестілеуден бұрын айтарлықтай жоғары балл жинады ($p < 0,05$).

Қорытынды. Негізгі, кеңейтілген жүрек-өкпе реанимациясы және жарақат реанимациясы ең маңызды және қажетті медициналық араласулардың бірі болып табылады. Біздің зерттеуіміз бұл модельдеу негізіндегі жаттығулар медициналық университетте оқуды аяқтауға дайындалып жатқан медицина студенттерінің білімі мен дағдыларын айтарлықтай жақсартқанын және олардың қанағаттану деңгейіне оң әсер еткенін көрсетті.

Түйінді сөздер: *Негізгі жүрек-өкпе реанимациясы, кеңейтілген жүрек-өкпе реанимациясы, кеңейтілген жарақат реанимациясы, оқыту, қанағаттану.*

Дәйексөз үшін:

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Introduction

Sudden cardiac arrest is one of the leading causes of death worldwide [10]. «Cardiopulmonary Arrest (CPA)» refers to the sudden cessation of spontaneous respiration and/or circulation due to any cause. “Cardiopulmonary Resuscitation (CPR)” consists of a series of simple yet knowledge- and experience-dependent sequential procedures performed to provide adequate respiration and circulation and to restore life in a person whose breathing and/or circulation has stopped [3].

In 2018, a total of 421,164 deaths were reported in Turkey. Among these, 161,920 were due to cardiovascular diseases, while 18,462 were trauma-related [16]. Several studies have shown that medical students’ knowledge and skills regarding cardiac life support are not at a sufficient level [2]. Effective and high-quality CPR can significantly reduce not only mortality but also morbidity rates. Similarly, the training of pre-hospital medical care providers and emergency service personnel plays a crucial role in reducing trauma-related deaths.

The purpose of this study is to evaluate and assess the success and satisfaction levels of sixth-year medical students who received Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and Advanced Trauma Life Support (ATLS) training.

Resuscitation practices have evolved and undergone rapid changes, particularly over the last two centuries [16]. In 1732, William Tossach performed the first mouth-to-mouth ventilation on a coal miner [8]. In 1773, a method known as the “barrel method” was developed. A barrel was placed under the chest of a presumed CPA victim and rolled back and forth to apply pressure on the lungs and heart, in an attempt to revive the patient [4].

In 1803, another method known as the “Russian method” involved placing victims under snow or ice to slow down metabolism, aiming to protect the brain and heart [7]. Historical records from 1812 indicate that some drowning victims were placed on horses and revived by galloping, which aimed to expel aspirated water from the lungs and provide a form of cardiac massage through the rhythmic movement [4].

In 1740, the Académie des Sciences de Paris (Paris Academy of Sciences) recommended mouth-to-mouth ventilation for drowning victims [13]. Later, Kouwenhoven, Knickerbocker, and Jude introduced the first definition of “modern CPR” in medical literature, which emphasized the combination of mouth-to-mouth ventilation and external chest compressions for effective resuscitation [8]. External defibrillation, first described by Kouwenhoven in 1957, was subsequently incorporated into Basic Life Support (BLS) guidelines [23]. The American Heart Association (AHA) officially endorsed CPR in 1963 and, in 1966, established standardized CPR guidelines for non-professional rescuers [23].

Sudden cardiac death accounts for approximately 15% of all deaths in the United States and other industrialized countries [5]. In 1999, the estimated number of sudden cardiac deaths in the United States was reported to be around 450,000 [15].

During advanced life support interventions, rescuers must be able to identify reversible causes of cardiac arrest and perform the necessary corrective actions [11]. It is also critical for lay rescuers in the community to recognize cardiac arrest early in the absence of medical personnel, promptly call local emergency services, initiate high-quality CPR without delay, use an automated external defibrillator (AED) correctly if available, and perform defibrillation when indicated, all of which are vital steps before the arrival of well-equipped healthcare professionals [19].

Training in Basic and Advanced Life Support emphasizes correct procedural performance, teamwork, and labor distribution, all of which have been shown to significantly improve participants skills [9].

Materials and Methods

This descriptive and retrospective study was conducted at the Karadeniz Technical University (KTU) Center for Good Medical Practice and Simulation. Ethical approval for the study was obtained from the KTU Clinical Research Ethics Committee (Decision No. 152, dated 2020) and the Directorate of the Center for Good Medical Practice and Simulation.

The study population consisted of 124 sixth-year medical students who were undergoing their emergency medicine internship at KTU Faculty of Medicine between September 2019 and February 2020. No sampling method was employed, as it was planned to include the entire population. A total of 120 students who agreed to participate in the study and successfully completed the simulation-based Advanced Cardiac Life Support (ACLS), Basic Life Support (BLS), and Trauma Life Support (TLS) trainings were included in the final analysis. Students who did not complete all training modules, did not provide appropriate data, or did not volunteer to participate were excluded.

Data were collected retrospectively from the records of the KTU Center for Good Medical Practice and Medical Simulation. The study included students who participated in BLS, ACLS, and trauma training sessions during the 2019–2020 academic year within the Department of Emergency Medicine internship block. Each participant completed a multiple-choice knowledge test both before and after the training sessions to assess their cognitive knowledge levels. Additionally, a post-training satisfaction questionnaire was administered to evaluate their satisfaction with the courses.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Parametric tests were used for normally distributed variables, and non-parametric tests were used for data that did not meet normality assumptions.

Results

This study was conducted to evaluate the success and satisfaction levels of sixth-year medical students at Karadeniz Technical University Faculty of Medicine who received BLS, ACLS, and Trauma training during the 2019–2020 academic year. Table 1 presents the socio-demographic characteristics of the participants. Accordingly, 76.7% (n = 92) of participants were between 20–25 years of age. The majority were female (60%, n = 72), while males comprised 40% (n = 48) of the group. In terms of marital status, 98.3% (n = 118) were single.

Table 1.

Sociodemographic Data.

Features		n	%
Age	20-25 years old	92	76,7
	26-30 years old	27	22,5
	31-35 years old	0	0
	35 years and older	1	0,8
Gender	female	72	60
	Male	48	40
Marital status	Single	118	98,3
	Married	2	1,7
Previous education status	Yes	78	65
	No	42	35
Nationality	Turkish	118	98,3
	Foreigner	2	1,7
Satisfaction with being at the Faculty of Medicine	Yes	95	79,2
	No	25	20,8
Wanting to become an Emergency Medicine Specialist	Yes	12	10
	No	53	44,2
	Undecided	55	45,8

Among the students, 65% (n = 78) reported having previously received BLS and ACLS training, 79.2% (n = 95) stated that they were satisfied with studying at the Faculty of Medicine, and 10% (n = 12) expressed their intention to specialize in emergency medicine.

Cardiopulmonary Resuscitation

After the BLS/ACLS trainings, a satisfaction questionnaire consisting of 19 items (rated as: very poor, poor, fair, good, very good) was administered. The results are presented in Table 2.

According to the findings, 73.4% (n = 88) of the participants rated the training duration as good (n = 44) or very good (n = 44). 43.3% (n = 52) evaluated the scheduling and timing of the course as good (n = 25) or very good (n = 27).

86.7% (n = 104) considered the course content appropriate and sufficient (good n = 54; very good n = 50). 81.7% (n = 98) rated the teaching methods, techniques, and comprehensibility as good (n = 56) or very good (n = 42).

86.7% (n = 104) found the adequacy of tools, equipment, and materials used during training to be good (n = 42) or very good (n = 62).

98.3% (n = 118) found the training venue appropriate (good n = 40; very good n = 78).

Table 2.

BLS/ACLS Training Satisfaction Survey Data.

Questions		n	%
1	2	3	4
Was the course duration sufficient?	very poor	5	4,2
	poor	6	5,0
	fair	21	17,5
	good	44	36,7
	very good	44	36,7
Was the date (timing) of the course suitable?	very poor	17	14,2
	poor	29	24,2
	fair	22	18,3
	good	25	20,8
	very good	27	22,5
Was the content of the course appropriate and sufficient for the training?	very poor	1	0,8
	poor	2	1,7
	fair	13	10,8
	good	54	45,0
	very good	50	41,7
Were the training methods and techniques appropriate for understanding the subject?	very poor	3	2,5
	poor	1	0,8
	fair	18	15,0
	good	56	46,7
	very good	42	35,0
Were the course materials (tools/equipment/documents) sufficient?	very poor	1	0,8
	poor	2	1,7
	fair	13	10,8
	good	42	35,0
	very good	62	51,7
Was the venue where the course was held suitable for training?	very poor	0	0
	poor	0	0
	fair	2	1,7
	good	40	33,3
	very good	78	65,0
Did the educators have sufficient knowledge and expertise on their subject?	very poor	2	1,7
	poor	4	3,3
	fair	13	10,8
	good	42	35,0
	very good	59	49,2
Has the topic been presented using appropriate methods and techniques?	very poor	1	0,8
	poor	3	2,5
	fair	12	10,0
	good	55	45,8
	very good	49	40,8
Was time used effectively and efficiently?	very poor	6	5,0
	poor	7	5,8
	fair	40	33,3
	good	44	36,7
	very good	23	19,2
Were the topics covered clearly, understandably, and appropriately for your level?	very poor	1	0,8
	poor	6	5,0
	fair	17	14,2
	good	51	42,5
	very good	45	37,5
Was it possible to ensure active participation of all participants in the training?	very poor	1	0,8
	poor	1	0,8
	fair	16	13,3
	good	57	47,5
	very good	45	37,5

Continuation of Table 2.

1	2	3	4
Were visual and audio aids used effectively in presentations?	very poor	3	2,5
	poor	7	5,8
	fair	10	8,3
	good	50	41,7
	very good	50	41,7
Did the course contribute positively to your professional development?	very poor	1	0,8
	poor	2	1,7
	fair	4	3,3
	good	42	35,0
	very good	71	59,2
Did the course contribute positively to your personal development?	very poor	1	0,8
	poor	7	5,8
	fair	7	5,8
	good	40	33,3
	very good	65	54,2
Did the course provide new knowledge and skills?	very poor	1	0,8
	poor	1	0,8
	fair	13	10,8
	good	41	34,2
	very good	64	53,3
Did the course increase your motivation?	very poor	2	1,7
	poor	3	2,5
	fair	22	18,3
	good	37	30,8
	very good	56	46,7
Did the course provide new professional knowledge and skills that you can share with your colleagues?	very poor	1	0,8
	poor	1	0,8
	fair	10	8,3
	good	46	38,3
	very good	62	51,7
Did the course increase your interest in the subject?	very poor	2	1,7
	poor	2	1,7
	fair	9	7,5
	good	44	36,7
	very good	63	52,5
How would you evaluate the course in general?	poor	2	1,7
	fair	4	3,3
	good	34	28,3
	very good	68	56,7
	Excellent	12	10,0

84.2% (n = 101) rated the instructors' knowledge and subject mastery as good (n = 42) or very good (n = 59).

86.6% (n = 104) evaluated the methods and techniques used in instruction as good (n = 55) or very good (n = 49). 55.9% (n = 67) believed that the allocated time was used efficiently (good n = 44; very good n = 23).

80% (n = 96) stated that the topics were explained clearly and at an appropriate level for students (good n = 51; very good n = 45).

85% (n = 102) reported that active student participation in the courses was good (n = 57) or very good (n = 45).

83.4% (n = 100) stated that visual and auditory materials were effectively used in the presentations (good n = 50; very good n = 50).

94.2% (n = 113) believed that the course positively contributed to their professional development (good n = 42; very good n = 71).

87.5% (n = 105) stated that the course contributed positively to their personal development (good n = 40; very good n = 65).

87.5% (n = 105) evaluated the acquisition of new knowledge and skills as good (n = 41) or very good (n = 64).

77.5% (n = 93) reported that the training significantly increased their motivation (good n = 37; very good n = 56). 90% (n = 108) indicated that the course provided new knowledge and skills they could share with colleagues (good n = 46; very good n = 62).

89.2% (n = 107) stated that the trainings increased their interest in the subjects (good n = 44; very good n = 63). Finally, 95% (n = 114) of the participants evaluated the overall BLS/ACLS training as good (n = 34), very good (n = 68), or excellent (n = 12).

In conclusion, the aspect participants were most satisfied with was the suitability of the training venue (98.3%, n = 118). Furthermore, 94.2% (n = 113) reported that the courses had a positive impact on their professional development. The lowest satisfaction rate was related to the scheduling and timing of the courses, with 43.3% (n = 52) rating this aspect as good or very good.

Trauma Training Satisfaction Survey and Achievement Findings

Following the trauma trainings, a 19-item satisfaction questionnaire (rated as: very poor, poor, fair, good, very good) was administered to the students. The results of the trauma training satisfaction survey are presented in Table 3. According to this survey, 77.5% (n = 93) of participants stated that the training duration was very good (n = 41) or good (n = 52). 41.7% (n = 50) characterized the scheduling and timing of the course as good (n = 29) or very good (n = 21). 84.1% (n = 101) reported that the appropriateness and adequacy of the course content were good (n = 67) or very good (n = 34). 80% (n = 96) rated the training methods, techniques, and comprehensibility as good (n = 71) or very good (n = 25), and 80% (n = 96) evaluated the adequacy of the tools, equipment, and documents used during training as good (n = 59) or very good (n = 37).

93.4% (n = 112) of the trainees rated the suitability of the training venue as good (n = 65) or very good (n = 47). 84.2% (n = 101) assessed the instructors' command of the subject and adequacy of knowledge as good (n = 57) or very good (n = 44).

Table 3.

Post-Trauma Training Satisfaction Survey.

Questions		n	%
1	2	3	4
Was the course duration sufficient?	very poor	4	3,3
	poor	11	9,2
	fair	12	10,0
	good	52	43,3
	very good	41	34,2
Was the date (timing) of the course suitable?	very poor	31	25,8
	poor	19	15,8
	fair	20	16,7
	good	29	24,2
	very good	21	17,5
Was the content of the course appropriate and sufficient for the training?	very poor	1	,8
	poor	3	2,5
	fair	15	12,5
	good	67	55,8
	very good	34	28,3
Were the training methods and techniques appropriate for understanding the subject?	very poor	1	,8
	poor	5	4,2
	fair	18	15,0
	good	71	59,2
	very good	25	20,8
Were the course materials (tools/equipment/documents) sufficient?	very poor	1	,8
	poor	6	5,0
	fair	17	14,2
	good	59	49,2
	very good	37	30,8
Was the venue where the course was held suitable for training?	very poor	0	0
	poor	2	1,7
	fair	6	5,0
	good	65	54,2
	very good	47	39,2
Did the educators have sufficient knowledge and expertise on their subject?	very poor	0	0
	poor	4	3,3
	fair	15	12,5
	good	57	47,5
	very good	44	36,7
Has the topic been presented using appropriate methods and techniques?	very poor	0	0
	poor	7	3,3
	fair	10	12,5
	good	67	47,5
	very good	36	36,7

Continuation of Table 3.

1	2	3	4
Was time used effectively and efficiently?	very poor	7	5,8
	poor	14	11,7
	fair	25	20,8
	good	46	38,3
	very good	28	23,3
Were the topics covered clearly, understandably, and appropriately for your level?	very poor	1	,8
	poor	4	3,3
	fair	13	10,8
	good	66	55,0
	very good	36	30,0
Was it possible to ensure active participation of all participants in the training?	very poor	1	,8
	poor	10	8,3
	fair	33	27,5
	good	40	33,3
	very good	36	30,0
Were visual and audio aids used effectively in presentations?	very poor	2	1,7
	poor	3	2,5
	fair	26	21,7
	good	49	40,8
	very good	40	33,3
Did the course contribute positively to your professional development?	very poor	0	0
	poor	3	2,5
	fair	16	13,3
	good	46	38,3
	very good	55	45,8
Did the course contribute positively to your personal development?	very poor	0	0
	poor	6	5,0
	fair	14	11,7
	good	51	42,5
	very good	49	40,8
Did the course provide new knowledge and skills?	very poor	0	0
	poor	2	1,7
	fair	11	9,2
	good	50	41,7
	very good	57	47,5
Did the course increase your motivation?	very poor	3	2,5
	poor	4	3,3
	fair	29	24,2
	good	45	37,5
	very good	39	32,5
Did the course provide new professional knowledge and skills that you can share with your colleagues?	very poor	1	,8
	poor	3	2,5
	fair	11	9,2
	good	49	40,8
	very good	56	46,7
Did the course increase your interest in the subject?	very poor	1	,8
	poor	4	3,3
	fair	21	17,5
	good	45	37,5
	very good	49	40,8
How would you evaluate the course in general?	poor	1	,8
	fair	11	9,2
	good	39	32,5
	very good	61	50,8
	Excellent	8	6,7

84.2% (n = 103) described the methods and techniques used in instruction as good (n = 67) or very good (n = 36).

61.6% (n = 74) evaluated the efficient and effective use of the allocated time as good (n = 46) or very good (n = 28). 85% (n = 102) rated the clarity of the topics and their suitability for the student level as good (n = 66) or very good (n = 36). 63.3% (n = 76) considered active participation in the trainings to be good (n = 40) or very good (n = 36). 74.1% (n = 89) stated that visual and auditory media were effectively used in the presentations (good n = 49; very good n = 40). 84.1% (n = 101) indicated that the course had a positive effect on their professional development (good n = 46; very good n = 55), while 83.3% (n = 100) reported a positive effect on personal development (good n = 51; very good n = 49).

89.2% (n = 107) evaluated the acquisition of new knowledge and skills as good (n = 50) or very good (n = 57). 70% (n = 84) stated that the course increased their motivation at good (n = 45) or very good (n = 39) levels. 87.5% (n = 105) rated the gains in new knowledge and skills that could be shared with colleagues as good (n = 49) or very good (n = 56). 78.3% (n = 94) reported that the trainings increased their interest in the topics (good n = 45; very good n = 49). Ultimately, 90% (n = 108) evaluated the trauma trainings overall as good (n = 39), very good (n = 61), or excellent (n = 8). Based on the trauma course satisfaction survey, 93.4% (n = 112) reported being most satisfied with the suitability of the training venue. Additionally, 87.5% (n = 105) stated that they had gained new knowledge and skills they could share with colleagues. The least satisfactory aspect was the course date and scheduling, with 41.7% (n = 50) reporting satisfaction in this dimension.

The participants' mean pre-test and post-test scores for BLS and ACLS were 60.44 ± 11.84 and 87.93 ± 10.54, respectively, indicating a statistically significant difference between the pre- and post-test mean scores. The post-test mean scores were significantly higher ($p < 0.05$) (Table 4). As indicated in the table, the minimum score observed in the pre-test was 12, while the minimum score in the post-test after training was 48. The maximum pre-test score was 86, whereas the maximum post-test score was 100.

Table 4.

Comparison of BLS and ACLS Course Pre-Test-Post-Test Scores Averages.

Tests	$\bar{x}$ ± S.S.	Min-Max	Test Statistics	p value
Pre-Test	60,44±11,84	12-86	Z=-9,417	0,000
Post-Test	87,93±10,54	48-100		

**$\bar{x}$: Arithmetic Mean, S.D.: Standard Deviation, Min: Minimum, Max: Maximum, Z: Wilcoxon Test.*

For trauma training, the participants' mean pre-test and post-test scores were 62.35 ± 13.73 and 78.41 ± 9.38, respectively, with a statistically significant difference between the two ($p < 0.05$). The post-test mean scores were significantly higher (Table 5). In the table, the minimum pre-test score was 28, while the minimum post-test score after training was 59. The maximum pre-test score was 90, and the maximum post-test score was 100.

Table 5.

Comparison of Trauma Course Pre-Test-Post-Test Mean Scores.

Tests	$\bar{x}$ ± S.S.	Min-Max	Test Statistics	p value
Pre-Test	62,35±13,73	28-90	Z=-8,944	0,000
Post-Test	78,41±9,38	59-100		

Z: Wilcoxon Test, Min: Minimum, Max: Maximum.

Comparisons of BLS and ACLS pre- and post-test results according to the socio-demographic characteristics of the final-year medical students are provided in Table 6. Accordingly, female participants had a mean pre-test score of 61.83 ± 11.68, while male participants had 58.35 ± 11.89; the difference was not statistically significant ($p = 0.060$). For the post-test, females scored 88.45 ± 10.21 on average and males 87.14 ± 11.08, with no statistically significant difference ($p = 0.480$). Based on these findings, gender did not exert a statistically significant effect on scores in either the pre- or post-test.

When pre- and post-test results were compared according to whether participants had previously received BLS and ACLS training, those with prior training had a mean pre-test score of 60.41 ± 11.94, while those without prior training had 60.50 ± 11.79, with no statistically significant difference ($P = 0.654$). In the post-test, the mean score was 88.23 ± 10.55 for those with prior training and 87.38 ± 10.62 for those without, again with no statistically significant difference ($P = 0.660$). Thus, in our study, prior training did not produce a statistically significant effect on the average scores obtained in either the pre- or post-test.

Regarding satisfaction with studying at the Faculty of Medicine, the pre-test mean score was 59.87 ± 11.59 among those satisfied and 62.60 ± 12.73 among those not satisfied; the difference was not statistically significant ($P = 0.198$). In the post-test, however, the mean score was 86.90 ± 10.88 for those satisfied and 91.84 ± 8.18 for those not satisfied, indicating a statistically significant difference ($P = 0.038$). Accordingly, a significant difference in mean exam scores between satisfied and dissatisfied students was observed only in the post-test.

For the intention to specialize in emergency medicine, the BLS/ACLS pre-test mean scores were 55 ± 16.37 among those who wished to specialize, 61.75 ± 10.40 among those who did not, and 60.36 ± 11.91 among those undecided, with no statistically significant difference ($P = 0.301$).

In the post-test, the mean scores were 85 ± 7.26 (wish to specialize), 89.39 ± 11.63 (do not wish), and 87.16 ± 9.95 (undecided), with no statistically significant difference ($P = 0.051$).

When the undecided group was excluded and a pairwise comparison was made between those who wished to specialize in emergency medicine and those who did not, the post-test mean scores for BLS/ACLS were, contrary to expectations, significantly higher among those who did not wish to specialize in emergency medicine ($p = 0.029$).

Table 6.

Comparison of socio-demographic characteristics and BLS and ACLS pre-test-post-test mean scores.

Features		Pre-Test	Post-Test
Gender	female	61,83±11,68	88,45±10,21
	Male	58,35±11,89	87,14±11,08
Test statistics		U=1378,500	U=1597,500
p		p=0,060	p=0,480
Previous education status	Yes	60,4103±11,94	88,23±10,55
	No	60,5000±1179	87,38±10,62
Test statistics		U=1557,000	U=1559,000
p		P=0,654	P=0,660
Satisfaction with being at the Faculty of Medicine	Yes	59,87±11,59	86,90±10,88
	No	62,60±12,73	91,84±8,18
Test statistics		U=989,000	U=870,500
p		P=0,198	P=0,038
Wanting to become an Emergency Medicine Specialist	Yes	55±16,37	85±7,26
	No	61,75±10,40	89,39±11,63
	Undecided	60,36±11,91	87,16±9,95
Test statistics p		χ^2=2,399	χ^2=5,954
		P=0,301	P=0,051

χ^2: :Kruskal Wallis test statistic, U:Mann Whitney U test statistic

In summary, based on the data obtained in our study, there were no statistically significant differences between gender, prior BLS/ACLS training, or the desire to specialize in emergency medicine with respect to BLS/ACLS pre- and post-test mean scores. However, there was a statistically significant difference between satisfaction with studying in the Faculty of Medicine and post-test mean scores for BLS/ACLS: post-test scores of students not satisfied with studying in the Faculty were significantly higher than those who were satisfied (P = 0.038).

Comparisons of trauma pre- and post-test mean scores according to participants' socio-demographic characteristics are provided in Table 7. Female participants had a mean pre-test score of 63.20 ± 12.74, while males scored 61.06 ± 15.13; this difference was not statistically significant (p = 0.410). In the post-test, females scored 78.81 ± 9.92 on average and males 77.81 ± 8.59, with no significant difference (p = 0.647). Thus, gender did not produce a statistically significant effect on trauma scores in either the pre- or post-test.

Table 7.

Comparison of Socio-Demographic Characteristics and Trauma Pre-Test-Post-Test Mean Scores.

Features		Pre-Test	Post-Test
Gender	Female	63,20±12,74	78,81±9,92
	Male	61,06±15,13	77,81±8,59
Test statistics		U=1574,500	U= 1643,000
P		p=0,410	p=0,647
Previous education status	Evet Yes	62,12±13,17	78,35±8,42
	No	62,76±14,86	78,52±11,06
Test statistics		U=1536,500	U=1574,500
P		P=0,576	P=0,725
Satisfaction with being at the Faculty of Medicine	Yes	63,65±13,43	79,18±9,03
	No	57,40±13,99	75,48±1028
Test statistics		U=876,500	U=905,500
P		P=0,044	P=0,067
Wanting to become an Emergency Medicine Specialist	Yes	68,83±15,78	80,83±5,37
	No	63,05±12,03	77,94±8,60
	Undecided	60,25±14,52	78,34±10,75
Test statistics		χ^2=3,751	χ^2=0,920
P		P=0,153	P=0,631

χ^2: Kruskal Wallis test statistic, U:Mann Whitney U test statistic

When trauma pre- and post-test results were compared based on prior training status, those with prior training had a mean pre-test score of 62.12 ± 13.17, while those without had 62.76 ± 14.86, with no statistically significant difference (P = 0.576). In the post-test, the mean score was 78.35 ± 8.42 for those with prior training and 78.52 ± 11.06 for those without, again not statistically significant (P = 0.725). Therefore, prior training did not produce a statistically significant effect on trauma test scores in either assessment.

Regarding satisfaction with studying at the Faculty of Medicine, the trauma pre-test mean score was 63.65 ± 13.43 among those satisfied, and 57.40 ± 13.99 among those not satisfied — a statistically significant difference (P = 0.044). In the post-test comparison, the mean scores were 79.18 ± 9.03 (satisfied) and 75.48 ± 10.28 (not satisfied), with no significant difference (P = 0.067). Thus, a statistically significant difference between satisfied and dissatisfied students was observed only in the pre-test for trauma.

In this comparison, the pre-test mean scores were 63.05 ± 12.03 for those who wished to specialize in emergency medicine, 63.05 ± 12.03 for those who did not, and 60.25 ± 14.52 for the undecided; no statistically significant difference was found (P = 0.153). In the post-test, the mean scores were 80.83 ± 5.37 (wish to specialize), 77.94 ± 8.60 (do not wish), and 78.34 ± 10.75 (undecided), with no significant difference.

In summary, in the present study there were no statistically significant differences in trauma pre- and post-test mean scores with respect to gender, prior training, or the desire to specialize in emergency medicine. The only statistically significant difference observed was between satisfaction with studying in the Faculty of Medicine and trauma pre-test mean scores: students who were satisfied had significantly higher trauma pre-test scores than those who were not.

Discussion

Resuscitation has been practiced throughout human history and continues to evolve today. Basic Life Support (BLS), Advanced Cardiac Life Support (ACLS), and Advanced Trauma Life Support (ATLS) can be defined as standardized, algorithm-based efforts implemented worldwide to restore life to a victim or casualty. BLS aims to sustain circulation and breathing with fundamental interventions until advanced life support conditions are available, with the goals of saving life and preventing clinical deterioration [9]. Because BLS constitutes the first step in the treatment of patients with cardiac arrest, it is a sequence of procedures that must be known and competently performed by physicians, nurses, and other healthcare professionals working in high-risk settings. There is a direct relationship between adequate training of healthcare personnel in this field and reductions in mortality and morbidity.

Çelik O.G. et al. conducted a survey study examining the educational needs of nurses working in emergency departments. The study included 199 nurses employed in university, state, and private hospitals within a single province. Of these nurses, 64.6% (n = 128) reported receiving in-service training; however, 62.8% (n = 123) considered these programs insufficient [6].

Consistent with these findings, in our study the majority of students reported that the trainings were good or very good, contributed substantially to their knowledge and skills, and markedly increased their motivation.

In a study by *Laco R.B. and colleagues* involving 18 participants consisting of physicians, nurses, and medical technicians, BLS skills and team strategies were evaluated through simulation-based training. The mean BLS score increased from 45.42 before simulation to 89 afterward; this difference was statistically significant (p = 0.000) [14]. While our study encompassed three modular trainings - BLS, ACLS, and trauma - *Laco R.B.* et al. focused exclusively on BLS skills. Similar to their results, we found a statistically significant difference between pre- and post-test scores for BLS and ACLS among our participants.

In another study by *Lima S.G. et al.* including 213 healthcare workers (nurses, nursing assistants, and technicians), the effects of theoretical and practical BLS/ACLS trainings on knowledge levels were evaluated [18]. The mean score increased from 4.1 before the course to 7.26 after the course. In our study, post-test scores were likewise significantly higher (p = 0.000). In addition to BLS and ACLS, trauma training was also provided. Furthermore, a post-training satisfaction questionnaire demonstrated that participants were generally satisfied with all trainings.

Passali C. et al. evaluated knowledge of BLS and ACLS guidelines among 216 participants (nurses and physicians) and demonstrated knowledge gaps regarding current guidelines [21]. In that study, participants who had previously received BLS/ACLS training answered significantly more questions correctly than those without prior training (p < 0.0001). In contrast, in our study there was no statistically significant difference between those with and without prior training in either pre- or post-test mean scores.

Türkmen E. et al. assessed expectations from BLS training and the impact of a BLS course on knowledge, skills, and satisfaction among 125 nursing students [22]. Those with prior BLS training performed better on the pre-test, and post-course knowledge scores increased significantly compared with pre-course scores (pre-test mean 59.5 ± 17.9; post-test mean 97.9 ± 3.2; p < 0.05). They concluded that BLS training improved students' knowledge and skills, met expectations, and yielded high satisfaction. Unlike that study - conducted among nursing students - our study included final-year medical students in an emergency medicine internship, with both pre- and post-training knowledge assessments and comparisons. Similar to *Türkmen E. et al.* we observed significantly higher post-test compared with pre-test scores among participants who completed BLS and ACLS trainings (p = 0.000).

Aekka A. et al. evaluated the effectiveness of simulation- and video-based trauma trainings among 48 non-physician healthcare workers using pre- and post-training questionnaires [1]. They reported statistically significant improvements in knowledge and skills across all domains of trauma management. Relative to *Aekka A. et al,* our study involved a larger cohort of final-year medical students, which strengthens the reliability and validity of our findings. In our sample, the mean trauma pre-test score was 62.35 ± 13.73 and the post-test score was 78.41 ± 9.38, demonstrating a statistically significant improvement.

In a study by *Li Q. et al.* the impact of pre-training assessment and feedback on BLS knowledge and skills among third-year medical students was investigated [17]. Forty students were randomized equally into a control group and an assessment-and-feedback group. The control group received theoretical BLS instruction followed by practical training. The intervention group, after theoretical instruction, underwent a video-based pre-assessment using a simulated cardiac arrest scenario, followed by a 15-minute group debrief and BLS practice. Both groups were then

evaluated with a 3-minute simulated cardiac arrest scenario and a multiple-choice examination. The assessment-and-feedback group achieved significantly higher performance scores (82.9 ± 3.2% vs. 63.9 ± 13.4%; $p < 0.01$). Unlike our design, *Li Q. et al.* [17] randomized cohorts to classical training versus classical training plus video-based scenarios and group debriefing.

Overall, our findings align with the literature indicating that simulation-based resuscitation trainings - across BLS, ACLS, and trauma domains - significantly enhance knowledge and skills and are well-received by learners. The convergence of evidence across diverse healthcare learner populations (nursing students, non-physician providers, and medical students) underscores the educational value and generalizability of simulation-enhanced curricula for resuscitation education.

Özçete E. et al. conducted a study to evaluate the educational quality and the knowledge levels of intern doctors regarding resuscitation. The study included three hours of didactic instruction and one hour of simulated manikin-based training on BLS, ACLS, and arrhythmias. Pre- and post-training test results were compared [20]. In this prospective study, 185 interns participated in the pre-test and 128 in the post-test. The comparison showed that post-test scores on BLS, ACLS, and arrhythmia topics were significantly higher than pre-test scores.

In contrast, our study also provided both theoretical and practical training in trauma management, and participants' satisfaction levels were assessed through questionnaires. Overall, both studies demonstrate that, in addition to traditional medical curricula, simulation-based resuscitation training positively impacts medical students' knowledge and skills in BLS and ACLS. Furthermore, researcher-designed demographic information forms were completed by the participants.

Our study's single-center design limited the ability to evaluate larger intern groups. Additionally, due to scheduling differences, some interns received the training at the beginning of their emergency medicine rotation while others received it later, preventing full temporal standardization. This limitation hindered the design of a more structured and homogeneous study, rendering the results and subsequent analyses more open to interpretation. Complete standardization of instructors and educational materials was also not achieved. Moreover, the long-term theoretical and practical retention of participants after these courses could not be assessed, and no longitudinal progression curve could be established in this respect.

Conclusion

BLS and ACLS are among the most critical medical interventions, and the management of trauma patients also holds great clinical importance. These interventions must be performed by knowledgeable and experienced practitioners. However, they are not always implemented successfully worldwide. Numerous studies in the literature emphasize the importance of repeated training in these medical interventions. In many developed countries, such trainings are provided within nationally standardized frameworks, resulting in far more favorable outcomes compared to developing and underdeveloped nations. This is particularly significant for Turkey, a developing country.

Globally, medical education is undergoing a rapid transition from traditional, intensive, and exhausting models to digital, advanced, simulation-based approaches. Many physicians still graduate from medical schools without adequate training opportunities, direct patient exposure, or simulation-based skill acquisition. Consequently, new graduates or near-graduates often experience serious loss of self-confidence, occupational stress, adaptation difficulties, and increased vulnerability to medicolegal challenges. More importantly, such deficiencies can lead to preventable deaths, permanent disabilities, and conditions that impose substantial material and moral burdens on individuals, families, and society.

From this perspective, lifelong learning—particularly pre-graduation learning—teamwork, skill development, and new skill acquisition become invaluable. It is evident that suitable educational environments must be established and staffed with educators, technicians, and academics who are competent in modern teaching methodologies.

In our study, a simulation-based educational methodology was implemented for final-year medical students. Pre-tests, post-tests, and satisfaction surveys were administered, and the findings were shared with the medical literature. These trainings were found to produce high satisfaction among participants and significantly increase their knowledge levels. We believe that conducting similar studies on larger populations and among other healthcare professionals could contribute to the implementation of more advanced and effective training methods both in Turkey and worldwide. Moreover, further studies comparing video-based and online education, virtual reality (VR), and augmented reality (AR) modalities—as defined in the literature—are essential. Reviewing previous research and identifying the most accurate and applicable educational methods for healthcare professionals, particularly physicians, is of utmost importance to ensure that those entrusted with human health receive the highest possible quality of training.

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THE EFFECT OF PRECONCEPTION CARE ON PERINATAL OUTCOMES OF THE MOTHER-PLACENTA-FETUS SYSTEM

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Abstract

Relevance. Examining the placenta could provide valuable insights into the effectiveness of preconception care, inform pregnancy management strategies, and aid in planning future pregnancies.

Objective: comparative clinical and morphological characteristics of the "mother-patient-fetus" system in women with preconception care and women without preconception care.

Methods. A prospective study compared maternal, perinatal and placental outcomes in a group of women who received preconception 6 months prior to their current pregnancy and women who did not receive preconception prior to their current pregnancy, provided that they also had placental histology. Clinical data were obtained from the medical records of the mother and newborn in a comprehensive health information system. The examination of the placenta and the collection of placental tissue fragments were carried out in accordance with the consensus recommendations of the Amsterdam Placental Workshop Group.

Results. Women with preconception care suffered less from serious pregnancy complications, such as Preeclampsia (4.3% vs. 11.6%; p=0.015) or gestational hypertension (7.9% vs. 15.2%; p=0.039). In the group of newborns from women with preconception care, young children for gestational age are less common (10.4% vs. 19.5%; p=0.021), newborns have fewer respiratory complications (14.0% vs. 23.8%; p=0.025) and antenatal fetal mortality (0.6% vs. 6.1%; p=0.006). Histopathological results of maternal vascular malperfusion (12.8% vs. 29.9%; p<0.01), acute inflammation of the placenta (4.9% vs. 11.6%; p=0.028) and chronic inflammation of the placenta (5.5% vs. 12.8%; p=0.022) are rare in the placentas of women with preconception care, as well as macrophages are rare. chorial with meconium in the lamina and amniotic membranes (7.9% vs. 16.5%; p=0.019).

Conclusion. Preconception care, aimed at improving the health of the mother, leads to a decrease in histopathological findings in the placentas and an improvement in the perinatal outcome. Morphological examination of the placenta should be an integral part of the strategy aimed at mitigating the adverse outcomes of current and subsequent pregnancy and childbirth in women without preconception care.

Keywords: *preconception care, placenta, perinatal outcome.*

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Резюме

ВЛИЯНИЕ ПРЕГРАВИДАРНОЙ ПОДГОТОВКИ НА ПЕРИНАТАЛЬНЫЕ ИСХОДЫ СИСТЕМЫ «МАТЬ-ПЛАЦЕНТА-ПЛОД»

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Актуальность. Исследование плаценты может дать ценную информацию об эффективности подготовки к зачатию, помочь в разработке стратегий ведения беременности и планировании будущих беременностей.

Цель исследования: сравнительная клиническая и морфологическая характеристика системы «мать-пациента-плод» у женщин с прегравидарной подготовкой и женщин без прегравидарной подготовки.

Методы. В проспективном исследовании сравнивали материнский, перинатальный исход и морфологические данные плаценты группы женщин у которых за 6 месяцев до текущей беременности была проведена прегравидарная подготовка и женщин, не проходивших прегравидарную подготовку до наступления текущей беременности, при условии, что у них также проводилось гистологическое исследование плаценты. Клинические данные были получены из медицинских записей матери и новорожденного в комплексной медицинской информационной системе. Исследование плаценты и отбор фрагментов ткани плаценты проводились в соответствии с рекомендациями консенсуса Amsterdam Placental Workshop Group.

Результаты. Женщины с прегравидарной подготовкой реже страдали от таких тяжелых осложнений беременности как преэклампсия (4.3% против 11.6%; p=0.015) или гестационная гипертензия (7.9% против 15.2%; p=0.039). В группе новорождённых от женщин с прегравидарной подготовкой реже встречалась малые для гестационного возраста новорожденные (10.4% против 19.5%; p=0.021), реже наблюдались респираторные осложнения у новорожденных (14.0% против 23.8%; p=0.025) и случаи антенатальной гибели плода (0.6% против 6.1%; p=0.006). В плацентах женщин с прегравидарной подготовкой реже встречались гистопатологические находки материнской сосудистой мальперфузии (12.8% против 29.9%; p<0,01), острого воспаления плаценты (4.9% против 11.6%; p=0,028) и хронического воспаления плаценты (5.5% против 12.8%; p=0,022), а также реже обнаруживались макрофаги с меконием в хориальной пластинке и амниотических оболочках (7.9% против 16.5%; p=0,019).

Выводы. Прегравидарная подготовка, направленная на улучшение здоровья матери, приводит к уменьшению гистопатологических находок в плацентах и улучшению перинатального исхода. Морфологическое исследование плаценты должно составлять неотъемлемую часть стратегии, направленной на смягчение неблагоприятных исходов текущей и последующей беременности и родов у женщин без прегравидарной подготовки.

Ключевые слова: *прегравидарная подготовка, плацента, перинатальный исход.*

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Түйіндеме

ПРЕГРАВИДАЛЬДЫ ДАЙЫНДЫҚТЫҢ "АНА-ПЛАЦЕНТА-ҰРЫҚ"ЖҮЙЕСІНІҢ ПЕРИНАТАЛДЫҚ НӘТИЖЕЛЕРІНЕ ӘСЕРІ

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Өзектілігі. Плацентарлы зерттеу жүктілікке дейінгі күтімнің тиімділігі туралы құнды ақпарат бере алады, жүктілікті басқару стратегияларын жасауға және болашақ жүктілікті жоспарлауға көмектеседі.

Зерттеудің мақсаты: прегравидальды дайындығы бар әйелдерде және прегравидальды дайындығы жоқ әйелдерде "ана-пациент-ұрық" жүйесінің салыстырмалы клиникалық және морфологиялық сипаттамасы.

Әдістері. Перспективалық зерттеуде қазіргі жүктіліктен 6 ай бұрын прегравидарлық дайындықтан өткен әйелдер тобы мен қазіргі жүктілікке дейін прегравидарлы дайындықтан өтпеген әйелдердің, егер олар плацентаға гистологиялық зерттеу жүргізген болса, аналық, перинаталдық және плацентарлы морфологиялық нәтижелерін

салыстырды. Клиникалық деректер кешенді медициналық ақпараттық жүйедегі ана мен жаңа туған нәрестенің медициналық жазбаларынан алынды. Плацентаны зерттеу және плацента тінінің сынықтарын таңдау Amsterdam Placental Workshop Group консенсусының ұсыныстарына сәйкес жүргізілді.

Нәтижесі. Преэклампсия (4.3% қарсы 11.6%; p=0.015) немесе гестациялық гипертензия (7.9% қарсы 15.2%; p=0.039) сияқты жүктіліктің ауыр асқынуларынан прегравидальды дайындығы бар әйелдер аз зардап шекті. Прегравидальды дайындығы бар әйелдерден шыққан жаңа туған нәрестелер тобында гестациялық жасқа арналған кішкентай нәрестелер сирек кездеседі (10.4% қарсы 19.5%; p=0.021), жаңа туған нәрестелерде респираторлық асқынулар (14.0% қарсы 23.8%; p=0.025) және ұрықтың антенатальды өлімі жағдайлары (0.6% қарсы 6.1%; p=0.006) аз байқалды.

Прегравидальды дайындығы бар әйелдердің плаценталарында аналық тамырлы малперфузияның гистопатологиялық нәтижелері (12.8% қарсы 29.9%; p<0,01), плацентаның жедел қабынуы (4.9% қарсы 11.6%; p=0,028) және плацентаның созылмалы қабынуы (5.5% қарсы 12.8%; p=0,022) сирек кездеседі, сонымен қатар хориальды пластинада және амниотикалық қабықшаларда (7.9% қарсы 16.5%; p=0,019) меконийі бар макрофагтар аз кездеседі.

Қорытынды. Ананың денсаулығын жақсартуға бағытталған прегравидарлы дайындық плацентадағы гистопатологиялық нәтижелердің төмендеуіне және перинаталдық нәтиженің жақсаруына әкеледі. Плацентаның морфологиялық зерттеуі прегравидарлы дайындықсыз әйелдерде ағымдағы және кейінгі жүктілік пен босанудың қолайсыз нәтижелерін азайтуға бағытталған стратегияның ажырамас бөлігі болуы керек.

Түйін сөздер: *прегравидальды дайындық, плацента, перинаталдық нәтиже.*

Дәйексөз үшін:

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Introduction

Making sure both the mother and newborn stay healthy is a key focus for public health systems around the world. The preconception period—before or between pregnancies—provides a crucial window of opportunity to improve women's health, promote healthy lifestyles, and identify risk factors for targeted interventions. Growing evidence suggests that the health status of both partners during this period plays a significant role in fertility and perinatal outcomes [3, 29, 32, 30, 28]. However, adverse birth outcomes remain a major global public health challenge, contributing to increased morbidity, mortality, and healthcare costs.

Preconception care has been shown to reduce the risk of preterm birth, low birth weight, congenital anomalies, and intrauterine growth restriction. However, most previous studies have focused on clinical characteristics rather than investigating the impact of preconception preparation on placental histopathology in relation to maternal and fetal conditions. Examining the placenta in this context could provide valuable insights into the effectiveness of preconception care, inform pregnancy management strategies, and aid in planning future pregnancies.

This study aims to compare the clinical and morphological characteristics of the Maternal-Placental-Fetal system in women who underwent preconception preparation versus those who did not.

Materials and methods

Study design

This prospective study included women who received medical care for delivery - either by vaginal birth or cesarean section - at the Regional Clinical Hospital in Karaganda, Kazakhstan, between January 1, 2018, and January 1, 2023. The study was approved by the Bioethics Committee of Karaganda Medical University (06.02.2022 №6) and written informed consent was obtained from all participants for the use of their clinical and placental morphological data for research purposes.

In accordance with the study objectives, participants were divided into two groups: "with preconception preparation" and "without preconception preparation."

The preconception preparation group included women who had undergone preconception care at least six months before their current pregnancy and whose placentas underwent histological examination.

The non-preconception preparation group included women who had not undergone preconception care before their current pregnancy, but whose placentas were also subjected to histological examination.

Placentas were sent for histological examination based on the following indications:

1. Maternal factors: Thyroid disorders, autoimmune diseases, hypertensive disorders, hypothyroidism, kidney disease, coagulopathies chronic and conditions such as diabetes.

2. Pregnancy complications: Gestational hypertension, Gestational diabetes and preterm birth.

3. Fetal/newborn factors: Antenatal fetal death or early neonatal death, birth weight below the 10th percentile, suspected infection or sepsis, an Apgar score of ≤6 at 5 minutes, or the need for respiratory support beyond 10 minutes.

4. Placental abnormalities: Deviations in placental mass or umbilical cord length, marginal or membrane insertion of the umbilical cord, and structural abnormalities of the placenta.

Exclusion Criteria: women with multiple pregnancies, chromosomal abnormalities, or congenital malformations of the newborn were excluded from the study.

Collection of clinical and morphological data

Clinical data were obtained from maternal and neonatal medical records within an integrated medical information system.

Obstetric data included gestational age at delivery, mode of delivery, and the presence of pregnancy-related pathologies. Maternal conditions assessed included hypertensive disorders and diabetes mellitus, while fetal and neonatal conditions included small for gestational age (SGA) and macrosomia.

Neonatal data encompassed clinical diagnoses of perinatal asphyxia and neonatal infections requiring intensive care, as well as antenatal fetal demise and neonatal death.

Morphological data were obtained from perinatal pathologists who conducted histopathological examinations of the placentas.

A summary of the clinical data for the study groups is presented in Table 1.

Table 1.

Demographic and clinical characteristics of the study groups.

Variables	Preconception preparation n (%) (n=164)		Non-preconception preparation n (%) (n=164)		P-value
Women's age, year	18-30	106 (64.6)	18-30	121 (73.8)	0.106
	31-40	48 (29.3)	31-40	39 (23.8)	
	41-45	10 (6.1)	41-45	4 (2.4)	
BMI, kg/м^2	<18.5	24 (14.6)	<18.5	32 (19.5)	0.136
	18.5-24.9	89 (54.3)	18.5-24.9	79 (48.2)	
	25-30	39 (23.8)	25-30	48 (29.3)	
	>30	12 (7.3)	>30	5 (3.0)	
Systolic blood pressure/ Diastolic blood pressure before pregnancy	>129 / >84	11 (6.7) / 9 (5.5)	<129 / <84	9 (5.5) /6 (3.7)	0.413 /0.603
	120-129 / 80-84	79 (48.2) /114 (69.5)	120-129 / 80-84	91 (55.5) / 121 (73.8)	
	<120 / <80	74 (45.1) /41 (25.0)	<120 / <80	64 (39.0) / 37 (22.5)	
Smoking	yes	4 (2.4)	yes	10 (6.1)	0.102
	no	160 (97.6)	no	154 (93.9)	
Alcohol consumption before pregnancy (≥2 times per month)	yes	3 (1.8)	yes	5 (3.0)	0.475
	no	161 (98.2)	no	159 (97.0)	
Mother's education	school	25 (15.2)	school	37 (22.6)	0.091
	higher	139 (84.8)	higher	127 (77.4)	
Gestation period, weeks	<28	8 (4.9)	<28	17 (10.4)	0.128
	28-31	14 (8.5)	28-31	11 (6.7)	
	32-36	42 (25.6)	32-36	51 (31.1)	
	>36	100 (61.0)	>36	85 (51.8)	
Prelabor rupture of amniotic membranes	yes	19 (11.6)	yes	11 (6.7)	0.204
	no	145 (88.4)	no	153 (83.5)	
Placental abruption	yes	6 (3.7)	yes	5 (3.0)	0.760
	no	158 (96.3)	no	159 (97.0)	
Delivery	vaginal birth	133 (81.1)	vaginal birth	129 (78.7)	0.573
	planned CS	14 (8.5)	planned CS	12 (7.3)	
	emergency CS	17 (10.4)	emergency CS	23 (14.0)	
Gender of the newborn	male	89 (54.3)	male	85 (51.8)	
	female	75 (45.7)	female	79 (48.2)	

Abbreviations: CS – cesarean section.

** p1<0.05 statistically significant differences between the group with pregravid preparation and the group without pregravid preparation.*

Definitions

Preconception care refers to a set of interventions designed to identify and modify biomedical, behavioral, and social risk factors that may impact a woman's health or pregnancy outcome. These interventions focus on prevention and management, emphasizing factors that should be addressed before conception to improve maternal and fetal health [7, 34].

Definitions of Maternal Conditions

Preeclampsia was defined as blood pressure ≥140/90 mmHg after 20 weeks of gestation, accompanied by

proteinuria (>0.3 g per day) or severe symptoms in a previously normotensive woman [9].

Chronic arterial hypertension (CAH) was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two separate occasions before 20 weeks of gestation [20].

Gestational hypertension was defined as newly diagnosed systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, measured at least twice, 4 hours apart, after 20 weeks of gestation, persisting up to one week postpartum, in the absence of systemic maternal organ damage [20].

Pregestational diabetes mellitus was diagnosed before pregnancy, based on a glycosylated hemoglobin (HbA1c) level >6.5% [44].

Gestational diabetes mellitus was diagnosed in pregnant women without a prior history of diabetes if at least two of the following criteria were met during a 3-hour, 100 g oral glucose tolerance test conducted between 24 and 28 weeks of gestation: fasting glucose ≥95 mg/dL, 1-hour glucose ≥180 mg/dL, 2-hour glucose ≥155 mg/dL, or 3-hour glucose ≥140 mg/dL [44].

Definitions of Neonatal and Perinatal Outcomes

Gestational age was determined based on the last menstrual period and confirmed by ultrasound. If first-trimester ultrasound dating differed by more than one week from menstrual dating, ultrasound measurements were used exclusively [15].

Small-for-gestational-age (SGA) neonates were defined as having a birth weight below the 10th percentile for gestational age at delivery.

Macrosomia is when a baby is born with a weight that is significantly higher than average of ≥4000 g at birth [5, 8].

Perinatal asphyxia was defined as a clinical diagnosis of birth asphyxia in the neonatal intensive care unit (NICU).

Birth asphyxia was characterized by progressive hypoxemia, hypercapnia, metabolic acidosis, and multiple organ failure.

Neonatal infection was defined as a clinical diagnosis of infection in the NICU.

Early neonatal death refers to the death of a newborn within the first seven days after birth.

Antenatal fetal death was defined as fetal demise occurring after 20 weeks of gestation, confirmed via ultrasound before delivery [2, 50].

Early neonatal death was defined as the death of a live-born infant within the first seven days of life.

Placental abruption was diagnosed based on clinical findings, including vaginal bleeding, abdominal pain, and the presence of a retroplacental blood clot unrelated to placenta previa or uterine rupture [10].

Placental Histopathology

Placental injury patterns were categorized based on the Amsterdam criteria [24]:

Maternal vascular malperfusion (MVM) was diagnosed based on histopathological findings indicative of impaired maternal blood flow to the placenta. These included:

- Central or peripheral infarctions affecting >10% of placental villi
- Acute atherosis of the basal plate or decidual arteries
- Hypertrophy of the muscular layer of basal plate arteries
- Thickening of arteriolar walls in the amniotic membranes [18, 38, 42].

Fetal vascular malperfusion (FVM) refers to a condition where there is reduced or no blood flow to the fetal part of the placenta. Diagnostic criteria included:

- Two or more medium-to-large areas of avascular villi or villi with stromal-vascular karyorrhexis
- Three or more small areas of avascular villi or villi with stromal-vascular karyorrhexis
- Thrombosis within large fetal vessels and/or vascular obliteration in stem villi [39, 37, 40, 48, 49].

Acute inflammatory placental injury was diagnosed by the presence of neutrophilic infiltration in the chorionic plate, fetal membranes (chorioamnionitis), or fetal vessels (funisitis) [24].

Chronic inflammatory placental damage is a lesion of the chorionic villi, characterized by the accumulation of small lymphocytes with a stromal reaction in the terminal chorionic villi and an increased number of fetal macrophages [16, 22].

Histological examination of the placenta

Placental examination and tissue collection were conducted in accordance with the Amsterdam Placental Workshop Group consensus recommendations [24]. Immediately after delivery, placentas were submitted for examination and processed following standard biosafety protocols.

Placentas were fixed in 10% formalin for 24–48 hours before undergoing routine histological processing. Each placenta was systematically evaluated, including:

- Photographic documentation of both the maternal and fetal surfaces
- Measurement and weighing (excluding amniotic membranes)
- Macroscopic examination of sectioned surfaces

For histological examination, the following tissue samples were collected:

- Two rolls of amniotic membranes
- Two umbilical cord fragments
- Two full-thickness placental sections
- Representative samples of any identified lesions

All tissue samples were processed using standard histological techniques and stained with hematoxylin and eosin (H&E) according to a standardized protocol.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics 22. Group differences were assessed using the Mann–Whitney U test and the χ^2 test. A p-value < 0.05 was considered statistically significant.

Results

A comparison of the maternal part of the Maternal-Placental-Fetal system

The clinical conditions found in women from the study groups are summarized in the table 2.

In the preconception preparation group, hypertensive disorders were diagnosed in 29 (17.7%) cases, including preeclampsia in 13 (44.8%), chronic arterial hypertension in 9 (31%), and gestational hypertension in 7 (24.2%). Diabetes mellitus was observed in 15 (9.2%) women, of whom 6 (40%) had pregestational diabetes mellitus (type 1 or type 2), and 9 (60%) had gestational diabetes mellitus. Other chronic

conditions, such as chronic pyelonephritis and thyroid disease, were reported in 27 (16.5%) cases. The postpartum period was complicated by bleeding in 3 (1.8%) cases, but there were no maternal deaths in this group.

In the non-preconception preparation group, hypertensive disorders were more prevalent, affecting 50 (38.0%) women. Among them, preeclampsia occurred in 19 (38%), CAH in 6 (12.0%), and gestational hypertension in 25 (50.0%). Diabetes mellitus was diagnosed in 16 (9.8%) women, equally distributed between pregestational diabetes mellitus (8 cases, 50%) and gestational diabetes mellitus (8 cases, 50%). Other chronic conditions, including chronic pyelonephritis and thyroid disease, were recorded in 34 (20.7%) cases. Postpartum bleeding was observed in 5 (3.0%) cases. Notably, there was one maternal death in this group, attributed to bilateral purulent-necrotic pyelonephritis with abscess formation, complicated by the development of a systemic inflammatory response.

Comparative Analysis of the Fetal Compartment in the Maternal-Placental-Fetal System

The diagnoses of newborns and cases of perinatal mortality in the study groups are presented in Table 2.

Table 2.

The clinical and morphological characteristics of the maternal, fetal, and placental compartments of the «Maternal – Placental – Fetal» system.

	Clinical and morphological characteristics, n (%)	Preconception preparation (n=164)	Non-preconception preparation (n=164)	P-value
«Mother»	Preeclampsia	7 (4.3)	19 (11.6)	**0.015***
	Chronic arterial hypertension	9 (5.5)	6 (3.7)	0.428
	Gestational hypertension	13 (7.9)	25 (15.2)	**0.039***
	Pregestational diabetes mellitus	6 (3.7)	8 (4.9)	0.585
	Gestational diabetes mellitus	9 (5.5)	8 (4.9)	0.804
	Other chronic conditions[1]	27 (16.5)	34 (20.7)	0.321
	Postpartum hemorrhage	3 (1.8)	5 (3.0)	0.475
	Maternal death	0	1 (0.6)	0.317
«Fetus/ newborn»	SGA	17 (10.4)	32 (19.5)	**0.021***
	Macrosomia	14 (8.5)	23 (14.0)	0.117
	Perinatal Asphyxia	8 (4.9)	19 (11.6)	**0.028***
	Neonatal Infection	14 (8.5)	25 (15.2)	0.061
	Respiratory Problems[2]	23 (14.0)	39 (23.8)	**0.025***
	Antenatal Fetal Death	1 (0.6)	10 (6.1)	**0.006***
	Early Neonatal Death	3 (1.8)	2 (2.4)	0.653
«Placenta»	Maternal Vascular Malperfusion	21 (12.8)	49 (29.9)	**<0,01***
	Fetal Vascular Malperfusion	12 (7.3)	18 (11.0)	0.251
	Acute Inflammatory Lesions	8 (4.9)	19 (11.6)	**0.028***
	Chronic Inflammatory Lesions	9 (5.5)	21 (12.8)	**0.022***
	Meconium[3]	13 (7.9)	27 (16.5)	**0.019***

Abbreviations: SGA – Small for Gestational Age (SGA)

1 – Chronic diseases of the kidneys (e.g., pyelonephritis), thyroid gland (e.g., hypothyroidism, hyperthyroidism, and autoimmune thyroiditis).

2 – Respiratory complications in newborns, including transient tachypnea of the newborn, meconium aspiration, respiratory distress syndrome, asphyxia, and the need for oxygen therapy or intubation.

3 – Macrophages containing meconium in the chorionic plate and amniotic membranes.

p1<0.05 – Statistically significant differences between the group with preconception care and the group without preconception care.

In the group with preconception care, there were 17 (10.4%) cases of fetal growth restriction and 14 (8.5%) cases of macrosomia. Perinatal asphyxia was diagnosed in 8 (4.9%) cases. Neonatal infection was identified in 14 (8.5%) newborns. Respiratory problems, including transient tachypnea of the newborn, meconium aspiration, respiratory distress syndrome, asphyxia, and the need for oxygen therapy or intubation, were observed in 23 (14.0%) newborns. There was 1 (0.6%) case of antenatal fetal death and 3 (1.8%) cases of early neonatal mortality in this group.

In the group without preconception care, there were 32 (19.5%) cases of FGR and 23 (14.0%) cases of macrosomia. Perinatal asphyxia was diagnosed in 19 (11.6%) cases. Neonatal infection was identified in 25 (15.2%) newborns. Respiratory problems were observed in 39 (23.8%) newborns. There were 10 (6.1%) cases of antenatal fetal death and 2 (2.4%) cases of neonatal mortality.

Comparative analysis of placental findings

Histopathological findings in the placentas are presented in Table 2.

In the group that received preconception care, maternal vascular malperfusion was found in 21 (12.8%) placentas, while fetal vascular malperfusion was found in 12 (7.3%) placentas. Acute inflammatory issues, such as chorioamnionitis, funisitis, and inflammation of the blood vessels in the chorionic plate, were present in 8 (4.9%) placentas. Chronic inflammation was observed in 9 (5.5%)

placentas. Macrophages containing meconium in the chorionic plate and amniotic membranes were observed in 13 (7.9%) placentas.

In the group without preconception care, maternal vascular malperfusion was detected in 49 (29.9%) placentas. Signs of fetal vascular malperfusion were found in 18 placentas (11.0%). Acute inflammation was present in 19 placentas (11.6%), while chronic inflammation was observed in 21 placentas (12.8%). Macrophages containing meconium were found in the chorionic plate and amniotic membranes of 27 placentas (16.5%).

Discussion

This study presents a comparative clinical and morphological analysis of the "Maternal-Placental-Fetal" system in women who underwent preconception care at least six months before the current pregnancy and those who did not receive preconception care before the current pregnancy.

The clinical data showed that women who didn't receive preconception care were more likely to experience severe pregnancy complications compared to those who did. Specifically, they had higher rates of preeclampsia (11.6% vs. 4.3%; p=0.015) and gestational hypertension (15.2% vs. 7.9%; p=0.039). These results align with other studies that link preconception care to a lower risk of maternal complications. Our findings are consistent with those of other studies that associate preconception care with a reduced risk of maternal complications [1, 14, 17, 36].

Secondly, we found that women without preconception care were more likely than those who underwent preconception care to give birth to SGA newborns (19.5% vs. 10.4%; p=0.021). Additionally, respiratory complications in newborns, including transient tachypnea of the newborn, meconium aspiration, respiratory distress syndrome, asphyxia, and the need for oxygen therapy or intubation, were more frequently observed (23.8% vs. 14.6%; p=0.025), along with perinatal asphyxia (11.6% vs. 4.9%; p=0.028) and antenatal fetal death (6.1% vs. 0.6%; p=0.006). These findings are consistent with previously published studies indicating that the absence of preconception care is associated with increased neonatal morbidity and mortality, stillbirth, and low birth weight [19, 33, 45, 47]. We believe that this is primarily due to maternal health conditions, which serve as a predisposing background factor in the antenatal period, increasing the vulnerability of the fetal nervous and cardiovascular systems in postnatal life. Birth and the transition from intrauterine to independent existence are significant stressors for the fetus and newborn. In the presence of maternal infections, these stressors may disrupt compensatory-adaptive mechanisms, leading to episodes of sudden neonatal asphyxia and postnatal collapse of the vascular and respiratory systems.

Furthermore, we observed a significant increase in the frequency of maternal vascular malperfusion (MVM) in the placentas of women without preconception care (29.9% vs. 12.8%; p<0.01). Notably, preconception blood pressure did not differ between the groups, indicating that the observed maternal vascular malperfusion in the group without preconception care was not related to any preexisting hypertensive condition that could have influenced the results.

Maternal vascular malperfusion represents a placental abnormality affecting maternal vascular function and blood circulation, often associated with an increased risk of adverse fetal outcomes [6, 18, 35, 41] as well as maternal hypertensive disorders and cardiovascular diseases [43, 46]. As expected [11, 13, 27, 31], our study found that women with placental signs of maternal vascular malperfusion were more likely to have chronic diseases, develop preeclampsia, and give birth to preterm babies.

It's important to note that not all women with maternal vascular malperfusion developed these complications. Also, in the group without preconception care, placental signs of maternal vascular malperfusion were more commonly seen in pregnancies where no maternal diseases were diagnosed. This suggests that, in some cases, the vascular abnormalities in this group may indicate a specific vascular susceptibility phenotype and/or undiagnosed maternal cardiovascular risk factors before or during pregnancy.

We also observed an increased frequency of acute placental inflammation in the group without preconception care (11.6% vs. 4.9%; p=0.028), which in some cases may be attributed to undiagnosed infections prior to conception. Additionally, we found a higher frequency of chronic inflammatory placental lesions of unknown etiology in women without preconception care (12.8% vs. 5.5%; p=0.022). The etiology of chronic placental inflammation remains unclear; however, it is believed to involve chronic microbial infection and the maternal immune response to fetal antigens [26]. We hypothesize that, in some cases in our study, the increased frequency of chronic inflammatory placental lesions in women without preconception care may be linked to pre-pregnancy maternal health conditions that affect the body's ability to adapt adequately to pregnancy. This idea is indirectly supported by the trend we observed, where smoking was more common in the group without preconception care. Smoking may contribute to increased systemic inflammation [4, 12, 21]. Further research is needed to better understand the pathophysiological links between maternal preconception care and chronic placental inflammation.

In this study was found an increased frequency of placentas with macrophages containing meconium in the chorionic plate and amniotic membranes in women without preconception care (16.5% vs. 7.9%; p=0.019). This may be associated with fetal distress, such as hypoxia or infection, as demonstrated in previous studies [23, 25].

Taken together, these findings suggest that placental morphological examination should be an integral part of strategies aimed at mitigating adverse pregnancy and birth outcomes in women without preconception care.

The strengths of this study include the comparative analysis of clinical and morphological factors within the "mother-placenta-fetus" system in the context of preconception care versus its absence. An additional advantage is the systematic data collection and placental sample examination conducted in accordance with a strict protocol.

A limitation of this study is that, although we applied the criteria of the Amsterdam Consensus Statement [24], which include sub classification by stage and/or severity, we only assessed the presence or absence of each pathological feature without considering its stage or severity. A more detailed evaluation of the impact of the stage and/or

severity of each placental pathological finding on adverse outcomes is an important objective for future research.

Thus, we found that women without preconception care were more likely to experience severe pregnancy complications such as preeclampsia and gestational hypertension. In the newborns of women without preconception care, there was a higher incidence of small-for-gestational-age babies, respiratory complications, and cases of antenatal fetal death. Taken together, these results confirm that preconception care leads to improved perinatal outcomes.

We also identified that women without preconception care were at increased risk for maternal vascular malperfusion, chronic placental inflammation, and more frequent presence of macrophages containing meconium in the chorionic plate and amniotic membranes, which indicates chronic or prolonged fetal hypoxia and placental dysfunction. These findings complement and expand the understanding of the impact of preventive medical interventions prior to pregnancy on structural placental changes.

The results of the study confirm that preconception care aimed at improving maternal health reduces histopathological findings in placentas and improves perinatal outcomes.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions *YP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. LS: Conceptualization, Supervision, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. DK: Conceptualization, Writing – review & editing. YK: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft. ZA: Data curation, Writing – original draft. RS: Supervision, Writing – original draft, Writing – review & editing. OZ: Writing – original draft, Writing – review & editing, Formal analysis, KN: original draft, Writing – review & editing.*

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Data Availability *Statement Data is unavailable due to ethical restrictions.*

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MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND ABLATION IN THE MANAGEMENT OF SYMPTOMATIC ADENOMYOSIS: ASSESSMENT OF CLINICAL EFFICACY, SAFETY, AND IMPACT ON FERTILITY. A CASE SERIES

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Abstract

Introduction Adenomyosis is a common cause of chronic pelvic pain and impaired fertility in women. Traditional radical treatments, such as hysterectomy, are unacceptable for patients who wish to preserve reproductive function. The implementation of organ-sparing, non-invasive methods, such as Magnetic Resonance-guided Focused Ultrasound (MRgFUS), is highly relevant, especially given the limited experience in regional medical centers in Kazakhstan.

Materials and Methods A prospective case series study was conducted, including 69 patients with symptomatic adenomyosis treated with MRgFUS (ExAblate 2100 system) from 2022 to 2024. Inclusion criteria were strictly limited to ensure safety and technical applicability. Primary outcomes were assessed by the dynamics of pain syndrome by Visual Analogue Scale (VAS) and menstrual bleeding by Pictorial Blood Loss Assessment Chart (PBAC). Secondary outcomes included objective efficacy (Non-Perfused Volume, NPV via MRI at 3 and 6 months), safety, and pregnancy rate.

Results All 69 patients successfully tolerated the procedure. A significant clinical response was achieved in the majority: 85% reported reduced pain (VAS: 7.2 to 3.0), and 76% reported reduced menorrhagia. Objective efficacy was confirmed by NPV formation averaging 74% by 6 months. No late complications were registered. Three pregnancies were reported within 12 months post-procedure, two of which resulted in successful live births, indicating the preservation of reproductive function.

Conclusion MRgFUS is a highly effective, non-invasive, and safe organ-sparing treatment for symptomatic adenomyosis. The results align with international data, confirming its suitability, particularly for women interested in preserving fertility. This initial clinical experience in Kazakhstan demonstrates the need for further integration of MRgFUS into national clinical practice.

Keywords: *Adenomyosis, MRgFUS, Focused Ultrasound, Non-Invasive Treatment, Dysmenorrhea, Fertility, Non-perfused Volume.*

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Резюме

МАГНИТНО-РЕЗОНАНСНАЯ ТОМОГРАФИЯ-КОНТРОЛИРУЕМАЯ ФОКУСИРОВАННАЯ УЛЬТРАЗВУКОВАЯ АБЛАЦИЯ (МРФУЗ) В ЛЕЧЕНИИ СИМПТОМАТИЧЕСКОГО АДЕНОМИОЗА: ОЦЕНКА КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ, БЕЗОПАСНОСТИ И ВЛИЯНИЯ НА ФЕРТИЛЬНОСТЬ. СЕРИЯ СЛУЧАЕВ.

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Актуальность Аденомиоз является распространенной причиной хронической тазовой боли и нарушения фертильности у женщин. Традиционные радикальные методы лечения, такие как гистерэктомия, неприемлемы для пациенток, желающих сохранить репродуктивную функцию. Внедрение органосохраняющих, неинвазивных методов, таких как МРФУЗ, является крайне актуальным, особенно в контексте ограниченного опыта в региональных медицинских центрах Казахстана.

Методы Проведено проспективное исследование серии случаев, включающее 69 пациентки с симптоматическим аденомиозом, пролеченных методом МРФУЗ (система ExAblate 2100) с 2022 по 2024 год. Критерии включения были строго ограничены для обеспечения безопасности и технической применимости. Первичные исходы оценивались по динамике болевого синдрома по Визуально-аналоговой шкале (ВАШ) и менструальных кровотечений по Иллюстрированной таблице оценки кровопотери (ИТОК). Вторичные исходы включали объективную эффективность (Объем неперфузии, (НПО) по МРТ через 3 и 6 месяцев), безопасность и частоту наступления беременности

Результаты Все 69 пациентки успешно перенесли процедуру. Значительный клинический ответ был достигнут у большинства: 85% сообщили о снижении болевого синдрома (ВАШ: 7.2 до 3.0), 76% – об уменьшении меноррагии. Объективная эффективность подтверждена формированием НПО в среднем 74% к 6 месяцам. Не зарегистрировано поздних осложнений. Отмечено наступление трех беременностей в течение 12 месяцев после процедуры, две из которых завершились успешными родами, что свидетельствует о сохранности репродуктивной функции.

Выводы МРФУЗ является высокоэффективным, неинвазивным и безопасным органосохраняющим методом лечения симптоматического аденомиоза. Результаты согласуются с международными данными, подтверждая его целесообразность, особенно для женщин, заинтересованных в сохранении фертильности. Данный первый клинический опыт в Казахстане демонстрирует необходимость дальнейшего внедрения МРФУЗ в национальную клиническую практику.

Ключевые слова: *Аденомиоз, МРФУЗ, фокусированный ультразвук, неинвазивное лечение, дисменорея, фертильность, объем неперфузии*

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Түйіндеме

СИМПТОМАТИКАЛЫҚ АДЕНОМИОЗДЫ ЕМДЕУДЕГІ МАГНИТТІ-РЕЗОНАНСТЫҚ ТОМОГРАФИЯМЕН БАСҚАРЫЛАТЫН ФОКУСТАЛҒАН УЛЬТРАДЫБЫСТЫҚ АБЛАЦИЯ (МРФУД): КЛИНИКАЛЫҚ ТИІМДІЛІГІН, ҚАУІПСІЗДІГІН ЖӘНЕ ФЕРТИЛЬДІККЕ ӘСЕРІН БАҒАЛАУ. КЕЙСТЕР СЕРИЯСЫ

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Өзектілігі Аденомиоз әйелдерде созылмалы жамбас қуысындағы ағзалардың ауырсынуы мен фертильдіктің бұзылуының жиі себебі болып табылады. Гистерэктомия сияқты дәстүрлі радикалды емдеу әдістері репродуктивті функцияны сақтағысы келетін пациенттер үшін қолайсыз. МРФУД сияқты ағзаны сақтайтын, инвазивті емес әдістерді енгізу, әсіресе Қазақстанның аймақтық медициналық орталықтарында тәжірибе шектеулі болғандықтан, өте өзекті.

Әдістері 2022-2024 жылдар аралығында МРФУД әдісімен емделген (ExAblate 2100 жүйесі) симптоматикалық аденомиозы бар 69 пациентті қамтитын проспективті кейстер сериясы зерттеуі жүргізілді. Қауіпсіздік пен техникалық қолданылуын қамтамасыз ету үшін қосу критерийлері қатаң шектелді. Негізгі нәтижелер ауырсыну синдромының Көрнекі аналогтық шкаласымен (КАШ) және етеккір қан кетуінің қан жоғалтуды бағалаудың суретті кестесі (ҚЖБСКҚ)динамикасы бойынша бағаланды. Қосымша нәтижелер объективті тиімділікті (3 және 6 айдан кейінгі МРТ бойынша перфузияланбаған көлем, ПК), қауіпсіздікті және жүктілік жиілігін қамтыды.

Нәтижелер Барлық 69 пациент процедураны сәтті өткізді. Көпшілігінде айтарлықтай клиникалық жауап алынды: 85%-ы ауырсыну синдромының төмендеуін (КАШ: 7.2-ден 3.0-ке дейін), 76%-ы меноррагияның азайғанын хабарлады. Объективті тиімділік 6 айға қарай орташа есеппен 74% ПК қалыптасуымен расталды. Кеш асқынулар тіркелген жоқ. Процедурадан кейінгі 12 ай ішінде үш жүктілік тіркелді, оның екеуі сәтті босанумен аяқталды, бұл репродуктивті функцияның сақталғанын көрсетеді.

Қорытынды МРФУЗ симптоматикалық аденомиозды емдеудің жоғары тиімді, инвазивті емес және ағзаны сақтайтын қауіпсіз әдісі болып табылады. Нәтижелер халықаралық деректермен сәйкес келеді, бұл оның мақсаттылығын, әсіресе фертильдікті сақтауға мүдделі әйелдер үшін, растайды. Қазақстандағы осы алғашқы клиникалық тәжірибе МРФУЗ-ті ұлттық клиникалық практикаға одан әрі енгізу қажеттілігін көрсетеді

Түйіндеме сөздер Аденомиоз, МРФУЗ, фокусталған ультрадыбыс, инвазивті емес емдеу, дисменорея, фертильдік, перфузияланбаған көлем.

Дәйексөз үшін:

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Introduction

Adenomyosis is a prevalent form of internal endometriosis characterized by the invasion of endometrial tissue into the thickness of the myometrium. This condition significantly impairs the quality of life for women of reproductive age, standing as a leading cause of chronic pelvic pain, abnormal uterine bleeding (hypermenorrhea), and impaired reproductive function [10; 13].

The management of patients with symptomatic adenomyosis requires a differentiated approach. When conservative therapy (hormonal agents) proves ineffective, the question of surgical intervention often arises. However, traditional radical procedures, such as hysterectomy, result in the loss of the organ, which is unacceptable for patients who wish to preserve fertility. Consequently, modern gynecology is actively focusing on the development of organ-sparing and minimally invasive treatment modalities that can provide effective symptom relief with minimal risk while preserving reproductive potential.

In recent years, interest has grown significantly in Magnetic Resonance-guided Focused Ultrasound Ablation (MRgFUS) as a promising, non-invasive alternative. The MRgFUS technology is based on the remote delivery of high-intensity focused ultrasound energy. Under precise MRI guidance, the ultrasound beam is focused on the pathological lesion within the myometrium. The resulting local heating causes thermal necrosis (ablation) of the pathological tissue, while surrounding healthy structures remain intact [15]. Thus, MRgFUS adheres to the principles of organ-sparing and non-invasive treatment, making it particularly valuable for patients planning future pregnancies.

According to current literature, MRgFUS is an effective and safe method for treating adenomyosis, demonstrating encouraging outcomes, particularly in terms of fertility preservation. A number of studies and meta-analyses suggest that the rates of pregnancy and live birth following MRgFUS are comparable to those following other conservative methods [3; 4; 6–9; 12]. Nevertheless, the evidence base is still limited by a lack of large prospective studies, and some authors note a potentially higher frequency of re-interventions compared to surgical options [3; 7; 14].

Despite the global experience, data regarding the efficacy, safety, and impact on reproductive function of MRgFUS in domestic clinical practice, and specifically in regional medical centers of Kazakhstan, are scarce.

This paper presents an analysis of the first clinical experience with the application of MRgFUS in the management of symptomatic adenomyosis, conducted at the "Multidisciplinary Center of Oncology and Surgery" in Ust-Kamenogorsk city — the sole center in Kazakhstan utilizing this technology.

Objective: To evaluate the immediate and medium-term clinical efficacy, safety, and impact on reproductive function of Magnetic Resonance-guided Focused Ultrasound Ablation in the management of patients with symptomatic adenomyosis.

Materials and Methods

This study included 69 patients diagnosed with symptomatic adenomyosis. The research constitutes a prospective case series analysis and reflects the early clinical experience with MRgFUS application at the "Multidisciplinary Center of Oncology and Surgery" in Ust-Kamenogorsk city during the period from 2022 to 2024. The cohort comprised all patients who met the strict inclusion criteria and underwent the procedure within the specified time frame.

The diagnosis of adenomyosis was verified based on comprehensive clinical and instrumental data, including patient history, transvaginal ultrasound (TVUS), and Magnetic Resonance Imaging (MRI) of the pelvis with contrast enhancement.

Inclusion criteria were: age between 25 and 48 years, preserved menstrual cycle, presence of symptoms (dysmenorrhea, hypermenorrhea, pelvic pressure sensation), and refusal of radical surgical treatment (hysterectomy). Exclusion criteria included: suspicion of malignancy, presence of an intrauterine device (IUD), severe adhesive disease, presence of a submucosal component of adenomyosis, or inadequate acoustic access.

The high specificity of the selection criteria, particularly technical limitations, resulted in a relatively small sample size, which is characteristic of studies involving the implementation of new high-technology methods.

The MRgFUS Procedure

Ablation procedures were performed using the ExAblate 2100 system (InSightec) in conjunction with a GE 3.0T Magnetic Resonance Imaging scanner. Standard planning protocols for the target zone were utilized, involving step-by-step MR-visualization and real-time temperature monitoring. All interventions were conducted on an outpatient basis, without the use of general or local anesthesia. The average duration of the MRgFUS session was 180 minutes.

Treatment efficacy was assessed based on pre-defined primary and secondary outcomes:

Primary Outcome

Clinical response, defined as the elimination or significant reduction of the primary adenomyosis symptoms. This assessment included:

1.Dynamics of pain syndrome using the Visual Analog Scale (VAS).

2.Dynamics of menstrual bleeding, assessed via The Pictorial Blood Loss Assessment Chart (PBAC), which possesses high sensitivity in detecting abnormal uterine bleeding [5].

Secondary Outcomes

1.Objective (Radiological) Efficacy: Reduction in the volume of the pathological focus according to MRI data, specifically the evaluation of the Non-Perfused Volume (NPV). Control MRI scans were performed at 3 and 6 months post-procedure.

2.Safety: Recording of complications during the procedure and in the early/delayed postoperative periods.

3.Impact on Reproductive Function: Frequency of pregnancy and delivery outcomes during the follow-up period.

4.Overall Tolerability: Assessment of the subjective reduction in complaints and return to normal physical activity.

The study was approved by the Local Ethics Committee (Protocol Number: № [Insert Protocol Number]; Date: [Insert

Date]). Informed consent for participation in the study and data processing was obtained from all patients.

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (SD) for normally distributed data or as the median with interquartile range (IQR) for non-normal distributions. Categorical variables are presented as frequencies (percentages). The Student's t-test was used to compare groups for normally distributed continuous variables, and the Mann-Whitney U test was used for non-normal continuous or ordinal data. Fisher's exact test was applied to compare categorical variables.

A two-sided p-value ≤0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics, Version 26 (Armonk, NY, USA) software.

Results

The study included 69 patients with symptomatic adenomyosis. The mean age of the patients was 43.14±3.82 years (range 38–47 years), which corresponds to the peak incidence of the disease (Table 1).

Analysis of the main clinical symptoms before treatment showed that for all patients the primary reason for seeking treatment was the sensation of pelvic pressure. Menstrual cycle disorders included menorrhagia in 19 women, while dysmenorrhea (menstruation-related pain) was noted in 14 patients. Non-menstruation-related pelvic pain was reported by 3 women. The mean number of myomatous nodes per patient was 2.03 (range 1–11). The mean total volume of fibroids in this group was 203.15 cm^3.

Table 1:

Baseline Demographic and Clinical Characteristics of Patients (n=69)

Variables	Values
Age, years	43,14 (38-47)
Symptoms	
Pressure on the bladder, n	33
Menorrhagia, n	19
Dysmenorrhea, n	14
Pelvic pain, n	3
Number, Location, and Volume of Fibroids	
Total number of fibroids per patient, n	2,03 (1-11)
Submucosal (FIGO Classification), n	3
Intramural < 50% (FIGO Classification), n	20
Intramural > 50% интрамуральная (FIGO Classification), n	34
Interstitial-submucosal node (FIGO Classification), n	3
Intramural fibroid (FIGO Classification), n	4
Subserosal-intramural node (FIGO Classification), n	4
<50 cm^3, n	24
≥50 и ≤80 cm^3, n	20
>80 cm^3, n	25
Fibroid Volume, cm^3	203,15

Primary Outcome

All 69 patients successfully tolerated the MRgFUS procedure. During the first 3 months of follow-up, 58 out of 69 patients (85%) reported a significant reduction in pain severity: the mean VAS score decreased from 7.2±1.1 to 3.0±1.4. A reduction in the duration and intensity of menstrual bleeding was observed in 52 patients (76%). The sensation of pelvic pressure completely resolved in 44 women (64%).

Table 2:

Primary Outcome.

Symptom	Before	After	p-value
Pain Syndrome (VAS score reduction)	7,2 ± 1,1	3,0 ± 1,4	p<0.001
Duration and Intensity of Menstrual Bleeding (PBAC score reduction)	9,2 ± 1,3	7,1 ± 1,0	p<0.05
Complaint, n	69	21	p<0.05

Secondary Outcomes

Control MRI with contrast enhancement performed at 3 months post-procedure registered the formation of a non-perfused volume (NPV) averaging 67% of the initial lesion volume. This further increased to 74% in 40 patients (58%) at 6 months, correlating with a continued improvement in the clinical picture **Figure 1**.

In no case was a repeat procedure or transition to an alternative treatment method required, and none of the patients reported complaints indicative of late complications. Three patients reported achieving pregnancy within 12 months after the procedure (all following focal adenomyosis treatment), two of which resulted in uncomplicated live births.

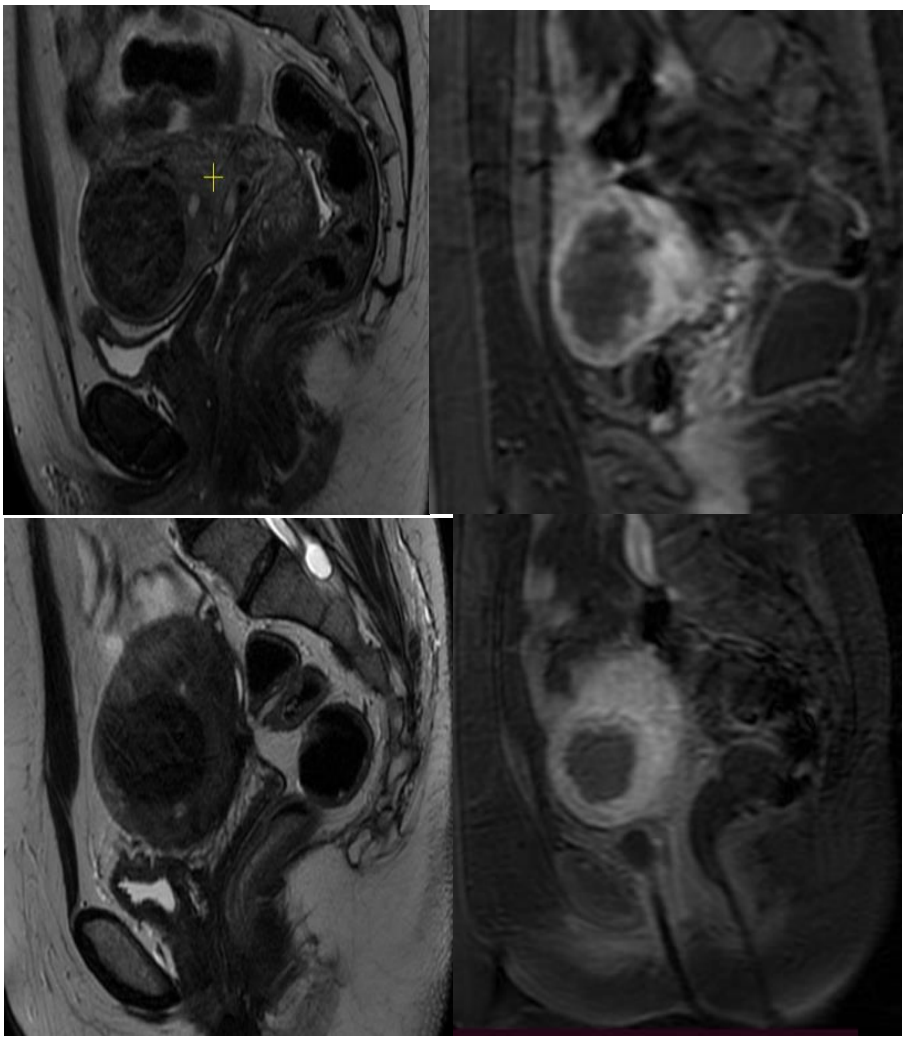


Figure 1: Fibroid Volume before (left) and after (right) MRgFUS procedure.

Discussion

The obtained results convincingly affirm the high clinical efficacy of the MRgFUS method in managing symptomatic adenomyosis. A significant majority of patients (85%) reported a marked reduction in pain syndrome, and 76% noted a decrease in the volume of menstrual bleeding. The mean VAS score decreased by more than 50%, which is consistent with previously published international data. For instance, in a study by Chin W. et al. (2016), clinical improvement was observed in 80–85% of patients during the first half-year [15].

The clinical success directly correlates with objective radiological indicators. Control MRI scans recorded the formation of a significant Non-Perfused Volume (NPV), reaching 74% by 6 months of follow-up. This indicator falls within the range noted in the works of Duc N.M. and Huy H.Q. (2018), confirming thermal destruction of the adenomyotic tissue as the key pathogenetic mechanism for symptom regression [11]. The observed increase in the non-perfused zone by 6 months suggests an ongoing process of necrosis and tissue remodeling, which correlates with further clinical improvement.

MRgFUS offers several unique advantages compared to surgical and endovascular methods: it is a non-invasive procedure, requiring no incisions or general anesthesia. We noted the absence of complications in our cohort, and all procedures were performed on an outpatient basis, ensuring rapid rehabilitation and preserved working capacity for the patients. The method allows for the preservation of the myometrial and endometrial architecture, which is critically important for women of reproductive age.

Thus, our data confirm the high safety profile and excellent tolerability of MRgFUS, while common but non-treatment-requiring side effects (such as pelvic pain or nausea, described in [1; 2; 11; 15]) were minimal and did not lead to procedure cancellation or hospitalization.

One of the most valuable outcomes of our study is the evaluation of reproductive results. The fact that three pregnancies occurred in patients treated with MRgFUS, with two successful live births within 12 months, holds great clinical significance. These findings attest to the preservation of reproductive function after MRgFUS and support the feasibility of considering this method as a promising alternative to hysterectomy, as well as myomectomy or uterine artery embolization (UAE), in women planning pregnancy. Unlike UAE, MRgFUS is associated with a potentially lower risk of miscarriage and abnormal placentation [3; 7; 8; 12; 14].

Study Limitations and Unique Experience

The main limitations of this study are its non-randomized nature (case series) and the relatively small

sample size (n=69). However, it should be emphasized that this sample reflects the entire cohort of patients treated at our center over a three-year period. The small number of observations is due to the high specificity of indications for MRgFUS and the necessity of adhering to strict technical requirements, which confirms the study's focus on safety and the initial experience of introducing the technology.

A crucial aspect is that this study represents the first and unique clinical experience of MRgFUS application in the treatment of adenomyosis in Kazakhstan, as the procedure is exclusively available at the KGP on PHV VKO "Multidisciplinary Center of Oncology and Surgery" in Ust-Kamenogorsk. This underscores the relevance of further dissemination of the technology, which requires careful patient selection and the development of national clinical protocols.

Conclusion

MRgFUS is a highly effective, non-invasive, and organ-sparing method for treating adenomyosis, demonstrating a sustained reduction in clinical symptoms, improved quality of life, and a positive impact on reproductive function. The results obtained in the Kazakhstan clinical practice are consistent with international data and confirm the safety of the technology, its applicability in outpatient settings, and its promise for women interested in preserving fertility. Given the urgency of the problem and the availability of the method in only one center in the country, it is necessary to expand access to MRgFUS and further integrate it into national clinical guidelines.

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VALIDATION OF THE RUSSIAN AND KAZAKH VERSIONS OF THE PSQ-18: ADAPTED INSTRUMENT FOR PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS

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Abstract

Background: Gestational diabetes mellitus (GDM) is a growing public health concern associated with adverse maternal and neonatal outcomes. Patient satisfaction represents an essential indicator of quality of care, particularly within primary healthcare settings responsible for screening, diagnosis, and follow-up of GDM. The Patient Satisfaction Questionnaire-18 (PSQ-18) is widely used internationally; however, no validated Kazakh or Russian versions tailored for pregnant women with GDM previously existed.

Aim: To adapt and validate the PSQ-18 for use among pregnant women with GDM in Kazakhstan.

Methods: A cross-sectional study was conducted. Forward–backward translation, expert review, and cultural adaptation processes were performed for Kazakh and Russian versions. The questionnaire was pilot-tested among 100 pregnant women with GDM (50 for each language version) in outpatient clinics in Aktobe. Internal consistency was assessed using Cronbach's alpha.

Results: Minor linguistic and conceptual adjustments were introduced to improve clarity and cultural relevance. Cronbach's alpha demonstrated acceptable internal consistency for both versions: 0.821 (Russian) and 0.758 (Kazakh). Pilot results confirmed comprehensibility and usability of the adapted tool in routine antenatal care settings.

Conclusion: The Kazakh and Russian versions of the PSQ-18 are reliable and culturally appropriate instruments for evaluating patient satisfaction among pregnant women with GDM in Kazakhstan's outpatient settings. Their use may support quality improvement and patient-centered care initiatives in primary healthcare.

