Online ISSN: 3007 – 0244
Print ISSN: 2410 – 4280
www.newjournal.ssmu.kz

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ ПРЕЗИДЕНТІНІҢ ЖАНЫНДАҒЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫ

Science & Healthcare

PEER-REVIEWED MEDICAL SCIENTIFIC JOURNAL

РЕЦЕНЗИРУЕМЫЙ МЕДИЦИНСКИЙ
НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ

Наука и Здравоохранение

Ғылым және Денсаулық Сақтау

РЕЦЕНЗИЯЛАНАТЫН МЕДИЦИНАЛЫҚ
ҒЫЛЫМИ-ПРАКТИКАЛЫҚ ЖУРНАЛ



Volume 27
Issue 4
2025

Министерство здравоохранения Республики Казахстан
Учредитель: НАО «Медицинский университет Семей»
Основан в 1999 году.

Журнал зарегистрирован в Министерстве информации и коммуникаций Республики Казахстан Комитете информации **№ 17773-Ж.**

Входит в Перечень изданий, рекомендуемых Комитетом по обеспечению качества в сфере науки и высшего образования МНиВО Республики Казахстан для публикации основных результатов научной деятельности **(Приказ №603 от 12.07.2024г.)**

Включен в **Ulrich's Periodicals Directory**, **Global Health, CAB Abstracts, InfoBase Index, Directory of Research Journals Indexing, Российский индекс научного цитирования (РИНЦ), E-library.ru, Cyberleninka.ru, Norwegian register for scientific journals (NSD), Всесоюзный институт научной и технической информации Российской академии наук (ВИНИТИ РАН), Ассоциацию CONEM, РАЦС, DataBase Indexing, ICI World of Journals, Crossref.**

Подписной индекс 74611
в каталоге «Казпочта»
Цена свободная

Сайт http://newjournal.ssmu.kz
e-mail: selnura@mail.ru

Адрес редакции:
071400, г. Семей
ул. Абая Кунанбаева, 103
контактный телефон:
(7222) 56-42-09 (вн. № 1054)
факс: (7222) 56-97-55

Выпускающий редактор:
Сапаргалиева Э.Ф.
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При цитировании материалов ссылка на журнал обязательна.

Отпечатано в типографии Медицинского университета Семей
Подписано в печать: 28.08.2025г.
Формат 60x90/8.
Печать цифровая. Усл.п.л 33,8
Тираж 500 экз., зак.189

Online ISSN: 3007 – 0244
Print ISSN: 2410 – 4280

НАУКА И ЗДРАВООХРАНЕНИЕ

РЕЦЕНЗИРУЕМЫЙ МЕДИЦИНСКИЙ НАУЧНО-ПРАКТИЧЕСКИЙ ЖУРНАЛ

Том 27 №4, 2025

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The Ministry of Healthcare of the Republic of Kazakhstan

Publisher: NCJSC «Semey Medical University»

Established in 1999

Journal is registered in Ministry of Information and Communication of the Republic of Kazakhstan in the Committee of Information. Certificate of registration of a periodical printed publication **№ 17773-Ж.**

The journal is included in the List of publications recommended by the Committee for Quality Assurance in the Field of Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan for the publication of the main results of scientific activity **(Order from 12.07.2024 №603)**

The journal is indexed in **Ulrich's Periodicals Directory**, **Global Health, CAB Abstracts, InfoBase Index, Directory of Research Journals Indexing, Russian Science Citation Index, Scientific electronic library E-library.ru, Cyberleninka.ru, NSD (Norwegian register for scientific journals), VINITI RAN, CONEM, RASS, DataBase Indexing, ICI World of Journals, Crossref.**

Subscription index in catalogue of "Kazpost" 74611

Open price.

Website http://newjournal.ssmu.kz

e-mail: selnura@mail.ru

Address of editor office and publisher:
071400, Semey, Abay st. 103,
Tel. (7222) 56-42-09 (in1054)
Fax: (7222) 56-97-55

Publishing editor:
Sapargaliyeva Einura

Translators:
Shuakbaeva Zhuldyz,
Konabekov Bakhytzhan

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In case of citation of materials, a link on the journal is required.

Printed by printing office of Semey medical university

Signed in press on August, 28, 2025

Format 60x90/8. 38,8 Digital printing.

Circulation 500 copies, ord. 189

Online ISSN: 3007 – 0244

Print ISSN: 2410 – 4280

SCIENCE & HEALTHCARE

PEER-REVIEWED SCIENTIFIC-PRACTICAL MEDICAL JOURNAL

Volume 27 №4, 2025

«Science & Healthcare» is a peer-reviewed scientific-practical medical journal, which publishes original articles, literature reviews, clinical case, short communications and conference reports covering all areas of clinical medicine and public health. The primary audience of the journal includes medical scientific community, practicing physicians, doctoral- and master - students in the fields of medicine and public health.

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Құрылтайшы: КеАҚ «Семей медицина университеті» 1999 негізі салынды

Журнал Қазақстан Республикасы ақпарат және комуникациялар министрлігі, Ақпарат комитетінде тіркелген. Мерзімді баспасөз басылымын есепке қою туралы куәлігі **№ 17773-Ж**

Журнал Ғылыми еңбектің негізгі нәтижелерін жариялау үшін Қазақстан Республикасы Ғылым және жоғары білім министрлігінің Ғылым және жоғары білім саласында сапаны қамтамасыз ету комитеті ұсынатын ғылыми басылымдар Тізбесіне кіреді (Бұйрық №603 12.07.2024ж.)

Ulrich's Periodicals Directory, Global Health, CAB Abstracts, InfoBase Index, Directory of Research Journals Indexing, Ғылыми дәйектеу Ресейлік индекс (РИНЦ), E-library.ru. - Ғылыми электронды кітапханаға, Cyberleninka.ru, NSD (Norwegian register for scientific journals), ВИНИТИ РАН, CONEM, РАЦС, DataBase Indexing, ICI World of Journals, Crossref енгізілді.

Каталогтағы жазылу индексі «Казпочта» 74611

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Сайт http://newjournal.ssmu.kz

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Баспаның және баспагердің мекен-жайы:
071400, Семей қаласы,
Абай көшесі, 103.
тел. (87222) 56-42-09 (ішкі 1054);
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Материалдарды дәйектеу кезінде журналға сілтеме жасау міндетті.

Семей медицина университетінің баспаханасында басылған

Баспаға қол қойылды 28.08.2025.
Формат 60x90/8. Баспа сандық.
Шартты-баспа парағы 38,8
Таралуы 500 дана. Зак.189

Online ISSN: 3007 – 0244
Print ISSN: 2410 – 4280

ҒЫЛЫМ ЖӘНЕ ДЕНСАУЛЫҚ САҚТАУ

РЕЦЕНЗИЯЛАНАТЫН МЕДИЦИНАЛЫҚ ҒЫЛЫМИ-ПРАКТИКАЛЫҚ ЖУРНАЛ

Том 27 №4, 2025

«Ғылым және денсаулық сақтау» журналы - рецензияланатын медициналық ғылыми-практикалық журнал, клиникалық медицина мен қоғамдық денсаулықпен байланысты бірегей зерттеулер нәтижелерін, әдеби шолуларды, кең шеңберлі сұрақтар бойынша конференциялар туралы қысқа мәлімдемелер мен есептерді жариялайды. Медициналық ғылыми қоғамдастық, тәжірибелік дәрігерлер, медицина мен қоғамдық денсаулық саласындағы докторанттар мен магистранттар журналдың негізгі оқырман аудиториясы болып табылады.

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ERRATUM

266-266 ***ИСПРАВЛЕНИЕ***

Received: 16 April 2025 / Accepted: 14 June 2025 / Published online: 29 August 2025

DOI 10.34689/SH.2025.27.4.001

UDC 616.1-036.22(574)

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REPROGRAMMING EXPERIENCE OF BLOOD MONONUCLEAR CELLS INTO INDUCED PLURIPOTENT STEM CELLS (IPSCS) IN A PATIENT WITH CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

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Abstract

Introduction. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a severe inherited arrhythmia linked to RYR2 mutations. CPVT is a major cause of sudden cardiac death in the young. Here we outline the experience of induced pluripotent stem cells (iPSCs) generation from a healthy donor and a patient with CPVT. By establishing iPSCs from affected individuals, this study can reveal mechanisms of disease pathophysiology and the potential of iPSC technology to develop cardiogenetic research and personalized medicine.

Aim. To investigate experimental methods used to generate and validate iPSCs derived from a healthy donor with wild-type RYR2 and a patient with RYR2 mutation.

Materials and methods. A 33-year-old female patient with CPVT was genetically screened using Sanger sequencing, revealing a de novo RYR2 mutation (c.13892A>T; p.D4631V). Peripheral blood mononuclear cells of a healthy donor and a patient were isolated by density gradient centrifugation and reprogrammed into iPSCs using the Sendai virus method. Cells were cultured under feeder-free conditions in Essential 8™ Flex medium. Pluripotency was confirmed via several methods, such as immunocytochemistry and G-banding karyotyping.