Keywords: *questionnaire, validation, gestational diabetes mellitus, primary healthcare, satisfaction.*

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Резюме

ВАЛИДАЦИЯ РУССКОЙ И КАЗАХСКОЙ ВЕРСИЙ PSQ-18: АДАПТИРОВАННЫЙ ИНСТРУМЕНТ ДЛЯ БЕРЕМЕННЫХ ЖЕНЩИН С ГЕСТАЦИОННЫМ САХАРНЫМ ДИАБЕТОМ

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Актуальность: Гестационный сахарный диабет (ГСД) является актуальной проблемой общественного здравоохранения и связан с неблагоприятными материнскими и перинатальными исходами. Удовлетворённость пациентов является важным индикатором качества медицинской помощи, особенно на уровне первичной медико-санитарной помощи, где осуществляются скрининг, диагностика и наблюдение беременных с ГСД. Опросник удовлетворённости пациентов PSQ-18 широко используется в международных исследованиях, однако до настоящего времени не существовало валидированных казахской и русской версий для беременных с ГСД.

Цель: Адаптировать и валидировать опросник PSQ-18 для беременных женщин с ГСД в Казахстане.

Методы: Проведено поперечное исследование. Выполнены прямой и обратный перевод, экспертная оценка и культурная адаптация казахской и русской версий опросника. Пилотирование проведено среди 100 беременных женщин с ГСД (50 — русская версия, 50 — казахская) в амбулаторных организациях здравоохранения г. Актобе. Внутренняя согласованность оценивалась с использованием коэффициента альфа Кронбаха.

Результаты: В анкету внесены незначительные лингвистические и концептуальные корректировки для повышения ясности и культурной релевантности. Значения альфа Кронбаха составили 0,821 для русской версии и 0,758 для казахской, что свидетельствует о приемлемой внутренней согласованности. Пилотирование подтвердило понятность и применимость инструмента в условиях амбулаторной акушерской помощи.

Заключение: Казахская и русская версии PSQ-18 являются надёжными и культурно адаптированными инструментами для оценки удовлетворённости медицинской помощью среди беременных женщин с ГСД в амбулаторных условиях Казахстана. Использование данного инструмента позволит поддержать процессы улучшения качества и пациент-ориентированности на уровне ПМСП.

Ключевые слова: *анкета, валидация, гестационный сахарный диабет, первичная медико-санитарная помощь, удовлетворённость.*

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Түйіндеме

PSQ-18 САУАЛНАМАСЫНЫҢ ҚАЗАҚ ЖӘНЕ ОРЫС ТІЛДЕРІНДЕГІ НҰСҚАЛАРЫН ВАЛИДИЗАЦИЯЛАУ: ГЕСТАЦИЯЛЫҚ ҚАНТ ДИАБЕТІ БАР ЖҮКТІ ӘЙЕЛДЕРГЕ БЕЙІМДЕЛГЕН ҚҰРАЛ

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Өзектілігі: Гестациялық қант диабеті (ГҚД) – ана мен нәресте денсаулығына кері әсер ететін өзекті қоғамдық денсаулық сақтау мәселесі. Пациенттердің қанағаттануы медициналық көмектің сапасының маңызды көрсеткіші болып табылады, әсіресе ГҚД бар жүкті әйелдерді скринингтеу, диагностикалау және бақылауды жүзеге асыратын алғашқы медициналық-санитариялық көмек (АМСК) деңгейінде. PSQ-18 науқастардың қанағаттануын бағалау сауалнамасы халықаралық зерттеулерде кеңінен қолданылады, алайда осы уақытқа дейін ГҚД бар жүкті әйелдер үшін бейімделген және валидтелген қазақ және орыс нұсқалары болмаған.

Мақсаты: Қазақстандағы ГҚД бар жүкті әйелдер арасында PSQ-18 сауалнамасының қазақ және орыс тіліндегі нұсқаларын бейімдеу және валидтеу.

Әдістер: Көлденең зерттеу жүргізілді. Сауалнама қазақ және орыс тілдеріне тікелей және кері аударылып, сараптамалық бағалау мен мәдени бейімдеу жүргізілді. Пилоттық сынақ Актөбе қаласындағы амбулаториялық ұйымдарда ГҚД диагнозы бар 100 жүкті әйел арасында (50 — орысша, 50 — қазақша нұсқа) жүргізілді. Ішкі сәйкестігі Кронбах альфа коэффициенті арқылы бағаланды.

Нәтижелер: Сауалнама элементтерінің түсініктілігін арттыру үшін неғұрлым айқын және мәдени тұрғыдан сәйкес тұжырымдарға түзетулер енгізілді. Кронбах альфа коэффициенті орыс нұсқасы үшін 0,821 және қазақ нұсқасы үшін 0,758 құрады, бұл шкалалардың жеткілікті ішкі сәйкестігіне дәлел. Пилоттық зерттеу сауалнаманың амбулаториялық акушерлік көмек жағдайында қолдануға қолайлы және түсінікті екенін көрсетті.

Қорытынды: PSQ-18 сауалнамасының қазақ және орыс тілдеріндегі нұсқалары ГҚД бар жүкті әйелдердің медициналық көмекке қанағаттануын бағалауға арналған сенімді және мәдени тұрғыдан бейімделген құрал болып табылады. Бұл құралды пайдалану АМСК деңгейінде пациентке бағдарланған көмекті және медициналық қызмет сапасын жақсарту бастамаларын қолдауға мүмкіндік береді.

***Түйінді сөздер**: сауалнама, валидизация, гестациялық қант диабеті, алғашқы медициналық-санитариялық көмек, қанағаттану.*

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Introduction

Gestational diabetes mellitus (GDM) is a disorder of carbohydrate metabolism first identified during pregnancy, which has gained increasing attention in global healthcare in recent years due to its rising prevalence [1]. According to the International Diabetes Federation (IDF), the global prevalence of GDM is approximately 16.7% [2]. The prevalence of GDM is predominantly observed in low- and middle-income countries [3]. GDM is associated with an increased risk of maternal complications, including preeclampsia, cesarean delivery, and the subsequent development of type 2 diabetes, as well as adverse perinatal outcomes such as macrosomia, neonatal hypoglycemia, and respiratory distress [4-6]. The growing burden of GDM is driven by a combination of factors, among which advanced maternal age, urbanization, changes in dietary patterns, and reduced physical activity play a major role [7-10].

Primary healthcare (PHC) plays a crucial role in the healthcare system and serves as the first point of contact for pregnant women [11]. PHC performs key functions in managing GDM: organizing screening and early diagnosis, ensuring referral to specialized professionals and laboratories, and providing continuous monitoring, education, and support throughout pregnancy [12]. Effective management of GDM largely depends on the degree of patient engagement, the quality of communication with healthcare professionals, access to specialized care, and the level of satisfaction with received services. Patient satisfaction is widely recognized as a key indicator of healthcare quality and a predictor of treatment adherence, compliance with recommendations, and maintenance of therapeutic regimens.

This study involved the adaptation and pilot testing of the Patient Satisfaction Questionnaire-Short Form (PSQ-18) in Kazakh and Russian among pregnant women with GDM receiving outpatient care. PSQ-18 is a brief version of the classic PSQ-III developed by RAND Health Care, covering seven domains of patient satisfaction. The tool is widely used in international research on the quality of outpatient care and patient-centeredness, includes standardized scoring, and is available in open access along with scoring instructions on the official RAND website [13].

Despite the rising prevalence of GDM in the Republic of Kazakhstan and the need to strengthen outpatient management for affected pregnant women, research assessing patient satisfaction with healthcare services remains limited. Existing international satisfaction assessment tools require adaptation to the national context and evaluation of their psychometric properties in the target population. The aim of this study was to assess the clarity, cultural relevance, and reliability of the instrument, enabling its further use for monitoring healthcare quality and guiding improvement initiatives.

Materials and Methods

Study design: cross-sectional study. Quantitative, statistical, and analytical research methods were used.

Stage 1. Questionnaire development.

The “Patient Satisfaction Questionnaire, Short Form (PSQ-18),” which is publicly available, was used as the primary instrument. Since the questionnaire covers general satisfaction with medical care, the items were adapted for pregnant women with gestational diabetes mellitus to ensure clearer understanding of the context and research objectives.

The questionnaire consists of 18 items, divided into seven subscales: General Satisfaction (items 3 and 17); Technical Quality (items 2, 4, 6, and 14); Interpersonal Manner (items 10 and 11); Communication (items 1 and 13); Financial Aspects (items 5 and 7); Time Spent with Doctor (items 12 and 15); and Accessibility and Convenience (items 8, 9, 16, and 18). Some PSQ-18 items are phrased such that agreement indicates satisfaction with medical care, whereas in others agreement indicates dissatisfaction. All items must therefore be reverse-coded where appropriate so that higher scores consistently reflect higher satisfaction. After recoding, items within each subscale are averaged to obtain seven final scale scores.

Responses are rated on a five-point Likert scale: “strongly agree,” “agree,” “uncertain,” “disagree,” “strongly disagree”.

The instrument was prepared using a forward- and back-translation methodology [14]. First, two independent qualified translators translated the questionnaire from English into Kazakh and Russian. Then, reverse translations into English were performed by independent translators who were unaware of the original version. The resulting versions were reviewed by experts proficient in English, Kazakh, and Russian.

Next, translations were discussed with the research team to verify their accuracy and equivalence to the original English instrument. Necessary modifications were introduced to ensure semantic adequacy. For example, in the Russian version of item 1 (“Doctors are good about explaining the reason for medical tests”), the broader term “medical examinations” was used instead of the narrower “medical tests”. In Russian practice, the term “medical tests” typically refers only to laboratory analyses and excludes instrumental/functional studies, imaging procedures, and physical examinations. The broader wording preserves conceptual scope and maintains content validity and comparability with the original PSQ-18. In the Kazakh version, the term “medical examinations” was used for the same purpose.

In the Russian version, all statements and Likert-scale anchors were deliberately written in the feminine form (e.g., “agree”, “disagree”, “strongly disagree”) because the target sample consisted of pregnant women. This linguistic decision aimed to improve readability and reduce cognitive burden while preserving the constructs, polarity of items, and scoring scheme, including reverse-coded items.

Stage 2. Pilot testing.

A pilot survey was conducted among pregnant women diagnosed with gestational diabetes mellitus. The sample included 50 respondents for the Russian version and 50 respondents for the Kazakh version. Each participant received an informed consent form and study information sheet describing the study title, purpose, procedures, expected benefits, confidentiality, and researcher contact details. Surveys were administered in urban outpatient clinics in Aktobe before or after consultations with obstetrician-gynecologists, without disrupting clinical workflow. Participation was anonymous, voluntary, and followed the signing of informed consent.

The objectives of this phase were to assess the clarity of questionnaire items, identify translation discrepancies, correct them, and refine wording. Based on pilot results, translation errors were corrected and necessary adjustments were introduced. Questionnaire reliability was assessed using internal consistency, calculated by Cronbach’s alpha. An alpha coefficient above 0.7 is considered acceptable and indicates good internal consistency [14].

This study was approved by the Bioethics Committee of the West Kazakhstan Marat Ospanov Medical University (Protocol No. 5, June 5, 2025).

Results

A total of 50 respondents participated in the pilot study for each language version of the questionnaire (Kazakh and Russian). Based on the results of preliminary testing, minor clarifications were introduced into the wording of several items and response options to enhance clarity for the target population.

The internal consistency of the instrument was evaluated using Cronbach’s alpha for all thematic subscales. The obtained Cronbach’s alpha values were 0.821 for the Russian version (Table 1) and 0.758 for the Kazakh version (Table 2), indicating an acceptable level of internal consistency across scales.

Table 1.

Cronbach’s Alpha reliability results (Russian version).

№	Item wording	Mean	SD	Corrected item–total correlation	Cronbach’s alpha if item deleted
1	2	3	4	5	6
1	Doctors are good about explaining the reason for medical examinations related to my GDM.	3,00	1,370	0,329	0,816
2	I think my doctor’s office has everything needed to provide complete medical care for pregnant women with GDM.	3,02	1,421	0,397	0,813
3	The medical care I have been receiving for my GDM is just about perfect.	3,02	1,378	0,134	0,827
4	Sometimes doctors make me wonder if their diagnosis of GDM is correct.	2,88	1,365	0,584	0,802
5	I feel confident that I can get the medical care I need for my GDM without being set back financially.	3,10	1,403	0,398	0,813
6	When I go for medical care for my GDM, they are careful to check everything when treating and examining me.	3,12	1,394	0,591	0,801
7	I have to pay for more of my medical care for GDM than I can afford.	3,10	1,460	0,409	0,812
8	I have easy access to the medical specialist I need for my GDM.	3,08	1,397	0,639	0,799
9	Where I get medical care for my GDM, people have to wait too long for emergency treatment.	2,92	1,426	0,591	0,801
10	Doctors act too businesslike and impersonal toward me when providing care related to my GDM.	3,06	1,346	0,422	0,811

Continuation of Table 1.

1	2	3	4	5	6
11	My doctors treat me in a very friendly and courteous manner when caring for me during my pregnancy with GDM.	3,06	1,346	0,347	0,815
12	Those who provide my medical care for GDM sometimes hurry too much when they treat me.	2,96	1,370	0,455	0,809
13	Doctors sometimes ignore what I tell them about my GDM.	2,80	1,471	0,290	0,819
14	I have some doubts about the ability of the doctors who treat me for my GDM.	2,98	1,378	0,194	0,824
15	Doctors usually spend plenty of time with me when managing my GDM.	3,00	1,471	0,270	0,820
16	I find it hard to get an appointment for medical care for my GDM right away.	3,04	1,277	0,329	0,816
17	I am dissatisfied with some things about the medical care I receive for my GDM.	2,94	1,391	0,397	0,813
18	I am able to get medical care for my GDM whenever I need it.	3,04	1,293	0,134	0,827

Table 2.

Cronbach's Alpha reliability results (Kazakh version).

№	Item wording	Mean	SD	Corrected item–total correlation	Cronbach's alpha if item deleted
1	Doctors are good about explaining the reason for medical examinations related to my GDM.	3,04	1,442	,469	,736
2	I think my doctor's office has everything needed to provide complete medical care for pregnant women with GDM.	3,02	1,421	,286	,751
3	The medical care I have been receiving for my GDM is just about perfect.	3,08	1,291	,278	,751
4	Sometimes doctors make me wonder if their diagnosis of GDM is correct.	3,02	1,407	,429	,739
5	I feel confident that I can get the medical care I need for my GDM without being set back financially.	3,08	1,275	,424	,740
6	When I go for medical care for my GDM, they are careful to check everything when treating and examining me.	3,04	1,442	,348	,746
7	I have to pay for more of my medical care for GDM than I can afford.	2,96	1,525	,183	,760
8	I have easy access to the medical specialist I need for my GDM.	3,10	1,374	,378	,744
9	Where I get medical care for my GDM, people have to wait too long for emergency treatment.	2,96	1,456	,168	,761
10	Doctors act too businesslike and impersonal toward me when providing care related to my GDM.	2,96	1,399	,316	,749
11	My doctors treat me in a very friendly and courteous manner when caring for me during my pregnancy with GDM.	2,92	1,322	,090	,765
12	Those who provide my medical care for GDM sometimes hurry too much when they treat me.	3,02	1,421	,448	,738
13	Doctors sometimes ignore what I tell them about my GDM.	2,96	1,414	,341	,746
14	I have some doubts about the ability of the doctors who treat me for my GDM.	3,00	1,400	,345	,746
15	Doctors usually spend plenty of time with me when managing my GDM.	2,98	1,270	,469	,736
16	I find it hard to get an appointment for medical care for my GDM right away.	2,96	1,324	,286	,751
17	I am dissatisfied with some things about the medical care I receive for my GDM.	3,04	1,309	,278	,751
18	I am able to get medical care for my GDM whenever I need it.	3,04	1,428	,429	,739

Discussion

The results demonstrate that the adapted PSQ-18 is a valid instrument for assessing satisfaction with healthcare services among pregnant women with gestational diabetes mellitus receiving outpatient care in Kazakhstan. The forward–backward translation procedure, expert review, and pilot testing ensured cultural and linguistic equivalence, while the adjustments introduced improved terminology accuracy and naturalness of phrasing.

High Cronbach's alpha values for the Russian (0.821) and Kazakh (0.758) versions indicate good internal consistency of the scales and are comparable to the performance of the original instrument. Minor revisions made after the pilot phase improved item clarity without altering the scale structure or content.

The findings align with international experience using the PSQ-18 across diverse healthcare domains and countries. The instrument has been adapted and applied in Spain (dermatology) [15], Ethiopia (ophthalmology) [16], Indonesia (dentistry) [17], as well as in Malaysia and the United States for assessing satisfaction with prenatal counseling and antenatal care [18,19]. Our procedures for translation, expert evaluation, and pilot administration follow the ISPOR "Principles of Good Practice" for translation and cultural adaptation of PRO instruments [20], ensuring comparability with global research.

Thus, the adapted PSQ-18 can serve as a reliable instrument for monitoring the quality of outpatient care for pregnant women with GDM and for informing strategies aimed at strengthening patient-centeredness and healthcare effectiveness.

Conclusion

The adapted Kazakh and Russian versions of the PSQ-18 demonstrated sufficient clarity for the target population, and the linguistic modifications ensured cultural and terminological accuracy. The internal consistency indicators obtained (α = 0.821 for the Russian version and α = 0.758 for the Kazakh version) confirm the reliability of the scales and compliance with methodological requirements for instruments measuring patient satisfaction with healthcare services.

The adapted PSQ-18 may be used to evaluate the quality of outpatient care for pregnant women with gestational diabetes mellitus and can serve as a foundation for further implementation of patient-centered monitoring tools in Kazakhstan's primary healthcare system.

Ethical approval and consent to participate. *This study was approved by the Ethics committee of West Kazakhstan Marat Ospanov Medical University (Protocol no. 5 from June 5, 2025). All participants provided written informed consent before conducting the interviews.*

Availability of data and materials. *Original data can be provided by West Kazakhstan Marat Ospanov Medical University upon reasonable request.*

Conflict of interest. *The authors declare that there is no conflict of interest.*

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METHODOLOGICAL STUDY VALIDATION OF THE INSTRUMENT «ORGANIZATIONAL ASPECTS OF URO-ANDROLOGICAL CARE» FOR USE BY HEALTHCARE ORGANIZATION SPECIALISTS

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Abstract

Introduction: Sociological questionnaires play a crucial role in most studies in the field of healthcare, as the validity, reproducibility, and interpretability of research findings largely depend on the quality of the measurement instrument. Incorrectly developed and/or non-validated instruments may lead to systematic measurement errors, distortion of the true characteristics of the phenomenon under study, and, consequently, to inappropriate organizational and managerial decisions. The lack of internationally validated questionnaires aimed at identifying organizational barriers in the provision of uro-andrological care, as well as at building an evidence base for optimizing healthcare services for men, highlights the need for the development and validation of such an instrument.

Aim of the Study: to scientifically substantiate the validation process of a multi-aspect questionnaire entitled «Organizational Aspects of Uro-Andrological Care» for its subsequent use by healthcare organization specialists.

Materials and Methods: A multi-stage validation procedure was conducted, including the following phases: conceptual (theoretical) validity; face validity; content validity; cognitive validity (pilot study); assessment of internal consistency reliability; and finalization of the questionnaire.

Results: The results of the conceptual and face validity assessments demonstrated favorable outcomes. High content validity was confirmed by a panel of eight experts (I-CVI = 0.875–1.00; S-CVI/Ave = 0.987–1.00; S-CVI/UA = 0.895–1.00). The pilot study (n = 10) indicated a high level of interpretative clarity of the questionnaire items. The internal consistency of the instrument was satisfactory (Cronbach's alpha = 0.739 for 23 included items), indicating an acceptable level of reliability at the pilot testing stage.

Conclusions: The developed multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care» underwent a comprehensive, multi-level validation process. These findings confirm the methodological soundness and scientific applicability of the instrument for use by healthcare organizers in further research aimed at examining organizational aspects of male reproductive health, particularly at the regional level.

Keywords: *multi-aspect questionnaire; instrument; validation; uro-andrological care; reproductive health; men; region.*

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Резюме

МЕТОДОЛОГИЧЕСКАЯ ВАЛИДАЦИЯ ИНСТРУМЕНТА «ОРГАНИЗАЦИОННЫЕ АСПЕКТЫ УРОАНДРОЛОГИЧЕСКОЙ ПОМОЩИ» ДЛЯ ИСПОЛЬЗОВАНИЯ СПЕЦИАЛИСТАМИ МЕДИЦИНСКИХ ОРГАНИЗАЦИЙ

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Введение: Социологические опросники играют ключевую роль в большинстве исследований в области здравоохранения, поскольку валидность, воспроизводимость и интерпретируемость результатов во многом зависят от качества измерительного инструмента. Некорректно разработанные и/или невалидированные инструменты могут приводить к систематическим ошибкам измерения, искажению истинных характеристик изучаемого явления и, как следствие, к принятию неадекватных организационно-управленческих решений. Отсутствие международных валидированных опросников, направленных на выявление организационных барьеров при оказании уро-

андрологической помощи, а также на формирование доказательной базы для оптимизации медицинской помощи мужчинам, обуславливает необходимость разработки и валидации такого инструмента.

Цель исследования: научно обосновать процесс валидации мультиаспектной анкеты «Организационные аспекты уро-андрологической помощи» для его последующего использования специалистами организаций здравоохранения.

Материалы и методы: Проведена многоэтапная процедура валидации, включавшая следующие этапы: концептуальная (теоретическая) валидность; внешняя валидность; содержательная валидность; когнитивная валидность (пилотное исследование); оценка надежности внутренней согласованности; окончательная доработка опросника.

Результаты: Результаты оценки концептуальной и внешней валидности продемонстрировали благоприятные показатели. Высокая содержательная валидность была подтверждена экспертной панелью из восьми специалистов (I-CVI = 0,875–1,00; S-CVI/Ave = 0,987–1,00; S-CVI/UA = 0,895–1,00). Пилотное исследование (n = 10) показало высокий уровень интерпретационной ясности формулировок вопросов. Внутренняя согласованность инструмента была удовлетворительной (α Кронбаха = 0,739 для 23 включенных пунктов), что свидетельствует о приемлемом уровне надежности на этапе пилотного тестирования инструмента.

Заключение: Разработанный мультиаспектный опросник «Организационные аспекты уро-андрологической помощи» прошел комплексную многоуровневую процедуру валидации. Полученные результаты подтверждают методологическую состоятельность и научную применимость инструмента для использования организаторами здравоохранения в дальнейших исследованиях, направленных на изучение организационных аспектов охраны репродуктивного здоровья мужчин, в частности, на региональном уровне.

Ключевые слова: *мультиаспектный опросник; инструмент; валидация; уро-андрологическая помощь; репродуктивное здоровье; мужчины; регион.*

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Түйіндеме

ӘДІСНАМАЛЫҚ ЗЕРТТЕУ «УРО-АНДРОЛОГИЯЛЫҚ КӨМЕКТІҢ ҰЙЫМДАСТЫРУШЫЛЫҚ АСПЕКТІЛЕРІ» ҚҰРАЛЫН ДЕНСАУЛЫҚ САҚТАУ ҰЙЫМДАРЫ МАМАНДАРЫНЫҢ ҚОЛДАНУЫ ҮШІН ВАЛИДАЦИЯЛАУ

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Кіріспе: Әлеуметтік-сауалнамалық құралдар денсаулық сақтау саласындағы көптеген зерттеулерде шешуші рөл атқарады, себебі зерттеу нәтижелерінің валидтілігі, қайталанғыштығы және интерпретациялануы өлшеу құралының сапасына тікелей байланысты. Дұрыс әзірленбеген және/немесе валидтелмеген құралдар жүйелі өлшеу қателіктеріне, зерттелетін құбылыстың шынайы сипаттамаларының бұрмалануына және соның салдарынан тиімсіз ұйымдастырушылық-басқарушылық шешімдердің қабылдануына әкелуі мүмкін. Уро-андрологиялық көмекті көрсету барысында ұйымдастырушылық кедергілерді анықтауға, сондай-ақ ерлерге медициналық көмекті оңтайландыру үшін дәлелді базаны қалыптастыруға бағытталған халықаралық валидтелген сауалнамалардың болмауы осындай құралды әзірлеу мен валидтілігін анықтау қажеттілігін айқындайды.

Зерттеу мақсаты: «Уро-андрологиялық көмектің ұйымдастырушылық аспектілері» атты көпқырлы сауалнаманы денсаулық сақтау ұйымдарының мамандары қолдануы үшін валидтілігін анықтау үдерісін ғылыми тұрғыдан негіздеу.

Материалдар мен әдістер: Келесі кезеңдерді қамтитын көпсатылы валидтілікті анықтау жүргізілді: концептуалдық (теориялық) валидтілік; сыртқы валидтілік; мазмұндық валидтілік; когнитивтік валидтілік (пилоттық зерттеу); ішкі келісімділік сенімділігін бағалау; сауалнаманы түпкілікті жетілдіру.

Нәтижелер: Концептуалдық және сыртқы валидтілікті бағалау нәтижелері қолайлы көрсеткіштерді көрсетті. Жоғары мазмұндық валидтілік сегіз сарапшыдан тұратын панельмен расталды (I-CVI = 0,875–1,00; S-CVI/Ave = 0,987–1,00; S-CVI/UA = 0,895–1,00). Пилоттық зерттеу (n = 10) сауалнама сұрақтарының интерпретациялық айқындығының жоғары деңгейін көрсетті. Құралдың ішкі келісімділігі қанағаттанарлық болды (23 енгізілген тармақ бойынша Кронбах α = 0,739), бұл пилоттық тестілеу кезеңінде сенімділіктің қабылданатын деңгейін көрсетеді.

Қорытынды: «Уро-андрологиялық көмектің ұйымдастырушылық аспектілері» атты әзірленген көпқырлы сауалнама кешенді, көпдеңгейлі валидтілікті растау рәсімінен өтті. Алынған нәтижелер құралдың әдіснамалық негізділігін және ғылыми қолданбалылығын растайды және оны ерлердің репродуктивті денсаулығының

ұйымдастырушылық аспектілерін, әсіресе аймақтық деңгейде зерттеуге бағытталған болашақ зерттеулерде денсаулық сақтау ұйымдастырушыларының қолдануына мүмкіндік береді.

Түйінді сөздер: *көпқырлы сауалнама; құрал; валидтілік; уро-андрологиялық көмек; репродуктивті денсаулық; ерлер; аймақ.*

Дәйексөз үшін:

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Relevance

At present, a steady upward trend in the prevalence of infertile marriages has been observed, representing a serious medico-social problem [19]. Despite the fact that 45.0–52.0% of infertility cases are associated with disorders of the male reproductive system [6] [14], issues related to male reproductive health and the state of uro-andrological care have long remained outside the focus of professional attention. A number of studies emphasize the existence of a crisis [8] and the so-called «relative neglect» [25] with regard to male fertility health, highlighting the need for organizational and functional modernization of uro-andrological services [1], [9], [18].

In this context, there is an urgent need to study the opinions and attitudes of urologists and andrologists toward the organizational aspects of uro-andrological care as an integrated system. However, to date, no unified, standardized, and validated instrument exists that adequately meets this requirement.

Numerous studies have employed internationally recognized questionnaires; however, these instruments are characterized by a narrow thematic focus, addressing specific conditions such as varicocele [26], idiopathic infertility [5], [16], erectile dysfunction [13], assessment of quality of life among men experiencing fertility difficulties [3], and evaluation of primary healthcare physicians' knowledge regarding the management of urological diseases [22], among others. None of these questionnaires is designed to provide a comprehensive assessment of the organizational aspects of uro-andrological care.

Moreover, one of the key objectives of sociological research is to establish the validity and reliability of the measurement instrument. Validity reflects the extent to which a measurement tool assesses what it is intended to measure, while reliability indicates the degree of reproducibility of the results obtained through measurement [4], [17]. In light of the above, there is an objective need for the development and validation of an instrument capable of adequately assessing the relevant aspects of the problem under investigation.

Aim of the Study: to scientifically substantiate the validation process of a multi-aspect questionnaire entitled «Organizational Aspects of Uro-Andrological Care» for its subsequent use by healthcare organization specialists.

Materials and Methods: To ensure methodological rigor and improve the quality of the multi-aspect questionnaire designed to assess the organizational aspects of uro-andrological care at the regional level, a multi-stage validation procedure was conducted. This process included the following stages:

1.conceptual (theoretical) validity;

2.face validity;

3.content validity;

4.cognitive validity (pilot study);

5.assessment of internal consistency reliability;

6.finalization of the questionnaire.

The preliminary version of the instrument, i.e., the prototype questionnaire entitled «Organizational Aspects of Uro-Andrological Care», was developed in two languages – Russian and Kazakh – and consisted of 45 items. For the professional translation of the instrument into the Kazakh language, two certified linguists who were native speakers and had practical experience working with medical terminology were involved.

Following the assessment of conceptual validity, which included a detailed analysis of the questionnaire's content structure – namely, the removal of duplicate items, exclusion of questions with overlapping meanings, and elimination of formulations that were not aligned with the study objective – the final version of the questionnaire was established on May 13, 2025. The finalized version comprised 38 items.

At the initial stage, between May 14 and May 16, 2025, an assessment of face validity was conducted to evaluate the clarity, comprehensibility, and unambiguity of the questionnaire items. Representatives of the target population – practicing specialists, namely urologists-andrologists (n=5) – participated in this procedure. Participants were asked to assess each item according to criteria of clarity, logical consistency, and relevance to the stated topic. No substantial comments were identified as a result of the face validity assessment.

The expert evaluation of the instrument was carried out in accordance with the methodologies proposed by Waltz and Bausell (1981) and Lynn (1986) during the period from May 25 to June 3, 2025. Content validity was assessed by eight independent experts using a four-point rating scale. Based on the expert assessment, the following indices were calculated:

I-CVI (Item-Level Content Validity Index) – the proportion of experts who rated an item as 3 or 4; a threshold value of I-CVI≥0.78 is considered acceptable when the number of experts is ≥6–10;

S-CVI/Ave (Scale Content Validity Index, Average) – the average I-CVI across all items of the questionnaire; a threshold value of S-CVI/Ave≥0.90 is considered acceptable for ≥6–10 experts;

S-CVI/UA (Scale Content Validity Index, Universal Agreement) – the proportion of items for which all experts were in complete agreement; a threshold value of S-CVI/UA ≥0.80 is considered acceptable for ≥6–10 experts.

According to the analysis, all three indices reached the required levels of content validity. Based on expert comments, selected item formulations and/or response options were refined.

Following these revisions, a pilot study was conducted between June 9 and June 13, 2025, among a sample of urologists-andrologists (n=10) representing the target population (pilot testing on a small sample). The primary aim of the pilot testing was to assess the applicability and practical feasibility of the instrument. The average time required to complete the questionnaire ranged from 15 to 20 minutes. No structural errors were identified, with the exception of an inaccuracy in item No.34, which confirmed the overall suitability of the instrument for the main study. Item No.34 and its response options were subsequently rephrased. Given that the sample size was ≤50, conducting factor analysis was deemed inappropriate.

To assess the internal consistency, or reliability, of the questionnaire scales, Cronbach's alpha coefficient was calculated. The analysis was performed using IBM SPSS Statistics version 20, both for the questionnaire as a whole and for individual items. An alpha value of ≥0.70 is considered acceptable for social and medical research. The Cronbach's alpha value calculated based on the pilot sample should be interpreted as preliminary.

Based on the results of the above-described validation stages, the final version of the multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care» was established. In addition, a certificate of registration in the State Register of Rights to Copyright-Protected Objects was obtained (No. 62500, dated September 29, 2025).

Results: Questionnaire-based studies are neither purely quantitative nor purely qualitative in nature; rather, they are designed to collect data of various types depending on the research questions being addressed.

For the purpose of developing and validating the multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care» intended for specialists involved in organizational issues of male reproductive health, the following procedures were carried out.

Conceptual (Theoretical) Validity of the Questionnaire

At this stage of validation, content optimization of the preliminary version of the questionnaire was performed. This process included a detailed analysis of item wording, removal of overlapping and duplicate questions, and exclusion of non-relevant items that did not correspond to the study objectives. As a result, the number of items was reduced from 45 to 38.

The multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care», designed for specialists involved in male reproductive health issues, was developed for subsequent use in the identification, scientific justification, and prioritization of key directions for the development of the male reproductive health protection system at the regional level.

The questionnaire consists of two main sections and several sub-sections:

1.Sociodemographic and professional characteristics;

2.Organization of uro-andrological care, including the following domains:

– organization of the uro-andrological care system for the regional population (patient routing, interdisciplinary coordination);

– accessibility of urological and andrological care for the regional population;

– rehabilitation and dispensary follow-up of men with urological and andrological conditions;

– material and technical resources for the diagnosis and treatment of male reproductive health disorders;

– monitoring of men's health status and collection of patient feedback;

– workforce capacity and professional workload of medical specialists;

– organizational aspects of diagnostics and screening of male reproductive health at the regional level;

– reproductive behavior and gender attitudes toward childbearing;

– informatization and digitalization of the uro-andrological care system;

– scientific, educational, and preventive programs for healthcare professionals and the regional population.

The above-mentioned domains of the questionnaire enable comprehensive identification of key organizational-processual and sociocultural barriers affecting the functioning of the existing uro-andrological care system in the region, as well as assessment of their impact on the accessibility, quality, and effectiveness of specialized medical care.

Face Validity

Face validity represents one of the important stages of instrument validation and is based on the external appearance, format, and structural organization of the questionnaire. This stage is aimed at assessing the clarity, correctness, and unambiguity of item wording, as well as the overall comprehensibility of the questions for the target audience.

Taking into account feedback not only from experts but also from members of the target research population is considered essential [7], as the evaluation provided by potential respondents contributes to improving the acceptability, relevance, and overall quality of the instrument [32].

The face validity assessment involved practicing specialists – urologists-andrologists (n=5) – representing the target population but not included in the expert panel. Participants were selected using a random sampling method.

The respondents were asked to evaluate each questionnaire item according to the following criteria:

1) clarity (yes/no);
2) absence of ambiguity (yes/no);
3) appropriateness of wording (yes/no).

Based on the results of the face validity assessment, no substantial comments or concerns were identified. The evaluation was documented in written form using a standardized assessment sheet.

Content Validity (Expert Evaluation)

There is no single standardized or universally approved format for expert evaluation, as each instrument and questionnaire is inherently unique. Research objectives, questionnaire structure, and item content vary; therefore,

the expert evaluation form should accurately reflect the specific content of the instrument being assessed. In the present study, the ultimate purpose of the questionnaire «Organizational Aspects of Uro-Andrological Care» was to develop and scientifically substantiate priority directions for the male reproductive health protection system.

In addition, internationally recognized methodological frameworks – such as those proposed by Waltz and Bausell (1981) [31], Lynn (1986) [20], and Polit and Beck (2006) [24] – provide general principles for conducting expert evaluation rather than a fixed template.

The aim of the expert evaluation was to determine the content validity of the questionnaire, that is, the extent to which each item corresponds to the study objectives, is clear and appropriate for the target population, and is supported by high-quality response options. Unlike other forms of validity, content validity plays a decisive role in the interpretation of research findings and their practical application [20].

Accordingly, experts selected for content validation were required to possess in-depth knowledge of the subject matter and prior experience in the validation of sociological instruments. Lynn (1986) recommended involving between 3 and 10 experts in the content validation process [20].

For the assessment of content validity of the multi-aspect questionnaire, an expert panel consisting of eight specialists with academic degrees was formed. The panel included practicing urologists as well as scientific and methodological experts from different regions of the country, all of whom had professional experience in both academic research and practical healthcare. This composition ensured a balance between knowledge of regional specificities in uro-andrological care delivery and an independent scientific and methodological perspective.

Each expert was provided with the questionnaire, a description of the study objectives, an expert evaluation form, and detailed instructions for its completion.

Experts evaluated each questionnaire item using a four-point Likert scale (from 1 to 4) according to the following assessment domains:

Objective relevance – the extent to which an individual item reflects the stated objective of the questionnaire and measures the intended construct:

1 – not relevant, does not reflect the questionnaire objective, requires complete revision;

2 – partially relevant, requires substantial revision;

3 – generally relevant, minor revisions possible;

4 – fully relevant, no revision required.

Clarity – the degree to which an item is clearly, grammatically, and logically formulated and understandable to potential respondents:

1 – unclear or ambiguous, requires complete revision;

2 – partially clear, requires substantial revision;

3 – generally clear, minor revisions possible;

4 – completely clear, no revision required.

Appropriateness – the extent to which an item is appropriate within the professional, cultural, and contextual framework of the target population:

1 – inappropriate, requires complete revision;

2 – partially appropriate, requires substantial revision;

3 – generally appropriate, minor revisions possible;

4 – fully appropriate, no revision required.

Quality of response options – the accuracy, completeness, and logical structure of the proposed response options, enabling respondents to adequately express their opinions or select appropriate answers:

1 – incorrect and/or incomplete, requires complete revision;

2 – partially correct, requires substantial revision;

3 – generally correct, minor revisions possible;

4 – fully correct, no revision required.

Experts were also given the opportunity to provide qualitative comments and recommendations aimed at optimizing item wording and improving the overall quality of the questionnaire.

In accordance with the methodology proposed by Waltz and Bausell (1981), expert ratings were dichotomized: items rated as 3 or 4 were assigned a value of «1», indicating relevance, whereas items rated as 1 or 2 were assigned a value of «0», indicating non-relevance and the need for further revision.

Based on the expert ratings and subsequent dichotomization, the Item-Level Content Validity Index (I-CVI) was calculated for each questionnaire item. The I-CVI represents the proportion of experts who considered a given item to be relevant and was calculated using the following formula:

I-CVI = (number of experts rating the item as 3 or 4) / (total number of experts)

According to methodological recommendations, an I-CVI value ≥0.78 is considered acceptable when the number of experts ranges from 6 to 10; items with I-CVI <0.78 require revision [27].

In the present study, the vast majority of questionnaire items demonstrated an I-CVI of 1.00, indicating a high level of relevance of both item wording and response options. For items No. 18, 19, 27, and 28, the I-CVI for objective relevance was 0.875, which exceeds the recommended threshold of ≥0.78 and indicates acceptable content validity (Figure 1. I-CVI Objective Relevance). No items with I-CVI values below 0.78 were identified; therefore, no further item revision was required.

Next, the Scale-Level Content Validity Index (S-CVI) was calculated to assess the overall content validity of the questionnaire. It is important to note that two types of S-CVI are distinguished in the methodological literature [11]:

1) S-CVI/Ave (Scale Content Validity Index, Average) – reflects the average content validity of the entire scale and is calculated as the mean value of all item-level content validity indices (I-CVI). Formula for S-CVI/Ave:

S-CVI/Ave = (sum of I-CVI values) / (total number of items)

2) S-CVI/UA (Scale Content Validity Index, Universal Agreement) – represents the proportion of items for which universal agreement among experts was achieved, that is, the share of items rated as 3 or 4 by all experts. Formula for S-CVI/UA:

S-CVI/UA = (number of items rated 3 or 4 by all experts) / (total number of items)

The recommended threshold values for acceptable content validity are S-CVI/Ave >0.90 and S-CVI/UA >0.80.

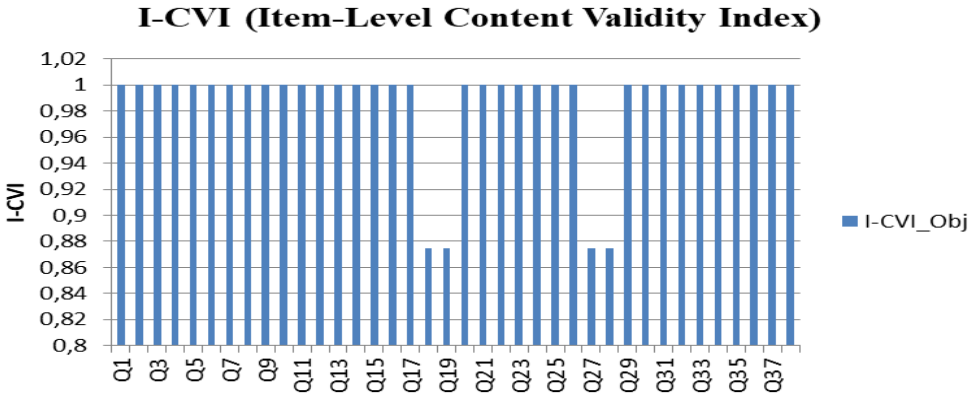


Figure 1. I-CVI Objective Relevance

The results of the calculations indicate a high level of expert agreement across all questionnaire domains. Specifically, for the domains «Clarity», «Appropriateness», and «Quality of Response Options», both indices reached a value of 1.00. For the domain «Objective Relevance», the values of S-CVI/Ave and S-CVI/UA were 0.987 and 0.895, respectively. Thus, all domains of the instrument demonstrated excellent content validity, and the questionnaire structure can be considered methodologically and conceptually sound.

During the content validation process, experts conducted not only a quantitative assessment but also a qualitative evaluation of each questionnaire item, providing detailed comments and recommendations. These comments addressed aspects such as clarity of wording, terminological accuracy, semantic refinement of items, and clarification of response options. All expert feedback was systematically organized and subjected to qualitative analysis. Based on these recommendations, selected items and/or response options were rephrased, which contributed to improved content validity and enhanced cognitive accessibility of the instrument.

Cognitive Validity (Pilot Study)

A pilot study is a preliminary investigation conducted prior to the actual survey or experiment and is designed to examine various aspects of the research process. In sociological research, pilot studies are typically carried out to assess the feasibility and suitability of a research instrument – namely, a questionnaire – before its application in a larger-scale study. In addition, pilot testing allows for the evaluation of key parameters of the chosen study design and methodology, participant selection criteria, and other operational strategies [21].

Conducting a large-scale survey is generally resource-intensive. Any substantial errors identified during a full-scale survey are highly likely to result in inefficient use of resources, including time, workforce, and financial costs. Therefore, a pilot study serves as an essential preparatory stage prior to the main survey, ensuring that the primary study can be implemented with realistic prospects of achieving its research objectives.

The present instrument is intended for use in the implementation of the third objective of the scientific start-up project «Model of a Digital Platform for Improving the Male Reproductive Health Protection System», namely, to identify current barriers within the existing healthcare organization related to male reproductive health. To achieve this objective, a questionnaire survey is planned among urologists and andrologists in the eastern region of the Republic of Kazakhstan (hereinafter referred to as the RK).

One of the fundamental considerations in planning a pilot study is the determination of the minimum sample size required to assess instrument reliability. According to official data from the Republican State Enterprise on the Right of Economic Management «Salidat Kairbekova National Scientific Center for Healthcare Development» of the Ministry of Health of the Republic of Kazakhstan, as of 2024, the number of practicing urologists and andrologists was 12 in the Abai Region, 18 in the East Kazakhstan Region and 23 in the Pavlodar Region.

Given that the target population in the present study was relatively small (n=53), it was decided to recruit 10 specialists to participate in the pilot testing of the questionnaire. Respondents were selected using a random sampling method, which ensured sample representativeness.

At this stage, the assessment focused on the clarity of item wording, verification of the logical sequence of questions, identification of potential difficulties in questionnaire completion, and determination of the time required to complete the questionnaire.

The allotted time for comprehensive and accurate questionnaire completion (15–20 minutes) was deemed sufficient. Overall, respondents did not report difficulties in completing the questionnaire. However, 7 out of 10 respondents (70%) experienced difficulty when answering Item No. 34: «How do you assess the level of organization of preventive examinations and screening programs for men compared with similar programs for women?»

The original response options were as follows:

1.significantly higher

2.somewhat higher

3.at the same level

4.somewhat lower

5.significantly lower

Considering the difficulties identified in interpreting the original wording of Item No. 34, and in order to enhance clarity and improve the validity of responses, a decision was made to modify the original formulation as follows: «In your opinion, the level of organization of preventive examinations and screening for male reproductive health is:»

The revised response options were:

1.significantly lower than that for women

2.somewhat lower than that for women

3.approximately at the same level

4.higher than that for women

5.difficult to answer

Thus, based on the results of the pilot study conducted on a small sample, no substantial content-related concerns were identified by respondents. The overall structure of the instrument, as well as the wording of questionnaire items and corresponding response options, was approved for subsequent use.

Assessment of Internal Consistency Reliability (Cronbach's Alpha)

The internal consistency of the questionnaire was assessed using Cronbach's alpha coefficient, which describes the extent to which all items of a test measure the same underlying construct and, consequently, reflects the interrelatedness of the items within the instrument. Internal consistency should be established prior to the use of a test for research purposes in order to ensure its validity. In addition, reliability estimates indicate the magnitude of measurement error in a test. In other words, reliability may be interpreted as the correlation of the test with itself. Cronbach's alpha coefficient ranges from 0 to 1 [30], with values closer to 1 indicating higher reliability of the scale.

The calculation of Cronbach's alpha on the pilot sample (n=10) was performed to identify potentially problematic questionnaire items and should be regarded solely as a preliminary indicator of the internal consistency of the instrument.

Cronbach's alpha was calculated and analyzed for the questionnaire as a whole as well as for individual items. The literature reports various acceptable alpha values, typically ranging from 0.70 to 0.95 [30]. Low alpha values may be associated with a small number of items, weak inter-item correlations, or heterogeneity of the measured constructs.

In accordance with the recommendations of Jum C. Nunnally (1978) [23] and Keith S. Taber (2018) [29], the following classification and interpretation of Cronbach's alpha values were applied:

α ≥ 0.90 – excellent internal consistency;

α = 0.80–0.89 – good internal consistency;

α = 0.70–0.79 – satisfactory internal consistency;

α < 0.70 – revision required.

In line with psychometric requirements, only scale (ordinal) items were included in the calculation of Cronbach's alpha. Sociodemographic («passport») questions, as well as items that were non-measurement in nature and not suitable for internal consistency assessment, were excluded from the analysis.

The obtained Cronbach's alpha value was 0.739 (based on 23 included items), which is considered a satisfactory level of internal consistency for social and medical research and indicates an acceptable level of instrument reliability at the pilot testing stage.

Cronbach's alpha values calculated after deleting individual items ranged from 0.691 to 0.818 (Table 1. Item–Total Statistics). Higher alpha values observed after item deletion indicate relatively weaker consistency of specific items with the overall scale.

Table 1.

Item–Total Statistics

Item number	Scale mean if item deleted	Scale variance if item deleted	Corrected item–total correlation	Cronbach's alpha if item deleted
Q9	59.00	60.667	.555	.708
Q11	59.20	65.956	.441	.724
Q12	60.20	62.400	.631	.709
Q13	59.40	62.711	.694	.709
Q14	59.00	60.000	.599	.704
Q15	59.20	59.733	.562	.706
Q16	58.80	57.733	.571	.702
Q18	59.30	59.789	.544	.707
Q19	59.40	64.489	.236	.736
Q20	59.10	67.878	.050	.756
Q21	58.90	59.878	.575	.705
Q22	59.80	58.622	.812	.691
Q23	58.60	66.267	.363	.727
Q24	59.60	69.378	.088	.741
Q25	59.20	88.844	-.899	.818
Q26	59.70	72.456	-.219	.751
Q27	58.30	62.678	.487	.715
Q29	60.20	75.733	-.356	.772
Q31	59.60	65.156	.656	.718
Q33	59.20	70.622	.013	.742
Q34	60.50	79.833	-.747	.782
Q35	59.00	59.778	.614	.703
Q36	58.80	58.844	.794	.693

Pilot testing of the questionnaire made it possible to identify several items that demonstrated negative or extremely low correlations with the total scale score, specifically Items Q25, Q26, Q29, and Q34. Removal of these items could have increased Cronbach's alpha (to values ranging from 0.751 to 0.818), thereby improving the internal consistency coefficient of the instrument. However, it is important to consider that the questionnaire is multi-aspect in nature; therefore, exclusion of these items would be methodologically unjustified, as they are conceptually meaningful and reflect key dimensions of the construct under investigation. In addition, the small sample size renders the Cronbach's alpha coefficient unstable.

One of the methods commonly used to justify item removal or modification is item–total correlation. The values of this psychometric indicator, which reflects the extent to which an individual item is consistent with or correlated to the overall scale, ranged from –0.899 to 0.812. The vast majority of item–total correlation values were considered good and acceptable (>0.30), confirming their consistency with the overall scale. Although certain items demonstrated low or even negative correlations, their removal would be methodologically inappropriate, as these items play a conceptual role within the measured construct. This approach is consistent with the recommendations of DeVellis (2003) [12], who emphasized that conceptually important items should not be excluded solely for the purpose of increasing Cronbach's alpha.

Overall, the results of the analysis indicated that the obtained Cronbach's alpha coefficient met established reliability criteria, thereby confirming the internal consistency of the developed instrument. Based on the above considerations, a decision was made to retain these items in the final version of the questionnaire.

Finalization of the Instrument

Following the comprehensive validation process, the final version of the questionnaire was established. The finalized instrument consists of 38 items and is intended to assess the organizational aspects of uro-andrological care.

It should be noted that the informed consent form for respondents was included as part of the materials of the doctoral dissertation entitled «Organizational and Functional Model of the Male Reproductive Health Protection System» and was approved at a meeting of the Local Ethics Committee (Protocol No. 2, dated December 5, 2024).

The informed consent form provided respondents with detailed information regarding the study objectives, the number of questionnaire items, the format of questions and response options, and the approximate time required to complete the questionnaire. In addition, potential participants were informed about the voluntary nature of participation, the anonymity of the survey, and guarantees of confidentiality of the collected data. The informed consent explicitly stated that all collected information would be used exclusively for research purposes.

Thus, it can be concluded that the multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care», designed for specialists involved in organizational issues of male reproductive health, represents a validated and reliable instrument ready for use in the development and scientific substantiation of priority directions in the male reproductive health protection system.

In addition, a certificate of registration in the State Register of Rights to Copyright-Protected Objects was obtained for this questionnaire (Registration No. 62500, dated September 29, 2025).

Discussion

The development and validation of an instrument for sociological research aimed at identifying key organizational-processual and sociocultural barriers affecting the functioning of the existing uro-andrological care system represent an important step toward establishing scientifically grounded approaches to improving specialized medical care.

One of the main limitations of the present study is the absence of standardized and validated instruments that comprehensively cover all organizational aspects of uro-andrological care for the male population, which complicates direct comparison of findings with other measurement tools.

Validity and reliability constitute two fundamental components of measurement instrument evaluation. Validity refers to the extent to which an instrument measures what it is intended to measure, whereas reliability refers to the instrument's ability to produce stable and consistent results. It should be noted that reliability is closely related to validity: an instrument cannot be valid if it is not reliable; however, reliability does not depend on validity [23]. To ensure methodological rigor, a multi-stage validation procedure was conducted, including conceptual (theoretical) validity, face validity, content validity, cognitive validity (pilot study), assessment of internal consistency reliability, and finalization of the questionnaire.

Methodological emphasis during the validation process was placed on content validity, that is, qualitative validation. From the perspective of content validity, many questionnaire items demonstrated maximum values (I-CVI=1.00), indicating complete expert agreement regarding item relevance and confirming that the questions adequately reflected the intended content of the instrument. I-CVI values of 0.875 observed for certain items also exceeded the recommended threshold of 0.78. The obtained S-CVI/Ave (0.987–1.00) and S-CVI/UA (0.895–1.00) values met established standards for content validity (S-CVI/Ave≥0.90; S-CVI/UA≥0.80). Assessment of content validity represents a critical stage in the psychometric evaluation and pilot testing of sociological instruments, as it ensures alignment between questionnaire items and the stated research objectives. In other words, the content validation process involves not only quantitative but also qualitative expert assessment of each item, which is particularly important given the small sample size (n=10).

Considering the professional competence of respondents and the unambiguous wording of questionnaire items, as confirmed by the results of content validity analysis, conducting additional cognitive interviews and/or think-aloud procedures was deemed unnecessary. Moreover, the high content validity indices indicate the absence of problematic item formulations, rendering further cognitive interviewing redundant.

Given that the target population size was ≤ 50, conducting factor analysis – both exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) – was considered inappropriate, as small sample sizes negatively

affect the quality and reliability of such analyses [10]. A commonly accepted rule of thumb suggests that at least 10 participants are required per item, resulting in an optimal respondent-to-item ratio of 10:1 [2], [15].

The Cronbach's alpha coefficient, reflecting the level of internal consistency among items, yielded a value of 0.739, which represents a satisfactory level and corresponds to an acceptable degree of internal reliability. It is important to emphasize that Cronbach's alpha is a property of test results obtained from a specific sample. Given that the pilot testing phase involved a small sample (n=10), test–retest reliability was not assessed. Small sample sizes directly affect the stability of Cronbach's alpha estimates. Such limitations are considered acceptable in the context of developing and validating sociological instruments. Therefore, researchers advise against relying solely on published alpha coefficients and recommend calculating alpha for each new application of the instrument [28].

During pilot testing, several items were identified as negatively correlated with the total scale score. However, it must be considered that the developed instrument is multi-aspect in nature, whereas the calculation of Cronbach's alpha assumes unidimensionality. Excluding conceptually important items solely for statistical reasons is regarded as a methodological error [12]. These items are conceptually essential for measuring organizational-processual and sociocultural domains and ensure adequate content representation of the construct.

Taken together, the comprehensive set of validation procedures confirms that the developed questionnaire is methodologically sound, content-relevant, and psychometrically acceptable for assessing the current state of uro-andrological care, identifying barriers, and designing organizational interventions aimed at improving healthcare services for men with reproductive health problems.

Conclusions

The use of valid and reliable instruments in sociological research is a key prerequisite for ensuring the accuracy of findings and the overall quality of research outcomes. The developed multi-aspect questionnaire «Organizational Aspects of Uro-Andrological Care», intended for specialists in healthcare organization, underwent a comprehensive, multi-level validation process, including assessment of conceptual, face, content, and cognitive validity, as well as evaluation of internal consistency reliability.

The obtained results confirm the methodological robustness and scientific applicability of the instrument for use in subsequent research, including multicenter studies in the field of male reproductive health. The questionnaire is suitable for identifying organizational barriers within the uro-andrological care system and for building an evidence base to optimize healthcare services for the male population at both regional and national levels of the Republic of Kazakhstan.

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FACTORS OF LIMITED DIAGNOSIS OF PHARAMACORESISTANT EPILEPSY

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Abstract

Background: Drug-resistant epilepsy (DRE) remains a serious clinical challenge, especially in settings with limited access to specialized care. A significant proportion of patients in Kazakhstan do not receive timely diagnosis or referral to specialized centers.

Objective: The aim of this study is to identify, using the example of the Epilepsy center's work, the barriers that limit access to specialized treatment, particularly the timely establishment of a diagnosis of drug-resistant epilepsy.

Materials and methods: This retrospective observational study included 560 Kazakh patients with DRE who presented to the Center between 2017 and 2023. Clinical and demographic data, social status, place of residence, and access to specialized care were analyzed. Statistical processing was performed using non-parametric methods and the χ^2 test, with a significance level of $p < 0.05$.

Results: In the overall patient group, delayed identification of drug resistance was associated with marital status and region of residence. Among patients whose diagnosis was first established at the Epilepsy center, unmarried individuals predominated ($p < 0.006$). A statistically significant predominance of individuals from Astana who received specialized care was observed ($p < 0.0001$). Examination of the association between DRE diagnosis and different epilepsy duration groups revealed no significant relationship in any group. Analysis of factors contributing to delayed DRE diagnosis in patients with disease duration over 20 years showed that men were almost 1.5 times more likely to experience delayed diagnosis compared to women (OR, 95% CI: 1.12 (1.02–1.31), $p = 0.02$), and lack of social protection reduced the likelihood of receiving specialized care (OR, 95% CI: 0.65 (0.54–0.79), $p < 0.0001$).

Conclusions: Timeliness of DRE diagnosis in Kazakhstan is determined by a combination of sociodemographic and regional factors. Patients from Astana and those with social support have better access to specialized care. Systemic measures are needed to improve patient referral pathways, reduce regional disparities, and combat stigmatization.

Keywords: *drug-resistant epilepsy, epilepsy duration, delayed diagnosis, specialized care.*

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Резюме

ФАКТОРЫ ОГРАНИЧЕННОЙ ДИАГНОСТИКИ ФАРМАКОРЕЗИСТЕНТНОЙ ЭПИЛЕПСИИ

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Введение. Фармакорезистентная эпилепсия (ФРЭ) остаётся серьёзной клинической проблемой, особенно в условиях ограниченного доступа к специализированной помощи. Значительная часть пациентов в Казахстане не получает своевременную диагностику и направление в специализированные центры.

Целью данного исследования является на примере работы Центра выявить барьеры, ограничивающие доступ к специализированному лечению, в частности своевременное установление диагноза фармакорезистентной эпилепсии.

Материалы и методы. Ретроспективное наблюдательное исследование включало 560 пациентов казахской национальности с ФРЭ, обратившихся в Центр с 2017 по 2023 гг. Анализировались клинико-демографические данные, социальный статус, место проживания и доступ к специализированной помощи. Статистическая обработка данных проводилась с использованием непараметрических методов и χ^2-теста, уровень значимости $p < 0,05$.

Результаты. В общей группе пациентов с несвоевременным выявлением фармакорезистентности были связаны семейное положение и регион проживания пациента. Среди пациентов, у которых диагноз впервые установлен в Центре эпилепсии, преобладали неженатые/незамужние ($p<0,006$). Наблюдается статистически значимое преобладание лиц в Астане, получивших специализированную помощь ($p<0,0001$). Изучение ассоциации с диагнозом фармакорезистентности в разных группах в зависимости от продолжительности эпилепсии не показала значимой связи ни в одной из групп. Анализ факторов несвоевременной постановки диагноза фармакорезистентности в группе пациентов с длительностью заболевания более 20 лет показал, что среди мужчин почти в 1,5 раза была вероятность несвоевременного диагностирования по сравнению с женщинами (OR, 95% CI: 1,12 (1,02-1,31), p=0,02) и отсутствие социальной защиты уменьшает шансы на получение специализированной помощи (OR, 95% CI: 0,65 (0,54-0,79), p<0,0001).

Выводы. Своевременность диагностики ФРЭ в Казахстане определяется сочетанием социально-демографических и региональных факторов. Пациенты из Астаны и социально защищённые лица обладают более высокой доступностью специализированной помощи. Необходимы системные меры по улучшению маршрутизации пациентов, снижению регионального неравенства и борьбе со стигматизацией.

Ключевые слова: *фармакорезистентная эпилепсия, длительность эпилепсии, несвоевременная диагностика, специализированная помощь.*

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Түйіндеме

ФАРМАКОРЕЗИСТЕНТТІ ЭПИЛЕПСИЯНЫҢШЕКТЕУЛІДИАГНОСТИКАЛЫҚФАКТОРЛАРЫ

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Кіріспе. Фармакорезистентті эпилепсия (ФРЭ), әсіресе мамандандырылған көмекке қол жетімділік шектеулі жағдайларда, маңызды клиникалық мәселе болып қала береді. Қазақстандағы пациенттердің едәуір бөлігі уақтылы диагноз қойып, мамандандырылған орталықтарға жолдама алмайды.

Мақсат. Бұл зерттеудің мақсаты орталық жұмысының мысалында мамандандырылған емдеуге қол жеткізуді шектейтін кедергілерді анықтау, атап айтқанда фармакорезистентті эпилепсия диагнозын уақтылы анықтау болып табылады.

Материалдар мен әдістер. Ретроспективті байқау зерттеуі 2017 жылдан 2023 жылға дейін Орталыққа жүгінген ФРЭ бар қазақ ұлтының 560 пациентін қамтыды. Статистикалық деректерді өңдеу параметрлік емес әдістер мен сынақтың көмегімен жүргізілді σ2, маңыздылық деңгейі p < 0,05.

Нәтижелер. Фармакорезистенттілігі уақтылы белгіленбеген пациенттердің жалпы тобында пациенттің отбасылық жағдайы мен тұратын аймағы байланысты болды. Эпилепсия орталығында алғаш диагноз қойылған пациенттер арасында үйленбеген / үйленбеген адамдар басым болды (p<0,006). Астанада мамандандырылған көмек алған адамдардың статистикалық маңызды артықшылығы байқалады (p<0,0001). Эпилепсияның ұзақтығына байланысты әртүрлі топтардағы фармакорезистенттілік диагнозымен байланысты зерттеу екі топта да айтарлықтай байланыс таппады. Аурудың ұзақтығы 20 жылдан асатын пациенттер тобындағы фармакорезистенттілік диагностикасының уақтылы емес факторларын талдау ер адамның уақтылы диагноз қою ықтималдығы әйелдерге қарағанда шамамен 1,5 есе жоғары екенін көрсетті (OR, 95% ci: 1,12 (1,02-1,31), p=0,02), ал әлеуметтік қорғаудың болмауы мамандандырылған көмек алу ықтималдығын төмендетеді (OR, 95% ci: 0,65 (0,54-0,79), p<0,0001).

Қорытынды. Қазақстанда ФРЭ диагностикасының уақтылығы әлеуметтік-демографиялық және өңірлік факторлардың үйлесімімен айқындалады. Астанадан келген пациенттер мен әлеуметтік қорғалған адамдар мамандандырылған көмектің жоғары қолжетімділігіне ие. Пациенттердің маршруттауын жақсарту, аймақтық теңсіздікті азайту және стигматизациямен күресу үшін жүйелі шаралар қажет.

Түйінді сөздер: *фармакорезистентті эпилепсия, эпилепсияның ұзақтығы, уақтылы диагностика, мамандандырылған көмек.*

Дәйексөз үшін:

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Introduction

Epilepsy is one of the most prevalent neurological disorders, particularly in low- and middle-income countries [5]. In most cases (approximately 60–70%), seizures can be successfully controlled with antiseizure medication; however, in about one third of patients, pharmacoresistant epilepsy (PRE) develops a condition in which seizures persist despite adequate pharmacological therapy [12].

Pharmacoresistant epilepsy is defined as the failure to achieve complete or near-complete seizure control despite the use of two “appropriate” antiepileptic drug (AED) regimens, administered either as monotherapy or in combination. The prevalence of PRE ranges from 15% in children to up to 34% in adults [4, 14, 17]. This condition leads to severe consequences, including psychosocial dysfunction, reduced quality of life, increased risk of injury, and premature mortality. Patients often become preoccupied with their condition, experience a significant decline in quality of life, and develop psychiatric comorbidities such as depression and anxiety. In addition, academic performance may deteriorate, social interactions become restricted, and in some cases, complete social isolation may occur [2,18].

Particular attention in clinical practice and research is given to focal epilepsy, in which the issue of pharmacoresistance is especially critical. In cases with confirmed structural abnormalities and well-localized epileptogenic foci, surgical intervention may represent a radical and effective treatment option [7]. As emphasized in clinical guidelines, for pharmacoresistant focal epilepsy, surgical treatment often has advantages over continued pharmacological therapy alone [8].

Nevertheless, despite clear indications and proven efficacy, epilepsy surgery remains insufficiently implemented in several Central Asian countries, including Kazakhstan. The most commonly identified barriers include diagnostic, infrastructural, socioeconomic, and organizational factors that hinder timely access to specialized care for patients with PRE [9, 15]. A particularly important issue is limited diagnostic capacity: decision-making regarding surgery requires high-quality neuroimaging (high-field MRI), video-EEG monitoring, and often invasive electrocorticography. In settings with limited resources and restricted availability of these modalities, significant obstacles arise that impede appropriate selection of surgical candidates. Collectively, these factors exacerbate the problem, as patients with pharmacoresistant focal epilepsy fail to receive timely surgical treatment, adversely affecting their quality of life as well as their cognitive and social functioning.

It is well established that specialized epilepsy care is provided through dedicated epilepsy centers. In Kazakhstan, three epilepsy centers are currently operating, with the primary aim of delivering comprehensive diagnostic and therapeutic services for patients with epilepsy. All preoperative and postoperative procedures are covered by the patient, whereas the surgical intervention itself is funded by the state. The Epilepsy Center of the Medical Center Hospital of the President’s Affairs Administration of the Republic of Kazakhstan (hereinafter referred to as the Center) began its operations in 2018 and is based on interdisciplinary collaboration among specialists from various fields, including epileptologists, neurosurgeons, experts in neurophysiology and neuroimaging, and pathologists. Despite these developments, recently published data indicate that only approximately 25–30% of patients with pharmacoresistant epilepsy in Kazakhstan have access to surgical treatment [1]. Consequently, only a limited proportion of patients with epilepsy receive specialized care at such centers, and the diagnosis of pharmacoresistant epilepsy may remain unrecognized for a prolonged period.

The aim of this study is to identify, using the experience of a Center as an example, the barriers that limit access to specialized care, with particular emphasis on the timely diagnosis of pharmacoresistant epilepsy.

Materials and Methods

This retrospective observational study included 560 patients with pharmacoresistant epilepsy who were referred to the Epilepsy Center of the Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan between early 2017 and late 2023. Patients were divided into two groups: those in whom pharmacoresistance was first diagnosed at the Center (n = 467) and those with previously established pharmacoresistant epilepsy (n = 93). All study participants were of Kazakh ethnicity. A retrospective analysis of clinical and anamnestic data was performed. Clinical information was obtained from the epilepsy surgery database and through review of hospital medical records. To ensure data specificity and accuracy, all records were additionally verified through manual review for consistency with the diagnosis as well as inclusion and exclusion criteria.

Individual participant data included date of birth, sex, ethnicity, age at epilepsy onset, age at obtaining the Center's diagnostic conclusion, age at initiation of antiseizure medication (ASM) therapy, duration and status of epilepsy and pharmacoresistance, and, in cases of surgical treatment, age at the time of surgery. In addition, information on patients' social status, place of residence, and distance from the Center was collected.

Regions of residence were categorized into four groups based on their distance from the Center: Group 1 - Astana; Group 2 - outside Astana up to 500 km; Group 3 - outside Astana at a distance of 500–999 km; and Group 4 - outside Astana 1,000 km or more. However, for analytical purposes, place of residence was ultimately dichotomized into Astana versus other regions.

Inclusion criteria were as follows: age ≥18 years at the time of referral to the Center; pharmacoresistant epilepsy (failure of ≥2 adequately tried and tolerated antiseizure medications); diagnosis consistent with the International League Against Epilepsy (ILAE) criteria for pharmacoresistant epilepsy; and Kazakh ethnicity.

Exclusion criteria included the presence of malignancy, any chronic disease in a decompensated stage, non-focal forms of epilepsy, and incomplete medical records.

Pharmacoresistant epilepsy (PRE) was defined as the failure to achieve sustained seizure remission despite treatment with two well-tolerated, appropriately selected, and adequately dosed antiepileptic drugs, administered either as monotherapy or in combination. In this context, the results of therapeutic drug monitoring of valproic acid and carbamazepine (Finlepsin), available at the Center, were evaluated.

*Ethical Considerations.*This study was conducted in accordance with an extended protocol for the secondary analysis of anonymized medical data and received ethical approval from the Local Bioethics Committee of the hospital, as stated in Protocol No. 4 dated December 20, 2024, and in compliance with the Declaration of Helsinki.

*Statistical Analysis.*Statistical analysis was performed using SPSS (IBM) version 26.0. Quantitative data were analyzed as continuous variables and presented as medians with lower and upper quartiles, Me (Q1; Q3), as well as means with standard deviations (M ± SD), where appropriate. Qualitative data were presented as frequencies and proportions and were dichotomized for analysis.

Quantitative data with non-normal distribution were analyzed using the nonparametric Mann–Whitney U test for independent groups, with results reported as medians (Q1; Q3). Data normality was assessed using the Shapiro–Wilk test. Dichotomous and categorical variables were analyzed using the chi-square (χ^2) test. A p-value of <0.05 was considered statistically significant. Associations between factors and pharmacoresistance were assessed using Pearson's chi-square (χ^2) test and odds ratios (ORs) with 95% confidence intervals (CIs).

Results

The results of our study demonstrated that the mean age at which pharmacoresistant epilepsy was first identified at the Center was significantly younger than that of patients with previously established pharmacoresistance. The age at seizure onset among patients with newly diagnosed pharmacoresistant epilepsy was younger than in those with a previously established diagnosis; however, these differences did not reach statistical significance. The duration of epilepsy was significantly longer in the group with a previously established diagnosis compared to patients in whom pharmacoresistance was first identified at the Center.

The proportion of male patients was higher in the group with a previously known diagnosis of pharmacoresistant epilepsy. In contrast, women slightly predominated among patients with newly diagnosed pharmacoresistance; however, no statistically significant association between sex and the timing of pharmacoresistant epilepsy diagnosis was observed.

Marital status, however, was associated with delayed diagnosis. Among patients whose diagnosis of pharmacoresistant epilepsy was first established at the Center, the proportion of unmarried individuals was higher than that of married patients.

Place of residence was not associated with the timeliness of diagnosis. In both the newly diagnosed and previously known pharmacoresistant epilepsy groups, urban residents predominated.

In both groups, the majority of patients were unemployed or not formally organized in the workforce. The proportion of socially unprotected patients exceeded that of socially protected individuals in both groups; however, no statistically significant differences between the groups were identified.

Our findings also indicated that, compared with the city of Astana, the number of patients with timely diagnosis in other regions was substantially lower. These differences were statistically significant and reflect a predominance of individuals in Astana who received specialized medical care.

Regarding the overall duration of epilepsy, both in the group with newly diagnosed pharmacoresistant epilepsy at the Epilepsy Center and in the group with a previously established diagnosis of pharmacoresistant epilepsy, the duration of the disease exceeded 20 years. However, in the group with a previously known diagnosis of pharmacoresistant epilepsy, the disease duration was statistically significantly longer than in the group with a newly established diagnosis.

As shown in Table 1, the proportion of patients with an epilepsy duration of up to 5 years was higher among those with

previously established pharmacoresistant epilepsy, whereas a disease duration of 5 to 10 years was more frequently observed among patients in whom pharmacoresistance was first identified at the Center. Patients with an epilepsy duration of 10 to 20 years were more common in the group with previously known pharmacoresistance. The largest proportion of patients belonged to the group with a disease duration exceeding 20 years. In this category, the proportion of patients was equal in both groups - those with newly identified pharmacoresistance and those with previously established pharmacoresistance.

However, no statistically significant association between the timeliness of pharmacoresistance detection and epilepsy duration was identified in either group. Although certain trends were observed when comparing the 5–10-year and 10–20-year subgroups, these associations did not reach statistical significance due to the application of Bonferroni correction for six pairwise comparisons.

Table 1.

Clinical and Demographic Indicators and Comparative Characteristics Based on the Detection of Pharmacoresistance.

Indicators	Newly Diagnosed Pharmacoresistance	Previously Known Pharmacoresistance	p
Gender	467	93	
Male	233(49,9%)	53(56,9%)	0,21
Female	234(50,1%)	40(43,1%)	
Marital Status	467	93	
Married	213(45,6%)	57(61,3%)	<0,006
Unmarried	254(54,4%)	36(38,7%)	
Average age, years	36,0 (31,0-41,0)	39,0(41,0-56,0)	<0,0001
Age at seizure onset, years	13,0(7,0-19,0)	21,0(13,0-33,0)	0,31
Duration of epilepsy, years	23,0(16,0-29,0)	27,0(16,0-32,5)	0,009
Place of residence	467	93	
City	371 (79,4%)	81 (87,1%)	0,09
Village	96 (20,6%)	12 (12,9%)	
Employment status	467	93	
Employed	156 (33,4%)	31 (33,3%)	0,99
Unemployed	311 (66,6%)	62 (66,7%)	
Social support	467	93	
Has group	189 (40,5%)	40 (43,1%)	0,65
No group	278 (59,5%)	53 (56,9%)	
Region	467	93	
Astana	213 (45,6%)	66 (70,9%)	<0,0001
Other regions	254 (54,4%)	27 (29,1%)	

Table 2.

Distribution of Patients by Epilepsy Duration and Comparison of Risk Indicators (Odds Ratio, OR) for Newly Diagnosed and Previously Established Pharmacoresistance.

Duration of epilepsy	Newly DiagnosedPR (n=467)	Previously Established PR (n=93)	OR (95% CI)	p
Upto 5 years	32 (6.85%)	7 (7.53%)	3,28 (0,63-17,1)	0,14
From 5 to 10 years	28 (6.0%)	1 (1.1%)		
From 5 to 10 years	28(6.0%)	1(1.1%)	1,25 (1,09-1,44)	0,05
From 10 to 20 years	89 (19.1%)	20 (21.5%)		
From 10 to 20 years	89(19.1%)	20(21.5%)	1,07 (0,61-1,88)	0,82
Over 20 years	318 (68.1%)	65 (69.9%)		
Upto 5 years	32(6.85%)	7(7.53%)	1,00 (0,39-2,61)	0,99
From 10 to 20 years	89(19.1%)	20(21.5%)		
From 5 to 10 years	28(6.0%)	1(1.1%)	0,33 (0,08-1,40)	0,11
Over 20 years	318 (91,9%)	65 (98,5%)		
Upto 5 years	32 (6.85%)	7 (7.53%)	1,07 (0,45-2,53)	0,88
Over 20 years	318 (68.1%)	65 (69.9%)		

Given that the largest number of patients was observed in the group with an epilepsy duration exceeding 20 years, we further analyzed factors associated with delayed diagnosis of

pharmacoresistant epilepsy within this subgroup. The analysis demonstrated that sex and social protection status were statistically significant factors associated with prolonged non-detection of pharmacoresistance. Male patients had approximately a 1.5-fold higher likelihood of delayed diagnosis of pharmacoresistant epilepsy compared with female patients. Lack of social protection reduced the likelihood of receiving specialized care and timely diagnosis.

Other factors, including marital status, place of residence (urban vs. rural), employment status (employed vs. unemployed), and region, were not associated with the timeliness of diagnosis among patients with long-standing disease. Although a tendency toward a higher number of undiagnosed cases was observed in regions geographically distant from Astana, these differences did not reach statistical significance. The detailed data are presented in Table 3.

Table 3.

Factors Associated with Prolonged Epilepsy: A Comparative Analysis.

Factors	Disease duration over 20 years	Disease duration up to 20 years	OR (95% CI)	p
Gender	n=318	n=149	1,12 (1,02-1,31)	0,02
Male	171 (53,8%)	63 (42,3%)		
Female	147 (46,2%)	86 (57,7%)		
Marital Status				
Married	168 (52,8%)	86 (57,7%)	1,15 (0,88-1,50)	0,32
Unmarried	150 (47,2%)	63 (42,3%)		
Place of residence				
City	247 (77,7%)	124 (83,2%)	1,27 (0,88-1,83)	0,19
Village	70 (22,3%)	25 (16,8%)		
Employment status				
Employed	100 (31,5%)	55 (36,9%)	1,18 (0,89-1,55)	0,24
Unemployed	218 (38,5%)	94 (63,1%)		
Social support				
Has group	258 (81,1%)	88 (59,1%)	0,65 (0,54-0,79)	<0,0001
No group	60 (18,9%)	61 (40,9%)		
Region				
Astana	139 (43,7%)	75 (50,3%)	1,31 (0,88-1,93)	0,18
Other regions	179 (56,3%)	74 (49,7%)		

Discussion

The present study identified several sociodemographic and geographic factors that limit access to specialized care and contribute to delayed diagnosis of pharmacoresistant epilepsy (PRE). The proportion of delayed PRE diagnosis was higher among unmarried individuals and among patients residing in regions geographically distant from Astana. Moreover, we observed a proportional increase in the number of patients with longer disease duration, with more than half of newly diagnosed PRE cases being identified only after 20 years of disease progression. Among patients with an epilepsy duration exceeding 20 years, male sex and lack of social protection were significant factors associated with delayed diagnosis.

Although patients with newly diagnosed PRE in our cohort were younger and differed in disease duration compared with those with previously established pharmacoresistance, they nevertheless had a substantial duration of epilepsy (median 23 years). These findings highlight the issue of late recognition of PRE and are consistent with data from previous studies. It is well documented that, on average, patients wait 15–20 years from seizure onset before being referred for specialized diagnostic evaluation or surgical treatment, which substantially exceeds the recommended threshold of two years of treatment failure with two appropriately selected antiseizure medications, as defined by the International League Against Epilepsy (ILAE) [10].

We identified an association between marital status and the likelihood of timely diagnosis, with unmarried patients being more prevalent among those whose PRE was first diagnosed exclusively at the Center. According to international studies, having a partner is associated with better treatment adherence and more regular follow-up visits among patients with epilepsy [13]. However, within our sociocultural context, this finding may also be explained by disease-related stigma. Epilepsy remains one of the most highly stigmatized neurological disorders, and patients often conceal their diagnosis due to fear of discrimination and anxiety related to the unpredictable occurrence of seizures [6,16].

A statistically significant predominance of timely diagnosed cases was observed in Astana compared with other regions of Kazakhstan. Geographic disparities in access to specialized epileptological care have also been reported in other countries. Several studies indicate that patients living far from specialized epilepsy centers have significantly lower chances of receiving timely diagnosis and referral for epilepsy surgery [19]. Therefore, the regional differences observed in our study are not unique to Kazakhstan and likely reflect broader structural barriers within healthcare systems.

Despite the high proportion of patients with an epilepsy duration exceeding 20 years, no statistically significant association was found between disease duration and the timeliness of PRE diagnosis across epilepsy duration

subgroups. Nevertheless, the observed trends—such as more frequent delayed diagnosis among patients with disease duration of 10–20 years—warrant further investigation in a larger cohort. The predominance of disease duration exceeding 20 years in more than half of patients whose PRE was first diagnosed at the Center is particularly concerning and should alert clinicians to the risk of prolonged under-recognition of pharmacoresistance.

Despite the absence of an overall association between sex and the detection of pharmacoresistant epilepsy (PRE) in the entire cohort, male patients in the subgroup with long-standing disease duration (>20 years) were nearly 1.5 times more likely to experience delayed diagnosis of PRE. Recent meta-analytic evidence indicates no overall differences between men and women in access to specialized epilepsy care [11]. The sex-related effect on the timeliness of PRE diagnosis observed in our study among patients with disease duration exceeding 20 years may therefore reflect specific social and cultural characteristics of our country.

With regard to the impact of social support on the timeliness of PRE diagnosis in patients with long-standing epilepsy (>20 years), available literature indicates that individuals with lower socioeconomic status receive specialized care significantly less frequently [3], and low socioeconomic status is associated with a longer duration of uncontrolled seizures [20].

Conclusion

This study revealed pronounced social and regional disparities in the timeliness of pharmacoresistant epilepsy diagnosis and access to surgical treatment in Kazakhstan. Socially protected patients and residents of Astana demonstrated significantly higher likelihood of receiving specialized care. These findings highlight the need for comprehensive healthcare system interventions aimed at reducing social inequality, improving patient referral pathways through optimization of primary care practices, and eliminating regional barriers by enhancing communication systems and implementing health information technologies. In addition, educational and awareness-raising initiatives are required to address epilepsy-related stigma.

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Author Contributions

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PSYCHOLOGICAL AND SOCIAL ASPECTS OF SYNTHETIC PSYCHOACTIVE SUBSTANCE USE AMONG INDIVIDUALS WITH BORDERLINE MENTAL DISORDERS: A COMPARATIVE ANALYSIS

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Abstract

Relevance. The growing prevalence of synthetic psychoactive substance use, particularly among young people, is accompanied by an increase in patients with severe forms of dependence and comorbid mental disorders, including borderline personality disorders. Identifying the psychological and social characteristics of this group is crucial for developing targeted support programs.

Objective: to conduct a comparative analysis of synthetic psychoactive substance users with and without signs of borderline personality disorders and to identify key psychological and social differences between the groups.

Materials and Methods. The present study employed a cross-sectional comparative design and was conducted over the period from January 2023 to December 2024 at the Almaty City Mental Health Center, Republic of Kazakhstan. The study was conducted in 2023–2024 at the Mental Health Center in Almaty. A total of 500 respondents were surveyed using a structured questionnaire. The sample was divided into two equal groups: individuals with borderline personality disorders (n=250) and those without (n=250). Data were analyzed using Spearman's rank correlation method.

Results. In the group with BPD, emotional disorders (88%), psychotic symptoms (40%), panic attacks (84%), suicidal thoughts (72%) and attempts (44%) were significantly more common. Significant correlations have been established between the frequency of use, the severity of addiction symptoms, mood changes, and the risks of suicidal behavior. The effectiveness of treatment in patients with BPD was lower (20% versus 36% in the group without BPD).

Conclusion. Users of synthetic psychoactive substances with borderline personality disorders demonstrate a more severe clinical profile and a lower response to therapy. These findings highlight the need for integrated assistance programs that include psychotherapeutic and social interventions, with a focus on prevention, early detection, and motivation enhancement.

Keywords: *synthetic drugs, borderline personality disorder, addiction, psychopathology, prevention.*

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Резюме

ПСИХОЛОГИЧЕСКИЕ И СОЦИАЛЬНЫЕ АСПЕКТЫ УПОТРЕБЛЕНИЯ СИНТЕТИЧЕСКИХ ПСИХОАКТИВНЫХ ВЕЩЕСТВ У ЛИЦ С ПОГРАНИЧНЫМИ ПСИХИЧЕСКИМИ РАССТРОЙСТВАМИ: СРАВНИТЕЛЬНЫЙ АНАЛИЗ

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Актуальность. Рост распространённости синтетических психоактивных веществ, особенно среди молодёжи, сопровождается увеличением числа пациентов с тяжёлыми формами зависимости и сопутствующими психическими расстройствами, включая пограничные расстройства личности. Выявление психологических и социальных особенностей этой группы имеет важное значение для разработки целевых программ помощи.

Цель: провести сравнительный анализ потребителей синтетических психоактивных веществ с признаками пограничных психических расстройств личности и без таковых, выявить ключевые психологические и социальные отличия между группами.

Материалы и методы. Настоящее исследование представляло собой кросс-секционное (поперечное) сравнительное исследование, проведённое в период с января 2023 по декабрь 2024 года на базе Центра психического здоровья города Алматы, Республика Казахстан. Анкетирование охватило 500 респондентов, разделённых на две равные группы: с пограничными расстройствами личности (n=250) и без таковых (n=250). Использовалась структурированная анкета. Применён корреляционный анализ по Спирмену.

Результаты. В группе с ПРЛ достоверно чаще встречались эмоциональные нарушения (88%), психотические симптомы (40%), панические атаки (84%), суицидальные мысли (72%) и попытки (44%). Установлены значимые корреляции между частотой употребления, выраженностью симптомов зависимости, изменениями настроения и рисками суицидального поведения. Эффективность лечения у пациентов с ПРЛ была ниже (20% против 36% в группе без ПРЛ).

Заключение. Потребители синтетических ПАВ с пограничными психическими расстройствами личности демонстрируют более тяжёлую клиническую картину и низкий отклик на терапию. Это подчёркивает необходимость внедрения комплексных программ помощи, включающих психотерапевтические и социальные интервенции, с акцентом на профилактику, раннее выявление и поддержку мотивации к лечению.

Ключевые слова: *синтетические наркотики, пограничные психические расстройства, зависимость, психопатология, профилактика.*

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Түйіндеме

ШЕКАРАЛЫҚ ПСИХИКАЛЫҚ АУЫТҚУЛАРЫ БАР АДАМДАР АРАСЫНДА СИНТЕТИКАЛЫҚ ПСИХОАКТИВТІ ЗАТТАРДЫ ҚОЛДАНУДЫҢ ПСИХОЛОГИЯЛЫҚ ЖӘНЕ ӘЛЕУМЕТТІК АСПЕКТІЛЕРІ: САЛЫСТЫРМАЛЫ ТАЛДАУ

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Өзектілігі. Синтетикалық психоактивті заттарды, әсіресе жастар арасында қолданудың өсіп келе жатқан таралуы — тәуелділіктің ауыр түрлерімен және қатар жүретін психикалық бұзылулармен, соның ішінде шекаралық тұлғалық бұзылулармен ауыратын науқастар санының артуымен қатар жүреді. Осы топтың психологиялық және әлеуметтік ерекшеліктерін анықтау — мақсатты қолдау бағдарламаларын жасау үшін өте маңызды.

Мақсаты: Тұлғаның шекаралық бұзылыстарының белгілері бар және онсыз синтетикалық психоактивті заттарды қолданушыларға салыстырмалы талдау жүргізу, сондай-ақ топтар арасындағы негізгі психологиялық және әлеуметтік айырмашылықтарды анықтау.

Материалдар мен әдістер. Бұл зерттеу көлденең (кросс-секциялық) салыстырмалы сипатта жүргізілді және 2023 жылғы қаңтардан 2024 жылғы желтоқсанға дейінгі кезеңде Алматы қаласының Психикалық денсаулық орталығының базасында өткізілді. Зерттеуге барлығы 500 респондент қатысып, олар екі тең топқа бөлінді: шекаралық тұлғалық бұзылыстары барлар (n=250) және ондай бұзылыстары жоқтар (n=250). Зерттеу барысында құрылымдық сауалнама қолданылды. Алынған деректерге Спирменнің рангілік корреляция талдауы жүргізілді.

Нәтижелер. Шекаралық бұзылулары бар топ эмоционалдық бұзылулардың (88%), психотикалық белгілердің (40%), дүрбелең шабуылдарының (84%), суицидтік ойлардың (72%) және әрекеттердің (44%) айтарлықтай жоғары таралғанын хабарлады. Сондай-ақ қолдану жиілігі, тәуелділік белгілерінің ауырлығы, көңіл-күйдің өзгеруі және суицид қаупі арасында айтарлықтай корреляция анықталды. Шекаралық тұлғалық бұзылыстары бар топта емдеудің тиімділігі төмен болды — 20% қарсы 36%..

Қорытынды. Шекаралық тұлғалық бұзылыстары бар синтетикалық психоактивті заттарды қолданушылар неғұрлым ауыр клиникалық профильмен және терапияға төмен жауап беруімен ерекшеленеді. Бұл нәтижелер алдын алуға, ерте анықтауға және мотивацияны арттыруға бағытталған психотерапиялық әрі әлеуметтік араласуды қамтитын кешенді көмек бағдарламаларының қажеттілігін көрсетеді.

Кілт сөздер: *синтетикалық препараттар, шекаралық тұлғаның бұзылуы, тәуелділік, психопатология, алдын алу.*

Дәйексөз үшін:

Козыбаева К.А., Козыбаева Ж.А., Субханбердина А.С., Бурибаева Ж.К., Изекенова А.К Шекаралық психикалық ауытқулары бар адамдар арасында синтетикалық психоактивті заттарды қолданудың психологиялық және әлеуметтік аспектілері: салыстырмалы талдау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 109-117. *doi 10.34689/SH.2025.27.6.013*

Introduction

According to the World Health Organization (WHO), there has been a steady increase in the number of individuals using narcotic substances over recent decades [24]. Several studies emphasize that drug use is becoming more widespread among young people, which is associated with the availability of synthetic drugs and a low level of awareness about the risks involved [9]. Contemporary epidemiological research shows that the prevalence of drug addiction is influenced by various factors, including socio-economic status, level of education, and accessibility of medical care [18]. For example, in developed countries, a decline in the use of traditional drugs (such as heroin and cocaine) has been observed, alongside a rise in the popularity of synthetic psychoactive substances (PAS) [1]. This article presents the results of a comparative study of two groups of synthetic PAS users — those with borderline mental disorders (BMD) and those without. Drawing on a dataset of 500 participants and subsequent correlation testing, we observed pronounced contrasts in how often psychopathological signs appear, how well individuals adapt socially, the prevalence of suicidal thoughts, and the strength of treatment motivation. These insights highlight the imperative for a holistic, cross-disciplinary strategy to both manage and prevent addictive behaviors in people living with borderline mental disorders.

Keywords: synthetic drugs, borderline personality disorders, addictive behavior, psychotic symptoms, correlation analysis

Over the past decade clinicians and public-health specialists in Kazakhstan have recorded a steady rise in the use of clandestinely produced synthetic stimulants such as α-PVP and mephedrone. Early reports suggest that people who meet DSM-5 criteria for borderline personality disorder (BPD) begin experimenting at a younger age, consume more frequently and suffer more pronounced social fallout than users without the disorder. To examine these differences, we surveyed 500 adults attending the Almaty City Narcological Centre, collecting data on age of first use, weekly intake, and the occurrence of mood, anxiety and psychotic symptoms with a structured interview adapted from the WHO ASSIST. We also documented work absenteeism, family conflict and contact with law-enforcement. Analysing these variables side by side should clarify how synthetic stimulants interact with the affective instability that typifies BPD and help frontline services - psychiatric clinics, narcological dispensaries and primary-care practices - shape more targeted prevention and treatment plans. These observations make it clear that piecemeal remedies will not suffice; an effective response must weave together psychiatric treatment, structured psychological interventions, social-service support, and community education so that medical, behavioral, and environmental factors are addressed in concert.

Materials and Methods

The present study employed a cross-sectional comparative design and was conducted over the period from January 2023 to December 2024 at the Almaty City Mental Health Center, Republic of Kazakhstan. The research protocol was reviewed and approved by the Ethics Committee of the Kazakh Medical University of Continuing Education (Protocol No. 02-23, dated March 12, 2023). All study procedures adhered to the ethical standards of the Declaration of Helsinki (2013 revision). The research was aimed at identifying and comparing the clinical, psychological, and social characteristics of individuals using synthetic psychoactive substances, with and without the presence of borderline personality disorders.

The total study sample comprised 500 adult participants aged 18 to 50 years. Respondents were recruited from among outpatients and inpatients who were receiving diagnostic, therapeutic, or rehabilitation services at the Mental Health Center during the study period. A purposive sampling strategy was used to ensure adequate representation of both clinical subgroups. Group I included 250 individuals diagnosed with borderline personality disorders according to the International Classification of Diseases, 10th Revision (ICD-10 codes F32–F39, F40–F48, and F60), while Group II comprised 250 respondents who reported a history of synthetic psychoactive substance use but had no psychiatric diagnosis corresponding to borderline disorders. Participation in the research was entirely voluntary, and all respondents provided written informed consent after receiving detailed information about the purpose, methods, and confidentiality conditions of the study.

Eligibility criteria required participants to be within the specified age range, to have a history of synthetic psychoactive substance use for at least six months, and to possess medical documentation confirming a diagnosis of substance dependence or a borderline mental disorder. Individuals experiencing acute intoxication, withdrawal, or psychotic decompensation at the time of data collection, as well as those with cognitive impairments preventing reliable self-reporting, were excluded. Respondents who declined participation or provided incomplete data were also excluded from the final analysis.

Data collection was conducted using a structured author-designed questionnaire, developed specifically for this study to examine the psychological and social aspects of synthetic psychoactive substance use among individuals with and without borderline personality disorders. The questionnaire was based on the analysis of clinical experience and previous sociological research in psychiatry and addiction medicine and was pre-tested on a pilot group to ensure clarity and reliability of responses. It contained sections addressing respondents' sociodemographic characteristics, clinical manifestations associated with substance use, and psychological and behavioral features relevant to borderline personality traits.

The questionnaire included questions about the type, duration, and frequency of psychoactive substance use, as well as the presence of emotional instability, anxiety, panic attacks, psychotic symptoms, suicidal ideation, and social adaptation difficulties. Additional items assessed family and social relationships, motivation for treatment, and perceived effectiveness of previous rehabilitation attempts. The survey was conducted in Russian, with questions formulated in clear and neutral language to minimize misinterpretation. Most items were closed-ended, allowing respondents to select one or more predefined options, while several questions permitted short written comments to capture qualitative nuances.

Each participant completed the questionnaire independently in a confidential setting under the supervision of a trained researcher. The average completion time was 20–25 minutes. After the survey, all forms were checked for completeness and accuracy. In total, 500 valid responses were included in the final statistical analysis.

To minimize reporting bias and ensure data accuracy, all surveys were administered in private consultation settings under the supervision of trained researchers who provided clarification when necessary but refrained from influencing participants' responses. All participants were informed of their right to withdraw from the study at any stage without any consequences for their treatment or ongoing therapy.

Statistical analysis was performed using IBM SPSS Statistics version 26. Descriptive statistics were used to summarize the socio-demographic and clinical characteristics of the sample, including mean values, standard deviations, and frequency distributions. To identify associations between the frequency of psychoactive substance use, the severity of withdrawal and dependence symptoms, affective and psychotic manifestations, and indicators of suicidal behavior, Spearman's rank correlation coefficient was applied. Differences between the two groups were analyzed using non-parametric methods (Mann–Whitney U test) for continuous variables and the chi-square (χ^2) test for categorical data. The level of statistical significance was set at $p < 0.05$.

Throughout the study, strict adherence to ethical research principles was maintained. Confidentiality of personal data was ensured by assigning anonymous identification codes to each participant and by storing all electronic and paper-based materials in secure locations accessible only to the research team. The findings were used exclusively for scientific purposes, and no identifying information was disclosed in any publication or presentation. The methodological approach adopted in this research allowed for a detailed comparative assessment of psychological and social determinants of synthetic psychoactive substance use, depending on the presence or absence of borderline personality pathology, thus ensuring both the scientific rigor and ethical integrity of the investigation.

Results

Drug addiction is accompanied by severe somatic consequences, including liver damage, cardiovascular diseases, and immunodeficiency conditions [13, 17, 20]. The analysis of the survey data from users of synthetic drugs without borderline personality disorders revealed that the predominant substances were synthetic cannabinoids (50%) and synthetic cathinones (30%). The analysis of the survey data revealed that the predominant substances were synthetic cannabinoids and synthetic cathinones (Figure 1).

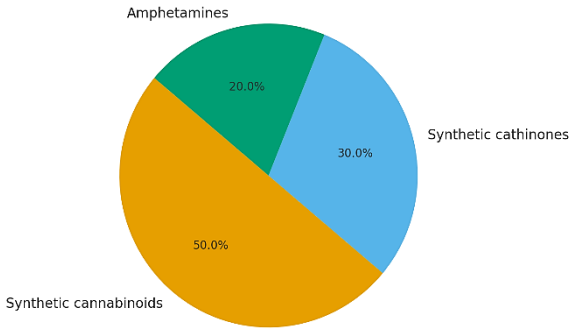


Figure 1. Distribution of Synthetic Psychoactive Substances

The most common reasons for initial use were curiosity (40%) and peer influence (35.2%), both of which can be viewed as negative motivational factors. These motives point to limited understanding of the risks involved and to poorly developed skills for resisting peer influence.

A vast majority of participants (80%) mentioned feelings of euphoria or relaxation after taking the drugs—sensations that can strongly reinforce repeated use and, in turn, elevate the likelihood of addiction.

Similarly, eight in ten respondents acknowledged an urge to consume the substances again, signalling that psychological dependence is taking hold and that stopping without help is exceptionally hard.

Frequent intake - reported by 60% of the sample as occurring several times a week or even daily—inevitably harms both mind and body, sharply raising the chance of entrenched addiction and secondary psychiatric problems.

Finally, the high rate of failed quit attempts (44.8%) reveals deficits in self-regulation and underscores the urgency of a comprehensive treatment programme that tackles psychological as well as social dimensions of use.

About one-half of the participants - roughly 50 percent- reported episodes of intrusive, anxious rumination ranging from occasional to almost constant. Such thoughts weigh heavily on psychological well - being and can pave the way for chronic anxiety conditions, underscoring the need to weave cognitive - behavioural techniques and structured anxiety-management modules into any full-scale rehabilitation plan.

Although psychotic features such as hallucinations and delusional ideas appeared in a smaller subgroup (close to 30 percent), their impact is profound: these symptoms erode mental health and markedly diminish quality of life. Even a minority showing such signs constitutes a serious clinical red flag. These manifestations require immediate medical intervention and long-term psychiatric care to prevent severe mental health deterioration.

Mood changes, including sudden shifts (40%), irritability (30%), and depression (20%), negatively affect respondents' social adaptation and personal functioning, confirming the impact of psychoactive substances on affective disorders. The presence of mood disturbances in a significant portion of respondents indicates serious psycho-emotional consequences of drug use. An important task is the early detection of such disorders and the provision of adequate psychological assistance aimed at improving emotional well-being and social integration. These findings are illustrated in Figure 2, which presents the prevalence of key psychological and psychiatric manifestations among respondents.

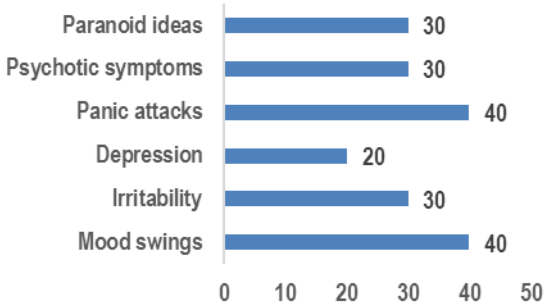


Figure 2. Prevalence of major psychological and psychiatric manifestations among synthetic PAS users (n = 500).

Drug addiction poses not only medical but also significant social consequences. The psychological aspects of addiction include the development of depressive and anxiety disorders, cognitive decline, and personality distortion [15]. Recent findings point squarely to psychosocial stress as a principal driver of substance dependence, reinforcing the case for robust prevention initiatives and prompt psychological aid [12]. Within our sample, six out of ten users admitted that their dosage crept upward over time - a trajectory that undermines both physical and mental health by accelerating tolerance and deepening addiction. Taken together, these insights argue strongly for proactive screening and ongoing follow-up of synthetic PAS consumers, ensuring that preventive and therapeutic support can be deployed without delay.

Ingesting psychoactive substances (PAS) on an empty stomach - a behavior acknowledged by 40 percent of participants - is particularly hazardous, because it amplifies each compound's toxicity within the body and hastens the pathway to dependency. These data highlight the urgency of comprehensive, ongoing, community-focused educational initiatives that alert users to such risks while advancing evidence-based harm-reduction practices.

Roughly four out of five participants - about 80 percent - described withdrawal discomfort ranging from mild unease to severe distress, a plainly harmful consequence. These symptoms usually point to a blend of physical and psychological dependence, and the literature consistently notes how hard it is to manage withdrawal without assistance. Reaching specialist services and evidence-based pharmacological support can greatly soften this phase and measurably raise the likelihood of lasting recovery.

Roughly two in five participants - around 40 percent - described experiencing panic episodes of differing intensity, a pattern that demonstrably erodes both quality of life and everyday social engagement. Panic phenomena linked to psychoactive-substance use greatly diminish a person's capacity to relate effectively to their surroundings and therefore demand focused therapeutic attention. If left unaddressed, such episodes can evolve into chronic anxiety and agoraphobic avoidance, further intensifying social withdrawal and narrowing the prospects for long-term recovery.

Memory and attention problems, reported by nearly 50% of respondents, also adversely affect their daily functioning, as well as their social and professional activity.

The expressed desire for self-harm among 30% of respondents indicates a pronounced level of emotional instability and despair associated with substance use.

Suicidal thoughts, although reported by 20% of respondents, are unequivocally a critical risk factor that necessitates active monitoring and timely psychological intervention, indicating a high risk of suicidal behavior.

Suicide attempts, recorded in 15% of respondents, underscore the detrimental impact of PAS use on mental health.

These findings are illustrated in Figure 3, which presents the distribution of self-harming urges, suicidal thoughts, and suicide attempts among respondents.

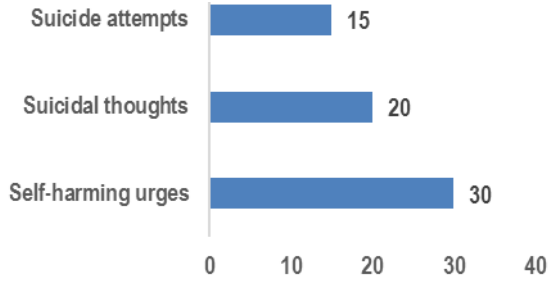


Figure 3. Indicators of self-harming and suicidal behavior among respondents (n = 500).

Feelings of persecution or paranoid symptoms, though less frequent (around 30%), are alarming indicators that negatively affect psychological well-being.

The nature of family relationships is assessed as positive by the majority of respondents (50%), which is a favorable factor contributing to successful rehabilitation and social reintegration. However, the presence of conflictual or absent family relationships among a significant portion (20%) highlights the need for family therapy and social support to restore and strengthen family bonds.

Relationships with friends are also predominantly positive (60%), representing an important source of social

support. Nevertheless, superficial or conflict-laden friendships, as well as the absence of close social connections among the remaining respondents, are negative indicators that require targeted efforts to foster a supportive social environment.

The pronounced call for both psychological counselling and pharmacological support among participants underscores the value of a truly integrated model of addiction care - one capable of meeting the many-sided needs of those grappling with substance dependence. Yet the data show that only about 40 percent have actually reached out to addiction clinicians or mental-health professionals, hinting at either limited service accessibility or lingering scepticism toward formal treatment. Encouragingly, half of the respondents expressed a desire to stop using drugs, revealing a reservoir of motivation that well-designed interventions could actively cultivate.

The correlation analysis based on the survey results revealed several significant relationships and trends. Spearman's method was used to conduct the correlation analysis. It was found that the frequency of psychoactive substance use is positively correlated with the severity of addiction symptoms. Respondents with a higher frequency of use more often reported intense cravings, severe discomfort during withdrawal attempts, and a need to increase dosage over time.

Volkow N.D. et al. [22] note that frequent use intensifies changes in the brain's neurotransmitter systems, which in turn exacerbates addiction symptoms. *Petrov V.S.* [16] emphasizes that regular consumption of synthetic drugs accelerates the development of dependence, increasing both cravings and withdrawal-related discomfort.

A significant association was found between the frequency of substance use and the severity of psychiatric symptoms, such as sudden mood swings, irritability, and depression. An increase in dosage was also linked to a higher frequency of psychotic symptoms, including hallucinations and paranoid ideation. *Kuzmin A. et al.* [8] report that prolonged use of synthetic drugs significantly increases the risk of psychotic episodes, as well as persistent changes in the emotional domain.

Table 1.

Spearman's correlation coefficients.

Variables correlated	Spearman's r	p-value	Interpretation
Frequency of use ↔ Severity of dependence	0.84	<0.01	Strong positive correlation
Frequency of use ↔ Psychiatric symptoms (mood, irritability, depression)	0.72	<0.01	Strong positive correlation
Dosage increase ↔ Psychotic symptoms	0.68	<0.05	Moderate positive correlation
Psychotic symptoms ↔ Suicide attempts	0.90	<0.01	Very strong correlation
Mood dysregulation ↔ Suicidal ideation	0.77	<0.01	Strong correlation
Frequency of use ↔ Cognitive impairment	0.65	<0.05	Moderate correlation

Particular attention was paid to the study of suicide risk. The analysis revealed a strong correlation between the severity of psychiatric and psychotic manifestations and the frequency of suicidal thoughts and suicide attempts among respondents. Nelson et al. [12] emphasize that mental disorders and psychoactive substance abuse are key risk factors for suicidal behavior.

Furthermore, a correlation was identified between the regular use of psychoactive substances and a decline in cognitive functioning, particularly memory and attention impairment.

In recent years, treatment methods for substance dependence have expanded significantly, including pharmacotherapy, psychotherapeutic interventions, and rehabilitation programs [4]. The effectiveness of treatment largely depends on a comprehensive approach that integrates medical management of withdrawal symptoms, cognitive-behavioral therapy, and social rehabilitation [10].

The highest risks to mental and physical health were observed among respondents with a high frequency of use, pronounced symptoms of dependence, and the need for gradual dose escalation. At the same time, respondents in older age groups demonstrated a greater degree of social stability, which may serve as a protective factor against severe manifestations of addiction.

These findings highlight the critical need for an integrated treatment approach that combines psychological support, pharmacological therapy, and social assistance, aimed at mitigating the adverse effects of synthetic drug use.

The modern consumer of synthetic psychoactive substances (PAS) with borderline personality disorders is represented by an approximately equal gender distribution: 52% male (130 individuals) and 48% female (120 individuals). The age category is predominantly young, with a majority between the ages of 18 and 25 (44%), followed by those aged 26 to 35 (36%). Individuals over the age of 35 are less commonly represented. Most respondents reported having a secondary (48%) or vocational education (32%), while only 20% had attained higher education. The employment rate among participants was low: approximately half were unemployed (48%), 36% were employed, and 16% were still in education.

The predominance of males (52%) is notable; however, the significant proportion of females (48%) points to a narrowing gender gap in the use of synthetic PAS and the associated psychopathology. Marital status indicates a low level of social adaptation: the majority of respondents (68%) are single or not in a formal relationship. Family relationships are predominantly formal or conflictual (64%), which may act as a risk factor for further social maladjustment and a barrier to successful rehabilitation. Drug use often leads to family breakdown, loss of employability, and social marginalization [9, 25]. Several studies have also identified a strong correlation between substance dependence and criminal activity, particularly among adolescents and young adults [5, 6, 23].

The average user of synthetic drugs with borderline personality disorders has a history of use spanning 3 to 5 years and primarily consumes synthetic cannabinoids

(52%), synthetic cathinones (36%), and amphetamines (24%). A significant proportion of respondents (around 88%) use drugs regularly, with the vast majority consuming them daily or several times per week.

The most common motive for using synthetic PAS is the desire to experience euphoria and joy (44%), while a portion of users (20%) report feelings of anxiety and panic following use. This highlights the complexity of the users' psycho-emotional state and the ambiguity of the perceived effects of the substances.

Initial attempts to stop using drugs are rarely successful: the majority (56%) report relapses despite undergoing treatment. Only 12% of respondents have managed to abstain from use for an extended period. Additionally, more than half (60%) experience moderate to severe discomfort when attempting to quit, indicating the presence of a pronounced withdrawal syndrome.

Among psychopathological manifestations, emotional disturbances are the most prevalent: 48% of respondents reported sudden mood swings, 32% experienced irritability, and 16% suffered from depressive states. Psychotic symptoms were also prominent, with 40% of respondents reporting psychotic episodes of varying frequency (from occasional to regular occurrences).

Particularly alarming is the high prevalence of suicidal tendencies: 44% of respondents reported having attempted suicide (24% once, 20% multiple times), and approximately 56% regularly experience self-harming urges.

Feelings of persecution (76%) and panic attacks (84%) were also frequently reported, indicating pronounced anxiety-paranoid and panic disorders associated with the use of synthetic drugs.

Approximately half of the respondents (48%) had previously sought help; however, in most cases (32%), treatment was reported as ineffective. Notably, nearly half (48%) had never sought specialized assistance at all, reflecting either limited access to services or a lack of trust in mental health systems.

Less than half of the participants (48%) expressed a desire to stop using drugs, while a significant portion remained undecided (24%) or were not ready to quit (28%), complicating prospects for rehabilitation and social reintegration in this patient population.

The correlation matrix analysis of the survey results among respondents who use synthetic drugs and have borderline personality disorders revealed several important relationships. A strong positive correlation was identified between age at first use and frequency of use ($r = 0.87$).

This may indicate that the earlier an individual begins using synthetic drugs, the more frequently and intensely they tend to consume them. A very strong positive linkage emerged between the presence of psychotic features and actual suicide attempts ($r = 0.90$), while mood dysregulation showed a sizable association with suicidal ideation ($r = 0.77$). In light of these results - derived from an in-depth survey of synthetic PAS users meeting criteria for borderline personality disorder - there is a compelling rationale for conducting a head-to-head comparison. Such an analysis would clarify both the distinctive and overlapping psychopathological, social, and clinical profiles of individuals who do and do not have BPD, ultimately informing finely tuned prevention and treatment strategies for each subgroup.

Nearly nine in ten participants who met diagnostic criteria for borderline personality disorder (BPD) - about 88 percent - described intense emotional turbulence, including irritability, dramatic mood swings, and depressive spells; by contrast, only 41 percent of those without BPD reported similar difficulties. This stark gap illustrates how powerfully BPD magnifies affective instability and reinforces the case for sustained, high-intensity psychological and psychotherapeutic support.

The pattern is echoed in psychotic symptoms. Roughly two-fifths of the BPD group (40 percent) admitted to hallucinations or delusional ideas, whereas such experiences were noted by just 15 percent of the non-BPD cohort. These figures argue strongly for integrated care plans that blend appropriate pharmacotherapy with targeted psychotherapy to curb psychosis and restore emotional equilibrium.

Among individuals diagnosed with borderline personality disorder (BPD), panic episodes are reported with striking frequency - 84 percent - compared with just 18 percent in those without the diagnosis. This stark disparity points to severe anxiety-phobic disturbances intertwined with emotional volatility and social apprehension. It strongly supports the proactive roll-out of cognitive-behavioural therapy (CBT) and dialectical behaviour therapy (DBT) programs.

In the group living with borderline personality disorder, close to three-quarters (72 %) acknowledged thoughts of suicide, while the rate in the comparison group barely reached 9 %. This stark gulf signals a sharply elevated threat of self-harm for individuals with BPD and demands swift preventive action alongside vigilant clinical surveillance for this high-risk population.

Criminal behavior is more prevalent among patients with borderline personality disorders (48%) compared to those without BPD (24%). This highlights the severity of social maladaptation in the BPD group and underscores the need for the development of specialized programs focused on social reintegration, legal support, and the prevention of criminal behavior.

Nearly two-thirds of participants living with BPD - around 64 percent - described their family ties as conflicted or altogether absent, versus only 36 percent in the comparison cohort. This stark imbalance underscores the urgency of weaving robust family involvement, structured counselling, and family-centred rehabilitation schemes into any truly comprehensive care plan.

Therapeutic drive sits at a middling level in both cohorts - about 48 percent of those with BPD and 44 percent of those without report willingness to pursue care. Even so, ambivalence and hesitation surface more often among the BPD participants, suggesting heavier dependence and a thinner layer of self-awareness. Such dynamics complicate treatment and point to the need for bespoke motivational interviewing and stepped-up engagement tactics.

Therapeutic outcomes split sharply between the two cohorts. Roughly 36 percent of participants without BPD attained a moderate level of benefit, whereas efficacy in the BPD subgroup dropped to just 20 percent—an alarmingly low figure. This highlights the urgent need to revise therapeutic approaches by increasing the duration, intensity, and multidimensionality of treatment for patients with borderline personality disorders.

Discussion

Our comparative findings reinforce current evidence that the co-occurrence of borderline personality disorder and substance use disorders reflects overlapping disturbances in emotion regulation, stress reactivity, and reward processing, which together amplify impulsive drug use, relapse, and suicidality in dual-diagnosis patients. Contemporary comprehensive reviews further underscore the broad comorbidity burden in BPD - spanning mood, anxiety, psychotic-spectrum, and substance-related problems - consistent with the more severe psychiatric load, social maladaptation, and cognitive difficulties we observed in the BPD subgroup [10].

The substance profile in our cohort (predominance of synthetic cannabinoids and cathinones) aligns with recent toxicological syntheses. Synthetic cannabinoids are increasingly linked to acute anxiety, psychosis, and measurable decrements in attention and memory - effects that plausibly intensify affective lability and psychotic features among individuals with BPD [11]. Synthetic cathinones, meanwhile, are now the second most frequently seized class of new psychoactive substances; their neurotoxic potential (neuroinflammation, monoaminergic dysregulation) and sympathomimetic toxicity contribute to clinical instability and relapse risk in this population [2]. These mechanistic liabilities help explain the stronger symptom load and heightened clinical risk we documented in the BPD group [2, 11].

The external risk environment is also evolving. Early-warning surveillance in 2025 points to the rapid global emergence of high-potency nitazene opioids, often encountered as adulterants, which complicates clinical triage and magnifies overdose risk for people using synthetic stimulants or cannabinoids [19]. Integrating such early-warning intelligence into assessment, patient education, and relapse-prevention plans is therefore essential for dual-diagnosis services [21].

Therapeutically, our observation that standard addiction programs yield limited benefit in the BPD subgroup converges with current efficacy syntheses: dialectical behavior therapy shows the strongest, most consistent evidence for reducing self-harm, suicidal ideation, and service utilization in BPD, with growing support for SUD-focused adaptations (e.g., dialectical abstinence, “clear mind,” contingency strategies). These data argue for integrated, DBT-informed care pathways delivered by joint addiction–psychiatry teams, supplemented by pharmacological support and family-inclusive interventions, to address the multi-determinant risk profile evident in our sample.

Limitations and future directions. The cross-sectional design limits causal inference, and self-report may underdetect polysubstance exposure. Prospective studies should track dynamic couplings among emotion dysregulation, exposure to high-potency synthetics, and suicidality, pairing repeated neurocognitive measures with toxicology. Pragmatic trials comparing DBT-informed integrated care versus standard addiction treatment in BPD+SUD - stratified by synthetic cannabinoid/cathinone exposure - would directly test the clinical propositions emerging here.

Conclusion

Individuals with borderline personality disorders (BPD) who use synthetic psychoactive substances are significantly more vulnerable to severe forms of addiction and complex psychopathological manifestations. The high prevalence of suicide attempts, pronounced anxiety-depressive and psychotic symptoms, and low responsiveness to standard treatments underscores the urgent need for a comprehensive care model. This model should combine pharmacotherapy, evidence-based psychotherapy -including dialectical behavior therapy (DBT) and cognitive-behavioral therapy (CBT) - as well as structured social rehabilitation to address the multifaceted needs of this high-risk population.

Future efforts to address this issue must include the expansion of access to specialized treatment and rehabilitation centers, the training of qualified professionals in psychotherapy and social work, and the development of preventive programs aimed at early identification of high-risk groups.

An important area of focus is increasing public awareness about the consequences of synthetic PAS use and involving patients’ close social networks in the rehabilitation process.

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ASSESSING RETINOBLASTOMA AWARENESS ACROSS PRIMARY HEALTH CARE PHYSICIANS

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Abstract

Objective. To assess the level of awareness of retinoblastoma among primary health care (PHC) physicians, identify areas of insufficient knowledge, compare the awareness of general practitioners (GPs) and pediatricians, and determine strategies to improve awareness.

Materials and methods. A cross-sectional online survey was conducted from January to February 2025. The study involved 90 PHC physicians (49 GPs and 41 pediatricians). The questionnaire included 18 questions on clinical suspicion, diagnosis, referral pathways, and treatment of retinoblastoma. Statistical analysis was performed using SPSS software.

Results. Most respondents were aware of retinoblastoma (81.6% of GPs and 92.7% of pediatricians). However, clinical experience with the disease was limited (20.4% of GPs and 31.7% of pediatricians). Pediatricians were more likely to encounter suspected retinoblastoma cases (51.2% vs. 26.5%, p=0.024) and refer children with a family history of the disease to an ophthalmologist (87.8% vs. 69.4%, p=0.032). The "white pupil" reflex was known to 90.2% of pediatricians and 63.3% of GPs (p=0.003). Only 14.3% of GPs and 34.7% of pediatricians were aware of modern organ-sparing treatments (p=0.027).

Conclusions. The study revealed an insufficient level of awareness of retinoblastoma among PHC physicians, particularly among GPs. To improve early diagnosis of retinoblastoma, it is recommended to implement mandatory continuing medical education courses for physicians, with an emphasis on rare pediatric oncological diseases. Additionally, public awareness campaigns and media outreach are recommended to increase clinical suspicion. These measures also contribute to achieving Sustainable Development Goal 3 (SDG 3), which aims to reduce child mortality and ensure universal health.

Keywords: *retinoblastoma, SDG 3, early diagnosis, primary health care, awareness, pediatricians, general practitioners.*

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Резюме

ОЦЕНКА ИНФОРМИРОВАННОСТИ ВРАЧЕЙ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ О РЕТИНОБЛАСТОМЕ

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Цель. Оценить уровень информированности врачей ПМСП о ретинобластоме, выявить области недостаточной осведомленности, сравнить осведомленность врачей общей практики (ВОП) и педиатров, а также определить стратегии повышения осведомленности.

Материалы и методы. Проведено поперечное исследование в форме онлайн-опроса с января по февраль 2025 года. Участвовали 90 врачей ПМСП (49 ВОП и 41 педиатр). Опросник включал 18 вопросов по клинической настороженности, диагностике, маршрутизации и лечению ретинобластомы. Статистическая обработка осуществлялась в программе SPSS.

Результаты. Большинство респондентов знали о ретинобластоме (81,6% ВОП и 92,7% педиатров). Однако клинический опыт был ограничен (20,4% ВОП и 31,7% педиатров). Педиатры чаще сталкивались с подозрениями на ретинобластому (51,2% против 26,5%, p=0,024) и направляли детей с отягощенным анамнезом к офтальмологу

(87,8% против 69,4%, p-0,032). Симптом «белого свечения» зрачка был известен 90,2% педиатров и 63,3% ВОП (p=0,003). Только 14,3% ВОП и 34,7% педиатров знали о современных органосохраняющих методах лечения (p=0,027).

Выводы. Выявлен недостаточный уровень информированности о ретинобластоме среди врачей ПМСП, особенно среди ВОП. В целях улучшения ранней диагностики ретинобластомы рекомендуется внедрить обязательные курсы повышения квалификации для врачей с акцентом на редкие онкологические заболевания у детей. Дополнительно рекомендуется усилить информационную работу через просветительские кампании и медиа для повышения настороженности. Эти меры также способствуют достижению Цели устойчивого развития 3 (ЦУР 3), направленной на снижение детской смертности и обеспечение всеобщего здоровья.

Ключевые слова: *ретинобластома, ЦУР 3, ранняя диагностика, первичная медико-санитарная помощь, информированность, педиатры, врачи общей практики.*

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Түйіндеме

БАСТАПҚЫ МЕДИЦИНАЛЫҚ-САНИТАРИЯЛЫҚ КӨМЕК ДӘРІГЕРЛЕРІНІҢ РЕТИНОБЛАСТОМА ЖӨНІНДЕГІ ХАБАРДАРЛЫҒЫН 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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Background

Retinoblastoma is a highly aggressive malignant neoplasm of the retina that primarily affects children under the age of 5. Approximately 8,000 new cases are diagnosed globally each year [7]. The incidence and survival rates vary depending on the region, the quality of healthcare, and the availability of early diagnosis [10, 15, 18, 22, 23]. Early diagnostic procedures are crucial for successful treatment and improving patient survival. This objective aligns with the United Nations Sustainable Development Goal 3 (SDG 3), which includes a focus on reducing preventable mortality in children under 5 through timely access to effective healthcare. The age at diagnosis is a key prognostic factor: children diagnosed with retinoblastoma before the age of one have better survival rates compared to older children [5, 13].

However, late diagnosis remains a serious problem, especially in countries with insufficient medical awareness and limited access to ophthalmological care [9]. In Central Asian countries, for example, advanced stages (T3 and T4) accounted for 60% of cases [12]. In the Republic of Kazakhstan, advanced stages made up 86% of cases in the early 2000s [3].

Primary healthcare (PHC) physicians play a key role in the early detection of retinoblastoma, as they are often the first to see these patients. Their level of awareness of the symptoms and diagnostic methods can significantly influence the timely referral of patients to specialists, and consequently, the chances of preserving the child's vision and life [14]. Research shows that a lack of knowledge among PHC physicians is one of the main barriers to early detection [20]. Specifically, the importance of skills in performing pediatric eye exams and taking a patient history is highlighted, as early detection can lead to up to 95% survival [19]. Studies emphasize that PHC physicians are key figures in the retinoblastoma diagnostic process and should be trained to recognize symptoms such as leukocoria and strabismus [6]. Improving the awareness of retinoblastoma signs among PHC physicians is a necessary condition for early diagnosis and effective treatment.

The objective of this study is to assess the level of awareness of retinoblastoma among PHC physicians, identify areas of insufficient knowledge, compare the awareness of general practitioners (GPs) and pediatricians, and determine strategies to improve awareness. Ultimately, these efforts should contribute to early diagnosis and improved treatment outcomes for patients.

Materials and methods

A cross-sectional survey was conducted among primary health care (PHC) physicians from January to February 2025. General practitioners (GPs) and pediatricians participated in the study. Participants were recruited through professional groups on messenger and social media.

The questionnaire was developed by the research team, peer-reviewed by specialists with experience working with retinoblastoma patients, and approved by the local ethics committee of the Asfendiyarov Kazakh National Medical University (IRB00011496), protocol No. 21 (157) of November 1, 2024.

The questionnaire included 18 questions designed for a comprehensive assessment of PHC physicians' awareness of retinoblastoma. It contained both general questions about retinoblastoma awareness and more specific questions about clinical experience, suspicion, and knowledge of disease diagnosis and treatment. Specifically, the survey included the following sections:

*General Awareness***:** Knowledge of retinoblastoma as a malignant tumor of the retina, its hereditary nature, understanding of the seriousness of the disease, and the level of confidence in their own knowledge.

*Practical Experience***:** Experience with retinoblastoma patients in clinical practice, frequency of encountering suspected cases, and management of children from families with a history of the disease.

*Clinical Suspicion***:** Respondents' knowledge of retinoblastoma symptoms such as leukocoria (white pupil reflex), strabismus; understanding that the glow can be noticed in a flash photograph; and the practice of performing ophthalmoscopy and referring for additional examinations.

Knowledge of Patient Management and Referral: Information about modern organ-sparing treatments and patient referral pathways when retinoblastoma is suspected.

The survey was conducted using a Google Form in both Kazakh and Russian languages. Participation in the study was voluntary and anonymous. Informed consent was placed at the beginning of the questionnaire, and completing the survey was considered confirmation of consent to participate. A total of 115 questionnaires were registered, of which 90 were included in the analysis as 25 contained incomplete data.

Statistical analysis was performed using SPSS software. Descriptive statistics and comparative analysis methods were used to evaluate the differences in retinoblastoma knowledge between physician groups (GPs and pediatricians). The significance of differences was determined using the χ^2 test for categorical variables and Student's t-test for quantitative data. A p-value of <0.05 was considered statistically significant.

Results

Table 1 presents the sociodemographic characteristics of the respondents. The study included 49 GPs and 41 pediatricians. Most respondents were female (91.8% of GPs and 85.4% of pediatricians). The age group under 40 predominated in both samples (69.4% of GPs and 61% of pediatricians). 42.9% of GPs and 61% of pediatricians had more than 10 years of work experience, while more GPs had less than 5 years of experience (22.4% vs. 9.8% of pediatricians). GPs were almost evenly distributed between urban and rural areas (51% and 49%), while most pediatricians worked in cities (70.7%).

Table 2 provides a comparative analysis of the survey results regarding GPs' and pediatricians' awareness of retinoblastoma.

General Awareness. The study shows that the vast majority of respondents, regardless of their specialization, are aware of retinoblastoma as a malignant neoplasm of the retina in children: 81.6% of GPs and 92.7% of pediatricians ($p>0.05$).

Regarding the level of confidence in their knowledge about retinoblastoma (on a scale of 1 to 5), both groups showed moderate levels of confidence. The most common answer among GPs was a score of "3" (38.3%), indicating

an average level of awareness. However, more than a quarter of GPs (26.5%) admitted to being completely unsure of their knowledge (a score of "1"), which is concerning. The distribution of answers among pediatricians was more balanced: a score of "3" was also the most common (41.5%), but the proportion of those who chose a low level of confidence ("1") was significantly smaller, at only 7.3%. At the same time, 34.1% of pediatricians rated their confidence level as "2" ($p>0.05$).

Table 1.

Socio-demographic characteristics of respondents.

Characteristic	Value	GPs (N =49)		Pediatricians (N =41)	
		N	%	N	%
Age	≤ 40 years	34	69,4	25	61
	41–60 years	13	26,5	14	34,1
	> 60 years	2	4,1	2	4,9
Sex	Male	4	8,2	6	14,6
	Female	45	91,8	35	85,4
Work experience	< 5 years	11	22,4	4	9,8
	5–10 years	17	34,7	12	29,3
	> 10 years	21	42,9	25	61
Place of residence	Urban	25	51	29	70,7
	Rural	24	49	12	29,3
Place of work	Hospital	1	2	12	29,3
	Polyclinic	43	87,8	21	51,2
	Private clinic	5	10,2	8	19,5

Table 2.

Awareness, clinical experience, and management tactics of retinoblastoma among general practitioners and pediatricians.

Question / Response	GPs (N=49)		Pediatricians (N=41)		p value
	N	%	N	%	
1	2	3	4	5	6
Do you know about the disease retinoblastoma — a malignant tumor of the retina in children?					
Yes	40	81,6	38	92,7	p>0,05
No	9	18,4	3	7,3	
Have you encountered retinoblastoma during your practice or studies?					
Yes	10	20,4	13	31,7	p>0,05
No	39	79,6	28	68,3	
How often do you encounter suspected cases of retinoblastoma in your practice?					
Rarely	13	26,5	21	51,2	p=0,024
Never	36	73,5	19	46,3	
Often	0	0	1	2,4	
Do you consider retinoblastoma a serious pediatric condition?					
Yes	44	89,8	40	97,6	p>0,05
No	1	2	1	2,4	
Unsure	4	8,2	0	0	
How confident are you in your knowledge of retinoblastoma? (1 = not confident, 5 = fully confident)					
1	13	26,5	3	7,3	p>0,05
2	7	14,3	14	34,1	
3	19	38,3	17	41,5	
4	7	14,3	4	9,8	
5	3	6,1	3	7,3	
Do you know that retinoblastoma is a hereditary disease?					
Yes	24	49	24	58,5	p>0,05
No	25	51	17	41,5	
Do you refer to an ophthalmologist a child born in a family with a history of retinoblastoma (parents, siblings)?					
Yes	34	69,4	36	87,8	p=0,032
No	15	30,6	5	12,2	
Do you think you have sufficient information about modern diagnostic and treatment methods for retinoblastoma?					
Yes	9	18,4	10	24,4	p>0,05
No	19	38,8	14	34,1	
Rather yes	5	10,2	9	22,0	
Rather no	16	32,7	8	19,5	

Continuation of Table 2.

1	2	3	4	5	6
How often do you examine a child born in a family with retinoblastoma?					
Once a month	5	10,2	6	14,6	p>0,05
Once every 3 months	7	14,3	10	24,4	
Once every 6 months	4	8,2	2	4,9	
Once a year	6	12,2	3	7,3	
When symptomatic	16	32,7	12	29,3	
Not at all	11	22,4	8	19,5	
Which signs of retinoblastoma do you know?					
Leukocoria	30	61,2	37	90,2	p>0,05
Strabismus	17	34,7	13	31,7	
Exophthalmos	3	6,1	9	21,9	
Others	17	34,7	4	9,8	
Have you heard of the retinoblastoma symptom “white pupillary reflex”?					
Yes	31	63,3	37	90,2	p=0,003
No	18	33,7	4	9,8	
Do you know that strabismus can be a symptom of retinoblastoma?					
Yes	24	49	27	65,9	p>0,05
No	25	51	14	34,1	
Do you perform wide-pupil ophthalmoscopy in all children with strabismus?					
Yes	8	16,3	13	31,7	p>0,05
No	41	83,7	28	68,3	
Do you know that a pupillary reflex can be noticed in flash photography?					
Yes	27	55,1	31	75,6	p>0,05
No	22	44,9	10	24,4	
Do you refer for ocular ultrasound in suspected retinoblastoma?					
Yes	29	59,2	32	78,0	p>0,05
No	20	40,8	9	22,0	
Do you refer for MRI or CT of the brain in suspected retinoblastoma?					
Yes	30	61,2	27	65,9	p>0,05
No	19	38,8	14	34,1	
Are you familiar with modern organ-preserving methods for retinoblastoma treatment?					
Yes	7	14,3	14	34,1	p=0,027
No	42	85,7	27	65,9	
Where do you refer patients in suspected retinoblastoma?					
NCPDCH (National Center for Maternal and Child Health)	6	12,2	3	7,3	p>0,05
KazRIEB (Kazakh Research Institute of Eye Diseases)	27	55,1	31	75,6	
Oncologist	9	18,4	6	14,6	
Other	7	14,3	1	2,4	

The analysis of knowledge regarding the hereditary nature of the disease showed that this aspect remains insufficiently known in both professional groups: 49% of GPs and 58.5% of pediatricians (p>0.05). However, in practice, pediatricians are more likely than GPs to refer children from families with a history of retinoblastoma to an ophthalmologist (87.8% vs. 69.4%, p=0.032), which can be explained by greater clinical suspicion among pediatricians.

Regarding confidence in their knowledge of modern diagnostic and treatment methods for retinoblastoma, both groups demonstrated low confidence: over 70% of GPs and over 50% of pediatricians (p>0.05). This confirms the need for regular knowledge updates and specialized training.

Practical Experience. Clinical experience with retinoblastoma patients was limited. Only 20.4% of GPs and 31.7% of pediatricians reported such cases in their professional practice (p>0.05), which highlights the rarity of the disease and the potential difficulty of its timely detection. It is interesting to note that the frequency of retinoblastoma suspicion in daily practice differed significantly between the two groups. Among pediatricians, 51.2% noted that they periodically encounter suspicious symptoms, while among GPs, this figure was 26.5% (p=0.024). This statistically significant difference may be due to better awareness of pediatric eye disease symptoms among pediatricians. At the same time, the vast majority of physicians recognize the seriousness of this pathology (89.8% and 97.6%, p>0.05).

Clinical Suspicion. The retinoblastoma symptom of leukocoria or the "white pupil" reflex, which is one of the key signs of retinoblastoma, is more known to pediatricians (90.2%) than to GPs (63.3%) (p=0.003), a statistically significant difference. Awareness of strabismus as a possible symptom of retinoblastoma is lower in both groups but higher among pediatricians (49% of GPs vs. 65.9% of pediatricians, p>0.05), and also requires improvement. Knowledge of the possibility of detecting leukocoria with a flash photograph was also higher among pediatricians (75.6%) compared to GPs (55.2%), although the difference was not statistically significant (p>0.05).

Knowledge of Patient Management and Referral. In cases of suspected retinoblastoma, the primary diagnostic referrals are eye ultrasound and brain MRI/CT. These methods are recognized as fundamental in the diagnostic algorithm. The majority of physicians in both specialties refer for these types of examinations when retinoblastoma is suspected, but the percentages are higher among pediatricians. 78% of pediatricians and 59.2% of GPs refer for eye ultrasound ($p>0.05$), and 65.9% of pediatricians and 61.2% of GPs refer for brain MRI/CT ($p>0.05$), which may confirm better knowledge of retinoblastoma diagnostics among pediatricians.

The question regarding awareness of modern organ-sparing treatments for retinoblastoma is particularly noteworthy. A generally low level of awareness was found, which is lower among GPs than among pediatricians (14.3% and 34.1%, respectively, $p=0.027$), indicating a serious knowledge gap, especially among general practitioners.

An analysis of preferred specialists for referral showed that 64% choose the Kazakh Research Institute of Eye Diseases as the priority institution, 10% choose the Scientific Center for Pediatrics and Pediatric Surgery, 17% choose an oncologist, and 9% choose other options ($p>0.05$)

Discussion

This study reveals the level of awareness of retinoblastoma, a malignant retinal tumor primarily affecting young children, among primary healthcare (PHC) physicians. It is crucial to emphasize that GPs and pediatricians are often the first to encounter patients exhibiting initial signs of the disease. Therefore, their knowledge of early retinoblastoma symptoms plays a pivotal role in timely detection. With sufficient knowledge and clinical suspicion among PHC physicians, it is possible to significantly increase the rate of early referrals to an ophthalmologist and, consequently, improve the disease prognosis.

Our research indicates that a significant portion of physicians struggle to recognize key symptoms and determine the appropriate next steps for patient management. This is a serious concern, as timely diagnosis and referral to an ophthalmologist are critical at this stage. These difficulties are consistent with other studies showing low awareness of retinoblastoma and other rare diseases among physicians in many countries [8, 24].

The experience of countries with high retinoblastoma diagnosis rates demonstrates that comprehensive strategies aimed at improving physician awareness and the availability of early screening can significantly enhance treatment outcomes. Educational programs, especially when combined with telemedicine, have proven effective. For example, a centralized diagnosis and remote consultation program in Jordan substantially reduced mortality and increased eye preservation rates in children with retinoblastoma [24]. Similarly, the implementation of national guidelines for retinoblastoma diagnosis in the UK, which included mandatory red reflex testing during pediatric examinations, significantly reduced the proportion of cases detected at late stages [11]. Furthermore, the integration of digital technologies opens new possibilities for telemedicine screening and patient monitoring in areas with limited access to ophthalmologists, expanding population coverage and accelerating the diagnostic process [25].

A key finding of our study is the low level of knowledge among surveyed physicians regarding modern retinoblastoma treatment methods. This is a significant concern, given that treatment approaches have evolved considerably. While enucleation was previously the standard of care in most cases, indications for this radical procedure have narrowed. The priority now is on organ-sparing methods that aim to preserve not only the eye but also the patient's vision. In Kazakhstan, methods such as intra-arterial chemotherapy, laser transpupillary thermotherapy, cryotherapy, and intravitreal chemotherapy have been successfully implemented [1, 2]. Modern research confirms the high efficacy of these methods, with intra-arterial chemotherapy achieving over 95% eye preservation [4].

The low awareness of modern treatment approaches among PHC physicians points to a serious gap in the continuous medical education system. Updating educational programs, integrating current clinical guidelines, and conducting targeted training on contemporary retinoblastoma diagnostics and treatment are essential steps to improve the situation. This can significantly improve patient outcomes through timely referral to specialized care.

Another key finding was that pediatricians demonstrated better awareness of retinoblastoma compared to general practitioners. In the past, Kazakhstan reformed its medical education system by closing pediatric faculties, which led to a reduction in specialists with a focused background in childhood diseases. Studies show that children initially examined by pediatricians receive an oncology diagnosis significantly faster than those seen by general practitioners [21].

This is linked to a pediatrician's specialized knowledge and experience with children, whereas GPs are generally less familiar with the age-specific clinical manifestations of pediatric tumors, which can lead to diagnostic delays [17].

The closure of pediatric faculties may have negatively impacted the early diagnosis and treatment of rare childhood diseases, including retinoblastoma. Restoring specialized pediatrician training appears to be a justified step to improve the quality of medical care for children.

The study's limitations include a low response rate from some regions of Kazakhstan, which may affect the representativeness of the sample and limit the generalizability of the results. Specifically, the insufficient number of responses from certain regions prevented a full comparative analysis of physician awareness based on geography, and consequently, the identification of regional differences in knowledge of symptoms, diagnosis, and treatment approaches for retinoblastoma.

Furthermore, the study was based solely on a survey, which carries the risk of subjective assessments and socially desirable responses. Surveys also do not allow for the evaluation of a physician's practical skills or their actual behavior when faced with a patient with suspected retinoblastoma.

Future research could focus on increasing the survey's reach and ensuring a more uniform distribution across regions. Another promising direction is to correlate

knowledge levels with actual patient clinical outcomes and to evaluate the effectiveness of educational interventions and reforms in the medical education system.

Conclusion

The findings of this study confirm that the level of awareness of retinoblastoma among primary healthcare (PHC) physicians remains insufficient, both in recognizing early symptoms and in knowledge of modern treatment methods. This represents a significant barrier to the timely diagnosis of a disease that is critically important for preserving a child's vision and life. The comparative analysis also showed that pediatricians are significantly better informed about retinoblastoma than general practitioners, which highlights the importance of specialized training in pediatrics.

Given the identified challenges, it is advisable to revise the educational programs for continuing medical education courses for PHC physicians to include topics on retinoblastoma. Special attention should also be given to the training of undergraduate and postgraduate students, by strengthening modules on rare oncological diseases and restoring specialized pediatric training.

Furthermore, an important strategy is to intensify public awareness campaigns. This can be achieved through publications in non-medical media, appearances in mass media, social networks, and educational campaigns during International Retinoblastoma Awareness Week.

These comprehensive measures, we believe, are capable of significantly improving the diagnosis and timely treatment of retinoblastoma, reducing the number of advanced cases, and consequently, decreasing the rates of disability and mortality among children. These efforts will contribute to achieving SDG 3, which aims to reduce preventable child mortality and ensure universal health and well-being.

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LONG-TERM RESULTS AND QUALITY OF LIFE AFTER SURGICAL TREATMENT OF DIFFUSE TOXIC GOITER

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Abstract

This study is devoted to improving the results of surgical treatment of patients with diffuse toxic goiter by justifying the choice of thyroid residue volume and predicting thyroid status in the long term. The work is based on the study of the long-term results of surgical treatment of 90 patients suffering from diffuse toxic goiter.

Aim: to study the long-term results of surgical treatment of CTD based on quality of life (QOL) and determination of the optimal amount of surgical intervention.

Materials and methods of research: From 2013 to September 2024, 90 patients with diffuse toxic goiter were operated in the surgical department of the University Hospital NCJSC «Semey Medical University».

All patients were divided into 2 groups: I — the main group, which included 63 patients who underwent subtotal subfascial resection of the thyroid gland (PCF) with the removal of thyroid tissue, II — the control group, in which 27 patients underwent thyroidectomy (TE).

There were 78 (86.6%) women and 12 (13.4%) men among the patients. The age of the patients ranged from 20 to 69 years and averaged 41.9±10.58 years. In 46 cases, accounting for 51.1% of all patients, DTT was combined with endocrine ophthalmopathy (EOP)

Results: Based on a clinical and hormonal examination conducted between 3 and 11 years after breast cancer (group I), it was found that 4 (4.7%) patients developed a recurrence of thyrotoxicosis, 65 (76.5%) patients developed hypothyroidism, and only 16 (18.8%) patients retained their euthyroid state. Hypothyroidism was achieved in all 40 patients after TE.

We did not find an effect of the age, gender of patients, average duration of the disease, severity of thyrotoxicosis, hormonal parameters (T3, T4, TSH), antibody titer to thyroid peroxidase (AT to TPO) before surgery, as well as the morphological structure of thyroid tissue on the long-term results of surgical treatment of DTP.

There were no fatal outcomes among the patients of both the main and control groups.

Conclusions: With an equal thyroid balance, different outcomes of subtotal thyroid resection are possible: hypothyroidism (76.5%), euthyroidism (18.8%) and thyrotoxicosis recurrence (4.7%). The main factors that increase the likelihood of recurrence of diffuse toxic goiter after subtotal resection of the thyroid gland are: preoperative antibody levels to the thyroid-stimulating hormone receptor of more than 30 U / l, combination of DTT with endocrine ophthalmopathy.

The quality of life of DTT patients 6 months after surgical treatment does not significantly differ in many indicators from the quality of life of healthy people.

Key words: *Diffuse toxic goiter, thyroidectomy, thyroid resection. quality of life, hypothyroidism, thyroxine, postoperative complications.*

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Резюме

ОТДАЛЕННЫЕ РЕЗУЛЬТАТЫ И ВЛИЯНИЕ ХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА НА КАЧЕСТВО ЖИЗНИ ПАЦИЕНТОВ С ДИФФУЗНЫМ ТОКСИЧЕСКИМ ЗОБОМ

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Данное исследование посвящено улучшению результатов хирургического лечения больных диффузным токсическим зобом путем обоснования выбора объема тиреоидного остатка и прогнозирования тиреоидного статуса в отдаленные сроки. В основе работы лежит изучение отдаленных результатов хирургического лечения 90 пациентов, страдающих диффузным токсическим зобом.

Цель: Оценка отдалённых результатов хирургического лечения диффузного токсического зоба на основе показателей качества жизни и обоснование оптимального объёма оперативного вмешательства.

Материалы и методы исследования: В хирургическом отделении УГ НАО «МУС» с 2013 года по сентябрь 2024 года было прооперировано 90 больных с диффузно-токсическим зобом.

Все пациенты были разделены на 2 группы: I — основную, в которую вошли 63 больных, выполнена субтотальная субфасциальная резекция щитовидной железы (СРЩЖ) с оставлением ткани щитовидной железы, II— контрольную, в которой 27 больным – тиреоидэктомия (ТЭ).

«Среди 90 пациентов, включённых в исследование, большинство составили женщины — 78 (86,6%), мужчин было 12 (13,4%). Возраст обследованных находился в диапазоне от 20 до 69 лет и в среднем составлял 41,9 ± 10,58 года. У 46 пациентов (51,1%) диффузный токсический зоб сочетался с эндокринной офтальмопатией.»

Результаты: По результатам клинико-гормонального обследования, проведённого в сроки от 3 до 11 лет после субтотальной резекции щитовидной железы (I группа), у 4 пациентов (4,7%) отмечен рецидив тиреотоксикоза, у 65 (76,5%) сформировался гипотиреоз, а у 16 (18,8%) сохранялось эутиреоидное состояние. Во всех 40 случаях после тотальной тиреоидэктомии был достигнут гипотиреоз.

Анализ показал, что такие факторы, как возраст и пол пациентов, средняя продолжительность заболевания, тяжесть тиреотоксикоза, предоперационные уровни гормонов (св. Т3, св. Т4, ТТГ), титр антител к тиреоидной пероксидазе (АТ к ТПО), а также морфологическая структура ткани щитовидной железы, не оказывали существенного влияния на отдалённые результаты хирургического лечения диффузного токсического зоба.

Летальных исходов среди больных как основной, так и контрольной групп не было.

Выводы: При одинаковом объёме оставленной ткани щитовидной железы исходы субтотальной резекции оказались неоднородными: в 76,5% случаев формировался гипотиреоз, в 18,8% — сохранялся эутиреоз, а в 4,7% развивался рецидив тиреотоксикоза. К числу факторов, ассоциированных с повышенной вероятностью рецидива диффузного токсического зоба, относились предоперационный уровень антител к рецептору тиреотропного гормона выше 30 Ед/л и сочетание заболевания с эндокринной офтальмопатией.

Оценка качества жизни показала, что через 6 месяцев после хирургического лечения у пациентов с диффузным токсическим зобом большинство показателей не имели достоверных отличий от соответствующих показателей у здоровых лиц.

Ключевые слова: *диффузно-токсический зоб, тириоидэктомия, резекция щитовидной железы. качество жизни, гипотиреоз, тироксин, послеоперационные осложнения*

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Түйіндеме

ДИФФУЗДЫ ТОКСИКАЛЫҚ ЖЕМСАУДЫ ХИРУРГИЯЛЫҚ ЕМДЕУДЕН КЕЙІНГІ ҰЗАҚ МЕРЗІМДІ НӘТИЖЕЛЕРІ МЕН ӨМІР САПАСЫ

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Бұл зерттеу диффузды токсикалық жемсаумен ауыратын науқастарды хирургиялық емдеу нәтижелерін қалқанша безінің қалдық көлемін таңдауды және қалқанша безінің күйін ұзақ мерзімде болжауды негіздеу арқылы жақсартуға арналған. Жұмыстың негізінде диффузды токсикалық жемсаумен ауыратын 90 науқасты хирургиялық емдеудің ұзақ мерзімді нәтижелерін зерттеу жатыр.

Жұмыстың мақсаты: өмір сапасына (ӨС) негізделген ДТЖ хирургиялық емдеудің ұзақ мерзімді нәтижелерін зерттеу және хирургиялық араласудың оңтайлы көлемін анықтау.

Зерттеу материалдары мен әдістері: Мақалада "СМУ" КЕАҚ УГ хирургиялық бөлімшесінде 2013 жылдан бастап 2024 жылдың қыркүйегіне дейін диффузды-токсикалық жемсауы бар 90 науқасқа ота жасалды.

Барлық пациенттер 2 топқа бөлінді: I — негізгі топқа 63 науқас кірді, бұл топтағы науқастарға қалқанша безінің субтотальды субфассиялық резекциясы, яғни қалқанша безінің тінін қалдырды, жасалды, II— бақылау тобында 27 науқасқа – тиреоидэктомия жасалынды.

Науқастар арасында 78-і (86,6%) әйелдер және 12 (13,4%) ер адамдар болды. Науқастардың жасы 20-дан 69 жасқа дейін болды және орташа есеппен 41,9±10,58 жасты құрады. Ал 46 науқаста (51,1%), эндокриндік офтальмопатиямен кездесті.

Зерттеу нәтижелері: Қалқанша безінің субтотальды субфассиялық резекциясы жасалған (I топ) науқастарда 3 жылдан 11 жылға дейінгі мерзімде жүргізілген клиникалық-гормондық тексеру негізінде науқастардың 4-де (4,7%) тиреотоксикоздың қайталануы байқалды, 65- науқаста (76,5%) гипотиреоз, тек 16 -. (18,8%) эутиреоидты жағдай сақталғаны анықталды. ТЭ-ден кейінгі барлық 40 науқаста гипотиреоз анықталды.

Біз науқастардың жасына, жынысына, аурудың орташа ұзақтығына, тиреотоксикоздың ауырлығына, гормоналды көрсеткіштерге (бос.Т3, бос.Т4,ТТГ), операцияға дейін қалқанша безінің пероксидазасына (АТ к ТПО) антиденелер титріне, сондай-ақ қалқанша без тінінің морфологиялық құрылымына ДТЖ хирургиялық емдеудің ұзақ мерзімді нәтижелеріне әсерін таппадық.

Негізгі және бақылау топтары бар науқастар арасында өлім болған жоқ.

Қорытынды: Қалқанша безінің қалдықтары тең болған кезде қалқанша безінің субтотальды резекциясының әртүрлі нәтижелері болуы мүмкін: гипотиреоз (76,5%), эутиреоз (18,8%) және тиреотоксикоздың қайталануы (4,7%). Қалқанша безінің субтотальды резекциясынан кейін диффузды уытты зобтың қайталану ықтималдығын арттыратын негізгі факторлар: қалқанша безді ынталандыратын гормон рецепторына антиденелердің операцияға дейінгі деңгейі 30 бірл/л-ден асады, дтз эндокриндік офтальмопатиямен үйлесуі. 6 айдан кейін диффузды уытты зобпен ауыратын науқастардың өмір сапасы. хирургиялық емдеуден кейін көптеген көрсеткіштер бойынша Дені сау адамдардың өмір сүру сапасынан сенімді түрде ерекшеленбейді.

Түйінді сөздер: *диффузды токсикалық жемсау, тиреоидэктомия, қалқанша безінің резекциясы, өмір сүру сапасы, гипотиреоз, тироксин, операциядан кейінгі асқынулар*

Дәйексөз үшін:

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Relevance

This study is devoted to improving the results of surgical treatment of patients with diffuse toxic goiter by justifying the choice of thyroid residue volume and predicting thyroid status in the long term. The work is based on the study of the long-term results of surgical treatment of 90 patients suffering from diffuse toxic goiter.

Aim: to study the long-term results of surgical treatment of CTD based on quality of life (QOL) and determination of the optimal amount of surgical intervention.

Materials and methods: From 2019 to September 2022, 90 patients with diffuse toxic goiter were operated in the surgical department of the University Hospital NCJSC «Semey Medical University».

All patients were divided into 2 groups: I — the main group, which included 63 patients who underwent subtotal subfascial resection of the thyroid gland (PCF) with the removal of thyroid tissue, II — the control group, in which 27 patients underwent thyroidectomy (TE).

There were 78 (86.6%) women and 12 (13.4%) men among the patients. The age of the patients ranged from 20 to 69 years and averaged 41.9±10.58 years. In 46 cases, accounting for 51.1% of all patients, DTT was combined with endocrine ophthalmopathy (EOP)

The duration of the disease before surgery ranged from 4 months to 36 years (median 3 years).

Patients in the study groups I and II were examined before surgery and for a period of 6 months to 11 years after surgery

The examination of patients included: clinical examination, laboratory and instrumental examination (hormonal and immunological blood tests, electrocardiography, ultrasound examination of the thyroid gland, radiography of the cervical-thoracic space with contrast of the esophagus), consultation of specialists: otolaryngologist (with mandatory indirect laryngoscopy), oculist (to determine the severity of EOP).

In order to study the quality of life in the postoperative period, a study was conducted using the methodology developed in the PHC, with the calculation of the so-called quality of life index (QIQ) PHC, which studies both the general level of quality of life (QOL) and its individual components [4]. In order to determine only the general level of QOL and as an express method, we used a linear analog scale (LASH). In the second group of patients, the study was conducted using a double test method, while the quality of life of patients before surgery and after surgical treatment was studied in a comparative aspect. Using this technique allowed us to conduct a comparative assessment of the condition of patients before surgical treatment and in the postoperative period.

Long-term results were studied from 6 months to 11 years after surgery. A control group of practically healthy individuals (n= 45) consisting of 25 women and 20 men was used to compare the indicators of QOL after various types of operations for DTP. The age range ranged from 21 to 41 years (average 31±7.03).

Two modules were included in the questionnaire: universal and specific (29 and 11 questions, respectively). The questions of the universal module covered the following aspects of QOL: physical activity; social function; sex life; economic security; intellectual activity; emotional function; perception of one's health and well-being; perception of the treatment process and its consequences. The specific module included questions about the effect of the underlying disease on the patient and the consequences of surgical treatment. In the questionnaire we used, we included questions related to a specific module and related to the effect of the underlying disease on the patient, i.e. DTP, as well as subtotal resection of the thyroid gland or thyroidectomy performed in this regard.

A universal questionnaire module was used for the control group, excluding the issue of perception of the treatment process and its consequences. In the answers to the ICJ questions, healthy people were asked to replace the phrase "after surgery" with the words "because of your well-being." The total number of questions included in the questionnaire was 40.

It is based on the standard 5–rank R. Likert scale: "never", "rarely", "often", "very often", "constantly" – which corresponds to values from 0 to 4 points. The final result was calculated by summing up all the values obtained for each question in the questionnaire. The values of the individual components of the quality of life were calculated by summing up the scores of the relevant questionnaire questions. The hypothetically possible range of total points can range from 0 to 112 points - the first part of the questionnaire (before surgery); from 0 to 160 – the second part of the questionnaire (after surgery). The level of quality of life is directly dependent on the amount of points. Questionnaires to determine the quality of life were sent by mail, which significantly increased the number and reduced the duration of the research (the time to review the questions is 20-25 minutes).

To measure the overall level of quality of life, the LASH was used, represented by a straight line 200 mm long, on the diametrical sections of which the opposite possible conditions of the patient are marked: "the happiest", "the healthiest" (the right part of the segment) and "the most unhappy", "the sickest" (the left part of the segment). than happiness and health, they are interconnected and inseparable. On a straight line segment, patients were asked to put a label (with an X or a dot) that would correspond to their self-assessment of their current condition. The test result was evaluated by measuring the distance in millimeters from the left (zero) edge of the segment to the mark made by the subjects.

The closer this marker was placed to the right edge of the segment, the greater the distance in millimeters from the left edge of the segment to it, the higher the level of quality of life. The rating range is from 0 to 200 conventional units.

Statistical data processing was performed using the SPSS for Windows 11.5 program (SPSS inc., USA). The comparison of patients with different outcomes of surgical treatment of DTP was carried out using the Kruskal-Wallis criterion for quantitative variables and the chi-square criterion for qualitative variables. Multiple comparisons of quantitative variables were carried out using the Newman-Keiles criterion. The Spearman coefficient was used as the correlation coefficient (r) between variables belonging to the ordinal scale, and the Pearson correlation coefficient was used for variables belonging to the interval scale. In order to identify predictive factors, logistic regression analysis was

applied with the calculation of regression coefficients, odds ratio, individual risk indicators and the calculation of a 95% confidence interval. The critical significance level when testing statistical hypotheses was assumed to be 0.05.

Results

Based on clinical and hormonal examinations conducted 3–11 years after subtotal thyroid resection (Group I), recurrence of thyrotoxicosis was observed in 4 patients (4.7%). Hypothyroidism developed in 65 patients (76.5%), while only 16 patients (18.8%) retained a euthyroid state. Hypothyroidism was achieved in all 40 patients after thyroidectomy.

We did not find an effect of the age, gender of patients, average duration of the disease, severity of thyrotoxicosis, hormonal parameters (T3, T4, TSH), antibody titer to thyroid peroxidase (AT to TPO) before surgery, as well as the morphological structure of thyroid tissue on the long-term results of surgical treatment of DTP.

The outcome of the operation also did not depend on the initial volume of the thyroid gland. There were no statistically significant differences between the initial volume of thyroid residue (TO) in the groups with different outcomes of surgical treatment of DTP.

According to our data, the most important prognostic factor for the development of thyrotoxicosis recurrence, as the main unfavorable outcome of DTP treatment, is the level of AT to RTG before surgery of more than 30 U/l and the combination of DTP with EOP.

When comparing the incidence of permanent recurrent laryngeal nerve (RLN) palsy and permanent hypoparathyroidism, no statistically significant differences were found between patients who underwent subtotal thyroid resection and those who underwent thyroidectomy. Permanent hypoparathyroidism developed in 3 patients (3.5%) after subtotal thyroid resection and in 1 patient (2.5%) after thyroidectomy. Permanent recurrent laryngeal nerve palsy occurred in 2 patients (2.3%) after subtotal thyroid resection and in 1 patient (2.5%) after thyroidectomy.

We conducted a study of the results of surgical treatment of CTD, in accordance with the recommendations of WHO experts, based on a study of the quality of life of operated patients.

At the preoperative stage, we interviewed DTP patients included in the prospective study group (n=40). At the same time, it was revealed that the disease had a negative effect on many aspects of QOL (Table 1). On average, the patients' IQ before surgery was only 104.8±11.6 points. The lowest values among all QOL components (less than 60% of the maximum possible value) were recorded when the patient assessed conservative treatment (45%) and his health (52.5%), as well as his economic condition (58.7%).

Table 1.

Dynamics of quality of life before surgery and at different times after surgery in patients with diffuse toxic goiter.

Indicator	Before the operation	After the operation		
		after 6 months	after 1 year	after 2 year
Quality of life index	104,8±11,6	125,3±15,07	131,1±9,7	132,3±7,7
Intelligent function	10,7±1,5	13,5±1,9	14,3±1,3	14,3±1,37
Emotional function	20,3±2,9	23,2±3,8	22,9±3,3	24,6±3,07
Physical activity	16,9±3,3	20,2±3,9	21,26±3,2	22,8±2,4
Perception of health	4,2±0,7	5,8±1,2	5,8±1,08	5,9±1,08
Symptoms of the disease	35,8±4,7	40,8±4,2	41,9±3,1	42,6±2,05
Sexual function	2,7±0,5	3±07	3,1±0,3	3,1±0,4
Social function	8,1±1,3	10±1,6	10,4±1,2	10,4±1,4
Economic condition	4,7±0,6	5,9±1,4	6,3±1,2	6,4±1,2
Perception of treatment	1,8±0,4	2,9±0,8	3,1±0,5	3,1±0,5

The values of such QOL indicators as physical condition, emotional function, intellectual function, social function, economic status, as well as the perception of one's health and well-being in patients before surgery differed statistically significantly from the values of the corresponding QOL components in healthy individuals (p0,001) (Table 2).

Table 2.

Quality of life of patients with Diffuse toxic goiter in the preoperative period and 6 months after surgery in comparison with healthy individuals.

Quality of life indicators	Groups of surveyed			Reliability	
	Health	Before the operation	After the operation	P1	P2
Physical activity	23,82±2,29	16,92±3,36	20,22±3,98	< 0,001	< 0,001
Social function	10,17±1,03	8,17±1,33	10,0±1,67	< 0,001	> 0,05
Sexual function	3,15±0,48	2,72±0,55	3,0±0,71	< 0,001	> 0,05
Economic condition	6,87±0,72	4,75±0,63	5,90±1,46	< 0,001	< 0,001
Intelligent function	13,45±1,41	10,77±1,52	13,55±1,90	< 0,001	> 0,05
Emotional function	28,85±1,21	20,30±2,91	23,25±3,84	< 0,001	< 0,001
Perception of health	7,0±0,71	4,22±0,76	5,82±1,25	< 0,001	< 0,001

Note: The significance of the differences is indicated for healthy individuals.:

p1 – with patients before surgery, p2 – with patients after TE

Statistical processing of the obtained results indicates the presence of a moderate inverse correlation between the level of IQ and the duration of the disease (r = -0.687, p0.001), i.e., the longer the disease, the lower the QOL.

The hypothesis of a possible negative effect of severe thyrotoxicosis on the level of heart failure is also confirmed by mathematical calculations: a moderate inverse correlation was found (r = -0.610, p0.001).

However, the result of the study did not reveal a correlation between the age, gender of patients, the presence of EOP and the quality of life in the preoperative period.

All patients in this group underwent thyroidectomy. A repeat survey of patients 6 months after surgery showed a significantly significant improvement in quality of life (Tables 1, 2, Fig. 1)

The average IQ of patients 6 months after surgery was 125.3±15.07 points. The best results (more than 80% of the maximum possible value of QOL) were found in the following parameters: intellectual function (84.3%), social function (84.1%), severity of symptoms of DTD (85%). When examining other aspects: physical condition, emotional function, economic condition, the impact of treatment on the perception of one's health and well-being, the QOL level ranged from 70 to 80% of the maximum possible value. Differences in the average values of the above-mentioned QOL indicators in patients before surgery and 6 months after surgery are statistically significant (p<0.001). After surgical treatment of patients with DTP, such indicators of QOL as social, intellectual, and sexual function became commensurate with the corresponding indicators in the control group of healthy people (p>0.05) (Table 2).

A survey of patients one year and 2 years after surgery revealed a tendency towards a further increase in QOL (Table 1, Fig.1).

Thus, surgical treatment with DTP significantly improves the quality of life of patients. A noticeable improvement is observed already 6 months after the operation.

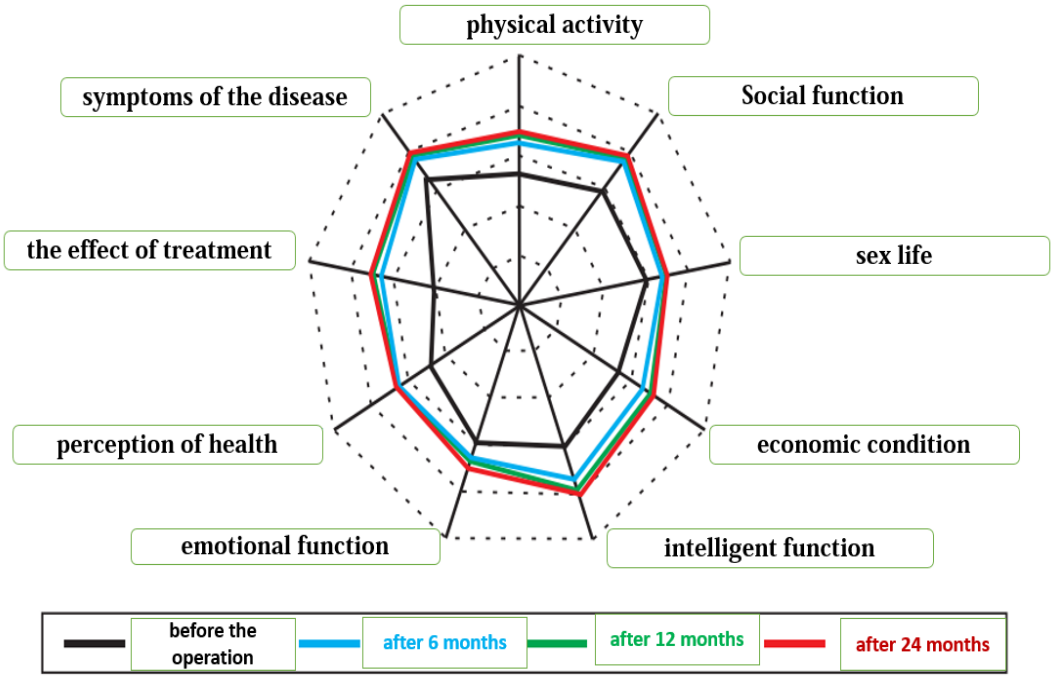


Figure 1. Dynamics of quality of life parameters before and at different times after surgery in patients with DTG.

Table 3.

Parameters of quality of life (ICG, LAS) before and after surgery in patients with diffuse toxic goiter.

Indicator	Before the operation	After the operation		
		after 6 months	after 1 year	after 2 year
Quality of life index	123,6 ± 15,5	127,1 ± 14,3	129,6 ± 13,05	131,05 ± 13,06
linear analog scale	30,95 ± 14,59	156,42 ± 18,80	162,70 ± 12,31	165,32 ± 9,72

The results obtained when patients answered the questions of the ICG FCC and LASH questionnaire correlate and allow us to conclude that these methods are highly reliable and sensitive in studying the quality of life of DTZ patients (Table 3). The correlation of the ICG and LASH questionnaire was r=0.85 (p=0.0001).

When studying the long-term results of surgical treatment of CTD, it was determined that there were no significantly significant differences in the group of patients who underwent prostate cancer (group I) and in the group of patients who underwent TE (group II): the total number of points in group I averaged 119.41±18.73, in group II 121.52±19.17 (p>0.05). There were also no significant differences when considering individual QOL indicators (Table 4)

The results closest to the maximum possible value of QOL (more than 70%) were in patients of groups I and II according to the following indicators: intellectual function, physical activity, severity of symptoms, sexual function, social function, economic well-being. In the second group of patients, the indicators of their perception of health and well-being and the impact of treatment were also brought closer to the maximum possible results (Table 4).

Table 4.

Quality of life and changes in its individual indicators depending on the volume of thyroid resection.

Indicator	Volume of thyroid resection		The validity of the differences P
	Subtotal Resection Of The Thyroid Gland	Thyroidectomy	
PHC Quality of Life Index *	119,41±18,73	121,52±19,17	p >0,05
Intelligent function **	80,6	78,7	p>0,05
Emotional function **	68,1	67,5	p>0,05
Physical activity **	71,07	69,6	p>0,05
Perception of health **	66,2	71,2	p>0,05
Symptoms of the disease **	80,4	83,7	p>0,05
Sexual function **	72,5	75	p>0,05
Social function **	78,3	79,1	p>0,05
Economic condition **	70,1	70	p>0,05
Perception of treatment **	67,5	72,5	p>0,05

***** as a unit

****** in % of the maximum possible value.

Primary hypothyroidism was achieved in 109 of the studied patients (87.2%) as a result of DTP treatment. To determine the possible effect of hormone replacement therapy on the level of QOL, a comparison was made between the IQ of patients taking L-thyroxine preparations and the IQ of patients who do not receive replacement therapy. At the same time, there were no significant differences in the results obtained: the IQ was 120.46±17.90 cont.units and 114.44±24.31 conl.units, respectively (p>0.05).

Summarizing the above, we can conclude that, despite the absence of significant differences in quality of life and frequency of postoperative complications in patients of the two study groups, subtotal surgery 1. Aristarkhov V.G., Kirillov Yu.B., Panteleev I.V., Voronina T.A., in contrast to thyroidectomy, led to different results: rare preservation of stable euthyroid postoperative hypothyroidism and recurrence of thyrotoxicosis, which required repeated surgical intervention and radioiodine therapy. At the same time, postoperative hypothyroidism was easily compensated by L-thyroxine preparations and did not lead to a decrease in the quality of life of patients. In this regard, thyroidectomy should be recognized as the most optimal and pathogenetically justified volume of surgical intervention for DTT.

Discussion

Long-term clinical and hormonal assessment conducted 3–11 years following subtotal thyroid resection (Group I) demonstrated thyrotoxicosis recurrence in 4 patients (4.7%). Hypothyroidism was identified in 65 patients (76.5%), whereas only 16 patients (18.8%) maintained euthyroid function. In contrast, hypothyroidism was observed in all 40 patients after thyroidectomy.

Comparative analysis of the rates of permanent recurrent laryngeal nerve (RLN) palsy and permanent hypoparathyroidism revealed no statistically significant differences between patients undergoing subtotal thyroid resection and those undergoing thyroidectomy. Permanent hypoparathyroidism was observed in 3 patients (3.5%) following subtotal thyroid resection and in 1 patient (2.5%) after thyroidectomy. Permanent RLN palsy developed in 2 patients (2.3%) after subtotal thyroid resection and in 1 patient (2.5%) after thyroidectomy.

The responses obtained from patients on the ICG FCC and LASH questionnaires were highly correlated, indicating that both instruments are reliable and sensitive for assessing quality of life in DTZ patients (Table 3). The correlation between the ICG and LASH questionnaires was r = 0.85 (p = 0.0001).

At the preoperative stage, patients with DTP included in the prospective study group (n = 40) were interviewed. The results demonstrated that the disease adversely affected multiple domains of quality of life (QOL) (Table 1). The mean preoperative IQ score was 104.8 ± 11.6. The lowest scores across all QOL domains (below 60% of the maximum possible value) were observed in patients' evaluations of conservative treatment effectiveness (45%), perceived health status (52.5%), and economic well-being (58.7%).

As a result of DTP treatment, primary hypothyroidism was induced in 109 patients (87.2%). To assess the potential impact of hormone replacement therapy on quality of life (QOL), IQ scores were compared between patients receiving L-thyroxine therapy and those not undergoing replacement treatment. No statistically significant differences were identified between the groups: mean IQ values were 120.46 ± 17.90 conventional units in patients receiving L-thyroxine and 114.44 ± 24.31 conventional units in those not receiving replacement therapy (p > 0.05).

Conclusions: With an equal thyroid balance, different outcomes of subtotal resection of the thyroid gland are possible.:hypothyroidism (76.5%), euthyroidism (18.8%) and recurrent thyrotoxicosis (4.7%). The main factors that increase the likelihood of a recurrence of diffuse toxic effects after subtotal thyroid surgery are: preoperative levels of antibodies to the thyroid-stimulating hormone receptor of more than 30 U/l, combination of DTT with endocrine ophthalmopathy.

The quality of life of DTP patients 6 months after surgical treatment in many respects does not significantly differ from the quality of life of healthy people.

The volume of DTP surgery does not have a significantly significant effect on the quality of life of patients. However, given that thyroidectomy is the most pathogenetically justified operation that eliminates the recurrence of thyrotoxicosis and does not lead to an

increase in the frequency of postoperative complications, this intervention should be considered the operation of choice for DTT.

Postoperative hypothyroidism, provided adequate hormone replacement therapy, does not lead to a deterioration in the quality of life of patients.

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MPOX: FROM EPIDEMIOLOGICAL TRENDS TO MODERN IMMUNOPROPHYLAXIS STRATEGIES. LITERATURE REVIEW

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Abstract

Introduction. Mpox (the disease caused by the MPXV virus) gained global significance during the 2022–2025 outbreak; as of the analysis period, 97,281 laboratory-confirmed cases had been reported in 118 countries, and the WHO declared the situation a Public Health Emergency of International Concern (PHEIC) on 14 August 2024. The expanded geographic circulation and the presence of vulnerable groups necessitate reassessment of control measures and vaccination strategies.

Objective. To analyse current features of Mpox spread and to evaluate the effectiveness of available preventive vaccine measures in the context of importation risk.

Search strategy. A critical review of peer-reviewed literature and official reports published between 2010 and 2025 was conducted; included sources comprised scientific publications, regulatory documents and surveillance data. Analysis was structured around mpox epidemiology and spread, risk groups and clinical features, and vaccine platforms (licensed products and candidates), with data classified as preclinical or clinical.

Results. Clinical presentation ranges from typical staged cutaneous eruptions to atypical anogenital forms; disease is more severe in people living with HIV. No confirmed cases were reported in Kazakhstan (July 2025). Regarding vaccines: the non-replicating MVA-BN shows a favourable profile (two doses - seroconversion ≈89%; estimated effectiveness ≈82%, 95% CI 72-92%; one dose ≈76%, 95% CI 64-88%); ACAM2000 is highly immunogenic (seroconversion ≈94-97%) but limited by safety concerns; LC16-KMB is an alternative in specific scenarios. Emerging candidates (attenuated dBTF, mRNA BNT166, VLP constructs) demonstrate promising preclinical / early clinical results, but data are limited by small sample sizes and lack of direct comparative studies.

Conclusions. Priorities include ensuring access to non-replicating vaccines and targeted PrEP/PEP programmes, strengthening surveillance and laboratory readiness, standardizing correlates of protection, and conducting head-to-head and large non-human primate (NHP) / clinical studies to enable evidence-based ranking of vaccine platforms.

Keywords: *Monkeypox virus (MPXV); epidemiology; vaccines.*

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Резюме

МРОХ: ОТ ЭПИДЕМИОЛОГИЧЕСКИХ ТЕНДЕНЦИЙ К СОВРЕМЕННЫМ СТРАТЕГИЯМ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Мрох (болезнь, вызванная вирусом MPXV) приобрёл глобальное значение в ходе вспышки 2022-2025 гг.; по состоянию на период анализа зарегистрировано 97 281 лабораторно подтверждённый случай в 118 странах, а ВОЗ 14 августа 2024 г. объявила ситуацию PHEIC. Расширение географии циркуляции и наличие уязвимых групп требуют переоценки мер контроля и стратегий вакцинации.

Цель исследования. Проанализировать актуальные особенности распространения Mpox и оценить эффективность доступных профилактических вакцинных мер в контексте риска заноса инфекции.

Стратегия поиска. Критический обзор рецензируемой литературы и официальных отчётов за период 2010-2025 гг.; включены публикации, регуляторные документы и данные надзорных служб. Анализ проводился по направлениям: эпидемиология и распространение инфекции, группы риска и клинические особенности, вакцинные платформы (зарегистрированные препараты и кандидаты) с разделением данных на доклинические и клинические.

Результаты. Клиническая картина варьирует от типичных стадийных кожных высыпаний до атипичных аногенитальных форм; у лиц с ВИЧ течение тяжелее. В Казахстане подтверждённых случаев нет (июль 2025). По вакцинам: нереплицирующаяся MVA-BN демонстрирует благоприятный профиль (две дозы - сероконверсия ≈89%; оценочная эффективность ≈82%, 95% ДИ 72-92%; одна доза ≈76%, 95% ДИ 64-88%); ACAM2000 высокоиммуногенна (сероконверсия ≈94-97%) но ограничена рисками; LC16-KMB - альтернатива в отдельных сценариях. Новые кандидаты (аттенуированные dBTF, mRNA-BNT166, VLP) показывают многообещающие доклинические/ранние клинические результаты, но данные ограничены по размерам выборок и отсутствуют прямые сравнительные исследования.

Выводы. Приоритеты - обеспечение доступа к нереплицирующимся вакцинам и таргетных PrEP/PEP-программ, усиление эпиднадзора и лабораторной готовности, стандартизация коррелятов защиты и проведение head-to-head и крупных NHP/клинических исследований для обоснованного ранжирования платформ.

Ключевые слова: *вирус оспы обезьян (MPXV); эпидемиология; вакцины.*

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Түйіндеме

MPOX: ЭПИДЕМИОЛОГИЯЛЫҚ ҮРДІСТЕРДЕН ЗАМАНАУИ ИММУНОПРОФИЛАКТИКА СТРАТЕГИЯЛАРЫНА ДЕЙІН. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Mpox (MPXV вирустың туындатқан ауруы) 2022-2025 жж. болған эпидемия барысында жаһандық маңызға ие болды, талдау кезеңіне сәйкес 118 елде 97 281 зертханалық расталған жағдай тіркелді, ал ДСҰ 2024 ж. 14 тамызда жағдайды Халықаралық маңызы бар қоғамдық денсаулық сақтау төтенше жағдайы (PHEIC) деп жариялады. Географиялық кеңеюі мен осал топтардың болуы бақылау шаралары мен вакцинация стратегияларын қайта қарауды талап етеді.

Мақсат. Mpox таралуының қазіргі ерекшеліктерін талдап, инфекцияның әкетілу қаупі контекстінде қолжетімді алдын алу вакциналық шаралардың тиімділігін бағалау.

Іздеу стратегиясы. 2010-2025 жж. жарияланған рецензияланған әдебиеттер мен ресми есептерге сыни шолу жүргізілді, талдау ғылыми жарияланымдарды, реттеуші құжаттарды және эпидемиологиялық қадағалау деректерін қамтыды. Талдау mpox эпидемиологиясы мен инфекцияның таралуы, қауіп топтары мен клиникалық ерекшеліктері, вакциналық платформалар (тіркелген препараттар және кандидаттар) бойынша, деректерді доклиникалық және клиникалық деңгейлерге бөле отырып жүргізілді.

Нәтижелер. Клиникалық көріністер типтік кезеңделген тері бөртпелерінен атиптік аногенитальды формаларға дейін өзгеріп отырады, ВИЧ-пен өмір сүретін адамдарда ауру ауырырақ өтеді. Қазақстанда расталған жағдайлар тіркелмеген (шілде 2025). Вакциналар жайлы: репликацияланбайтын MVA-BN жағымды профиль көрсетеді (екі доза - сероконверсия ≈89%; бағаланған тиімділік ≈82%, 95% сенімді интервал 72-92%; бір доза ≈76%, 95% СИ 64-88%), ACAM2000 жоғары иммуногенді (сероконверсия ≈94-97%) бірақ қауіпсіздік мәселелерімен шектелген; LC16-KMB кейбір сценарийлерде балама болып табылады. Жаңа кандидаттар (аттенуирленген dBTF, mRNA BNT166, VLP конструкциялары) доклиникалық/ерте клиникалық зерттеулерде үмітті нәтиже көрсетуде, алайда деректер үлгілерінің шағындығымен және тікелей салыстыру зерттеулерінің болмауымен шектеледі.

Қорытынды. Басты басымдықтар - репликацияланбайтын вакциналарға қолжетімділікті қамтамасыз ету және мақсатты PrEP/PEP бағдарламаларын енгізу, эпидемиялық бақылау мен зертханалық дайындықты күшейту,

қорғаныс корреляттарын стандарттау және вакциналық платформаларды дәлелді түрде рейтингтеу үшін тікелей салыстырулы (head-to-head) және ірі адам емес примат (NHP) / клиникалық зерттеулер жүргізу.

Түйінді сөздер: *маймыл шешегі вирусы (MPXV); эпидемиология; вакциналар.*

Дәйексөз үшін:

Туяков А. М., Жаппарова Г.А., Тленчиева Т.М., Мырзахметова Б.Ш., Жугунисов К.Д., Кутумбетов Л.Б., Омарбекова Ж.Е., Шабдарбаева Д.М. Мрох: эпидемиологиялық үрдістерден заманауи иммунопрофилактика стратегияларына дейін. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 135-148. *doi 10.34689/SH.2025.27.6.016*

Introduction

Monkeypox virus (MPXV) was first isolated in 1959 from cynomolgus macaques imported into Denmark; the first clinically confirmed human case was reported in 1970 in the Democratic Republic of the Congo. In 1970–1979, 47 confirmed cases were described in Central and West Africa, predominantly in children; in individual foci, secondary transmission was estimated at 3-7%, and case fatality reached ≈17%. Over time, both an expansion of the geographic range and changes in the demographic structure of cases were observed-the mean age increased from ≈4 years in the 1970s to >20 years in 2010-2019-which has been attributed to the cessation of mass smallpox vaccination, urbanization, and weakening of epidemiological surveillance [70, 9, 3, 4].

These long-term trends were highlighted by the 2022 outbreak, during which MPXV spread beyond its traditional endemic regions: cases were reported in previously non-endemic countries, and a proportion of transmission events occurred without obvious epidemiological links to travel to endemic areas, indicating cryptic circulation. According to WHO data, by 8 May 2023, 87,377 laboratory-confirmed cases and 140 deaths had been reported; the subsequent decline in the number of new diagnoses in February-April 2023 reflected the effect of response measures but did not eliminate the risk of further spread. Chronic resource shortages and weak surveillance in endemic regions facilitate the establishment of the virus in the ecological niche vacated after smallpox eradication, while the emergence of new genetic variants (including Clade IIb / B.1 lineages) calls for continuous monitoring and reevaluation of prevention strategies [3, 4, 24, 22].

Taxonomically, MPXV belongs to the genus Orthopoxvirus (family Poxviridae) and is divided into three clades: Clade I (Central African), Clade IIa (West African), and Clade IIb; the B.1 lineage predominated in the 2022 outbreak and was characterized by an increased substitution rate compared with preceding strains. The MPXV genome is a linear double-stranded DNA (~196–211 kb, ≈190 ORFs) with a conserved central region and variable terminal repeats; virions have a brick-shaped morphology (~200–250 nm) and exist in several biological forms (IMV, IEV/EEV), with IMV being the most stable in the external environment and playing a key role in inter-host transmission. Understanding genomic variability and the biological properties of these forms is important for interpreting changes in pathogenicity and transmission [31, 89, 38, 35, 15].

The clinical presentation of MPXV is broadly typical of poxvirus infections: fever, headache, myalgia, and a characteristic rash that progresses through the stages macules → papules → vesicles → pustules → crusts; the incubation period averages 10–16 days, and in most patients the rash appears within the first few days after fever onset. During the 2022 outbreak, atypical presentations were also documented (limited anogenital lesions or complete absence of rash), which complicated diagnosis and contributed to delayed detection. Severe complications include bronchopneumonia, encephalitis, sepsis, and secondary bacterial infections; in immunocompromised individuals (including people living with HIV), the disease course is generally more severe. Case fatality varies by clade (Clade I-up to ≈10%, Clade II-substantially lower) [16, 47, 33, 29].

This review summarizes historical and contemporary aspects of the epidemiology of monkeypox virus (MPXV) from its isolation in 1959 up to the global outbreak of 2022. Particular attention is paid to the evolution of vaccine platforms-from classical first-generation replicating vaccines to modern attenuated, non-replicating, and innovative constructs based on mRNA and virus-like particles. Comparison of the immunological characteristics and safety profiles of different platforms will make it possible to assess their potential for practical use and to develop recommendations within the framework of a national strategy for the prevention of and preparedness for orthopoxvirus infections.

Search strategy. The present study is a literature review addressing issues of the epidemiology, clinical manifestations, and prevention of MPOX. The search for publications was carried out in the international databases PubMed, Scopus, Web of Science, Elsevier ScienceDirect, Google Scholar, as well as in peer-reviewed journals. The review included original articles, reviews, and official communications of international organizations (WHO, CDC, ECDC), published predominantly in 2010-2025. Priority was given to full-text sources; abstracts of reports, newspaper publications, unpublished observations, non–peer-reviewed materials, and articles not relevant to the topic of the study were excluded. The sources were analyzed in the following main areas: epidemiology and spread of infection, routes of transmission, pathogenesis, clinical presentation, and prevention. As the study is based on an analysis of published data, separate ethical approval was not required.

Epidemiology and spread of MPOX

The monkeypox outbreak recorded in the Democratic Republic of the Congo (formerly Zaire) in 1980-1985 comprised 282 confirmed cases. The vast majority of patients (about 90%) were children younger than 15 years, with a mean age of 4.4 years. Case fatality among unvaccinated individuals was about 11%, and in children younger than 15 years up to 15%. No deaths were recorded

among individuals who had previously received smallpox vaccination [33, 32].

From February 1996 to October 1997, 511 suspected monkeypox cases were reported in the Katako-Kombe and Lodja areas (Kasai Oriental, Democratic Republic of the Congo), 419 of them in October 1997 alone [13]. Most patients (85%) were children aged up to 16 years. The disease was characterized by a severe course with high fever, diarrhea, generalized rash (often >100 lesions), lymphadenopathy, and impairment of ability to work for more than three days. Despite the pronounced symptomatology, case fatality remained relatively low-1.5% [74]. It was established that 22% of cases were of zoonotic origin, whereas 78% resulted from human-to-human transmission, predominantly within households and neighborhoods [45]. The scale of this outbreak, the largest until 2022, was probably related to increasing population susceptibility following the cessation of smallpox vaccination [29].