Results. The isolated cells showed optimal morphology, with cell colonies displaying smooth, well-defined edges and a rounded shape. The cells within the colonies were densely packed. Immunostaining confirmed the expression of the pluripotency marker TRA-1-60. Karyotype analysis revealed that all derived cell lines maintained stable chromosomal integrity.

Conclusions. iPSCs were successfully generated from a healthy donor to serve as a "control" for comparison with patient-derived iPSCs carrying a de novo heterozygous RYR2 mutation (c.13892A>T; p.D4631V). This iPSC-based model offers a valuable platform for investigating CPVT pathophysiology and testing potential therapeutic approaches.

Keywords: *iPSCs, CPVT, cardiac arrhythmia, mutation, disease modeling, personalized medicine*.

For citation:

Satvaldina N.N., Tolymbekova A., Rakhimova S.E., Abilova Zh.M., Akilzhanova A.R. Reprogramming experience of blood mononuclear cells into induced pluripotent stem cells (iPSCs) in a patient with catecholaminergic polymorphic ventricular tachycardia (CPVT) // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 7-13. doi 10.34689/SH.2025.27.4.001

Резюме

ОПЫТ РЕПРОГРАММИРОВАНИЯ МОНОНУКЛЕАРНЫХ КЛЕТОК КРОВИ В ИНДУЦИРОВАННЫЕ ПЛЮРИПОТЕНТНЫЕ СТВОЛОВЫЕ КЛЕТКИ (ИПСК) У ПАЦИЕНТА С КАТЕХОЛАМИНЕРГИЧЕСКОЙ ПОЛИМОРФНОЙ ЖЕЛУДОЧКОВОЙ ТАХИКАРДИЕЙ (КПЖТ)

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Введение. Катехоламинергическая полиморфная желудочковая тахикардия (КПЖТ) - это тяжелая наследственная аритмия, связанная с мутациями RYR2. КПЖТ — одна из основных причин внезапной сердечной смерти у молодых людей. Здесь мы описываем опыт генерации индуцированных плюрипотентных стволовых клеток (иПСК) от здорового донора и пациента с КПЖТ. Благодаря получению иПСК от пациентов это исследование может раскрыть механизмы патофизиологии заболевания и потенциал технологии иПСК для развития кардиогенетических исследований и персонализированной медицины.

Цель. Исследовать экспериментальные методы, используемые для создания и валидации иПСК, полученных от здорового донора с диким типом RYR2 и пациента с мутацией RYR2.

Материалы и методы. Пациентка 33 лет с КПЖТ прошла генетический скрининг с использованием секвенирования по Сэнгеру, выявив мутацию RYR2 de novo (c.13892A>T; p.D4631V). Мононуклеарные клетки периферической крови здорового донора и пациента были выделены центрифугированием в градиенте плотности и перепрограммированы в иПСК с использованием метода вируса Сендай. Клетки культивировались в условиях без фидера в среде Essential 8™ Flex. Плюрипотентность была подтверждена несколькими методами, такими как иммуноцитохимия и кариотипирование с G-бэндингом.

Результаты. Изолированные клетки продемонстрировали оптимальную морфологию, при этом клеточные колонии имели гладкие, четко очерченные края и округлую форму. Клетки внутри колоний были плотно упакованы. Иммуноокрашивание подтвердило экспрессию маркера плюрипотентности TRA-1-60. Анализ кариотипа показал, что все полученные линии клеток сохраняли стабильную хромосомную целостность.

Выводы. иПСК были успешно получены от здорового донора, чтобы служить «контролем» для сравнения с iPSC, полученными от пациента, несущими гетерозиготную мутацию RYR2 de novo (c.13892A>T; p.D4631V). Эта модель на основе иПСК предлагает ценную платформу для исследования патофизиологии КПЖТ и тестирования потенциальных терапевтических подходов.

Ключевые слова: *иПСК, КПЖТ, сердечная аритмия, мутация, моделирование заболеваний, персонализированная медицина.*

Для цитирования:

Сатвалдина Н.Н., Толымбекова А., Рахимова С.Е., Абилова Ж.М., Акильжанова А.Р. Опыт репрограммирования мононуклеарных клеток крови в индуцированные плюрипотентные стволовые клетки (иПСК) у пациента с катехоламинергической полиморфной желудочковой тахикардией (КПЖТ) // Наука и Здравоохранение. 2025. Т.27 (4), С. 7-13. doi: 10.34689/SH.2025.27.4.001

Түйіндеме

КАТЕХОЛАМИНЕРГИЯЛЫҚ ПОЛИМОРФТЫ ҚАРЫНШАЛЫҚ ТАХИКАРДИЯ (КПҚТ) БАР НАУҚАСТЫҢ ҚАН МОНОНУКЛЕАРЛЫ ЖАСУШАЛАРЫН ИНДУКЦИЯЛАНҒАН ПЛЮРИПОТЕНТТІ ДІҢ ЖАСУШАЛАРЫНА (ИПДЖ) ҚАЙТА БАҒДАРЛАМАЛАУ ТӘЖІРИБЕСІ

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Кіріспе. Катехоламинергиялық полиморфты қарыншалық тахикардия (КПҚТ) RYR2 мутацияларымен байланысты ауыр тұқым қуалайтын аритмия болып табылады. КПҚТ жас ересектердегі кенеттен жүрек өлімінің негізгі себебі болып табылады. Мұнда біз сау донордан және КПҚТ бар науқастан индукцияланған плюрипотентті дің жасушаларын (иПДЖ) генерациялау тәжірибемізді баяндаймыз. Зардап шеккен адамдардан иПДЖ алу арқылы бұл зерттеу аурудың патомеханизмдері туралы түсінік бере алады және иПДЖ технологиясының кардиогенетикалық зерттеулер мен дербес медицинаны дамыту мүмкіндігін көрсетеді.

Мақсаты. Жабайы типті RYR2 бар сау донордан және RYR2 мутациясы бар науқастан алынған иПДЖ генерациялау және тексеру үшін қолданылатын эксперименттік әдістерді зерттеу.

Материалдар мен әдістер. КПҚТ-мен ауыратын 33 жастағы әйел науқаста Сэнгер секвенирлеу арқылы генетикалық скрининг нәтижесінде жаңа RYR2 мутациясы анықталды (c.13892A>T; p.D4631V). Дені сау донор мен пациенттен алынған перифериялық қан мононуклеарлы жасушалары градиенті центрифугалау арқылы бөліп алынып, Сендай вирусы әдісімен иПДЖ-ға қайта бағдарламаланды. Жасушалар Essential 8™ Flex ортасында фидерсіз жағдайда өсірілді. Плюрипотенттілігі иммуноцитохимия және G-бэнд кариотиптеу сияқты әдістермен расталды.

Нәтижелері. Жасушалар оңтайлы морфологияны көрсетті, жасуша колониялары тегіс, шеттері анық және дөңгелек пішінді. Колониялардағы жасушалар тығыз орналасқан. Иммуноцитохимия әдісі TRA-1-60 плюрипотентті маркердің экспрессиясын көрсетті. Кариотиптік талдау барлық жасуша линиялары тұрақты хромосомалық тұтастықты сақтайтынын көрсетті.

Қорытынды. иПДЖ-да жаңа гетерозиготалы RYR2 мутациясы (c.13892A>T; p.D4631V) бар пациенттен алынған иПДЖ-мен салыстыру үшін «бақылау» ретінде қолдану үшін сау донордан сәтті алынды. Бұл иПДЖ негізіндегі модель КПҚТ патофизиологиясын зерттеу және ықтималды емдік әдістерді сынау үшін құнды платформаны ұсынады.

Түйін сөздер: *иПДЖ, КПҚТ, жүрек аритмиясы, мутация, ауруды модельдеу, дербес медицина.*

Дәйексөз үшін:

Сатвалдина Н.Н., Толымбекова А., Рахимова С.Е., Абилова Ж.М., Акильжанова А.Р. Катехоламинергиялық полиморфты қарыншалық тахикардия (КПҚТ) бар науқастың қан мононуклеарлы жасушаларын индукцияланған плюрипотентті дің жасушаларына (иПДЖ) қайта бағдарламалау тәжірибесі // Ғылым және Денсаулық. 2025. Т.27 (4), Б. 7–13. doi: 10.34689/SH.2025.27.4.001