In 2003, from 15 May to 20 June, the first monkeypox outbreak outside Africa was recorded in the United States [54, 40]. A total of 72 confirmed and probable cases (37 of them laboratory confirmed) were identified in humans in six Midwestern states. The median age of patients was 28 years (range 1–55 years), and no deaths were reported. All patients had contact with infected prairie dogs (Cynomys spp.) [54]. The investigation showed that the likely source of MPXV introduction into the USA was an international shipment consisting of about 800 small mammals from Ghana to Texas. The shipment contained about 800 small mammals of nine different species, including six genera of African rodents. In response to the outbreak, importation and sale of African rodents and prairie dogs were temporarily suspended, and extensive epidemiological and virological investigations were carried out [11]. Genetic analysis revealed that the virus belonged to the West African clade [40].

From 22 September 2017 to 16 September 2018, Nigeria experienced the largest recorded MPOX outbreak in the country, 39 years after the last reported case [92, 56]. A total of 122 confirmed and probable cases were registered in 17 states, including the capital, and 7 (6%) deaths. The median age was 29 years, and 84 (69%) were men [91, 58]. The causative agent was a West African clade MPXV, with transmission occurring via both zoonotic routes and human-to-human transmission chains [91, 59]. In response, measures were implemented within the One Health framework: laboratory diagnostics and intersectoral collaboration between public health and veterinary services, and an electronic outbreak response and analysis system was introduced to improve digitalization and the timeliness of surveillance [56, 46]. Three MPOX cases detected in 2018–2019 in the United Kingdom and Israel were found to be associated with importation of infection by travelers from Nigeria [91, 68].

The global MPOX outbreak in 2022–2023 was the first of such magnitude outside endemic regions, affecting 111 countries and leading to tens of thousands of confirmed infections. The first confirmed MPOX case in the 2022 outbreak was identified in the United Kingdom on 7 May in a patient who had recently returned from Nigeria [67]. As of 8 August 2022, 2,914 confirmed and 103 probable monkeypox cases had been reported in the United Kingdom-a total of 3,017 [67]. On 21 May 2022, WHO issued an emergency communication regarding the onset of a multi-country MPOX outbreak in non-endemic countries. At that time, 92 confirmed and 28 suspected cases had been reported in 12 countries, including Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, the United Kingdom, and the United States [81]. There are suggestions that MPOX virus may have been circulating unnoticed in European countries long before its official identification in May 2022, which indicates the possibility of underestimated or unrecognized transmission in the early stages of the outbreak [57]. On 23 July 2022, the MPOX outbreak was officially declared by WHO a public health emergency of international concern (PHEIC). The decision was taken by the WHO Director-General against the background of a rapid increase in the number of cases-over 16,000 in 75 countries [87]. On 11 May 2023, WHO announced that the global MPOX outbreak was no longer considered a public health emergency of international concern (PHEIC), based on the sustained decline in case numbers and the stability of the clinical picture. The Emergency Committee emphasized the need to shift from emergency response to long-term control strategies, including integration of MPOX into national programs for surveillance, vaccination, and research [49]. (Figure 1).

According to WHO data, from 1 January 2022 to 8 May 2023, a total of 87,377 laboratory-confirmed MPOX cases, including 140 deaths, were reported in 111 countries across all six WHO regions (Figure 2). Since the previous report (27 April 2023), 264 new cases (an increase of 0.3%) and 10 deaths had been recorded, with some cases reported retrospectively [80]. Among MPOX cases with available data on sex, 96.2% (77,834 of 80,872) were men, and the median age of patients was 34 years. The distribution by sex and age remained stable throughout the outbreak. Among patients with known age, 1.3% (1,108 of 83,460) were children under 18 years, including 324 cases (0.4%) in children younger than 5 years. Among cases with available information on sexual orientation, 84.1% (25,871 of 30,761) identified themselves as gay, bisexual, or other men who have sex with men (MSM). Despite minor fluctuations, this proportion consistently exceeded 75%, indicating predominant circulation of the virus in this risk group during the outbreak. In cases where data on sexual orientation were unavailable, the high proportion of male patients may also indicate hidden transmission among MSM [80]. The causative agent of the global MPOX outbreak in non-endemic countries was a Clade IIb virus, predominantly lineage B.1, and less frequently A.1. At the same time, in endemic regions such as the Democratic Republic of the Congo and Nigeria, Clade I and Clade IIa viruses continued to circulate [80]. Following the onset of the MPOX outbreak, urgent measures were implemented: surveillance was strengthened, PCR diagnostics expanded, vaccination of risk groups was organized (primarily using MVA-BN), and isolation of patients was introduced [43, 81, 14]. Leading countries launched information campaigns among key communities aimed at counteracting stigmatization, and WHO ensured international coordination [89].

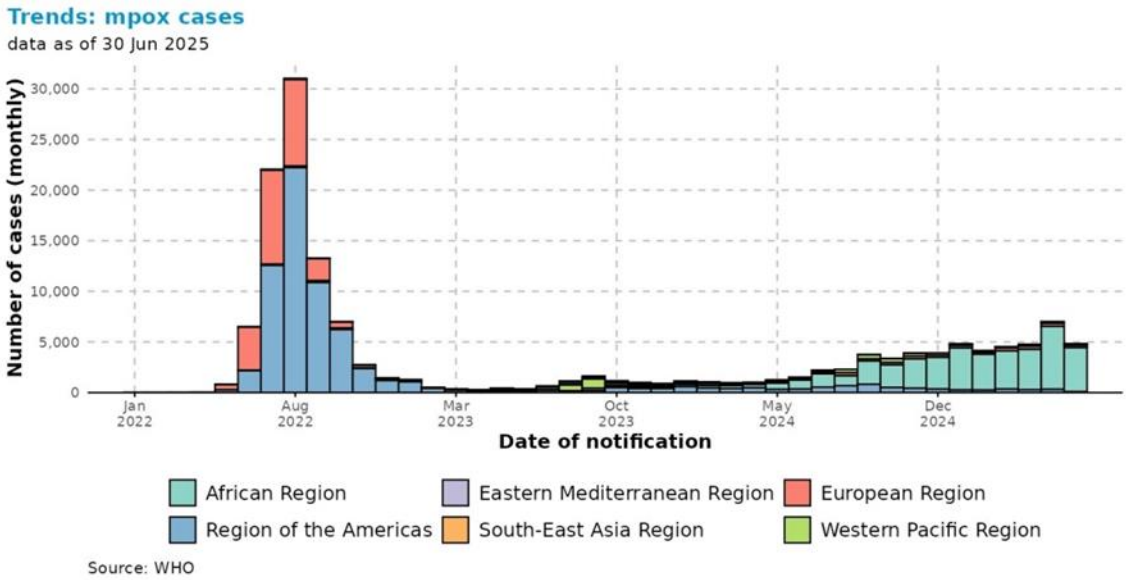


Figure 1. Dynamics of MPOX incidence by world region (January 2022 – June 2025). Source: World Health Organization, 2025, Global Mpox Trends.

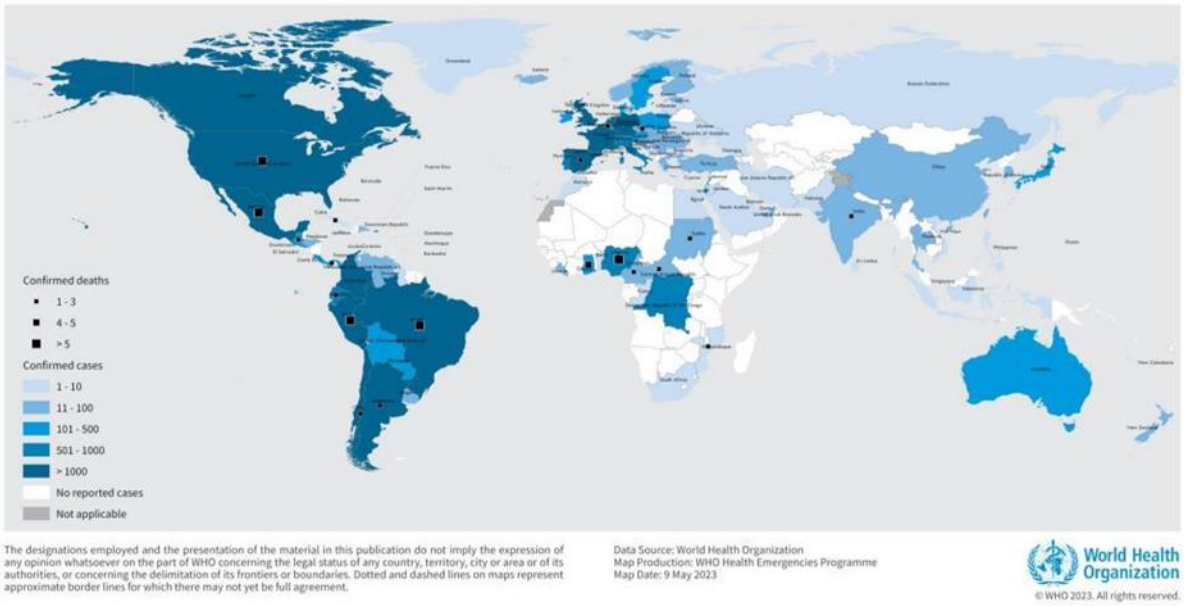


Figure 2. Geographic distribution of confirmed monkeypox cases reported or identified by WHO from official public sources for the period 1 January 2022 to 8 May 2023. Source: World Health Organization, 2023, External Situation Report 22.

In August 2023, the first confirmed MPOX cases were reported in Kinshasa, the capital of the Democratic Republic of the Congo. The index patient arrived by river transport from the endemic province of Maïndombe; his diagnosis was laboratory confirmed on 18 August. Subsequently, infection was detected in several of his close contacts [79]. From 1 January 2024 to 28 July 2024, 13,791 MPOX cases and 450 deaths were reported in the Democratic Republic of the Congo, accounting for 96.3% and 97%, respectively, of all cases and deaths in Africa. Morbidity affected 25 of the country's 26 provinces, with 68% of cases and 85% of deaths occurring in children under 15 years of age. More generally, from 1 January 2022 to 28 July 2024, 37,583 MPOX cases and 1,451 deaths were reported in 15 African Union member states, corresponding to an overall case fatality of 3.9% [3]. During the outbreak, Clade II viruses (including subclade IIa) continued to circulate, and active transmission of a new clade, Ib, more adapted to human-to-human transmission, was documented, predominantly in the eastern part of the Democratic Republic of the Congo. Genomic analysis showed that all investigated MPOX virus isolates obtained during the outbreak in South Kivu Province (eastern Democratic Republic of the Congo) belonged to Clade Ib and formed three distinct clusters. Mutations were identified in viral genomes, predominantly driven by APOBEC3 activity, indicating sustained human-to-human transmission [39]. Against the background of the rapid spread of this new MPOX clade, on 14 August 2024 the WHO Director-General declared the outbreak in the Democratic Republic of the Congo and several African countries a public health emergency of international concern (PHEIC) [86].

As of the period from 1 January to July 2025, MPOX continues to circulate predominantly in African countries. Since the beginning of the year, 30,022 confirmed cases and 119 deaths have been reported in 79 countries, with 28,152 cases and 133 deaths occurring in 24 African countries, accounting for 94% of all global cases. The highest numbers of cases have been recorded in the Democratic Republic of the Congo (13,927), Uganda (6,230), and Sierra Leone (4,876). Despite an overall decline in global incidence, active local outbreaks persist in several regions [83]. Clade Ib viruses dominate in eastern and central Africa, whereas Clade IIb continues to circulate mainly in West Africa and beyond. Isolated imported Clade Ib cases have been reported in Australia, the United Kingdom, and China (Figure 3), confirming the continuing risk of international spread of the infection [73].

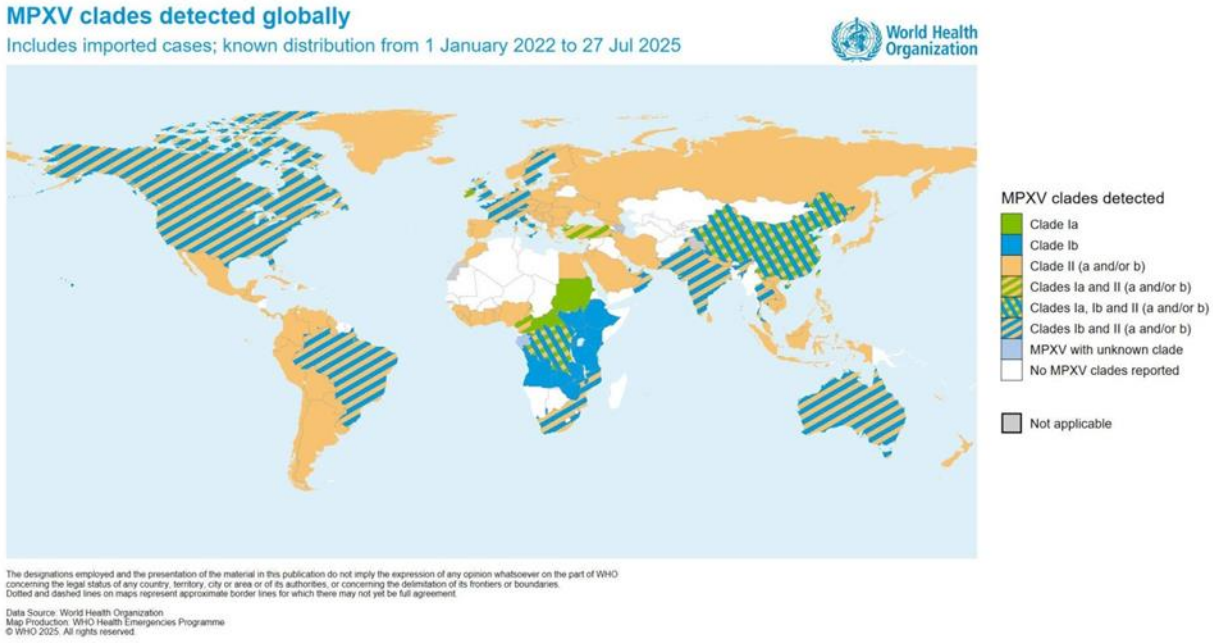


Figure 3. Geographic distribution of monkeypox virus clades, including imported cases, for the period 1 January 2022 to 27 July 2025.
Source: World Health Organization, 2025, Global Mpox Trends.

According to WHO data for the period from 1 July 2024 to 30 June 2025, outside Africa MPOX predominantly affected men of working age. The highest incidence was observed in the 30–39 and 18–29 year age groups. Women accounted for only a small proportion in all age categories. After 50 years of age, incidence declined substantially: in the 50–59 year age group, 353 cases were recorded in men and only 13 in women. Among children and adolescents <18 years, 55 cases were reported over the entire observation period (Figure 4) [73].

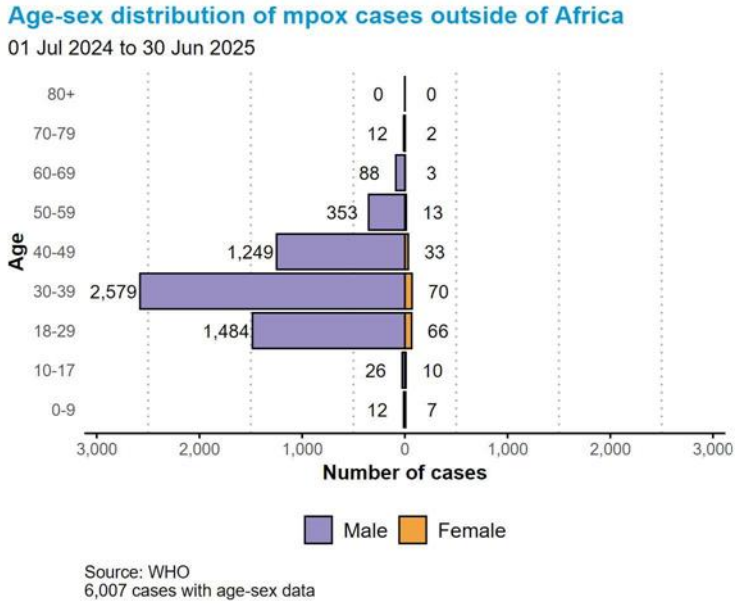


Figure 4. Distribution of confirmed MPOX cases by sex and age outside Africa for the period 1 July 2024 to 30 June 2025.
Source: World Health Organization, 2025, Global Mpox Trends.

In the endemic provinces of the Democratic Republic of the Congo, the epidemiological profile of MPOX cases differs from that observed outside Africa. According to data for the period from 1 January 2024 to 25 July 2025, cases of infection were registered in all age groups (Figure 5). Particularly high incidence was observed among children and adolescents: the 5-9, 10-14, and 15-19 year age groups showed the largest numbers of reported cases. In contrast to the pattern in non-endemic countries, where MPOX predominantly affected men, in the DRC the sex distribution is more balanced-the proportions of men and women are approximately equal in most age groups. A substantial number of cases was also noted in the 20-39 year age group, with a gradual decline in incidence with increasing age. The lowest number of cases was recorded among individuals older than 45 years [73].

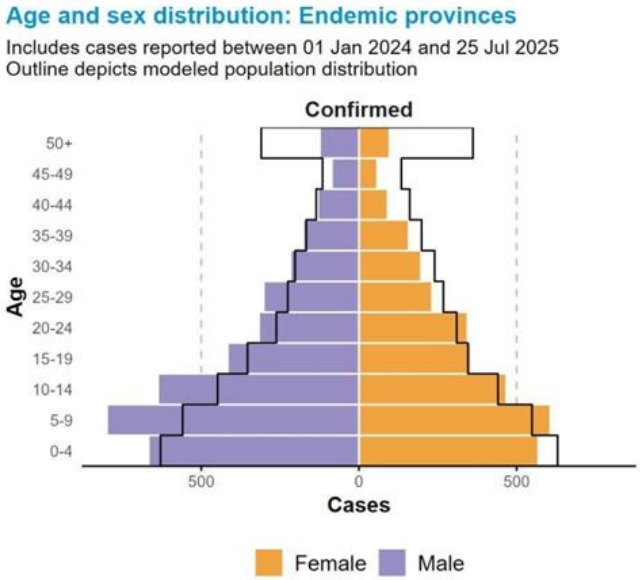


Figure 5. Distribution of confirmed MPOX cases by sex and age in the endemic provinces of the Democratic Republic of the Congo for the period 1 January 2024 to 25 July 2025. (Endemic provinces include: Equateur, Sankuru, Tshuapa, Tshopo, Nord-Ubangi, Bas-Uélé, Sud-Ubangi, Mongala, Kwilu, Maïndombe, and Maniema) Source: World Health Organization, 2025, Global Mpox Trends.

Vaccines

Although immune memory after smallpox vaccination is long-lasting and provides cross-protection, the first two generations of vaccines have critical drawbacks: replicating VACV strains occasionally cause severe complications in individuals with immunodeficiency, eczema, and in transplant recipients; first-generation products also had problems with production standardization. The spread of MPXV beyond endemic regions and the large number of people without residual immunity make it necessary to develop safer, standardized platforms with comparable immunogenicity.

*Classification of vaccine platforms (*Table 1).

Dryvax®, APSV®, Lancy-Vaxina®, and L-IVP® belong to first-generation vaccines (produced before the 1970s-1980s) and contained live vaccinia virus in various pharmaceutical forms-lyophilized, “frozen-liquid,” and calf-lymph [35]. Despite differences in manufacturing technology and type of substrate, all of these products demonstrated comparably high clinical efficacy: the development of the characteristic “take” served as a universal empirical correlate of protection and was accompanied by pronounced humoral and cellular responses that ensured long-term immune memory. At the same time, differences in production approaches led to lot-to-lot variability and affected safety: whereas Dryvax® and L-IVP® were characterized by relatively stable immunogenicity, calf-lymph vaccines (Lancy-Vaxina®) were more frequently associated with technological heterogeneity and a risk of contamination. Overall, all replicating products were associated with frequent mild reactions (≈5-80%) and rare but clinically significant complications: fatal outcomes ≈1-2 × 10^{-6}, postvaccinal encephalitis ≈3-9 × 10^{-6}, eczema vaccinatum ≈2-35 × 10^{-6}, generalized vaccinia ≈40–200 × 10^{-6}; in later series, myopericarditis was reported with a frequency on the order of 10^{-4}. Thus, despite their high efficacy, differences in standardization and safety rendered these vaccines poorly suited to modern mass immunization programs, which in turn led to the development and introduction of second- and third-generation vaccines-cell culture-based and non-replicating-aimed at improving safety while maintaining immune protection [35].

Second-generation vaccines retained the same biological basis-VACV strains close to the original ones-but shifted production to controlled cell culture systems and introduced purification and standardization (e.g., ACAM2000, Elstree-BN). This improved product quality and predictability; however, it did not fundamentally change the risk associated with replication of the vaccine virus: second-generation replicating vaccines still have limitations in use among vulnerable groups and require a cautious approach to mass immunization. ACAM2000, produced in MRC-5 cells and administered as a single dose using a bifurcated needle, demonstrates high seroconversion (≈94-97%) and proven protection in preclinical models and retrospective studies. However, it retains the typical risks of a replicating platform-the possibility of transmission of the vaccine virus and contraindications in children, pregnant women, and immunocompromised individuals (rate of serious adverse events ≈20.25 per 100,000) [18, 71, 55, 28, 41, 42, 35].

Table 1.

Comparative characteristics of vaccine platforms against MPOX.

Vaccine / platform	Type	Regimen and dose of administration	Immunology (seroconversion / NT_{50} / T-cell)	Efficacy / protection (key results)	Risks / safety	Development status
Dryvax®, APSV®, Lancy–Vaxina®, L-IVP®	Live replicating VACV (1st generation)	1 dose, ≈15 punctures, ~10^6–10^8 PFU/mL, scarification	Robust humoral and cellular responses; "take" as an empirical correlate	High historical clinical effectiveness	Frequent mild reactions (≈5–80%); rare serious complications (mortality ~1–2×10^{-6}; encephalitis 3–9×10^{-6}; eczema vaccinatum 2–35×10^{-6}; myopericarditis ~10^{-4})	Historical (withdrawn from widespread vaccination)
ACAM2000	2nd generation, replicating	1 dose, ≈15 punctures, ≈0.0025 mL × 2.5–12.5 × 10^5 PFU, scarification	Seroconversion ≈94–97% in clinical series	Demonstrated protection in retrospective data/model studies	Retains replication-related risks (possibility of transmission; contraindicated in children, pregnant individuals, and the immunocompromised); serious reactions ≈20.25/100,000.	Licensed / in strategic stockpiles
MVA-BN (JYNNEOS / IMVANEX)	3rd generation, non-replicating MVA	2 doses, 0.5 mL, ≈10^8 $TCID_{50}$, subcutaneous (SC)	Seroconversion ≈89% after 2 doses; effectiveness in meta-analysis ~82% (95% CI 72–92%) for the two-dose regimen; one dose ≈76% (64–88%).	Reduction in clinical disease during the outbreak; good tolerability	High safety profile; can be used in individuals with contraindications to replicating vaccines	Licensed; included in stockpiles and recommendations
LC16m8	3rd generation, attenuated partially replicating	1 dose, 0.5 mL, ≈1.5×10^4–10^5 PFU, scarification	Seroconversion ≈70–72% by day 28 after 1 dose	Protection after a single dose in historical/field data	Partial replication → earlier immune response, but caution required in immunocompromised individuals	Licensed in Japan; used in emergency situations
dBTF (Tiantan-derived attenuated)	Replicating, genetically attenuated	Not applicable (preclinical study)	High binding and neutralizing titers; enhancement of cGAS/STING and IFN response	A single vaccination produced a marked reduction in clinical burden: on day 10, control macaques had hundreds of lesions (452, 156, 75), while vaccinated animals had 6, 5, and 1; plasma/tissue viral loads were reduced; NT_{50} values correlated with protection.	Replicating candidate — regulatory risks for immunocompromised individuals; requires thorough safety evaluation.	Advanced preclinical stage (NHP), no clinical data
BNT166 (multi-antigen mRNA-LNP)	Non-replicating mRNA-LNP	Not applicable (preclinical study)	High seroconversion; strong $CD4^+$/$CD8^+$ responses; NT_{50} correlate with protection	In NHP, BNT166 provided 100% prevention of death and suppression of skin lesions under a Clade I challenge	Expected safety of the mRNA platform; needs clinical confirmation	Early clinical trials (phase I/II, NCT05988203)
SpyCatcher003-mi3 VLP (Belghith et al.)	Non-replicating VLP	Not applicable (preclinical study)	Very high NT_{50} (in mice and NHP); in macaques VLP NT_{50} ≈2× higher than JYNNEOS; strong humoral and adequate cellular response	Complete protection in mouse models; in NHP higher NT_{50} values than JYNNEOS; passive transfer of serum from VLP-vaccinated macaques provided better protection in mice than serum from JYNNEOS recipients	High safety (no genome); manufacturing and large-scale trials are necessary	Predominantly preclinical (small NHP groups); no clinical data

Third-generation vaccines represent a transition from replicating viral platforms to safer and more technologically controlled solutions, where the key goal is to reduce the risk of adverse reactions while maintaining adequate immunogenicity. Two of the most illustrative examples are MVA-BN (a non-replicating modified Ankara platform) and LC16m8 (an attenuated temperature-sensitive VACV strain. Both vaccines have inherited the cross-protection characteristic of classical smallpox vaccines, but differ in their biological properties as well as in their practical use profile. MVA-BN, which is unable to replicate in human cells, demonstrates the best safety profile: it does not cause vaccine viremia and can be used in individuals with contraindications to replicating vaccines. According to clinical observations, two doses of the vaccine induce seroconversion in ≈89% of previously unvaccinated individuals and provide protective effectiveness of about 82% (meta-analysis: 82%, 95% CI 72-92%); the effectiveness after a single dose in one review was estimated at approximately 76% (95% CI 64-88%) [50]. LC16m8, by contrast, retains a limited ability to replicate, which promotes more pronounced early activation of the immune response-according to Japanese trials, seroconversion reached 70-72% by day 28-but at the same time requires greater caution in immunocompromised and pregnant individuals. With comparable overall tolerability, LC16m8 is somewhat inferior to MVA-BN in terms of safety profile, but potentially induces a broader cellular response due to preserved, albeit attenuated, replication. Thus, both platforms reflect different strategic approaches: MVA-BN is aimed at maximizing safety and universality of use, whereas LC16m8 seeks a compromise between immunogenicity and controlled replication, which may be important for target groups at high risk of infection [1, 22, 23]. Differences in seroconversion levels between LC16m8 and MVA-BN partly reflect not only the biology of the platforms themselves but also the specifics of study design. LC16m8 was evaluated after a single dose with a relatively short follow-up period (28 days), whereas MVA-BN studies focused on a two-dose regimen with a longer evaluation interval (≈90 days). In addition, serological testing methods and cohort compositions also differed. Consequently, the higher seroconversion observed for MVA-BN in certain series appears to be related to differences in vaccination regimens and time points of measurement rather than necessarily to a fundamental advantage of the platform [71, 21, 17, 6, 63, 65, 21, 17, 51, 75, 84, 44].

An experiment in a black-tailed prairie dog model, in which animals were intranasally infected with an MPXV strain at moderate and extremely high exposure, demonstrated differences in the practical effect of vaccine platforms in post-exposure immunization. In a comparison of the non-replicating MVA-BN (JYNNEOS/IMVAMUNE) and the replicating ACAM2000, both vaccines induced neutralizing antibodies and could delay death when administered after exposure; at the same time, early administration (day 1) of MVA-BN produced more pronounced clinical attenuation compared with administration on day 3, although antibody levels in the different groups were comparable-which likely reflects the specifics of vaccination schedules and timing of measurements. At a very high challenge dose, neither vaccine provided complete protection, underscoring the limited window for effective PEP and the need for prompt intervention. In practical terms, this means that in the PEP setting the non-replicating platform has operational advantages, especially in individuals with contraindications to replicating vaccines [59].

Candidates and promising platforms

The recent attenuated candidate dBTF (Tiantan-derived; deletions J2R/TK, F4L, B2R) demonstrates pronounced single-dose protection in NHP models: a single IM vaccination (2.5×10^5 PFU) led to a significant reduction in the number of skin lesions and viral load at the standard control time point (day 10) and correlated with high NT_{50} values, indicating strong prophylactic efficacy in the acute phase of infection [90]. In parallel, two non-replicating platforms-a multi-antigenic mRNA-LNP vaccine (BNT166) and a nanocage VLP (SpyCatcher003-mi3)-showed comparable protective efficacy in preclinical models but with differing immunological profiles: BNT166 provided complete prevention of death and suppression of skin lesions in mouse and NHP models and has already advanced to early clinical trials (phase I/II), whereas the VLP construct elicited particularly high humoral responses (neutralizing titers in macaques were higher than in JYNNEOS recipients) and excellent passive protection in transmission models but remains predominantly at the preclinical stage and requires large-scale NHP studies to confirm tolerability and long-term durability of the response [93, 8].

Comparing these data reveals clear differences in profiles and translational trajectories: dBTF occupies an intermediate niche between replicating and fully non-replicating platforms-combining enhanced immunogenicity with modified (reduced) replication and a promising safety profile; the mRNA platform (BNT166) shows the advantage of “rapid” clinical translation and a strong multi-epitope T-cell response; the VLP stands out for its particularly potent humoral activity and promise as a safe non-replicating booster. An important methodological remark: direct inter-platform comparison is complicated by differences in models (mice vs CAST vs NHP), challenge doses, endpoints used (death, clinical burden, local replication), and methods for measuring immune correlates (NT_{50}, time points). Consequently, robust ranking of platforms is currently difficult: there are no standardized head-to-head preclinical studies in NHP and no unified clinical trials with harmonized serological and cellular endpoints, nor a systematic assessment of tolerability in vulnerable groups.

Limitations of available data and research needs

Despite promising preclinical and early clinical results for several platforms, the current evidence base on MPXV vaccines has obvious limitations: many studies involve small group sizes (small n), use different formats of neutralization assays and time points of measurement, and there is an almost complete absence of direct comparative (head-to-head) studies, which makes reliable inter-platform comparison difficult. Priority tasks remain the standardization of methods and the search for correlates of protection (including unification of neutralization formats for NT_{50} and harmonization of parameters for assessing T-cell responses), as well as the conduct of large preclinical studies in non-primate species and randomized comparative clinical trials with unified clinical and serological endpoints. In parallel, well-designed observational studies and sustainable pharmacovigilance programs are needed to assess real-world effectiveness and safety profiles in different populations. Only by

combining standardized laboratory methods, large preclinical series, direct clinical comparisons, and systematic post-registration monitoring will it become possible to reasonably rank platforms according to the criteria of "replication-immunogenicity-safety" and make balanced decisions in shaping national vaccination programs and preparedness strategies.

Conclusions

Monkeypox, first described in 1958 in laboratory monkeys, for a long time remained an endemic zoonosis of Central and West Africa [70, 10]. Since the early 2000s, and especially after 2017, imported and localized cases in non-endemic countries have become more frequent, which has led to a reassessment of global risk; the culmination was a large international outbreak in 2022 that affected more than 100 countries and demonstrated the virus's capacity for wide-scale spread [34, 19, 67, 79].

As of July 2025, no confirmed MPOX cases have been reported in Kazakhstan, but the absence of notifications does not exclude the country's vulnerability given its transit position between Europe and Asia and dense transport and trade links with regions where cases have been recorded (including China, the Russian Federation, and European countries) [73, 83]. Additional concern is raised by the Clade Ib variant, which is actively circulating in Eastern and Central Africa, shows signs of enhanced human-to-human transmission, and has already been detected outside the continent (China, the United Kingdom, Australia) [39, 73].

Particularly important from an epidemiological standpoint are vulnerable groups-men who have sex with men (MSM), people living with HIV and other forms of immunodeficiency, as well as sex workers-as confirmed by analyses of the 2022–2024 outbreaks [58, 57, 80]. The 2022–2023 outbreak demonstrated the key role of close skin-mucosal contacts (including sexual) in transmission; at the same time, detection of viral DNA in semen rarely correlates with the presence of replication-competent virus. The routes of MPXV introduction are not limited to human-to-human transmission: zoonotic events (including the 2003 episode in the USA associated with the import of infected rodents) and natural foci involving reservoir animals remain important sources of new outbreaks. The main mechanisms of transmission are direct contact with skin lesions and biological secretions, fomite transmission (linen, clothing, surfaces), and, with prolonged close contact, the droplet-aerosol route; vertical transmission has been described rarely but is possible. Taken together, these data indicate the need not only for control of the trade in wild animals, but also for strengthening surveillance, rapid identification and isolation of cases, as well as targeted communication and preventive measures for high-risk groups [76, 73, 30, 27, 53, 69, 7, 58, 58, 40, 82].

Modern MPOX vaccines are represented by several platforms that embody trade-offs between immunogenicity, safety, and practical accessibility, so the choice should be context dependent. Non-replicating platforms (MVA-BN / JYNNEOS / IMVANEX) are prioritized-they are preferred for PEP and targeted PrEP in risk groups (laboratory and clinical staff, specific population clusters) due to their favorable safety profile and the possibility of use in individuals with contraindications to replicating vaccines [21, 51, 85]; a two-dose MVA-BN schedule provides a more sustained serological response for planned PrEP, whereas a single dose is applicable in an emergency PEP regimen. LC16-KMB may be considered a useful alternative in scenarios where partial replication is acceptable (including some pediatric groups) [75, 84, 85], whereas ACAM2000, despite its high immunogenicity, is appropriate only under strictly limited indications and with careful selection of recipients [41].

At the same time, significant gaps remain in the evidence base: there are insufficient data on effectiveness in different populations and almost no direct comparative studies. Priorities include standardizing assessment methods and identifying correlates of protection, conducting head-to-head and large-scale NHP/clinical trials, as well as clinical validation of promising mRNA, VLP, and attenuated candidates. Until such data accumulate, it is reasonable for national strategies to be built around ensuring access to vaccines and targeted PrEP/PEP programs for high-risk groups, including: (1) priority development and stockpiling of replicating and non-replicating vaccines; (2) rapid PEP protocols for contacts (optimally within the first 4 days); (3) targeted PrEP campaigns for high-risk occupational groups; (4) systematic data collection for subsequent policy adjustment and platform selection.

Thus, despite the absence of registered MPOX cases in Kazakhstan, maintaining epidemiological vigilance, ensuring the functioning of early detection and laboratory confirmation systems, as well as forming strategic vaccine stockpiles and advancing their development, training healthcare personnel, and conducting targeted information and educational activities among high-risk groups remain priority areas for the national biosafety system.

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POST-STROKE DEPRESSION: IMPACT ON ADHERENCE TO SECONDARY PREVENTION OF ISCHEMIC STROKE AND THE EFFECTIVENESS OF THERAPEUTIC INTERVENTIONS AT THE LEVEL OF PRIMARY HEALTH CARE. LITERATURE REVIEW

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Abstract

Introduction. Post-stroke depression (PSD) is the most common psychiatric complication following a cerebrovascular event. In every second or third patient after a stroke, slowing recovery and worsening clinical outcomes. Despite the availability of validated screening instruments, PSD remains underdiagnosed and underestimated in routine practice.

Objective. To review current literature on post-stroke depression (PSD), its influence on adherence to secondary stroke prevention, and therapeutic interventions at the level of primary health care (PHC).

Search strategy. This review is based on the analysis of publications addressing the impact of PSD on adherence to secondary prevention of ischemic stroke, rehabilitation processes, and clinical outcomes, as well as screening and diagnostic methods applicable in primary health care. The literature search was conducted in PubMed, Scopus, eLibrary, and Cochrane Library databases for the period 2015–2025 using the following keywords: *stroke, post-stroke depression, PHQ-9, Beck Depression Inventory, primary care, screening, rehabilitation*.

Results. According to the literature, PSD is highly prevalent among stroke survivors. In post-Soviet countries, mental health problems remain stigmatized, leading to underrecognition and delayed diagnosis of PSD. Rehabilitation efforts are predominantly focused on motor and cognitive recovery, while depressive symptoms are often overlooked. PSD is associated with decreased treatment adherence, poorer rehabilitation outcomes, cognitive decline, and reduced quality of life.

Conclusion. Early detection and a comprehensive approach to PSD management at the PHC level improve adherence to secondary prevention and rehabilitation measures. Screening programs should be expanded and systematically integrated into routine follow-up care. Timely identification and treatment of PSD improve the quality of life for patients and caregivers engaged in the rehabilitation process.

Keywords: *stroke, depression, screening, secondary prevention, rehabilitation.*

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Резюме

ПОСТИНСУЛЬТНАЯ ДЕПРЕССИЯ: ВЛИЯНИЕ НА ПРИВЕРЖЕННОСТЬ К ВТОРИЧНОЙ ПРОФИЛАКТИКЕ ИШЕМИЧЕСКОГО ИНСУЛЬТА И ЭФФЕКТИВНОСТЬ ТЕРАПЕВТИЧЕСКОГО ВМЕШАТЕЛЬСТВА НА УРОВНЕ ПЕРВИЧНОЙ МЕДИКО-САНИТАРНОЙ ПОМОЩИ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Постинсультная депрессия наиболее частое психическое нарушение после перенесенной мозговой катастрофы. По данным разных источников, постинсультная депрессия развивается у каждого второго-третьего пациента, пережившего инсульт, замедляя восстановление и утяжеляя исходы. Несмотря на наличие доступных валидизированных инструментов диагностики, постинсультная депрессия остается нераспознанным и недооцененным состоянием.

Цель. Обзор современных литературных данных посвященных постинсультной депрессии (ПИД), ее влиянию на приверженность к вторичной профилактике инсульта и терапевтическим вмешательствам на уровне первичной медико-санитарной помощи (ПМСП).

Стратегия поиска. Настоящий обзор основан на анализе публикаций, посвященных влиянию постинсультной депрессии (ПИД) на приверженность вторичной профилактике ишемического инсульта, реабилитационный период и клинические исходы, методам диагностики (инструментам скрининга) на уровне первичной медико-санитарной помощи (ПМСП). Поиск источников осуществлялся из баз данных PubMed Scopus e-Library, Cochrane Library за период с 2015-2025гг. с использованием ключевых слов: Stroke, post-stroke depression, PHQ-9, Beck Depression Inventory, primary care, screening, rehabilitation.

Результаты. Согласно литературным данным, ПИД имеет высокую распространенность среди пациентов, перенесших инсульт. В постсоветских странах проблема психического здоровья остается стигматизированной, что приводит к недооценке и поздней диагностике постинсультной депрессии. При этом реабилитационные мероприятия постинсультных пациентов направлены на восстановление утраченных физических функций и когнитивного дефицита, тогда как депрессивные расстройства часто игнорируется.

Выводы: Ранняя диагностика и комплексный подход в лечении ПИД на уровне ПМСП улучшает приверженность пациентов к вторичной профилактике и реабилитационным мероприятиям. Необходимо развивать программы скрининга и интегрировать их на уровень ПМСП. Чем раньше начато лечение ПИД, тем лучше качество жизни пациентов и их родных, вовлеченных в реабилитацию.

Ключевые слова: *инсульт, депрессия, скрининг, вторичная профилактика, реабилитация.*

Для цитирования:

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Түйіндеме

ПОСТИНСУЛЬТТІК ДЕПРЕССИЯ: ИШЕМИЯЛЫҚ ИНСУЛЬТТІҢ ҚАЙТАЛАМА ПРОФИЛАКТИКАСЫНА БЕЙІЛДІЛІККЕ ӘСЕРІ ЖӘНЕ БАСТАПҚЫ МЕДИЦИНАЛЫҚ-САНИТАРИЯЛЫҚ КӨМЕК ДЕҢГЕЙІНДЕГІ ТЕРАПИЯЛЫҚ АРАЛАСУЛАРДЫҢ ТИІМДІЛІГІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Постинсульттік депрессия – инсульттан кейін жиі кездесетін психикалық бұзылыс. Әдеби деректер бойынша, постинсульттік депрессия инсультті басынан өткерген науқастардың әр екінші–үшінші жағдайында дамиды, қалпына келу қарқынын баяулатып, клиникалық нәтижелерді нашарлатады. Қолжетімді және валидтелген скрининг құралдары бар болғанына қарамастан, постинсульттік депрессия әлі де жиі анықталмайды және жеткіліксіз бағаланады.

Мақсат. Постинсульттік депрессияның (ПИД) қазіргі ғылыми деректерін, оның инсульттің қайталама профилактикасына науқастардың бейілділігіне әсерін және бастапқы медициналық-санитариялық көмек (БМСК) деңгейіндегі терапиялық араласуларды талдау.

Іздеу стратегиясы. Бұл шолу PubMed, Scopus, e-Library және Cochrane Library деректер базаларындағы 2015–2025 жж. жарияланған материалдарды талдауға негізделді. Кілт сөздер: *stroke, post-stroke depression, PHQ-9, Beck Depression Inventory, primary care, screening, rehabilitation.* Талдауға ПИД-тің таралуы, оның клиникалық нәтижелерге және қайталама профилактикаға бейілділікке әсері, сондай-ақ БМСК деңгейінде скрининг әдістері жөніндегі деректер енгізілді.

Нәтижелер. Әдебиеттер көрсеткендей, ПИД инсульттан кейінгі науқастар арасында кең таралған. Посткеңестік елдерде психикалық денсаулық проблемалары жиі стигматизацияға ұшырайды, бұл ПИД-тің кеш анықталуына әкеледі. Реабилитациялық шаралар көбінесе қозғалыс функцияларын және когнитивтік тапшылықты қалпына келтіруге бағытталғанымен, депрессивті бұзылыстар көбіне назардан тыс қалады.

Қорытынды. ПИД-ті ерте кезеңде анықтау және БМСК деңгейінде кешенді емдеу науқастардың қайталама профилактикаға және реабилитациялық шараларға бейілділігін жақсартады. Скрининг бағдарламаларын дамыту және оларды БМСК жүйесіне енгізу қажет. ПИД-ті уақтылы емдеу пациенттердің және оларды күтетін жақындарының өмір сүру сапасын арттырады.

Түйінді сөздер: *инсульт, депрессия, скрининг, қайталама профилактика, реабилитация.*

Дәйексөз үшін:

Ким Е.Д., Кондыбаева А.М., Изекенова А.К., Оспанбекова Д.М., Исмаилов А.К., Нурбекова Г.Б., Мырзахайрова А.О., Мадишева Д.И. Постинсульттік депрессия: ишемиялық инсульттің қайталама профилактикасына бейілділікке әсері және бастапқы медициналық-санитариялық көмек (БМСК) деңгейіндегі терапиялық араласулардың тиімділігі. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 149-158. *doi 10.34689/SH.2025.27.6.017*

Introduction

According to data provided by the World Health Organization (WHO), mortality from cardiovascular diseases continues to rise, increasing from 14 million deaths in 2000 to 17.9 million in 2019 [6]. Stroke and myocardial infarction together account for 85% of all cardiovascular deaths [6], with stroke remaining the second leading cause of mortality globally.

Post-stroke depression (PSD) is an affective disorder that develops at various time points after a stroke and is characterized by anhedonia (loss of the ability to experience pleasure), apathy (loss of interest and emotional indifference), anergia (reduced or lost ability to engage in purposeful activity), as well as cognitive and somatic symptoms [45]. According to ICD-10, this condition is coded under F06.3 "Organic mood (affective) disorders" in the Republic of Kazakhstan [5].

PSD is the most common and clinically significant neuropsychiatric complication of stroke [8]. Its prevalence varies widely, from 20% to 60% across different studies [27]. Underrecognition and delayed diagnosis contribute to reduced adherence to treatment and rehabilitation programs, thereby worsening clinical outcomes [14]. PSD is also associated with more pronounced cognitive impairment and a significantly reduced quality of life [22]. High-risk groups include women and patients with severe motor and cognitive deficits [8,14,15,27]. Approximately one in three stroke survivors develops depressive symptoms within three months to two years after the event [27], and PSD is considered a potential predictor of mortality.

Despite the availability of validated depression assessment tools, early detection of PSD remains challenging [20]. This is largely due to symptom overlap with post-stroke cognitive impairment and the absence of epidemiological data specific to Kazakhstan.

Aim: to analyze current literature to assess the impact of post-stroke depression on the rehabilitation process, adherence to secondary prevention, and outcomes of ischemic stroke, as well as to determine the feasibility of integrating early screening instruments into the practice of primary health care (PHC).

Materials and methods

Study design: literature review.

A comprehensive analysis of scientific publications in Russian and English was conducted using international databases, including PubMed, Scopus, eLibrary, and the Cochrane Library, as well as official resources of the World Health Organization (WHO). Particular emphasis was placed on studies published within the past ten years that provide contemporary evidence on post-stroke depression (PSD) and its impact on the outcomes of ischemic stroke.

Inclusion criteria: peer-reviewed publications presenting data on the epidemiology, pathophysiology, and clinical impact of PSD on rehabilitation processes and outcomes of ischemic stroke; studies describing validated tools for early PSD detection and therapeutic interventions applicable in primary health care (PHC). The analysis included major systematic reviews, clinical trials, and recommendations issued by leading international organizations.

Exclusion criteria: studies lacking clinical data, publications with low levels of evidence, duplicates, articles without full-text access, and research focused on hemorrhagic stroke.

Search strategy:

The following keyword combinations were used:

- ("Post-stroke depression" OR "PSD" OR "Post-stroke rehabilitation" OR "Secondary prevention") AND
- ("Stroke" OR "Ischemic stroke") AND
- ("Diagnostic scales" OR "Depression scales")

Boolean operators **AND**, **OR**, and **NOT** were applied.

Additional filters (English and Russian):

- **Type of publication:** review, meta-analysis, clinical trial, guideline, systematic review
- **Topic areas:** neurology, psychiatry, rehabilitation, public health
- **Age group:** adult, older adult

Results of the review

Despite the high prevalence and clinical significance of this complication, no official statistical data on post-stroke depression (PSD) are available in the Republic of Kazakhstan. The average estimated frequency of PSD in Kazakhstan is presumed to be comparable to global rates; however, objective assessment of its true prevalence requires data from national stroke registries.

More than 49,000 stroke cases are recorded annually in the country, of which 80% are ischemic [2]. According to epidemiological data reported by *Kairatova G.K. et al.* (2022), the incidence of stroke in Kazakhstan has been steadily increasing, rising more than twofold - from 189 per 100,000 population in 2011 to 433 per 100,000 in 2020 [1]. Mortality has reached 180 deaths per 100,000 population per year.

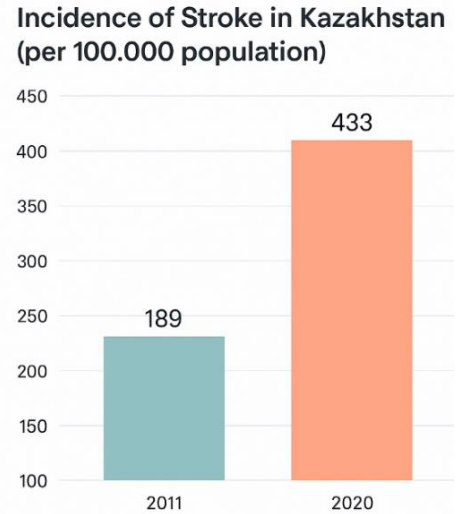


Figure 1. Stroke incidence in the Republic of Kazakhstan

Approximately 29% of all stroke patients are younger than 60 years, representing individuals of active working age. High disability rates (unofficially estimated at 49–80%) in Kazakhstan create a substantial socio-economic burden for the state [1].

Given these data, assessing the true prevalence of PSD remains challenging. The absence of official statistics on the occurrence and impact of PSD on post-stroke recovery in the Republic of Kazakhstan underscores the need for a systematic analysis of contemporary literature and the

implementation of validated early screening tools in the acute and subacute post-stroke period.

Pathophysiological mechanisms of post-stroke depression

The pathophysiological mechanisms of post-stroke depression (PSD) are multifactorial and arise from a combination of ischemic brain injury, psychological stress, and disrupted neurobiological processes [45].

1. Neuroanatomical factors: lesion location and infarct volume

Earlier hypotheses suggested an association between PSD and lesions of the left frontal lobe or basal ganglia, regions responsible for emotional regulation in healthy individuals [16,46]. However, studies by Caeiro [17] and Aben [11] did not confirm a consistent relationship. At the same time, several investigations have demonstrated that larger infarct volume is associated with an increased risk of PSD development [49,51].

2. Monoaminergic neurotransmitter imbalance

Reduced levels of monoaminergic neurotransmitters - serotonin (5-HT), dopamine (DA), and norepinephrine (NE) [43] - result from ischemic injury to ascending brainstem pathways [39,40], forming a core neurobiological basis of PSD.

Experimental PSD models frequently employ middle cerebral artery occlusion (MCAO) [30,41]. MCAO-induced activation of calcium-activated potassium channels (SK channels) in the ventral tegmental area suppresses dopaminergic neuron activity and promotes depression-like behavior, whereas pharmacological inhibition of these channels produces an antipsychotic effect [50].

3. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis

Excessive production of pro-inflammatory cytokines following stroke leads to hyperactivation of the HPA axis and persistent hypercortisolemia [52]. This contributes to impaired neuroplasticity and reduced neurogenesis in emotion-regulating structures, including the hippocampus and prefrontal cortex [37]. Chronic hypercortisolemia is considered a significant risk factor for PSD, particularly when sustained for several months [23].

Prolonged HPA axis activation also disrupts the Keap1-Nrf2 signaling pathway, a key component of the antioxidant defense system, further contributing to PSD development [38].

4. Glutamate-mediated neurotoxicity

Acute elevations in extracellular glutamate - the primary excitatory neurotransmitter [44] - trigger excitotoxic cascades involving cellular swelling, activation of calcium-dependent enzymes, apoptosis, and neuronal death [56]. Elevated serum glutamate concentrations in patients with PSD correlate with greater severity of depressive symptoms [19].

5. Neuroinflammation

Neuroinflammation is a central mechanism of neuronal injury in the post-stroke period [18]. It triggers the release of pro-inflammatory mediators - chemokines, cytokines (IL-6, TNF-α), adhesion molecules, and reactive oxygen species (ROS) - which, despite their initial protective role in ischemic tolerance, ultimately worsen tissue damage [13].

Overactivation of perivascular astrocytes and excessive secretion of cytokines such as IL-6, TNF-α, and MMP-9 disrupt the integrity of the blood–brain barrier [21] and exacerbate necrotic processes. Collectively, these mechanisms contribute to the clinical expression and severity of PSD [28].

Mechanisms by which PSD influences adherence to secondary prevention

The key psychopathological manifestations of post-stroke depression (PSD) that affect patient adherence to secondary prevention measures are outlined below.

1) Anhedonia and apathy (impaired motivation and goal-directed behavior)

PSD is frequently accompanied by anhedonia, apathy, sleep disturbances, and increased fatigability. These symptoms reduce motivation and impair the performance of essential self-management behaviors such as medication intake, participation in physical training, and regular self-monitoring [35]. Notably, antidepressants are not always effective in treating apathy [25].

2) Cognitive and communicative deficits /depressive–executive dysfunction syndrome

PSD is associated with executive dysfunction, aphasia, and low health literacy, which impair planning and complicate adherence to complex treatment regimens. These difficulties often lead to the need for external assistance [34]. Clear explanations and educational materials have been shown to improve adherence to preventive measures.

3) Low patient activation and reduced self-efficacy

PSD diminishes patients' confidence in their ability to manage their condition. Lower engagement in rehabilitation and preventive strategies, as well as negative attitudes toward medical treatment, are independently associated with poorer medication adherence among stroke survivors [48]. Additional barriers - including anxiety, inconvenience of treatment regimens, and concerns about medication side effects - further reduce adherence, often to a greater extent than sociodemographic factors [34].

4) Social isolation and lack of support

Depression correlates with reduced social activity. Research demonstrates a strong association between depression, social support, and the effectiveness of secondary prevention, as well as the benefits of caregiver and family involvement [55]. Living alone and polypharmacy are also linked to lower adherence, amplifying the negative impact of PSD [47].

Impact of post-stroke depression on adherence to secondary prevention of ischemic stroke

Given that PSD occurs in approximately one-third of stroke survivors, the AHA/ASA recommends routine depression screening for all patients following a stroke. A study conducted among older adults (n = 102) demonstrated that higher PHQ-9 scores - indicating more severe depressive symptoms - were associated with lower medication adherence at the 6-month follow-up [47].

Furthermore, a 2019 meta-analysis conducted by a group of Chinese researchers showed that the presence of PSD was associated with an increased risk of recurrent stroke (relative risk ≈ 1.48) [54].

PSD and medication adherence (adherence to anticoagulants, antiplatelet agents, statins, and antihypertensive therapy)

A multicenter cohort study conducted in France demonstrated that PSD identified using the HADS scale (8–

10 points) was associated with incomplete adherence to the full range of secondary prevention measures: OR 1.90; 95% CI 1.05–3.44 [29]. The lowest adherence was observed for statin therapy, which led to poorer vascular outcomes [12].

Influence of PSD on lifestyle and rehabilitation

Large-scale international studies indicate that up to 90% of strokes are attributable to ten major risk factors, either individually or in combination [42].

Key modifiable risk factors include healthy diet, regular physical activity, maintaining a normal BMI, moderate alcohol consumption, and smoking cessation.

PSD significantly reduces adherence to secondary prevention and impairs effective management of modifiable risk factors. The presence of two or more uncontrolled risk factors substantially worsens prognosis [33].

Diagnosis of post-stroke depression at the primary healthcare level

Early detection of PSD within primary healthcare settings is of critical importance. Short, validated, and easy-to-administer screening tools are particularly relevant, as they allow timely identification of at-risk patients without requiring mandatory involvement of a psychiatrist.

Table 1.

Diagnostic tools for post-stroke depression.

Scale	Advantages	Threshold	Sensitivity / Specificity
PHQ-9	Brief, easy to administer (including self-administration), and readily integrable into primary healthcare workflows	≥ 10 (AUC=0,96)	91%/89% (Williams L.S., 2005)
BDI-FS	Complements the PHQ-9 and excludes stroke-related somatic symptoms	≥ 10 (AUC=0,93)	94%/90% (Furlanetto LM, 2005)

These scales are recommended for screening and dynamic monitoring of groups at high risk for developing post-stroke depression.

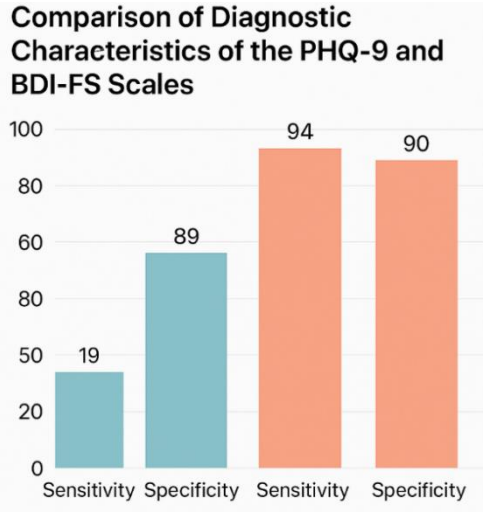


Figure 2. Comparison of Diagnostic Scales

Therapeutic interventions for post-stroke depression at the primary healthcare level

The primary goals of PSD therapy include reducing depressive symptoms, strengthening self-management and motivation, and improving adherence to secondary prevention of ischemic stroke.

Management strategy for patients with PSD in primary healthcare (PHC):

1.Screening for PSD in PHC settings is recommended for all stroke survivors without pronounced cognitive impairment [32].

2.During the initial visit, screening is performed by neurologists and general practitioners using the PHQ-9 and BDI-FS scales. Screening may also be conducted by appropriately trained mid-level healthcare personnel.

3.Repeat assessment of PSD and evaluation of medication adherence (using the MMAS scale) should be performed at 4–6 weeks and subsequently at 3, 6, and 12 months of follow-up [32].

4.All post-stroke patients and their family members must be informed about the risk of developing PSD, which includes patient education during consultations and the provision of informational materials.

5.Prescribing antidepressants is permitted for neurologists and general practitioners in accordance with the Ministry of Health Order № ҚР ДСМ-224/2020

6.*"On the Approval of the Standard for Medical and Social Care in the Area of Mental Health for the Population of the Republic of Kazakhstan"* [7].

Table 2.

Management strategy for patients with post-stroke depression at the primary healthcare level.

Scale	Score range	Degree of depression	Management strategy	Level of evidence
PHQ-9	5-9	Mild	Psychological counseling, cognitive-behavioral therapy (CBT) monotherapy	B
BDI FS	10-15			
PHQ-9	10-14	Moderate	CBT, with antidepressants if required	B
BDI FS	16-19			
PHQ-9	15-19	Severe	Psychiatric consultation, mandatory initiation of antidepressant therapy, and hospitalization in a specialized unit if necessary	A
BDI FS	20-29			
PHQ-9	20-27	Very severe (high suicide risk)	Urgent psychiatric consultation and hospitalization in a psychiatric/neurological facility with selection of combined therapy: pharmacotherapy + psychotherapy.	A
BDI FS	30-39			

Note: Levels of evidence (A, B, C) correspond to the Canadian Stroke Recommendations system (2021) [10].

Key Therapeutic approaches to post-stroke depression in accordance with the AHA/ASA Clinical Guidelines (2017) [8] and Cochrane systematic reviews (2021) [9], include the following components:

1.The primary therapeutic objective is to achieve a clinically significant reduction in depressive symptoms, defined as a decrease of more than 5–6 points on the PHQ-9 and BDI-FS scales within 6–8 weeks of treatment.

2.Completion of all stages of post-stroke rehabilitation, including timely initiation of PSD treatment, contributes to a reduction in depressive severity and accelerates functional recovery.

3.High adherence to rehabilitation measures and secondary prevention strategies is essential for effective PSD management and is associated with improved cognitive and emotional outcomes.

4.Developing self-management skills plays a critical role. These include maintaining a blood pressure diary, adhering to dietary recommendations, and optimizing physical activity. Such measures help achieve target blood pressure levels and lipid profiles (LDL < 1.7 mmol/L), thereby reducing the risk of recurrent ischemic events.

5.Cognitive-behavioral therapy (CBT) is effective both as a treatment modality and as a preventive strategy for PSD in high-risk individuals (those with a history of depressive episodes, significant cognitive or motor impairments, or social isolation).

6.Antidepressants may be prescribed, considering safety and tolerability, for patients with moderate PSD who do not respond sufficiently to CBT. First-line agents include selective serotonin reuptake inhibitors (SSRIs) [8,9].

7.Severe forms of PSD require multimodal therapeutic approaches, incorporating long-term pharmacotherapy with antidepressants, CBT, and additional non-pharmacological interventions (motivational programs, physical activity, and comprehensive psychoeducation).

8.Gradual tapering of antidepressants over 1–2 months is recommended to prevent withdrawal syndrome and minimize the risk of relapse of depressive symptoms

Thus, early diagnosis and timely initiation of treatment for post-stroke depression lead to improved functional and clinical outcomes following ischemic stroke.

Discussion

The prevalence of post-stroke depression (PSD) ranges from 18% to 33%, yet its true occurrence remains difficult to estimate due to insufficient diagnostic practices and low clinical awareness among healthcare providers. These factors contribute to delays in initiating treatment, which negatively affects stroke outcomes.

Established risk factors include female sex, a history of depression, extensive or recurrent strokes, a stroke occurring within the past year, severe disability, and limited social support. These factors should be considered during early risk stratification at the level of primary healthcare (PHC).

The pathophysiological mechanisms of PSD are multifactorial, reflecting the variability of clinical presentations and the heterogeneity of treatment response.

Evidence regarding the effectiveness of preventive interventions remains limited and inconsistent, preventing the formulation of a universal prevention strategy for all stroke survivors. Further research is needed to establish standardized approaches to PSD prevention.

According to current AHA/ASA guidelines and Cochrane reviews, optimal management of PSD includes cognitive-behavioral therapy (CBT) and psychological counseling, either as standalone interventions in mild cases or as part of combined therapy. Selective serotonin reuptake inhibitors (SSRIs) are considered first-line pharmacological agents for moderate and severe depression.

Timely identification of PSD at the primary care level using validated screening tools is of particular importance. For Kazakhstan, key priorities include implementing standardized PSD management protocols within the PHC system, training general practitioners and mid-level healthcare personnel in the use of screening instruments, and integrating depression assessment into the clinical pathway for post-stroke patients.

Study limitations

1.Lack of unified methodological approaches for diagnosing post-stroke depression, including variability in diagnostic criteria, assessment scales, and timing of evaluation.

2.The chronological interval following the stroke is a key factor influencing the clinical course of PSD; its variability complicates comparison across studies.

3.Insufficient research on the diagnosis and management of PSD in outpatient settings (PHC) and in the post-stroke population of Kazakhstan.

4.Limited number of studies evaluating the effectiveness of comprehensive intervention programs (pharmacotherapy + psychotherapy + motivational interventions) within primary healthcare.

5.Lack of national epidemiological data on PSD and its impact on adherence to secondary prevention in the Republic of Kazakhstan.

Conclusions

1.Post-stroke depression is a common complication, occurring in approximately one-third of stroke survivors and significantly impairing functional recovery.

2.PSD is an independent predictor of adverse outcomes, including reduced adherence to secondary prevention, worsening cognitive status, and increased risk of mortality.

3.Early diagnosis and timely treatment of PSD at the PHC level are crucial for successful rehabilitation, as they enhance patient engagement in secondary prevention programs and improve overall prognosis.

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THE ROLE OF INTERVENTIONAL RADIOLOGY IN THE COMPLEX MANAGEMENT OF PORTAL HYPERTENSION COMPLICATIONS. LITERATURE REVIEW

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Abstract

Introduction. Portal hypertension in cirrhosis remains a cause of complications (variceal bleeding, ascites, hypersplenism, hepatic encephalopathy); minimally invasive interventional tactics are indicated in a significant proportion of patients.

Purpose of the study. To summarize data on the efficacy and safety of TIPS, BRTO/PARTO/CARTO, PTHVE and partial splenic artery embolization (PSE), as well as on portal pressure monitoring and postoperative management.

Search strategy. Review (2005–2025) in PubMed/MEDLINE, Scopus, Web of Science, eLIBRARY; RCTs, cohort/retrospective studies, meta-analyses were included; observational studies, abstracts and outdated reviews were excluded. A total of 315 studies were identified, 58 of which were included in the analysis.

Results. Endoscopic ligation provides primary hemostasis in 90–95% and, when combined with β-blockers, reduces recurrence by 40–50%; PTHVE – hemostasis 85–95%, 1-year recurrence ~15–20%, serious complications 3–5%; TIPS prevents recurrence in 80–90% of patients, PE 25–35%; the addition of embolization to TIPS reduces the risk of rebleeding (RR≈0.58), with post-TIPS PPG >12 mmHg – HR≈0.47; for gastric varices BRTO – success 90–95%, PE <5%, PARTO/CARTO are comparable; in refractory ascites TIPS reduces the recurrence rate by more than 70%; PSE increases platelet count by 40–60%: effect lasts ≥6–12 months. Optimization and monitoring: 8 mm stents reduce PE rate; success – HVPG reduction by ≥20–30% or <12 mmHg; Doppler signs of dysfunction – velocity <90 cm/s or >50% gradient; CT/MRI control at 4–6 weeks, ultrasound every 3 months.

Conclusions. Interventional radiology is central; novelty – PPG-guided stratification (>12 mmHg), monitoring, solutions for PE reduction (8 mm stents); questions of transhepatic pressure measurement standardization and optimal intervention sequence remain, requiring prospective studies.

Keywords: *portal hypertension, liver cirrhosis, interventional radiology, hypersplenism, esophageal varices, TIPS*

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Резюме

РОЛЬ ИНТЕРВЕНЦИОННОЙ РАДИОЛОГИИ В КОМПЛЕКСНОМ ВЕДЕНИИ ОСЛОЖНЕНИЙ ПОРТАЛЬНОЙ ГИПЕРТЕНЗИИ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Портальная гипертензия при циррозе остаётся причиной осложнений (варикозные кровотечения, асцит, гиперспленизм, печёночная энцефалопатия); у существенной доли пациентов показана минимально инвазивная интервенционная тактика.

Цель исследования. Обобщить данные об эффективности и безопасности TIPS, BRTO/PARTO/CARTO, PTHVE и частичной эмболизации селезёночной артерии (PSE), а также о мониторинге портального давления и послеоперационном ведении.

Стратегия поиска. Обзор (2005–2025) в PubMed/MEDLINE, Scopus, Web of Science, eLIBRARY; включались РКИ, когортные/ретроспективные исследования, мета-анализы; исключались наблюдения, тезисы и устаревшие обзоры. Идентифицировано 315 работ, в анализ вошли 58.

Результаты. Эндоскопическое лигирование обеспечивает первичный гемостаз в 90–95% и при сочетании с β-блокаторами снижает рецидивы на 40–50%; PTHVE – гемостаз 85–95%, годичный рецидив ~15–20%, серьёзные осложнения 3–5%; TIPS предотвращает рецидив у 80–90% пациентов, ПЭ 25–35%; добавление эмболизации к TIPS уменьшает риск повторного кровотечения (RR≈0,58), при пост-TIPS PPG >12 мм рт. ст. – HR≈0,47; для желудочных вариксов BRTO – успех 90–95%, ПЭ <5%, PARTO/CARTO сопоставимы; при рефрактерном асците TIPS снижает частоту рецидивов более чем на 70%; PSE повышает уровень тромбоцитов на 40–60%: эффект ≥6–12 мес. Оптимизация и мониторинг: стенты 8 мм уменьшают частоту ПЭ; успех – снижение HVPG на ≥20–30% или <12 мм рт. ст.; допплер-признаки дисфункции – скорость <90 см/с или >50% градиент; контроль КТ/МРТ на 4–6-й неделе, УЗИ каждые 3 месяца.

Выводы. Интервенционная радиология занимает центральное место; новизна – PPG-ориентированная стратификация (>12 мм рт. ст.), мониторинг, решения для снижения ПЭ (8-мм стенты); остаются вопросы стандартизации чреспечёночного измерения давления и оптимальной последовательности вмешательств, требующие проспективных исследований.

Ключевые слова: *портальная гипертензия, цирроз печени, интервенционная радиология, гипертспленизм, варикозное расширение вен пищевода, TIPS.*

Для цитирования:

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Түйіндеме

ПОРТАЛДЫ ГИПЕРТЕНЗИЯНЫҢ АСҚЫНУЛАРЫН КЕШЕНДІ БАСҚАРУДАҒЫ ИНТЕРВЕНЦИЯЛЫҚ РАДИОЛОГИЯНЫҢ РӨЛІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Цирроз кезіндегі порталдық гипертензия асқынулардың себебі болып қалады (варикозды қан кету, асцит, гиперспленизм, бауыр энцефалопатиясы); аз инвазивті араласу тактикасы пациенттердің айтарлықтай бөлігінде көрсетілген.

Мақсаты. TIPS, BRTO/PARTO/CARTO, PTHVE және ішінара көкбауыр артериясының эмболизациясының (PSE), сондай-ақ портал қысымын бақылау және операциядан кейінгі басқарудың тиімділігі мен қауіпсіздігі туралы деректерді жинақтау.

Іздеу стратегиясы. Шолу (2005–2025) PubMed/MEDLINE, Scopus, Web of Science, eLIBRARY; RCT, когорттық/ретроспективті зерттеулер, мета-талдаулар қосылды; бақылау зерттеулері, тезистер мен ескірген шолулар алынып тасталды. Барлығы 315 зерттеу анықталды, оның 58-і талдауға қосылды.

Нәтижелер. Эндоскопиялық байлау 90–95% біріншілік гемостазды қамтамасыз етеді және β-блокаторлармен біріктірілгенде қайталануды 40–50% төмендетеді; PTHVE – гемостаз 85–95%, 1 жылдық қайталану ~15–20%, ауыр асқынулар 3–5%; TIPS пациенттердің 80–90%, PE 25–35% қайталануды болдырмайды; TIPS-ке эмболизацияны қосу қайта қан кету қаупін азайтады (RR≈0,58), TIPS кейінгі PPG >12 мм.сын.бағ. – HR≈0,47; асқазанның варикозды BRTO үшін – табыс 90–95%, PE <5%, PARTO/CARTO салыстырмалы; отқа төзімді асцитте TIPS қайталану жиілігін 70% -дан астамға төмендетеді; PSE тромбоциттер санын 40–60%-ға арттырады: әсері ≥6–12 айға созылады. Оңтайландыру және бақылау: 8 мм стенттер PE жылдамдығын төмендетеді; табыс – HVPG ≥20–30% немесе <12 мм рт.ст.-ға төмендеуі; Дисфункцияның доплерологиялық белгілері – жылдамдық <90 см/с немесе >50% градиент; 4-6 аптада КТ/МРТ бақылау, 3 ай сайын ультрадыбыстық.

Қорытынды. Интервенциялық радиология орталық болып табылады; жаңалық – PPG-басқаруымен стратификация (>12 мм.сын. бағ.), мониторинг, ПЭ азайту шешімдері (8 мм стенттер); Транс-бауыр қысымын өлшеуді стандарттау және оңтайлы араласу реттілігі мәселелері перспективалық зерттеулерді қажет етеді.

Түйін сөздер: *порталдық гипертензия, бауыр циррозы, интервенциялық рентгенология, гиперспленизм, өңештің варикоздары, TIPS.*

Дәйексөз үшін:

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Relevance

Portal hypertension (PH) most often occurs in the context of liver cirrhosis and is a significant cause of morbidity and mortality [7, 15]. Its complications – esophageal and gastric varices, ascites, hypersplenism, and hepatic encephalopathy – determine the clinical course and prognosis of the disease [8, 23].

According to the World Health Organization, approximately 500 million people worldwide are infected with hepatitis B and C viruses – the main etiologic causes of cirrhosis and, consequently, portal hypertension. In 2019 alone, hepatitis-related diseases resulted in more than 1.1 million deaths [47], highlighting the scale of the global burden and the need for improved treatment approaches.

Despite advances in pharmacological and endoscopic treatments, their effectiveness remains limited in a significant proportion of patients. According to a systematic review and Bayesian network meta-analysis of 40 RCTs, TIPS (transjugular intrahepatic portosystemic shunt) and DSRS (distal selective splenorenal shunt) are better at preventing recurrent bleeding, but are associated with a risk of hepatic encephalopathy and do not demonstrate a convincing survival benefit compared with endoscopic or medical therapy [9, 58].

Interventional radiological techniques include TIPS, BRTO (balloon-occluded retrograde transvenous obliteration), PARTO/CARTO (vascular plug/coil-assisted retrograde transvenous obliteration), PTHVE (percutaneous transhepatic variceal embolization), and splenic artery embolization; they represent effective, minimally invasive approaches to the treatment of PH and its complications. Successful variceal and collateral obliteration, portal pressure reduction, and clinical stabilization of patients with a wide range of complications have been described [5, 42].

Several meta-analyses, including a contemporary review of TIPS with variceal embolization, have shown that the combined strategy reduces the risk of rebleeding (RR ≈ 0.58) without affecting the incidence of shunt dysfunction, hepatic encephalopathy, and mortality [29]. In a large retrospective study in patients with post-TIPS portal hypertension (PPG > 12 mmHg, the addition of variceal embolization reduced the likelihood of rebleeding (HR = 0.47) [11].

However, the following tasks remain open: determining the optimal sequence of interventions, unifying methods for monitoring portal pressure, and developing highly accurate transhepatic methods for measuring PPG, which will allow for the establishment of stricter criteria for indications and contraindications for interventional procedures [22].

Therefore, conducting a review analysis of the role of interventional radiology in the treatment of portal hypertension complications – with an emphasis on efficacy, safety, and monitoring methods, including new transhepatic pressure measurement techniques – seems highly relevant. Systematization of current data facilitates the refinement of diagnostic and treatment algorithms and improves the clinical prognosis in patients with liver cirrhosis and portal hypertension.

Purpose of the study. To study and systematize current data on the role of interventional radiology in the diagnosis and treatment of complications of portal hypertension in patients with cirrhosis, with an emphasis on the effectiveness, safety and prospects for the clinical use of minimally invasive interventions.

Search strategy

The literature search was aimed at identifying and analyzing publications on the use of interventional radiological methods in the diagnosis and treatment of complications of portal hypertension in liver cirrhosis. The search period of 2005–2025 was chosen because it was during this period that major technological and methodological advances occurred in interventional radiology for portal hypertension: the introduction of covered stents for TIPS, standardization of HVPG measurement, the development and widespread use of BRTO and its modifications (PARTO, CARTO), clarification of indications for PSE, as well as the revision and updating of international consensuses (Baveno VI–VII) and clinical guidelines for the management of patients with cirrhosis. Studies from the last twenty years include large RCTs, meta-analyses, and national/international guidelines based on modern pharmacotherapy regimens (including the use of direct antiviral agents for viral hepatitis), ensuring their consistency with current clinical practice. The choice of this time interval, on the one hand, eliminates the use of outdated data based on early, technically imperfect interventions, and on the other, allows for the monitoring of long-term outcomes and assessment of the safety profile of interventional techniques in a real-world patient population. The search was performed in Russian and English using the following databases and resources: PubMed (MEDLINE), Scopus, Web of Science, Google Scholar, eLIBRARY, and CyberLeninka. In some cases, references to earlier publications of historical significance to the issue under study are provided.

The search strategy used keywords and their logical combinations:

- in Russian: «портальная гипертензия», «цирроз печени», «интервенционная радиология», «эмболизация варикозных вен», «селезёночная артерия», «TIPS», «чреспечёночная эмболизация варикозно-расширенных вен»;
- in English:portal hypertension, cirrhosis, interventional radiology, transjugular intrahepatic portosystemic shunt (TIPS), splenic artery embolization, esophageal varices, portal pressure measurement, BRTO, PARTO, PTHVE, CARTO, embolization.

Inclusion criteria:

- randomized controlled trials (RCTs);
- cohort and retrospective studies;
- systematic reviews and meta-analyses;
- clinical guidelines and consensus documents;
- original papers with clinical and/or experimental data on the topic.

Exclusion criteria:

- isolated clinical cases without generalization;
- conference abstracts;
- unverified sources (newspaper publications, advertisements);
- duplicate or outdated reviews without new data.

The initial search yielded 315 sources. After removing duplicates and applying inclusion/exclusion criteria, 58 publications with the most relevant and representative data were retained for the final analysis (Figure 1).

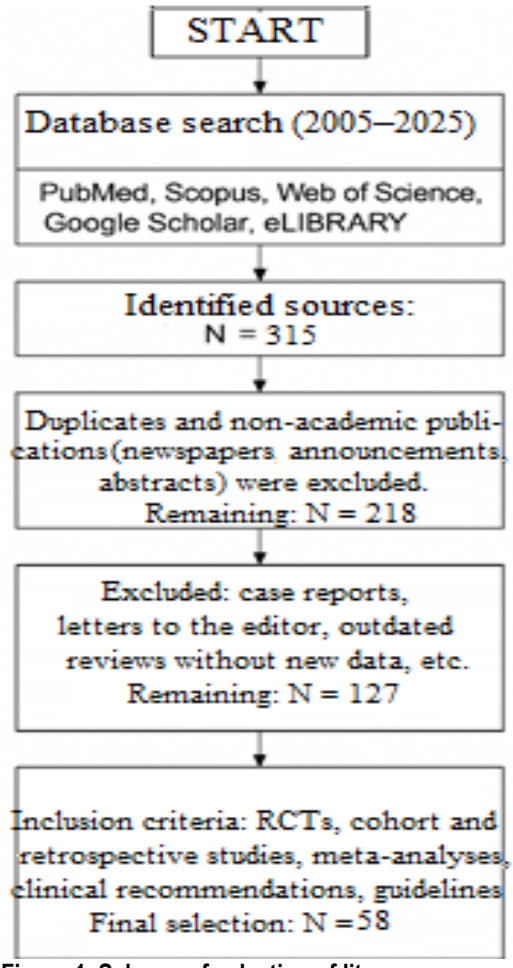


Figure 1. Scheme of selection of literary sources.

Results and discussions

Evolution of interventional methods in portal hypertension

In 1951, R. Myers and D. Taylor were the first to propose indirectly assessing portal pressure: by measuring the gradient between the weighted and free hepatic venous pressure (WHVP), they obtained an approximation to the pressure in the portal vein and thus laid the basis for stratification prognosis in portal hypertension [43].

The first attempts to create an intrahepatic portosystemic shunt without open surgery date back to the early 1980s. In 1983, R. Colapinto (University of Toronto) performed balloon dilation in a human patient to create a connection between the hepatic and portal veins; however, without a metal stent, the shunt quickly collapsed [20]. Clinically stable results were only achieved with the introduction of metal stents.

A turning point was the use of the covered Palmaz stent in TIPS in January 1990, performed by the group of G. M. Richter, Nöldge G., J. Palmaz and M. Rössle at the University of Freiburg (Germany). The use of a metal stent finally eliminated the problem of bypass tract obstruction and ensured the widespread clinical use of the method [48].

In parallel, selective embolization methods for the treatment of complications of portal hypertension were improved. In 1973, F.E. Maddison first described complete embolization of the splenic artery to control bleeding from varicose veins, which became the basis for the subsequent development of partial splenic embolization (PSE) [38]. Within the Soviet/Russian tradition, a significant step in the development of endovascular techniques was made by A. Granov, P.G. Tarazov and V.K. Ryzhkov, who showed that tumor-related arterioportal fistulas may cause hyperkinetic variants of portal hypertension with variceal hemorrhage and demonstrated options for their endovascular treatment [25]. In the same line, a structured account of angiographic diagnostics and endovascular management of portal-hypertensive complications (variceal bleeding, hypersplenism and others) was provided in the monograph by A.M. Granov and A.E. Borisov “Endovascular Surgery of the Liver” (1986), which for many years remained a key reference for surgical and radiological strategies in the treatment of portal hypertension [2].

At the turn of the 1990s, the BRTO (balloon-occluded retrograde transvenous obliteration) method was developed based on the idea of retrograde variceal obliteration. The first series of clinical BRTO interventions were performed in December 1999 by D. Sze and M. D. Dake at Stanford University, using a balloon and a sclerosant (Gelfoam + ethanolamine oleate) [53].

In the early 2010s, modifications of BRTO were proposed that eliminate the need for prolonged balloon retention:

- PARTO (plug-assisted RTO) – Gwon et al., 2013: bypass obliteration using vascular plugs [27];
- CARTO (coil-assisted RTO) – Lee et al., 2012: embolization coils are used instead of a balloon, simplifying the technique and reducing the risk of complications [34].

The evolution of interventional technologies demonstrates a shift from experimental approaches to standardized and highly effective procedures that now form the basis for treating complications of portal hypertension. However, choosing the optimal approach is impossible without understanding the pathogenesis and clinical and hemodynamic typology of the disease. Therefore, it is appropriate to further review the generally accepted classification of portal hypertension, based on the location of portal blood flow blockage and the degree of pressure increase. This serves as the basis for diagnosis, prognosis, and selection of interventional strategies (Table 1).

The table shows that portal hypertension has both etiopathogenetic and hemodynamic classifications, forming the basis for comprehensive diagnosis and treatment. Based on the location of the block, presinusoidal, sinusoidal, postsinusoidal, and suprahepatic variants are distinguished, each with its own causes and clinical features [4]. Sinusoidal portal hypertension is of the greatest clinical significance in liver cirrhosis, as it most often leads to decompensation and complications.

However, presinusoidal forms can be accompanied by severe portal hypertension with normal HVPG, requiring additional diagnostic methods. Classification by HVPG allows for risk stratification: values ≥ 10 mmHg are associated with a high risk of variceal development, while values ≥ 12 mmHg are associated with the likelihood of life-threatening bleeding. Thus, the presented systematization has practical value, facilitating the choice of optimal treatment tactics, prediction of complications and substantiation of indications for interventional procedures.

Table 1.

Classification groups of portal hypertension.

Criteria	Type / Gradation	Characteristics / Main Causes
By block localization	Presinusoidal	Obstruction of the portal or splenic vein (thrombosis, congenital anomalies, schistosomiasis).
	Sinusoidal	The most common cause in liver cirrhosis; increased resistance develops at the level of the hepatic sinusoids.
	Post Sinusoidal	Obstruction at the level of the hepatic veins/small venules (veno-occlusive disease, alcoholic hepatitis).
	Suprahepatic	Obstruction of the hepatic veins or inferior vena cava (Budd-Chiari syndrome, membranous occlusion).
By severity (HVPG)	Norm	≤ 5 mmHg
	Portal hypertension	> 5 mmHg
	Clinically significant portal hypertension (CSPH)	≥ 10 mmHg; high risk of variceal development.
	Critical portal hypertension	≥ 12 mmHg; high risk of variceal bleeding.

Consequently, the transition from early experimental interventions to standardized modern techniques (TIPS, PSE, BRTO, and their modifications) reflects a focus on improving treatment safety and effectiveness. Current classifications, taking into account both the block location and the HVPG level, allow for complication risk stratification and justification for optimal treatment decisions. Combining pathogen-targeted diagnostics with interventional approaches ensures personalized therapy for portal hypertension, increasing survival and improving patient quality of life.

Diagnosis of portal hypertension

Methods for diagnosing portal hypertension can be invasive and non-invasive.

Invasive methods. HVPG is recognized as the "gold standard" for assessing the severity of portal hypertension. The method is based on catheterization of the hepatic vein: first, free venous pressure is measured, then, after balloon occlusion of the ostium, the weighted pressure is measured; their difference is the portal system gradient. Indications include decompensation risk stratification in cirrhosis and an objective assessment of the effectiveness of interventions (TIPS, selective variceal embolization). Limitations: an experienced interventional radiologist, specialized equipment, and an angiographic unit are required; invasive complications (bleeding, infection) are possible. Furthermore, in presinusoidal forms and portal vein thrombosis, HVPG may be incorrect, since it does not reflect extrahepatic pressure [36].

Non-invasive methods. Transient elastography (FibroScan) measures the velocity of ultrasound (shear) waves in the liver, which is directly related to tissue stiffness. Increased stiffness indicates fibrosis and increased intrahepatic resistance, indirectly indicating portal hypertension. This method is suitable for mass screening of patients at risk of cirrhosis decompensation and for monitoring progression during therapy. Results may be affected by venous congestion in the liver (e.g., in heart failure), cholestasis, as well as obesity and severe ascites, which make measurements difficult [32].

Contrast-enhanced ultrasound (CEUS) supplements standard ultrasound by incorporating microbubble contrast, allowing for qualitative and quantitative assessment of liver vascularization and portal blood flow characteristics. Portal hypertension is characterized by delayed portal vein emptying and changes in hepatic sinusoid and collateral filling. CEUS is used to clarify the severity of portal hypertension, predict decompensation, and select optimal candidates for interventional procedures. Limitations include the need for contrast (contraindicated in severe heart failure and allergies) and significant operator-dependent interpretation [39].

Portal vein Doppler ultrasonography allows for the assessment of blood flow velocity and direction, vein diameter, and splenic artery resistive index. These parameters reflect the degree of portal hypertension and are used for initial diagnosis, as well as for follow-up after TIPS or selective embolization. The method depends on the quality of the equipment and the experience of the specialist: with significant ascites, significant obesity, or an unfavorable acoustic window, accuracy is reduced, so the results should be interpreted with caution and, if in doubt, confirmed by other methods [40].

CT and MRI play an important role in the diagnosis of portal hypertension. Multiphase contrast-enhanced CT allows for a detailed assessment of the anatomy of the portal and hepatic veins, identifying thromboses, collaterals, and varicose veins of the stomach and esophagus, as well as associated complications (ascites, hepatocellular carcinoma). MRI, including MR angiography, provides high information content in the study of the vascular bed without radiation exposure and allows for dynamic assessment of portal blood flow. Modern MR elastography quantitatively measures the stiffness of the liver and spleen, which correlates with the severity of portal hypertension and the risk of variceal development. Limiting factors include high cost, limited availability, and contraindications to MRI (implanted devices, claustrophobia) [55].

General treatment tactics

Treatment of portal hypertension is carried out in a stepwise manner, moving from minimally to maximally invasive interventions. Initially, drug therapy is prescribed, followed by endoscopic methods if necessary. If conservative and endoscopic approaches are ineffective, TIPS or surgical bypass procedures are performed [24].

A generalized algorithm for treatment tactics for complicated portal hypertension, reflecting the sequence of interventions and their clinical outcomes, is shown in Figure 2.

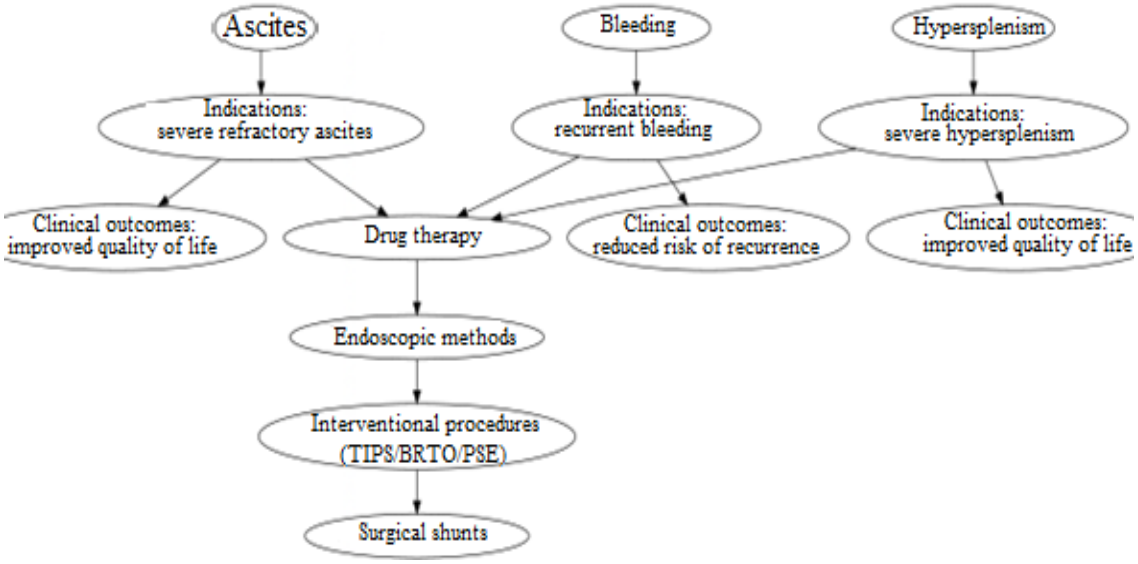


Figure 2. Generalized algorithm for choosing treatment tactics for complicated portal hypertension.

The treatment algorithm for complicated portal hypertension presented in Fig. 2 is based on a stepwise approach: from drug and endoscopic therapy to interventional and, if necessary, surgical procedures. For each complication (ascites, variceal bleeding, hypersplenism), indications and expected outcomes are outlined, emphasizing the individualization of the approach. Interventional techniques (TIPS, BRTO/PARTO/CARTO, PTHVE, PSE) occupy a central place as a link between the conservative and surgical stages. Assessment of clinical outcomes – reduced risk of recurrence and improved quality of life – allows the effectiveness of interventions to be balanced against their invasiveness and potential risks.

Drug therapy is based on the administration of non-selective β-blockers (propranolol, nadolol), antispasmodic nitrates, and vasopressin/terlipressin to reduce portal blood flow and pressure. The main indications are the prevention of primary and secondary bleeding from varicose veins; contraindications are severe bronchial asthma, severe bradycardia, and unstable heart failure [24].

For acute or refractory bleeding from esophageal and gastric varices, endoscopic ligation (EVL) or sclerotherapy are used. Endoscopy provides direct control of the bleeding source and is the first-line therapy in acute episodes, and is also used in combination with β-blockers as an alternative or adjunctive method [24].

If bleeding persists despite optimal medical and endoscopic therapy, the next step is transhepatic variceal vein embolization (PTHVE). This method allows for targeted obliteration of the esophagogastric varices and collaterals. If PTHVE is ineffective or recurrent, TIPS is indicated for the following indications:

- refractory variceal bleeding not controlled by medical and endoscopic therapy;
- secondary bleeding prevention in high-risk patients (Child–Pugh C < 14 points);
- refractory ascites or hydrothorax requiring frequent paracentesis;
- hepatorenal syndrome and pulmonary complications of portal hypertension in selected cases.

TIPS is a key element of interventional tactics: it allows for the control of bleeding and refractory ascites. The choice of technique is based on the liver's functional reserve and the risk of hepatic encephalopathy [41, 46].

To reduce the risk of recurrent bleeding, TIPS is often supplemented with variceal embolization. According to a meta-analysis, this combination almost halves the relative risk of recurrent bleeding without significantly increasing the incidence of shunt dysfunction or encephalopathy [56].

If TIPS is impossible or contraindicated (e.g., severe liver failure, unfavorable venous access anatomy), surgical shunting procedures are performed – distal splenorenal shunt (DSRS) or paraportal portocaval shunt. They provide long-term decompression of the portal system, but require open surgery and are associated with higher periprocedural risk; therefore, they are primarily indicated for young patients with good general condition and an expected survival of more than 5 years [45].

Complications of portal hypertension and their management

Varicose veins of the esophagus and stomach

Endoscopic variceal ligation (EVL) is a first-line treatment for acute bleeding from esophageal and gastric varices. In RCTs, the method provided primary bleeding control in 90–95% of cases and, when combined with non-selective β-blockers, reduced the risk of recurrence by 40–50% [4]. Limitations include the need for repeat sessions (an average of 3–4) and the risk of local complications, such as post-ligation ulcers and esophageal stenosis [1, 3].

The first successful series of transhepatic interventions were described in 1974, after which the method became firmly established in clinical practice as an effective way to stop and prevent recurrent bleeding in portal hypertension. PTHVE is performed by percutaneous catheterization of the portal or splenic vein through the liver parenchyma, followed by the passage of microinstruments into the left gastric vein. Microcoils, adhesive compositions (Histoacryl), sclerosing agents (ethanolamine, polidocanol), or combinations thereof are used to obliterate varices.

According to large retrospective series [23, 28], primary hemostasis in acute bleeding is achieved in 85–95% of cases, and the risk of recurrence within the first year is approximately 15–20%. An additional advantage is the possibility of combined

intervention – simultaneous embolization of collaterals and thrombectomy in portal vein thrombosis.

Limitations of this method include invasive access, the risk of intra-abdominal bleeding, and bile duct damage; however, with modern ultrasound and fluoroscopic guidance, the incidence of serious complications typically does not exceed 3–5%. In Asian and Eastern European countries, transhepatic embolization is often used as a first-line intervention for recurrent variceal bleeding, while BRTO is primarily used for types II–III gastric varices.

If endoscopic treatment is ineffective or bleeding recurrs, TIPS is indicated. Multicenter data confirm that TIPS without embolization prevents recurrent bleeding in 80–90% of cases; however, the risk of hepatic encephalopathy is 25–35% [2, 46]. The addition of variceal embolization to TIPS further reduces the relative risk of recurrence by almost half (RR ≈ 0.58) without a statistically significant increase in the incidence of shunt dysfunction or encephalopathy [12].

Retrograde obliteration techniques are increasingly being used for patients with type II–III gastric varices, particularly in cases of failed endoscopy or in the presence of large gastrorenal bypass grafts:

- BRTO provides a 90–95% clinical success rate in stopping bleeding and almost completely prevents recurrence; the risk of encephalopathy is <5% [44];
- PARTO and CARTO simplify the BRTO technique, eliminating the need for prolonged balloon retention. PARTO has been shown to have comparable efficacy to BRTO and a favorable safety profile (recurrence <10%, encephalopathy <3%) [27], while CARTO demonstrates similar results with a shorter procedure time and a lower sclerosant dose [35].

Table 2 provides a comparative analysis of the main interventional techniques for PG according to key clinical criteria.

Table 2.

Interventional treatment methods for PG.

Method	Main indications	Brief Description of the Technique	Clinical efficacy level	Main risks	Special Notes
TIPS	Prevention of recurrent bleeding	Creation of an intrahepatic portosystemic shunt	70–80%	Encephalopathy, shunt dysfunction	Not used in severe liver failure
BRTO	Gastric varices types II–III	Injection of sclerosant into gastrorenal collaterals with temporary balloon occlusion	80–100%	Ascites, increased portal pressure	Preferred for large gastrorenal bypasses
PARTO	Recurrent bleeding	Sclerotherapy using a vascular plug instead of a balloon	75–95%	Ascites	Simplifies the BRTO technique, reduces procedure time
CARTO	Recurrent bleeding	Sclerotherapy using embolization coils	75–85%	Ascites	Less sclerosant required, shorter procedure
PTHVE	Bleeding from varices after unsuccessful endoscopy; bridge to TIPS	Transhepatic approach; selective obliteration of varices/collaterals	85–95%	Invasiveness, bleeding, bile duct injury	Targeted obliteration; ± thrombectomy; bridge or alternative to TIPS
PSE	Hypersplenism, thrombocytopenia	Partial embolization of the splenic parenchyma	Increase in platelet count by 40–60%	Post-embolization syndrome, pleural effusion	Improves preparation for invasive procedures

The comparative table shows that each interventional technique for portal hypertension has clear indications and its own risk-benefit balance. TIPS remains a universal solution for controlling bleeding and refractory ascites, but is associated with an increased risk of encephalopathy. BRTO and its modifications (PARTO, CARTO) are particularly effective for gastric varices, providing a high rate of recurrence prevention; simplified PARTO/CARTO techniques offer advantages in terms of convenience and safety. PTHVE is appropriate when endoscopy is unsuccessful or unavailable as a bridge/alternative to TIPS, providing targeted obliteration of collaterals and, if necessary, combination with thrombectomy. PSE does not directly reduce portal pressure, but it reliably corrects hypersplenism and can serve as a preparatory step for other interventions. The choice of strategy should be individualized based on the anatomy, functional state of the liver, and clinical priorities.

Ascites

The first step in treating ascites in cirrhosis is drug therapy with diuretics and albumin. A combination of spironolactone (100–400 mg/day) and furosemide (40–160 mg/day) is typically used, which ensures a negative sodium balance and effective removal of excess fluid. In large paracenteses, simultaneous albumin infusion at a rate of 6–8 g/L of removed fluid reduces the risk of paracentesis-related circulatory dysfunction, maintains circulating volume, improves renal parameters, and reduces post-puncture complications [6, 13, 49].

In refractory ascites – when adequate doses of diuretics are ineffective or relapse occurs less than 4 weeks after large-volume paracentesis – regular therapeutic paracentesis with albumin replacement is indicated. Removal of up to 8–10 liters of ascitic fluid is performed under ultrasound guidance, which reduces the risk of bleeding and infectious complications [49].

In patients with refractory ascites, despite optimal diuretic regimens and repeated paracenteses, TIPS significantly improves outcomes. Multicenter RCTs have shown that, compared with paracentesis, TIPS reduces the rate of ascites recurrence by more than 70% and improves quality of life due to a smaller ascites volume, reduced hospitalizations, and better exercise tolerance [10, 18]. The main limitations of the method are the risk of hepatic encephalopathy (20–30%) and

the need for strict patient selection taking into account liver function and risk profile [17].

Hypersplenism

In portal hypertension, PSE is performed to correct hypersplenism accompanied by thrombocytopenia, leukopenia and anemia.

Indications for PSE:

- Thrombocytopenia (< 50 × 109 L) preventing safe endoscopic or surgical interventions;
- Severe hypersplenism with frequent bleeding or refractory ascites;
- Preparation for TIPS or liver transplantation with a risk of bleeding.

The technique involves percutaneous catheterization of the splenic artery under X-ray control, followed by embolization of 50–70% of the parenchyma with polyvinyl alcohol particles or microspheres. Selective or segmental embolization preserves the arterial buffer response and reduces the risk of necrosis of large areas of tissue [31].

Short-term results include a 40–60% increase in platelet counts within 1–2 weeks after the procedure, a reduction in the severity of ascites, and a decrease in the incidence of variceal bleeding. Typical adverse events include post-embolization syndrome (fever, pain in the left hypochondrium), which is usually relieved by analgesics and NSAIDs [31].

Long-term effects: a sustained increase in platelets by 30–50% persists for 6–12 months or longer, allowing for planned endoscopic and surgical interventions without a high risk of bleeding. The procedure also reduces the load on the portal system and is sometimes accompanied by a reduction in ascites volume [31].

Clinical experience in Kazakhstan confirms the high efficacy of PSE. In a series of more than 170 procedures performed in clinics in Almaty and Astana, regional interventional radiologists recorded an average increase in platelet count from 45 × 10^9L to 95 × 10^9L and a 35% reduction in the incidence of recurrent ascites in the first six months after the procedure. These data indicate the safety of the method and its suitability for inclusion in standard care for patients with complicated portal hypertension in domestic practice [54].

Hepatic encephalopathy

Hepatic encephalopathy (HE) is one of the most serious complications of decompensated cirrhosis, especially after TIPS. Lactulose and L-ornithine-L-aspartate (LOLA) are recommended for the prevention and treatment of minimal and mild HE in the pre- and post-procedural periods. A multicenter RCT demonstrated that lactulose improves cognitive function, reduces the frequency of minimal HE episodes, and modulates the intestinal microbiota, which is of key importance before TIPS and during follow-up [51].

The selection of technical parameters of TIPS, primarily the stent diameter, determines the balance between portal pressure reduction and the risk of PE. *Van K. et al.* showed that 8 mm covered stents are comparable to 10 mm in preventing recurrent variceal bleeding, but are significantly less likely to cause encephalopathy [37]. Similar data were presented by *Lo K. et al.,* confirming the feasibility of a smaller diameter for reducing neurological complications without losing the effectiveness of decompression [30].

In spontaneous portosystemic shunts leading to recurrent PE, interventional obliteration is used – PTO (percutaneous transhepatic obliteration) and PTS (percutaneous transhepatic sclerotherapy). According to Ishikawa T. et al., targeted elimination of the pathological shunt significantly reduces the frequency of PE episodes and improves the general neurological status of patients [50].

Other complications

Portosystemic shunt syndrome (PSS) occurs when excessive blood flow through TIPS or spontaneous portosystemic collaterals leads to recurrent PE, decreased liver perfusion, and cognitive impairment. For correction, embolization of pathological shunts is performed via a percutaneous transjugular or transhepatic approach using microcoils or vascular plugs. In a series of 28 patients by Saad V.E., complete obliteration of the shunts resulted in the resolution of encephalopathy in 85% of cases and improvement in liver function tests without a significant increase in portal pressure [50].

Rare but clinically important complications include splenorenal aneurysms, shunt thrombosis, and prosthetic infection.

Splenorenal aneurysms are often detected incidentally during follow-up examinations after selective splenic artery embolization. For most aneurysms <2 cm, dynamic observation is preferred, whereas aneurysms >2 cm or symptomatic ones are subject to endovascular occlusion with microcoils or vascular plugs [19, 21].

TIPS graft thrombosis occurs in 5–10% of cases and is manifested by increased portal pressure, recurrent ascites, or bleeding. Patency is restored by thrombolysis followed by angioplasty or implantation of an additional stent [52].

Prosthetic stent infection is rare (<1%) and is usually associated with bacteremia or hematogenous spread of microorganisms. Treatment involves a long course of broad-spectrum antibiotics and, if necessary, removal or replacement of the infected stent segment [15].

Algorithm for postoperative monitoring and criteria for early detection of obstruction

After TIPS, PSE, BRTO/PARTO, and PTHVE, a uniform follow-up protocol combining imaging and clinical assessment is required. At 4–6 weeks after the procedure, multiphase abdominal CT or MRI is performed to confirm graft patency, exclude bleeding, and monitor stent position [57]. Doppler ultrasound is performed every 3 months during the first year and then every 6 months. Blood flow velocity in the TIPS tract < 90 cm/s or a difference of > 50 cm/s between two adjacent segments indicates a stricture and requires angioplasty or stenting [33].

Indications for repeat interventions:

- An increase in portal gradient of more than 5 mmHg compared to baseline after TIPS;
- An increase in varicose vein sac volume on follow-up ultrasound/CT by more than 20% of the previous value;
- Recurrence of bleeding or ascites in the absence of signs of infection or non-compliance with therapy [58].

Success criteria: reduction of portal pressure by 20–30% or more (achieving HVPG < 12 mmHg), absence of recurrent variceal bleeding, and cessation or significant reduction of ascites without frequent paracentesis. Warning signs: appearance of new collaterals, slow or turbulent blood flow in the TIPS tract, as well as clinical decompensation (increased encephalopathy, increased ascites) with preserved shunt anatomy [16].

Conclusion

Interventional radiology plays a key role in the modern management of portal hypertension complications. Minimally invasive procedures – PTHVE, TIPS, BRTO/PARTO/CARTO, and selective splenic artery embolization – effectively reduce portal pressure, control recurrent variceal bleeding, reduce the incidence of refractory ascites, and correct hypersplenism, often providing faster clinical results and improved quality of life compared to traditional approaches.

The safety of interventions has significantly improved thanks to technological advances – the use of covered stents, precise optimization of bypass graft diameter, and the use of microcoils and vascular occluders. This has reduced the risk of encephalopathy and bypass dysfunction. Standardized imaging and clinical monitoring protocols allow for the timely detection of warning signs – such as bypass obstruction, variceal sac enlargement, and cognitive deterioration – and targeted repeat interventions.

Promising milestones include the development of transhepatic methods for direct portal pressure measurement, equipping stents with integrated flow/pressure sensors, and the implementation of AI models for individualized treatment. These approaches will enable more precise risk stratification, continuous hemodynamic monitoring, and informed selection of optimal interventional strategies for each patient.

Therefore, the combination of evidence-based interventional techniques, technological improvements, and digital predictive tools forms the basis for multidisciplinary management algorithms aimed at improving survival and quality of life in patients with liver cirrhosis and portal hypertension.

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THE STATE OF CARBOHYDRATE METABOLISM AND RENAL FUNCTION IN PATIENTS WITH ACUTE CORONARY SYNDROME. LITERATURE REVIEW

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Abstract

Introduction. Cardiovascular diseases (CVD) are the most common cause of morbidity and mortality worldwide [41,84]. In most cases, kidney pathology also develops in parallel with the conditions described above, manifesting as albuminuria and a reduction in glomerular filtration rate (GFR), which can progress to end-stage renal failure and a fatal outcome [37].

Objective. To summarize the literature on the state of carbohydrate metabolism and renal function in patients with acute coronary syndrome (ACS).

Search strategy. An analysis of open-access literature sources from the scientific databases PubMed, Medline, Google Scholar, Cyberleninka for the past 7 years (2018-2025) was conducted. The following keywords were used for the search: carbohydrate metabolism, diabetes mellitus, prediabetes, acute coronary syndrome, renal function, cardiorenal syndrome, cardiorenometabolic syndrome. This literature review included full-text articles in Russian and English. A total of 206 papers were analyzed, of which 100 met the study objectives and inclusion criteria.

Results. This literature review presents data on the state of carbohydrate metabolism and renal function in patients with ACS.

Conclusion. Based on the literature review, it was found that carbohydrate metabolism disorders (CMD) are quite common in patients with ACS - data vary from 11 to 67%. ACS is often accompanied by renal dysfunction (RDI). The incidence of renal dysfunction among patients with ACS, according to literature data, is 10 - 61%. Simultaneous damage to the cardiovascular system and kidneys in combination with CMD is called cardio-renometabolic syndrome, the presence of which significantly aggravates the prognosis.

Key words: *carbohydrate metabolism, diabetes mellitus, prediabetes, acute coronary syndrome, renal function, cardiorenal syndrome, cardiorenometabolic syndrome*

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Резюме

СОСТОЯНИЕ МЕТАБОЛИЗМА УГЛЕВОДОВ И ФУНКЦИИ ПОЧЕК У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Сердечно-сосудистые заболевания (ССЗ) являются наиболее распространенной причиной заболеваемости и смертности во всем мире [41,84]. В большинстве случаев параллельно с вышеописанными состояниями появляется и почечная патология в виде альбуминурии и снижения скорости клубочковой фильтрации (СКФ) вплоть до развития терминальной почечной недостаточности и летального исхода [37].

Цель. Обобщение литературных сведений о состоянии углеводного обмена и функции почек у пациентов с острым коронарным синдромом (ОКС).

Стратегия поиска. Проведен анализ литературных источников в открытом доступе из научных баз данных PubMed, Medline, Google Scholar, Cyberleninka за последние 7 лет (2018-2025 гг.). Для поиска использовались ключевые слова: углеводный обмен, сахарный диабет, предиабет, острый коронарный синдром, функция почек, кардиоренальный синдром, кардиоренометаболический синдром. В данный литературный обзор были включены полнотекстовые статьи на русском и английском языках. Всего проанализировано 206 работ, из них цели исследования и критериям включения соответствовала – 100.

Результаты. В данном литературном обзоре представлены данные о состоянии углеводного обмена и почечной функции у пациентов с ОКС.

Заключение. На основании проведенного обзора литературы установлено, что нарушения углеводного обмена (НУО) достаточно часто встречаются у пациентов с ОКС – данные варьируют от 11 до 67%. ОКС нередко сопровождается и нарушением функции почек (НФП). Частота встречаемости почечной дисфункции среди пациентов с ОКС согласно литературным данным составляет 10 - 61%. Одновременное поражение сердечно-сосудистой системы и почек в сочетании с НУО именуется термином кардио-рено-метаболический синдром, наличие которого значительно отягощает прогноз пациентов.

Ключевые слова: *углеводный обмен, сахарный диабет, предиабет, острый коронарный синдром, функция почек, кардиоренальный синдром, кардиоренометаболический синдром*

Для цитирования:

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Түйіндеме

КӨМІРСУ АЛМАСУЫНЫҢ ЖАҒДАЙЫ ЖӘНЕ БҮЙРЕК ҚЫЗМЕТІ ЖЕДЕЛ КОРОНАРЛЫҚ СИНДРОМЫ БАР НАУҚАСТАРДА. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Жүрек-қан тамырлары аурулары (ЖҚА) әлем бойынша сырқаттанушылық пен өлім-жітімнің ең кең таралған себебі болып табылады [41,84]. Көп жағдайда жоғарыда сипатталған жағдайлармен қатар альбуминурия және шумақтық сүзілу жылдамдығының (ШСЖ) төмендеуі түріндегі бүйрек патологиясы да пайда болады, бұл терминалдық бүйрек жеткіліксіздігінің дамуына және өлімге дейін әкелуі мүмкін [37].

Мақсаты. Жедел коронарлық синдромы (ЖКС) бар науқастарда көмірсу алмасуының жағдайы мен бүйрек қызметі туралы әдеби деректерді талдап, жинақтау.

Іздеу стратегиясы. Соңғы 7 жыл ішінде (2018–2025 жж.) PubMed, Medline, Google Scholar, CyberLeninka ашық ғылыми дерекқорларындағы әдеби дереккөздерге талдау жүргізілді. Іздеу барысында келесі негізгі сөздер пайдаланылды: көмірсу алмасуы, қант диабеті, предиабет, жедел коронарлық синдром, бүйрек қызметі, кардиоренальды синдром, кардиоренометаболикалық синдром. Шолу аясында қазақ және ағылшын тілдеріндегі толық мәтінді мақалалар қарастырылды. Жалпы 206 жұмыс талданып, оның 100-і іріктеу критерийлеріне сәйкес келді.

Нәтижелер. Әдеби шолуда ЖКС бар науқастарда көмірсу алмасуы мен бүйрек қызметінің жағдайына қатысты мәліметтер ұсынылған.

Қорытынды. Әдеби деректерді талдау ЖКС бар науқастар арасында көмірсу алмасуының бұзылыстары (КАБ) жиі кездесетінін көрсетті, олардың таралу жиілігі 11%-дан 67%-ға дейін. Сонымен қатар, ЖКС жиі бүйрек қызметінің бұзылуымен (БҚБ) қатар жүреді, оның таралу жиілігі 10%-дан 61%-ға дейін жетеді. Жүрек-қантамыр жүйесі мен

бүйректің бір мезгілде зақымдалуы, көмірсу алмасуының бұзылыстарымен бірге кардиореометаболикалық синдром деп аталады. Бұл синдромның болуы науқастың болжамын айтарлықтай нашарлатады.

Түйінді сөздер. *Көмірсу алмасуы, қант диабеті, предиабет, жедел коронарлық синдром, бүйрек қызметі, кардиоренальды синдром, кардиореометаболикалық синдром.*

Дәйексөз үшін:

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Introduction

Cardiovascular diseases (CVD) are the most common causes of morbidity and mortality worldwide [22]. Similarly, diabetes mellitus (DM) is also a major contributor to these adverse outcomes [73]. At the same time, global data on the prevalence of CVD among individuals with type 2 diabetes (T2D) remain insufficient. From this standpoint, the findings of the recent CAPTURE study are highly important: among 9,823 participants with T2D, more than one-third (n = 3,582; 36.5%) had confirmed CVD. Confirmed CVD was defined as the presence of any of the following conditions: coronary artery disease (CAD), cerebrovascular disease, heart failure, arrhythmias or cardiac conduction disorders, aortic disease, or peripheral or carotid artery disease [55]. The prevalence of CAD in patients with T2D reaches 21%. Noteworthy are also data demonstrating a high prevalence of prediabetes and T2D among individuals with CVD, particularly those with CAD [8]. The incidence of DM in the setting of acute coronary syndrome (ACS) ranges between 25–30% [13, 6]. It is also well known that many patients with CVD present with impaired renal function (IRF) [39].

Aim. To summarize the literature data on carbohydrate metabolism and renal function in patients with acute coronary syndrome.

Search Strategy

The literature search for the present review was conducted using major scientific databases, including PubMed, Medline, Google Scholar, and CyberLeninka. Publications from the last seven years (2018–2025) were considered. Selection was carried out among systematic reviews, meta-analyses, and original research articles published in both Russian and English. The search strategy was based on the use of the following key terms: «carbohydrate metabolism», «diabetes mellitus», «prediabetes», «acute coronary syndrome», «renal function», «cardiorenal syndrome» and «cardiorenometabolic syndrome».

The inclusion criteria were: articles published between 2018–2025, available in full-text format, written in either Russian or English, and classified as systematic reviews, meta-analyses, or original research studies. The exclusion criteria were: publications in other languages, materials presented in the form of theses or abstracts, as well as studies not relevant to the stated topic of the present review.

A total of 206 publications were identified through the search. The majority of the studies were retrieved from PubMed (96 publications) and CyberLeninka (54 publications). Google Scholar and Medline contained 30 and 26 publications respectively. At the stage of initial screening, 12 duplicate articles were excluded. Additionally, 58 studies published in foreign sources requiring paid access, as well as 36 publications unrelated to the research topic, were excluded. As a result of the selection, 100 publications that most comprehensively reflected current data on the studied issue were included in the analytical part of the review. The selection algorithm is presented in Fig. 1.

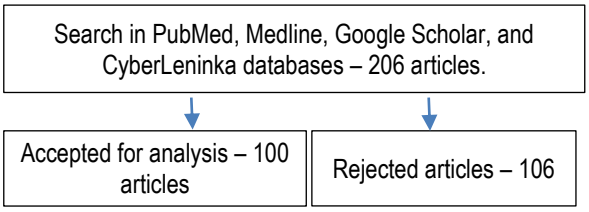


Figure 1. Flow diagram of materials extraction.

Definition and Classification of ACS

Acute coronary syndrome (ACS) is a modern synonym for the concept of acute coronary artery disease (CAD). CAD is a supra-nosological concept that may present in acute or chronic forms [9].

ACS includes the following conditions: myocardial infarction (MI), sudden coronary death, acute coronary thrombosis without MI development in the context of thrombolytic therapy (TLT) and/or percutaneous coronary intervention (PCI), and unstable angina (UA) [9].

According to the definition by Thygesen et al., ACS encompasses conditions characterized by acutely occurring clinical symptoms, 12-lead electrocardiogram (ECG) changes (with or without such changes), and marked elevation of cardiac troponin (cTn) concentrations (with or without such elevation) [87,40].

Patients with suspected ACS may be diagnosed with acute MI or unstable angina (UA). The diagnosis of MI is made according to the Fourth Universal Definition, which is based on the detection of elevated serum cTn levels in patients [87,3].

UA is an ACS manifesting with a characteristic clinical presentation (progression of exertional angina functional class, onset of rest angina, and a high likelihood of progression to MI) in the absence of biochemical markers of cardiomyocyte injury. The clinical and pathogenetic variants of UA are reflected in the Braunwald classification (Table 1) [27].

In patients presenting with sudden-onset acute chest pain or its equivalent and persistent ST-segment elevation or its equivalents, ST-segment elevation myocardial infarction (STEMI) is diagnosed. In most of these patients, myocardial necrosis and elevated cTn levels are observed.

In cases of anginal chest pain without persistent ST-segment elevation (or its equivalents) on ECG, a preliminary diagnosis of non–ST-segment elevation ACS (NSTE-ACS) is established. ECG changes may include the following: transient ST-segment elevation, persistent or transient ST-segment depression, T-wave abnormalities including hyperacute T-waves, T-wave inversion, biphasic or flattened T-waves, and T-wave pseudonormalization. In

some cases, the ECG may remain normal. In most such patients with characteristic rises and falls in cTn levels, non–ST-segment elevation myocardial infarction (NSTEMI) is diagnosed. In patients with normal cTn levels, unstable angina (UA) is diagnosed [21].

Table 1.

Classification of unstable angina by E. Braunwald.

Variants ⇩ ⇨ Causes Angina pectoris	A – presence of an external factor that increases ischemia Secondary UA (unstable angina)	B – no external factor causing angina Primary UA (unstable angina)	C – возникает в течение 2-х недель после инфаркта миокарда Постинфарктная НС
I – severe exertional angina (new-onset or progressive)	IA	IB	IC
II – angina within the past month, but not during the preceding 48 hours; subacute rest angina	IIA	IIB	IIC
III – rest angina during the preceding 48 hours; acute rest angina	IIIA	IIIB	IIIC

Importantly, at the Cardiology Congress held in London in 2024, it was emphasized that ACS may arise as a result of progression and destabilization of a condition referred to as chronic coronary syndrome (CCS). This term was first introduced in 2019 at the European Cardiology Congress in Paris, where it was adopted to replace the previous term «stable coronary (ischemic) disease». CCS represents a condition evolving from the formation of an atherosclerotic plaque to the development of functional coronary artery impairment. The mechanisms underlying CCS are associated with myocardial ischemia caused by diffuse atherosclerotic involvement rather than solely by flow-limiting stenoses [88,12].

Classification of Myocardial Infarction

The current MI classification distinguishes five types [25]:

Type 1. MI resulting from rupture or erosion of an atherosclerotic plaque (AP), leading to thrombus formation, significant reduction of blood flow distal to the affected AP, and development of myocardial necrosis. Less commonly, type 1 MI may be caused by the formation of an intraplaque hematoma with progressive enlargement and narrowing of the arterial lumen.

Type 2. Occurs due to ischemia either in the presence or absence of coronary atherosclerosis, and may result from embolism or spontaneous coronary artery dissection, hypoxia, arrhythmias, blood pressure fluctuations, and other causes.

Type 3. Type 3 MI corresponds to cases of acute MI confirmed at autopsy, as patients die before blood samples can be obtained to detect biochemical markers of myocardial necrosis. Supporting evidence for acute MI may include a history of ischemic symptoms and characteristic electrocardiographic changes.

Type 4a. MI associated with complications occurring during percutaneous coronary intervention (PCI) or within the first 48 hours following the procedure.

Type 4b. MI caused by coronary stent thrombosis confirmed by either coronary angiography (CAG) or autopsy. Depending on the time elapsed after stent implantation, stent thrombosis is classified as acute (0–24 h), subacute (>24 h–30 days), late (>30 days–1 year), and very late (>1 year).

Type 4c. MI due to restenosis in the artery corresponding to the necrosis zone, occurring in the absence of thrombosis and other lesions in the infarct-related artery.

Type 5. MI associated with coronary artery bypass grafting (CABG).

This MI classification takes into account several factors, including the underlying causes and mechanisms, updated ECG criteria, coronary imaging findings, and levels of high-sensitivity biomarkers.

In ESC member countries, cardiovascular diseases (CVD) account for approximately 2.2 million deaths among women and more than 1.9 million deaths among men. Among mortality causes attributed to CVD, coronary artery disease (CAD) accounts for 38% of deaths in women and 44% in men [86]. ACS is often the first clinical manifestation of CAD. According to expert data, in 2019, 5.8 million new cases of CAD were recorded across 57 ESC member countries [86].

Prevalence of Disorders of Carbohydrate Metabolism among Patients with ACS

A significant proportion of patients with cardiovascular diseases (CVD) have diabetes mellitus (DM). The risk of peripheral artery disease and the development of coronary artery disease (CAD) in DM is associated with a range of factors, primarily hyperglycemia, insulin resistance, and elevated levels of advanced glycation end-products (AGEs) [38,28,34,41,71,45,79,80].

It is well known that disorders of carbohydrate metabolism (DCM) are frequently detected in patients with ACS. According to registry data, DM in ACS patients is observed at a frequency of 22–65% [30,31,98,97].

Among patients with ST-segment elevation myocardial infarction (STEMI), one quarter had a previously documented diagnosis of DM, and more than 40% had prediabetes or newly diagnosed type 2 DM (T2DM) [56,82,37].

According to the results of a well-known epidemiological study, The Euro Heart Survey on Diabetes and the Heart (EHS), which included 2,107 ACS patients with no prior history of DCM, such disorders were identified in 58% of cases, with newly diagnosed T2DM in 22%. Even more

patients (36%) were found to have impaired glucose tolerance (IGT) [70].

In a study by *Rizaeva M.A.* [17], among 344 patients with MI aged 35 to 90 years, DCM were detected in 55% of cases.

Sheen M. et al. [76] found T2DM in 19.03% of 529 STEMI patients, of whom newly diagnosed T2DM accounted for 11.11%.

According to data from *Nikitina E.A.,* the prevalence of T2DM among patients with non–ST-segment elevation ACS (NSTE-ACS) was 12.17%, while in patients with ST-segment elevation ACS it was 13.89%.

The detection rate of DM among MI patients ranges from 14.3% to 40.9% [13].

According to *Shestakova M.V. et al.* [19], T2DM was identified in 8–14% of patients with CVD, and prediabetes in 14.6–36.4% of cases, which exceeds the corresponding population indicators reported in the NATION study (5.4% and 19.3%, respectively) [96].

In a study by *E.H. Ploumen et al.,* among 988 patients who underwent PCI, newly diagnosed T2DM was detected in 68 patients (6.8%), while 132 patients (13.4%) had prediabetes [66].

According to a meta-analysis conducted by *J. Yang et al.* in 2020, the prevalence of prediabetes among patients with ACS ranged from 26% to 38% [93].

In another study published by *L. Nguyen et al.* in 2020, approximately 34% of ACS patients had prediabetes [62].

According to a separate meta-analysis by N*. Laichuthai et al.*, the prevalence of prediabetes among patients with acute MI was 48.4% [50].

It is widely recognized that prediabetes is a major predictor of T2DM development. It has been demonstrated that T2DM develops in nearly all individuals with previously diagnosed prediabetes over the course of life, with one quarter of these patients progressing within the first 3–5 years. In addition to the high likelihood of T2DM development, individuals with prediabetes have an increased risk of both macrovascular and microvascular diabetes-related complications [44,59].

According to the literature, the course of ACS is significantly aggravated by the occurrence of another type of DCM known as «stress hyperglycemia». Stress hyperglycemia is a transient elevation of plasma glucose levels in critically ill patients, with or without pre-existing DM [29,26,35]. Critical states in this context include major surgical interventions, acute illnesses, life-threatening conditions requiring intensive care, and major trauma. According to the Consensus Statement of the American Association of Clinical Endocrinologists and the American Diabetes Association (ADA), stress hyperglycemia is defined as any elevation of blood glucose above 7.8 mmol/L in the absence of a history of diabetes [52].

The incidence of stress hyperglycemia in critically ill patients reaches 90%. In MI, its frequency, according to various authors, ranges from 20% to 80% [64,4]. According to another study, stress hyperglycemia during the acute phase of MI is observed in 44.4% of cases [14].

The pathogenesis of stress hyperglycemia is associated with stress-induced activation of the sympathetic nervous system, the release of insulin antagonists - particularly cortisol - and proinflammatory cytokines [96]. The relationship between stress hyperglycemia and elevated cortisol levels has been examined in detail in a study by *R.K. Pandey* [63].

In a well-known study [43], predictors of stress hyperglycemia in patients after cardiac surgery were analyzed. Among 3,658 medical records reviewed, 1,453 patients developed stress hyperglycemia postoperatively. The analysis demonstrated that the factors significantly associated with its development included female sex, older age, body mass index, elevated serum creatinine, left ventricular ejection fraction, history of cardiac surgery, and cardiogenic shock.

Confirmed biochemical predictors of stress hyperglycemia in patients with acute MI (AMI) include elevated glycated hemoglobin, hyperinsulinemia, and proinflammatory cytokines [72,20].

It is important to note that the adverse prognostic impact of disorders of carbohydrate metabolism in ACS patients has been well known for a long time. For example, according to a meta-analysis conducted in Sweden in 2007 that included 22 randomized clinical trials and 6,315 STEMI patients, mortality was higher in individuals with diabetes compared with those without [23].

Similar results were obtained by *Xu F. et al.* [92], who found that in-hospital MI mortality was significantly higher among patients with diabetes than among those without (16% vs. 6%, $P < 0.001$).

According to a meta-analysis by *M. Zeng et al.* [95], prediabetes also exerts a negative prognostic influence in MI patients. As in T2DM, mechanisms contributing to these adverse outcomes include insulin resistance, endothelial dysfunction, dyslipidemia, and oxidative stress. By promoting the formation of unstable atherosclerotic plaques, these mechanisms create a high risk of plaque rupture and erosion, and consequently acute coronary events, including MI. Glucotoxicity, leading to myocardial remodeling, is also considered relevant [95,51].

Renal Function in Patients with ACS

ACS is frequently accompanied by impaired renal function (IRF). The mechanism of kidney injury in MI is primarily associated with inadequate renal perfusion due to reduced cardiac output [99,100,18,5].

Another cause of IRF is exposure to radiographic contrast agents during coronary angiography (CAG), leading to contrast-induced nephropathy (CIN) [40,85,47]. CIN develops in approximately 3–19% of patients undergoing the procedure [34], and in about 1% of such cases, hemodialysis becomes necessary [74]. In patients with pre-existing chronic kidney disease (CKD) and additional risk factors, the likelihood of CIN development increases up to 50% [54].

Acute kidney injury (AKI) is a serious complication of MI [1]. This condition is observed in 10–60% of patients with ACS [16,22]. Renal impairment in ACS ranges from 4.4% to 13.2%, depending on the method used to calculate estimated glomerular filtration rate (eGFR) [89].

Roumeliotis S. et al. assessed the prevalence of unrecognized renal insufficiency in 12,830 ACS patients and found it to be 19.8% (defined as eGFR below 60 mL/min/1.73 m²) [70].

In a study by *Qi L. et al.,* the prevalence of IRF among ACS patients was 61% (1,146 out of 1,860). Specifically, mild IRF (eGFR 60–90 mL/min/1.73 m²) was present in 40.1% (746) of patients, while severe impairment was noted in 20% (400) [67].

In a joint Chinese-American research project, mild IRF was detected in 36.17% of cases, and significant impairment in 17.87% [91].

In another study involving a retrospective analysis of 314 ACS cases, mild renal impairment was more common in men (51.5%) than in women (42.7%). Moderate renal dysfunction was observed in 12.2% of men and 30.9% of women [18].

It has been demonstrated that IRF occurs more frequently in non–ST-segment elevation ACS (NSTE-ACS) cases (42.9%) compared to ST-segment elevation ACS (STE-ACS) (30.5%) [6,32]. Findings from various clinical studies indicate that 35-40% of ACS patients exhibit renal insufficiency of varying severity [92]. Other studies have also confirmed that ACS is often associated with reduced renal function [91,90,75].

In a meta-analysis conducted by *J.W. Pickering et al.* including 36 unique studies and 100,476 ACS patients, the prevalence of IRF reached 15.8%. The authors also reported that ACS complicated by AKI was associated with more than a threefold increase in early mortality and more than a twofold increase in long-term mortality [65].

In a study by *M. Zykov et al.,* aimed at establishing the clinical and prognostic significance of IRF in ACS patients, it was found that renal impairment assessed within the first 24 hours of ACS-regardless of initial treatment strategy-served as a predictor of cardiovascular complications during a three-year follow-up period [6].

According to another meta-analysis including 25 studies with a total of 254,408 adults with ACS, IRF was associated with an 86% increase in cardiovascular mortality risk, a 38% increase in major adverse cardiovascular events (MACE), and a 58% increase in heart failure risk [87].

Cardiorenal-Metabolic Continuum

The simultaneous involvement of the heart and kidneys against the background of metabolic disturbances is referred to as the cardiorenal-metabolic (cardiovascular) continuum (CRMC)**.** According to the definition by *Reznik E.V.,* «the cardiovascular continuum is a chain of interconnected changes in the cardiovascular system-from exposure to risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, etc.) through the gradual development and progression of endothelial dysfunction, atherosclerosis, left ventricular (LV) hypertrophy, coronary artery disease (CAD), myocardial infarction (MI), to the development of heart failure (HF) and death» [15]. Regardless of the etiological factor, endothelial dysfunction represents the initial («triggering») link in the formation of this syndrome.

In the setting of dysglycemia, the major causal factor of endothelial dysfunction is hyperglycemia, which induces activation of the polyol pathway, heparanase, heparan sulfate degradation, and non-enzymatic protein glycation [15,58].

Subsequently, increased activity of the local renin-angiotensin system (RAS) plays a significant role, leading to the development of systemic and intraglomerular hypertension. The latter is observed in 40% of patients with type 2 diabetes (T2DM). There is evidence suggesting an association between the risk of renal damage in T2DM patients and RAS-related genes, as well as genes encoding endothelial factors (eNOS3) [7].

One of the variants within the CRMC framework is the **cardiorenal syndrome (CRS).**

The concept of «cardiorenal syndrome» (CRS) was formulated in 2008. This term encompasses the bidirectional interaction of pathological processes between the cardiovascular system and the kidneys: acute or chronic dysfunction of one organ leads to acute or chronic dysfunction of the other. In CRS, the primary disease may involve the kidneys, resulting in renal failure and subsequently cardiovascular complications and heart failure. Conversely, primary cardiac pathology may lead to HF, which in turn causes renal dysfunction and injury, leading up to end-stage renal disease (ESRD) [81] (Table 2).

Acute Cardiorenal Syndrome (CRS Type 1)

Acute CRS refers to sudden kidney injury occurring in the setting of rapidly developing cardiac pathology, such as myocardial infarction with cardiogenic shock, decompensation of chronic heart failure, coronary angiography (CAG), or cardiac surgery. Chronic kidney disease (CKD) is usually a predisposing factor [69,48]. This condition is associated with an increased risk of mortality [42,9,70]. A significantly adverse prognostic factor is reduced left ventricular ejection fraction (LVEF) [77].

The abrupt decline in renal function reflects the severity of the patient's condition, as it is accompanied by activation of inflammatory cascades and an increased risk of mortality [84].

Table 2.

Classification of CRS [68].

Type	Title	Clinical situations
1	Acute cardiorenal syndrome	AKI in the setting of ACS, acute heart failure, decompensated chronic heart failure, pulmonary embolism, after coronary angiography, and cardiac surgery
2	Chronic cardiorenal syndrome	Chronic kidney disease (CKD) in patients with chronic heart failure secondary to coronary artery disease, hypertension, cardiomyopathies, valvular heart disease, and other etiologies
3	Acute renocardiac syndrome	Hypertension, acute coronary syndrome, acute heart failure, and neurohormonal activation in the setting of acute kidney injury
4	Chronic renocardiac syndrome	Cardiovascular pathology (hypertension, left ventricular hypertrophy, cardiac structural calcifications, valvular heart disease, myocardial infarction) in chronic kidney disease
5	Secondary cardiorenal syndrome	systemic disease involving both cardiac and renal systems

Chronic Cardiorenal Syndrome (CRS Type 2)

The development of chronic cardiorenal syndrome type 2 is usually caused by the presence of pre-existing chronic cardiac pathology (for example, chronic heart failure) with prolonged reduction of renal perfusion. However, hemodynamic disturbances are not the only reason for the decline in glomerular filtration rate. Neurohormonal shifts are also considered important, including disturbances in the balance between the production of vasoconstrictors and vasodilators, and the use of diuretics, which may lead to hypovolemia [49,60]. The onset of chronic kidney disease in such patients serves as a predictor of the development of systolic and diastolic left ventricular dysfunction and cardiovascular death [24].

Acute Renocardiac Syndrome (CRS Type 3)

Acute renocardiac syndrome develops as a consequence of sudden renal dysfunction that leads to acute impairment of cardiac function, including heart failure, arrhythmia, and ischemia. Such a situation may be observed in acute kidney injury, acute glomerulonephritis or pyelonephritis, acute tubular necrosis, or acute obstruction of the urinary tract [94,57].

Chronic Renocardiac Syndrome (CRS Type 4)

In chronic renocardiac syndrome type 4, the primary condition is chronic renal damage, which causes impairment of cardiac function in the form of left ventricular hypertrophy, diastolic dysfunction, and other abnormalities [55].

Secondary Cardiorenal Syndrome (CRS Type 5)

Cardiorenal syndrome type 5 is associated with pre-existing acute or chronic diseases that simultaneously affect both the heart and the kidneys. Such conditions may include sepsis, systemic connective tissue diseases, and sarcoidosis.

Chronic heart failure significantly increases the risk of deterioration of kidney function and adverse renal outcomes, particularly when associated with a rapid decrease in estimated glomerular filtration rate (more than 5 milliliters per minute per 1.73 square meters per year). In turn, reduction of kidney function and the occurrence of microalbuminuria increase the risk of developing heart failure.

Thus, the cardiorenal syndrome is part of the cardiorenal-metabolic axis [78]. Cardiorenal syndrome may be diagnosed in 32-90.3% of patients with heart failure. Impairment of kidney function has an unfavorable prognostic significance, as it leads to increased mortality in patients with heart failure.

Conclusion

The literature data on the prevalence of disorders of carbohydrate metabolism and renal impairment in acute coronary syndrome are characterized by considerable variability. The prevalence of disorders of carbohydrate metabolism in acute coronary syndrome ranges from 11% to 67%. With regard to renal pathology, its frequency among patients with acute coronary syndrome, according to different authors, ranges from 10% to 60%.

Meanwhile, timely detection of impaired renal function, as well as disorders of carbohydrate metabolism, in the context of acute coronary syndrome is extremely important from the standpoint of the possible development of cardiorenal syndrome in this category of patients. Considering the mechanisms of the formation of cardiorenal syndrome, cardiorenal syndrome in acute coronary syndrome most likely corresponds to type 1 and, consequently, requires immediate intervention aimed at eliminating hemodynamic, metabolic, and other disturbances [16].

In particular, in cases where type 2 diabetes mellitus is diagnosed in the setting of acute coronary syndrome, it is reasonable to prescribe medications that modify the course of the disease, specifically sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists. These classes of medications were originally developed as "hypoglycemic agents." However, in numerous studies assessing cardiorenal safety in patients with type 2 diabetes mellitus, they have convincingly demonstrated beneficial effects on both cardiovascular and renal outcomes. This is very important, since patients with type 2 diabetes mellitus exhibit a high association with adverse development of both microvascular and macrovascular complications [10,11]. By suppressing the reabsorption of glucose and sodium in the proximal renal tubules, sodium-glucose cotransporter 2 inhibitors contribute to a reduction in preload and afterload, improvement of energy metabolism, and cardiac remodeling. Clinically, this manifests as a decrease in arterial blood pressure, improvement of cardiac contractility, and reduction of heart failure symptoms [11,46].

At the same time, due to a decrease in intraglomerular pressure, the workload on the kidneys is reduced, which is expressed as stabilization of estimated glomerular filtration rate, reduction of ischemic kidney injury, and ultimately-improvement of renal function [33,36].

Despite the absence of a pronounced effect of glucagon-like peptide-1 receptor agonists on renal hemodynamic parameters, this class of medications demonstrates nephroprotective capacity by reducing albumin excretion in patients with type 2 diabetes mellitus. Presumably, their nephroprotective effect is associated with decreased formation of proinflammatory cytokines and reduction of oxidative stress, which contributes to prevention of damage to structures of the glomerular filtration barrier [43,92].

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MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND IN GYNECOLOGY: FUNDAMENTALS AND SAFETY, POTENTIAL IMPACT ON FERTILITY AND PREGNANCY OUTCOMES. LITERATURE REVIEW

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Abstract

Background and Objective. Uterine fibroids are the most common benign tumor in women of reproductive age (20-40%). Given the trend toward delayed childbearing and the high frequency of hysterectomies, organ-preserving, minimally invasive methods such as Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) ablation are becoming highly relevant. The objective of this review is to study and systematize publications on the use of MRgFUS technology, focusing on its impact on fertility and reproductive outcomes.

Methods. A comprehensive and systematic search of scientific literature from the last 10-20 years was conducted in databases (PubMed, Medline, Google Scholar, etc.) using keywords including "MRgFUS," "uterine fibroids," "fertility," and "HIFU." Out of 1247 identified studies, 46 of the most relevant publications meeting strict criteria were included in the final review.

Results. MRgFUS ablation is a safe and effective method based on the thermal coagulative necrosis of myoma tissue. Efficacy depends on the histological structure of the fibroid (hypointense on T2WI is preferred) and careful patient selection. Live birth rates after MRgFUS are encouraging, ranging from 41% to over 70%. The miscarriage rate (8-28%) is comparable to that following other conservative interventions and is lower than after Uterine Artery Embolization. MRgFUS preserves uterine integrity and does not increase the risk of uterine rupture or placental abnormalities. However, the reintervention rate may be higher than after myomectomy.

Conclusions. MRgFUS is a promising, minimally invasive option for fertility preservation in women with uterine fibroids. Reproductive outcomes are comparable to other conservative methods. Treatment success critically depends on strict patient selection and technical aspects. Large prospective randomized studies are necessary to clarify long-term reproductive outcomes and optimize protocols, especially in combination with Assisted Reproductive Technology.

Keywords: *radiological diagnostics, focused ultrasound, MRI, ablation, uterine fibroids, uterine adenomyosis, fertility, pregnancy.*

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Резюме

ПРИМЕНЕНИЕ ФОКУСИРОВАННОГО УЛЬТРАЗВУКА ПОД КОНТРОЛЕМ МАГНИТНО-РЕЗОНАНСНОЙ ТОМОГРАФИИ В ГИНЕКОЛОГИИ: ОСНОВЫ И БЕЗОПАСНОСТЬ, ПОТЕНЦИАЛЬНОЕ ВЛИЯНИЕ НА ФЕРТИЛЬНОСТЬ И ИСХОД БЕРЕМЕННОСТИ. ОБЗОР ЛИТЕРАТУРЫ

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Цель исследования. Миома матки - наиболее распространенная доброкачественная опухоль у женщин репродуктивного возраста (20-40%). Учитывая тенденцию к откладыванию деторождения и высокую частоту гистерэктомий, особую актуальность приобретают органосохраняющие, малоинвазивные методы, такие как абляция фокусированным ультразвуком под контролем МРТ (ФУЗ МРТ). Цель обзора - изучить и систематизировать публикации об использовании технологии ФУЗ МРТ, сфокусировавшись на ее влиянии на фертильность и репродуктивные результаты.

Методы. Проведен комплексный и систематический поиск научной литературы за последние 10-20 лет в базах данных (PubMed, Medline, Google Scholar и др.) с использованием ключевых слов, включая “MRgFUS”, “uterine fibroids”, “fertility”, и «ФУЗ МРТ». Из 1247 идентифицированных работ в финальный обзор были включены 46 наиболее релевантных публикаций, соответствующих строгим критериям.

Результаты. ФУЗ МРТ -абляция является безопасным и эффективным методом, основанным на термическом коагуляционном некрозе миоматозной ткани. Эффективность зависит от гистологической структуры миомы (предпочтительны гипоинтенсивные на T2WI) и тщательному отбору пациентов. Показатели живорожденияпосле MRgFUS обнадеживают, варьируясь от 41% до более 70%. Частота выкидышей (8-28%) сопоставима с таковой после других консервативных вмешательств и ниже, чем после эмболизации маточных артерий. ФУЗ МРТ сохраняет целостность матки и не повышает риск разрыва матки или аномалий плацентации. Однако, частота повторных вмешательств может быть выше, чем после миомэктомии.

Выводы. ФУЗ МРТ является перспективной, минимально инвазивной опцией для сохранения фертильности у женщин с миомой матки. Репродуктивные исходы сопоставимы с другими консервативными методами. Успех лечения критически зависит от строгого отбора пациентов и технических аспектов. Необходимы крупные проспективные рандомизированные исследования для уточнения долгосрочных репродуктивных результатов и оптимизации протоколов, особенно в сочетании с вспомогательными репродуктивными технологиями (ВРТ).

Ключевые слова: *лучевая диагностика, фокусированный ультразвук, МРТ, абляция, миома матки, аденомиоз матки, фертильность, беременность.*

Для цитирования:

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Түйіндеме

ГИНЕКОЛОГИЯДА МАГНИТТІ-РЕЗОНАНСТЫ ТОМОГРАФИЯ БАҚЫЛАУЫМЕН ФОКУСТЕЛГЕН УЛЬТРАДЫБЫСТЫ ҚОЛДАНУ: НЕГІЗДЕРІ МЕН ҚАУІПСІЗДІГІ, ФЕРТИЛЬДІККЕ ЖӘНЕ ЖҮКТІЛІК НӘТИЖЕЛЕРІНЕ ӘСЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Өзектілігі мен мақсаты. Жатыр миомасы - репродуктивті жастағы әйелдер арасында жиі кездесетін қатерсіз ісіктердің ең кең таралған түрі (20-40%). Репродуктивті функцияны кейінге қалдыру үрдісін және гистерэктомияның жоғары жиілігін ескере отырып, ағзаны сақтауға бағытталған, минималды инвазивті әдістердің, соның ішінде магниттік-резонанстық томография (МРТ) бақылауымен фокустелген ультрадыбыстық абляцияның (МРТ-БФУ) клиникалық маңыздылығы артып отыр.

Шолудың мақсаты - МРТ-БФУ технологиясын қолдану жөніндегі заманауи ғылыми жарияланымдарды талдау және жүйелеу, оның фертильдікке және репродуктивті нәтижелерге ықпалын бағалау.

Әдістері. Соңғы 10-20 жыл аралығында жарық көрген ғылыми дереккөздерінде (PubMed, Medline, Google Scholar және т.б.) «MRgFUS», «uterine fibroids», «fertility» және «ФУЗ МРТ» сөздері бойынша жүйелі және кешенді әдеби іздеу жүргізілді. Анықталған 1247 мақаланың ішінен іріктеу критерийлеріне сәйкес келетін 46 зерттеу талдауға енгізілді.

Нәтижелері. МРТ-БФУ - миоматозды тінге бағытталған жоғары қарқынды ультрадыбыстық энергияның әсерінен термокоагуляциялық деструкция туындататын қауіпсіз әрі тиімді репродуктивті ағзаны сақтау әдісі. Әдістің нәтижелілігі миоманың морфологиялы құрылымына (T2WI кескіндерінде гипоинтенсивті сигналдың басым болуы) және пациентті дұрыс таңдау тактикасына тәуелді.

МРТ-БФУ-дан кейін тірі босану жиілігі оң нәтижелер көрсетеді - 41%-дан 70%-ға дейін. Түсік тастау жиілігі (8-28%) басқа консервативті араласулардан кейінгі көрсеткіштермен салыстырмалы және жатыр артериясының эмболизациясынан қарағанда төмен.

МРТ-БФУ жатырдың анатомиялық және функционалдық тұтастығын сақтайды, миометрийдің перфорациясы мен плацентарлық имплантация ақауларының даму қаупін арттырмайды. Дегенмен, қайталама араласу қажеттілігі миомэктомиядан қарағанда жоғары болуы мүмкін.

Қорытындылар. МРТ-БФУ - жатыр миомасы бар әйелдерде репродуктивті функцияны сақтау тұрғысынан перспективті, минималды инвазивті емдеу әдісі. Репродуктивті нәтижелер тиімділігі бойынша басқа репродуктивті ағзаны сақтау тәсілдерімен салыстырмалы. Емнің тиімділігі пациентті дұрыс іріктеуге және процедураның техникалық параметрлеріне тікелей байланысты.

Ұзақ мерзімді репродуктивті нәтижелерді нақтылау және емдеу хаттамаларын, әсіресе көмекші репродуктивті технологиялармен (КРТ) үйлестіруді оңтайландыру үшін ірі проспективті рандомизацияланған зерттеулер қажет.

Түйінді сөздер: *сәулелік диагностика, фокустелген ультрадыбыс, МРТ, абляция, жатыр миомасы, аденомиоз, фертильдік, жүктілік.*

Дәйексөз үшін:

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Introduction

Uterine fibroids are the most prevalent benign tumors of the female reproductive tract, affecting between 20% and 40% of women during their reproductive years [31,39]. The incidence peaks in women over 35, with an overall prevalence reaching 90% in the 25-45 age group. In recent decades, there has been a noticeable trend toward detecting fibroids in women nearing the end of their childbearing potential. This phenomenon is largely attributed to social factors, particularly the decision by many to postpone childbearing until later in their reproductive period. Consequently, the proportion of surgical procedures for uterine fibroids in gynecological hospitals ranges from 41% to 74% [17].

The management of patients with uterine fibroids necessitates a differentiated approach, which is determined by a complex interplay of factors: the patient's age, clinical presentation, size and characteristics of the myomatous nodules, tumor growth rate, and the extent of the fibroid's impact on reproductive function.

The problem of uterine fibroid treatment remains a central focus in both national and global gynecology. While the necessity of radical surgical intervention is undisputed in cases involving acutely severe symptoms or giant nodules, there are persistent concerns regarding the high rate of hysterectomies and the optimal management strategy for asymptomatic fibroids. Given that approximately one in four women undergoing fibroid-related surgery is under the age of 40, the primary goal of surgical treatment, following myomectomy, is unequivocally the preservation of reproductive function. This underscores the increasing importance of organ-sparing and minimally invasive treatment modalities for young women.

One such relatively new technique that has entered clinical practice in recent years is Magnetic Resonance-Guided Focused Ultrasound (MRgFUS) ablation for uterine fibroids.

The MRgFUS technology is based on the remote delivery of high-intensity focused ultrasound energy. Using precise MRI navigation, the ultrasound beam is focused onto the pathological target area inside the body. Within a few seconds, the tissue at the focal point is heated to a temperature sufficient for thermal necrosis (ablation), while the surrounding healthy tissues remain unaffected (intact). This method achieves a non-invasive, strictly localized destruction of tumor cells, effectively meeting the criteria for an ideal surgical tool [45].

MRgFUS represents a non-invasive, organ-sparing treatment for uterine fibroids and adenomyosis, increasingly considered for women desiring fertility preservation. Current literature suggests that MRgFUS does not significantly impair fertility and is associated with encouraging pregnancy outcomes, including high live birth rates and a low incidence of severe complications. A number of studies and meta-analyses report that pregnancy and live birth rates after MRgFUS are comparable to those following other conservative treatments, with miscarriage rates similar to the general population or other interventions [10, 16, 18, 25, 28, 29, 37]. However, the evidence base is limited by a lack of large prospective trials, and some authors point to a higher rate of repeat interventions (reinterventions) compared to surgical options like myomectomy or Uterine Artery Embolization (UAE) [10,25,41]. Overall, MRgFUS appears to be a safe and effective fertility-preserving option, yet careful patient selection and further research are warranted to clarify long-term reproductive outcomes and optimize protocols [10, 16, 18, 25, 28, 29].

The aim of this study is to examine and systematize publications on the use of MRgFUS ablation technology for the subsequent refinement of this treatment method, specifically to investigate the impact of MRgFUS on female fertility and reproductive outcomes.

Methods

To achieve the stated objective-investigating the impact of MRgFUS ablation on fertility and reproductive outcomes-a comprehensive and systematic search of the scientific literature spanning the past 20 years was conducted. The key search terms used across both Russian- and English-language databases (PubMed, Medline, Cinahl, Embase, e-library, Cochrane, Health star, Google Scholar, and Consensus) included: “uterine fibroids”, “MRI for uterine fibroids”, “radiological diagnostics of uterine fibroids”, “pregnancy”, “MRgFUS for uterine fibroids”, “fertility”, “MRgFUS”, “HIFU” and “pregnancy outcomes”.

Inclusion Criteria:

The analysis included publications that met the following criteria:

- Publications available in both Russian and English languages.
- Articles addressing the application of MRgFUS for uterine fibroids and its influence on reproductive function predominantly published within the last 20 years (with the potential inclusion of older works deemed to hold significant scientific or historical value).
- Studies containing clearly formulated and statistically substantiated conclusions.
- Full-text articles retrieved from the aforementioned scientific databases.

Exclusion Criteria: The following were excluded from the review: meeting abstracts, newspaper articles, and personal communications.

The initial search, based on the key queries, encompassed over 100,000 scientific articles, which led to the identification of 1,247 potentially relevant works. Following a preliminary screening, 196 of the most relevant articles were selected for subsequent in-depth analysis (**Figure 1**).

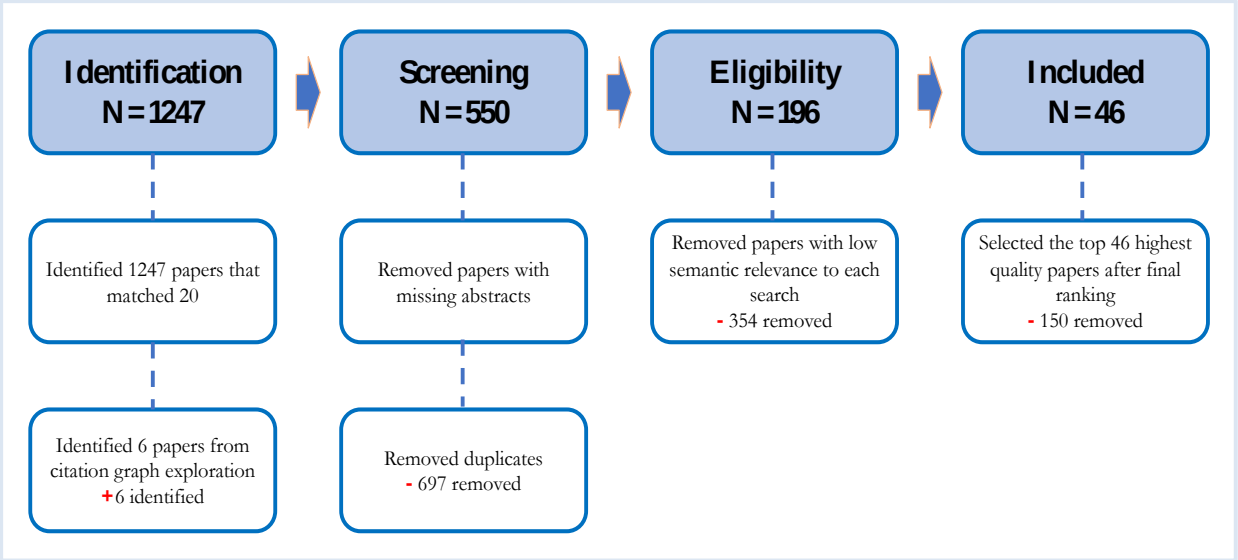


Figure 1: Flow diagram of the literature search and selection process. Four unique search strategies were used, combining terms for MRgFUS, fertility, pregnancy, and comparative treatments.

As a result of thorough screening and criterion assessment, 46 publications-representing the most authoritative and relevant studies-were ultimately included in this final review and served as its foundation.

Given the substantial volume and fragmented nature of the information available on this topic, particular emphasis within this review will be placed on the patient selection criteria, the technical principles of MRgFUS ablation, and its direct impact on fertility and reproductive outcomes.

Results

Physico-Biological Principles and Mechanism of MRgFUS Action

The continuous development of therapeutic options for treating uterine fibroids remains highly relevant [21]. Among the organ-sparing techniques, non-invasive focused ultrasound ablation (FUS) guided by Magnetic Resonance Imaging (MRI) holds a special place, as it often allows patients to avoid hospitalization [3, 11, 42].

The primary physiological effect of MRgFUS is thermal ablation. The temperature increase within the target tissue causes protein denaturation and irreversible cell damage, leading to coagulative necrosis, tumor growth arrest, and subsequent regression. The extent of thermal injury is dependent on the exposure time and the temperature reached [3, 7, 8, 35].

An important secondary mechanism is the occlusion of vessels supplying the tumor. This is achieved through the thermal closure of microvessels, the collapse of vessels due to the destruction of surrounding tissue followed by fibrosis, and the activation of thrombotic processes resulting from endothelial reaction or mechanical vessel damage by acoustic waves [7, 46].

Furthermore, focused ultrasound is capable of modulating the immune response and potentially suppressing carcinogenesis. This occurs through the antigenic properties of damaged tumor proteins, local inflammatory reactions generating effector cells, the release of heat shock proteins, and a reduction in immunosuppressive cytokines [20, 46]. Although these immunological effects may be insufficient for independent tumor growth control [43, 44], they contribute to the overall therapeutic efficacy.

The Role of MRI Guidance and Thermometry

The integration of therapeutic ultrasound with MRI visualization has established MRgFUS as one of the fastest-growing therapeutic technologies. MRI visualization enables precise localization of the target tumor and its margins, as well as clear visualization of the surrounding anatomy. A key feature of MRI is its ability to monitor temperature changes in real-time, thereby creating a closed-loop control system [8, 14, 32].

MR thermometry is based on the temperature-dependent shift in the resonance frequency of water protons, which makes it highly suitable for thermometry [15, 24]. Crucially, this temperature sensitivity is independent of the tissue type and the process of thermocoagulation, rendering MRI a reliable technology for non-invasive monitoring of FUS ablation [19, 26, 36]. The main limitations of the method include susceptibility to patient motion and inaccuracies in fatty tissues.

Overall Efficacy and Methodological Predictors

The treatment process, known as sonication, involves the pulsed delivery of FUS energy, with treatment duration varying from a few seconds up to 20 seconds, depending on the desired coagulation temperature [1, 23]. The software provides automatic configuration of the treatment zone, aiming for a sub-millimeter boundary between healthy and target tissue [5, 27, 30, 40]. MRI thermography allows for closed-loop control of energy deposition with high spatial and temporal resolution [6, 12, 38].

Numerous publications have confirmed the safety and efficacy of MRgFUS [1; 2; 5; 9; 14; 15; 19; 20; 23; 24; 26; 27; 30; 32; 36; 40; 43; 44; 46]. Clinical efficacy assessment has shown an increase in the Non-Perfused Volume (NPV) and a significant reduction in fibroid symptoms, as measured by the Symptom Severity Score (SSS) and Quality of Life (UFS-QOL) scale [38]. An increase in NPV strongly correlates with fibroid size reduction and a lower frequency of repeat interventions [3,24].

A meta-analysis of 10 studies reported that the overall improvement in SSS six months post-MRgFUS averaged 31.0 (95% CI 23.9-38.2), indicating substantial symptomatic relief.

Influence of Location and T2WI Signal Intensity

MRgFUS efficacy can be influenced by fibroid characteristics:

Location: Studies have shown that MRgFUS can treat fibroids of various locations, including submucosal fibroids and pedunculated subserosal fibroids [7,40]. For example, treatment of submucosal fibroids showed an average NPV of 80% and a size reduction of 90.1% at 24 months, though its superiority over hysteroscopic myomectomy has not been definitively proven yet [5].

T2WI Signal Intensity: MRI T2-weighted imaging is used for planning, as signal intensity correlates with vascularity and response to therapy. Hypointense fibroids on T2WI have been found to yield a higher average NPV (86.3%) and better long-term outcomes compared to hyperintense fibroids (67.6%) [3,9,38,45]. Slightly homogeneous hyperintense fibroids pose a particular challenge, with an average NPV of only 55.8%, potentially making them an exclusion criterion or requiring more meticulous selection [3,34,45].

Impact of MRgFUS on Fertility and Pregnancy Outcomes

Initially, MRgFUS was not offered to women planning future pregnancies, but current data have prompted multicenter studies in this group. Numerous studies confirm that women can successfully conceive and give birth after MRgFUS. Live birth rates are reported to range from 41% to over 70% across various cohorts [16, 18, 25, 28, 29, 37]. The mean time to conception following MRgFUS is 8 months [33]. A series described 54 pregnancies in 51 patients after MRgFUS [33], with 41% (22 patients) successfully carrying to term.

Pregnancy Complications and Comparative Efficacy

The rate of spontaneous abortions (miscarriages) after MRgFUS is generally between 8%-28%, which is comparable to rates in the general population or following other conservative interventions, and notably lower than after UAE [10,16,18,25,28,37]. Most studies show no significant increase in adverse pregnancy outcomes, such as preterm birth, placental abnormalities, or uterine rupture, compared to other treatments [10, 18, 25, 28, 29].

Efficacy Comparison: Compared to myomectomy, MRgFUS may result in a slightly lower overall pregnancy rate, but shows comparable rates of miscarriage and complications. Compared to UAE, MRgFUS is associated with a lower risk of miscarriage and abnormal placentation [10, 25, 37, 41]. MRgFUS preserves the structural integrity and function of the uterus, making it a favorable choice for women wishing to avoid surgery [10, 18, 25, 28, 29].

Reinterventions and Patient Selection

A controversial aspect is the rate of repeat interventions (reinterventions): some authors note that this rate may be higher after MRgFUS compared to surgical methods like myomectomy or UAE [10, 25, 41]. Consequently, meticulous patient selection and technical expertise are crucial for optimizing reproductive outcomes [3, 9, 34, 38, 45]. Pregnancy success after MRgFUS depends on factors such as patient age, history of infertility, and fibroid characteristics (size, location, vascularization) [14,18].

Discussion

The discussion of MRgFUS ablation efficacy begins with an understanding of its pathogenetic mechanism. The crucial finding is that the connective tissue within myomatous nodules acts as the primary absorber of focused ultrasound energy. This active energy absorption leads to intense heating of the stroma, while the destruction of myocytes occurs secondarily. Consequently, the treatment outcome is directly dependent on the histological structure and moisture content of the connective tissue: a drier connective tissue has higher FUS absorption, which paradoxically minimizes the destructive volume of myocytes and vascular elements [12].

MRgFUS induces a histological transformation of the fibroid tissue (myocytes and stroma convert into a state of wet coagulative necrosis), which leads to the arrest of nodule growth and symptom regression. For maximum efficacy, fibroids characterized by a parenchyma 1/stroma 3 structure (stroma-dominant) with minimal or no edema are preferred. In cases of significant edema or pronounced destructive changes (less than 30% viable tissue), the substrate available to absorb FUS energy is insufficient, thereby reducing procedural effectiveness [3, 22]. Inadequate connective tissue prevents the temperature (55-85°C) from being sustained long enough to induce coagulative necrosis in the myocytes, which inherently do not absorb FUS well. This explains the lower efficacy observed in the proliferative or atypical hyperplasia parenchyma 2/stroma 1 histotype.

MRgFUS is generally considered a highly safe procedure. However, like any medical intervention, it carries potential side effects. Common side effects that do not require medication include pelvic pain, nausea, vomiting, and fatty edema of the upper abdomen [3, 4, 34, 45].

Despite the overall high safety profile, rare but serious complications have been reported. The frequency of adverse events ranges between 0.003% and 0.088% of all treated cases. Severe complications include skin burns, bone destruction (successfully managed conservatively), and extremely rare cases of intestinal damage and acute renal failure (due to lysis of necrotic tumor masses) [3, 4, 34, 45]. Strict adherence to established protocols and the use of auxiliary measures are critically important to minimize these risks.

The accumulated data unequivocally suggest that MRgFUS is a promising, minimally invasive method for women with uterine fibroids who seek to preserve their fertility. Pregnancy and live birth rates after MRgFUS are encouraging, and the risk of serious obstetric complications, such as uterine rupture or placenta accreta, remains low [10,16,18,25,28,29,37]. Compared to UAE, MRgFUS is associated with a lower risk of miscarriage and abnormal placentation [10, 25, 28, 37, 41]. While myomectomy remains the "gold standard" for maximizing the chances of pregnancy, MRgFUS offers a less invasive alternative.

A major issue limiting the widespread adoption of MRgFUS in reproductive practice is the lack of large, prospective, randomized studies and the relatively short

follow-up periods in most published works [10, 13, 25, 28, 41].

Furthermore, several critical factors influence the success of the procedure and reproductive outcomes: Patient Age: The mean age of patients in earlier successful studies was around 43 years. Conversely, younger women (of prime reproductive age) more frequently present with hyperintense fibroids, which are more resistant to MRgFUS, complicating treatment in this key demographic. Technical Aspects: Success is closely linked to meticulous patient selection (including assessment based on T2WI signal intensity), technical expertise, and fibroid characteristics [10, 14, 18]. Assisted Reproductive Technology (ART): Data on Intrauterine Insemination (IUI) or In Vitro Fertilization (IVF) after MRgFUS remain limited. The optimal timing for pursuing ART post-treatment has also not been established.

Despite the encouraging current data on 35 live births following MRgFUS, the heterogeneity of these case series and the low enrollment levels in past clinical trials preclude definitive conclusions regarding rare and serious outcomes.

Conclusion

MRgFUS is a safe and effective organ-sparing method for the treatment of uterine fibroids. It provides clinical improvement and symptom regression through thermal ablation and coagulative necrosis, with a low risk of severe complications when protocols are strictly followed. Ultrasound ablation does not pose an obstacle to subsequent pregnancy. Pregnancy and live birth rates after MRgFUS are comparable to those of other conservative treatments, and the risk of spontaneous abortion and placental abnormalities is lower than after UAE. The success of treatment critically depends on careful patient selection, which includes evaluating age, history of infertility, and fibroid characteristics (predominantly hypointense fibroids on T2WI). MRgFUS represents a promising, minimally invasive option for fertility preservation in women with uterine fibroids. Further high-quality research is necessary to fully define its role in reproductive medicine, standardize treatment protocols, and refine patient selection criteria.

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MODERN ASPECTS OF PATIENT-CENTERED CARE IN INFERTILITY

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Abstract

Introduction. Infertility remains one of the pressing problems of modern medicine, affecting not only the physical health of patients but also their psycho-emotional state, social relationships, and overall quality of life. With the increasing prevalence of infertility and the widespread use of assisted reproductive technologies (ART), there is a growing need for a more humanistic and holistic approach to medical care. One of the key directions in improving treatment effectiveness is the implementation of patient-centered medicine principles. Patient-centered care implies active involvement of the patient in decision-making, respect for their values, provision of information, and ensuring comfortable treatment conditions. The application of such approaches is especially important in reproductive medicine, where every intervention touches upon deeply personal and socially sensitive aspects of patients' lives.

Aim. To conduct a review of current scientific literature devoted to the implementation of a patient-centered approach in infertility treatment.

Search strategy. The review included scientific publications addressing patient-centered approaches in infertility treatment using ART and in the organization of reproductive care. The search query included the following keywords: "patient-centered care," "infertility," "patient experience," "reproductive medicine," "ART," "shared decision-making," as well as their equivalents in Russian. The search was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases for the period from 2006 to 2024.

Results. Patients' experience of patient-centered care (PCC) in infertility treatment varies across different countries. To the best of our knowledge, no studies have been conducted in Kazakhstan to investigate the perceptions of healthcare professionals and patients regarding the implementation of patient-centered care in infertility.

Conclusion. The key components of the patient-centered model are active patient involvement in decision-making, provision of accessible and reliable information, emotional support, and individualization of the treatment process.

Keywords: *infertility, patient-centered care, assisted reproductive technologies, quality of medical care, doctor-patient communication.*

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Резюме

СОВРЕМЕННЫЕ АСПЕКТЫ ПАЦИЕНТОРИЕНТИРОВАННОЙ ПОМОЩИ ПРИ БЕСПЛОДИИ

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Введение. Бесплодие остается одной из актуальных проблем современной медицины, затрагивая не только физическое здоровье пациентов, но и их психоэмоциональное состояние, социальные отношения и качество жизни в целом. В условиях роста числа случаев бесплодия и широкого применения вспомогательных репродуктивных технологий (ВРТ) возрастает потребность в более гуманистичном, целостном подходе к оказанию медицинской помощи. Одним из ключевых направлений повышения эффективности лечения является внедрение принципов пациенториентированной медицины. Пациенториентированность подразумевает активное вовлечение пациента в процесс принятия решений, уважение к его ценностям, информированность, а также обеспечение комфортных условий лечения. Применение таких подходов особенно важно в репродуктивной медицине, где каждое вмешательство затрагивает глубоко личные и социально чувствительные аспекты жизни пациентов.

Цель. Провести обзор современной научной литературы, посвященной реализации пациенториентированного подхода в лечении бесплодия.

Стратегия поиска. Для проведения обзора использовались научные публикации, освещающие вопросы пациенториентированного подхода в лечении бесплодия с помощью ВРТ и организации репродуктивной помощи. Поисковый запрос включал ключевые слова: «patient-centered care», «infertility», «patient experience», «reproductive medicine», «ART», «shared decision-making», а также их эквиваленты на русском языке. Поиск проводился в базах данных Pubmed, Scopus, Web of Science, Google Scholarза период с 2006 по 2024 годы.

Результаты. Опыт пациентов в отношении PCC при лечении бесплодия будет различаться в разных странах. Насколько нам известно, на сегодняшний день в Казахстане не проводилось исследований, посвященных изучению восприятия медицинских работников и пациентов о проведении ориентированной на пациента помощи при бесплодии.

Выводы. Ключевыми компонентами пациенториентированной модели являются активное вовлечение пациента в процесс принятия решений, обеспечение доступной и достоверной информации, эмоциональная поддержка и индивидуализация лечебного процесса.

Ключевые слова: *бесплодие, пациенториентированный подход, вспомогательные репродуктивные технологии, качество медицинской помощи, коммуникация врач-пациент.*

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Түйіндеме

БЕДЕУЛІКТІ ЕМДЕУДЕ ПАЦИЕНТКЕ БАҒЫТТАЛҒАН КӨМЕКТІҢ ҚАЗІРГІ АСПЕКТІЛЕРІ

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Кіріспе. Бедеулік қазіргі медицинаның өзекті мәселелерінің бірі болып қалып отыр. Ол тек науқастардың физикалық денсаулығына ғана емес, сонымен қатар олардың психоэмоционалдық жағдайына, әлеуметтік қатынастарына және жалпы өмір сапасына әсер етеді. Бедеулік жағдайларының артуы және көмекші репродуктивтік технологиялардың (КРТ) кеңінен қолданылуы жағдайында медициналық көмекті көрсетуде гуманистік әрі кешенді көзқарастың қажеттілігі артып келеді. Емдеудің тиімділігін арттырудың негізгі бағыттарының бірі – пациентке бағытталған медицинаның қағидаттарын енгізу. Пациентке бағытталу науқасты шешім қабылдау

процесіне белсенді қатыстыруды, оның құндылықтарына құрметпен қарауды, ақпараттандыруды және жайлы жағдай жасауды қамтиды. Мұндай тәсілдердің қолданылуы репродуктивті медицинада ерекше маңызды, өйткені әрбір араласу пациенттердің жеке және әлеуметтік тұрғыдан сезімтал қырларын қозғайды.

Мақсаты. Бедеулікті емдеуде пациентке бағытталған тәсілді іске асыруға арналған қазіргі ғылыми әдебиеттерге шолу жүргізу.

Іздеу стратегиясы. Шолуды жүргізу үшін КРТ көмегімен бедеулікті емдеуде және репродуктивті көмекті ұйымдастыруда пациентке бағытталған тәсілге қатысты ғылыми жарияланымдар пайдаланылды. Іздеу сұрағына келесі кілт сөздер енгізілді: «patient-centered care», «infertility», «patient experience», «reproductive medicine», «ART», «shared decision-making» және олардың орыс тіліндегі баламалары. Іздеу Pubmed, Scopus, Web of Science, Google Scholar дерекқорларында 2006–2024 жылдар аралығында жүргізілді.

Нәтижелер. Пациенттердің бедеулікті емдеуде пациентке бағытталған көмекті қабылдау тәжірибесі әр елде әртүрлі болады. Біздің білуімізше, бүгінгі күнге дейін Қазақстанда бедеулікті емдеуде пациентке бағытталған көмекті жүзеге асыруға қатысты медицина қызметкерлері мен пациенттердің қабылдауын зерттеуге арналған жұмыстар жүргізілмеген.

Қорытынды. Пациентке бағытталған модельдің негізгі құрамдас бөліктері: науқасты шешім қабылдау процесіне белсенді тарту, қолжетімді әрі сенімді ақпаратпен қамтамасыз ету, эмоционалдық қолдау көрсету және емдеу процесін жекелендіру болып табылады.

Түйінді сөздер: *бедеулік, пациентке бағытталған тәсіл, көмекші репродуктивтік технологиялар, медициналық көмектің сапасы, дәрігер-пациент коммуникациясы.*

Дәйексөз үшін:

Куштекова А.Т., Ермуханова Л.С., Локшин В.Н., Нурбакыт А.Н., Корсак В.С., Достанова Ж.А., Киматова К.Н. Бедеулікті емдеуде пациентке бағытталған көмектің қазіргі аспектілері. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 193-201. *doi 10.34689/SH.2025.27.6.021*

Introduction

Infertility remains a pressing issue affecting many individuals. Modern medicine offers various methods for diagnosing and treating this condition; however, the influence of factors such as stress, lifestyle, and age highlights the importance and relevance of assisted reproductive technologies (ART). These technologies provide the possibility of biological parenthood for those facing infertility, a low probability of conception, or other medical challenges.

The prevalence of infertility in the Republic of Kazakhstan, according to various literature sources, ranges from 12% to 15.5%. In Kazakhstan, 23 infertility treatment centers provide ART services. ART clinics operate in major cities of the country, but the majority of them are located in Nur-Sultan (the capital) and Almaty, where the population exceeds 1 million people. The increase in the number of cycles is driven by the availability of information, the growth of household income, the development of private IVF clinics, and possibly the expansion of state subsidies for IVF [32].

The prevalence rates of infertility have been studied in several investigations: registered rates are 12% in the USA, 9% in the United Kingdom, and 12% in Portugal. Infertility is a serious health problem that can be treated; however, as some authors reporte, only 56% of infertile couples seek medical help [29].

The prevalence of infertility in the Republic of Kazakhstan, according to various literature sources, ranges from 12% to 15.5%. In Kazakhstan, 23 infertility treatment centers provide ART services. ART clinics operate in major cities of the country, but the majority of them are located in Nur-Sultan (the capital) and Almaty, where the population exceeds 1 million people. The increase in the number of cycles is driven by the availability of information, the growth of household income, the development of private IVF clinics, and possibly the expansion of state subsidies for IVF [32].

From the government's perspective, the average healthcare expenditures required to achieve one additional birth ranged from 2,599 USD in Ukraine to 5,509 USD in Belarus. The financial costs of having a child through IVF were as follows: Ukraine – 9,839 USD, Belarus – 21,702 USD, and Kazakhstan – 2,295 USD [35].

Infertility is classified by the World Health Organization as a disease, and this definition is supported by numerous professional associations, including the American Medical Association, the European Society of Human Reproduction and Embryology, the International Committee for Monitoring Assisted Reproductive Technologies (ICMART), and the American Society for Reproductive Medicine [35, 50, 15]. Infertility is a disease historically defined as the inability to achieve a successful pregnancy after 12 or more months of regular unprotected sexual intercourse or due to an individual's impairment in the capacity to reproduce, either alone or with a partner.

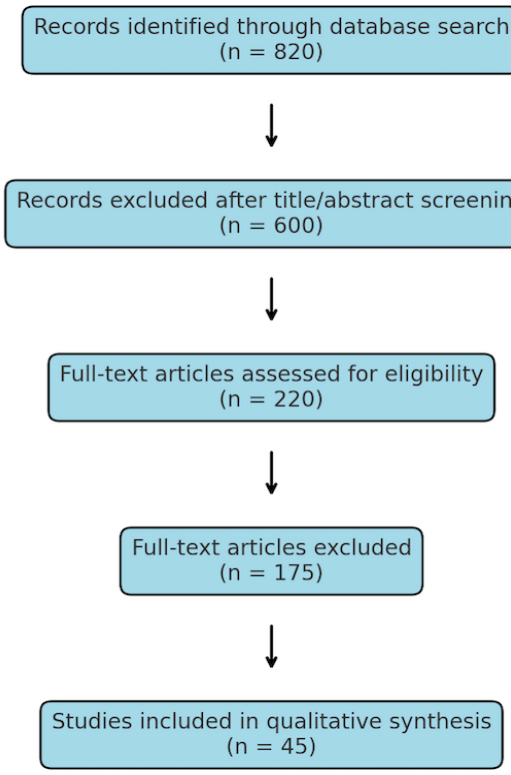
Infertility is a disease that leads to disability in the form of impaired function. Diagnostic testing for infertility should begin without delay in any patient with a medical, sexual, or reproductive history, advanced age, or physical findings suggesting a possible reproductive impairment. In the absence of relevant history or physical findings, evaluation and treatment may be initiated after 12 months in women under the age of 35, and after 6 months in women aged 35 years and older. Women over 40 years may require more immediate evaluation and treatment [1,53,2]. As of February 13, 2020, the American Medical Association (AMA) supports healthcare experts worldwide in recognizing infertility as a disease [1].

Infertility, defined as the inability to achieve pregnancy within 12 months after unprotected intercourse or therapeutic donor insemination in women under 35 years of age, or within 6 months in women over 35, affects up to 15% of couples. Diagnostic testing should begin without delay in the presence of risk factors such as age, medical, or reproductive history. Women over 40 years are recommended to undergo immediate evaluation and initiation of treatment.

Among the factors influencing reproductive function are stress, lifestyle, age, environmental conditions, and the presence of comorbidities. This emphasizes the need for a comprehensive approach to infertility treatment, in which the patient-centered model of care is becoming increasingly important. Such an approach implies respect for the individuality of the patient, consideration of their values, preferences, emotional state, and active involvement in medical decision-making.

Aim. To conduct a comprehensive review of current scientific literature on the application of a patient-centered approach in infertility treatment, with a particular focus on clinical, psychological, and organizational factors that shape the quality of care, enhance patient engagement, and influence overall satisfaction with treatment outcomes.

Search strategy. Scientific publications addressing patient-centered care in the treatment of infertility using ART and in the organization of reproductive care were used for the review. The search query included the following keywords: “patient-centered care,” “infertility,” “patient experience,” “reproductive medicine,” “ART,” “shared decision-making,” as well as their Russian equivalents. The search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for the period from 2010 to 2024. Refer to Picture 1.



Picture 1. Flowchart of study selection.

Both original studies and literature reviews were included if they contained analyses of the implementation of patient-centered practices, assessments of patient satisfaction, and the quality of communication and engagement in decision-making.

Inclusion criteria: publications containing data on the principles and implementation of patient-centered care in infertility; articles describing patients’ opinions, needs, and expectations; studies concerning physician–patient interaction within assisted reproductive technologies.

Exclusion criteria: works dealing only with the clinical effectiveness of infertility treatments without analysis of organizational and communication aspects.

Data analysis was performed using a qualitative approach with synthesis and systematization of key themes identified in the literature. Considering the predefined inclusion and exclusion criteria, all records retrieved from the databases were systematically screened and assessed for eligibility. After the full-text revision and exclusion of non-relevant publications, a total of 45 studies were finally included in the review.

Results

An infertility evaluation may be offered to any patient who, by definition, is infertile or at high risk of infertility. Women over the age of 35 are recommended to undergo expedited assessment and treatment after six months of unsuccessful attempts to conceive, or earlier if clinical indications exist, while women over 40 years often require immediate evaluation. Male factors account for approximately 40–50% of infertility cases, and unexplained infertility is diagnosed in about 30% of couples. In Kazakhstan, studies revealed that participants often lacked awareness of the impact of age on fertility decline, with more than half of women reporting being “shocked” to learn about their reduced chances of conception at older ages, although this alone does not fully explain the persistent socio-demographic trend toward delayed childbearing [13]. When analyzing infertility prevalence, 12.5% of women and 10.1% of men aged 16–74 years reported at least one unsuccessful attempt to conceive lasting one year or longer [15].

Psychological factors play a critical role in infertility outcomes. Women with fertility problems undergoing assisted reproductive technology (ART) procedures demonstrated high levels of stress, anxiety, and depression, all of which negatively influenced reproductive status [40]. A cross-sectional study of 89 infertile women using the FertiQoL and Hospital Anxiety and Depression scales revealed a mean overall FertiQoL score of 66.0 ± 14.5. Lower quality-of-life scores were associated with longer duration of infertility and higher numbers of IVF cycles, and a negative correlation was observed between treatment tolerability and indicators of anxiety and depression [29]. In a prospective cohort study of 304 infertile women in three Kazakhstani cities, more than 80% had CES-D scores above 16, suggesting a risk of clinical depression. Anxiety and stress levels were significantly higher among non-pregnant compared with pregnant women, and anxiety in particular was negatively associated with clinical pregnancy following IVF. Regional differences were also evident: in Aktobe, 91% of women were at risk of clinical depression,

and respondents reported significantly higher stress and anxiety compared with those from Nur-Sultan [5,8].

Socio-demographic and health-related variables were strongly linked with infertility. Prevalence was lowest among younger participants and highest in women aged 35–44 years (17.7%), while for men it extended from 35 to 54 years. Infertility was more frequent among married or cohabiting individuals, and in women it was positively associated with older age at first cohabitation. Treatment for depression in the previous year showed a borderline association with infertility in women, while in men infertility was associated with prior sexually transmitted infections, particularly chlamydia (AOR 1.39, 95% CI 1.02–1.88). Data from the United Kingdom further indicated that one in eight women and one in ten men reported infertility, with higher prevalence among individuals of higher education and social status, as well as those who had children later in life. Women under 50 years with infertility were more likely to report depression symptoms and dissatisfaction with their sexual life (AOR 1.81, 95% CI 1.15–2.84) [15]. In patients with natural infertility and chronic salpingitis, endocrine disorders such as thyroid dysfunction were among the most frequently detected comorbidities (15.38%) [6].

Quality-of-life assessment tools have provided deeper insight into the psychosocial burden of infertility. The FertiQoL questionnaire has become a gold standard, demonstrating good internal consistency across domains (Cronbach's $\alpha \approx 0.8$). A Kazakhstani cross-sectional study of 453 women undergoing IVF showed that respondents with secondary infertility reported significantly higher emotional, social, environmental, and treatment domain scores compared with those with primary infertility. However, women with low income had the lowest overall FertiQoL scores, and prolonged infertility duration was associated with worse outcomes. The mean overall FertiQoL score among Kazakhstani women was 59.6 ± 11.5, which is considerably lower than in European countries [17,27].

Infertility was consistently described as a stressful life event with wide-ranging social and personal consequences [12,45]. Although ART has offered hope to many couples, access remains limited due to financial and insurance barriers, while medicalization of infertility has often overlooked patients' emotional responses, including distress, loss of control, stigmatization, and disruption of life trajectories. Patient-centered care (PCC) is therefore increasingly recognized as an essential element of infertility services, emphasizing respect for patients' preferences, needs, and values [15,52]. Despite its benefits, implementation faces barriers including insufficient professional training, underestimation of patient needs, lack of time and resources, and rigid organizational cultures [33,14].

Patient-centered infertility care is structured around both systemic and human dimensions. Systemic priorities include provision of information, competence of staff, coordination and continuity of care, accessibility, and physical comfort, while human factors encompass communication, patient involvement, confidentiality, and emotional support. Evidence indicates that attention to these factors improves satisfaction, adherence to treatment, and quality of life [28, 51,39]. However, significant gaps remain between patients' expectations and providers' perceptions. Providers often underestimate patients' needs for information and emotional support, as demonstrated in a Dutch study of 1189 infertile couples and 194 healthcare professionals. Specialists consistently underestimated communication, patient involvement, and competence, while overestimating continuity of care, misjudging 29 aspects of treatment quality overall [4,21].

Systematic reviews further suggest that while evidence linking PCC directly to improved clinical outcomes remains mixed, its benefits for patient satisfaction, empowerment, and self-management are consistently strong [44,38]. PCC has been identified as one of the six determinants of healthcare quality by the Institute of Medicine, and its key elements - information, communication, physical and emotional support, family involvement, continuity of care, and access - are particularly important for patients undergoing prolonged and emotionally demanding infertility treatment [10, 28,51]. In Israel, PCC has been formally introduced as a quality metric by the Ministry of Health. In Kazakhstan, the Healthcare Development Concept 2026 prioritizes the integration of PCC into reproductive services, with emphasis on patient support programs, digital health solutions, and provider training. Furthermore, contracting policy reforms aim to strengthen accountability and prioritize patient-centered services within the State Guaranteed Benefits Package and the Mandatory Social Health Insurance [42].

Finally, studies highlight variability in perceptions of PCC between patients and providers. While overall agreement exists regarding its importance, discrepancies persist in prioritization: patients place more weight on information and communication, whereas providers emphasize coordination and integration. Some studies suggest providers underestimate their own effectiveness, while others highlight the opposite [30,9,23,13,16]. To date, no published research in Kazakhstan has directly examined how healthcare professionals and patients perceive PCC in infertility care, underlining the need for further investigations in this field.

Discussion

Moving from Biomedical to Patient-Centered Models

The findings of this review demonstrate that infertility, traditionally defined in biomedical terms as the inability to conceive after one year of unprotected intercourse, is increasingly being understood as a multidimensional condition that encompasses clinical, psychological, social, and cultural dimensions. Our results show that infertility affects both men and women, with male factors accounting for 40–50% of cases and unexplained infertility diagnosed in nearly one-third of couples. These data are consistent with global epidemiological studies, which confirm that infertility is not exclusively a female condition but a shared reproductive health challenge requiring joint approaches to care [26,36].

Despite this well-established biomedical knowledge, many patients remain unaware of risk factors, particularly age-related fertility decline. Our review of studies conducted in Kazakhstan revealed that more than half of women were "shocked" to learn that their chances of conception decreased substantially with age. This lack of awareness aligns with international reports showing that fertility literacy

remains limited even in high-income countries [31]. Such findings underscore the importance of patient-centered care (PCC), in which accessible information and patient education are prioritized alongside biomedical interventions.

Infertility Prevalence and Socio-Demographic Determinants

The prevalence of infertility observed in our review - 12.5% among women and 10.1% among men aged 16–74 - corresponds closely with international estimates, where approximately one in eight women and one in ten men experience infertility [15]. Age remains the strongest predictor: infertility peaks among women aged 35–44 and men aged 35–54. Marital and cohabitation status also show significant associations, with infertility more frequently reported among married or cohabiting individuals.

Notably, in men, infertility has been linked to a history of sexually transmitted infections (particularly chlamydia), while in women, prior depression treatment showed borderline associations. These findings emphasize the interplay between biological, psychological, and behavioral health determinants. They also highlight the need for multidisciplinary infertility care that integrates gynecological, urological, and mental health expertise.