Introduction

Primary electrical heart disorders (PED), also referred as cardiac channelopathies, are a group of inherited genetic conditions that affect the electrical activity of cardiomyocytes. PED includes various diseases such as long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome, early repolarization syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and idiopathic ventricular fibrillation [1]. One of the deleterious consequences of PED may be sudden cardiac death, especially in young individuals. According to the World Health Organization (WHO) sudden cardiac death is an unexpected death that occurs within the first 1 hour of symptom onset. The genetic basis of the disease includes specific rare mutations in genes encoding cardiac ion channels or their subunits. Mutations in ion channel genes include sodium, potassium, calcium channels, and mutations in regulatory proteins [2]. CPVT is an extremely severe type of inherited arrhythmia characterized by a typically normal electrocardiogram (ECG) and triggered by physical or emotional stress. The main arrhythmogenic mechanism consists of unusual calcium release from the sarcoplasmic reticulum (SR). In a healthy heart, calcium (Ca^{2+}) transients occur following the initiation of an action potential, as calcium influx through L-type calcium channels triggers calcium release from the SR. In contrast, in CPVT, mutations in the associated genes alter the function of the encoded proteins, resulting in spontaneous Ca^{2+} transients [3]. CPVT is marked by sudden cardiac arrest and accounts for nearly 15% of sudden cardiac deaths in young individuals. If left undiagnosed, it is highly fatal, with a mortality rate reaching up to 50% by the age of 35. The main disease-causing gene, which occurs in approximately 60-70% of patients with CPVT is the gene encoding ryanodine receptor 2 (RYR2). Most RYR2 mutations are missense variants that result in the accumulation of calcium and its sudden release into the cytoplasm. Such release triggers delayed afterdepolarizations, leading to ventricular arrhythmias. Genetic analysis revealed other mutations in genes like CASQ2, TRDN, TECRL, KCNJ1, CALM1, CALM2, CALM3, SCN5A, PKP2, and ANK2, but their prevalence is less than 5% [4]. In the frame of our previous research projects, we studied 35 patients, 33 of whom were diagnosed with idiopathic ventricular tachycardia by mutations in the RYR2 gene. We observed a novel heterozygous missense mutation in the RYR2 gene (c.13892A>T; p.D4631V; case #239) with high pathogenic potential (high in-silico, de-novo prediction scores, reference databases negative) in a patient with classic clinical features of CPVT. The de novo penetrance of this variant should be considered high due to the early age of onset, characteristic, and severe clinical course [5]. It is challenging to functionally prove the relationship of such deleterious mutations with the phenotypic manifestations of the disease. Only patient-specific models in inherited cardiac diseases may partially unveil the mechanism of disease formation and progression. Induced pluripotent stem cell (iPSC) technology may serve as a promising tool for mirroring a patient's genetic blueprint.

The development of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka in 2006 marked a groundbreaking achievement, made possible by the collective contributions of past and present researchers in related scientific fields [6]. Human induced pluripotent stem cell (hiPSC) technology has advanced significantly since Yamanaka and colleagues first demonstrated that human fibroblasts could be reprogrammed by the forced expression of four transcription factors: octamer-binding protein 3/4 (OCT3/4; also known as POU5F1), SOX2, c-MYC (Myc proto-oncogene protein), and Krüppel-like factor 4 (KLF4). This pioneering method was subsequently validated by other research groups, either using the same set of factors or modified versions. Like human embryonic stem cells (hESCs), hiPSCs exhibit the key properties of self-renewal and pluripotency, enabling differentiation into derivatives of all three germ layers. Unlike hESCs, however, hiPSCs are generated without the use of human embryos, thereby avoiding many of the ethical controversies that have historically impeded hESC research. Additionally, because hiPSCs can be derived from individual patients, they retain unique genomic characteristics, making them valuable for modeling patient-specific disease phenotypes [7-10].

This article **aims** to summarize the experimental methodologies employed in the generation and characterization of iPSCs derived from a healthy donor and a patient exhibiting a CPVT phenotype. Within the scope of this article, we wanted to share our experience in the

implementation of this complex but promising technology in the field of cardiogenetics with the scientific community of Kazakhstan. We are pioneering the use of iPSC technology in Kazakhstan, with the expectation that it will contribute to the advancement of personalized medicine in the field of cardiovascular disorders.

Materials and methods

CPVT case and genetic analysis

The research was performed in accordance with the principles of the Declaration of Helsinki. The research protocol was approved at a meeting of the Local Ethics Committee of the Private Institution "National Laboratory Astana", protocol No. 05-2022 dated 10.21.2022. Informed written consent was obtained from the participant. The CPVT case included a 33-year-old female individual. The onset of symptoms occurred at the age of 13, characterized by recurrent episodes of syncope and the emergence of distinctive ECG patterns, including mono- and polymorphic ventricular premature beats, which progressed to bidirectional ventricular tachycardia and episodes of polymorphic ventricular tachycardia. We performed Sanger sequencing of hot-spot regions of the RYR2 gene for this patient. Our targeted genomic sequencing revealed de-novo heterozygous missense RYR2 mutation (c.13892A>T; p.D4631V) in a 33-year-old female patient with CPVT.

Isolation of peripheral blood mononuclear cells (PBMC)

PBMCs were isolated from whole blood using a density gradient centrifugation method with Histopaque-1077 (Sigma-Aldrich). Briefly, the blood was diluted with PBS and layered carefully over Histopaque-1077, followed by centrifugation at 400 × g for 30 minutes at room temperature without brake. The mononuclear cell layer was collected, washed twice with PBS, and centrifuged to remove platelets and residual plasma. The isolated PBMCs were counted, viability assessed, and the cells were either used immediately for reprogramming or cryopreserved in freezing medium containing 10% DMSO and FBS.

Reprogramming of PBMC

Peripheral blood mononuclear cells (PBMCs) were reprogrammed into induced pluripotent stem cells (iPSCs) using the CytoTune™-iPS 2.0 Sendai Reprogramming Kit (Life Technologies). After isolation, PBMCs were cultured in StemPro™-34 medium (Life Technologies) supplemented with cytokines to promote cell expansion and viability. On day 4, cells were transduced with Sendai virus vectors encoding the reprogramming factors OCT4, SOX2, KLF4, and c-MYC at a multiplicity of infection (MOI) of 7:7:7, respectively. The transduction was performed in 24-well plates and centrifuged at 750 × g for 45 minutes. Following transduction, cells were maintained in the same medium for an additional 2 days. On day 6, transduced cells were transferred onto Matrigel-coated 6-well plates. Media were changed, and emerging iPSC colonies were manually picked between days 18–21 and cultured in Essential 8™ medium (Life Technologies) under feeder-free conditions. All procedures were performed under sterile conditions.

Immunocytochemistry (ICC)

For pluripotency marker analysis, fixed iPSC were stained using immunocytochemistry. The TRA-1-60 Alexa Fluor™ 488 antibody (Life Technologies) was diluted 1:50 and added to the cell culture medium. Then incubated with the diluted antibody solution at 37°C for 30 minutes in a humidified incubator with 5% CO_2. Following incubation, cells were gently washed three times with FluoroBrite DMEM to remove unbound antibody. Imaging was performed using a Celena X fluorescence microscope to confirm the expression of pluripotency markers.

Karyotyping

To check chromosomal stability, iPSCs were subjected to G-banding karyotyping. Cells were treated with colcemid to arrest them in metaphase, followed by hypotonic treatment with 0.075 M KCl. After fixation with methanol:acetic acid (3:1), cells were dropped onto chilled slides and air-dried. Slides were stained with Giemsa and analyzed under a microscope to determine karyotypic stability.

Results

Peripheral blood mononuclear cells (PBMCs) were successfully isolated using Histopaque-1077–based density gradient centrifugation method, which was selected as the optimized protocol due to its improved yield, clarity of cell layer separation, and processing efficiency. In this method, whole blood was diluted 1:1 with sterile PBS and gently layered onto Histopaque-1077, followed by centrifugation at 400 × g for 30 minutes at room temperature without brake. This approach resulted in a well-defined buffy coat layer containing PBMCs. Following two rounds of washing with PBS and centrifugation at 250 × g for 10 minutes, cells exhibited high viability, minimal erythrocyte contamination, and formed a clean pellet. The simplified layering technique and avoidance of mechanical disruption helped preserve cell morphology and integrity. Overall, the optimized method provided good results in terms of PBMC purity, yield, and ease of isolation, and was therefore selected for subsequent experiments. Peripheral blood mononuclear cells (PBMCs) were successfully reprogrammed into induced pluripotent stem cells (iPSCs) using Sendai virus vectors, which demonstrated efficiency, reproducibility, and cell viability. In this reprogramming method, freshly isolated PBMCs were cultured in a defined medium without prior cell-type selection, and transduced directly with Sendai virus vectors carrying the Yamanaka factors. Colonies with typical iPSC morphology emerged between days 18–21, and were manually picked for expansion. This method required minimal manipulation, allowing for a workflow with reduced handling time and lower contamination risk. Furthermore, the use of Essential 8 medium under feeder-free conditions supported robust colony growth and maintenance of the TRA-1-60 pluripotency marker. Overall, the modified protocol of reprogramming proved to be more efficient and practical, yielding a higher reprogramming success rate and healthier iPSC colonies suitable for downstream applications such as disease modeling and cardiomyocyte differentiation. Therefore, this method was selected as the optimized reprogramming approach in our study. As a result of reprogramming, we were able to obtain iPSC colonies with good morphology, well-defined edges, and shape (Fig.1). As a validation, we stained iPSCs with the pluripotency marker TRA-1-60 and identified expression of the marker under the fluorescent microscope (Fig.2). Moreover, karyotype examination of iPSCs showed stable chromosomal integrity (Fig.3).