Psychological Distress and Mental Health Correlates

A striking result of this review is the very high prevalence of psychological distress among infertile women in Kazakhstan. More than 80% of respondents in one prospective cohort study had CES-D scores above 16, indicating risk for clinical depression, while in the city of Aktobe as many as 91% of women were at risk. Stress and anxiety scores were significantly higher among non-pregnant women compared to those who conceived, and logistic regression analyses confirmed negative associations between anxiety levels and clinical pregnancy outcomes.

These findings reinforce the global evidence that infertility is a profound psychological stressor. International studies consistently demonstrate elevated rates of depression and anxiety in infertile populations, often exceeding those observed in patients with other chronic illnesses such as cancer or cardiovascular disease. Psychological distress is not merely an outcome of infertility but may itself reduce the likelihood of treatment success, creating a vicious cycle [37].

The review also demonstrates that quality of life is substantially reduced in infertile women. Mean FertiQoL scores among Kazakhstani women were 59.6 ± 11.5, significantly lower than European benchmarks, with longer infertility duration and repeated ART cycles further lowering scores. These results mirror international findings: Boivin et al. reported global FertiQoL averages around 66–70, suggesting that women in Kazakhstan face disproportionate psychosocial burdens [11]. Such disparities may be influenced by cultural expectations regarding motherhood and limited availability of psychosocial support services.

Quality of Life, Adherence, and Patient-Reported Outcomes

The FertiQoL data underscore that infertility treatment outcomes cannot be judged solely by clinical pregnancy rates. Women with lower quality of life scores were more likely to drop out of treatment, reported higher emotional distress, and demonstrated poorer adherence to medical recommendations. International research has confirmed that patient-reported outcomes (PROs), including well-being, satisfaction, and psychological state, are strong predictors of both adherence and treatment continuation [20].

The importance of integrating PROs into infertility care is therefore twofold. First, it ensures that the full impact of infertility is measured, not only its biological manifestations. Second, it provides clinicians with actionable insights into patients' needs, enabling individualized and empathetic responses. In Kazakhstan, where ART cycles are rapidly increasing, incorporating FertiQoL and CES-D tools into routine practice could serve as a critical step in patient-centered quality monitoring.

Communication, Information, and Shared Decision-Making

One of the most consistent themes emerging from both the reviewed literature and our results is the central role of effective communication. Many patients in Kazakhstan and abroad lacked clear understanding of age-related fertility decline or the psychosocial risks of infertility, indicating insufficient counseling. Studies in Europe and North America confirm that patients often perceive information provision as inadequate, while providers may underestimate the importance of communication [14,18].

Shared decision-making has been shown to enhance patient satisfaction and treatment adherence. Patients involved in selecting their treatment options report feeling more respected, empowered, and optimistic about outcomes. Conversely, when communication is overly paternalistic, patients may feel alienated and distrustful of medical services (69). In our context, the fact that so many women were unaware of fundamental fertility risks illustrates the urgent need for culturally sensitive, accessible educational strategies.

Gender and Cultural Considerations

The results also illustrate the importance of cultural and gender dimensions in patient-centered infertility care. Women and men experience and express infertility differently: women tend to report higher levels of distress, fear of failure, and feelings of social stigma, while men often underreport psychological burden due to cultural norms surrounding masculinity [34]. These patterns were observed in Kazakhstan as well, where gendered expectations strongly shape reproductive experiences.

Cross-cultural studies further demonstrate that infertility is perceived not merely as a medical condition but as a deeply social phenomenon. In some societies, infertility is associated with stigma, moral judgment, or even marital instability, making psychosocial support a critical component of treatment [25]. Therefore, PCC must be tailored to the cultural context, ensuring that communication, counseling, and support services resonate with patients' lived realities.

Organizational and Systemic Barriers

Despite clear benefits, multiple barriers impede the implementation of PCC in infertility care. Our review found that outdated organizational models, limited institutional resources, and insufficient staff training often reduce care to a formalized process with limited personalization. These obstacles are consistent with international reports, which highlight that hierarchical provider-patient relationships,

time constraints, and financial pressures hinder the uptake of PCC principles [47].

Nevertheless, innovative approaches are emerging. Digitalization of care - through telemedicine consultations, mobile health applications, and electronic diaries - offers new ways to engage patients, particularly in geographically remote or resource-limited settings. In Kazakhstan, where ART services are expanding beyond major cities, such digital platforms may prove instrumental in ensuring equitable access to information and continuity of care.

Implications for Kazakhstan and Global Context

The findings of this review hold specific implications for Kazakhstan. The expansion of ART services, combined with government support through the Healthcare Development Concept until 2026, creates an enabling environment for PCC implementation. Policy priorities now include patient satisfaction monitoring, effective communication, and the integration of health information technologies into care delivery.

Internationally, similar policy frameworks have accelerated the institutionalization of PCC. In Israel, patient-centeredness is formally monitored as a quality indicator in infertility clinics, while in the United Kingdom, the Human Fertilisation and Embryology Authority incorporates patient feedback into clinic ratings [48,24]. Kazakhstan has the opportunity to draw on these international experiences while adapting PCC principles to its unique cultural and health system context.

Future Directions

The integration of PCC in infertility care requires systemic transformation. Training programs for healthcare providers must prioritize communication skills, empathy, and shared decision-making, alongside technical expertise. Multidisciplinary teams should include not only gynecologists and urologists but also psychologists, social workers, and patient navigators. Furthermore, patient feedback systems must be institutionalized to provide continuous quality improvement. Future research should examine the cost-effectiveness of PCC interventions, as well as their impact on long-term adherence, dropout rates, and overall efficiency of ART programs. Comparative cross-cultural studies will also be essential to identify scalable models of PCC that respect cultural diversity while maintaining evidence-based standards.

Conclusions

The patient-centered approach in infertility treatment represents an important direction in the development of reproductive medicine, aimed at improving the quality and effectiveness of medical care. The results of the review showed that the key components of such a model are the active involvement of the patient in the decision-making process, the provision of accessible and reliable information, emotional support, and the individualization of the treatment process.

The implementation of patient-centered principles contributes not only to increased patient satisfaction but also to improved adherence to treatment, reduced psychological burden, and enhanced overall quality of life. At the same time, in some cases, unresolved issues remain regarding the training of medical personnel, organizational conditions, and interdisciplinary interaction.

Further work is needed on the development of standards, training programs, and assessment tools that would allow the integration of patient-centered practices into everyday clinical activities. Greater attention to the needs and expectations of patients should become an integral part of the strategy for improving the accessibility and quality of infertility care.

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COMPARATIVE REVIEW OF INTERNATIONAL MODELS FOR MEDICINE DISPOSAL: CHALLENGES, SOLUTIONS, AND PUBLIC HEALTH IMPLICATIONS. LITERATURE REVIEW

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Abstract

Background: Unused and expired medicines pose both environmental and epidemiological risks, particularly when improperly disposed of by the public. Leading countries have implemented various models for the collection and safe disposal of pharmaceutical waste to mitigate harm to human health and the environment. This article presents a comparative analysis of international strategies for household medicine disposal, focusing on regulatory frameworks, public behavior, and program effectiveness. The need for systematic approaches in countries lacking established practices is emphasized.

Objective. To compare international models of household medicine disposal, identify effective practices, regulatory approaches, and key challenges, and assess their relevance to public health and environmental safety.

Search strategy. A targeted search of scientific and official literature was conducted for the period 2019–2025. Sources included PubMed, Scopus, and Google Scholar, as well as materials from international organizations (WHO, European Commission, OECD), national health authorities, and environmental agencies. The selection focused on peer-reviewed articles, regulatory documents, and analytical reports containing information on household medicine disposal practices, government policies, citizen involvement, and environmental impacts.

Results and conclusions. Many countries have implemented government or pharmacy-based drug return programs. Their effectiveness depends on regulation and public engagement. In developing regions, such systems are lacking, increasing environmental risks. Structured medicine disposal is essential for health and environmental safety. Adapting successful international models is necessary where such systems are underdeveloped.

Keywords: *medicine disposal, pharmaceutical waste, public health, environmental safety, drug take-back, international experience, pharmacies, community involvement*

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Резюме

СРАВНИТЕЛЬНЫЙ ОБЗОР ЗАРУБЕЖНЫХ МОДЕЛЕЙ УТИЛИЗАЦИИ ЛЕКАРСТВ: ПРОБЛЕМЫ, РЕШЕНИЯ И ЗНАЧЕНИЕ ДЛЯ ОХРАНЫ ЗДОРОВЬЯ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Неиспользованные и просроченные лекарственные средства представляют экологическую и эпидемиологическую угрозу, особенно в условиях их неправильной утилизации населением. Ведущие страны мира внедряют различные модели сбора и обезвреживания фармацевтических отходов, направленные на минимизацию

вреда здоровью и окружающей среде. Настоящая статья представляет сравнительный анализ международных стратегий утилизации лекарств на уровне населения, рассматривает нормативные подходы, поведение граждан и эффективность программ. Обоснована необходимость внедрения системного подхода в странах, где такая практика не развита.

Цель. Сравнить зарубежные модели утилизации лекарственных средств на уровне населения, выявить эффективные практики, нормативные подходы и ключевые проблемы, а также оценить их значение для охраны здоровья и окружающей среды.

Стратегия поиска. Для проведения обзора был осуществлён целенаправленный поиск научной и официальной литературы за период 2019–2025 годов. Использовались базы данных PubMed, Scopus и Google Scholar, а также материалы международных организаций (ВОЗ, Европейская комиссия, ОЭСР), национальных агентств здравоохранения и экологических платформ. Отбор включал рецензируемые статьи, нормативно-правовые документы и аналитические отчёты, содержащие данные о практике утилизации лекарств населением, государственном регулировании, вовлечённости граждан и экологических последствиях.

Результаты и выводы. Во многих странах действуют государственные или аптечные программы возврата лекарств от населения. Эффективность обеспечивается нормативной базой и участием граждан. В развивающихся странах такие системы развиты слабо, что увеличивает экологические риски. Системная утилизация лекарств — важный компонент охраны здоровья и экологии. Необходима адаптация успешных международных практик в странах с недостаточно развитой инфраструктурой.

Ключевые слова: *утилизация лекарств, фармацевтические отходы, общественное здравоохранение, экологическая безопасность, возврат медикаментов, международный опыт, аптеки, участие населения*.

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Түйіндеме

ДӘРІЛІК ЗАТТАРДЫ ЖОЮДЫҢ ШЕТЕЛДІК МОДЕЛЬДЕРІНІҢ САЛЫСТЫРМАЛЫ ШОЛУЫ: МӘСЕЛЕЛЕР, ШЕШІМДЕР ЖӘНЕ ҚОҒАМДЫҚ ДЕНСАУЛЫҚ ҮШІН МАҢЫЗЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Пайдаланылмаған және мерзімі өткен дәрілік заттар халық тарапынан дұрыс жойылмаған жағдайда, экологиялық және эпидемиологиялық қауіп тудырады. Әлемнің дамыған елдері дәрі-дәрмек қалдықтарын жинау мен қауіпсіз түрде жою бойынша әртүрлі үлгілерді енгізуде, бұл қоғамдық денсаулық пен қоршаған ортаны қорғауға бағытталған. Бұл мақалада тұрғындар деңгейінде дәрілік заттарды кәдеге жарату бойынша халықаралық стратегиялардың салыстырмалы талдауы ұсынылады. Нормативтік тәсілдер, халықтың мінез-құлқы және бағдарламалардың тиімділігі қарастырылады. Мұндай тәжірибе дамымаған елдерде жүйелі тәсілді енгізу қажеттігі негізделеді.

Мақсаты: Тұрғындар деңгейінде дәрілік заттарды жою бойынша шетелдік үлгілерді салыстыру, тиімді тәжірибелерді, нормативтік тәсілдерді және негізгі мәселелерді анықтау, сондай-ақ олардың қоғамдық денсаулық пен қоршаған ортаға әсерін бағалау.

Іздеу стратегиясы: 2019–2025 жылдар аралығындағы ғылыми және ресми әдебиеттерге мақсатты іздеу жүргізілді. Дереккөздер ретінде PubMed, Scopus және Google Scholar мәліметтер базалары, сондай-ақ ДДСҰ, Еуропалық комиссия, ЭЫДҰ сияқты халықаралық ұйымдардың, ұлттық денсаулық сақтау органдары мен экологиялық агенттіктердің материалдары пайдаланылды. Таңдап алынған деректерге халық деңгейінде дәрі-дәрмектерді дұрыс жою тәжірибесі, мемлекеттік реттеу, азаматтардың қатысуы және экологиялық салдарлар туралы мәліметтері бар рецензияланған мақалалар, нормативтік құжаттар мен талдамалық есептер кірді.

Нәтижелер мен қорытындылар: Көптеген елдерде халықтан дәрі-дәрмектерді қайтару бойынша мемлекеттік немесе дәріханалық бағдарламалар бар. Тиімділік нормативтік база мен халықтың қатысуына байланысты. Дамушы елдерде мұндай жүйелер жеткіліксіз, бұл экологиялық қауіптерді арттырады. Дәрі-дәрмектерді жүйелі

түрде кәдеге жарату — денсаулық пен экологияны қорғаудың маңызды бөлігі. Мұндай тәжірибесі әлсіз елдерде халықаралық тиімді үлгілерді бейімдеу қажет.

Кілт сөздер: *дәрілерді жою, фармацевтикалық қалдықтар, қоғамдық денсаулық, экологиялық қауіпсіздік, дәріні қайтару, халықаралық тәжірибе, дәріханалар, халықтың қатысуы.*

Дәйексөз үшін:

Хисметова З.А., Искакова Н.С., Сахариев Е.Д., Ерланұлы Е., Молдабаева А., Ахметова К.М. Дәрілік заттарды жоюдың шетелдік модельдерінің салыстырмалы шолуы: мәселелер, шешімдер және қоғамдық денсаулық үшін маңызы. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 202-211. *doi 10.34689/SH.2025.27.6.022*

Introduction. The issue of unused and expired medicine disposal has garnered growing attention in recent years due to its direct implications for public health and environmental sustainability. Improper disposal methods—such as throwing pharmaceuticals in household waste or flushing them into sewage systems—contribute to water pollution, antimicrobial resistance, and the risk of accidental ingestion. Recent literature increasingly explores government strategies, pharmacy-based initiatives, and behavioral factors influencing medicine disposal at the household level.

Countries vary widely in their approaches, ranging from well-structured national programs with robust regulatory frameworks (e.g., in the United States, Canada, EU countries, and Japan) to fragmented or underdeveloped systems in parts of the Global South. Scientific studies highlight both the achievements of drug take-back programs and ongoing challenges, such as low public awareness, inadequate infrastructure, and limited intersectoral coordination.

Objective. To compare international models of household medicine disposal, identify effective practices, regulatory approaches, and key challenges, and assess their relevance to public health and environmental safety.

Search strategy. A targeted search of scientific and official literature was conducted for the period 2019–2025. Sources included PubMed, Scopus, and Google Scholar, as well as materials from international organizations (WHO, European Commission, OECD), national health authorities, and environmental agencies. The selection focused on peer-reviewed articles, regulatory documents, and analytical reports containing information on household medicine disposal practices, government policies, citizen involvement, and environmental impacts.

Search results and their discussion.

EU Strategy and Regulatory Framework

At the supranational level, the European Union sets the policy framework. As early as Directive 2004/27/EC, EU Member States were required to implement appropriate systems for the collection of expired or unused medicines. In March 2019, the European Commission adopted the EU Strategic Approach to Pharmaceuticals in the Environment (PiE), a comprehensive action plan covering all stages of the pharmaceutical life cycle—from production to disposal. This approach was endorsed by the EU Council and the European Parliament, which called for new measures, including both legislative and educational initiatives [30].

In particular, discussions in the EU have included the introduction of a “Do not flush” pictogram on medicine packaging and the organization of pan-European awareness campaigns. The use of extended producer responsibility (EPR) mechanisms has also been recommended to fund medicine take-back systems and public environmental education [21].

Between 2020 and 2023, the implementation of the PiE strategy progressed significantly. Guidelines were developed for national authorities on how to establish medicine return schemes, the exchange of best practices among countries was encouraged, and under the European Green Deal, environmental sustainability requirements for the pharmaceutical industry were strengthened. Pharmaceutical consumption continues to grow constantly. Unused/expired pharmaceuticals are disposed of to the municipal sewage system or waste disposal [34]. Consequently, many countries have implemented a system of collecting pharmaceutical waste, with pharmacies playing an important role. It is important to educate consumers on rational consumption and the appropriate disposal of unused/expired pharmaceuticals and to identify the level of public awareness. Two studies were conducted in Poland to estimate the problem of collection and disposal of expired/unused pharmaceuticals. The survey was aimed to identify patients’ attitudes regarding expired/unused pharmaceuticals at home. Of the respondents who participated in in survey I, almost 74% indicated that analgesics were among the over-the-counter drugs they purchased. Group of pharmaceuticals 65% of the respondents purchased were medicines for treating flu symptoms. Almost 68% of the respondents said they usually disposed of expired pharmaceuticals in their household waste or by flushing them down the toilet. In survey II more than 35% reported that they disposed of pharmaceuticals in the same ways. Of all respondents, ~30% returned their expired pharmaceuticals to pharmacies. Most respondents (over 65%) who participated survey I indicated that they were aware that pharmaceutical waste can be returned to pharmacies. It should be noted that local governments are currently not obliged by law to work with or compensate pharmacies in the collection and proper disposal of unused pharmaceuticals [2], [45].

In parallel, the pharmaceutical sector and environmental organizations launched initiatives to raise public awareness. For example, the pan-European #MedsDisposal campaign provides information on national medicine disposal systems and proper ways to discard unwanted pharmaceuticals [10].

International institutions such as the World Health Organization (WHO) and the OECD have also issued recommendations on the safe handling of pharmaceutical waste. The 2022 OECD report emphasizes that while the complete avoidance of pharmaceutical waste generation is

unlikely, proper separation and destruction remain necessary to prevent the release of hazardous substances into the environment.

France serves as a model example of a state-managed pharmaceutical waste disposal system. Since 2007, the national mandatory scheme Cyclamed has covered 100% of pharmacies in the country. All pharmacies accept unused medicines from the public free of charge, placing them into special containers provided by distributors. These are then centrally transported to Cyclamed facilities for disposal. The collected waste is incinerated with energy recovery (i.e., generating steam and electricity) [48].

The program is funded through the Extended Producer Responsibility (EPR) mechanism: pharmaceutical companies cover the costs through levies. With mandatory participation from all parties—over 22,000 pharmacies and approximately 190 pharmaceutical companies—France collected around 17,600 tons of pharmaceutical waste in 2018 (about 260 grams per capita). An estimated 62% of all unused medicines from households are returned via pharmacies—one of the highest rates in Europe [11].

To maintain public engagement, Cyclamed conducts regular awareness campaigns. Posters are displayed in pharmacies, prescription slips are stamped with return reminders, and advertisements are placed in public transport. This system demonstrates both environmental and social benefits: it reduces pharmaceutical substances in solid waste and wastewater, increases producer accountability (based on the "polluter pays" principle), and actively involves the population in environmental protection [28].

Belgium also operates a long-standing national program. Since 2000, a centralized collection scheme has functioned through pharmacies, financed by the pharmaceutical industry and distributors. Wholesalers provide pharmacies with containers and handle the transport and incineration of returned medicines, while producers cover these costs proportionally to their market share [16].

In 2011, Belgium disposed of 572 tons of medicines—equivalent to about 111 kg per pharmacy. Surveys showed that by 2013, 78% of citizens were aware of the program, though barriers such as a lack of information on procedures and insufficient collection points remained. Nevertheless, 96% of respondents stated they would use the system if clear instructions were available, underlining the importance of education for the success of such programs [3].

Germany lacks a unified national scheme, but most regions ensure safe medicine disposal through high-temperature municipal waste incineration. As the country bans landfilling of non-incinerated waste, nearly all solid household waste is incinerated. Consequently, it is legally acceptable to dispose of unused medicines in household trash (Restmüll), which meets environmental standards due to incineration [24].

Nonetheless, citizens are advised not to flush medicines down the drain and, where possible, to return them to pharmacies or municipal hazardous waste collection points. In about 95% of German municipalities, pharmacies voluntarily accept expired medications. However, these programs are not mandatory and are funded by local authorities, leading to variability between regions [13].

Efforts are underway to standardize practices, such as the Ecologic Institute's interactive map, which informs residents on proper disposal methods in each German region. A key challenge is raising awareness, as surveys show that many people still incorrectly discard medicines despite the availability of safe options [4].

The United Kingdom, though no longer part of the EU, maintains a similar established system. Under contracts with the National Health Service (NHS), all pharmacies are required to accept unwanted or expired medicines from patients. NHS local units contract specialized companies to regularly collect the waste and ensure environmentally safe incineration [33].

Pharmacies sort the waste (e.g., tablets, liquids, aerosols) in accordance with the Hazardous Waste Regulations. The program is fully funded by the government via the NHS, effectively through taxpayers, reflecting a model of public service responsibility rather than producer responsibility [23].

Although well-established, the issue persists: studies indicate a significant portion of UK residents still dispose of medicines in the general waste stream or flush them down the drain, despite the option to return them to pharmacies. Promoting correct disposal is a key component of NHS campaigns aimed at reducing medicinal waste and saving public funds (annual losses from unused medicines are estimated in the tens of millions of pounds) [37].

The Nordic and Northern European countries have long placed strong emphasis on the environmental aspects of pharmaceutical waste management. Sweden was a pioneer in this field, establishing a medicine return system in pharmacies as early as 1971. Initially introduced by the state-owned pharmacy chain Apoteket AB, the system aimed to prevent improper household medication disposal. In 2009, Sweden legally mandated Extended Producer Responsibility (EPR) for pharmaceutical companies (Regulation SFS 2009:1031). In practice, all pharmacies accept returned medicines free of charge, and pharmaceutical companies fund the collection and destruction through a collective organization [27].

A distinctive feature of the Swedish model is its incentive-based approach: many pharmacy chains offer loyalty points or discounts to customers who return expired medicines. As a result, Sweden achieves very high return rates, collecting approximately 1,300 tons of unused medicines from the public annually—one of the highest per capita volumes in Europe. In terms of collection efficiency relative to pharmaceutical market size, Sweden competes with France: about 270 mg of pharmaceutical waste is collected for every USD 1,000 spent on medicines, far surpassing most other countries [7].

Sweden also invests in education: for example, eco-labels and “green medicine” guides are being developed to help prescribers and patients consider environmental impacts when selecting treatments. However, despite the maturity of the system, improper disposal still exists: Swedish studies estimate that 10–20% of the population continues to discard medicines in the trash or down the drain, although overall awareness is high [18].

Norway and Denmark implement similar approaches through national-level return schemes. In Norway, the system is publicly funded, pharmacies accept medicines

free of charge, and centralized incineration is the primary disposal method. Finland also collects medicines mainly through pharmacies, with funding provided by municipalities and supported by national environmental programs. Finnish pharmacies actively participate in ecological initiatives: nearly every pharmacy offers medicine return services as part of their commitment to "a cleaner environment" [35].

In recent years, Finland has also proposed an eco-classification system for pharmaceuticals to inform both healthcare professionals and patients about the environmental impact of specific drugs and to encourage more responsible consumption [5].

In the Baltic States (Estonia, Latvia, Lithuania), mixed models are used. Legislation generally requires the availability of return points—typically within pharmacies—but funding and coverage vary. For example, in Lithuania, all pharmacies are mandated to accept returned medicines; however, actual public participation remains low. Research indicates that in Lithuania and some other Eastern European countries, a significant portion of the population continues to dispose of medications improperly (in household waste or wastewater), despite the formal existence of collection systems. This highlights the urgent need to strengthen public awareness campaigns and improve access to convenient return points [49].

Over the past decades, Southern European countries have developed effective national pharmaceutical waste management systems based on cooperation between government and industry. Spain, since the early 2000s, has implemented the SIGRE program (Sistema Integrado de Gestión y Recogida de Envases), which covers all pharmacies in the country. For over 24 years, SIGRE has offered citizens a convenient way to dispose of expired medicines: each pharmacy is equipped with a Punto SIGRE container where medications and their packaging can be returned free of charge [38].

The system is financed by pharmaceutical companies and distributors under the Extended Producer Responsibility (EPR) principle. Pharmacists play a central role by informing customers and encouraging them to return unused medicines, emphasizing the health risks of improper storage or disposal. Due to the proximity and trust in pharmacies, the habit has become deeply rooted: surveys from the 2020s show that 3 out of 4 Spanish households regularly use the SIGRE system. This represents a remarkable level of public engagement. Returned medications are sent for centralized destruction (thermal treatment), while recyclable packaging is recovered [46].

The Spanish experience demonstrates how long-term education efforts and public–private collaboration can successfully integrate environmentally responsible behavior into daily life. Portugal adopted a similar model under the Valormed program. Since 2001, national legislation has required pharmaceutical producers and distributors to establish a country-wide medicine waste collection system. Companies finance the non-profit organization Valormed, which supplies pharmacies with containers and organizes the collection and destruction of returned medicines [1].

As a result, Portugal has achieved one of the highest participation rates in Europe, comparable to Sweden. The EPR model has relieved municipalities of financial burdens by shifting costs to the pharmaceutical industry, in line with the "polluter pays" principle. According to statistics, Portugal's per capita and market-adjusted collection volumes rank among the top in the EU. Nevertheless, a portion of the population remains unreached, particularly in rural areas, highlighting the continued need for awareness campaigns [12].

Italy has organized medicine waste collection largely through local governments and pharmacies. Since the 1980s, the sector has relied on cooperation between trade associations: the Assinde consortium brings together producers, wholesalers, and pharmacies to manage the removal of expired medicines from both pharmacy stock and household waste. Pharmacists receive partial compensation for returned expired medicines, encouraging timely withdrawal from circulation [17].

In all Italian regions, collection points have been set up: in most cities, municipal containers for household pharmaceutical waste are installed in or near pharmacies. Municipalities are responsible for collection and disposal, working with licensed waste operators. In 2016, Italy's Ministry of Environment signed an agreement with Assinde to enhance monitoring of pharmaceutical waste flows and ensure environmental compliance. The system now covers nearly all populated areas, although public participation levels vary [50].

Italian experts identify a key challenge: reducing the volume of unnecessary medicines through improved prescribing and packaging, as significant pharmaceutical waste continues to accumulate despite a widespread collection infrastructure [14].

Greece has more recently established a national system. Until the 2010s, pharmaceutical waste collection was sporadic, but in 2019, a new national program was launched under the Institute of Pharmaceutical Research and Technology (IFET) with support from the Ministry of Health. Special green containers were installed in all pharmacies, allowing citizens to return expired or unwanted medicines [32].

When a container fills, the pharmacist notifies the local pharmaceutical cooperative, which dispatches certified staff to collect the sealed bag. The bags are then sent to an IFET warehouse and redirected to authorized high-temperature incineration facilities. The entire process is digitally tracked, and destruction is documented with formal reports. In 2019 alone, approximately 120 tons of pharmaceutical waste were collected through this system, covering an estimated 45% of medicines disposed of nationwide.

Greece has also launched educational campaigns. The Pharmacists' Association, in collaboration with the Ministry of Education, conducts school-based programs highlighting the environmental risks of improper medicine disposal. Public outreach materials encourage people—especially youth—not to discard medicines in trash but to return them to pharmacies. Additionally, Greek pharmacists have begun promoting the safe disposal of vaccination-related waste (e.g., needles, syringes) to prevent injuries and environmental contamination.

Greece's key achievement over the past five years has been the creation of disposal infrastructure from scratch and initial public engagement, although a large portion of unused medicines is still improperly discarded due to public inertia and lack of awareness.

In Central and Eastern European countries—including new EU members and neighboring states—medicine disposal systems have developed under the influence of EU directives, yet their effectiveness varies widely.

Poland, for instance, has legislated that medicines from households may be returned to pharmacies or designated collection points. However, for a long time, there were no uniform procedures. Municipalities are required to provide citizens access to hazardous waste disposal points, including for medicines, and often place containers in selected pharmacies or clinics. Yet not all pharmacies participate: formally, they are not obliged to accept medicines unless they have an agreement with local authorities, and there is no financial compensation for doing so.

A 2016–2019 study showed that only about 30% of Poles returned medicines to pharmacies, even though around 65% were aware of this option. A majority—up to 68%—admitted to disposing of expired medications in regular trash or flushing them down the toilet, indicating both insufficient public awareness and limited convenience. Since 2005, Poland's Waste Act has allowed pharmacies to accept medicine waste from the population, while responsibility for safe destruction lies with local authorities. However, the lack of funding and clear operational guidelines has led to inconsistent practices.

In recent years, the Polish government and NGOs have taken steps to improve the situation: local awareness campaigns have been launched, and some provinces have introduced pilot programs offering free pharmacy take-back. Still, Poland exemplifies a key regional challenge—the gap between regulatory requirements and actual implementation. Further effort is needed to transform formal "schemes" into fully operational services for the public [40] .

By contrast, Hungary has successfully implemented an EPR-based system. Since 2005, the national Recyclomed program has operated under a government-industry partnership. According to Hungarian law (20/2005 [VI.10]), all pharmacies must accept expired medications, and the collection and disposal are funded by pharmaceutical companies through a specialized producer responsibility organization (PRO). Collection points also exist in other healthcare facilities, enhancing accessibility.

As a result, government data indicate that a significant share of household pharmaceutical waste is collected annually. Hungary's per capita collection volumes are among the highest in Eastern Europe, though still lower than in Western countries. The EPR model has made Hungary a regional example, demonstrating that shifting financial responsibility to manufacturers encourages corporate participation in environmental initiatives and provides pharmacies with resources to fulfill their role without burdening public budgets.

Slovakia and Slovenia have chosen a different model, emphasizing public funding. In Slovakia, national and municipal authorities are jointly responsible for collection: pharmacies accept medicines, while the state covers transport and disposal costs. The scheme is nationwide, though funding is limited. Slovenia combines pharmacy-based and municipal collection: urban areas have public medicine bins, hazardous waste collection stations, and pharmacy-based return programs. While this improves access, the fragmented infrastructure may cause confusion among residents.

In non-EU Balkan countries (e.g., Serbia, North Macedonia, Montenegro), systems are still emerging. These countries are currently drafting regulations—often with support from the WHO and EU—aimed at establishing public take-back systems. However, implementation is still in its early stages: citizens are encouraged to return medicines to pharmacies or hospitals, but infrastructure is limited.

Turkey, partially located in Europe, adopted a 2020 regulation mandating pharmacy-based take-back of expired household medicines, but practical implementation remains hampered by logistical and organizational challenges [41], [29].

Overall, many Eastern European countries face similar issues: lack of funding, weak coordination between authorities and pharmacies, and low public awareness. However, the presence of a shared EU regulatory framework and increasing participation in international knowledge-sharing initiatives are gradually improving conditions.

For example, Latvia, in recent years, has launched several EU-supported public campaigns, which increased awareness. According to 2021 surveys, about 60% of Latvians knew that medicines should not be discarded in regular trash—though fewer than half actually returned them to pharmacies.

Regulatory Framework and Initiatives in the United States and Canada

In the United States, a key role is played by the nationwide initiative National Prescription Drug Take Back Day, organized twice a year by the Drug Enforcement Administration (DEA). These events allow the public to anonymously return both prescription and over-the-counter medications for safe disposal. The volume of collected pharmaceuticals is significant; for instance, in October 2020, during the program's 10th anniversary, a record was set with nearly 1 million pounds (≈493 metric tons) of medications collected nationwide [42].

Since the launch of the initiative in 2010, approximately 13.7 million pounds (over 6,800 metric tons) of unwanted medicines have been collected in total. DEA data confirms that such campaigns are in high public demand and successfully remove large quantities of potentially dangerous substances from circulation [51].

In addition to Take Back Days, the U.S. has established a network of permanent drug collection sites: as of 2019, about 11,000 DEA-authorized take-back locations were operating across the country (including in pharmacies, hospitals, and police stations). Thanks to this infrastructure, approximately 70% of the U.S. population lives within 5 miles of a drug disposal location [39].

Beyond federal initiatives, major pharmacy chains have voluntarily implemented their own disposal programs. For example, since 2019, Walgreens has offered year-round medicine disposal in all of its 9,000+ stores via either dedicated kiosks or by providing in-home disposal kits (absorbent pouches) to customers. Similar services have been introduced by CVS and other retail pharmacy chains [26].

Each year, during National Drug Take Back Week, local initiatives also participate in partnership with the DEA and public health agencies—often involving volunteers, NGOs, and law enforcement [8].

Canada operates a nationwide medicine return program through pharmacies. Every pharmacy in the country accepts expired or unused medications from the public year-round. This model is supported at the provincial and territorial levels, often in partnership with industry associations. For example, in British Columbia, Ontario, Manitoba, and Prince Edward Island, the Medications Return Program is managed by the Health Products Stewardship Association (HPSA).

Residents can return prescription drugs, over-the-counter medications, and natural health products free of charge to designated pharmacies. The collected products are then centrally incinerated, typically through high-temperature combustion. Additionally, some municipalities and police departments periodically organize special medicine collection days to supplement the pharmacy-based system.

Nevertheless, as noted by Health Canada, existing initiatives only capture a portion of unused medications—a substantial share still ends up in the environment (soil and water) or remains stored in households. This highlights the need to expand the reach and effectiveness of medicine return programs.

Despite the availability of disposal programs, behavioral studies point to a gap between official recommendations and the actual practices of citizens. Many people continue to throw medications in the trash, flush them down the toilet, or stockpile expired pills at home. According to recent surveys, a significant share of Americans are unsure how to properly dispose of medications: more than half of respondents reported difficulties or a lack of awareness about the existence of safe disposal methods. An analysis of practices related to unused opioids showed that between one-quarter and three-quarters of patients do not dispose of the remaining drugs, instead keeping them at home for potential future use or losing track of them altogether. Only a minority intentionally return medications to pharmacies or take-back events. As a result, surplus medicines become accessible for misuse: U.S. federal statistics show that up to 85% of intentional nonmedical use of prescription painkillers occurs with the knowledge of the original patient (for example, by giving away or selling leftover pills). In Canada, similar trends are observed—review data indicate that most residents have traditionally disposed of medicines with household waste or stored them at home, and only a small proportion have regularly returned them to pharmacies. However, a positive trend is emerging: as public awareness grows, the number of people using pharmacy return programs is gradually increasing. Studies identify several key factors influencing public participation. First, awareness and education: many citizens are simply unaware of these programs or underestimate the risks of improper disposal. Targeted campaigns (via public service announcements, counseling by physicians and pharmacists) can increase participation. Second, the availability of infrastructure: people are more likely to return medications if a collection site is nearby and the process is convenient. Accessibility is especially important for residents of rural and remote areas, where it can be difficult to find a pharmacy or police station with a disposal bin; long distances and transport issues often discourage visits or participation. As the American Farm Bureau notes, many farmers find it inconvenient to drive dozens of kilometers just to dispose of medicines and therefore tend to keep excess drugs "for later." In surveys of rural U.S. residents, many admitted to keeping unnecessary prescription medications out of fear they might not be able to obtain them again when needed, or simply due to lack of knowledge about disposal options. To address this issue, alternative, more convenient solutions are being implemented—such as free mail-back envelopes for sending drugs for incineration or distribution of special deactivation pouches to farming families for at-home use. Third, motivation and risk perception: when people understand that storing medicines at home can lead to child poisoning, accidental ingestion by the elderly, or misuse, they are more likely to dispose of them. Gradually, the public is becoming more aware of the risks, particularly regarding opioids and other high-abuse-potential drugs. This shift is being driven by information campaigns: for example, U.S. media often reports cases of children poisoned by vitamin supplements or pets harmed by discarded pills, which encourages responsible disposal. Therefore, increasing public engagement in proper medication disposal requires a comprehensive approach—improving awareness, ensuring easy access to drop-off locations, and offering convenient solutions tailored to various population groups (urban, rural, young, elderly) [15].

Regulatory Framework and Initiatives in Asian countries

In many countries around the world, collecting unused medications through dedicated programs is recognized as an effective method of safe disposal [47]. In recent years, Asian countries have also begun implementing similar initiatives at both national and local levels [19]. Government-run take-back programs typically involve setting up infrastructure to accept expired and surplus medicines from the public—such as collection points at pharmacies, hospitals, or designated centers—where the drugs are sent for destruction, most commonly through controlled incineration. Voluntary initiatives, often supported by pharmaceutical companies or environmental organizations, complement public measures in places where mandatory regulations are lacking [2]. By the 2020s, several Asian countries had already established official take-back programs. For instance, in Malaysia, the Ministry of Health launched the Return Your Medicines Programme, which enables patients to return unused medications to government pharmacies and clinics for safe disposal [43]. Despite the existence of such a program, its reach remains limited: a survey in the state of Selangor showed that only 25.2% of households returned medications through the official mechanism, although 73.8% of respondents agreed that pharmaceutical waste should be separated from regular trash. Many residents continue to dispose of medications with household waste (about half of respondents), while 10–12% flush them down the drain, unaware of the environmental harm. A majority (82.5%) acknowledged a lack of information on proper disposal methods. These findings highlight the need to expand and promote take-back programs in Malaysia [6]. Another

example is China, where since 2004, a large-scale annual campaign has been conducted to collect expired drugs from the public. The initiative, launched by the state-owned Guangzhou Pharmaceutical Holdings, has evolved into a nationwide voluntary take-back effort. Every year in March–April, over 6,000 pharmacies in 200 Chinese cities collect expired medications from citizens for proper disposal [31]. Over the past 20 years, more than 1,600 tons of medicines have been collected and safely destroyed. Citizens are encouraged to participate: those returning old medications receive small gifts such as basic over-the-counter medicine kits or pharmacy discount coupons. Thanks to this campaign, awareness of the issue is gradually increasing, with more residents recognizing the environmental and health risks of discarding expired drugs in regular trash. While most participants are older adults, youth participation is also visible, indicating the success of educational outreach [53]. In the Republic of Korea, both legislative and corporate initiatives exist for collecting pharmaceuticals. Since 2017, all pharmacies have been legally required to maintain special containers for expired and unused medications from the public, with local governments responsible for collection and destruction. The private sector is also involved; for example, in 2021, leading pharmaceutical company Dong-A Pharmaceutical signed an agreement with the Korean Pharmaceutical Association and the city of Dangjin to launch a joint household-level medication take-back project. Under this project, pharmacies accept expired medications from the public, and logistics company Yongma Logis centrally transports the collected drugs to an incineration facility. The initiative aims to protect public health and the environment, as disposing of medications with household waste poses serious risks (such as water and soil pollution and pharmaceutical residues entering the food chain). Estimates indicate that in 2018, approximately 4,690 tons of medications were discarded in Korea, a figure projected to rise to 6,700 tons by 2025 due to population aging. As such, these programs are seen as timely interventions. A photo captures the signing of the agreement between representatives of the pharmaceutical company and the Korean Pharmaceutical Association, exemplifying a partnership model involving industry, professional bodies, and local government to address pharmaceutical waste. Even in Asian countries lacking official take-back programs, some steps are being taken. For example, Japan still does not have a dedicated national system for collecting expired medications from households. Unused drugs are typically disposed of by Japanese residents with regular waste (as burnable garbage) or returned to physicians during follow-up visits. Nonetheless, government authorities advise citizens not to flush medicines and, where possible, to bring hazardous waste to municipal drop-off points. Some prefectures in Japan have launched pilot projects for household-level separation of medical waste, but a uniform system has yet to be established. Similar situations exist in other East Asian countries, where local initiatives or non-binding recommendations fill the role of official take-back programs [22].

Behavioral aspects of medication disposal largely determine the success of any take-back program. Studies show that even when safe disposal options are available, people do not always use them. The reasons vary—from lack of awareness about the existence of such programs to reluctance to make a separate trip to a pharmacy or collection point. A review of 12 studies conducted in South and Southeast Asia between 2013 and 2023 revealed a significant gap between public attitudes and actual practices [44]. Overall, people recognize the dangers of improper drug disposal and express support for safe disposal initiatives—most respondents were in favor of pharmaceutical take-back programs. However, actual behavior lags behind: a significant portion of respondents continue to throw medications in the trash or flush them down the drain [20]. Nine out of the twelve studies in the review reported insufficient public knowledge about proper disposal methods and limited access to reliable information. Surveys across various Asian countries show that many citizens are simply unaware that take-back programs exist or that medicines should not be discarded with regular waste [52]. For example, in Thailand, about 80% of respondents had never heard of designated medicine collection points. In Bangladesh, only one-third of respondents were aware of the environmental harm caused by pharmaceutical waste. On the other hand, the willingness to participate in solving the problem is quite high—provided people are informed and the process is convenient. When individuals are told that they can return medicines to a pharmacy and are educated on environmental risks, many act responsibly. In China, thanks to a large-scale information campaign, by 2023 citizens began planning visits to pharmacies specifically to return expired medicines—pharmacy staff report that residents now ask about the dates of upcoming campaigns and deliberately collect drugs for that purpose. Thus, education and awareness efforts play a decisive role. Most of the Asian population responds positively to appeals for safe disposal, but a lack of practical opportunities (such as nearby drop-off points or convenient hours) and insufficient information prevent people from changing established habits [9]. Therefore, changing behavior requires a comprehensive approach: expanding the accessibility of programs (more return locations, integration with municipal waste services), along with active public education on the dangers of improper disposal [25], [36].

Conclusion

The review highlights that while many countries have established pharmaceutical take-back programs, significant gaps remain in public awareness, infrastructure accessibility, and behavioral adherence. Successful models—such as those in parts of Europe, North America, and emerging efforts in Asia—demonstrate that integrating regulatory frameworks with public education and convenient disposal options leads to higher participation rates. However, in many regions, particularly in Asia and Eastern Europe, the effectiveness of these systems is still limited by inconsistent implementation and lack of public engagement. Addressing these challenges requires a coordinated strategy that combines legislation, industry responsibility, public outreach, and cross-sector collaboration to ensure safe and environmentally sound medication disposal practices worldwide.

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QUALITY OF LIFE AND MENTAL HEALTH OF PATIENTS WITH RHEUMATOID ARTHRITIS. LITERATURE REVIEW

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease marked by persistent inflammation, joint damage, pain, and progressive functional limitations. These symptoms substantially reduce patients' health-related quality of life (HRQoL), affecting physical functioning, emotional well-being, social participation, and work capacity. In addition to physical impairment, RA is strongly associated with mental health problems. Depression, anxiety, chronic stress, and sleep disturbances occur significantly more often in RA patients than in the general population. Psychological distress not only develops as a reaction to chronic pain and disability but also contributes to increased disease activity, heightened pain perception, and reduced adherence to treatment. The relationship between mental health and quality of life in RA is complex and bidirectional: poor psychological well-being worsens physical outcomes, while disease progression further aggravates emotional difficulties. Understanding this interplay is essential for developing effective biopsychosocial management strategies. This review summarizes current evidence on the quality of life and mental health of individuals with RA and identifies key factors influencing these outcomes.

Aim. To review current literature on the quality of life and mental health of patients with rheumatoid arthritis, identifying key determinants and the interplay between psychological status and health-related quality of life.

Search strategy. A literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar using keywords: "rheumatoid arthritis," "quality of life," "mental health," "depression," "anxiety," "HRQoL." Inclusion criteria: articles published in the last 10 years, in English, focused on adult RA populations. Narrative review methodology was applied.

Results and conclusions. Evidence shows that reduced quality of life in RA is strongly associated with pain, functional limitations, fatigue, and psychological distress. Depression and anxiety are reported in up to one-third of patients and substantially worsen disease outcomes. Multidisciplinary management - including optimized pharmacotherapy, patient education, psychological support, and physical activity – d emonstrates effectiveness in improving both mental health and quality of life. Further research is needed to develop integrated biopsychosocial interventions.

Keywords: *rheumatoid arthritis, quality of life, mental health, depression, anxiety, HRQoL, chronic disease.*

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Резюме

КАЧЕСТВО ЖИЗНИ И ПСИХИЧЕСКОЕ ЗДОРОВЬЕ ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Ревматоидный артрит (РА) — хроническое аутоиммунное заболевание, характеризующееся стойким воспалением, повреждением суставов, болью и прогрессирующими функциональными ограничениями. Эти симптомы существенно снижают качество жизни, связанное со здоровьем (HRQoL), влияя на физическое функционирование, эмоциональное благополучие, социальную активность и трудоспособность. Помимо физических нарушений, РА тесно связан с проблемами психического здоровья. Депрессия, тревога, хронический стресс и нарушения сна встречаются у пациентов с РА значительно чаще, чем в общей популяции. Психологический дистресс формируется не только как реакция на хроническую боль и инвалидизацию, но и способствует повышению активности заболевания, усилению восприятия боли и снижению приверженности лечению.

Взаимосвязь психического здоровья и качества жизни при РА является сложной и двусторонней: ухудшение психологического состояния негативно отражается на физических исходах, тогда как прогрессирование заболевания усиливает эмоциональные трудности. Понимание этих взаимодействий имеет ключевое значение для разработки эффективных биопсихосоциальных стратегий ведения пациентов. Настоящий обзор обобщает современные данные о качестве жизни и психическом здоровье пациентов с РА и выявляет ключевые факторы, влияющие на эти показатели.

Цель. Проанализировать современную литературу, посвящённую качеству жизни и психическому здоровью пациентов с ревматоидным артритом, определить ключевые детерминанты и взаимосвязь психологического статуса с качеством жизни, связанным со здоровьем.

Стратегия поиска. Поиск литературы проводился в базах PubMed, Scopus, Web of Science и Google Scholar с использованием ключевых слов: «rheumatoid arthritis», «quality of life», «mental health», «depression», «anxiety», «HRQoL». Критерии включения: статьи, опубликованные за последние 10 лет, на английском языке, посвящённые взрослой популяции пациентов с РА. Использовался нарративный метод обзора.

Результаты и выводы. Данные показывают, что снижение качества жизни при РА тесно связано с болью, функциональными ограничениями, утомляемостью и психологическим дистрессом. Депрессия и тревожные расстройства отмечаются почти у трети пациентов и значительно ухудшают течение заболевания. Междисциплинарное ведение, включая оптимизированную фармакотерапию, обучение пациентов, психологическую поддержку и физическую активность, демонстрирует эффективность в улучшении психического здоровья и качества жизни. Необходимы дальнейшие исследования для разработки интегрированных биопсихосоциальных вмешательств.

Ключевые слова: *ревматоидный артрит, качество жизни, психическое здоровье, депрессия, тревога, HRQoL, хроническое заболевание.*

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Түйіндеме

РЕВМАТОИДТЫ АРТРИТІ БАР ПАЦИЕНТТЕРДІҢ ӨМІР САПАСЫ МЕН ПСИХИКАЛЫҚ ДЕНСАУЛЫҒЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Ревматоидты артрит (РА) – созылмалы аутоиммунды ауру, оны ұзаққа созылатын қабыну, буындардың зақымдануы, ауырсыну және үдемелі функционалдық шектеулер сипаттайды. Бұл симптомдар пациенттердің денсаулыққа қатысты өмір сапасын (HRQoL) айтарлықтай төмендетіп, олардың физикалық белсенділігіне, эмоционалдық әл-ауқатына, әлеуметтік қатысуына және еңбек қабілетіне әсер етеді. Физикалық бұзылыстардан бөлек, РА психикалық денсаулық проблемаларымен тығыз байланысты. Депрессия, мазасыздық, созылмалы стресс және ұйқының бұзылыстары РА бар пациенттерде жалпы халыққа қарағанда әлдеқайда жиі кездеседі. Психологиялық дистресс тек созылмалы ауырсыну мен мүгедектікке реакция ретінде ғана емес, сонымен қатар ауру белсенділігінің артуына, ауырсынуды күшейте қабылдауға және емге бейімділіктің төмендеуіне әкеледі.

Психикалық денсаулық пен өмір сапасының өзара байланысы күрделі және екіжақты: психологиялық жағдайдың нашарлауы физикалық нәтижелерді төмендетеді, ал аурудың үдеуі эмоционалдық қиындықтарды арттырады. Бұл өзара байланысты түсіну тиімді биопсихосоциалдық басқару стратегияларын әзірлеу үшін маңызды. Бұл шолу РА бар пациенттердің өмір сапасы мен психикалық денсаулығына қатысты қазіргі зерттеулерді қорытындылап, осы нәтижелерге әсер ететін негізгі факторларды анықтайды.

Мақсаты: Ревматоидты артриті бар пациенттердің өмір сапасы мен психикалық денсаулығы туралы заманауи әдебиеттерді талдау, негізгі детерминанттарды және психологиялық мәртебе мен денсаулыққа қатысты өмір сапасының өзара байланысын анықтау.

Іздеу стратегиясы: Әдебиеттерді іздеу PubMed, Scopus, Web of Science және Google Scholar деректер базаларында «rheumatoid arthritis», «quality of life», «mental health», «depression», «anxiety», «HRQoL» кілт сөздерін пайдалану арқылы жүргізілді. Қосу критерийлері: соңғы 10 жылда ағылшын тілінде жарияланған, ересек РА пациенттеріне арналған мақалалар. Шолу нарративті тәсіл бойынша жүргізілді.

Нәтижелер мен қорытындылар: Деректер РА кезіндегі өмір сапасының төмендеуі ауырсынумен, функционалдық шектеулермен, қажумен және психологиялық күйзеліс деңгейімен тығыз байланысты екенін көрсетеді. Депрессия мен мазасыздық шамамен үштен бір пациентте кездеседі және аурудың ағымын едәуір нашарлатады. Көпсалалы басқару – оңтайландырылған фармакотерапия, пациенттерді оқыту, психологиялық қолдау және дене белсенділігі – психикалық денсаулық пен өмір сапасын жақсартуда тиімді екенін дәлелдейді. Интеграцияланған биопсихосоциалдық араласуларды әзірлеу үшін қосымша зерттеулер қажет.

Кілт сөздер: *ревматоидты артрит, өмір сапасы, психикалық денсаулық, депрессия, мазасыздық, HRQoL, созылмалы ауру.*

Дәйексөз үшін:

Тогизбаев Г.А., Жандарбекова Б.Б., Ногаева М.Г., Нургалиева Б.К., Самарова У.С., Искакова Н.С. Ревматоидты артриті бар пациенттердің өмір сапасы мен психикалық денсаулығы Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 212-219. *doi 10.34689/SH.2025.27.6.023*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, pain, and functional disability. Beyond its physical manifestations, RA substantially affects multiple dimensions of patients' lives, including social functioning, work capacity, emotional well-being, and daily activities. As a result, health-related quality of life (HRQoL) in individuals with RA is significantly lower compared with the general population and many other chronic diseases.

In recent years, increasing attention has been directed toward the psychological aspects of RA. Numerous studies have demonstrated that mental health disorders -particularly depression, anxiety, stress, and sleep disturbances - are highly prevalent among RA patients, with rates exceeding those in other inflammatory and non-inflammatory chronic conditions. These psychological factors not only arise as consequences of chronic pain, fatigue, disability, and social limitations but also play a critical role in the disease course. Evidence suggests that poor mental health is associated with increased disease activity, higher pain perception, reduced treatment adherence, and greater functional impairment.

The interplay between psychological well-being and quality of life in RA is complex and bidirectional. Mental health problems exacerbate physical symptoms and negatively affect self-management, while worsening physical health further contributes to emotional distress. This highlights the need for a comprehensive biopsychosocial approach to managing RA, integrating medical, psychological, and social support measures.

Given the growing body of research and the clinical significance of this issue, a structured analysis of existing literature is essential for understanding the determinants of quality of life and mental health in RA and for identifying effective intervention strategies.

Aim. To review current literature on the quality of life and mental health of patients with rheumatoid arthritis, identifying key determinants and the interplay between psychological status and health-related quality of life.

Search strategy. A literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar using keywords: "rheumatoid arthritis," "quality of life," "mental health," "depression," "anxiety," "HRQoL." Inclusion criteria: articles published in the last 10 years, in English, focused on adult RA populations. Narrative review methodology was applied.

Search results and their discussion.

Quality of Life in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease marked by persistent synovial inflammation, causing joint pain, stiffness, swelling and eventually erosive joint damage [43]. Over time this leads to functional disability and substantial limitations in daily activities and work performance. Consequently, RA patients report markedly lower health-related quality of life (HRQoL) than age- and sex-matched general populations, especially in physical health domains [31]. For example, fatigue has been identified as "one of the most important symptoms" in RA and is strongly associated with reduced HRQoL. In sum, the chronic pain, disability, and fatigue of RA impose heavy burdens on patients' physical, emotional and social well-being [40].

Physical Functioning and Disability. Physical symptoms and functional limitations are key determinants of QoL in RA. Chronic joint pain and stiffness directly impair mobility and independence. In one recent analysis, RA patients with poorer physical function (higher HAQ scores) were far more likely to fall into a "poor HRQoL" subgroup. Likewise, severe disease activity correlates with dramatically worse QoL: for instance, a meta-analysis found mean EQ-5D utility of ~0.78 in remission versus only ~0.47 in high-activity RA [17]. In cohort studies, higher HAQ disability and DAS28 activity scores predict worse SF-36 and EQ-5D outcomes. Notably, achieving low disease activity or remission yields substantial gains: Ma et al. reported that RA patients in sustained remission had significantly better SF-36, HAQ and EQ-5D scores than those in merely low-

activity states [18]. In general, higher disease activity, greater disability and any comorbid conditions each produce independent decrements in HRQoL. Thus, controlling inflammation and preserving function are critical to improving the physical dimension of QOL in RA [27].

Fatigue in RA is pervasive and debilitating, often reducing QoL beyond the impact of joint symptoms [37]. It is experienced as overwhelming and persistent, feeding a vicious cycle of inactivity. Studies show that fatigue levels correlate with pain, disability, and mood disorders. Psychosocial factors further compound QoL reduction: anxiety and depression are very common in RA and independently predict worse HRQoL scores. For example, Katchamart et al. found that higher depression and anxiety scores were strongly associated with lower EQ-5D utilities, even after adjusting for disease severity. Social and demographic factors also matter: having employment, higher income and education is linked to better QoL, whereas older age and work disability amplify the burden [14]. In summary, fatigue and mental health profoundly affect RA patients' well-being; comprehensive care must address pain and mobility as well as emotional and social support.

Modern RA therapies have markedly improved QoL outcomes. Treat-to-target strategies aim for remission, since remission status strongly correlates with patient-reported health. Ma et al. showed that even intermittent remission yields better SF-36, HAQ and fatigue scores than low disease activity, and sustained remission yields the greatest gains. Biologic DMARDs in particular produce large improvements. Recent evidence suggests that adding biologics (e.g. TNF inhibitors, IL-6 or JAK inhibitors) significantly reduces pain, fatigue and disability while boosting physical and mental function [8]. In a narrative review, Mamasaidov et al. found that biologic therapy "significantly improve[d] QoL in RA patients by reducing pain, fatigue, and disability while enhancing physical function and mental well-being". Real-world cohorts confirm these benefits. For example, a Palestinian study found that patients treated with the TNF inhibitor etanercept had significantly higher EQ-5D indices (better HRQoL) and lower HAQ disability scores than those not on biologics. In general, more effective disease control (whether by conventional DMARDs or biologics) translates into improved HRQoL. However, treatment response varies: therapy side-effects, comorbid illnesses, and socioeconomic factors can moderate the gains in QoL. Overall, the evidence from randomized trials and cohorts indicates that aggressive therapy (aiming for remission) is associated with meaningful improvements in patients' quality of life [51].

Measurement of QoL in RA. HRQoL in RA is assessed using validated generic and disease-specific instruments. The 36-item Short-Form survey (SF-36) is widely used in RA research. It yields component scores (Physical Function, Role Physical, Bodily Pain, Vitality, etc.) that have consistently shown much larger deficits in physical domains for RA patients than in mental or social domains [9]. Functional disability is often quantified by the Health Assessment Questionnaire (HAQ) Disability Index; higher HAQ indicates more impairment. Generic utility measures like the EuroQol EQ-5D are also commonly used, especially in cohort and economic studies, to capture overall health status on a 0–1 scale. For example, Katchamart et al. used the EQ-5D in a Thai RA registry and found mean utility ~0.87, with problems in pain/discomfort and usual activities rising sharply as DAS28 and HAQ increased. Likewise, Al-Jabi et al. used the EQ-5D-5L alongside HAQ-DI and HAQ pain VAS to quantify QoL in a Palestinian cohort. These instruments are reliable and responsive: pooled analyses confirm that RA patients score far below population norms on SF-36 physical domains and have HAQ scores that worsen as disease progresses [11]. In practice, studies often report multiple measures (e.g. SF-36 PCS/MCS, HAQ-DI, EQ-5D utility) to fully capture patient-reported outcomes.

In summary, extensive literature from large cohorts, trials and meta-analyses uniformly shows that RA significantly impairs physical functioning and overall well-being. Pain, fatigue and disability are the principal drivers of low QoL in RA. Effective treatments – particularly when they achieve sustained remission – tend to restore HRQoL toward normal levels [38]. Validated instruments like the SF-36, HAQ and EQ-5D are essential for quantifying these outcomes. Ongoing research emphasizes the multifaceted nature of QoL in RA and the need for comprehensive management to address both the physical and psychosocial dimensions of this chronic disease.

Mental Health in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is associated with a strikingly high prevalence of mood disturbances. Studies report that depression affects roughly 20–40% of RA patients and anxiety affects 25–70%, far above general population rates [34]. These disorders are often *underdiagnosed*. For example, one cross-sectional study found only 10% of RA patients had a recorded depression diagnosis, but standardized screening revealed depression in 30–34% and anxiety in ~32% [22]. Risk factors for depression in RA include longer disease duration, low income or education, and chronic inflammation [4]. Importantly, RA with depression or anxiety is linked to worse clinical outcomes: higher pain and DAS28 activity scores, more fatigue and disability, lower treatment adherence, and higher mortality. In one large study, RA patients with depression had significantly worse DAS28 (4.36 vs 3.70), greater fatigue, and poorer physical function than those without [30]. Overall, "depression and anxiety are highly prevalent and underreported in the RA population and are associated with higher levels of pain, physical disability, and disease activity". Clinicians are urged to screen routinely for mood disorders since they predict *poorer quality of life and increased disease severity* in RA [6].

Depression and anxiety in RA often occur together and exacerbate one another. Many RA patients report chronic stress and worry about disease flares, disability and future health, which can trigger or worsen mood symptoms. Coping resources vary: RA patients commonly use active problem-solving, planning, acceptance, and (more so than controls) religious coping. However, under high stress or inflammation, patients may resort to denial or catastrophizing, which are maladaptive. For example, one study found that RA patients with high stress had *twice* the inflammatory marker (CRP) levels of those with low stress [48], and as CRP/DAS28 rose, patients increasingly used denial coping. In general, positive coping (support-seeking, acceptance) is linked to better outcomes, whereas catastrophizing leads to more pain, fatigue and disability [19]. These findings suggest that stress management could be key to controlling inflammation in RA.

Sleep disorders are strikingly common in RA and interwoven with mood. Across studies, 30–42% of RA patients report poor sleep quality or insomnia. Poor sleep is strongly associated with anxiety and depression: one cross-sectional analysis found anxiety increased the odds of poor sleep by ~5× and depression by ~9× [24]. Compared to healthy controls, RA patients have significantly shorter sleep duration, lower sleep efficiency, and more sleep disruptions, along with much higher

daytime sleepiness [33]. As disease activity rises, sleep quality consistently worsens. The interaction is bidirectional: poor sleep can amplify pain perception and mood symptoms, and mood disorders further impair sleep. For example, women with RA and depressive symptoms had significantly poorer Pittsburgh Sleep Quality Index scores (10.1 vs 7.3) and more fatigue than those without depression [41].

Poor sleep and mood combine to erode quality of life. RA patients commonly report sleep disturbance contributing to chronic fatigue and functional impairment. In one study, high disease activity was correlated with worse sleep and higher anxiety/depression scores, while both worse mood and poor sleep strongly predicted lower physical and mental health on the SF-36 survey [20]. Clinicians should assess sleep (e.g. with the PSQI) especially in depressed or anxious patients, as treating insomnia may improve overall outcomes.

Beyond depression and anxiety, RA carries elevated risk for other psychiatric conditions. Population studies show that RA patients have higher incidence of bipolar disorder and possibly other mood-spectrum illnesses. One cohort study found that RA patients were significantly more likely than matched controls to develop depression, anxiety disorders, and bipolar disorder over time. Women and socioeconomically disadvantaged RA patients are particularly at risk. In practice, chronic pain syndromes also overlap – e.g. up to ~40% of RA patients screen positive for fibromyalgia, which often coexists with depression and anxiety (though not fully covered here). Overall, RA should be viewed as a systemic illness in which psychiatric comorbidities are part of the disease burden, leading to worse prognosis and highlighting the need for integrated care [32].

Effective coping skills can mitigate psychological distress. Studies show RA patients often use active coping, planning and acceptance strategies; religious coping is also more common in RA than in controls. Engagement coping (seeking emotional/instrumental support, positive reframing) is reported by many patients, especially women. In contrast, denial or escape coping tends to surface when patients feel overwhelmed – a pattern that correlates with higher CRP and disease activity [10]. Maladaptive coping (helplessness, rumination, catastrophizing) is linked to increased pain and fatigue. Interventions such as coping skills training and patient education aim to teach adaptive strategies (problem solving, relaxation, realistic goal-setting) to reduce stress and perceived pain. Indeed, trials of structured self-management programs (often including education and coping skills) have shown improvements in adherence, mood and function in RA [7].

Evidence strongly supports the benefit of psychological treatments in RA. A recent meta-analysis of 21 trials found that psychological interventions (CBT, relaxation, education, etc.) produced a *moderate* average effect size (Hedges' g≈0.40) on RA outcomes [36]. In practice, cognitive-behavioral therapy (CBT) and mindfulness-based programs are most studied. For instance, a 2025 randomized trial of online CBT vs mindfulness-based stress reduction (MBSR) found both approaches significantly reduced pain interference and depression compared to a waitlist. Notably, MBSR outperformed CBT in improving functional ability and reducing *fear of disease progression*, while CBT yielded a slight edge in reducing pain intensity by 6-month follow-up. Both treatments had effect sizes comparable to in-person therapy [42]. In another trial, a digital CBT program ("Reclarit") significantly improved the SF-36 mental score over usual care, and led to reductions in depression, anxiety, fatigue and work/social impairment [3].

Guidelines now endorse integrating psychosocial care. EULAR and ACR recommend multidisciplinary management of RA, including nonpharmacologic strategies. In particular, CBT has demonstrated consistent benefits for mood and fatigue in RA. Mindfulness-based interventions (MBSR, MBCT) have likewise been shown to ease psychological distress and even pain perception, making them valuable options [49]. Patient education and self-management programs, which often include coping skills training, have been found to enhance self-efficacy and treatment adherence. Overall, psychosocial therapies in RA can improve quality of life, mood, and sometimes even disease activity, supporting a holistic biopsychosocial approach to care [29].

Key Points: Depression and anxiety are very common in RA and worsen pain, disability and quality of life. Sleep problems and fatigue often coexist with mood symptoms. Stress and maladaptive coping (e.g. denial, catastrophizing) are linked to higher inflammation. Effective interventions (CBT, mindfulness, education) have moderate-to-large effects on psychological outcomes in RA. Treating mental health in RA is crucial: distress predicts higher disease activity and mortality [50], so integrated mental health support is recommended to improve overall RA outcomes.

Interplay Between Quality of Life and Mental Health in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease causing joint inflammation, pain, fatigue and disability, all of which can profoundly impair a patient's health-related quality of life (HRQoL). HRQoL encompasses physical, mental and social well-being, and in RA it reflects the combined impact of pain, functional loss and psychological distress [35]. In practice, the physical burden of RA (pain, fatigue, disability) often serves as a chronic stressor that triggers depression and anxiety. Several studies note that RA patients report much higher levels of psychological stress than healthy individuals. In one case–control study, RA patients had significantly higher depression, anxiety and stress scores (assessed by DASS-21) than age-matched controls. Thus, pain and fatigue inherent to RA can diminish QoL and precipitate mental health problems [26], creating a complex clinical picture where physical and emotional burdens reinforce each other.

Psychological comorbidities are common in RA. Cross-sectional surveys estimate that depression affects roughly one-quarter to one-half of RA patients, and anxiety is similarly common. For example, Uda *et al.* (2021) reported that 17.6% of RA patients had anxiety symptoms and 27.7% had depression symptoms (defined by HADS≥8) [46]. Other studies report even higher figures: 26–46% of patients experience anxiety and 15–34% report depressive symptoms. In early arthritis cohorts, nearly 48% of newly diagnosed RA patients had moderate-to-severe depression (versus 27–32% in pre-RA arthralgia/undifferentiated arthritis). These high rates underscore that RA patients are at elevated risk for mood disorders [45]. Importantly, the mental health burden is not merely a reaction to disease: even after adjusting for demographics and disease activity, RA patients show higher prevalence of depression and anxiety than the general population [23].

Depression, anxiety and chronic stress exert powerful negative effects on HRQoL in RA. Numerous studies link poor psychological health to worse QoL scores across multiple

domains. In a nationally representative U.S. survey, Alwhaibi (2025) found that RA patients with *comorbid* depression and/or anxiety had significantly lower HRQoL than those with RA alone. In that study, patients with both depression and anxiety had the lowest scores on both physical and mental HRQoL scales, even after controlling for age, comorbidities and lifestyle factors [16]. Similarly, Beşirli *et al.* (2020) used the Hospital Anxiety and Depression Scale (HADS) and SF-36 in 50 RA patients and found strong negative correlations between HADS anxiety/depression and *all* SF-36 domains. In other words, higher anxiety or depression scores were associated with poorer physical function, role limitations, vitality, social function, etc., on the SF-36. The study concluded that "anxiety, depression, quality of life, disease activity and suicidal ideation are related" in RA, and that patients with both anxiety and depression had significantly lower SF-36 scores in every dimension [5].

Stress and psychological distress have similar effects. Khan *et al.* (2021) reported that RA patients had significantly higher perceived stress than healthy subjects. Chronic stress in RA often comes from ongoing pain and fatigue, which in turn can amplify feelings of helplessness or depression. High stress and mood symptoms contribute to sleep disturbances and fatigue, further degrading QoL. One recent survey of RA patients on biologic therapy found alarmingly low QoL and high distress: mean QoL scores (on a disease-specific scale) were "low" and psychological distress (Kessler scale) was "very high," with extreme depression observed in many participants. Notably, this study found a strong inverse correlation between QoL and distress levels – patients with poorer QoL had much higher depression/anxiety scores. Taken together, these findings indicate that mental health disorders substantially magnify the HRQoL burden of RA [39].

The relationship is bidirectional: not only do depression and anxiety worsen QoL, but the converse is also true. Persistent RA symptoms, disability and social limitations can erode self-esteem and resilience, fueling depression and anxiety. For example, chronic pain and functional loss – key components of low QoL – serve as continuous stressors that may precipitate psychological distress [15]. Conversely, several large cohort studies show that depression in RA leads to worse physical outcomes, suggesting a vicious cycle. In the JAMA Network Open cohort, Jeon *et al.* (2024) note that comorbid depression is linked to *"exacerbation of pain, increased disease activity, [and] poor health-related quality of life"* in RA [47]. In other words, depression can amplify the perception of pain and disability, further lowering QoL. This vicious cycle has been quantified: the risk of depression onset is ~1.7-fold higher in RA patients than in controls, and conversely depressed individuals have an elevated incidence of developing RA. Torlinska *et al.* (2024) explicitly note the bidirectional association: having RA increases depression risk, while pre-existing depression increases future RA risk. In early RA cohorts, even subclinical depression or anxiety symptoms predict poorer response to treatment and lower QoL over time [1].

In summary, a negative feedback loop can arise in RA: chronic joint pain and disability reduce QoL and induce stress, which can trigger depression/anxiety; those mood disorders then worsen pain perception and coping, leading to further QoL decline. Clinically, this means that low HRQoL and mental distress often reinforce each other, underscoring the need for comprehensive care. As Jeon *et al.* conclude, "preventing and managing depression can be an effective approach to enhancing overall health and quality of life in [RA] patients" [44], and many authors advocate integrating rheumatologic and psychiatric treatment to break the cycle.

Researchers use a variety of validated instruments to measure HRQoL and mental health in RA:

- SF-36 (Short Form-36 Health Survey) – A generic HRQoL tool yielding physical and mental component scores. For example, Beşirli *et al.* found that RA patients with higher HADS anxiety/depression had uniformly lower SF-36 subscale scores [2]. SF-36 allows comparison to population norms and other diseases.
- EQ-5D – A health utility index (mobility, self-care, pain, etc.). Torlinska *et al.* used EQ-5D to show that HRQoL in RA patients was significantly lower than in general population or those with less severe arthritis [13]. EQ-5D scores in their RA cohort were comparable to those of severe chronic conditions, illustrating the QoL impact.
- HAQ-DI (Health Assessment Questionnaire–Disability Index) – An RA-specific measure of physical function. Higher HAQ-DI means more disability. Uda *et al.* reported that HAQ-DI >0.5 was strongly associated with both anxiety and depression symptoms in RA (OR≈3.5 for anxiety) [12]. HAQ-DI is widely used to link disability with QoL and mood.
- PHQ-9 (Patient Health Questionnaire-9) – A 9-item depression screener. Many RA studies classify patients by PHQ-9 score: for instance, Torlinska *et al.* defined "moderate-to-severe depression" as PHQ-9 ≥10 and found 48% of early RA patients met this threshold [21]. PHQ-9 is sensitive for depressive symptom severity in RA.
- HADS (Hospital Anxiety and Depression Scale) – A 14-item scale with separate anxiety (HADS-A) and depression (HADS-D) subscales, designed for patients with medical illness. Both Beşirli *et al.* and Uda *et al.* used HADS in RA cohorts [28]. In Beşirli's study, every SF-36 domain correlated negatively with HADS-A/D, illustrating how HADS can quantify mental health impacts on QoL [25].

These tools allow standardized assessment. For example, in the cited studies: SF-36 and EQ-5D quantified QoL, HAQ-DI measured disability, PHQ-9 and HADS measured depression/anxiety, and all were significantly interrelated in RA patients. Consistently, worse scores on mental health scales corresponded to lower QoL scores on SF-36 or EQ-5D [52].

Conclusion. In adult RA patients, depression, anxiety and chronic stress profoundly erode quality of life, and conversely poor physical and social functioning can worsen psychological well-being. Observational studies and cohorts show that up to half of RA patients struggle with mood disorders, and that these comorbidities are linked to significantly lower HRQoL across physical and mental domains. The relationship is bidirectional: RA markedly increases the risk of subsequent depression, and depression/anxiety predict worse RA outcomes (more pain, higher disease activity and reduced treatment response) and further QoL decline.

These findings underscore that RA management must address mental health as well as physical symptoms. Routine screening for depression and anxiety (e.g. with PHQ-9 or HADS) and interventions such as psychotherapy or integrated care can improve overall HRQoL. Ultimately, breaking the negative cycle of pain–poor QoL–depression can enhance both psychological well-being and functional outcomes in rheumatoid arthritis.

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THE EVOLUTION AND IMPLEMENTATION OF THE ADVANCED PRACTICE NURSE MODEL IN DEVELOPED AND DEVELOPING COUNTRIES. LITERATURE REVIEW

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Abstract

Introduction: There has been exponential growth in demand for advanced nursing services worldwide. Experience from other countries demonstrates that the adoption of a patient-centered healthcare model is accompanied by an increase in the professional workload and functional responsibilities of nursing staff. According to the World Health Organization, a shortage of nursing staff is prevalent in most countries worldwide, but this problem is particularly severe in developing countries.

Aim. The experience of developing advanced practice nursing in developed countries around the world.

Search strategy: We studied publicly available articles covering 8 years in depth and using the following databases and specialized search engines: PubMed, Google Scholar, Cochrane Library, Web of Science, and Scopus.

Results. A review highlights that developing a positive professional environment is essential to maintaining healthy and safe working conditions for healthcare workers, including nurses. The safety and quality of healthcare delivery are directly impacted by this setting. Additionally, successful adoption of the advanced practice nurse model relies on a stable regulatory framework, a high standard of professional education, and effective collaboration across various disciplines. In nations that fulfill these prerequisites, the implementation of advanced practice nursing results in better clinical outcomes, greater access to healthcare services, and a decreased burden on the overall healthcare system.

Conclusions. Thus, international experience shows that the successful implementation of the advanced practice nurse model is possible with regulatory support, high-quality training, and a supportive professional environment, leading to improved access to and quality of healthcare.

Keywords: *advanced practice nurse, barriers, working conditions, professional development, practicing nurse.*

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Резюме

ЭВОЛЮЦИЯ И РЕАЛИЗАЦИЯ МОДЕЛИ МЕДСЕСТРЫ РАСШИРЕННОЙ ПРАКТИКИ В РАЗВИТЫХ И РАЗВИВАЮЩИХСЯ СТРАНАХ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Во всем мире наблюдается экспоненциальный рост спроса на услуги передовой сестринской практики. Анализ международного опыта показывает, что реализация модели медицинской помощи, ориентированной на потребности пациента, сопровождается возрастанием профессиональной нагрузки на медицинских сестер, а также расширением спектра их функциональных обязанностей. Согласно данным Всемирной организации здравоохранения, дефицит медицинских сестер наблюдается в большинстве стран мира, однако наибольшую остроту эта проблема приобретает в развивающихся государствах.

Цель: Изучение опыта развития расширенной практики медицинских сестер в развитых странах мира.

Стратегия поиска: Изучены статьи, находящиеся в открытом доступе, глубиной за 8 лет, с использованием следующих баз данных научных публикаций и специализированных поисковых систем: PubMed, Google Scholar, Cochrane Library, Web of Science, Scopus.

Результаты. Проведённый нами обзор научной литературы показывает, что положительная профессиональная среда имеет решающее значение для обеспечения здоровых и безопасных условий труда медицинских работников, включая медсестер, что напрямую отражается на качестве и безопасности медицинской помощи. Кроме того, успешная реализация модели медсестры расширенной практики возможна только при наличии устойчивой нормативно-правовой базы, высокого уровня профессионального образования и эффективного междисциплинарного взаимодействия. В странах, где эти условия соблюдены, расширенная практика приводит к улучшению клинических результатов, увеличению доступности услуг и снижению нагрузки на систему здравоохранения.

Выводы. Таким образом, международный опыт свидетельствует, что успешная реализация модели медсестры расширенной практики возможна при наличии нормативной поддержки, качественной подготовки и благоприятной профессиональной среды, что приводит к повышению доступности и качества медицинской помощи.

Ключевые слова: *медсестра расширенной практики, барьеры, условия труда, развитие профессий, практикующая медсестра.*

Для цитирования:

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Түйіндеме

ДАМЫҒАН ЖӘНЕ ДАМУШЫ ЕЛДЕРДЕГІ КЕҢЕЙТІЛГЕН ТӘЖІРИБЕЛІК МЕЙІРГЕР МОДЕЛІНІҢ ЭВОЛЮЦИЯСЫ ЖӘНЕ ЖҮЗЕГЕ АСЫРЫЛУЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Бүкіл әлемде мейіргер ісінің озық қызметтеріне сұраныстың экспоненциалды өсуі байқалады. Халықаралық тәжірибені талдау пациенттің қажеттіліктеріне бағдарланған медициналық көмек моделін іске асыру мейіргерлердің кәсіптік жүктеменің ұлғаюымен, сондай-ақ олардың функционалдық міндеттерінің спектрінің кеңеюімен қатар жүретінін көрсетеді. Дүниежүзілік денсаулық сақтау ұйымының мәліметтері бойынша, мейіргерлердің тапшылығы әлемнің көптеген елдерінде байқалады, бірақ бұл мәселе дамушы елдерде ең өткір болып табылады.

Зерттеу мақсаты: әлемнің дамыған елдеріндегі кеңейтілген тәжірибе мейіргерлерінің даму тәжірибесін зерттеу.

Іздеу стратегиясы: Ғылыми жарияланымдар мен мамандандырылған іздеу жүйелерінің келесі дерекқорларын қолдана отырып, 8 жыл ішінде ашық қол жетімді мақалалар зерттелді: PubMed, Google Scholar, Cochrane Library, Web of Science, Scopus.

Нәтижелер. Біз жүргізген ғылыми әдебиеттерге шолу көрсеткендей, оң кәсіби орта мейіргерлерді қоса алғанда, денсаулық сақтау қызметкерлері үшін салауатты және қауіпсіз жұмыс жағдайларын қамтамасыз етуде шешуші рөл атқарады, бұл тікелей денсаулық сақтау сапасына және қауіпсіздігіне әсер етеді. Сонымен қатар, деректерді талдау көрсеткендей, жоғары тәжірибелі мейіргер моделінің сәтті енгізілуі тек тұрақты нормативтік-құқықтық орта, жоғары кәсіби білім және тиімді салааралық ынтымақтастық жағдайында ғана мүмкін. Осы талаптар орындалған елдерде жоғары тәжірибелі мейіргер қызметі клиникалық нәтижелерді жақсартып, қызметтерге қолжетімділікті арттырып, денсаулық сақтау жүйесіне түсетін жүктемені азайтады.

Қорытынды. Осылайша, халықаралық тәжірибе көрсеткендей, реттеуші қолдау, жоғары сапалы оқыту және қолайлы кәсіби орта болған жағдайда жоғары білікті мейіргер моделінің сәтті енгізілуі мүмкін, бұл денсаулық сақтау қызметтеріне қолжетімділікті және олардың сапасын жақсартуға әкеледі.

Түйінді сөздер: *кеңейтілген мейіргер, кедергілер, еңбек жағдайлары, кәсіптерді дамыту, мейіргер тәжірибесі.*

Дәйексөз үшін:

Болатова М.Б., Смаилова Д.С., Жуманбаева Ж.М., Кайратова Г.К., Серикова-Есенгельдина Д.С., Аскарова М.М., Сыдыкова Б.Қ., Актаева Л.М., Байгожина З.А., Кисина Р.М. Дамыған және дамушы елдердегі кеңейтілген тәжірибелік мейіргер моделінің эволюциясы және жүзеге асырылуы. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 220-230. *doi 10.34689/SH.2025.27.6.024*

Introduction

Global transformation of healthcare systems is marked by an increase in chronic diseases, shortages of medical staff, and the pressing need to ensure access to high-quality care that is why the development of the Advanced Practice Nurse (APN) role has become increasingly crucial. This model, introduced in response to evolving population needs and the pursuit of more efficient resource allocation, has gradually become a cornerstone of modern healthcare systems in developed countries. Advanced practice nurses possess in-depth clinical expertise and expanded authority in diagnosis, treatment, and patient management. They play a vital role in primary healthcare, disease prevention, and the coordination of interdisciplinary collaboration.

In many countries, nurses make up half of all health care professionals and have a vital role in how health actions are organized and applied, both at the front-line and managerial levels. They are often the first and sometimes only health professional a patient will see, and the quality of their initial assessment and subsequent care is vital to strong health outcomes [62].

One of the priority tasks for the development of nursing services in the Republic of Kazakhstan is to strengthen the role of nurses in the healthcare system. This includes expanding their clinical authority and emphasizing the importance of their independent professional activities. Nurses play a key role in the prevention of chronic non-communicable diseases, making their independent practice an important component of the functioning of practical healthcare [63, 28].

The growing need to prevent health problems and pandemics, as well as to reduce health inequalities, and ongoing changes in population structure, are affecting healthcare worldwide. There is a need to expand the diversity of career opportunities for nurses [24] and to retain nursing staff in health care [49, 17]. In addition, it is necessary to improve the professional competence of nurses and introduce advanced nursing practices to ensure and improve the quality and accessibility of health care. The development of advanced nursing practice roles is part of the WHO Global Strategy on Human Resources for Health: Workforce 2030 [12, 61, 25].

Aim to study the experience of developing advanced practice nurses in the developed countries of the world.

Search strategy

We studied publicly available articles covering 8 years in depth and using the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Cochrane Library, Web of Science, and Scopus.

The information search was conducted by keywords: advanced practice nurse, barriers, nursing care, independent nursing appointment, and nurse practitioner.

Inclusion criteria: Publications of the level of evidence A, B: meta-analyses, systematic reviews, cohort, and cross-sectional studies.

The exclusion criteria were conference materials, collections of abstracts containing a limited amount of information, articles with paid access, and articles published before 2015.

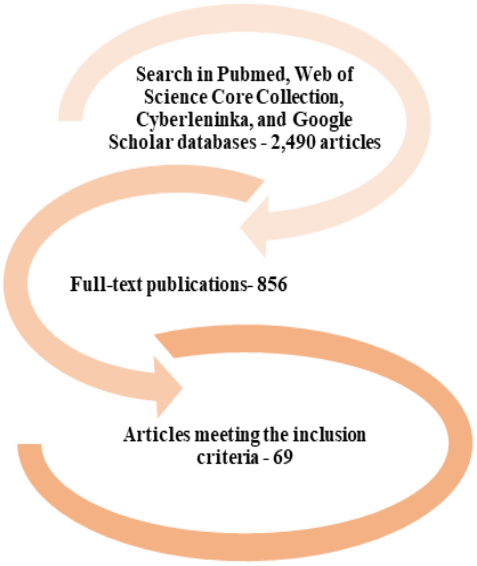


Figure 1. Article selection algorithm.

Research results.

Becoming an advanced practice nurse in developed and developing countries.

Health systems continue to transform and expand access to healthcare and improve the quality of health services and health outcomes for populations around the world [40]. In many countries, the role of non-physician service providers, such as Advanced Practice Nurses (APNs), has been introduced to achieve universal health coverage [10, 64] and improve patient health outcomes [51, 54, 32, 21]. However, the implementation of APNs in many countries faced difficulties and thus required actions to promote proper implementation [52, 4, 18]. An international study aimed to assess the implementation of advanced practice nursing rules worldwide found large differences in educational requirements, rules, and scope of practice in 26 countries in North America, Europe, Asia, South America, and Africa [20]. Out of the 16 countries that have implemented the role of nurse practitioner (NP), only 9 countries have regulated the role of NP. Only six of the thirteen countries that have adopted the role of clinical nurse specialist (CNS) have regulated it [18]. Out of the 10 countries that have implemented common APN roles, without specifying whether this applies to NP or CNS, only 5 countries have regulated APNs [18].

According to the World Health Organization (WHO), it was estimated that there will be a shortage of 7.2 million health workers to deliver healthcare services worldwide, and by 2035, the demand for nurses will reach 12.9 million [65]. The inadequate supply of nurses has notably created many negative impacts not only on RNs but also on patient health-related outcomes and on efforts to fight disease and improve health, resulting in increased workload for nurses and, later, decreased quality of nursing care [22, 35].

In response to the growing need for greater access to healthcare amid declining resources, more than 70 countries have implemented or plan to implement advanced nursing practices (International Council of Nurses [ICN]) [26]. The ICN defines APNs as those who have acquired, through master's- or doctoral-level education, complex decision-making skills, as well as advanced clinical expertise and competencies to provide direct patient and family care [23]. CNS and NP are included in this definition; their roles and responsibilities depend on the healthcare setting in which they are integrated. While APNs typically work autonomously, make diagnoses, prescribe new medications, and serve a broad patient population, the scope of practice of a CNS is more specialized and assumes that an initial medical diagnosis has been made; it also includes a large proportion of non-clinical responsibilities, such as research and education [53].

The social and economic environments have an impact on population health (Scanlon & Reinisch, World Health Organization). Countries identified as low-income countries (LICs) or lower-middle-income countries (LMICs) have insufficient healthcare resources and, as a result, have poorer population health outcomes. Nurses working in Advanced Practice Nursing or Advanced Nursing Practice roles can provide a wide range of care and treatment services and are an example of developing a workforce role that can address health care disparities. These nurses go by many role titles and have different skills, education, and regulatory requirements [66].

The first advanced nursing roles were developed in the US and Canada in the late 1960s/70s, in the UK in the 1980s, and in other high-income countries in the 1990s and beyond [26]. Subsequently, this advanced role continued to develop worldwide, albeit at varying speeds, often due to a recognized need to increase the number of practicing physicians in areas with insufficient resources and underserved populations. From the outset, nurses were used to provide primary health care, traditionally in underserved areas and for vulnerable populations. Their role has now been expanded to include other types of primary health care services [50], and this change has been implemented in several countries around the world [25].

Advanced Practice Nursing is currently expanding across the world. The APN's role is characterized by its heterogeneity, as the policies and strategies for its implementation differ depending on the country [26]. In Spain, some autonomous communities have included APNs in health care, mainly to deal with chronic diseases: the APN for Urgent Care of Minor Illnesses in Catalonia or the Advanced Clinical Nurse in the Basque Country [31]. In Andalusia, one of the largest communities in Spain, there are APN roles in six areas: diabetology, stomatherapy, oncology, palliative care, chronic wounds, and case management [27]. The latter is the most well-known by the population, as its functions are more established, and it was the first advanced practice nursing role on a regional and national level [33].

Internationally, APNs are recognized as generalist or specialized nurses who have completed a master's degree required for expert and enhanced clinical practice, including complex decision-making in managing patient care (International Council of Nurses [ICN]) [29]. The World Health Organization (WHO) has advocated for the expanded use of APNs across countries to strengthen their nursing workforce, increase access to care, and improve

the quality of care. In a recent review of the international literature, a substantive increase in the number of countries investing in advanced practice nursing roles over the last decade was noted, especially in high-income countries [10]. However, many countries, including France, are in the early stages of advanced practice nursing role development and implementation. The introduction of new healthcare providers, including APNs, is a complex process. Barriers to the effective implementation of advanced practice nursing roles are extensive and widely reported, even in countries where the roles are well established [6].

Factors that influence role implementation include role clarity, interprofessional collaboration, stakeholder involvement, regulation, funding, APN readiness, and organizational leadership and preparation for the roles. Failure to address these factors means that patients, healthcare providers, and organizations do not benefit from the full impact of the roles and has implications for APN job satisfaction, recruitment, and retention. In France, the government recently approved the credentialing requirements and introduction of APNs in priority areas of need [37]. To achieve optimal utilization and impact, it is essential to monitor how advanced practice nursing roles are being introduced into practice settings and to address barriers to effective role implementation [9].

By the 2000s, every province in Canada had legally recognized the role of nurse practitioners, and their numbers began to grow rapidly [28]. In the United Kingdom, the first nurse practitioner training program was launched by the Royal College of Nursing in the early 1990s. In the following decades, the concept of advanced nursing practice spread throughout the United Kingdom: by 2018, a significant number of advanced practice nurses were already working in England, Scotland, Wales, and Northern Ireland, both in primary care and in specialized services. In continental Europe, the introduction of advanced nursing practice began somewhat later: one of the first countries was the Netherlands, where this model began to develop in the mid-2000s in response to a predicted shortage of doctors. Over the past 20 years, approximately 2,750 nurse practitioners have been trained and registered in the Netherlands (as of 2016), and they have become firmly integrated into the system, improving the quality of care by combining medical and nursing approaches. In Finland, a national initiative for advanced nursing practice was launched in 2016. In China, the development of advanced nursing practice is in its infancy and faces a number of structural and regulatory challenges [47]. In recent years, this practice has been successfully implemented in various countries, such as Germany, Australia, New Zealand, Nigeria, and others [38]. In many of these countries, the introduction of advanced nursing practice has involved significant changes in legislation and professional regulation, as well as reforms to professional practice requirements and educational programs for nurses.

Similarly, in the Pacific Island Countries (PICs), nursing shortages are becoming a widespread problem [19]. In the Solomon Islands, Papua New Guinea, and Vanuatu, the density of health workers per 1,000 populations (mainly nurses and midwives) is well below the minimum density threshold (4.45 per 1,000 population) for maintaining basic health services [55].

Nursing reform in Kazakhstan is being implemented in stages and is already showing concrete results. In the Republic of Kazakhstan, bachelor's degrees in nursing have been offered since 2014. Currently, 37 medical colleges that have received the status of higher colleges provide this training. Graduates who have completed the applied bachelor's program are bachelor's degree holders in nursing, ready to work independently with patients. In 2007, all medical universities in Kazakhstan introduced an academic bachelor's degree program in nursing, and master's degree programs in nursing and doctoral programs in nursing science are also being implemented [1].

In July 2018, a pilot project was launched aimed at introducing a new model of nursing services in medical organizations. As part of this project, specialists with applied and academic bachelor's degrees in nursing were given expanded professional powers, moving from being executors of medical prescriptions to equal participants in the treatment process. Based on the results of the trials, the pilot project was deemed successful, and since 2020, the model of expanded nursing practice has been actively implemented in the primary health care system throughout the country. Expanded nursing practice in Kazakhstan contributes to the redistribution of responsibilities between doctors and nurses, which optimizes medical care, increases its effectiveness, and improves patient satisfaction. The introduction of this model brings the national healthcare system closer to international standards and contributes to raising the status of the nursing profession [13].

Factors causing a shortage of nursing staff.

There are many factors affecting the healthcare system as a result of nursing shortages. These include a decline in the number of nursing students enrolled in nursing programs and an increase in early retirement due to health problems [1, 67]. However, one of the main factors reported in many countries is inadequate workforce policy and planning [48].

In countries such as Tonga, Samoa, and Fiji, the main factors causing nursing shortages are the very high rates of migration of nurses to other countries, particularly Australia and New Zealand, in search of better working conditions and other opportunities. This has created problems and gaps that needed to be identified to better understand the extent of the nursing shortage and address it quickly and effectively [7].