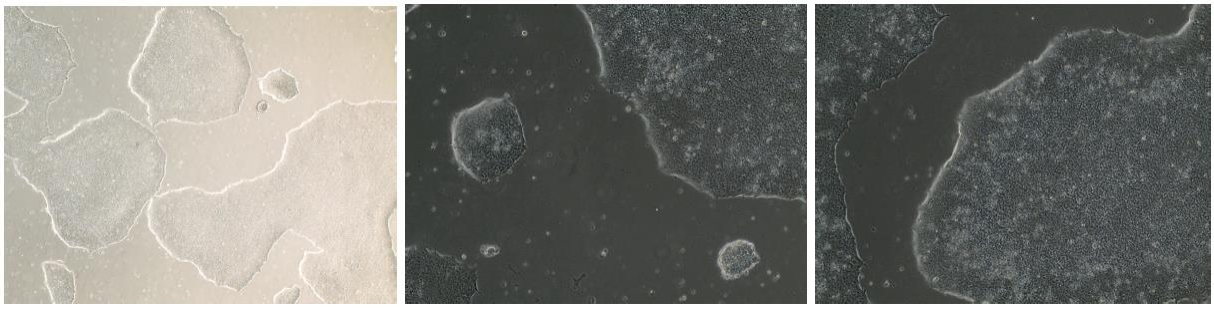


Figure 1. Stable induced pluripotent stem cells with optimal morphology.

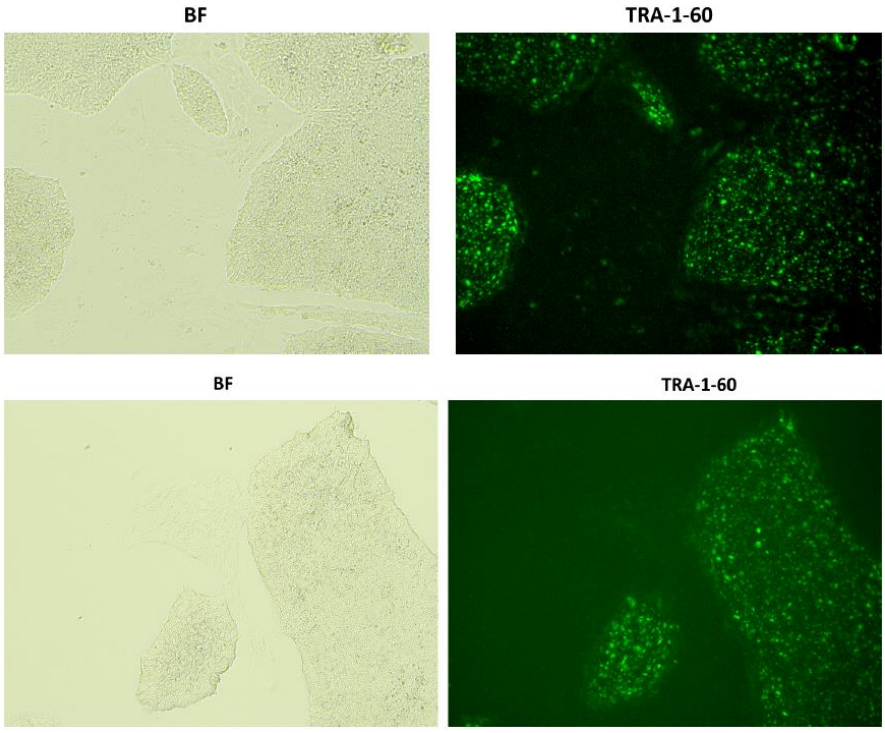


Figure 2. Immunocytochemistry of iPSCs for TRA-1-60 pluripotency marker.

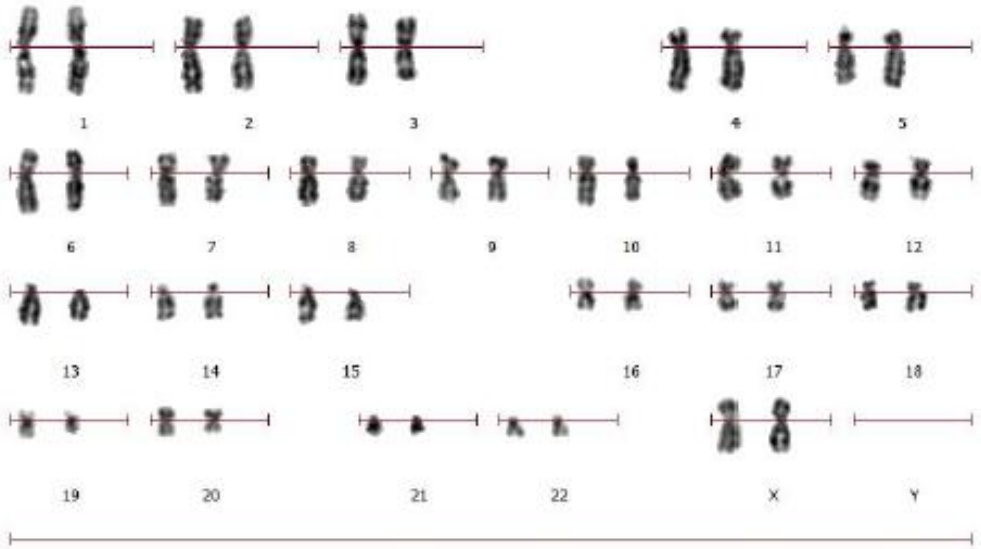


Figure 3. Karyotyping analysis of iPSCs.

Discussion

Primary electrical cardiac disorders or channelopathies are inherited genetic disorders affecting the electrical activity of cardiomyocytes, posing a risk of malignant arrhythmias that can result in sudden cardiac death. Channelopathies include heterogeneous diseases such as long QT syndrome (LQTS), short QT syndrome (SQTS), idiopathic ventricular fibrillation (IVF), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and early repolarization syndromes (ERS). CPVT is commonly linked to

mutations in genes involved in calcium handling within cardiac cells, such as the ryanodine receptor gene (RYR2) and the calsequestrin gene (CASQ2). If left untreated, CPVT carries a high risk of mortality, with around 30% of affected individuals experiencing at least one cardiac arrest and up to 80% suffering one or more syncopal episodes. In some cases, sudden death may be the initial presentation of the disease [11,12]. According to the guideline of European Society of Cardiology, "upgrade of genetic counseling and testing" is in the list of 10 novel key aspects of management of ventricular arrhythmias and prevention of sudden cardiac death. Future advancements in the evaluation of genetic variants are essential, as the number of variants of uncertain significance (VUS) and likely pathogenic variants continues to grow with the increasing use of genetic testing [13]. A number of specific genes have been strongly implicated in the pathophysiology of channelopathies. However, not all genetic variants within these genes are well characterized, especially those classified as VUS. From a fundamental research perspective, the underlying disease mechanisms are yet to be elucidated. In these terms, disease modeling tools such as induced pluripotent stem cell-derived cardiomyocytes can serve as an appropriate technology for studying the molecular basis of the disease. Here, we report the successful generation of induced pluripotent stem cells (iPSCs) from a healthy donor to serve as a control in disease modeling of catecholaminergic polymorphic ventricular tachycardia (CPVT). The induction of iPSCs from peripheral blood mononuclear cells (PBMCs) using the Sendai virus reprogramming method demonstrated efficiency and reproducibility. The colonies displayed classical iPSC morphology, expressed the pluripotency marker TRA-1-60, and maintained normal karyotype stability. These findings are consistent with previous reports indicating the efficacy of Sendai virus-based reprogramming systems in generating integration-free, pluripotent stem cells with reliability for downstream applications [14-16]. The case of the CPVT patient carrying a de novo heterozygous missense mutation in the RYR2 gene (c.13892A>T; p.D4631V) provides an opportunity to reveal pathogenic mechanisms associated with RYR2 dysfunction. RYR2 is a tetrameric protein embedded in the membrane of the sarcoplasmic reticulum (SR), where it facilitates ion release during systole. It is tethered to calsequestrin-2 (CASQ2) through associated regulatory proteins. The pathophysiology of CPVT is characterized by impaired calcium homeostasis resulting from mutations in critical calcium-handling proteins, such as RYR2 and CASQ2 [17,18]. As a rare but fatal arrhythmia with a normal resting ECG, CPVT represents significant diagnostic and therapeutic challenges. Therefore, an induced pluripotent stem cell (iPSC)-based model derived from the patient's genetic background may serve as a valuable platform for investigating the mechanisms underlying arrhythmia onset, disturbances in calcium handling, and individualized responses to pharmacological interventions [19,20].

Future differentiation of both control and mutant iPSC lines into cardiomyocytes will enable electrophysiological assessments and calcium imaging studies, providing functional validation of the disease phenotype and response to candidate drugs. Such patient-specific cardiomyocytes may also uncover genotype–phenotype relationships, contributing to improved risk stratification.