In Vanuatu, nurses make up only 58% or 12.0 per 10,000 populations, which is below the WHO-recommended ratio of 45 nurses per 10,000 populations. According to the annual report of the Vanuatu Ministry of Health (MoH) (2018), the number of nurses retiring will continue to increase over the next 10 years, but will be disproportionate to the number of qualified nurses graduating from the Vanuatu College of Nursing Education (VCNE), which will pose a serious challenge for the Vanuatu Ministry of Health in filling vacant positions. This will place a greater burden on nurses, which will affect their productivity. This study aims to examine nurses' perceptions of the impact of the nursing shortage and their productivity in providing quality care in the Republic of Vanuatu in 2020 [2].

In many countries, healthcare systems face serious challenges due to a persistent shortage of qualified medical

personnel [5]. The key factors contributing to this problem are limited investment in professional education, training, working conditions, remuneration, and management [41]. As a result, there is an acute shortage of specialists, high staff turnover, premature termination of professional activity, and significant internal and international migration of healthcare workers.

The World Health Organization currently considers nurses to be an important resource for meeting the growing needs of the population for accessible and quality healthcare. The modern healthcare system focuses on training a new generation of nurses [36], improving the regulatory framework, creating conditions for the full realization of their professional potential, and effective management of nursing practice [3].

Legislative framework for the professional activities of nurses in the Republic of Kazakhstan.

The Ministry of Health of the Republic of Kazakhstan has identified the reform of nursing as one of its strategic goals. This is evidenced by the policy documents adopted in the republic: the State Program for the Development of Healthcare in the Republic of Kazakhstan for 2020-2025, the Roadmap for the Modernization of Medical Education, aimed at developing nursing, and the Comprehensive Plan for the Development of Nursing in the Republic of Kazakhstan for 2020-2025 [11].

According to the order of the Ministry of Health of the Republic of Kazakhstan dated December 21, 2020, No. KR DSM -305/2020 “On the approval of the nomenclature of specialties and specializations in the field of healthcare, the nomenclature and qualification characteristics of healthcare workers' positions,” the training of specialists in the specialty of “nursing” is carried out at the level of higher and postgraduate medical education, post-secondary medical education, technical and vocational education [18].

Regulatory framework for the professional activities of advanced practice nurses in the Republic of Kazakhstan.

The regulatory framework for the activities of advanced practice nurses (APNs) in the Republic of Kazakhstan is a key element in the transformation of the healthcare system, aimed at expanding the functions of mid-level medical personnel and improving the effectiveness of primary health care (PHC). The legislative framework defines the professional status, powers, and functional responsibilities of nurses, as well as the standards for their training, certification, and clinical practice.

The central regulatory document governing the activities of EPNs is the Code of the Republic of Kazakhstan “On Public Health and the Healthcare System” of July 7, 2020. For the first time at the legislative level, it establishes the status of an advanced practice nurse as a specialist with post-secondary or higher education in nursing and the right to practice nursing independently. According to Article 127, advanced practice nurses have the right to independently conduct clinical assessments of patients, formulate nursing diagnoses, develop and implement nursing intervention plans, and monitor their effectiveness based on clinical protocols and guidelines [56]. In order to implement the provisions of the Code, subordinate legislation was approved, specifying the functions and powers of nurses. In particular, Order No. KR DSM -199/2020 of the Minister of Health of the Republic of Kazakhstan, dated November 23, 2020, approved the Rules for the Provision of Nursing Care, which officially enshrine the rights of MRPs to perform independent nursing interventions in accordance with clinical protocols and standards. Following this, Order No. KR DSM -305/2020 of December 21, 2020, established the position of APRN in the nomenclature of healthcare workers' positions and defined the qualification characteristics, educational requirements, and competencies [42].

An advanced practice nurse is a specialist with an applied bachelor's degree in nursing who has expanded clinical functions. Their activities include independent nursing consultations, dynamic monitoring, counseling, screening, vaccinations, and preventive measures, as well as participation in chronic disease management programs and the universal progressive model of patronage service (UPMS).

The regulatory framework continued to develop with the adoption of Order No. 49 of March 30, 2023, which approved the Standard for the Organization of Primary Health Care, and Order No. KR DSM-90 of August 24, 2021, which sets out the range of medical services provided by medical professionals with higher education. Order No. KR DSM -149/2020 of October 23, 2020, also defined the responsibility of primary healthcare providers for monitoring patients with chronic diseases, preventing complications, and reducing the frequency of hospitalizations [43].

However, despite the focus on internationally recognized models of nursing practice, the existing regulatory framework remains fragmented. Documents often contain only general provisions that do not reflect in detail the structure and algorithm of nursing care, without specifying a clear distribution of roles among members of the multidisciplinary team. This hinders the full implementation of the expanded functions of nurses in practice.

Of particular importance in the transformation of nursing is the maintenance of nursing documentation that reflects all stages of the nursing process, from assessing the patient's condition to analyzing the effectiveness of interventions. Systematic and accurate documentation helps ensure continuity of care, legal protection for medical staff, improved quality of medical care, and the development of clinical thinking and evidence-based decisions. In Kazakhstan, as part of standardization, the international CCC (Clinical Care Classification) classification was introduced, adapted to local conditions, containing 175 nursing diagnoses and 788 interventions. In addition, Order No. KR DSM-175/2020 of October 30, 2020, defined the forms of record keeping and instructions for filling them out for MRPs [54].

An analysis of the current regulatory framework suggests that, despite the existence of fundamental legal documents, the system for regulating the activities of MRPs requires further structural improvement. In particular, it is necessary to develop clearer standards for nursing care, algorithms for interprofessional interaction, and mechanisms for the implementation of clinical guidelines and electronic documentation. Currently, the legal status of MRPs does not fully ensure the implementation of the principles of autonomy and professional responsibility, which limits their potential contribution to the reform of primary health care.

Educational programs

Contemporary transformations in the nursing education system in the Republic of Kazakhstan: regulatory guidelines and institutional changes.

In recent decades, education systems in many countries around the world have undergone significant structural and substantive changes. Kazakhstan is no exception: in line with global modernization trends, the national medical education system is undergoing active reform, with particular attention being paid to integration into the European educational space, including in the field of nursing training. Large-scale reforms have already been implemented to improve the quality of nursing training, develop clinical competencies, and expand professional autonomy.

The modernization of the nursing education system in Kazakhstan covers all levels and is focused on compliance with international standards, including quality control of educational programs, the development of practice-oriented training models, and the formation of human resources for the practical healthcare system. Such processes reflect the global trend of raising the educational level of nursing staff -from secondary technical education to bachelor's, master's, and doctoral programs, which significantly expands the professional and career opportunities of specialists [44]. At the same time, despite significant successes, several systemic problems and challenges remain relevant, affecting the quality of nurse training in the country [45].

Table 1.

Key problems in the nursing training system.

Educational programs not meeting modern clinical practice requirements	In many institutions, curricula do not reflect current advances in medical science, technological innovations, and changing patient needs, which reduces the relevance of the knowledge gained.
Insufficient involvement of nurses in teaching.	Often, the educational process is carried out by doctors who do not have specific training in nursing. The lack of teachers with clinical experience in nursing practice in educational institutions hurts the training of future specialists.
Limited opportunities for clinical practice.	Students often face a shortage of training facilities and clinical placements, which makes it difficult to develop practical skills, especially in a real medical setting.
Low social and professional status of nurses	The lack of prestige associated with the profession, limited career advancement opportunities, low salaries, and a weak incentive system are leading to a decline in interest among young people and creating the risk of a future shortage of personnel.
Limited resources for professional development.	The rapid development of medicine requires regular updating of knowledge and skills, but the current system of postgraduate education does not always provide accessible and effective opportunities for continuing professional development (CPD), especially in the regions.
Adverse working conditions.	High workload, staff shortages, inadequate material and technical resources, and emotional burnout affect both professional stability and the quality of medical care.

A comprehensive approach is needed to overcome these challenges, involving the improvement of educational programs, strengthening cooperation between educational institutions, health care providers, and professional associations, creating incentives for professional growth, developing mentoring, and improving working conditions for nurses.

Thus, the implementation of comprehensive reforms in nursing education in Kazakhstan represents a systematic and strategically significant step towards the formation of a sustainable, competent, and patient-oriented nursing service capable of responding adequately to modern healthcare challenges.

Barriers.

Globally, barriers exist for advanced practice nurses (APNs) to practise to the full extent of their education and scope of practice (SOP) because of problems with legislation, role ambiguity, autonomy, and resistance to roles [57]. Kandrack, Barnes, and Martsolf [27] mention the limited APNs practice in many states of the United States (US) because of such SOP regulations that impose restrictions on nurse practitioner practice and prescriptive authority to protect the quality of care. These authors also observe that no differences were found in the quality of care provided by APNs in those US states without these restrictions. Similar to the US, SOP regulations in South Africa by the South African Nursing Council [39] govern the authority related to prescriptive and practice authority, which explains the extent to which professional nurses can independently diagnose, treat, and prescribe to patients. In the South African LMIC context, regulations and resources are not very adaptable, especially in areas of service delivery, where physician availability is juxtaposed with the needs of the growing population [15]. In the Western Cape, South Africa, national budget constraints compelled the Provincial Department of Health (WCDoH) to improve staff productivity and efficiency to safeguard health service delivery and patient care [61].

However, as with international experience, several systemic barriers need to be removed, including the standardization of educational standards, strengthening the legal status of nurses, introducing effective quality assessment mechanisms, and promoting the model through public information campaigns.

One of the key barriers to the full implementation of advanced nursing practice in Kazakhstan is the low public awareness of nurses' functional capabilities in independent practice. Patients do not always understand the role and authority of advanced practice nurses, which leads to low attendance at such consultations and reduced confidence in their professionalism. The historically established stereotype of nurses as assistants to doctors makes it difficult to accept the new model of nursing services. However, gradually informing patients and the active work of nurses themselves to explain their competencies will help to change this situation. This is confirmed by the results of

both this study and foreign publications, which emphasize the importance of educational work among patients [46].

Another significant limitation remains the unadapted working environment, which affects the efficiency of nurses' work. In particular, problems with the integration of medical information programs have been identified, which significantly complicates record keeping and increases the workload on specialists. Another important problem is the lack of separate rooms for private consultations, which hinders confidentiality and full interaction with patients. Resolving these issues could significantly improve the quality and convenience of nurses' work. Similar organizational barriers have previously been identified in other countries undergoing the adaptation of advanced nursing practice [8].

Working conditions.

Creating an optimal working environment for nurses is an important task not only for managers and supervisors, but also for those who determine national health policy [14]. Policy-makers must make systemic changes that prioritize the well-being of nurses. Necessary changes include increasing salaries and improving working conditions, providing opportunities for professional development and recognition, expanding nurses' rights and opportunities to provide medical care, and using technology to support nurses better [59]. McHuge et al. explain that pay is important for good nursing outcomes, but working conditions and staffing are even more important [30]. There are also large differences within Europe: pay levels in some Western countries are three times higher than in Eastern countries [58]. In the Slovenian example, salary was important, but not as important as career advancement and education opportunities. Respondents felt that their career advancement was hampered [16]. Gender inequality and structural racism persist in the European healthcare sector and contribute to the shortage of nurses. The gender pay gap in the European healthcare sector is 20%. In addition, women in healthcare, especially in nursing, face other inequalities, such as difficulties in balancing childcare and work, higher health risks, and insufficient visibility of women in leadership positions [69].

Beyond education and training, it is important to pay attention to nurses' working conditions, including high workloads, a lack of necessary resources, and unfavorable working conditions. These factors can negatively affect both the physical and emotional well-being of nurses and the quality of care they provide [34].

An effective solution to these issues requires a comprehensive approach that includes improving educational programs, introducing incentives for professional growth and career advancement, improving working conditions, and recognizing the contribution of nurses to the healthcare system. Working conditions and technical support must be improved to ensure high-quality medical care [60].

Conclusion

In conclusion, our article emphasizes that a positive professional environment is crucial for ensuring healthy and safe working conditions for healthcare workers, including nurses, to provide quality healthcare and patient safety. The vast majority of European countries are striving to accept nursing as a profession and as a science. There is still a shortage of nurses with bachelor's degrees and advanced practical skills, and clinical specializations for nurses are developing at the master's level. Attention should be paid to the recognition of nurses as an equal workforce in the health care field, who should be able to improve their profession and have opportunities for professional development. Necessary changes include increasing salaries and improving working conditions, providing opportunities for advanced training and professional recognition, expanding the rights and opportunities of nurses to provide medical care, and using technology to support nurses better. The decline in interest in nursing education and the often stereotypical and condescending view of the role and work of nurses in the healthcare team should be a warning sign for everyone working on healthcare reform.

The better the working conditions for nurses, the higher the quality of their professional life. Managers and decision-makers can focus on improving working conditions for nurses, which could become a new approach for managers to improve the quality of nurses' professional lives and stabilize the nursing team.

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IMPROVED RECOGNITION OF ADULT-ONSET COMMON VARIABLE IMMUNODEFICIENCY FOLLOWING A TARGETED EDUCATIONAL WORKSHOP: A CASE SERIES FROM KAZAKHSTAN

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Abstract

Common Variable Immunodeficiency (CVID) is the most common symptomatic Inborn Errors of Immunity in adults, characterized by hypogammaglobulinemia and impaired antibody responses. Despite its prevalence, limited clinical awareness frequently results in delayed diagnosis and preventable complications. We describe a case series of three adult patients identified shortly after a targeted educational workshop for family physicians in a low-awareness setting. All patients presented with recurrent respiratory tract infections as their initial clinical first major clinical manifestation. Complications included bronchiectasis, pleural empyema, chronic bronchitis, and, in one severe case, profound weight loss, chronic obstructive pulmonary disease, and cor pulmonale. Diagnostic delays ranged from 2 to 10 years. All patients demonstrated markedly reduced IgG, IgA, and/or IgM levels, meeting ESID diagnostic criteria. Immunoglobulin replacement therapy led to clinical stabilization and decreased infection burden. This series highlights the value of clinical education in improving CVID recognition and diagnostic delay.

Keywords: *Common variable immunodeficiency, CVID, Inborn Errors of Immunity, Adult, Diagnostic delay, Complications.*

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Резюме

УЛУЧШЕНИЕ ВЫЯВЛЯЕМОСТИ ОБЩЕЙ ВАРИАБЕЛЬНОЙ ИММУННОЙ НЕДОСТАТОЧНОСТИ С ДЕБЮТОМ ВО ВЗРОСЛОМ ВОЗРАСТЕ ПОСЛЕ ЦЕЛЕВОГО ОБРАЗОВАТЕЛЬНОГО СЕМИНАРА: СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ ИЗ КАЗАХСТАНА

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Общая вариабельная иммунная недостаточность (ОВИН) является наиболее распространенной симптоматической формой врожденных ошибок иммунитета у взрослых и характеризуется гипогаммаглобулинемией и нарушением антительного ответа. Несмотря на ее распространенность, недостаточная клиническая

осведомленность нередко приводит к поздней диагностике и развитию предотвратимых осложнений. В настоящем исследовании предоставлена серия клинических случаев трех взрослых пациентов, выявленных вскоре после проведения целевого образовательного семинара для врачей общей практики в условиях низкой осведомленности. У всех пациентов первичным клиническим проявлением были рецидивирующие инфекции дыхательных путей. Осложнения включали бронхоэктазы, плевральную эмпиему, хронический бронхит и, в одном тяжелом случае, выраженную потерю массы тела, хроническую обструктивную болезнь легких и легочное сердце. Задержка в постановке диагноза составляла от 2 до 10 лет. У всех пациентов выявлены значительно сниженные уровни IgG, IgA и/или IgM, соответствующие диагностическим критериям Европейского общества по иммунодефицитам (ESID). Назначение заместительной терапии иммуноглобулинами привело к клинической стабилизации и снижению частоты инфекций. Представленная серия случаев подчеркивает значимость клинического образования для улучшения распознавания ОВИН и уменьшения диагностической задержки.

Ключевые слова: *Общий вариабельный иммунодефицит, ОВИД, врожденные нарушения иммунитета, взрослые, задержка диагностики, осложнения.*

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Түйіндеме

МАҚСАТТЫ БІЛІМ БЕРУ СЕМИНАРЫНАН КЕЙІН ЕРЕСЕК ЖАСТА БАСТАЛАТЫН ЖАЛПЫ ВАРИАБЕЛЬДІ ИММУНДЫҚ ЖЕТКІЛІКСІЗДІКТІ ДИАГНОСТИКАЛАУДЫҢ ЖАҚСАРУЫ: ҚАЗАҚСТАННАН КЛИНИКАЛЫҚ ЖАҒДАЙЛАР СЕРИЯСЫ

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Жалпы вариабельді иммундық тапшылық (ЖВИТ) - ересектерде гипогаммаглобулинемиямен және антидене реакцияларының бұзылуымен сипатталатын туа біткен иммунитет ақауларының ең көп таралған түрі. Таралуына қарамастан, клиникалық хабардарлықтың шектеулі болуы көбінесе диагноздың кешіктіріліп қоюына және алдын алуға болатын асқынуларға әкеледі. Біз отбасылық дәрігерлерге арналған мақсатты білім беру семинарынан кейін көп ұзамай үш ересек пациенттің жағдайлар сериясының анықталғанын сипаттаймыз. Барлық пациенттер негізгі клиникалық көрінісі ретінде қайталанатын тыныс алу жолдарының инфекцияларымен келгендігі анықталды. Асқынулары бронхоэктаз, плевра эмпиемасы, созылмалы бронхит және бір ауыр науқаста салмақтың күрт төмендеуі, созылмалы обструктивті өкпе ауруы және өкпелік жүрек түрінде көрінді. Диагностикалық кешігулер 2 жылдан 10 жылға дейін болды. Барлық пациенттерде IgG, IgA және/немесе IgM деңгейлерінің айтарлықтай төмендегені байқалды, бұл ESID диагностикалық критерийлеріне сәйкес келеді. Иммуноглобулинді алмастыру терапиясы клиникалық тұрақтандыруға және инфекция жүктемесінің төмендеуіне әкелді. Бұл жағдайлар ЖВИТ тануды және диагностикалық кешігуді болдырмаудағы клиникалық білім берудің маңыздылығын көрсетеді.

Түйінді сөздер: *Жалпы вариабельді иммундық тапшылық, ЖВИТ, туа біткен иммунитет ақауы, ересек, диагностикалық кешігу, асқынулары.*

Дәйексөз үшін:

Абдушукурова Г., Кадырбаева Б., Әуелова Ә., Мирзабекова Ж., Ошибаева А., Бабаева К. Мақсатты білім беру семинарынан кейін ересек жаста басталатын жалпы вариабельді иммундық жеткіліксіздікті диагностикалаудың жақсаруы: Қазақстаннан клиникалық жағдайлар сериясы // Ғылым және Денсаулық сақтау. 2025. Vol. 27(6), Б. 231-236. *Doi 10.34689/SH.2025.27.6.025*

Introduction

Common Variable Immunodeficiency Disorder (CVID) is characterized by defective antibody production, presenting clinically as recurrent sinopulmonary infections, autoimmune complications, granulomatous diseases, enteropathy, and an increased risk of malignancy. The estimated prevalence varies between 1:25,000 and 1:50,000 worldwide [1, 2]. While the onset can occur at any age, a bimodal distribution is often observed, with a significant peak in adulthood (ages 20 and 40).

The hallmark of CVID management is early diagnosis to prevent structural lung damage (e.g., bronchiectasis) and associated morbidity. However, diagnostic delay remains a global challenge. The European Society for Immunodeficiencies (ESID) Registry indicate a mean delay of 8.8 years between onset and diagnosis. In developing healthcare systems, this delay is often longer due to limited immunological testing capabilities and low awareness among general practitioners [4].

To address this gap, a grant-funded educational initiative was launched in the southern region of Kazakhstan. A targeted educational workshop was conducted for family physicians (General practitioners), focusing on the clinical warning signs of IEIs, ESID diagnostic criteria, and referral pathways. This study reports on the first three adult CVID patients diagnosed in our center, all of whom were referred by workshop attendees shortly after the training, illustrating the direct translational impact of medical education on case detection.

Case description

All patients provided informed consent for the publication of their clinical data. The diagnosis of CVID was established based on the ESID criteria: marked decrease in IgG combined with reduced IgA and/or IgM, and exclusion of secondary causes of hypogammaglobulinemia.

Patient 1. The "Chronic obstructive pulmonary disease (COPD)" mimic.

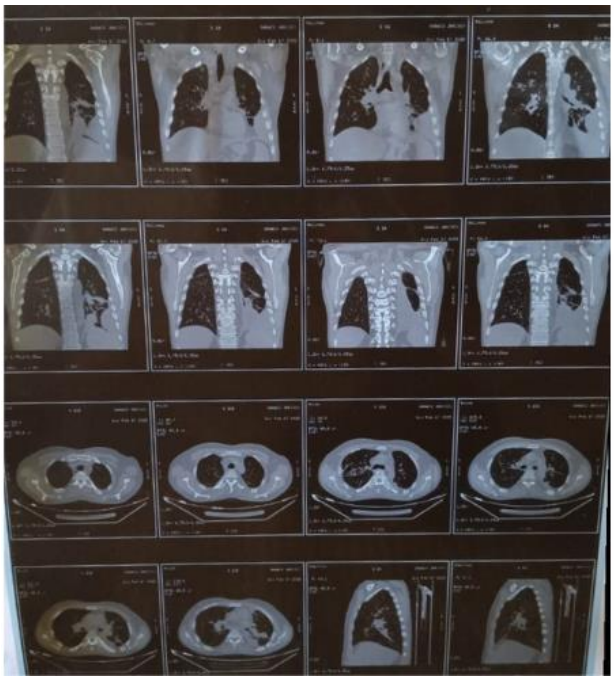
A 45-year-old male was referred in April 2025 with a history of recurrent respiratory tract infections, productive cough, and dyspnea (mMRC grade 2). His history included a documented pneumonia in May 2023, followed by 3-4 episodes in 2024 and another in January 2025. In early 2025, he was hospitalized in a pulmonary department in Almaty with diagnoses of left-sided loculated pleural effusion, pnemofibrosis, and COPD (Category B). He also had Type 2 diabetes mellitus.

Physical examination revealed a scattered wheezing. High-resolution chest Computed Tomography demonstrated bilateral post-inflammatory fibrosis, right-sided bronchiectasis, and signs of chronic bronchitis (Figure 1a, b). Immunological testing on March 3, 2025, confirmed profound hypogammaglobulinemia: IgG 0.7 g/L (reference: 7.0–16.0), IgA 0.6 g/L (reference 0.7–4.0), and IgM 1.08 g/L (reference 0.4–2.3). Secondary causes, including protein-losing enteropathy and lymphoproliferative malignancies, were excluded. The patient was commenced on immunoglobulin replacement therapy (IgRT).



a.

(a) Coronal Reconstructions: HRCT images demonstrating extensive post-inflammatory fibrosis (arrows) and architectural distortion in the lung parenchyma.



b.

(b) Axial View: HRCT image confirming the presence of cylindrical and traction bronchiectasis (starred areas) in the right lower lobe.

Figure 1. High-resolution Computed Tomography (HRCT) of the chest, Patient 1.

Patient 2. The decades-long diagnostic delay.

A 33-year-old male presented with a 4-month history of persistent cough, recent fever (39°C), and exertional dyspnea. He reported 3–4 episodes of pneumonia annual since the age of 20. Bronchiectasis had been diagnosed a decade prior (2015), yet no immunological workup was performed at that time.

Following the educational workshop, his primary care physician suspected IEI and referred him for evaluation. CT imaging revealed a "tree-in-bud" pattern, bilateral polysegmental pneumonia, and extensive bronchiectasis, particularly in the lower lobes (Figure 2). Immunological evaluation on January 2024 and 2025, revealed: IgA 0.11 g/L (reference: 0.7–4.0), IgG 0.67 g/L (7.0–16.0), and IgM 0.49 g/L (0.4–2.3). The patient had no history of systemic steroids or immunosuppressive drug use. The diagnosis of CVID was confirmed, ending a diagnostic delay of 13 years.

Patient 3. CVID enteropathy and severe sepsis.

A 21-year-old man presented in severe condition with fever, cachexia (weight loss of 7 kg over 2 months), and respiratory failure. His medical history was complex: he was diagnosed with celiac disease in 2015, and had suffered recurrent pneumonia since 2019. He had multiple prior hospitalizations for "severe COPD" and bronchiectasis.

On admissions in May 2025, he was cachetic (Weight 35 kg, Height: 1.38 m) with digital clubbing ("drumstick" fingers) and central cianosis (SpO2-70% on room air). Laboratory investigations revealed critical pan-hypogammaglobulinemia: IgA – 0.01 g/l (reference: 0.7–4.0), IgG – 0.15 g/l (reference: 7.0–16.0), IgM - 0.07 g/l (reference: 0.4–2.3), inflammatory markers were elevated (CRP - 208.4 mg/l (reference: 0-5)), and sputum culture was positive for Streptococcus pneumoniae (Table 1). Secondary protein loss via the kidneys was excluded (normal urinalysis). While the patient carried diagnosis of celiac disease, the severity of the IEI suggests this may represent CVID-associated enteropathy, a known phenotype of the disorder. He was immediately started in IVIG and broad-spectrum antibiotics.

A detailed summary comparing the demographic information, immunological profiles, diagnostic delays, and clinical complications for all three patients is provided in Tables 2 and 3.

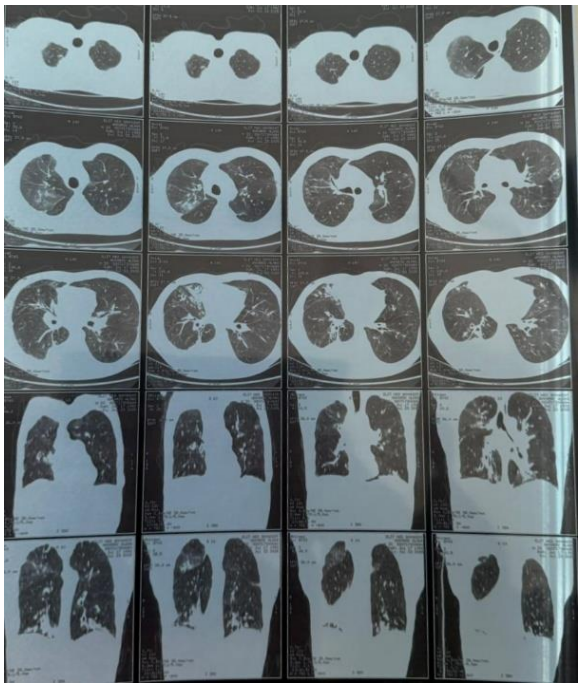


Figure 2. High-resolution Computed Tomography (HRCT) of the chest, Patient 2.

**** HRCT images demonstrating diffuse evidence of bronchiolitis, characterized by the "tree-in-bud" sign (small centrilobular nodular opacities with linear branching). Multiple lung segments exhibit established extensive cylindrical bronchiectasis, predominantly in the lower and mid-lung zones.***

Table 1.

Results of sputum culture and antimicrobial sensitivity profile (Patient 3).

Microorganism isolated	Antimicrobial agent	Sensitivity (S)/Resistance (R)
Streptococcus pneumoniae	Ceftazidime	S
	Cefepime	S
	Gentamicin	S
	Cefoperazone	S
	Ceftriaxone	S

**culture was performed on sputum sample collected upon admission on 14 May 2025. The organism showed pan-sensitivity to the tested cephalosporins.*

Table 2.

Comparative clinical and immunological characteristics of the diagnosed patients.

Characteristic	Patient 1	Patient 2	Patient 3
Demographics (Age/Sex)	45/Male	33/Male	21/Male
Age at Symptom Onset (years)	43	20	11 (Enteropathy)
Age at diagnosis (years)	45	33	21
Diagnostic delay (years)	2	13	10
Infectious manifestations	Recurrent pneumonia, pleural effusion	Recurrent pneumonia (3-4 years), "tree-in-bud" sign	Recurrent pneumonia
Structural lung damage	Pneumofibrosis, bronchiectasis	Extensive bilateral bronchiectasis	Severe bronchiectasis, cor pulmonale
Autoimmunity/Enteropathy	No	No	Celiac-like enteropathy, malabsorption
Referred following educational workshop?	Yes	Yes	Yes

Table 3.

Key laboratory parameters at diagnosis for all patients.

Test name	03/2025	01/2025	05/2025	Reference range	Unit
IgG serum	0.70	0.67	0.15	7.0-16.0	g/L
IgA serum	0.60	0.11	0.01	0.7-4.0	g/L
IgM serum	1.08	0.49	0.07	0.4-2.3	g/L
CRP	-	-	208.4	0-5	Mg/L

Discussion

The case series reports the first adult patients diagnosed with CVID in our clinical practice all identified as a direct result of a targeted educational workshop for family physicians. The study highlights two critical issues in the management of IEI: the heterogeneity of the disease and the effectiveness of educational interventions in settings with low awareness.

All three patients fulfilled the ESID diagnostic criteria for probable CVID. Key features included a marked reduction in IgG (all < 1.0 g/L in this cohort) and reduced IgA/IgM, alongside a clinical phenotype of reccurent bacterial infections [3]. In our patients, secondary causes of hypogammaglobulinemia – such as drug-induced suppression (e.g., steroids, rituximab), lymphoproliferative disorders, and severe protein-losing states – were clinically ruled out. Note: while vaccine response testing is often used to confirm impaired antibody production, the severity of hypogammaglobulinemia in these patients (IgG < 3.0 g/L) and the urgency of treatment necessitated the immediate initiation of IgRT, supporting the diagnosis based on baseline levels and clinical history alone.

The cases illustrate the progressive nature of undiagnosed CVID. Patient 2 experienced a diagnostic delay over a decade, resulting in established bronchiectasis. Patient 3 represents a severe "enteropathic" phenotype. Although previously diagnosed with celiac disease, his profound weight loss and malabsorption are likely manifestations of CVID enteropathy. Distinguishing between classical celiac disease and CVID-associated villous atrophy is challenging but vital, as CVID patients do not always respond to a gluten-free diet alone and require aggressive IgRT [5].

The most significant finding of this series is the mechanism of ascertainment. In Kazakhstan, recurrent pneumonia is typically managed by pulmonologists who may focus on structural damage (COPD, bronchiectasis) rather than underlying etiology. By training primary care providers to recognize "warning signs" – such as bronchiectasis without smoking history or recurrent infections in young adults – we successfully bridged the gap between primary care and specialized immunology services.

Conclusions

Early detection and timely initiation of immunoglobulin replacement therapy are essential to prevent irreversible organ damage in CVID. This series demonstrates that targeted education of family physicians is a highly effective, low-cost intervention to improve case detection in regions where adult IEIs are underrecognized.

Declarations

Disclaimer

This section states any applicable disclaimers.

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Author contributions

G.Z.: Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. A.A.: Conceptualization, Methodology, Visualization, Writing - original draft, Writing - review & editing. B.K.: Conceptualization, Data curation, Methodology, Writing - original draft. Z.M.: Conceptualization, Data curation, Methodology, Writing - original draft. A.O.: Conceptualization, Funding acquisition, Investigation. K.B.: Conceptualization, Data curation, Investigation.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee of Khoja Akhmet Yassawi International Kazakh-Turkish University Approval No. 121, Date: 02/09/2025.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Informed consent to publication was obtained from relevant participants.

Availability of data and materials

All data underlying the results of this case series are fully contained within the published article and accompanying tables. No additional source data are required.

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Abbreviations

CT: Computed tomography
CVID: Common Variable Immunodeficiency
ESID: European Society for Immunodeficiencies
IgRT: Immunoglobulin replacement therapy
IVIG: Intravenous immunoglobulin G
SCIG: Subcutaneous immunoglobulin G

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NEW TECHNIQUE OF ANTERIOR MITRAL LEAFLET PLICATION FOR CORRECTION OF SAM SYNDROME IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY. CLINICAL CASE

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Abstract

Background and Objective: A variety of surgical techniques have been developed to correct systolic anterior motion (SAM) of the mitral valve, typically performed in conjunction with septal myectomy for obstructive hypertrophic cardiomyopathy (oHCM). However, many of these approaches carry a substantial risk of postoperative functional complications. We present a novel technique for plication of the elongated mitral anterior leaflet designed to reduce left ventricular outflow tract (LVOT) obstruction and associated mitral regurgitation while preserving leaflet geometry and function, ultimately improving heart failure symptoms.

Materials and methods: The proposed technique is performed through an aortotomy and consists of targeted plication of the elongated A2 segment and its chordae, creating a controlled duplication that eliminates excess leaflet length without distortion. This approach restores physiologic coaptation of the mitral leaflets. A single plication loop is used for shortening up to 5 mm, whereas multiple interrupted sutures are applied for greater lengths.

Results: A 68-year-old female patient with progressive obstructive HCM, SAM syndrome, NYHA Class III functional status, and stage C heart failure (ACC/AHA) underwent anterior mitral leaflet plication using the described method combined with septal myectomy. The intervention significantly reduced the postoperative peak LVOT gradient (from 98 mmHg to 15 mmHg) and resolved mitral regurgitation (from grade III to grade 0).

Conclusion: This initial clinical experience with targeted anterior mitral leaflet plication for SAM correction in obstructive HCM suggests that the technique is both effective and safe in the short term. It substantially decreases the severity of SAM and mitral regurgitation while preserving valve function. Further research is required to define optimal patient selection and assess long-term outcomes.

Keywords: *obstructive hypertrophic cardiomyopathy; systolic anterior motion (SAM); mitral regurgitation; mitral valve plication.*

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Резюме

НОВЫЙ СПОСОБ ПЛИКАЦИИ ПЕРЕДНЕЙ СТВОРКИ МИТРАЛЬНОГО КЛАПАНА ДЛЯ КОРРЕКЦИИ SAM-СИНДРОМА ПРИ ОБСТРУКТИВНОЙ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Предпосылки и цель: Существует широкий спектр методов хирургической коррекции SAM-синдрома, выполняемых в сочетании с септальной миоэктомией при обструктивной гипертрофической кардиомиопатии. Однако данные вмешательства относятся к группе высокого риска развития послеоперационных функциональных нарушений. Мы предложили метод пликации удлиненного митрального клапана, который может уменьшить обструкцию выходного тракта левого желудочка (LVOT) и сопутствующую митральную регургитацию, тем самым

способствуя улучшению симптомов сердечной недостаточности, при этом сохранив функциональное состояние створок.

Материалы и методы: Предлагаемый метод выполняется через аортотомный доступ и предусматривает точечную пликацию удлинённого сегмента А2 и его хорд с формированием дупликатуры, что позволяет устранить избыточную длину створки без её деформации. Техника обеспечивает восстановление нормальной кооптации митральных створок и применяется с использованием одной пликационной петли при удлинении до 5 мм, так и с несколькими узловыми швами при большей протяжённости.

Результаты: Пациентке 68 лет с диагнозом гипертрофическая кардиомиопатия, обструктивный тип, прогрессирующая форма; SAM-синдром; ХСН 3ФК (NYHA), стадия С (ACC/AHA) проведена пликация передней створки митрального клапана по предложенному методу в сочетании с септальной миоэктомией. Процедура снизила послеоперационный максимальный градиент выносящего тракта левого желудочка (LVOT obstruction) (с 98 мм рт. ст. до 15 мм рт. ст.) и степень митральной регургитации (с III степень до 0).

Выводы: Первый опыт применения точечной пликации передней створки митрального клапана для коррекции SAM-синдрома при обструктивной гипертрофической кардиомиопатии показывает, что данный метод может быть эффективным для облегчения симптомов за счёт уменьшения выраженности SAM и митральной регургитации, оставаясь при этом безопасным с точки зрения краткосрочных функциональных исходов. Требуются дальнейшие исследования для уточнения целевых групп пациентов и оценки долгосрочных клинических результатов.

***Ключевые слова**: гипертрофическая кардиомиопатия, обструктивная форма, систолическое переднее движение (SAM), митральная регургитация, пликация.*

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Түйіндеме

ОБСТРУКТИВТІ ГИПЕРТРОФИЯЛЫҚ КАРДИОМИОПАТИЯДАҒЫ SAM-СИНДРОМДЫ ТҮЗЕТУГЕ АРНАЛҒАН МИТРАЛЬДЫҚ ҚАҚПАҚШАНЫҢ АЛДЫҢҒЫ ЖАПЫРЫҒЫН ПЛИКАЦИЯЛАУДЫҢ ЖАҢА ӘДІСІ. КЛИНИКАЛЫҚ ЖАҒДАЙ

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Кіріспе және мақсаты: Обструктивті гипертрофиялық кардиомиопатия кезінде септальды миоэктомиямен бірге орындалатын SAM-синдромды хирургиялық түзетудің кең ауқымды әдістері бар. Алайда бұл араласулар операциядан кейінгі функционалдық бұзылыстардың жоғары қаупімен байланысты. Біз митральдық қақпақшаның ұзарған алдыңғы жапырғысын пликациялаудың жаңа әдісін ұсынамыз, ол сол жақ қарыншаның шығу жолының (LVOT) обструкциясын және оған байланысты митральды регургитацияны азайтуға мүмкіндік береді, жүрек жеткіліксіздігі белгілерін жеңілдетеді және жапырғы функциясын сақтайды.

Материалдар мен әдістер: Ұсынылған әдіс аортотомиялық қолжетімділік арқылы жүзеге асырылады және ұзарған А2 сегменті мен оның хордаларына нүктелі пликация жүргізуді қамтиды. Дупликатура түзу арқылы жапырғының артық ұзындығын деформациясыз жоюға болады. Техника митральдық жапырғылардың қалыпты коаптациясын қалпына келтіреді және ұзындығы 5 мм-ге дейін болғанда бір пликациялық ілмекпен, ал одан ұзын болғанда бірнеше түйінді тігістермен орындалады.

Нәтижелері: 68 жастағы әйел пациентке «обструктивті түрдегі гипертрофиялық кардиомиопатия, үдемелі нысаны; SAM-синдром; ЖСЖ III ФК (NYHA), С сатысы (ACC/AHA)» диагнозымен ұсынылған әдіс бойынша митральды қақпақшаның алдыңғы жапырғысына пликация жасалды, процедура септальды миоэктомиямен біріктірілді. Операциядан кейін сол жақ қарыншаның шығу жолындағы максималды градиент 98 мм с.б.-дан 15 мм с.б.-ға дейін төмендеді, митральды регургитация III дәрежеден 0 дәрежеге дейін жойылды.

Қорытынды: Обструктивті гипертрофиялық кардиомиопатиядағы SAM-синдромды түзету үшін митральдық қақпақшаның алдыңғы жапырғысының нүктелі пликациясын қолданудың алғашқы тәжірибесі бұл әдістің SAM мен митральды регургитация айқындылығын төмендету арқылы симптомдарды жеңілдетуде тиімді әрі қысқа мерзімді функционалдық нәтижелер тұрғысынан қауіпсіз екенін көрсетеді. Пациенттердің мақсатты топтарын нақтылау және ұзақ мерзімді нәтижелерді бағалау үшін қосымша зерттеулер қажет.

Түйінді сөздер: *обструктивті гипертрофиялық кардиомиопатия, систолалық алдыңғы қозғалыс (SAM), митральды қақпақша жетіспеушілігі, пликация.*

Дәйексөз үшін:

Жакаев М.А., Төлеутаев Р.М., Сұлтанов Ғ.Б., Сергеева Е.Н. Обструктивті гипертрофиялық кардиомиопатиядағы sam-синдромды түзетуге арналған митральдық қақпақшаның алдыңғы жапырығын пликациялаудың жаңа әдісі. Клиникалық жағдай // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 237-243. *doi 10.34689/SH.2025.27.6.026*

Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder affecting approximately 1 in 500 individuals [5,10]. It is characterized by asymmetric myocardial hypertrophy, most commonly involving the basal portion of the interventricular septum, and is frequently accompanied by abnormalities of the mitral valve and subvalvular apparatus [7]. The obstructive form of HCM (oHCM) is defined by narrowing of the left ventricular outflow tract (LVOT) due to dynamic obstruction. The principal pathophysiological mechanism underlying this obstruction is systolic anterior motion (SAM) of the anterior mitral leaflet, which further narrows the LVOT and is frequently associated with mitral regurgitation (MR) [3].

In many patients with oHCM, the mitral leaflets are elongated compared to those of healthy individuals [1]. Typically, the elongated portion of the anterior leaflet extends beyond the coaptation plane, a feature central to the development of SAM [4]. These anatomical abnormalities of the mitral apparatus are increasingly recognized as a phenotypic expression of HCM and contribute to LVOT obstruction, particularly in patients whose basal septal thickness is only moderately increased [2]. During late diastole and early systole, blood flow is directed against the protruding leaflet, generating aerodynamic forces that displace it toward the septum [16]. Once contact occurs between the anterior leaflet and the interventricular septum, further systolic displacement into the outflow tract is driven by intraventricular pressure, thereby exacerbating the obstruction [17].

Transaortic septal myectomy (Morrow procedure), first introduced in 1968, remains the gold standard for surgical management of oHCM [21]. This technique – consisting of resection of the basal interventricular septum – achieves high rates of success in reducing gradients, improving symptoms, and ensuring long-term survival, with low operative mortality [14]. However, residual SAM and MR persist in a subset of patients after myectomy, underscoring the importance of mitral valve correction as an adjunctive or independent surgical intervention. Elongation of the anterior mitral leaflet is one of the major determinants of persistent SAM following septal reduction. Studies demonstrate that residual MR and SAM remain in approximately 10–15% of patients, tripling the risk of future reinterventions due to recurrent severe MR [15].

Multiple techniques for mitral valve modification have been described. Vertical plication (McIntosh–Cooley) reduces leaflet width by creating a vertical fold but often results in substantial leaflet deformation and impaired coaptation, leading to central MR [11]. Horizontal plication (Swistel), used when the anterior leaflet length exceeds 30 mm or 17 mm/m² of body surface area as part of the RPR (resection-plication-release) strategy, shortens leaflet height but also causes significant tissue trauma and may induce central regurgitation [4]. The edge-to-edge (Alfieri) repair effectively prevents SAM by approximating the A2 and P2 scallops [9], yet it is associated with progressive postoperative mitral stenosis. Retention plasty according to Hetzer provides additional fixation of leaflet edges, preventing anterior leaflet displacement [12], but requires extended exposure and is often followed by mixed dysfunction (stenosis and regurgitation).

Contemporary surgical management of oHCM increasingly emphasises individualised treatment strategies. In patients with pronounced mitral valve pathology, plication or shortening of the leaflets may be added to septal myectomy to address both the septal and valvular components contributing to SAM [19]. This approach aims to prevent persistent or recurrent obstruction after isolated septal reduction.

Given this anatomical and clinical heterogeneity, developing a plication technique for the anterior mitral leaflet that effectively eliminates SAM, improves leaflet coaptation, and avoids postoperative dysfunction is of substantial clinical importance. In this study, we introduce a new surgical method involving precise plication of the A2 segment of the anterior mitral leaflet. This localized technique targets only the elongated region, aiming to reduce SAM and improve hemodynamics without requiring extensive myectomy or complex mitral reconstructions.

Methods / Surgical Technique

Approbation of the Method

Clinical testing of the proposed mitral valve plication technique was performed in the Department of Cardiac Surgery with the Laboratory of Cardiopulmonary Bypass and the operating suite of the Research Institute of Cardiology and Internal Diseases (Almaty) from April 2023 to December 2024.

Technique of Anterior Mitral Leaflet Plication

The procedure is performed under standard conditions. A median sternotomy is followed by normothermic cardiopulmonary bypass using a single, dual-stage venous cannula placed through the right atrium. The left atrium is vented via the right superior pulmonary vein. Cardiac arrest is achieved with cold blood cardioplegia administered antegrade following transverse transection of the ascending aorta. Subsequent doses of cardioplegia are delivered selectively after aortotomy.

The aorta is opened obliquely in a transverse direction toward the base of the non-coronary sinus. Through the aortotomy, with gentle displacement of the aortic valve leaflets, the elongated portion of the anterior mitral leaflet and its elongated chordae – corresponding to the A2 scallop – is visualized (Fig. 1).

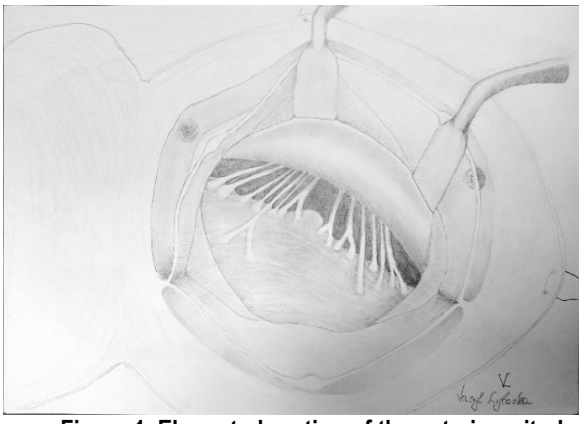


Figure 1. Elongated portion of the anterior mitral leaflet (A2 scallop) with lengthened chordae.

To correct the elongated segment of A2 that protrudes beyond the coaptation plane during systole, together with its elongated chordae, a targeted plication technique is applied. Using a 5-0 monofilament suture, the free edge of A2 is first pierced from the ventricular side toward the coaptation side at a point adjacent to the elongated chorda insertion. The second needle is similarly passed through the elongated chorda region on the opposite side. Both suture ends are then returned from the coaptation side toward the ventricular side, traversing the free edge of the leaflet over a narrower span. Subsequently, both sutures are passed superiorly through the body of the leaflet near the attachment of secondary chordae (Fig. 2).

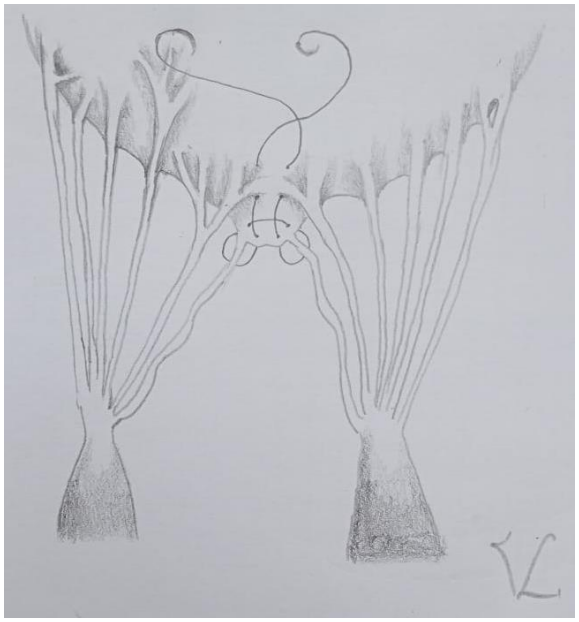


Figure 2. Formation of a plication loop on the elongated portion of the A2 scallop of the anterior mitral leaflet.

The suture loop is then tightened until the free edge approximates the leaflet body, creating a duplication fold (Fig. 3).

This single-loop plication technique is applied when the elongated segment measures up to 5 mm. For segments exceeding 5 mm (Fig. 4), separate interrupted sutures are placed according to the same principle.

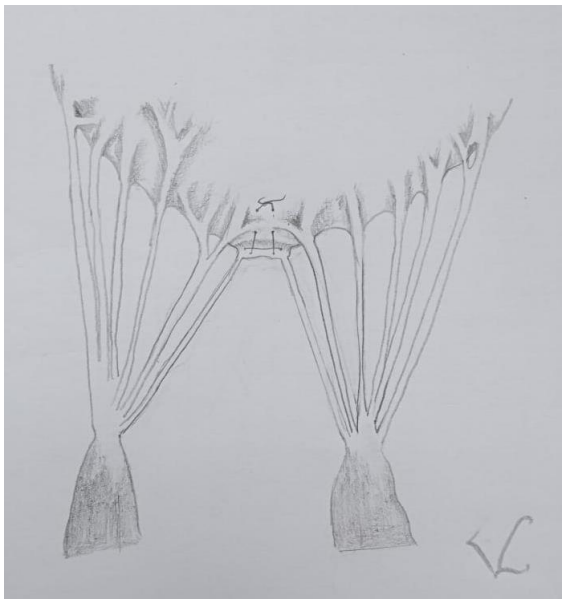


Figure 3. Plication of the elongated portion of the A2 scallop of the anterior mitral leaflet with tensioning of the elongated chordae.

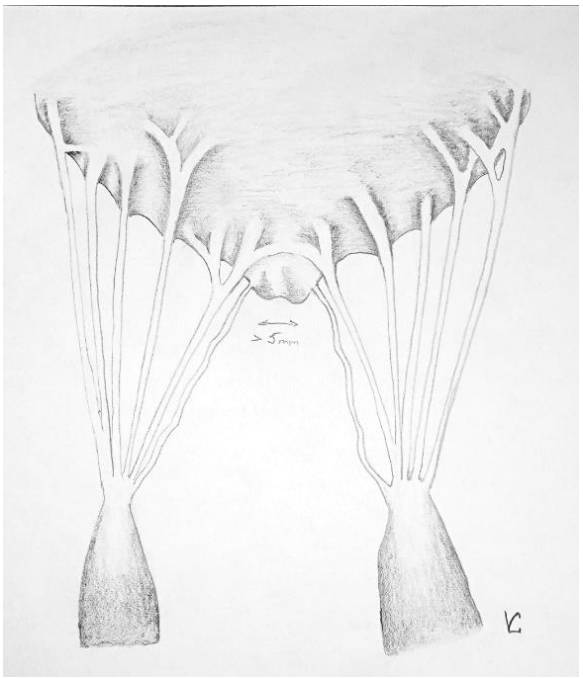


Figure 4. The elongated portion of the A2 scallop of the anterior mitral leaflet measuring greater than 5 mm in width.

Clinical Case

Patient S., a 68-year-old woman, was admitted to the Cardiac Surgery Department of the Research Institute of Cardiology and Internal Diseases with the following diagnosis: obstructive hypertrophic cardiomyopathy, progressive form; SAM syndrome; chronic heart failure, NYHA Class III, Stage C (ACC/AHA).

Preoperative echocardiography demonstrated severe left ventricular outflow tract (LVOT) obstruction with a peak gradient of 98 mmHg and grade III mitral regurgitation (Fig. 5c). A key pathophysiological feature in this patient was marked anterior displacement and elongation of the anterior mitral leaflet, leading to systolic anterior motion (Fig. 5a).

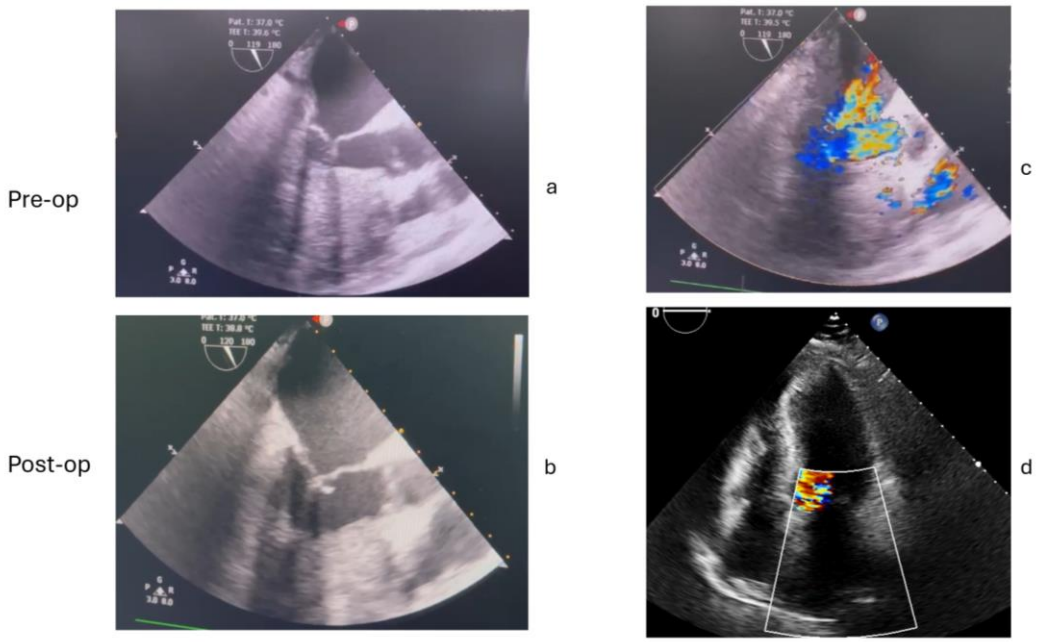


Figure 5. Echocardiographic images in obstructive hypertrophic cardiomyopathy before and after surgical correction: (a, b) systolic anterior motion (SAM); (c, d) mitral regurgitation (MR).

Given these anatomical characteristics, plication of the anterior mitral leaflet became a critical component of the operation. This intervention eliminated excessive leaflet mobility, restored proper coaptation, and significantly reduced the LVOT gradient when combined with septal myectomy. The patient was included in the cohort undergoing surgical correction of SAM syndrome using the proposed anterior mitral leaflet plication technique.

Ethics approval and consent to participate

The report was conducted in accordance with institutional ethical standards. Approval for publication of this case was obtained from the Bioethical Commission of Kazakh National Medical University named after S.D. Asfendiyarov (Protocol #1071, dated March 31, 2021), and written informed consent was provided by the patient.

Results

Clinical Case Description and Surgical Technique

The operation was performed via median sternotomy under normothermic cardiopulmonary bypass, using a single dual-stage venous cannula inserted through the right atrium. The left atrium was vented via the right superior pulmonary vein. Cardioplegic arrest was induced using cold blood cardioplegia administered antegradely after transverse transection of the ascending aorta. Subsequent doses of cardioplegia were delivered selectively following aortic dissection.

The ascending aorta was opened obliquely in a transverse direction toward the base of the non-coronary sinus. Revision and evaluation of the AML and its chordae were performed through the aortic root. At this stage, septal myectomy was carried out to reduce left ventricular outflow tract obstruction.

After confirming the presence of an elongated portion of the A2 segment of the AML with elongated chordae, targeted plication was performed. Using a 5-0 monofilament suture, the free edge of the A2 segment was first pierced from the ventricular side toward the coaptation plane at a point adjacent to the attachment of the elongated chord. The second needle was then passed in a similar manner through the elongated chord on the opposite side. Both suture ends were returned from the coaptation side toward the ventricular side, piercing the free edge over a narrower span. Subsequently, both sutures were passed superiorly through the leaflet body near the secondary chordal attachment. The plication loop was then tightened until the free edge approximated the leaflet body, creating a duplication of the elongated segment. The operation was completed in the standard manner.

Postoperative Outcomes

In the early postoperative period, echocardiography demonstrated complete resolution of SAM syndrome (Fig. 5b) and a significant reduction of mitral regurgitation to grade 0 (Fig. 5d). The LVOT gradient decreased from the preoperative value of 98 mmHg to 15 mmHg, reflecting effective relief of the obstruction. Echocardiographic assessment indicated restoration of mitral leaflet coaptation and stabilization of left ventricular function in the early postoperative phase.

Discussion

In our study, we describe a novel method for eliminating systolic anterior motion (SAM) in a patient with obstructive hypertrophic cardiomyopathy, aiming not only to abolish SAM but also to preserve maximal valvular and ventricular function in the postoperative period. The mechanism of action of the proposed A2 segment plication of the anterior mitral leaflet is based on targeted reduction of the protruding free-edge portion and stabilization of the coaptation line. The creation of a duplicate fold limits excessive anterior displacement of the anterior mitral leaflet into the left ventricular outflow tract, thereby reducing SAM and concomitant mitral regurgitation. The principal advantage of this technique is the establishment of a more stable coaptation line with minimal chordal tension while maintaining leaflet mobility, which minimizes the risk of

postoperative mitral stenosis. The procedure is simple, reproducible, and does not require complex reconstructions or implantation of additional material, facilitating standardization and broader clinical application.

Surgical correction of SAM, performed adjunctively with septal myectomy, remains a subject of ongoing debate. Despite advances in surgical techniques, the optimal approach to mitral valve correction continues to be discussed. For instance, recent data from Carvalho et al. indicate that anterior leaflet length does not always correlate directly with residual LVOT gradients or survival following isolated myectomy [8]. Conversely, other studies demonstrate that plication or "shortening" of the leaflets yields durable results, including long-term reduction of LVOT gradients, decreased MR, and favorable survival [19].

A retrospective analysis of 57 patients with oHCM who underwent combined sectoral myectomy and anterior leaflet retention plasty (ALRP) demonstrated significant reductions in LVOT gradient and septal thickness, while minimal MR was preserved in 87% of patients, and SAM was completely eliminated [22]. The main limitations of this study included its retrospective design, absence of a control group, requirement for left atrial access, and potential technical challenges in cases with complex subvalvular anomalies. These results support the efficacy of ALRP as an adjunct to myectomy; however, further studies are required to assess long-term safety and generalizability.

Interventions targeting the anterior mitral leaflet in SAM, including Resect-Plicate-Release (RPR) and AML shortening, have been shown to reduce valve length, decrease the protruding portion, eliminate LVOT gradients and SAM, reduce MR, and improve NYHA functional class [4,19]. Overall advantages of these approaches include verified echocardiographic efficacy, clinical improvement, and high procedural safety. Limitations include short- to medium-term follow-up, technical variability, retrospective study designs, and procedure-specific risks such as leaflet injury, thrombosis, or recurrent regurgitation. These findings support the development of point-specific plication techniques for the A2 AML to optimize SAM correction.

In a recent study, combining myectomy with targeted mitral valve correction (including anterior leaflet folding and interventions on the subvalvular apparatus) significantly reduced the incidence of residual SAM and MR compared to isolated myectomy: 5% vs 28% for SAM and 0% vs 15% for MR in a randomized comparison [6]. The main limitations of this study were its retrospective design and small, single-center sample size.

In a larger cohort treated with the "three-step" RPR method – comprising extended myectomy, horizontal AML plication, and correction of abnormal papillary muscle attachments - it was demonstrated that adjunctive AML plication markedly reduces residual SAM and MR while maintaining low operative mortality and favorable clinical outcomes [20].

Research on surgical correction of the anterior mitral leaflet as a primary treatment for patients with oHCM remains limited to case series and small observational studies. In the study by *Sorajja P. et al.,* non-surgical percutaneous (catheter-based) plication of the mitral valve was performed in five patients who were initially candidates for myectomy, aiming to reduce SAM and mitral regurgitation [18]. Overall, most studies have focused on the role of plication as an adjunct to septal myectomy [13,19,20].

Strengths and Limitations

The main strength of this study is the demonstration of the safety and efficacy of A2 segment plication of the anterior mitral leaflet in a specific clinical case. Careful intraoperative assessment of the mitral valve and chordae allowed precise identification of areas requiring correction and the establishment of a stable coaptation line postoperatively.

However, several limitations must be acknowledged. The findings are based on a single clinical observation, which limits the generalizability of the results to a broader patient population. Prospective studies with larger patient cohorts and long-term follow-up are necessary to confirm the reproducibility of the technique and the durability of its outcomes. Additionally, individual anatomical variations of the mitral valve may limit the effectiveness of plication, particularly in cases with markedly elongated AML or atypical chordal configurations. Despite these limitations, the described technique demonstrates potential as a targeted and safe strategy for correcting SAM in oHCM.

The proposed A2 segment plication is particularly indicated in patients with mitral-dependent LVOT obstruction, prolonged AML, and pronounced SAM. Limitations include the width of the elongated segment (>5 mm), potential variability in surgical technique among operators, and the lack of long-term outcome data. Further prospective studies with larger cohorts and extended follow-up are required to validate the safety and effectiveness of this method. Nevertheless, A2 segment plication shows substantial potential as a stand-alone or adjunctive procedure to correct SAM and reduce the risk of recurrent mitral regurgitation in patients with advanced AML elongation.

Conclusion

The proposed technique of mitral valve A2 segment plication effectively eliminates SAM syndrome, restores coaptation of the mitral valve leaflets, and preserves valvular function, thereby optimizing the clinical outcomes of surgical treatment in patients with obstructive hypertrophic cardiomyopathy.

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COMBINATION OF ATYPICAL HEMOLYTIC UREMIC SYNDROME AND IGA NEPHROPATHY : A CASE REPORT AND LITERATURE REVIEW

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Abstract

Atypical hemolytic uremic syndrome (aHUS), which is characterized by thrombotic microangiopathy, is distinct from Shiga-toxin-induced HUS and thrombotic thrombocytopenic purpura. aHUS is associated with dysregulation of the alternative complement system. Eculizumab, an anti-C5 antibody, is effective in limiting complement activation in patients with aHUS. In recent years, a link has been identified between aHUS and some other complement-mediated nephropathies, in particular C3 glomerulopathy and immune-complex–mediated membranoproliferative glomerulonephritis. A common genetic component may be a unifying factor in these situations. At the same time, the possible combination of aHUS with IgA nephropathy (IgAN) remains poorly understood. We herein report the case of a 10-year-old girl, who was admitted to our hospital with symptoms of jaundice, anemia, thrombocytopenia, and acute kidney injury. Clinical and laboratory assessments led to a diagnosis of atypical hemolytic uremic syndrome (aHUS). The patient was initially treated withplasma exchange and hemodialysis. Eculizumab treatment was initiated on hospital day 6.Remission of her thrombotic microangiopathy was achieved, however during her follow-up, the patient experienced several episodes of acute respiratory infections with macrohematuria. Kidney biopsy was performed and her histological findings were consistent with immunoglobulin A nephropathy (IgAN). The patient showed improvement following treatment with eculizumab and ramipril. This case prompts a discussion on the potential relationship between aHUS and IgAN.

Key words: *Hemolytic uremic syndrome, immunoglobulin A nephropathy, acute kidney injury, glomerulonephritis, childhood.*

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Резюме

СОЧЕТАНИЕ АТИПИЧНОГО ГЕМОЛИТИКО-УРЕМИЧЕСКОГО СИНДРОМА И IGA-НЕФРОПАТИИ. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И ОБЗОРЛИТЕРАТУРЫ.

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Атипичный гемолитико-уремический синдром (аГУС) обусловлен нарушением регуляции системы комплемента, приводящей к повышенной её активации по альтернативному пути. Этот механизм отличает аГУС от других вариантов тромботической микроангиопатии (ТМА), прежде всего таких, как гемолитико-уремический синдром, обусловленный шига-токсином (STEC-ГУС) и тромботической тромбоцитопенической пурпуры (ТТП). Экулизумаб, моноклональное антитело к С5, эффективно блокирует активацию комплемента у пациентов с аГУС. В последние годы была выявлена связь между аГУС и некоторыми другими нефропатиями, развитие которых опосредованно активацией системы комплемента, вчастности С3-гломерулопатией и иммунокомплексным мембранопролиферативным гломерулонефритом. Общий

генетический механизм может быть объединяющим фактором в этих ситуациях. В то же время возможное сочетание аГУС с IgA-нефропатией (IgAN) остаётся плохо изученным. В настоящем сообщении мы приводим наблюдение за 10-летней девочкой, которая поступила в нашу больницу с симптомами желтухи, анемии, тромбоцитопении и острого повреждения почек. Клинические и лабораторные исследования привели к диагностике аГУС. Первоначально пациентка получала лечение инфузиями свежезамороженной плазмы, плазмаобменом и гемодиализом. Лечение экулизумабом было начато на 6-й день госпитализации. Была быстро достигнута ремиссия ТМА, однако во время последующего наблюдения у пациентки сохранялись изменения в анализах мочи и отмечалось несколько эпизодов острых респираторных инфекций, сопровождавшихся кратковременными эпизодами макрогематурии. Была проведена биопсия почки. Гистологическое исследование выявило IgAN. С нефропротективной целью был добавлен пероральный рамиприл, что привело к стойкому улучшению анализов мочи. Мы приводим литературные данные, обсуждающие подобные клинические случаи и возможную связь между аГУС и IgAN.

Ключевые слова: *гемолитико-уремический синдром, иммуноглобулин А нефропатия, острое почечное повреждение, гломерулонефрит, детство.*

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Түйіндеме

АТИПИЯЛЫҚ ГЕМОЛИТИКО-УРЕМИЯЛЫҚ СИНДРОМ МЕН IGA НЕФРОПАТИЯСЫНЫҢ ҮЙЛЕСІМІ. КЛИНИКАЛЫҚ БАҚЫЛАУ ЖӘНЕ ӘДЕБИЕТКЕ ШОЛУ

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Атипиялық гемолитикалық-уремиялық синдром (аГУС) комплемент жүйесінің реттелуінің бұзылуымен байланысты, бұл оның альтернативті жол арқылы шамадан тыс белсендірілуіне әкеледі. Бұл механизм аГУС-ті тромботикалық микроангиопатияның (ТМА) басқа түрлерінен, ең алдымен шигатоксинмен байланысты гемолитикалық-уремиялық синдромнан (STEC-ГУС) және тромботикалық тромбоцитопениялық пурпурадан (ТТП) ерекшелендіреді. Экулизумаб - С5-ке қарсы моноклоналды антидене - аГУС-пен ауыратын науқастарда комплемент белсендірілуін тиімді түрде тежейді. Соңғы жылдары аГУС пен кейбір басқа нефропатиялар арасындағы байланыс анықталды, олардың дамуы комплемент жүйесінің белсендірілуімен байланысты, атап айтқанда, С3-гломерулопатия және иммундық кешенмен байланысты мембранопролиферативті гломерулонефрит. Бұл жағдайларда ортақ генетикалық механизм біріктіруші фактор болуы мүмкін. Сонымен қатар, аГУС пен IgA-нефропатиясының (IgAN) қатар жүруі әлі толық зерттелмеген. Осы мақалада біз сарғаю, анемия, тромбоцитопения және жедел бүйрек зақымдануы белгілерімен ауруханаға түскен 10 жастағы қыздың жағдайын сипаттаймыз. Клиникалық және зертханалық зерттеулер аГУС диагнозын растады. Бастапқыда науқас жаңа мұздатылған плазма инфузиясы, плазма алмасу және гемодиализ арқылы ем қабылдады. Экулизумабпен емдеу ауруханаға жатқызылғаннан кейін 6-шы күні басталды. ТМА ремиссиясына тез қол жеткізілді, алайда кейінгі бақылау кезеңінде науқастың зәр талдауларында өзгерістер сақталып, жедел респираторлық инфекция эпизодтарымен қатар жүретін қысқа мерзімді макрогематурия байқалды. Бүйрек биопсиясы жасалды. Гистологиялық зерттеу IgAN диагнозын көрсетті. Бүйрек қорғаушы мақсатта ішке қабылдайтын рамиприл қосылды, бұл зәр талдауларының тұрақты жақсаруына алып келді. Біз осындай клиникалық жағдайларды сипаттайтын әдеби деректерді ұсынып, аГУС пен IgAN арасындағы мүмкін байланыс мәселесін талқылаймыз.

Түйінді сөздер: *гемолитикалық-уремиялық синдром, иммуноглобулин А нефропатиясы, жедел бүйрек зақымдануы, гломерулонефрит, балалық шақ.*

Дәйексөзүшін:

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Hemolytic uremic syndrome (HUS) represents a group of disorders with diverse etiologies and pathogenic mechanisms. These conditions are grouped under the general term "thrombotic microangiopathy" (TMA), due to the formation of blood clots within the microcirculation. TMA is characterized not only by organ damage, but also by thrombocytopenia caused by platelet consumption and microangiopathic hemolytic anemia. The latter is characterized by the presence of more than 1% schistocytes (red blood cell fragments) in the blood, which can be easily detected by peripheral blood smear analysis. Other laboratory markers of intravascular hemolysis, such as increased lactate dehydrogenase (LDH) levels and decreased plasma haptoglobin, can also be detected [1].

Despite the similarity of clinical and morphological features, primary TMA can be divided into two main categories: thrombotic thrombocytopenic purpura (TTP) and HUS [2]. In the pathogenesis of TTP, a key role is played by a severe deficiency of the ADAMTS13 enzyme, which is responsible for cleaving large multimers of von Willebrand factor into smaller fragments with low thrombogenic capacity. ADAMTS13 deficiency may result from either genetic mutations or the presence of autoantibodies that inhibit its activity. This leads to the formation of uncleaved multimers of von Willebrand factor and the development of microthrombosis. The disease has a systemic nature and can affect various organs; however, ischemic involvement of the central nervous system often predominates in the clinical presentation, while acute kidney injury requiring dialysis is less common [3].

In contrast, HUS is a form of TMA in which the kidneys are the primary target organ. Therefore, severe acute kidney injury (“acute uremia”) becomes one of the main clinical features of this syndrome [2,4]. Historically, HUS has been classified into two forms: with (D+) and without (D-) diarrhea. D+ HUS was previously considered synonymous with HUS caused by Shiga toxin-producing E. coli (STEC). However, the current classification distinguishes between “typical HUS” (STEC-HUS), referring to the Shiga toxin-induced form, and “atypical HUS” (aHUS) for all other cases [4,5]. Atypical HUS is a rare condition characterized by uncontrolled activation of the alternative complement pathway. The pathogenesis of aHUS involves mutations in genes regulating complement activity (such as factor H, factor I, MCP, C3, factor B, and thrombomodulin) or the presence of autoantibodies against these proteins [2]. Potential triggers for disease onset include infections, pregnancy, childbirth, and surgical procedures.

Ideally, aHUS diagnosis should include genetic testing; however, about 40% of patients with clinical manifestations of aHUS have no detectable genetic mutations. This may be due to limitations of current diagnostic methods, as well as the fact that the full spectrum of genes involved in complement regulation is not yet completely understood. Therefore, a negative genetic test result does not exclude the possibility of aHUS diagnosis. Moreover, given the time-consuming nature of genetic testing and the need for prompt therapeutic decisions in active TMA, the diagnosis of aHUS should be based on clinical and laboratory findings after exclusion of other potential causes of TMA in a particular patient [4]. Children with TMA, TTP and STEC-HUS should be excluded first. For this purpose, it is especially important to determine ADAMTS13 activity: levels below 10% of the norm are indicative of TTP, whereas higher activity essentially rules out this diagnosis [6]. The presence of diarrhea during the prodromal phase, along with a positive Shiga toxin test or isolation of Shiga toxin-producing E. coli from feces, confirms the diagnosis of STEC-HUS [5,7].

In addition, it is important to exclude secondary forms of thrombotic microangiopathy (TMA), which may be associated with antiphospholipid syndrome, systemic lupus packed red blood cells, disseminated intravascular coagulation (DIC), and other conditions [8]. In recent years, an association has been established between atypical hemolytic-uremic syndrome (aHUS) and several other complement-mediated nephropathies, such as C3-glomerulopathy and immunocomplex membranoproliferative glomerulonephritis. A shared underlying factor in these cases may be a genetic predisposition [9,10]. At the same time, the coexistence of aHUS with IgA nephropathy (IgAN) remains insufficiently studied [11].

IgAN is the most common primary glomerular disease, particularly prevalent in countries of the Asia-Pacific region. It is characterized by dominant or co-dominant mesangial deposition of immune complexes containing IgA. Large cohort studies have identified distinctive light-optical histological changes, including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), interstitial fibrosis and tubular atrophy (T), and semilunar lesions (C). These findings formed the basis for the Oxford morphologic classification of IgAN [12,13].

In this paper, we present a rare case of the co-occurrence of aHUS and IgAN in a 10-year-old girl.

Clinical Observation. A 10-year-old girl was admitted in June 2024 to the regional children's hospital due to the acute vomiting, profound weakness, marked jaundice of the skin and sclera, and decreased diuresis. No diarrhea was observed. In addition to jaundice, examination revealed isolated petechiae on the trunk and arterial hypertension (BP 145/85 mm Hg). The heart rate was 94 beats per minute, respiratory rate 20 breaths per minute, and body temperature 36.5 ° C. Upon admission to the emergency department, a general blood test revealed anemia with Hb 76 g / L and thrombocytopenia 49 x 109 / L. A peripheral blood smear showed schistocytes of 3-4% (Figure 1) and reticulocytosis of 5%. Urinalysis (UA) revealed a high number of erythrocytes and proteinuria of 2.6 g/L. Biochemical analysis of blood confirmed high bilirubin levels (total bilirubin at 180 μmol/L, indirect fraction at 172 μmol/L) and acute kidney injury, with urea at 22 mmol/L and creatinine at 265 μmol/L. Ultrasound demonstrated bilateral diffuse increased echogenicity of the renal parenchyma. Liver ultrasound showed no signs of biliary obstruction, fibrosis, or any other damage. The patient was admitted to the intensive care unit. From the medical history, it was established that there was no hereditary history of kidney disease. The child had no previous health abnormalities, except for a single episode of macrohematuria that developed three years ago, due to which the patient was hospitalized in the pediatric urology unit with suspected urolithiasis.

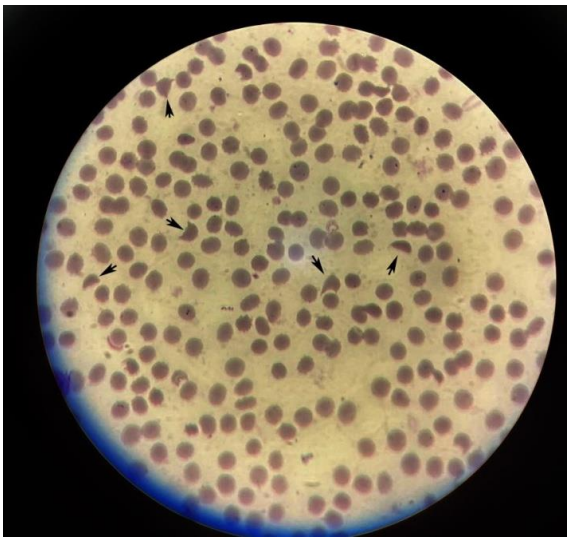


Figure 1. Schistocytes (indicated by arrows) in the patient's peripheral blood smear.

Hematuria spontaneously resolved after a few days and, although ultrasound of the urinary system did not reveal a calculus, this episode was assessed as a probable passage of a stone. Recommendations were given to increase the amount of fluid intake. Monitoring of urine tests was not performed subsequently. The hematuria resolved spontaneously within a few days and, although renal ultrasound did not reveal a calculus, this episode was interpreted as a probable passage of a stone. The patient was advised to increase fluid intake. No follow-up urinalysis monitoring was conducted thereafter. The examination in the intensive care unit revealed a high level of LDH at 2160 U / L (< 430). Other biochemical parameters remained within the reference levels: ALT - 18.3 IU/L (0.0 - 39.0), AST - 46.4 IU/L (0.0 - 47.0), CPK - 75.6 U/L (<247), complement factor 3 (C3) - 115 mg/dL (90-180), complement factor 4 (C4) - 34 mg/dL (10-40). There were no deviations in the coagulogram: APTT 28 seconds (24-35), prothrombin index 91% (70-120), fibrinogen 2.57 g/L (1.8-4.0), D-dimer 0.31 μg/ml (0-0.55). Testing for hepatitis A, B, C, CMV, and EBV returned negative results. Autoimmune screening, including antinuclear antibodies, antibodies to double-stranded DNA, ANCA, and antiphospholipid antibodies, did not reveal any values exceeding the reference ranges. Both direct and indirect Coombs tests were negative. ADAMTS13 activity was measured at 71% (93-113). The child was tested for antibody titers against factor H, which found to be within normal limits.

TMA was diagnosed. Over the following days, the patient received infusions of fresh frozen plasma and packed red blood cells. One plasma exchange session was performed with replacement of 60 ml/kg of the patient's plasma and, due to the developed hyperhydration, one hemodialysis session was required. Oral amlodipine was prescribed at a dose of 5 mg per day due to arterial hypertension. Given the absence of diarrheal prodrome, STEC- HUS was ruled out. ADAMTS13 activity level above 10% (blood for the study was taken before the start of plasma therapy) allowed to exclude TTP. Together with negative findings for antiphospholipid syndrome, DIC syndrome, immune hemolytic anemia, and systemic autoimmune diseases, these results allowed to reject other possible causes of TMA and diagnose aHUS, in connection with which complement-inhibiting therapy with eculizumab was initiated on the sixth day of the disease.

Eculizumab was given 600 mg weekly for two doses, then 900 mg every two weeks (maintenance) (patient weight 33 kg). Two days after the first dose, the patient demonstrated a marked increase in diuresis, from 200 ml to 1300 ml per day. This was followed by a rapid normalization of peripheral blood platelet counts, a more gradual decline in serum bilirubin, and eventual resolution of anemia and schistocytosis, with LDH levels decreasing to 280 U / L. Blood pressure normalized, allowing for the discontinuation of amlodipine therapy, and serum urea and creatinine returned to refence levels. However, despite the clear positive dynamics in general urine tests, hematuria (erythrocytes from 30-40 in sight to a large number) and proteinuria (albumin-to-creatinine ratio of 1.0-1.2 mg / mg in spot urine samples) persisted.

To investigate further, targeted next-generation sequencing was performed at the Medical Genetic Center of the National Medical Research Center of Children's Health in Moscow, focusing on genes associated with aHUS (CFH, CFI, MCP, C3, CFB, THBD). Pathogenic genetic variants were not identified. In September and October 2024, the patient experienced two episodes of macrohematuria during acute respiratory viral infection, which could not be explained by aHUS relapse, given the ongoing eculizumab therapy and the absence of laboratory signs of TMA activity. In this regard, in October 2024, 3.5 months after the TMA onset, a puncture biopsy of the lower pole of the left kidney was performed.

Light microscopy was conducted on paraffin sections stained with hematoxylin-eosin, PAS reaction, Masson's trichrome, and Jones methenamine silver stain. The nephrobiopsy material included both cortical and medullary tissue, with a total of 40 glomeruli. The glomeruli were mildly enlarged, with single-contour capillary wall and diffuse expansion of the mesangial space due to the extracellular matrix and its hypercellularity, but without signs of both endocapillary hypercellularity (E0) and formation of crescents (C0) (Figure 2).

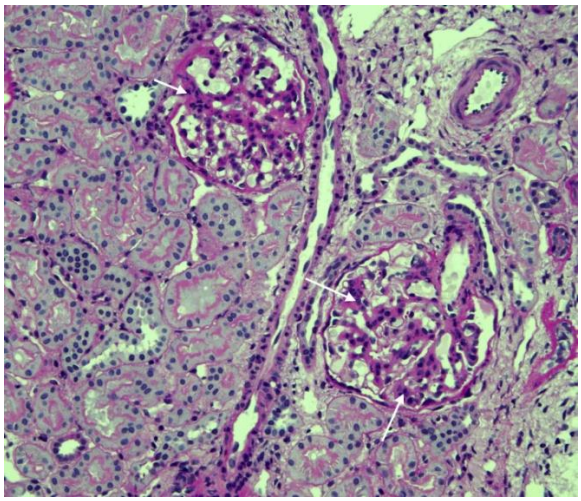


Figure 2. Histological examination of renal tissue. Mesangial proliferation and expansion of the mesangial matrix (indicated by arrows). PAS stain, magnification ×200.

The GBM was not visually thickened, had a single contour, and showed uniform silver impregnation. Segmental glomerulosclerosis (S1) was noted in 6 glomeruli (15%), without reaction of glomerular epithelium. Cytoplasm of tubular epithelium was granular, with preserved brush border, and tubular lumens were patent. There were no signs of tubular atrophy and interstitial fibrosis (T0). Arterioles and small-caliber arteries exhibited no pathological changes.

Immunofluorescence analysis was performed on cryostat sections using FITC-conjugated antibodies against human IgA, IgG, IgM, C3, C1q, fibrinogen, and kappa and lambda light chains. The staining revealed diffuse mesangial granular deposition of IgA graded as 3+ (Figure 3), along with C3 (1+), kappa (2+), and lambda (2–3+).

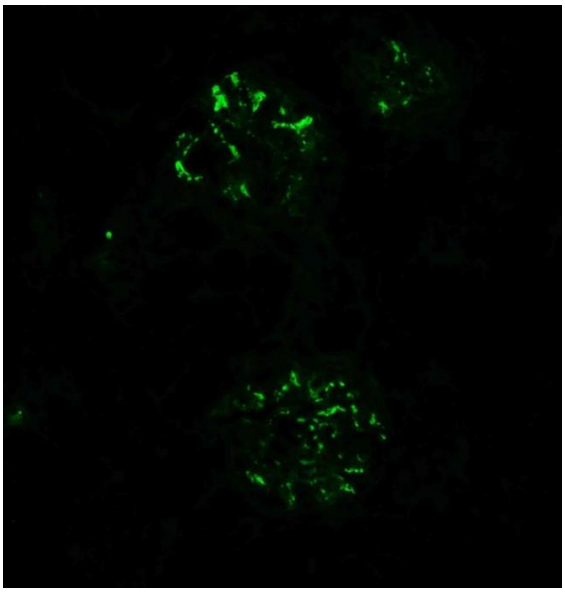


Figure 3. Immunofluorescence analysis of kidney biopsy, magnification ×100. Diffuse mesangial granular expression of IgA (+++).

Electron microscopy was performed on semithin sections stained with toluidine blue and ultrathin sections stained with uranyl acetate and lead citrate, with double contrast with osmium. Seven glomeruli were examined on semithin sections. All of them showed focal, mild mesangial hypercellularity; with no evidence of endocapillary hypercellularity or crescent formation. One glomerulus exhibited secondary segmental glomerulosclerosis. The GBM was of uniform thickness (240-260 nm), with preserved lamina densa, lamina rara interna and lamina rara externa, without signs of disorganization and with a smooth external contour. Podocyte foot processes were preserved and discretely arranged throughout, and the slit diagram between them was clearly visualized. Electron-dense deposits were determined in the mesangial matrix, mainly in the paramesangial area (Figure 4). No electron-dense deposits were found in the subendothelial or subepithelial spaces. No pathological inclusions were observed in the cytoplasm of epithelial, endothelial, or mesangial cells. A weakly expressed subendothelial edema was noted. CONCLUSION: IgA nephropathy, Oxford-2016 classification: M1E0S1T0C0. Mild subendothelial edema of glomerular capillaries is not a highly specific sign; however, in the context of a confirmed diagnosis of atypical HUS, it may be consistent with the disease.

After receiving the results of the histological examination, ramipril was added to eculizumab therapy at a dose of 2.5 mg per day for nephroprotective and antiproteinuric purposes, the dose of which was gradually increased to the maximum tolerated, reaching 5 mg per day. By November 2024, the patient's urine tests had normalized and remained within normal limits at the time of preparing this publication. In the absence of any signs of TMA activity, a decision was made to discontinue eculizumab therapy and continue nephroprotective treatment with ramipril.

Discussion. We present a case of a rare combination of IgAN and aHUS in a 10-year-old girl. Initially, we attributed all of the patient's symptoms solely to TMA; however, despite the prompt initiation of eculizumab therapy and complete resolution of hematologic abnormalities, hematuria and proteinuria persisted. This, combined with a prior unexplained episode of macroscopic hematuria three years earlier, led us to suspect glomerulonephritis and perform a nephrobiopsy. Histological examination revealed dominant, diffuse mesangial IgA (+++) deposition. Additionally, secondary segmental glomerulosclerosis was observed in 15% of glomeruli—characteristic of chronic IgAN. These findings suggest that the onset of glomerulonephritis likely preceded the development of aHUS, potentially dating back to the earlier episode of macroscopic hematuria noted in the patient's history.

Several publications report that TMA may be a histological finding in IgAN [14,15]. In such cases, TMA may either represent a direct complication of the glomerulonephritis—mediated by its underlying mechanisms—or an independent coexisting pathology such as TTP, aHUS, or STEC-HUS. The development of TMA as a complication of IgAN may require multiple contributing factors, with complement activation within the glomeruli—triggered by IgA deposition—being a key element. In these situations, TMA may manifest solely at the histological level without overt clinical signs [14,15]. In contrast, the pronounced clinical manifestations of TMA observed in our patient strongly suggest the presence of a second, distinct disease [14]. We believe that the rapid resolution of TMA symptoms following the initiation of eculizumab, and the absence of histological signs of TMA 3.5 months after disease onset under ongoing complement-inhibiting therapy, support the diagnosis of aHUS superimposed on pre-existing IgAN. An interesting question arises: should the co-occurrence of these two diseases be regarded as coincidental, or is there an underlying connection? Given that these two conditions did not arise simultaneously in our patient—with IgAN likely preceding aHUS—the most straightforward explanation is that the initial disease may have triggered the development of the second [16].

Nonetheless, several studies have identified genetically determined dysregulation of the complement system in some patients with isolated IgAN. This dysregulation may potentially contribute both to the pathogenesis of glomerulonephritis and to the development of aHUS. Cases reported by Nakamura H. et al., Hou W. et al., and Schmitt R. et al. describe various mutations in complement factor H associated with the co-occurrence of IgAN, TMA, and aHUS

[17, 19]. In such scenarios, eculizumab may provide therapeutic benefits for both diseases [16, 17].

Some reports also highlight elevated circulating levels of complement factor H-related proteins (CFHR1–5) in patients with IgAN, which further indicates activation of the alternative complement pathway. In the case presented here, eculizumab effectively and completely resolved the manifestations of TMA, but had no significant impact on the persistent hematuria and proteinuria, which were most likely driven by IgAN. The use of the maximally tolerated dose of ramipril led to marked improvement in urine parameters, offering hope for slowing disease progression.

In conclusion, we describe a patient with both clinical and histological features of aHUS and IgAN. Despite the rarity of this combination, this case underscores the importance of considering such a dual diagnosis to avoid misinterpretation and ensure appropriate management.

Author's contribution.

Mikhail Kagan *– conceptualization, literature search and analysis, text writing and editing, responsibility for the integrity of all parts of the article.*

Zhamilya Issanguzhina *– critical revision and editing of the article.*

Aniya Seipenova *– systematic review and analysis of the literature.*

Natalia Pukhovikova *–systematic review and analysis of the literature.*

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The authors declare no conflicts of interest.

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CORONARY ARTERY STENTING UNDER ECMO SUPPORT: A CASE SERIES DESCRIPTION

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Abstract

Objective: The use of Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) is a potentially life-saving strategy for patients with refractory cardiogenic shock (CS) secondary to ST-segment elevation myocardial infarction (STEMI)for whom standard therapy is ineffective. Data on the implementation of this method are scarce in the Republic of Kazakhstan (RK).

Aim of the Study To evaluate the feasibility and initial clinical outcomes of emergency percutaneous coronary intervention (PCI) supported by VA-ECMO under a unified protocol in patients with refractory cardiogenic shock in the Republic of Kazakhstan.

Methods A retrospective, single-center study was conducted, including a series of six consecutive patients with refractory CS due to STEMI who underwent emergency coronary artery stenting at the Pavlodar Regional Cardiology Center during the period from October 2024 to September 2025. PCI was performed with active peripheral VA-ECMO support via a femoral approach. The primary endpoint was survival to hospital discharge, and the secondary endpoint was the frequency of major complications.

Results The mean age of the patients was 71.3 years (men — 83.3%). Multivessel coronary artery disease was recorded in 100% of patients. The PCI procedure was technically successful in all 6 cases, achieving TIMI 3 flow. The mean duration of ECMO support during the intervention was 56 minutes (30–90 minutes). Hospital survival was 83.3%(5 out of 6 patients were discharged in satisfactory condition). Among discharged patients, 30- and 90-day survival was 100%. A complication in the form of femoral artery dissection was recorded in 1 patient (16.7%).

Conclusions The application of a unified perioperative management protocol allows for the successful performance of emergency PCI with VA-ECMO support in patients with refractory cardiogenic shock. The method is technically feasible and provides a high level of early survival comparable to international data, confirming its potential as a life-saving option.

Keywords: *Cardiogenic Shock, STEMI, VA-ECMO, PCI, Revascularization, Kazakhstan.*

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Резюме

СТЕНТИРОВАНИЕ КОРОНАРНЫХ АРТЕРИЙ В УСЛОВИЯХ ЭКМО: ОПИСАНИЕ СЕРИИ КЛИНИЧЕСКИХ СЛУЧАЕВ

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Использование вено-артериальной экстракорпоральной мембранной оксигенации (ВА-ЭКМО) является потенциально жизнесберегающей стратегией для пациентов с рефрактерным кардиогенным шоком (КШ) на фоне инфаркта миокарда с подъемом сегмента ST (ИМпST), для которых стандартная терапия неэффективна. В Республике Казахстан (РК) данные о внедрении данной методики отсутствуют.

Цель исследования: Оценить реализуемость и первоначальные клинические исходы экстренного чрезкожного коронарного вмешательства (ЧКВ) под поддержкой ВА-ЭКМО в условиях единого унифицированного протокола у пациентов с рефрактерным кардиогенным шоком на территории РК.

Методы: Проведено ретроспективное, одноцентровое исследование, включающее серию из шести последовательных пациентов с рефрактерным КШ на фоне ИМпST, которым было выполнено экстренное стентирование коронарных артерий в Павлодарском Областном Кардиологическом Центре в период с октября 2024 года по сентябрь 2025 года. ЧКВ выполнялось при активной периферической ВА-ЭКМО поддержке через бедренный доступ. Первичной конечной точкой была выживаемость до выписки из стационара, вторичной — частота основных осложнений.

Результаты: Средний возраст пациентов составил 71,3 года (мужчины — 83,3%). У 100% пациентов было зафиксировано многососудистое поражение. Процедура ЧКВ была технически успешной во всех 6 случаях, с достижением кровотока TIMI 3. Средняя длительность ЭКМО-поддержки во время вмешательства составила 56 минут (30–90 минут). Госпитальная выживаемость составила 83,3% (5 из 6 пациентов выписаны в удовлетворительном состоянии). Среди выписанных пациентов 30- и 90-дневная выживаемость составила 100%. Осложнение в виде диссекции бедренной артерии зафиксировано у 1 пациента (16,7%).

Выводы: Применение унифицированного протокола периоперационного ведения позволяет успешно проводить экстренное ЧКВ под поддержкой ВА-ЭКМО у пациентов с рефрактерным кардиогенным шоком. Методика технически реализуема и обеспечивает высокий уровень ранней выживаемости, сопоставимый с международными данными, что подтверждает ее потенциал в качестве жизнесберегающей опции.

Ключевые слова: *Кардиогенный шок, ИМпST, ВА-ЭКМО, ЧКВ, Реваскуляризация, Казахстан.*

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Түйіндеме

ЭКМО ЖАҒДАЙЫНДАҒЫ КОРОНАРЛЫҚ АРТЕРИЯЛАРДЫ СТЕНТТЕУ: КЛИНИКАЛЫҚ ЖАҒДАЙЛАР СЕРИЯСЫНЫҢ СИПАТТАМАСЫ

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Вено-артериялық экстракорпоралдық мембраналық оксигенацияны (ВА-ЭКМО) қолдану стандартты терапия тиімсіз болған ST сегментінің көтерілуімен болатын миокард инфарктісі (МКСК) аясындағы рефрактерлік кардиогенді шок (КШ) бар пациенттер үшін өмірді сақтауға қабілетті стратегия болып табылады. Қазақстан Республикасында (ҚР) осы әдісті енгізу туралы деректер жоқ.

Зерттеу мақсаты: ҚР аумағында рефрактерлік кардиогенді шок бар пациенттерде бірыңғай стандартталған хаттама жағдайында ВА-ЭКМО қолдауымен шұғыл тері арқылы коронарлық араласудың (ТКА) іске асырылуын және бастапқы клиникалық нәтижелерін бағалау.

Әдістер: 2024 жылдың қазан айынан 2025 жылдың қыркүйегіне дейінгі кезеңде Павлодар облыстық кардиологиялық орталығында шұғыл коронарлық артерия стенттеуі жүргізілген рефрактерлік КШ-пен 6 пациентті қамтитын ретроспективті, бір орталықты зерттеу жүргізілді. ТКА шұғыл перифериялық ВА-ЭКМО қолдауымен

(сандық қолжетімділік арқылы) орындалды. Негізгі соңғы нүкте стационардан шыққанға дейінгі өмір сүру ұзақтығы болды, ал екіншісі — негізгі асқынулардың жиілігі.

Нәтижелер: Пациенттердің орташа жасы 71,3 жасты құрады (ерлер — 83,3%). Пациенттердің 100%-ында көп тамырлы зақымдану тіркелді. ТКА процедурасы барлық 6 жағдайда техникалық тұрғыдан сәтті өтті, TIMI 3ағынына қол жеткізілді. Араласу кезіндегі ЭКМО қолдаудың орташа ұзақтығы 56 минутты (30–90 минут) құрады. Ауруханадағы өмір сүру ұзақтығы 83,3% (6 пациенттің 5-і қанағаттанарлық жағдайда шығарылды). Шығарылған пациенттер арасында 30 және 90 күндік өмір сүру ұзақтығы 100% құрады. Сандық артерияның диссекциясы түріндегі асқыну 1 пациентте (16,7%) тіркелді.

Қорытындылар: Периоперациялық жүргізудің бірыңғай хаттамасын қолдану рефрактерлік кардиогенді шок бар пациенттерде ВА-ЭКМО қолдауымен шұғыл ТКА-ны сәтті жүргізуге мүмкіндік береді. Әдіс техникалық тұрғыдан іске асырылады және халықаралық деректермен салыстыруға болатын ерте өмір сүрудің жоғары деңгейін қамтамасыз етеді, бұл оның өмірді сақтау мүмкіндігі ретіндегі әлеуетін растайды.

Түйін сөздер: *Кардиогенді шок, МКСК, ВА-ЭКМО, ТКА, Реваскуляризация, Қазақстан.*

Дәйексөз үшін:

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Introduction

Ischemic heart disease (IHD) remains a leading cause of mortality and disability worldwide, particularly among the working-age population. Its most critical manifestation is ST-segment elevation myocardial infarction (STEMI), which requires urgent restoration of coronary blood flow [11].

Despite advancements in reperfusion therapy (percutaneous coronary intervention (PCI), thrombolysis), the development of cardiogenic shock (CS) occurs in 5%–10% of patients with acute myocardial infarction, carrying an extremely poor prognosis. In-hospital mortality reaches 40%–50% and often higher [10, 14, 16].

Cardiogenic shock is defined as a critical condition resulting from an abrupt reduction in cardiac output and subsequent impairment of end-organ perfusion, unresponsive to standard treatments (inotropes, vasopressors). Patients with refractory cardiogenic shock present a particular challenge, as mortality approaches 100% without the application of mechanical circulatory support (MCS). It is this patient population—typically older, with low left ventricular ejection fraction (LVEF), multi-vessel coronary disease, and severe comorbidities—that is at maximum risk [5, 6, 8, 9, 12].

One potential solution is the use of Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO), which provides temporary circulatory and respiratory support. This allows therapeutic interventions to be performed in a setting of stabilized circulation. Several publications have demonstrated that combining ECMO and PCI can be life-saving for patients with severe myocardial dysfunction and high anatomical risk (e.g., left main coronary artery disease, chronic total occlusions) [3, 13, 15].

However, despite these technological advances, such interventions are associated with considerable risks. Hospital mortality in these complex patients can be as high as 23%, and long-term survival rarely exceeds 45%–50% [10]. Notably, successful PCI in this setting achieves complete revascularization rates of over 90%, and ECMO weaning is often feasible [13].

Published data remain limited to small case series and isolated retrospective studies. Crucially, no studies have been conducted or published within the Republic of Kazakhstan on this topic. Furthermore, randomized clinical trials directly comparing PCI under ECMO support versus coronary artery bypass grafting (CABG) in high-risk patients are lacking [2, 7]. Key questions remain unresolved, including optimal patient selection criteria, ideal timing for ECMO placement, anticoagulant management strategies, and long-term outcomes.

Study Hypothesis: We hypothesize that describing a series of clinical cases using a unified protocol will demonstrate that PCI under VA-ECMO support is a technically feasible and potentially life-saving procedure. Furthermore, this analysis will allow us to identify the key factors determining success in this patient cohort.

Aim of the Study: The aim of this study is to evaluate the feasibility and initial clinical outcomes of emergency percutaneous coronary intervention (PCI) with VA-ECMO support, utilizing a single unified protocol in patients with refractory cardiogenic shock within the Republic of Kazakhstan.

Materials and Methods

Study Design and Population

This retrospective, single-center study included six consecutive patients with refractory cardiogenic shock (CS) secondary to STEMI. All patients underwent emergency percutaneous coronary intervention (PCI) with active VA-ECMO support via femoral access at the Pavlodar Regional Cardiac Center (PRCC) between October 2024 and September 2025. All procedures were conducted in the hospital's third-level hybrid operating room.

Veno-Arterial ECMO Protocol and Procedure: ECMO was established peripherally via femoral access, guided by a unified institutional protocol (Figure 1). The procedure was performed jointly by interventional cardiologists, X-ray vascular surgeons, cardiac surgeons, and intensive care specialists.

ECMO Cannulation and Initiation: Patients presenting with hypotension, hemodynamic instability, clinical signs of CS, and/or requiring ongoing cardiopulmonary resuscitation (CPR) were immediately moved to the X-ray vascular operating room.

1. Anticoagulation: Intravenous heparin was administered at a dose of 150–200 IU/kg (e.g., 10,500–

14,000 IU for a 70 kg patient) prior to cannulation to maintain the Activated Clotting Time (ACT) control.

2. Surgical Access: Under sterile conditions (Figure 1A), a vertical incision (up to 7 cm) was made in the inguinal crease to expose the femoral artery and vein.

3. Arterial Cannulation: A purse-string suture (3 by 4 mm patches) was placed on the pulsatile femoral artery. An arterial cannula was inserted (Figure 1B, C), and the line was purged of air and secured with a Murphy clamp.

4. Venous Cannulation: A second purse-string suture was placed on the femoral vein, medial to the artery. The soft guidewire was advanced into the superior vena cava, ensuring the cannula tip reached the right atrium or stopped just short of the atrial roof to prevent injury (Figure 1D, E).

5. Circuit Connection: After clamping the ECMO circuit lines, the arterial cannula was connected to the red (arterial) line and the venous cannula to the blue (venous) line. Physiological saline was used to flush the connection sites to meticulously remove all air before removing the clamps.

6. ECMO Activation: The ECMO console was activated by turning the knob to a rotational speed of 6,500 rpm (Figure 1F). Oxygen flow was set to 2–3 L/min, with FiO2 maintained at 90%–100%. The heat exchanger was set to 37.3◦C.

7. Post-Procedure: Following successful PCI and ECMO stabilization, patients were transferred to the Critical Care Unit (CCU). Decisions regarding ECMO weaning were made by a multidisciplinary heart team.

Endpoints: Primary endpoints included successful revascularization (TIMI 3 flow) and survival rates until ECMO weaning and hospital discharge. Secondary endpoints included the incidence of major in-hospital complications (bleeding, stroke, limb ischemia) and survival at 30 and 90 days.

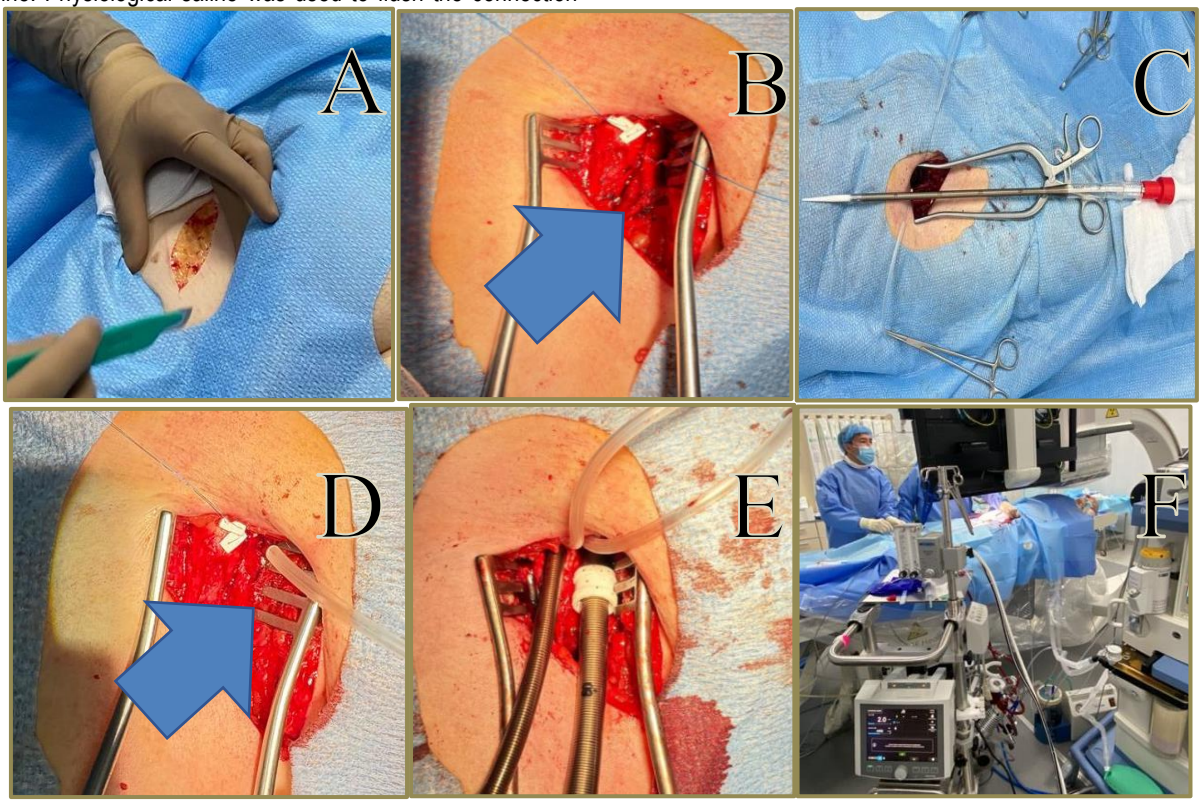


Figure 1. Stages of preparation for PCI under VA-ECMO support: (A) Access for peripheral VA cannulation, (B) Visual confirmation of cannulae, (C) Preparation and purse-string suture placement on the femoral artery (blue arrow), (D)Preparation and purse-string suture placement on the femoral vein (blue arrow), (E) Cannulation of the femoral artery and vein, (F) Team activity during the VA-ECMO procedure.

Results

Patient Characteristics and Baseline Data

This study included six patients, the majority of whom were male (83.3%). Their baseline characteristics are summarized in Table 1. The mean age of the cohort was 71.3 years (range: 59–84 years). Patients generally presented with overweight status, with a mean BMI of 25 kg/m2 (range: 19–29 kg/m2).

A significant portion of the cohort (83.3%) had a history of, or were admitted with, a previous MI. Three patients (50%) had undergone prior surgical revascularization in the form of Coronary Artery Bypass Grafting (CABG), and one patient (16.7%) had a history of Aorto-Femoral Bypass (AFB).

The following comorbidities were noted in the patient history: Arterial Hypertension (AH) – 6 patients (100%), Multifocal Atherosclerosis (MFA) – 5 patients (83.3%), Diabetes Mellitus (DM) – 1 patient (16.7%), Mitral Regurgitation (MR) – 2 patients (33.3%), Tricuspid Regurgitation (TR) – 4 patients (66.7%), Cardiac Rhythm Disorder (CRD) – 2 patients (33.3%), Chronic Venous Insufficiency (CVI) and Abdominal Aortic Aneurysm (AAA) – 1 patient (16.7%) each.

All six patients (100%) presented with multivessel coronary artery disease. Left Main Coronary Artery (LMCA)

involvement was noted in four cases (66.7%). The majority of patients had lesions in the Left Anterior Descending (LAD) artery (83.3%), the Circumflex Artery (Cx) (66.7%), and the Right Coronary Artery (RCA) (83.3%).

As detailed in Table 1, the mean Left Ventricular Ejection Fraction (LVEF) was 36.67% (range: 23%–57%). The average Glomerular Filtration Rate (GFR) was slightly reduced at 73.8 mL/min/1.73 m2 (range: 59–85 mL/min/1.73 m2). Laboratory markers indicated liver function near the upper limit of normal (ALT: 83 U/L, range 12–365 U/L), renal function also near the upper limit of normal (creatinine: 88.33 μmol/L, range 72–105 μmol/L), while cardiac markers (AST) were within the normal range (33.83 U/L, range 15–94 U/L).

Table 1.

Patient Characteristics.

Variable	Value
Male, n (%)	5 (83,3)
Age, mean (min-max) [years]	71,33 (59-84)
BMI,kg/m2	25 (19-29)
Ischemic Heart Disease (IHD), n (%)	6 (100)
History of Acute MI, n (%)	5 (83,3)
Prior Coronary Artery Bypass Grafting (CABG), n (%)	3 (50)
Arterial Hypertension (AH), n (%)	6 (100)
Multifocal Atherosclerosis (MFA), n (%)	5 (83,3)
Prior Aorto-Femoral Bypass (AFB), n (%)	1 (16,7)
Diabetes Mellitus (DM), n (%)	1 (16,7)
Mitral Regurgitation (MR), n (%)	2 (33,3)
Tricuspid Regurgitation (TR), n (%)	4 (66,7)
Cardiac Rhythm Disorder (CRD), n (%)	2 (33,3)
Chronic Venous Insufficiency (CVI), n (%)	1 (16,7)
Abdominal Aortic Aneurysm (AAA), n (%)	1 (16,7)
Left Main Coronary Artery (LMCA), n(%)	4 (66,7)
Left Anterior Descending Artery (LAD), n (%)	5 (83,3)
Circumflex Artery (Cx), n (%)	4 (66,7)

Procedure and Initial Outcomes

Complete coronary revascularization was successfully achieved in all six cases (100%) under ECMO support and hemodynamic stabilization.

The duration of ECMO support was remarkably short (Table 2), with a mean duration of only 56 minutes (range: 30 to 90 minutes), indicating its use as a temporary prophylactic/stabilizing tool during the PCI procedure.

Table 2.

VA-ECMO Parameters and Duration.

Variable	Value
ECMO Support Duration <1 day, n (%)	6 (100)
ECMO Support Duration, hours, mean (min-max)	0:56 (0:30-1:30)

Primary Outcomes (Table 3): Successful revascularization (achieving TIMI 3 flow) was observed in all 6 patients (100%) without major procedural complications. The mean length of hospital stay was 16 days (range: 3–31 days), with a mean stay in the Intensive Care Unit (ICU) of 3 days (range: 3–6 days). Five out of six patients were discharged from the hospital in a satisfactory condition.

Secondary Outcomes (Table 3): Thirty-day and ninety-day survival among the discharged patients was 100%. Only one complication was recorded in the entire cohort: a femoral artery dissection, which was managed successfully. No other complications were observed.

Table 3.

Primary and Secondary Outcomes.

Variable	Value
Primary Outcomes	
Successful Revascularization, n (%)	6 (100)
Length of Hospital Stay, days, mean (min-max)	16 (3-31)
Length of ICU Stay, days, mean (min-max)	3 (1-6)
Discharged, n (%)	5 (83,3)
Secondary Outcomes	
30-day Survival Rate, n(%)	5 (83,3)
90-day Survival Rate, n (%)	5 (83,3)
Femoral Artery Dissection, n(%)	1 (16,7)
Bleeding Events, n (%)	0
Stroke, n (%)	0
Limb Ischemia, n (%)	0

Discussion

The current study describes a sequential series of six patients with refractory cardiogenic shock (CS) secondary to STEMI, who underwent emergency percutaneous coronary intervention (PCI) with VA-ECMO support. The principal finding demonstrates that this complex intervention was technically feasible in all cases, leading to successful revascularization (TIMI 3 flow) and, crucially, the possibility of successful ECMO weaning in the majority of the cohort.

These results align favorably with previously published international data. Specifically, studies by Shaukat et al. (2018), Huang et al. (2022), and Bai et al. (2022) have reported high success rates (90%–100%) for PCI performed under ECMO support in patients presenting with severe multivessel disease and low LVEF [3, 4, 13]. Our findings further validate that the use of ECMO effectively stabilizes hemodynamics, permitting complete revascularization even in critically ill patients.

Consistent with the literature, we observed a measurable rate of complications (16.7%), which is characteristic of such high-risk procedures. The most significant complication encountered was vascular in nature, stemming from the percutaneous ECMO insertion. These observations are consistent with large retrospective registries where bleeding rates approach 20% and vascular complications reach up to 10% [7]. In our small series, we were able to minimize these complications through the implementation of a unified management protocol (strict ACT control, standardized access selection, and early detection of limb ischemia). However, the inherent risk remains substantial.

A key achievement was that the standardized protocol for anticoagulation and access site care allowed us to avoid fatal bleeding events and strokes, underscoring the vital importance of a multidisciplinary approach and patient management within a specialized center. These conclusions strongly echo the recommendations put forth by Zuin et al. (2019) and Griffioen et al. (2022), who emphasize the necessity of concentrating these complex interventions in tertiary care facilities [1, 17].

The practical significance of this study lies in confirming that PCI with ECMO support offers a viable pathway to acceptable clinical outcomes (hospital survival rate of approximately 83.3%), even in patients facing an extremely unfavorable prognosis (advanced age, multivessel disease, low LVEF). This evidence supports the view that the methodology should be considered a real alternative to surgical revascularization (CABG) for patients deemed non-candidates for conventional surgery.

Limitations

Our study is subject to several limitations. Firstly, the small sample size restricts the ability to draw statistically significant conclusions. Secondly, as a single-center study, the generalizability of these results is inherently limited. Thirdly, the absence of a dedicated control group (e.g., patients undergoing CABG or PCI without ECMO) prevents a direct assessment of the method's advantages.

Nevertheless, the data collected highlight the potential and promise of this approach and clearly demonstrate the need for further investigation. Future research should prioritize the optimization of patient selection criteria, refinement of the timing for ECMO placement, and the development of unified protocols for anticoagulation and perioperative management. These steps are crucial for the design of future multicenter studies and, ultimately, randomized clinical trials.

Conclusion

Revascularization performed with VA-ECMO support is a life-preserving procedure that necessitates a multidisciplinary approach, along with meticulous patient selection and management strategies. The feasibility and promising initial outcomes demonstrated here underscore the urgent requirement for further investigation, ideally in the form of multicenter randomized clinical trials.

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CLINICAL CASE OF INTUSSUSCEPTION AGAINST A BACKGROUND OF INTESTINAL INFECTION IN A CHILD. CLINICAL CASE

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Abstract

Intestinal intussusception is an intestinal obstruction caused by the insertion of one intestine into another. Intestinal intussusception is the most frequent form of acquired intestinal obstruction in childhood, accounting for 70-80% of all its types [2]. According to various authors, diagnostic errors in intestinal intussusception at the stage of primary care make up 34 - 88.8%, which determines late admission of patients and, of course, worsens the results of treatment. It should be emphasized that in recent decades there have been changes in the clinical picture and course of the disease, an increase in the number of recurrent intussusception [2].

In this article, we presented a case of fatal intestinal intussusception in a 2-month-old child registered in the pediatric department of the regional infectious disease hospital of Abay region, Republic of Kazakhstan. The development of intestinal obstruction against the background of acute intestinal infection is not uncommon, but is not often described in the literature [2].

The article will be interesting to medical workers who first meet with patients with intestinal intussusception, namely doctors of "emergency and urgent care", district pediatricians, general practitioners, doctors of infectious and somatic hospitals.

Keywords: *intussusception, children, intestinal infections.*

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Резюме

КЛИНИЧЕСКИЙ СЛУЧАЙ ИНВАГИНАЦИИ КИШЕЧНИКА НА ФОНЕ КИШЕЧНОЙ ИНФЕКЦИИ У РЕБЕНКА. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Инвагинация кишечника — непроходимость кишечника, обусловленная внедрением одной кишки в другую. Инвагинация кишечника является наиболее частой формой приобретенной кишечной непроходимости в детском возрасте, составляя 70—80% от всех ее видов [2]. По данным различных авторов, диагностические ошибки при инвагинации кишечника на этапе первичного звена составляют 34 - 88,8%, что определяет позднее поступление больных и, безусловно, ухудшает результаты лечения. Необходимо особо отметить, что в последние десятилетия происходят изменение клинической картины и течения заболевания, увеличение числа повторных инвагинаций [2].

В статье мы представили случай с летальным исходом, инвагинации кишечника у ребенка 2 месяцев, зарегистрированный в детском отделении областной инфекционной больницы области Абай, республика Казахстан.

Статья будет интерсна медицинским работникам, кто первыми встречаются с пациентами с инвагинацией кишечника, а именно врачам «скорой и неотложной помощи», участковым педиатрам, врачам общей практики, врачам инфекционных и соматических стационаров.

Ключевые слова: *инвагинация, дети, кишечные инфекции.*

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Түйіндеме

БАЛАДА ІШЕК ИНФЕКЦИЯСЫ ФОНЫНДА ІШЕК ИНВАГИНАЦИЯСЫНЫҢ КЛИНИКАЛЫҚ ЖАҒДАЙЫ. КЛИНИКАЛЫҚ ЖАҒДАЙ

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Ішектің инвагинациясы - бір ішектің екіншісіне енуіне байланысты ішек өтімсіздігі. Ішектің инвагинациясы балалық шақта жүре пайда болған ішек өтімсіздігінің ең көп таралған түрі болып табылады, оның барлық түрлерінің 70-80% құрайды [2]. Әр түрлі авторлардың пікірінше, бастапқы кезеңдегі ішек инвагинациясының диагностикалық қателіктері 34 - 88,8% құрайды, бұл пациенттердің кеш келуін анықтайды және емдеу нәтижелерін нашарлатады. Соңғы он жылдықтарда аурудың клиникалық көрінісі мен ағымының өзгеруі, қайталанған инвагинациялар санының артуы байқалады [2].

Мақалада біз Қазақстан Республикасы Абай облысы облыстық жұқпалы аурулар ауруханасының балалар бөлімшесінде тіркелген 2 айлық балада ішектің инвагинациясының өліммен аяқталған жағдайын ұсындық.

Мақала ішек инвагинациясы бар науқастармен алғаш кездескен медицина қызметкерлеріне, атап айтқанда "жедел және шұғыл көмек" дәрігерлеріне, үлескілік педиатрларға, жалпы тәжірибе дәрігерлеріне, жұқпалы және соматикалық стационарлардың дәрігерлеріне қызықты болады.

Түйінді сөздер: *инвагинация, балалар, ішек инфекциялар.*

Дәйексөз үшін:

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Relevance

Intestinal intussusception in children is the result of temporary age-related discoordination of intestinal peristalsis with the formation of areas of spasm, which contributes to the intrusion of the intestine. The most common causes of peristaltic discoordination are intestinal diseases (dysentery, dyspepsia), as well as improper feeding and complementary feeding in infants [6]. The onset of the disease is facilitated by certain anatomical features of the intestine in infants aged 3-9 months, more often in boys (common mesentery, functional insufficiency of the Bauhin valve), as well as an increase in lymph nodes and fatty plaques in the ileocecal angle, developing as a result of enterovirus infection [6]. Intussusception is the most common type of acute intestinal obstruction in children and can occur at any age. Intussusception is more common between the ages of 4 and 9 months (85–90% of cases). Boys are affected twice as often as girls [4].

According to various authors, diagnostic errors in intestinal intussusception at the primary care stage range from 34 to 88.8%, which determines the late admission of patients and, undoubtedly, worsens treatment outcomes [2]. In pediatric surgical hospitals, diagnostic errors reach 12-16%. The mortality rate for intussusception ranges from 0.5 to 1%, reaching 6 to 15% in complicated cases. The objective difficulties of diagnosis and treatment are largely associated with the presence of intercurrent diseases, as well as the limitations of traditional X-ray diagnostics [7,8].

The first to encounter patients with intussusception are emergency doctors, district pediatricians, and often doctors on duty at infectious disease and somatic hospitals. It is during the initial examination that it is important to make the correct diagnosis and take the appropriate decision. It should be noted that in recent decades there have been changes in the clinical picture and course of the disease, with an increase in the number of recurrent intussusceptions [2,8].

The objective difficulties in diagnosis and treatment are largely related to the presence of intercurrent diseases, the limitations of traditional X-ray diagnostics, and continuing disagreements regarding the choice of conservative or surgical treatment methods and their timing [7]. Traditionally, the indications for surgical treatment are considered to be: more than 12 hours since the onset of the disease, age over 1 year, and recurrence of intussusception [1,3,5].

Aim: to analyses the clinical case of a patient with intussusception.

Materials and methods: A retrospective analysis of the case was performed using the medical records of an in-patient. Diagnostic and therapeutic procedures were performed in accordance with the approved clinical protocol set out in the Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan. The consent of the patient's parents was obtained for all procedures performed. The publication of the treatment results has been approved by the clinic's management.

Results

A two-month-old boy was admitted to the pediatric ward of the regional infectious diseases hospital on the third day of illness with complaints of a rise in body temperature to 38°C, repeated vomiting and loose stools up to six times. From the medical history: the child had been ill for three days, starting with loose stools up to 3-4 times, followed by an increase in body temperature to 38°C, vomiting once, and restlessness. On the second day of illness, he was examined by a surgeon, and surgical pathology of the abdominal organs was ruled out. On the third day of the illness, the diarrhea increased to 6 times a day, and the mother and child went to the regional infectious disease's hospital. Upon admission to hospital: the child's general condition is moderate due to intoxication and diarrhea syndromes. Consciousness is clear. Well-being is moderately impaired, lethargic. According to the mother, the child feeds well. Meningeal signs are negative. Skin is pale, no rash. Skin folds smooth out immediately. Turgor is preserved. Eyes are normal. Tongue is dry, coated with white plaque. Lips are dry. Lungs: percussion reveals clear pulmonary sounds; auscultation reveals vesicular breathing, no rales. Respiratory rate 44 per minute. Saturation 98%. Heart sounds clear and rhythmic. Heart rate 132 per minute, blood pressure 80/50 mmHg. Abdomen soft, painless, palpable in all areas. Liver is not enlarged, painless on palpation. Spleen is not enlarged. Stools are loose, watery, without pathological impurities, up to 6 times a day. Anus is closed. Urination is preserved, painless. Considering the complaints, medical history and physical examination, a preliminary diagnosis was made: acute intestinal infection, moderate gastroenteritis. The child's condition is deteriorating, with delayed breathing, restlessness, increasing lethargy, abdominal distension and pain, and decreased urine output.

Table 1.

Dynamics of complete blood count indicators.

Indicators	Day of admission		
	first day	second day	third day
WBC (*10^9/л)	20,18	65,46	51,46
RBC (*10^{12}/л)	5,58	5,33	4,28
HBG (g/l)	152	148	113
PLT (*10^9/л)	565	726	598
Neu %	51,3	78,8	84,4
Lym %	39,1	14,4	8,1
Mon %	8,8	6,5	7,4
Eos %	0,8	0,3	0,1
ESR (mm/hour)	3	2	3

Upon admission, comprehensive treatment was provided: combined antibiotic therapy, oxygen therapy, anti-shock therapy (hormones, intravenous infusion), correction of acidosis, cardiotropic, anticonvulsants, immunotherapy (plasma, immunoglobulins).

Given the deterioration in condition, anxiety, bloating and abdominal pain, sharply inflammatory blood tests (hyperleukocytosis, neutrophilia), to rule out surgical pathology of the abdominal organs, intestinal developmental abnormalities, peritonitis, the patient was re-examined by a surgeon on the second day. The surgeon's conclusion: no evidence of surgical pathology of the abdominal organs was found.

On the third day of hospitalization: condition extremely serious, septic (according to blood tests, hyperleukocytosis, neutrophilia, thrombocytosis). Clinical signs of hemorrhagic syndrome, according to blood gas analysis - decompensated metabolic acidosis. Consciousness and well-being are severely impaired — deep lethargy. Skin is pale, extensive bruising at venipuncture sites (elbow bends, feet), bleeding from blood collection sites (stopped dynamically). Skin turgor and elasticity are reduced (especially on the thighs). Scrotal edema. Breathing is regular, pulse oximetry readings are normal with oxygen therapy. Breathing in the lungs is stiff, no wheezing. Heart sounds are muffled, rhythm is regular. Pulse in radial arteries is reduced. Blood pressure on the monitor is within normal limits. Abdomen is soft. Intestinal peristalsis is audible. Diarrhea of enteritic nature, stools are watery. Urinates through a catheter - urine is yellow. By decision of the consultation, a repeat consultation with a surgeon was scheduled to rule out surgical pathology of the abdominal organs. The surgeon ruled out surgical pathology of the abdominal organs and, due to the child's inability to be transported, recommended an ultrasound scan of the abdominal organs.

Results of abdominal ultrasound. Distended intestinal loops. Free fluid is located in the abdominal cavity, the contours of an atonic stomach with contents are visible. Moderate hepatomegaly. Effusion around the liver and lower abdomen.

An abdominal X-ray in the frontal projection shows no signs of intestinal obstruction or perforation of hollow organs. A small amount of air without fluid levels is visible in the intestines.

Despite comprehensive treatment and examination, and resuscitation measures carried out on the third day of hospitalization, death was confirmed. Cause of death: cerebral edema with occipital herniation.

During the autopsy, four invaginations of the small intestine were found, formed in areas where there were no circular muscles or nerve trunks. In addition, 40 ml of whitish fluid was found in the abdominal cavity, 21 ml of whitish fluid in the right pleural cavity, and 18 ml of whitish fluid in the left pleural cavity (Photo 1).

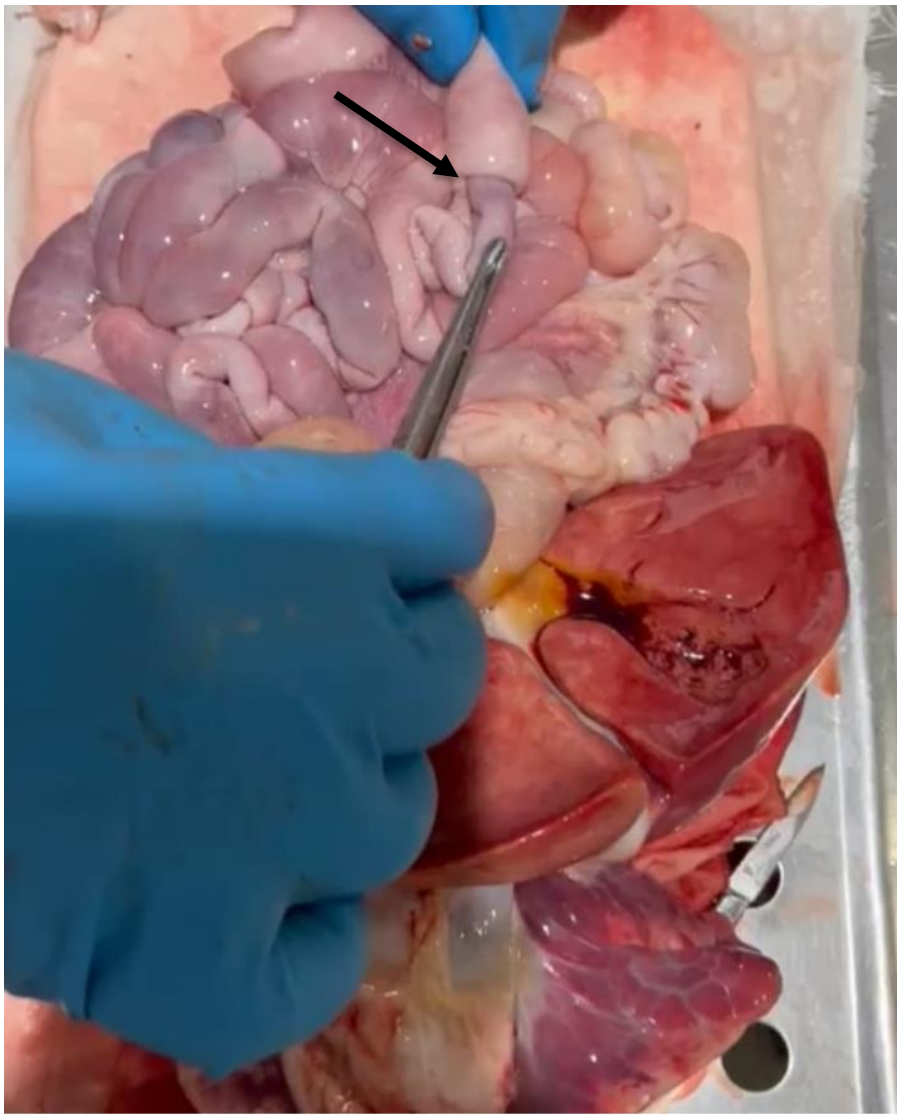


Photo 1. Intussusception in the intestine.

Based on anamnestic, clinical, laboratory and instrumental data, as well as the results of a pathological autopsy, the following post-mortem diagnosis was made: Primary diagnosis:

Combined disease:

1) Intussusception (in four places with an intussusception size ranging from 1.4 cm to 2.5 cm in the area of the Bauhin valve).

2) Acute intestinal infection, gastroenteritis, severe. Complications: Acute peritonitis. Toxic encephalopathy (grade 2 neurotoxicosis). Cerebral edema. Disseminated intravascular coagulation (defibrination phase). Grade 3 respiratory failure. Grade 3 cardiovascular failure. There is a coincidence between the clinical and pathological diagnoses.

Conclusion:

This clinical case demonstrates once again that intussusception is most severe in children during the first three months of life, who may lack typical symptoms and rapidly develop peritonitis and shock. Intestinal infection complicates the timely diagnosis of intussusception in young children [10].

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EFFECTS OF MATERNAL CYTOMEGALOVIRUS INFECTION ON FETAL IMMUNE ORGANS DEVELOPMENT. CLINICAL CASE

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Abstract

Introduction: Cytomegalovirus (CMV), a ubiquitous herpesvirus, causes congenital infection in 0.5–2% of live births, leading to severe manifestations like hepatosplenomegaly, microcephaly, and neurological damage. CMV evades immunity by manipulating apoptosis via Bcl-2 upregulation and p53 suppression, disrupting thymic and splenic development critical for T-cell education and peripheral immunity. This case report examines morphological changes and expression of apoptosis (Bcl-2, p53) and proliferation (Ki-67) markers in fetal thymus and spleen from a 23-week miscarriage due to maternal CMV infection.

Materials and Methods: Autopsy of fetus from a 28-year-old woman's fourth pregnancy (late miscarriage at 23 weeks) provided thymus and spleen samples. Macroscopic and microscopic assessments followed standardized algorithms. Immunohistochemistry used monoclonal antibodies (Bcl-2 Clone 124, p53 Clone DO-7, Ki-67 Clone MIB-1; DAKO) with LSAB2®-HRP and diaminobenzidine chromogen. Results were quantified via Histo score (McCarthy et al., 1985).

Results: Thymus showed enlargement, large lobules (cortex:medulla 2:1), preserved lymphocytes, and moderate Hassall's corpuscles. Spleen exhibited splenomegaly, white:red pulp 1:2, activated white pulp, and marginal zone clusters. Bcl-2 stained cytoplasmically in thymic medulla and splenic marginal zone; p53 was weakly positive in thymic cortex/medulla; Ki-67 was pronounced in thymic subcapsular cortex and splenic periarteriolar lymphoid sheaths.

Discussion: Thymic hyperplasia and preserved lymphocytes indicate CMV-driven proliferation over atrophy, with Bcl-2 medullary dominance suggesting impaired negative selection and autoreactive T-cell survival. Splenic white pulp expansion reflects immune activation, but disorganization and Bcl-2/Ki-67 upregulation imply exhaustion and dysregulation. A decrease in p53 levels may indicate a disruption of the apoptotic process.

Conclusion: CMV profoundly alters fetal thymus/spleen morphology and apoptosis/proliferation, disrupting T-cell repertoire and self-tolerance, contributing to long-term immunological sequelae.

Key Words: *CMV-infection, fetal thymus, spleen, Bcl-2, p53, Ki-67, apoptosis*

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Резюме

ВЛИЯНИЕ МАТЕРИНСКОЙ ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ НА РАЗВИТИЕ ИММУННЫХ ОРГАНОВ ПЛОДА. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Введение: Цитомегаловирус (ЦМВ), повсеместно распространенный герпесвирус, вызывает врожденную инфекцию у 0,5–2% новорожденных, приводя к тяжелым проявлениям, таким как гепатоспленомегалия, микроцефалия и неврологические повреждения. ЦМВ избегает иммунитета, манипулируя апоптозом посредством повышения уровня Bcl-2 и подавления p53, нарушая развитие тимуса и селезенки, критически важных для обучения Т-клеток и периферического иммунитета. В данном клиническом случае рассматриваются морфологические изменения и экспрессия маркеров апоптоза (Bcl-2, p53) и пролиферации (Ki-67) в тимусе и селезенке плода после выкидыша на 23-й неделе беременности, вызванного материнской ЦМВ-инфекцией.

Материалы и методы: Образцы тимуса и селезенки плода от четвертой беременности (поздний выкидыш на 23-й неделе) 28-летней женщины. Макроскопическая и микроскопическая оценка проводилась в соответствии со стандартизированными алгоритмами. Для иммуногистохимического исследования использовались моноклональные антитела (Bcl-2, клон 124, p53, клон DO-7, Ki-67, клон MIB-1; DAKO) с LSAB2®-HRP и окраской диаминобензидиновым хромогеном. Результаты количественно оценивались с помощью гисто-счета (McCarthy et al., 1985).

Результаты: Тимус показал увеличение линейных размеров, большие дольки (соотношение кора:мозговое вещество 2:1), сохраненное количество лимфоцитов и умеренное количество телец Гассалля. Селезенка показала

спленомегалию, соотношение белой и красной пульпы 1:2, активированную белую пульпу и скопления клеток в краевой зоне. Bcl-2 окрашивался цитоплазматически в мозговом веществе тимуса и краевой зоне селезенки; p53 был слабоположительным в коре/мозговом веществе тимуса; Ki-67 был выражен в субкапсулярной коре тимуса и периартериальных лимфоидных оболочках селезенки.

Обсуждение: Гиперплазия тимуса и нормальное количество лимфоцитов указывают на пролиферацию, вызванную ЦМВ, а не на атрофию, при этом доминирование Bcl-2 в мозговом веществе предполагает нарушение негативной селекции и выживаемости аутореактивных Т-клеток. Увеличение белой пульпы селезенки отражает активацию иммунной системы, но дезорганизация и повышение уровня Bcl-2/Ki-67 указывают на истощение и дисрегуляцию. Снижение уровня p53 может свидетельствовать о нарушении процесса апоптоза.

Заключение: ЦМВ существенно изменяет морфологию фетального тимуса/селезенки и апоптоз/пролиферацию, нарушая репертуар Т-клеток и аутотолерантность, способствуя развитию долгосрочных иммунологических последствий.

Ключевые слова: *ЦМВ-инфекция, фетальный тимус, селезенка, Bcl-2, p53, Ki-67, апоптоз*

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Түйіндеме

АНАЛЫҚ ЦИТОМЕГАЛОВИРУС ИНФЕКЦИЯСЫНЫҢ ҰРЫҚТЫҢ ИММУНДЫҚ МҮШЕЛЕРІНІҢ ДАМУЫНА ӘСЕРІ. КЛИНИКАЛЫҚ ЖАҒДАЙ

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Кіріспе: Цитомегаловирус (CMV), кең таралған герпесвирус, жаңа туған нәрестелердің 0,5–2%-ында туа біткен инфекцияны тудырады, бұл гепатоспленомегалия, микроцефалия және неврологиялық зақымдану сияқты ауыр көріністерге әкеледі. CMV Bcl-2 деңгейінің жоғарылауы және p53 басылуы арқылы апоптозды манипуляциялау арқылы иммундық жүйеден жалтарады, бұл Т жасушаларының жиналуы және перифериялық иммунитет үшін маңызды болып табылатын тимус пен көкбауырдың дамуын бұзады. Бұл клиникалық жағдай туралы есепте ананың CMV инфекциясынан туындаған жүктіліктің 23 аптасында түсік тастағаннан кейін ұрықтың тимус пен көкбауырындағы морфологиялық өзгерістер мен апоптоздық (Bcl-2, p53) және пролиферация (Ki-67) маркерлерінің экспрессиясы зерттеледі.

Материалдар мен әдістер: 28 жастағы әйелдің төртінші жүктілік кезіндегі (23 аптада кеш түсік тастаған) ұрықтың тимус және көкбауыр үлгілері пайдаланылды. Макроскопиялық және микроскопиялық бағалау стандартталған алгоритмдерге сәйкес жүргізілді. Иммуногистохимия үшін LSAB2®-HRP және диаминобензидин хромоген бояуы бар моноклоналды антиденелер (Bcl-2 клоны 124, p53 клоны DO-7, Ki-67 клоны MIB-1; DAKO) пайдаланылды. Нәтижелер гисто-балл арқылы сандық анықталды (McCarthy және т.б., 1985).

Нәтижелер: Тимус сызықтық өлшемдерінің ұлғаюын, үлкен бөлікшелердің (қыртыс:ми безінің қатынасы 2:1), лимфоциттер санының сақталуын және орташа Гассалл денешелерінің болуын көрсетті. Көкбауырда спленомегалия, ақ/қызыл пульпа қатынасы 1:2, белсендірілген ақ пульпа және шеткі аймақта жасушалық агрегаттар байқалды. Bcl-2 тимус ми безі мен көкбауырдың шеткі аймағында цитоплазмалық боялған; p53 тимус қыртысында/ми безінде әлсіз оң нәтиже көрсетті; Ki-67 субкапсулярлы тимус қыртысында және көкбауырдың периартериалды лимфоидты қабықтарында экспрессияланды.

Талқылау: Тимус гиперплазиясы және лимфоциттердің қалыпты саны атрофия емес, CMV тудырған пролиферацияны көрсетеді, ал милы затында Bcl-2 басым болуы аутореактивті Т- жасушаларының теріс іріктеуі мен тіршілік етуінің бұзылуын көрсетеді. Көкбауырдың ақ пульпасының ұлғайуы иммундық белсенділікті көрсетеді, бірақ ұйымдаспағандық және Bcl-2/Ki-67 деңгейінің жоғарылауы сарқылу мен реттелудің бұзылуын көрсетеді. p53 деңгейінің төмендеуі апоптоз процесінің бұзылуын көрсетуі мүмкін.

Қорытынды: CMV ұрықтың тимус/көкбауыр морфологиясын және апоптоз/пролиферациясын айтарлықтай өзгертеді, Т-жасушаларының репертуарын және өзін-өзі төзімділігін бұзады, ұзақ мерзімді иммунологиялық салдардың дамуына ықпал етеді.

Түйінді сөздер: *CMV инфекциясы, ұрықтың тимусы, көкбауыр, Bcl-2, p53, Ki-67, апоптоз*

Дәйексөз үшін:

Милюшина Я.А., Есболатова Г.М. Аналық цитомегаловирус инфекциясының ұрықтың иммундық мүшелерінің дамуына әсері. Клиникалық жағдай // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 263-270. *doi 10.34689/SH.2025.27.6.030*

Introduction

Cytomegalovirus (CMV) is the causative agent of one of the most common viral infections in the world, which is usually asymptomatic in immunocompetent individuals. CMV is a DNA herpesvirus belonging to the family Herpesviridae, characterized by its ability to establish lifelong latency despite immune surveillance. Presently, CMV can be encountered in every fourth woman of childbearing age, with seroprevalence rates exceeding 80% in some populations [1, 2]. Cytomegalovirus represents one of the most significant causes of congenital infection globally, affecting approximately 0.5–2% of all live births, making it the leading infectious cause of congenital disease worldwide [3, 4, 5].

Clinical manifestations in infants with symptomatic congenital CMV infection at birth are present in only 5–10% of intrauterinely infected infants, though this represents a significant proportion of symptomatic disease. The clinical spectrum includes hepatosplenomegaly (75%), petechiae (65–80%), growth retardation (70%), jaundice (65%), microcephaly (45–50%), and periventricular calcification of the brain (45%) [6, 7]. Congenital CMV infection can affect virtually every organ system, including the thymus and spleen - primary and secondary lymphoid organs crucial for immune system development and function.

CMV has evolved sophisticated strategies to evade host immune responses and promote survival of infected cells. A fundamental survival strategy involves biphasic regulation of cellular Bcl-2 family proteins - key arbiters of mitochondrially-mediated apoptosis [8]. The immediate-early (IE) and early viral proteins of CMV directly counteract apoptotic pathways: IE2 protein binds to and suppresses the transcriptional functions of p53, a critical tumor suppressor and apoptosis inducer, while other viral proteins (pUL36 and pUL37) directly inhibit procaspase-8 and pro-apoptotic proteins (Bax and Bak), respectively [9, 10].

CMV-infected cells exhibit upregulation of anti-apoptotic Bcl-2 and transient elevation of Mcl-1, followed by sustained Bcl-2 expression, creating a permissive intracellular environment for viral replication [8]. This is accomplished through integrin signaling pathways, wherein viral envelope glycoproteins (particularly the pentameric gH/gL/UL128-131 complex) engage cellular integrins to trigger pro-survival signaling cascades.

The thymus represents a primary lymphoid organ essential for T-lymphocyte development and education. Thymic development begins as early as week 8 of human gestation, with organized cortical and medullary regions by the second trimester. The first T-lymphocytes emigrate from the fetal thymus and populate the periphery by 12–14 weeks of gestation [11]. Humans accomplish most T-cell development in utero, with a dramatic increase in thymic cellularity during the third trimester.

Congenital CMV infection elicits marked immune responses despite the typically underdeveloped neonatal immune system. Infected fetuses generate strong CD8+ T cell responses that can be detected as early as 22 weeks of gestation, with oligoclonal expansions of CMV-specific CD4+ T cells displaying a Th1 phenotype [12, 13]. However, these responses demonstrate functional exhaustion characterized by elevated expression of the inhibitory receptor PD-1, reduced production of IL-2 and other effector cytokines, and high frequencies of terminally differentiated CD57+ CD28– cells [14, 15].

The purpose of this clinical report description is to present morphological changes in fetal thymus and spleen in a case of CMV infection during pregnancy and to study the expression of apoptosis markers: bcl-2, p 53 and the cell proliferation marker ki-67 in the lymphoid component of the thymus and spleen of human fetuses with congenital CMV infection.

Materials and methods

The following is a case report of a 28-year-old woman with clinically and laboratory confirmed cytomegalovirus infection, who was in her fourth pregnancy and experienced a late spontaneous miscarriage at 23 weeks' gestation. Using autopsy material, we assessed the morphological characteristics of the fetal thymus gland and spleen (macroscopic parameters and microscopy). Immunohistochemical studies were performed with primary monoclonal antibodies to bcl-2 (Clone: 124 “DAKO”), p 53 (Clone: DO-7 “DAKO”), and ki-67 (Clone: MIB-1 “DAKO”). For immunostaining of the reaction products, the Kit LSAB2® System-HRP (“DAKO”) visualization system was used with the chromogen diaminobenzidine, which yielded a dark brown stain. Nuclei were counterstained with hematoxylin. The results of the immunohistochemical reaction were assessed using the semiquantitative Histo score method according to *McCarthy et al.* (1985).

Research Results:

Autopsy examination revealed enlarged thymic dimensions measuring 3.2 × 2.7 cm with weight of 3.15 g, exceeding age-appropriate norms for 23-week gestation [16]. This thymic enlargement represents a critical finding, as an infection may potentially leads to a reactive lymphoid hyperplasia or an inflammatory response that disrupts the normal maturation of the fetal immune system. Linear dimensions and weight of the fetal spleen were markedly elevated above age-appropriate norms for 23-week gestation, and compiled 1,7 × 3,3 cm with weight of 2.10 g, that means pronounced enlargement (splenomegaly).

Microscopic Architecture:

Microscopic examination of the thymus was conducted in accordance with and based on the "Algorithm for Assessment of Morphological Features of the Thymus" developed by *Professor Yu.V. Pruglo* (1996). A predominance of large lobules was observed, with a cortex-to-medulla ratio of 2:1. The stroma was poorly defined, congestive hyperemia was observed, and there was no decrease in the lymphocyte count in the cortex or medulla. A moderate number of medium-sized Hassall's stratified corpuscles was observed per lobule. The ratio of white to red pulp of the spleen in the CMV-infected fetus was 1:2, demonstrating a predominance of red pulp but with paradoxical sharp increase and activation of white pulp structures. Numerous small forming lymphoid follicles without clear boundaries between individual nodules were observed, with clusters of cells conspicuously present in the marginal zone - the specialized microenvironment separating white and red pulp compartments.

Immunohistochemical Analysis of Apoptosis and Proliferation Markers

Bcl-2 Expression: Immunohistochemical analysis using monoclonal antibodies against Bcl-2 (Clone 124, DAKO) revealed a positive immunohistochemical reaction manifested by cytoplasmic staining of lymphocytes, predominantly localized to the thymic medulla with fewer immunopositive cells detected in the cortex. Bcl-2 Expression in Splenic White Pulp: a positive immunohistochemical reaction to Bcl-2 was observed with cytoplasm staining of lymphocytes, predominantly localized to the marginal zone. (Fig1, Fig 2).

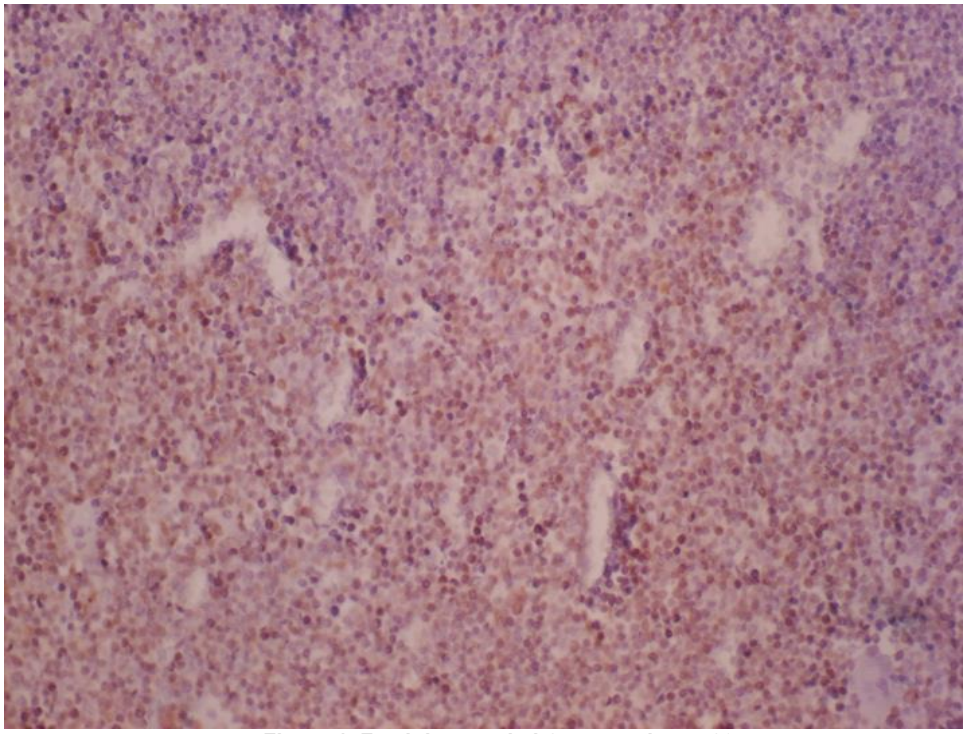


Figure 1. Fetal thymus, bcl-2 expression, x 20.

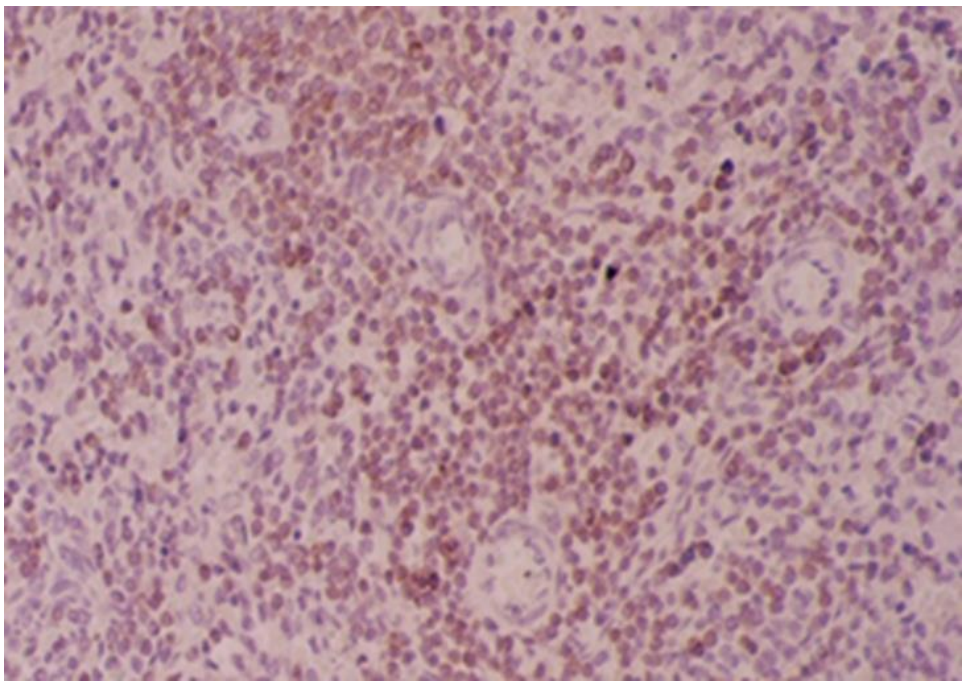


Figure 2. Fetal spleen, bcl-2 expression, x 20.

Ki-67 Expression:

Ki-67 expression was well expressed in lymphocytes in the cortex of the thymus, particularly pronounced in the subcapsular zone where early thymocyte precursors accumulate and proliferate. Ki-67 expression was pronounced in the periarterial lymphoid tissue (PALS) - the T-cell zones surrounding central splenic arteries. (Fig3, Fig 4).

p53 Expression: Expression of p53, the critical tumor suppressor and apoptosis-inducing transcription factor, was weakly positive in both cortical and medullary regions of the thymus (Fig5).

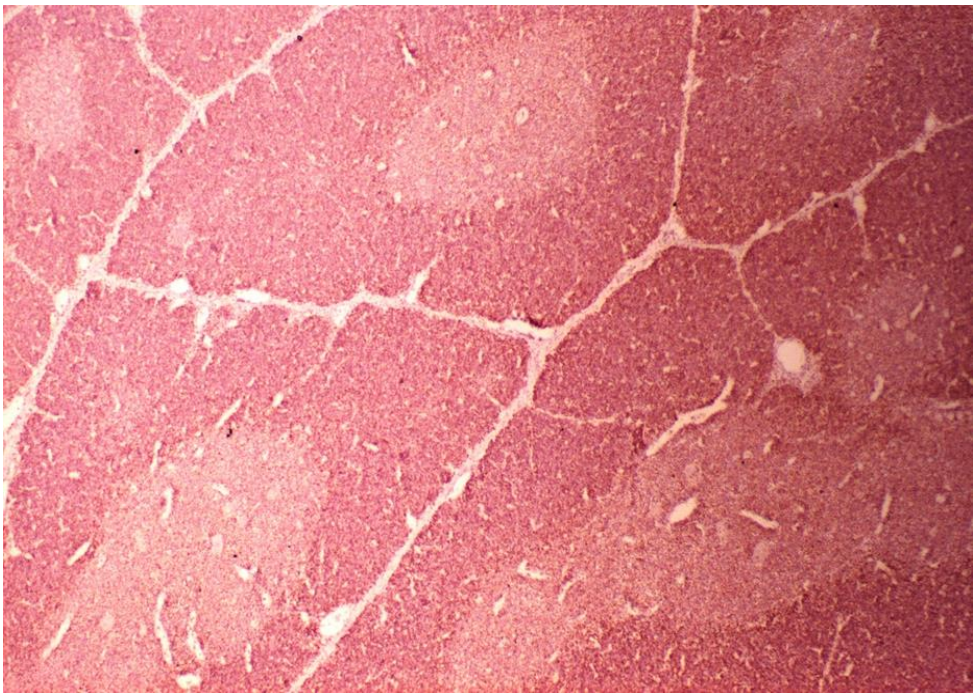


Figure 3. Fetal thymus, ki-67 expression, x 20.

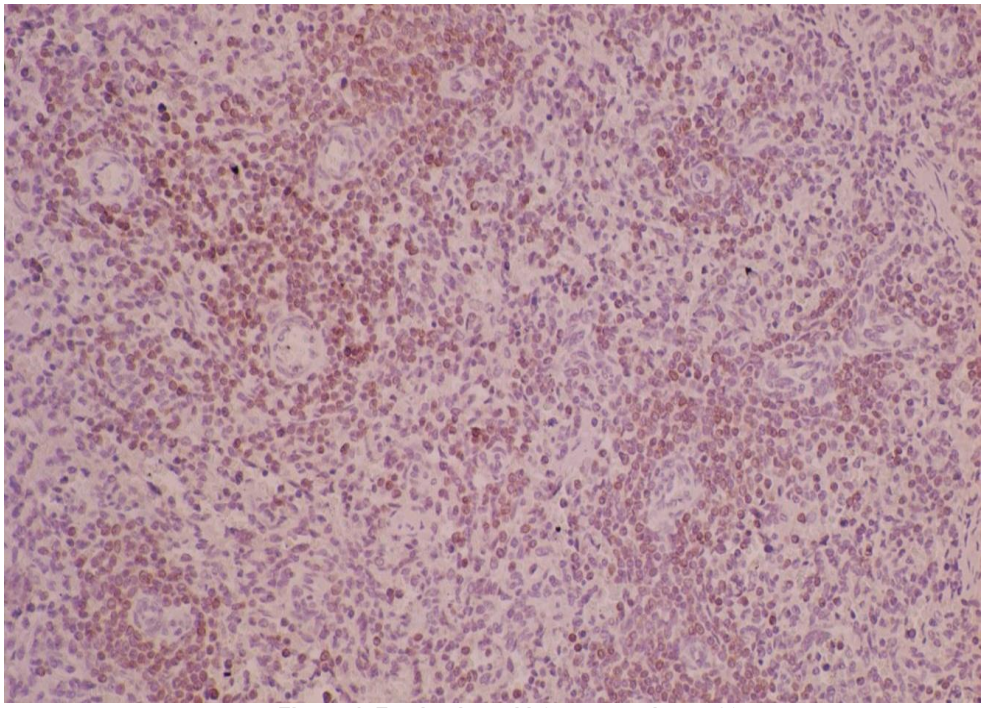


Figure 4. Fetal spleen, ki-67 expression, x 20.

Discussion

The macroscopic enlargement of the thymus in congenital CMV infection likely reflects a paradoxical response to infection: while the thymus normally exhibits involution (shrinkage) during systemic infection in older individuals, the developing fetal thymus may respond to viral infection with hyperplasia as an attempt to generate enhanced immune responses or alternatively due to infection-related disruption of normal developmental signals.

The splenomegaly represents one of the most common clinical signs of symptomatic congenital CMV infection, occurring in 75% of symptomatic neonates at birth.[50] The normal ratio white and res pulp at this gestational age is approximately 1:3, indicating relative expansion of white pulp in this infected specimen despite absolute increase in red pulp mass.

Detailed microscopic examination, conducted according to standardized morphological assessment algorithms, revealed significant architectural alterations compared to normal fetal thymus. This elevated cortex-to-medulla ratio indicates either relative expansion of the cortical (epithelial-rich) compartment or reduction of the medullary compartment.

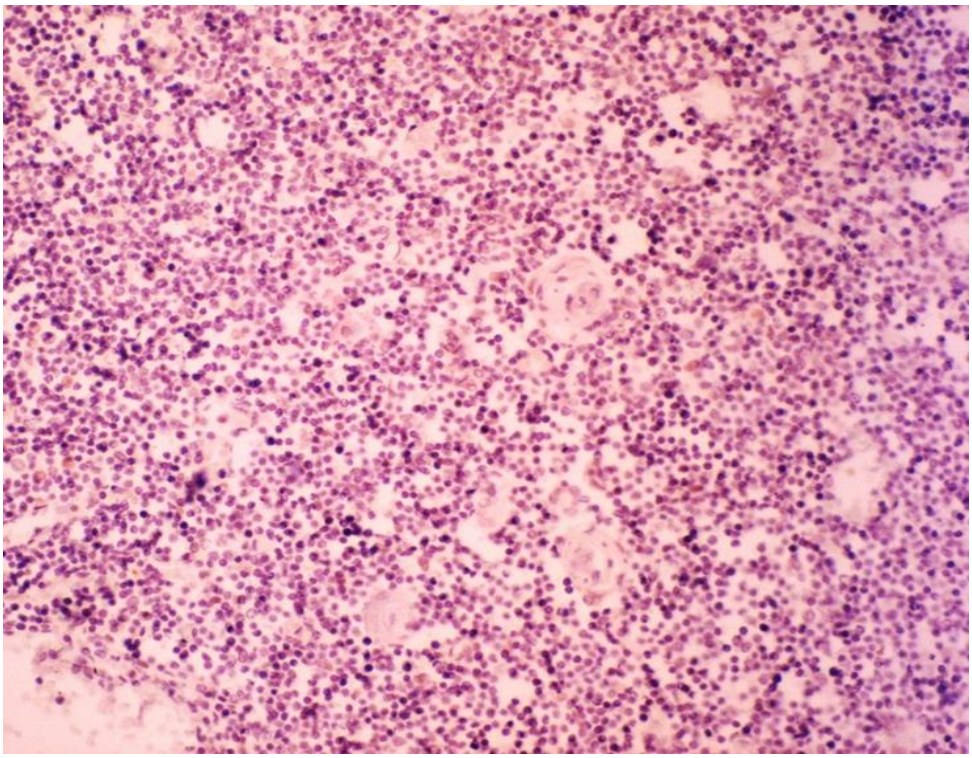


Figure 5. Fetal thymus, p 53 expression, x 20.

Critically, there was no decrease in lymphocyte count in either the cortex or medulla, distinguishing this case from classical viral-induced thymic atrophy characterized by rapid lymphocyte depletion. This preservation of lymphocyte numbers despite architectural distortion suggests that CMV primarily disturbs thymic epithelial organization rather than causing direct cytolytic elimination of thymocytes.

Hassall's corpuscles are aggregates of post-Aire differentiated medullary thymic epithelial cells (post-Aire mTECs), representing terminally differentiated epithelial structures that express thymic stromal lymphopoietin (TSLP) and contribute to the pro-inflammatory thymic microenvironment crucial for central tolerance induction [17]. The presence of intact Hassall's corpuscles, though numerically moderate, is notable, as severe viral infections can induce increased numbers of these structures and disarrangement of thymic epithelium.

The abnormal splenic architecture reflects profound splenic lymphoid hyperplasia in response to CMV infection. The white pulp comprises periarteriolar lymphatic sheaths (PALS) - T-cell zones surrounding central arteries - and lymphoid follicles containing B-lymphocytes [18]. Activation and proliferation of these white pulp structures indicates robust, albeit immature, splenic immune response to viral antigen.

The relative decrease in red pulp area, resulting primarily from a decrease in sinusoid volume, suggests that actively proliferating lymphoid tissue may have mechanically displaced normal erythrocyte-filtering capacity. The red pulp normally functions to filter erythrocytes and pathogens from circulating blood through open-ended capillaries lined with specialized endothelial cells and surrounded by reticular meshwork and resident macrophages. CMV infection results in marked disruption of normal splenic white and red pulp compartmentalization. The virus infects splenic stromal cells and endothelial cells, leading to transient reduction of CCL21 (a critical chemokine for splenic organization), which compromises the ability of lymphocytes to localize within appropriate T-cell zones [19].

The activation and expansion of marginal zone structures observed in this case likely represents early splenic immune response to CMV antigens: marginal zone macrophages and dendritic cells capture and present antigens to lymphocytes, initiating both innate and adaptive immune responses. However, the architectural disorganization suggests that CMV-induced inflammatory responses and cellular recruitment have overwhelmed normal splenic organization.

The distribution pattern of Bcl-2 expression has significant pathobiological implications.

Bcl-2, the founding member of the anti-apoptotic B-cell lymphoma family, prevents mitochondrial outer membrane permeabilization and caspase cascade activation, thereby blocking apoptosis through multiple mechanisms [20]. In normal thymic development, Bcl-2 expression is tightly regulated: DP thymocytes undergoing negative selection show low Bcl-2 expression, allowing apoptosis of autoreactive cells, while positively selected SP thymocytes and Tregs in the medulla express higher levels facilitating their survival [21].

The predominant medullary localization of Bcl-2 in this CMV-infected thymus raises important questions about how CMV affects thymic medullary development. CMV's known ability to upregulate Bcl-2 in infected cells suggests viral manipulation of medullary lymphocyte survival, potentially allowing survival of autoreactive or improperly selected thymocytes that would normally undergo apoptosis.

The preferential expression in marginal zones of the spleen is notable, as this compartment contains activated B

and T lymphocytes engaged in early immune responses. CMV-induced upregulation of Bcl-2 in marginal zone lymphocytes would promote survival of these activated cells, facilitating antibody production and cellular immune responses.

However, persistent Bcl-2 upregulation in the context of impaired p53 function could also prevent appropriate apoptosis of autoreactive or dysfunctional lymphoid cells, potentially contributing to abnormal splenic immune responses. The balance between protective anti-apoptotic signaling (facilitating anti-viral responses) and potential immune dysregulation (allowing autoreactive cell survival) represents a fundamental conflict during congenital CMV infection.

This weak p53 expression is consistent with CMV-mediated suppression of p53 functions through direct binding and transactivation inhibition by the viral IE2 protein, and potentially through other mechanisms [1, 22].

p53 normally functions as a critical regulator of selection processes in the thymus: in response to excessive TCR signaling or DNA damage signals, p53 triggers expression of pro-apoptotic Bcl-2 family members (Bax, PUMA, NOXA) and death receptors (Fas, TNF receptor), promoting apoptosis of improperly selected thymocytes [23]. The weak p53 expression observed in this case suggests impaired apoptosis signaling for eliminating autoreactive thymocytes, potentially contributing to abnormal T-cell repertoire generation.

Notably, CMV-mediated p53 suppression represents a fundamental molecular adaptation for persistent viral infection: p53-dependent apoptosis normally serves as an innate antiviral defense mechanism, inducing death of infected cells before productive viral replication completes. By suppressing p53, CMV promotes survival of infected cells and maximizes viral progeny production.

The combination of elevated Bcl-2 and reduced p53 activity creates a permissive intracellular environment markedly biased toward cell survival over apoptosis - a state beneficial for CMV replication but potentially harmful for normal thymic immune education processes.

The elevated Ki-67 expression in the cortex, particularly in subcapsular regions, suggests active proliferation of developing thymocytes despite architectural distortion. This is consistent with thymic hyperplasia (increased overall cell numbers and organ size) rather than thymic involution. The subcapsular zone normally contains cortical thymic epithelial cells and early CD4+CD8 – thymocyte precursors that have recently entered the thymus and are beginning TCR gene rearrangement and initial proliferation [24].

Elevated proliferation in this zone could reflect either: (1) normal developmental processes occurring despite concurrent infection, (2) compensatory proliferation attempting to replenish lymphocyte numbers lost to infection-induced apoptosis, or (3) CMV-driven proliferation of infected cells and recruited immune cells. CMV modulates cell cycle progression in infected cells to maximize availability of cellular DNA replication machinery, potentially affecting proliferation of infected thymic epithelial cells or resident myeloid cells within the thymus.

A central pathobiological consequence of CMV infection during thymic development is impairment of the critical thymic selection processes - positive and negative selection - that educate T lymphocytes and establish self-tolerance. CMV-induced disruption of thymic architecture, impaired p53-dependent apoptosis signaling for negative selection, and reduced capacity for generating regulatory T cells collectively impair thymic "learning."

PALS represent crucial sites of T-lymphocyte activation and proliferation in response to blood-borne antigens. The pronounced Ki-67 expression indicates active proliferation of splenic T lymphocytes, likely representing CMV-specific T cell responses attempting to control viral replication.

The enhanced proliferation in PALS regions is consistent with splenic CD8+ T cell expansion observed in congenital CMV infection, though these expanded T cells characteristically show reduced effector function due to T cell exhaustion mechanisms (PD-1+ expression, reduced IFN-γ and TNF-α production). The splenic CD8+ T cell response to CMV represents one of the few sites of robust adaptive immunity generation during congenital infection, likely aided by presentation of viral antigens by splenic dendritic cells and collaboration with maternal antibodies.

The profound effects of CMV on thymic and splenic development described in this case suggest significant disruption of adaptive immune system development.

Conclusion

This case of CMV infection during pregnancy with documented morphological changes in the fetal thymus and spleen illustrates the profound impact of this ubiquitous virus on developing immune organs. The enlarged thymus with preserved lymphocyte numbers but abnormal cortex-medulla ratio, combined with elevated anti-apoptotic Bcl-2 expression and reduced p53 function, suggests viral manipulation of thymic selection processes and impaired apoptosis signaling crucial for generating T-lymphocytes.

Similarly, the marked splenic white pulp hyperplasia with activation of marginal zone structures and pronounced Ki-67 expression in periarteriolar lymphoid tissue indicates vigorous splenic immune activation, yet compromised by architectural disorganization and likely functional exhaustion of CMV-specific lymphocytes.

At the molecular level, CMV-mediated modulation of BCL-2 family proteins (upregulated anti-apoptotic Bcl-2, downregulated pro-apoptotic functions) and suppression of p53 create a fundamentally altered cellular environment biased toward survival of infected cells and potentially dysregulated immune cells. This survival advantage for infected cells and impaired apoptosis of autoreactive or exhausted lymphocytes may explain the characteristic long-term sequelae of congenital CMV infection, particularly the persistent immunological dysfunction underlying susceptibility to secondary infections and late-appearing complications.

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INCA BONE AS A MORPHOLOGICAL PARAMETER IN THE FORENSIC IDENTIFICATION OF KAZAKH NATIONALITY PERSONS

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Abstract

Relevance: the article discusses the possibility of using Inca bones (os Incae) as an additional morphological parameter in the forensic identification by the skull of Kazakh nationality persons. It has been established that the frequency of occurrence of Inca bones in this population is low, however, this feature may be noticeable as an additional factor in identification algorithms.

Aim: to describe a clinical case of using a neural network model to analyze the morphometric parameters of the skull and their use in identifying the identity of a person of Kazakh nationality.

Research methods: This study is an observational one; no additional statistical data processing has been performed.

Discussion: The results of the study confirmed that the anatomical variability of the skull's occipital region is important for forensic identification. This feature reflects the features of the intertribal area's ossification, but does not have a strict racial diagnostic value. Nevertheless, the inclusion of the Inca bone as a morphological parameter in neural network identification algorithms increases the accuracy of ethnopopulation recognition. For the Kazakh population, characterized by a meso- and brachycranic type of skull with moderate occipital relief, the rare occurrence of this trait is consistent with Asian trends.

Conclusions: The Inca bone is rare in people of Kazakh nationality, which corresponds to the general trends for Asian populations. The feature can be used as an additional parameter for forensic identification by the skull. The integration of Inca bone data into neural network algorithms improves the accuracy of digital identity recognition.

Keywords: *Inca bone, forensic identification, skull, neural network model, Kazakh population, morphology.*

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Резюме

КОСТЬ ИНКОВ КАК МОРФОЛОГИЧЕСКИЙ ПАРАМЕТР ПРИ СУДЕБНО-МЕДИЦИНСКОЙ ИДЕНТИФИКАЦИИ ЛИЦ КАЗАХСКОЙ НАЦИОНАЛЬНОСТИ

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Актуальность: в статье рассматривается возможность использования кости Инков (os Incae) как дополнительного морфологического параметра при судебно-медицинской идентификации по черепу лиц казахской национальности. Установлено, что частота встречаемости кости Инков в данной популяции низкая, однако данный признак может быть полезен как дополнительный фактор в алгоритмах идентификации.

Цель: описать клинический случай применения нейросетевой модели для анализа морфометрических параметров черепа и их использования при отождествлении личности лица казахской национальности.

Методы исследования: Данное исследование является обсервационным, дополнительная статистическая обработка данных не проводилась.

Результаты исследования подтвердили, что анатомическая вариабельность затылочной области черепа имеет значение для судебно-медицинской идентификации. Данный признак отражает особенности окостенения межтеменной области, но не имеет строгого расово - диагностического значения. Тем не менее, включение кости Инков как морфологического параметра в алгоритмы нейросетевой идентификации повышает точность распознавания этнопопуляционной принадлежности. Для казахской популяции, характеризующейся мезо- и брахикранным типом черепа с умеренным затылочным рельефом, редкая встречаемость данного признака согласуется с азиатскими тенденциями.

Выводы: Кость Инков у лиц казахской национальности встречается редко, что соответствует общим тенденциям для азиатских популяций. Признак может быть использован как дополнительный параметр при судебно-медицинской идентификации по черепу. Интеграция данных о кости Инков в нейросетевые алгоритмы способствует повышению точности цифрового распознавания личности.

Ключевые слова: *кость Инков, судебно-медицинская идентификация, череп, нейросетевая модель, казахская популяция, морфология.*

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Түйіндеме

ИНКА СҮЙЕГІ ҚАЗАҚ ҰЛТЫ ТҰЛҒАЛАРЫН СОТ-МЕДИЦИНАЛЫҚ СӘЙКЕСТЕНДІРУ КЕЗІНДЕГІ МОРФОЛОГИЯЛЫҚ ПАРАМЕТР РЕТІНДЕ

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[3] Қазақстан Республикасы, Семей, Абай ауданының облыстық прокуратурасы.

Өзектілігі: мақалада Инка сүйегін (os Incae) ұлты қазақ адамдардың бас сүйегі бойынша сот-медициналық сәйкестендіру кезінде қосымша морфологиялық параметр ретінде пайдалану мүмкіндігі қарастырылады. Белгілі бір популяциядағы Инка сүйектерінің пайда болу жиілігі төмен екендігі анықталды, бірақ бұл белгі сәйкестендіру алгоритмдерінде қосымша фактор ретінде пайдалы болуы мүмкін.

Зерттеудің мақсаты: бас сүйегінің морфометриялық параметрлерін талдау және оларды қазақ ұлтының тұлғасын сәйкестендіру кезінде пайдалану үшін нейрондық желі моделін қолданудың клиникалық жағдайын сипаттау.

Зерттеу әдістері: бұл зерттеу бақылау болып табылады, деректерді қосымша статистикалық өңдеу жүргізілмеген.

Зерттеу нәтижелері бас сүйегінің желке аймағының анатомиялық өзгергіштігі сот-медициналық сәйкестендіруге әсер ететінін растады. Бұл белгі периодаралық аймақтың оссификациясының ерекшеліктерін

көрсетеді, бірақ қатаң нәсілдік диагностикалық маңызы жоқ. Дегенмен, нейрондық желіні сәйкестендіру алгоритмдеріне морфологиялық параметр ретінде Инка сүйегін қосу этнопопуляцияны тану дәлдігін арттырады. Бас сүйегінің мезо - және брахикрандық түрімен сипатталатын қазақ популяциясы үшін бұл белгінің сирек кездесуі азиялық тенденцияларға сәйкес келеді.

Қорытынды: ұлты қазақ адамдарда Инка сүйегі сирек кездеседі, бұл азиялық популяциялар үшін жалпы үрдістерге сәйкес келеді. Бұл белгіні бас сүйегінің сот-медициналық сәйкестендіруінде қосымша параметр ретінде пайдалануға болады. Инка сүйек деректерін нейрондық желі алгоритмдеріне біріктіру цифрлық тұлғаны тану дәлдігін арттыруға көмектеседі.

Түйінді сөздер: *Инка сүйегі, сот-медициналық сәйкестендіру, бас сүйек, нейрожелілік модель, қазақ халқы, морфология.*

Дәйексөз үшін:

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Relevance

Forensic identification of an individual based on bone remains is a difficult expert task, especially in the absence of personal data [15]. In Kazakhstan, as a multinational state, craniometric features may be important for determining the ethnicity of the remains [9,5].

Traditional identification methods include: Craniometric analysis: measurement of various cranial parameters to determine gender, age, and ethnicity. This method requires high qualifications and may be subject to subjective errors [5].

Craniofacial reconstruction: restoration of a lifetime appearance based on the structure of the skull. Both manual methods and computer technologies are used, but the accuracy of reconstruction depends on the specialist's experience and the quality of the source data [6].

Comparative morphological analysis: comparison of the skull with lifetime photographs or descriptions. This method also depends on subjective factors and the quality of the available materials [2].

Studies of the anthropological characteristics of skulls of various ethnic groups are important for correct identification. However, there is insufficient data in the available sources on the specific features of Kazakh skulls. This highlights the need for additional research aimed at studying the morphological and metric parameters of the skulls of the Kazakh population, which will improve the accuracy of identification in forensic practice. The Kazakh population is characterized by a mixed anthropological type, combining features of the Caucasoid and Mongoloid races [10]. Studies show the following features:

Skull shape: predominance of brachycephaly (short head) with rounded skull shape.

Facial skeleton: broad cheekbones, moderately prominent brow ridges, moderate prognathism (jaw protrusion).

Nasal region: relatively narrow nasal bone with a slight hump.

Orbital region: medium-sized eye sockets with a rounded or oval shape [1, 3].

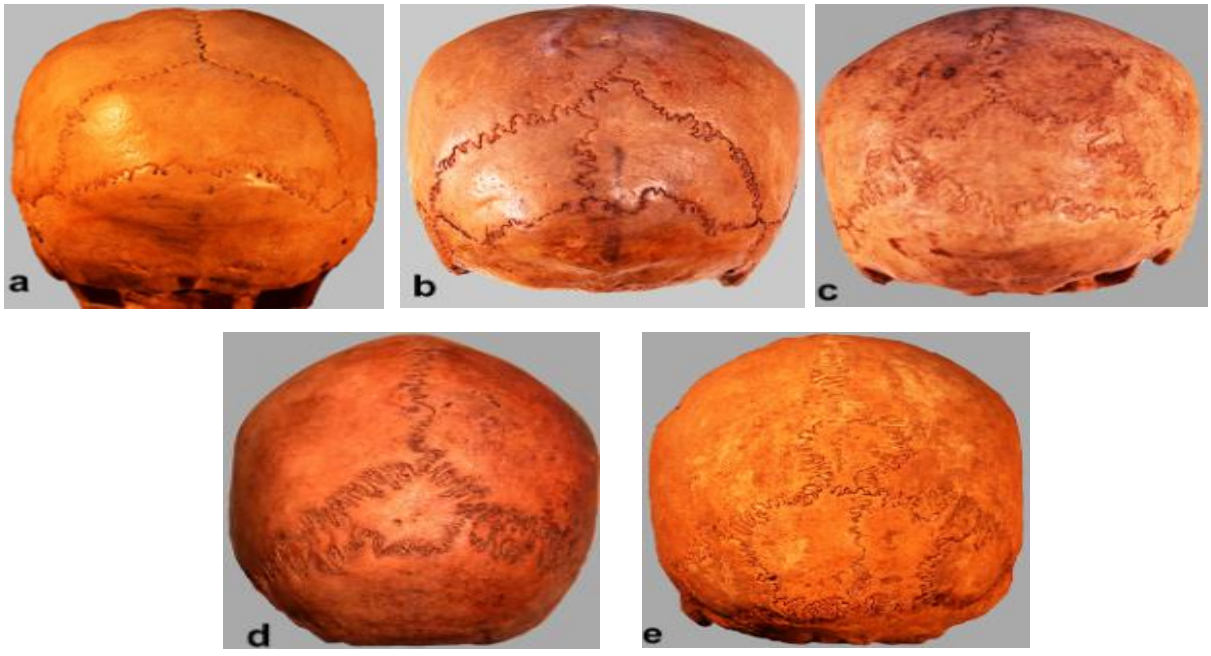


Figure 1. a) Complete Inca bone; b) bipartite Inca bone; c) Incomplete asymmetrical Inca bone; d) Incomplete symmetrical Inca bone; e) The quadripartite Inca bone and the pre-interparietal bone.

The forensic identification of a person during the examination of bone remains is based on a comprehensive assessment of the metric and non-metric features of the skull. In addition to traditional craniometric indicators, variant anatomical formations with individualizing value play an important role [14, 12]. One of these features is the Inca bone (Os incae), which is an additional bone element in the occipital region.

In modern scientific literature, the Inca bone is considered mainly in the context of physical anthropology, but its significance for forensic practice remains insufficiently studied, especially in relation to populations of Central Asia. The lack of systematic data on the frequency and morphological variants of Os incae in people of Kazakh nationality determines the relevance of this review [17].

The occipital bone is formed from several ossification centers, some of which are of membranous origin. Normally, in the process of postnatal development, their complete fusion occurs. When this process is disrupted, an inter - parietal bone is formed - the Inca bone, located between the parietal bones and the scales of the occipital bone in the area of the lambdoid suture [13,17].

From a morphological point of view, Os incae can be represented as a single bone plate, an asymmetric fragment, or a multipart formation. The variability of shape and size is due to the peculiarities of embryonic development and is probably genetically determined [14].

According to anthropological studies, the frequency of occurrence of Inca bones varies significantly in different populations. The greatest prevalence of this trait is noted among the indigenous peoples of Central and South America, where the frequency can reach 10-15% [14]. In populations of South Asia and the Middle East, the frequency of Os incae averages 1-4% [16, 11].

In European and North Asian populations, this indicator, as a rule, does not exceed 1-2% [14]. *Hanihara T. and Ishida H.* showed that the distribution of the Inca bone has a pronounced population character, which allows it to be considered as an additional ethnoanthropological marker [14].

In forensic medical practice, the Inca bone is important as a rare morphological feature that can be used to identify an individual. According to *Fujita M.Q. et al.,* the presence of Os incae can serve as an additional individualizing criterion when comparing antemortem and postmortem data, including the results of radiation research methods [12]. In addition, the Inca bone can mimic the fracture line of the occipital bone, which requires its differentiation from traumatic injuries during forensic examination [17, 7]. Taking this feature into account reduces the risk of diagnostic errors and increases the reliability of expert opinions.

Research methods: This study is an observational one, no additional statistical data processing has been performed.

Craniometric parameters were studied: the length and width of the skull, the craniality index, the shape of the occipital relief, and the variation of the intertribal region. Special attention was paid to the identification of the Inca bone (os Incae), an additional inter - parietal bone formed by incomplete fusion of the upper part of the occipital bone.

Aim: to describe a clinical case of using a neural network model to analyze the morphometric parameters of the skull and their use in identifying the identity of a person of Kazakh nationality.

A clinical case.

The circumstances of the receipt of the material

On November 09, 2022, skeletonized remains of a corpse were sent to the medical and forensic department of the branch of the RSE "Center for Forensic Examinations of the Ministry of Justice of the Republic of Kazakhstan" - the Institute of Forensic Examinations in the Abai region - for medical and forensic examination. The material was sent by a forensic medical expert. According to the direction, "On 11.08.2022, the duty station of the Zaton detention center received a message about the discovery of a human skull in the territory of the village of Karagaily."

The object of the study.

A human skull without soft tissues and articular cartilage was presented for the study. The skull is dry, brittle, yellow-brown in color, with pronounced signs of prolonged exposure to the ground. There was cracking and detachment of the outer bone plate, which indicated a significant age of burial.

Were missing:

- upper and lower jaws;
- mastoid processes;
- areas of the frontal, temporal and zygomatic bones;

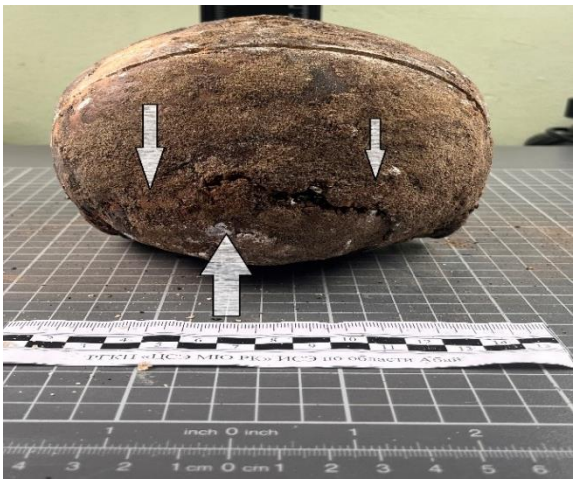


Figure 2. General view of the skull from behind before processing.

Research methods

During the examination, standard methods of medical and forensic examination were used:

- visual inspection;
- Measuring method;
- Stereomicroscopic examination;
- photographing;
- anatomical and morphological analysis.

The age was assessed according to the degree of obliteration of the skull sutures in accordance with classical forensic and anthropological methods.

Morphological features of the occipital region and the Inca bone

When examining the occipital region of the skull, pronounced features of the occipital suture formation were noted. The presence of an atypical configuration of bone structures in the area of the lambdoid suture suggests a variant development of the inter-parietal part of the occipital bone, which corresponds to the morphological features of the Inca bone (Os incae).



Figure 3. General view of the skull from above upon admission.

In conditions of partial fusion of the swept and occipital sutures, as well as the preservation of the metopic suture, the revealed feature acquires additional diagnostic significance. The Inca bone belongs to rare variant features and can be considered as a stable morphological marker, which is important for comparative analysis and identification.

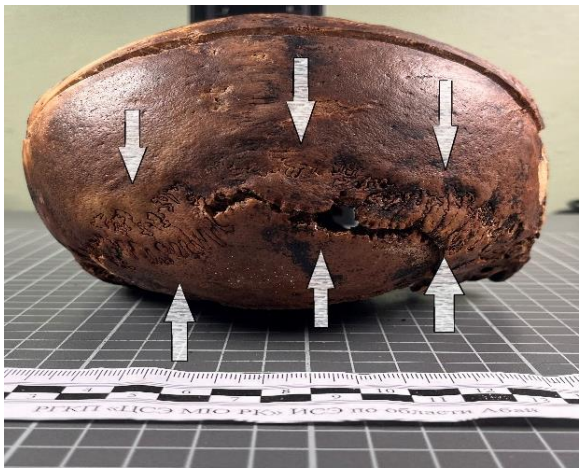


Figure 4. General view of the skull from behind after processing. The photograph shows the occipital region of the human skull with a variant configuration of bone structures in the area of the lambda suture. The arrows indicate the areas corresponding to the atypical development of the inter-parietal part of the occipital bone, which can be regarded as a manifestation of the Inca bone (Os incae)

Forensic medical assessment and the significance of the feature

In the presented clinical case:

• According to its anatomical and morphological features, the skull submitted for the study could belong to a male person of the Mongoloid race, the age of the skull was determined in the range of 30-40 years;

• the age of burial is estimated to be at least 25 years;



Figure 5. A detailed snapshot of the damaged and incomplete non-symmetrical Inca bone.

In such situations, the presence of variant anatomical formations, such as the Inca bone, can significantly increase the informative value of expert research. For the Kazakh population, characterized by a mixed anthropological type, consideration of such signs is especially relevant and requires further accumulation of clinical observations.

Discussion.

Inca bone is rarely considered in routine forensic practice, however, in conditions of limited identification data, it can serve as an additional morphological parameter. The presented clinical case demonstrates the expediency of including an analysis of the variant anatomy of the occipital region in the standard cranial examination protocol.

The formation of regional databases on the variant anatomy of the skull in persons of Kazakh nationality will in the future improve the accuracy of identification conclusions and expand the possibilities of forensic medicine.

Conclusions.

The presented clinical case confirms that the Inca bone can be considered as an additional morphological parameter in the forensic identification of a person. Given the limited amount of diagnostic features, consideration of variant cranial anatomy, including Os incae, is of practical importance and requires further systematic study in the population of Kazakhstan. Conducting targeted research among people of Kazakh nationality is a promising area for the further development of forensic medicine.

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