Conclusion

This study reports the successful generation of induced pluripotent stem cells (iPSCs) from a healthy donor, which will further be used as a "control" sample to compare it with the patient's iPSCs carrying RYR2 mutation. Currently, generation of iPSCs from patient with CPVT, carrying a de novo heterozygous missense mutation in the RYR2 gene (c.13892A>T; p.D4631V) is ongoing. This iPSCs model provides a valuable platform for studying the pathophysiology of CPVT and evaluating potential therapeutic interventions. Further experiments will be conducted to obtain patient-derived cardiomyocytes and assess their electrophysiological responses, calcium handling, and contractile functions.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

Funding: *This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grants AP19677442; AP23490249; BR24993023; BR24992841); and Nazarbayev University funding CRP grant 211123CRP1608.*

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Received: 16 April 2025 / Accepted: 14 June 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.002

UDC 614.2:575.17

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EXPERIENCE OF LONG-TERM OBSERVATION OF AN EXPOSED POPULATION: LESSONS FOR REGIONAL HEALTH MONITORING PROGRAMS

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Abstract

Background. Over two decades of medical observation have been conducted among residents living near the Semipalatinsk Nuclear Test Site, an area affected by chronic exposure to ionizing radiation. This study focuses on thyroid diseases, which are known to be among the most radiosensitive conditions following nuclear fallout.

Materials and Methods. A cohort of 3,240 individuals who underwent thyroid ultrasound examinations between 1998 and 2002 was selected for long-term follow-up. Vital status, clinical diagnoses, and registry data were regularly updated. In 2023–2024, a detailed questionnaire was administered to 1,099 surviving participants to evaluate lifestyle, behavioral, and reproductive risk factors. Individual thyroid radiation doses were retrospectively estimated based on age at exposure, place of residence, and dietary patterns.

Results. The overall prevalence of thyroid disorders reached 63%, with 33% of respondents reporting the use of hormone replacement therapy. The highest rates were observed among individuals with reconstructed thyroid doses in the range of 100–300 mGy. The integration of survey findings with clinical and dosimetric data allowed for a more comprehensive understanding of dose-dependent health effects.

Conclusion. The results confirm the long-term impact of low-to-moderate radiation exposure on thyroid health and support the importance of integrated health monitoring approaches. This experience offers practical lessons for developing regional health surveillance systems in other chronically exposed populations.

Keywords*: radiation exposure, health monitoring, thyroid gland, Semipalatinsk Nuclear Test Site, cohort study.*

For citation:

Apsalikov K.N., Massabayeva M.R., Lipikhina A.V., Tokanov A.M., Brait Yu.Y., Konovalova F.V., Mansarina A.E. Experience of long-term observation of an exposed population: lessons for regional health monitoring programs // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 14-20. *doi 10.34689/SH.2025.27.4.002*

Резюме

ОПЫТ МНОГОЛЕТНЕГО НАБЛЮДЕНИЯ ЗА ПОСТРАДАВШЕЙ ПОПУЛЯЦИЕЙ УРОКИ ДЛЯ РЕГИОНАЛЬНЫХ ПРОГРАММ МОНИТОРИНГА ЗДОРОВЬЯ

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Введение. На протяжении более 20 лет проводился мониторинг состояния здоровья населения, проживающего в районах, прилегающих к Семипалатинскому испытательному полигону. Основное внимание уделено заболеваниям щитовидной железы как органа, особенно чувствительного к радиационному воздействию.

Материалы и методы. В исследование включена когорта из 3240 человек, прошедших ультразвуковое обследование щитовидной железы в 1998–2002 годах. Сбор клинических данных, информации о vital-статусе и результатах диспансерного наблюдения продолжался в течение всего периода. В 2023–2024 гг. было проведено анкетирование 1099 живых участников для оценки поведенческих и репродуктивных факторов. Индивидуальные дозы облучения щитовидной железы были реконструированы с учетом возраста на момент воздействия, места проживания и особенностей питания.

Результаты. У 63% опрошенных ранее диагностированы заболевания щитовидной железы, 33% получали гормональную терапию. Наибольшая распространенность патологии отмечена среди лиц с реконструированной дозой облучения 100–300 мГр. Объединение анкетных, клинических и дозиметрических данных позволило выявить дозозависимые эффекты и поведенческие модификаторы риска.

Заключение. Результаты подтверждают отдаленное влияние хронического радиационного воздействия на эндокринное здоровье и подчеркивают необходимость комплексных региональных программ наблюдения за пострадавшими популяциями.

Ключевые слова: *радиационное воздействие, мониторинг здоровья, щитовидная железа, Семипалатинский испытательный ядерный полигон, когортное исследование.*

Для цитирования:

Апсаликов К.Н., Масабаева М.Р., Липихина А.В., Токанов А.М., Брайт Ю.Ю., Коновалова Ф.В., Мансарина А.Е. Опыт многолетнего наблюдения за пострадавшей популяцией уроки для региональных программ мониторинга здоровья // Наука и Здравоохранение. 2025. Vol.27 (4), С. 14-20. *doi 10.34689/SH.2025.27.4.002*

Түйіндеме

РАДИАЦИЯЛЫҚ ӘСЕРГЕ ҰШЫРАҒАН ХАЛЫҚТЫ КӨПЖЫЛДЫҚ БАҚЫЛАУ ТӘЖІРИБЕСІ: ӨҢІРЛІК ДЕНСАУЛЫҚ МОНИТОРИНГІ БАҒДАРЛАМАЛАРЫ ҮШІН САБАҚТАР

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Кіріспе. Семей ядролық сынақ полигонына жақын орналасқан елді мекендерде тұратын халықтың денсаулық жағдайы 20 жылдан астам уақыт бойы жүйелі түрде бақыланып келеді. Бұл зерттеуде радиациялық әсерге аса сезімтал ағзалардың бірі – қалқанша безі ауруларына ерекше назар аударылды.

Материалдар мен әдістер. Зерттеуге 1998–2002 жылдар аралығында қалқанша безінің ультрадыбыстық тексеруінен өткен 3240 адам енгізілді. Мониторинг барысында өмірлік мәртебе, клиникалық диагноздар және медициналық деректер тұрақты түрде жаңартылып отырды. 2023–2024 жылдары 1099 тірі қатысушы арасында сауалнама жүргізіліп, мінез-құлықтық және репродуктивті факторлар бағаланды. Жеке дозалар жас, тұрғылықты жер және тамақтану үлгілерін ескере отырып қайта есептелді.

Нәтижелер. Сауалнамаға қатысқандардың 63%-ында қалқанша безі ауруы анықталған, ал 33%-ы гормоналды терапия алған. Ең жоғары көрсеткіштер 100–300 мГр дозасын алғандар арасында тіркелді. Анкеталық, клиникалық және дозиметриялық деректерді біріктіру арқылы дозалық тәуелділік пен қауіп факторлары арасындағы байланыс айқындалды.

Қорытынды. Созылмалы радиациялық әсердің эндокриндік денсаулыққа ұзақ мерзімді әсері дәлелденді. Бұл зерттеу аймақтық деңгейде тұрақты денсаулық мониторингін дамыту қажеттігін көрсетеді және басқа да зардап шеккен өңірлерге үлгі бола алады.

Түйінді сөздер: *радиациялық әсер, денсаулықты бақылау, қалқанша безі, Семей ядролық сынақ полигоны, когорттық зерттеу.*

Дәйексөз үшін:

Апсаликов Қ.Н., Масабаева М.Р., Липихина А.В., Тоқанов А.М., Брайт Ю.Ю., Коновалова Ф.В., Мансарина А.Е. Жүрек және оның жүйке құрылымдарының морфофункциясы туралы заманауи көзқарас // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 14-20. *doi 10.34689/SH.2025.27.4.002*

Introduction

The Semipalatinsk Nuclear Test Site (SNTS), located in Eastern Kazakhstan, was the primary testing ground for the Soviet Union's nuclear weapons program from 1949 to 1989. Over 450 nuclear detonations were conducted at the site, including 116 atmospheric tests, resulting in widespread dispersion of radioactive materials. Estimates suggest that hundreds of thousands of residents in the surrounding areas were exposed to both external gamma radiation and internal exposure through inhalation and ingestion of radionuclides [1,5,7].

Unlike acute nuclear accidents, such as Chernobyl or Fukushima, the radiation exposure in the SNTS region occurred under peacetime conditions and often went unrecognized for years. Many communities remained in place during and after testing, receiving prolonged, low-to-moderate doses over time. This scenario created a unique epidemiological situation of chronic exposure, which continues to impact public health across generations [7].

In response to rising concerns about the long-term consequences of nuclear testing, the government of Kazakhstan launched a structured health monitoring initiative in the late 1990s [1,11]. A central focus was the thyroid gland—an organ known for its high radiosensitivity, particularly in individuals exposed during early childhood [2,6,12]. Early studies in the SNTS region and similar contexts (e.g., Belarus, French Polynesia, the Marshall Islands) have demonstrated elevated rates of thyroid nodules, hypothyroidism, and autoimmune conditions decades after exposure [3,6,13].

The cohort analyzed in this study was formed through extensive fieldwork conducted from 1998 to 2002, involving ultrasound screening and demographic data collection across radiation-affected settlements. In 2023–2024, a targeted follow-up was conducted to reassess a subsample of the cohort, enabling the integration of behavioral, clinical, and dosimetric data.

This article presents a comprehensive analysis of long-term health outcomes associated with radiation exposure in the SNTS region. Specifically, we examine the prevalence of thyroid disorders, explore potential risk modifiers including lifestyle and reproductive factors, and evaluate dose-response relationships using reconstructed individual radiation doses. The goal is to generate evidence-based insights that can inform the design of sustainable public health surveillance systems in chronically exposed populations.

Materials and Methods

2.1. Cohort Description and Data Sources

This analysis is based on a cohort of 3,240 individuals who underwent thyroid ultrasound examinations between 1998 and 2002 in rural settlements of Eastern Kazakhstan located near the SNTS. Participants were selected from communities classified as potentially radiation-affected areas, using records from regional healthcare institutions.

To verify participants' current status and to collect medical data, the following sources were utilized:

- the National Mortality Registry;
- information systems of the Ministry of Health of the Republic of Kazakhstan;
- outpatient clinic medical records;
- inpatient and outpatient medical journals;
- cancer and endocrine disease registries;
- results from follow-up field examinations conducted in 2023–2024.

2.2. Questionnaire Survey

To identify non-radiation-related risk factors, a structured survey was administered in 2023–2024 among 1,099 surviving members of the cohort. The questionnaire covered the following domains:

- thyroid disease history and treatment (hormone therapy, surgical interventions);
- lifestyle characteristics (tobacco use, alcohol consumption);
- reproductive history in women (number of pregnancies, age at menarche, and menopause);
- migration history (residence during atmospheric nuclear testing).

2.3. Clinical Indicators

Data on thyroid and other endocrine diseases were extracted from official medical records and validated by certified endocrinologists. Diagnoses were classified according to ICD-10 codes. The primary diagnostic categories included:

- nontoxic diffuse goiter (E04.0), multinodular goiter (E04.2), solitary thyroid nodule (E04.1);
- autoimmune thyroiditis (E06.3);
- hypothyroidism (E03 and subcodes);
- thyrotoxicosis (E05.0);
- thyroid cancer (C73 and C73.9);
- type 2 diabetes mellitus (E11);
- obesity (E66 and subcodes).

2.4. Radiation Dose Estimation

For 2,713 participants (83.7% of the cohort), individual thyroid radiation doses were reconstructed based on the following parameters:

- age at the time of exposure;
- geographic location of residence;
- dietary patterns (particularly the consumption of milk and dairy products);
- deposition data for radioactive iodine isotopes.

Dose calculations employed the ECOSYS-87 radioecological transfer model [9], along with region-specific adaptations [4,10]. Both external gamma radiation and internal exposure due to radionuclide incorporation were considered.

2.5. Statistical Analysis

All statistical analyses were performed using the R software environment (version 4.3.0). Descriptive statistics, logistic regression, and multivariate analysis were applied to assess the association between radiation dose and endocrine morbidity. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed. A p-value of less than 0.05 was considered statistically significant.

Results

Cohort Monitoring Database

An electronic database was developed to support long-term health monitoring of individuals exposed to radiation in the Semipalatinsk region. The dataset included 3,240 participants who underwent thyroid ultrasound examinations between 1998 and 2002. By the time of the most recent follow-up, 1,099 individuals (33.9%) were confirmed to be

alive, allowing for renewed data collection via structured questionnaires and clinical reassessment.

The database incorporated key demographic identifiers, as well as detailed information on residence history and migration patterns – essential for accurate reconstruction of individual radiation exposure. This structure enabled comprehensive longitudinal analysis of health outcomes in high-risk subgroups within the cohort.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Sysid	Gender	Ethnicity	Date of birth	Vital status	Date of last information	Cause of death	Profession	Settlement 1	Settlement code	Settlement status	Entry date 1	Departure date 1
149	4002	2	2	02.08.1949	3	31.12.2015		1	KANONERKA	1	1	02.08.1949	31.12.1966
150	4024	2	2	12.01.1947	3	31.12.2005		1	KANONERKA	1	1	12.01.1947	31.12.2005
151	4065	2	6	09.12.1945	2	27.02.2021	I11	1	UKRAINA	3	2	09.12.1945	31.12.1959
152	4092	2	2	11.09.1940	2	05.06.2015	E66	1	KANONERKA	1	1	11.09.1940	05.06.2015
153	4120	2	2	30.07.1930	2	17.06.2014	I67.2	1	KANONERKA	1	1	30.07.1930	17.06.2014
154	4130	2	2	07.12.1936	2	02.02.2014	I25.8	1	SEMIYARKA	1	1	07.12.1936	31.12.1958
155	4140	2	2	25.05.1932	2	29.01.2021	G93.8	1	KANONERKA	1	1	25.05.1932	23.09.2002
156	4141	1	2	02.05.1931	2	20.07.2013	C38.3	1	KANONERKA	1	1	02.05.1931	04.04.1951
157	4147	2	2	16.07.1949	2	11.11.2005	I11	2	KANONERKA	1	1	16.07.1949	11.11.2005
158	4149	2	3	11.03.1938	1	20.07.2023		1	RUSSIA	3	1	11.03.1938	31.12.1948
159	4154	2	2	10.06.1942	3	31.12.2005		2	KANONERKA	1	1	10.06.1942	31.12.2005
160	4158	1	2	10.12.1948	2	01.12.1998	I21	1	KANONERKA	1	1	10.12.1948	01.12.1998
161	4170	2	2	13.04.1942	1	20.07.2023		1	KANONERKA	1	1	13.04.1942	20.07.2023
162	4176	2	2	05.09.1947	3	25.09.2002		1	KANONERKA	1	1	05.09.1947	25.09.2002
163	4216	2	2	29.09.1935	1	17.07.2023		1	PAVLODAR REGION	3	1	29.09.1935	31.12.1944
164	4221	2	2	29.08.1941	1	17.07.2023		2	KANONERKA	1	1	29.08.1941	31.12.1960
165	4267	2	2	01.07.1938	2	05.07.2018	I20.8	1	KANONERKA	1	1	01.07.1938	05.07.2018
166	4298	2	2	20.03.1930	2	09.10.2013	I25.8	1	KANONERKA	1	1	20.03.1930	09.10.2013
167	4323	2	2	21.09.1931	2	01.01.2015	G20	1	RUSSIA	3	1	21.09.1931	31.12.1952
168	4359	2	2	15.06.1930	2	09.10.2002	I11.0	1	KANONERKA	1	1	15.06.1930	09.10.2002
169	4370	2	2	11.11.1939	1	17.04.2023		2	BELOKAMENKA	2	1	11.11.1939	31.12.1948
170	4373	1	2	01.09.1938	1	17.04.2023		1	KANONERKA	1	1	01.09.1938	03.12.1957
171	4426	2	2	09.03.1930	2	11.10.2004	I24.9	1	KANONERKA	1	1	09.03.1930	11.10.2004
172	4446	2	2	12.04.1936	2	17.10.2015	C73	1	KANONERKA	1	1	12.04.1936	17.10.2015
173	4474	2	2	20.09.1935	2	07.04.2000	I21	1	KANONERKA	1	1	20.09.1935	07.04.2000
174	4556	2	2	22.04.1949	1	17.07.2023		2	KANONERKA	1	1	22.04.1949	17.07.2023
175	4586	2	2	15.04.1949	1	19.07.2023		1	KANONERKA	1	1	15.04.1949	31.12.1985
176	4587	1	2	02.08.1947	2	08.07.2020	I49	1	KANONERKA	1	1	02.08.1947	22.10.1966

Figure 1. Structure of the "Study Cohort" database used for long-term health monitoring.

This updated dataset provided the groundwork for the next stage of the study, which aimed to capture comprehensive behavioral and clinical insights via a structured survey.

Questionnaire-Based Monitoring

During this phase, all living members of the cohort (n = 1,099) were surveyed (Table 1). The questionnaire was designed to capture:

– personal and familial history of thyroid disorders;

– lifestyle factors (tobacco use, alcohol consumption);

– reproductive history in women.

Survey analysis revealed the following:

– 63% of respondents reported a physician-diagnosed thyroid disorder;

– 33% had received thyroid hormone replacement therapy;

– 2% had undergone thyroid surgery;

– 21% reported regular smoking, and 34% reported regular alcohol consumption;

– 96.2% of female participants had experienced at least one pregnancy, an important parameter for assessing hormonal risk factors.

The survey also revealed the presence of two main ethnocultural subgroups within the cohort, each exhibiting specific dietary habits and behavioral traits. These distinctions may influence both radiation-related and metabolic health risks, serving as potential modifying factors in exposure outcomes.

Integration of Survey and Dosimetric Data as a Component of Sustainable Regional Monitoring

One of the most informative aspects of this long-term study is the ability to link reconstructed individual thyroid radiation doses with personal health histories reported through the survey. This integration offers insight not only into the overall burden of thyroid disease but also into how behavioral and demographic factors may influence health outcomes in the context of radiation exposure.

Figure 2 illustrates the observed association between dose categories and self-reported thyroid conditions, including hormone therapy use. These findings highlight the value of stratifying participants by dose when interpreting long-term epidemiological data, and they support the effectiveness of this combined approach for guiding regional health monitoring strategies.

Even decades after radiation exposure, a significant portion of the surveyed population remains actively engaged in monitoring their thyroid health. According to the survey, 63% had been diagnosed with a thyroid disorder, and 33% had received hormone therapy, reflecting a sustained awareness of health risks and access to care.

The subgroup with reconstructed thyroid doses between 100 and 300 mGy – comprising 36.9% of the cohort proved particularly informative. Within this group, thyroid disorders and hormone use were reported at elevated rates, further supporting the link between radiation exposure and endocrine outcomes.

These results demonstrate the practical utility of structured questionnaires in long-term cohort studies and support the continued investment in regional health monitoring programs for chronically exposed populations.

Table 1.

Distribution of responses to key questionnaire items (n = 1,099).

Survey Question	Response Option	Number of Respondents (n)	% of Total
Have you been diagnosed with a thyroid disorder?	Yes	692	63.0%
	No	363	33.0%
	Do not remember	44	4.0%
Have you taken thyroid hormone medication?	Yes	363	33.0%
	No	725	66.0%
	Do not remember	11	1.0%
Have you undergone thyroid surgery?	Yes	22	2.0%
	No	1,077	98.0%
Have any of your close relatives had thyroid disease?	Yes	22	2.0%
	No	802	73.0%
	Do not know / Do not remember	275	25.0%
Have you ever smoked regularly?	Yes	231	21.0%
	No	868	79.0%
How often did you consume alcoholic beverages?	Once a month or less	242	22.0%
	2–3 times per month	88	8.0%
	Once a week	33	3.0%
	Several times a week	11	1.0%
	Do not consume alcohol	725	66.0%
How many pregnancies have you had? *(females only, n = 790)*	0	30	3.8%
	1	67	8.5%
	2	246	31.1%
	3	177	22.4%
	4	107	13.6%
	5	106	13.4%
	6	21	2.6%
	7	22	2.7%
	8		
	9	7	0,9

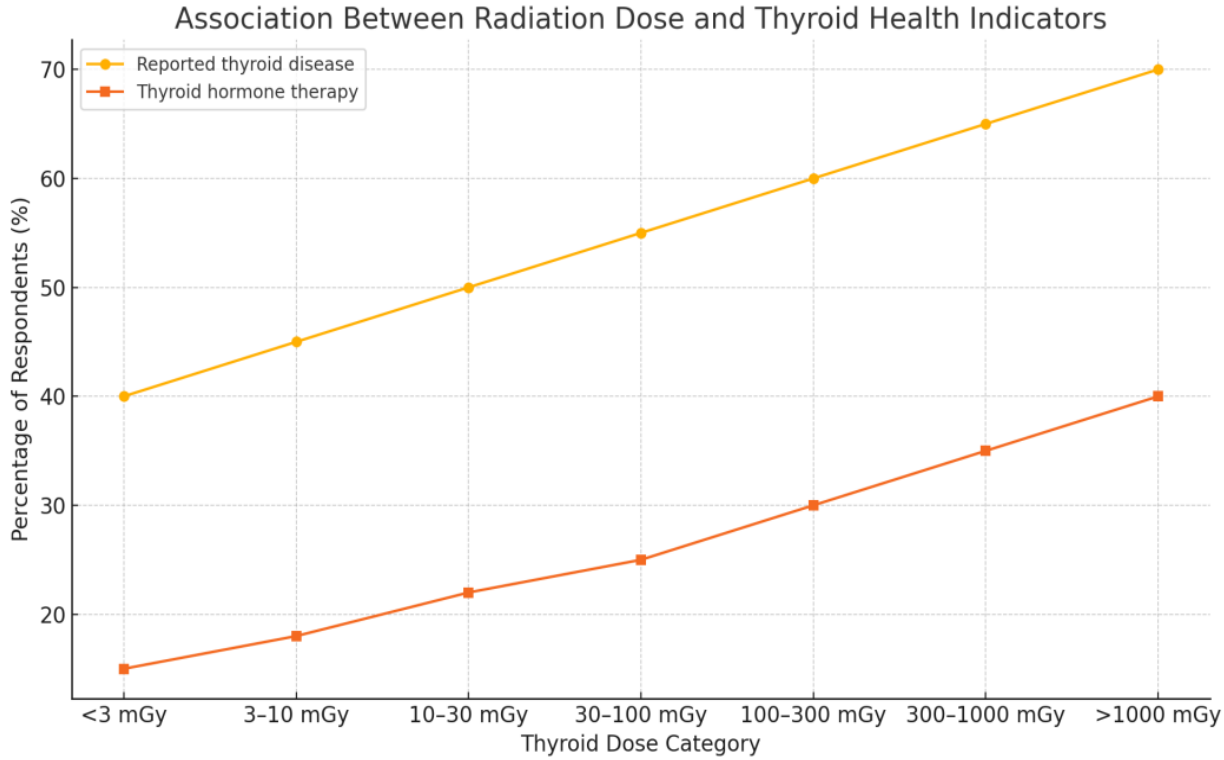


Figure 2. Association between thyroid radiation dose levels and self-reported survey indicators.

Discussion

This long-term observational study of a population exposed to radiation near the SNTS has generated a unique dataset encompassing demographic, clinical, behavioral, and dosimetric parameters. Such a comprehensive approach to health monitoring in radiation-affected communities remains rare in global practice, particularly considering the duration of follow-up, the inclusion of multiple generations, and the integration of diverse data sources, including medical registries, survey responses, and individualized dose reconstructions.

The survey findings, corroborated by official medical records, revealed a high prevalence of thyroid pathology: 63% of respondents reported a thyroid disorder, and 33% had received hormone therapy. These observations are consistent with findings from major cohort studies conducted after the Chernobyl disaster, which also demonstrated elevated rates of goiter, hypothyroidism, and autoimmune thyroiditis decades after exposure, especially among those irradiated during childhood [6,12,13].

A major strength of this study is the capacity to cross-reference survey data with reconstructed thyroid radiation doses. The highest prevalence of thyroid disorders and hormone use was observed among participants with doses in the 100–300 mGy range, confirming a dose-dependent effect previously documented in populations exposed during nuclear testing in French Polynesia [3], the Marshall Islands [7], and Belarus [2].

Unlike acute nuclear accidents such as Chernobyl or Fukushima, the SNTS population experienced protracted radiation exposure under peacetime conditions. This distinguishes the present study and enhances its relevance for understanding the effects of chronic low- and moderate-dose exposure. While the French Polynesian population shares a similar exposure context, the Kazakh cohort is notable for its methodical, multicomponent approach—leveraging historical data, medical registries, structured surveys, and radiation transport modeling to yield robust and reliable results [1,14].

An additional contribution of this study is its attention to modifying factors such as smoking, alcohol use, sex, age at exposure, and ethnocultural differences in diet and residential patterns. As demonstrated herein, these variables play a critical role in shaping long-term radiation health effects and must be integrated into screening and monitoring frameworks.

In summary, the findings from this extended health surveillance program highlight the importance of a multidisciplinary approach combining epidemiological tools, clinical diagnostics, registry analysis, and dosimetric modeling for assessing delayed health effects in radiation-exposed populations. Such strategies should serve as a model for developing regional public health responses in other territories affected by environmental radioactive contamination.

Conclusion

Long-term monitoring of the population exposed to radiation near the Semipalatinsk Nuclear Test Site demonstrated the high utility of an integrated approach that combines structured surveys, diagnostic evaluations, and dosimetric assessments. A high prevalence of thyroid disorders was identified, and a clear association with radiation dose levels was confirmed. These findings underscore the critical importance of sustainable regional health surveillance programs and offer a potential model for implementation in other areas affected by radiation exposure.

Acknowledgements

The authors express their gratitude to the field investigators and ultrasound specialists for conducting thyroid examinations during both the baseline and follow-up phases of the study.

Funding

This study was supported by the grant funding program for scientific startup projects of academic and teaching staff at NCJSC "Semey Medical University" for 2023–2025 (Agreement No. 4, dated January 20, 2023).

Conflict of Interest

The authors declare no conflicts of interest. This manuscript has not been published previously and is not under consideration for publication elsewhere.

Authors' contribution

All authors contributed equally to the conceptualization, methodology, data analysis, and manuscript preparation. All authors have reviewed and approved the final version of the manuscript.

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Received: 05 June 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.003

UDC 616.43

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PATTERNS OF DEVELOPMENT OF PATHOMORPHOLOGICAL TUMOR REGRESS AFTER NEOADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER: EXPERIENCE OF THE NATIONAL RESEARCH ONCOLOGY CENTER

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Abstract

Background: Gastric cancer remains one of the leading causes of cancer-related mortality worldwide. Perioperative neoadjuvant polychemotherapy (NAPCT) using the FLOT regimen has improved long-term outcomes; however, the prognostic value of pathological tumor regression grade (TRG) and its association with clinicopathological factors is not yet fully elucidated.

Objective: To evaluate the association between tumor regression grade (TRG) assessed by the Mandard system, clinicopathological characteristics, and overall (OS) and relapse-free survival (RFS) in patients with locally advanced gastric cancer treated with NAPCT using the FLOT regimen.

Materials and methods: A single-center retrospective cohort study was conducted, including 74 patients with stage II–III gastric adenocarcinoma treated with perioperative FLOT chemotherapy followed by surgery between 2020 and 2024. TRG was evaluated using the Mandard classification. Correlations were calculated using Spearman's coefficient. Survival was analyzed by Kaplan–Meier method with log-rank test and univariate Cox regression. Statistical significance was set at $p<0.05$.

Results: TRG was assessed in 70 resection specimens: TRG1 — 9 (12.9%), TRG2 — 2 (2.9%), TRG3 — 23 (32.9%), TRG4 — 10 (14.3%), TRG5 — 26 (37.1%). A clinically significant response (TRG1–2) was observed in 16% of patients. TRG showed significant correlation with ypT ($\rho=0.51$; $p<0.001$), ypN ($\rho=0.36$; $p=0.0037$), and the number of metastatic lymph nodes ($\rho=0.36$; $p=0.0025$). The presence of signet ring cells was associated with higher tumor grade ($\rho=0.308$; $p=0.008$) and ypT ($\rho=0.324$; $p=0.007$), but not with TRG. In univariate analysis, OS was significantly associated with ypN ($\rho=–0.24$; $p=0.048$) and the number of metastatic lymph nodes ($\rho=–0.28$; $p=0.021$). Median OS and RFS were not reached. Kaplan–Meier analysis demonstrated significantly better OS and RFS in responders (TRG1–2) compared to non-responders (log-rank $\chi^2=7.9$; $p=0.005$ and $\chi^2=10.86$; $p=0.001$, respectively).

Conclusions: A strong pathological response after FLOT-based NAPCT is associated with improved survival; however, residual lymph node metastasis (ypN and number of involved nodes) remains the dominant prognostic factor. TRG should be interpreted in the context of nodal status. Further prospective multicenter studies with standardized pathological assessment are warranted to validate the independent prognostic role of TRG.

Keywords: *tumor regression grade, gastric cancer, neoadjuvant chemotherapy.*

For citation: Bolsynbekova S.O., Tuleubayeva A., Ganieva E.D., Urezkova M.M., Gogolev A.B., Pak L.A. Patterns of development of pathomorphological tumor regress after neoadjuvant chemotherapy for gastric cancer: experience of the National Research Oncology Center // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 21-28. *doi 10.34689/SH.2025.27.4.003*

Резюме

ЗАКОНОМЕРНОСТИ РАЗВИТИЯ ПАТОМОРФОЛОГИЧЕСКОГО РЕГРЕССА ОПУХОЛИ ПОСЛЕ ПРОВЕДЕНИЯ НЕОАДЪЮВАНТНОЙ ХИМИОТЕРАПИИ ПРИ РАКЕ ЖЕЛУДКА: ОПЫТ НАЦИОНАЛЬНОГО НАУЧНОГО ОНКОЛОГИЧЕСКОГО ЦЕНТРА

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Введение. Рак желудка остаётся одной из ведущих причин онкологической смертности в мире. Периоперационная неоадъювантная полихимиотерапия (НАПХТ) по схеме FLOT улучшает отдалённые результаты лечения, однако прогностическая значимость степени патоморфологического регресса опухоли (tumor regression grade, TRG) и её связь с клинико-патологическими характеристиками остаются недостаточно изученными.

Цель исследования. Оценить взаимосвязь степени патоморфологического регресса по системе Mandard с клинико-патологическими параметрами, а также с показателями общей (ОВ) и безрецидивной выживаемости (БРВ) у пациентов с местнораспространённым раком желудка, получивших НАПХТ по схеме FLOT.

Материалы и методы. Проведено одноцентровое ретроспективное когортное исследование, включающее 74 пациента с аденокарциномой желудка II–III стадии, получивших лечение по схеме FLOT и последующую хирургическую резекцию (2020–2024 гг.). Степень регресса оценивали по системе Mandard. Корреляции рассчитывали с использованием коэффициента Спирмена. Выживаемость оценивали методом Каплана–Майера с применением лог-рангового теста и однофакторного анализа регрессии Кокса. Статистическая значимость принималась при $p<0,05$.

Результаты. TRG оценён у 70 пациентов: TRG1 — 9 (12,9%), TRG2 — 2 (2,9%), TRG3 — 23 (32,9%), TRG4 — 10 (14,3%), TRG5 — 26 (37,1%). Клинически значимый регресс (TRG1–2) наблюдался у 16% пациентов. Степень регресса достоверно коррелировала с остаточной стадией (ypT; $\rho=0,51$; $p<0,001$), статусом лимфоузлов (ypN; $\rho=0,36$; $p=0,0037$) и числом метастатически поражённых лимфоузлов ($\rho=0,36$; $p=0,0025$). Наличие перстневидноклеточного компонента ассоциировалось с более высоким грейдом опухоли ($\rho=0,308$; $p=0,008$) и большей стадией (ypT; $\rho=0,324$; $p=0,007$), однако не влияло на TRG. В однофакторном анализе на ОВ статистически значимо влияли ypN ($\rho=–0,24$; $p=0,048$) и число поражённых лимфоузлов ($\rho=–0,28$; $p=0,021$). Медианы ОВ и БРВ не были достигнуты. По данным анализа Каплана–Майера, пациенты с выраженным ответом (TRG1–2) имели лучшую ОВ и БРВ (лог-ранг $\chi^2=7,9$; $p=0,005$ и $\chi^2=10,86$; $p=0,001$ соответственно).

Выводы. Выраженный патоморфологический ответ после НАПХТ по схеме FLOT ассоциирован с улучшением выживаемости, однако ключевым прогностическим фактором остаётся остаточное лимфогенное метастазирование (ypN и число поражённых лимфоузлов). Оценку TRG целесообразно проводить в контексте узлового статуса. Для верификации независимой прогностической роли TRG необходимы проспективные многоцентровые исследования с унифицированным морфологическим подходом.

Ключевые слова: *патоморфологический регресс опухоли, рак желудка, неоадъювантная химиотерапия.*

Для цитирования:

Болсынбекова С.О., Тулеубаева А.А., Ганиева Е.Д., Урезкова М.М., Гоголев А.Б., Пак Л.А. Закономерности развития патоморфологического регресса опухоли после проведения неоадъювантной химиотерапии при раке желудка: опыт Национального Научного Онкологического Центра // Наука и Здравоохранение. 2025. Vol.27 (4), С.21-28. *doi 10.34689/SH.2025.27.4.003*

Түйіндеме

АСҚАЗАН ЫРЫҒЫНА НЕОАДЮВАНТТЫ ХИМИТЕРАПИЯДАН КЕЙІН ПАТОМОРФОЛОГИЯЛЫҚ ІСІКТЕРДІҢ РЕГРЕССІНІҢ ДАМУ ПЕРЕКШІЛЕРІ: ҰЛТТЫҚ ЗЕРТТЕУ ОНКОЛОГИЯ ОРТАЛЫҒЫНЫҢ ТӘЖІРИБЕСІ

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Кіріспе: Асқазан қатерлі ісігі дүниежүзі бойынша онкологиялық өлім-жітімнің негізгі себептерінің бірі болып саналады. FLOT сызбасы бойынша жүргізілетін периоперациялық неоадъювантты полихимиотерапия (НАХТ) ұзақ мерзімді нәтижелерді жақсартатыны дәлелденгенімен, ісіктің патоморфологиялық регрессия дәрежесінің (tumor regression grade, TRG) болжау маңыздылығы мен оның клиникалық-патологиялық көрсеткіштермен байланысы әлі толық зерттелмеген.

Зерттеу мақсаты: FLOT сызбасы бойынша НАХТ алған, жергілікті таралған асқазан аденокарциномасы бар науқастарда Mandard жүйесімен бағаланған TRG мен клиникалық-патологиялық сипаттамалардың, жалпы өмір сүру ұзақтығы (ӨСҰ) мен рецидивсіз өмір сүру ұзақтығының (РӨСҰ) арасындағы байланысты зерттеу.

Материалдар мен әдістер: 2020–2024 жылдар аралығында FLOT схемасы бойынша НАХТ және хирургиялық ем алған II–III кезеңдегі асқазан аденокарциномасы бар 74 науқастың қатысуымен бір орталықта ретроспективті когорттық зерттеу жүргізілді және TRG Mandard жүйесі бойынша бағаланды. Корреляциялық талдау Спирмен коэффициентімен, ал өмір сүру көрсеткіштері Каплан–Майер әдісі мен log-rank тестімен және бірфакторлы Кокс регрессиясымен есептелді. Статистикалық маңыздылық деңгейі – p<0,05.

Нәтижелер: TRG 70 резекцияланған препаратта анықталды: TRG1 — 9 (12,9%), TRG2 — 2 (2,9%), TRG3 — 23 (32,9%), TRG4 — 10 (14,3%), TRG5 — 26 (37,1%). Клиникалық маңызы бар регрессия (TRG1–2) 16% науқаста байқалды. TRG урТ (ρ=0,51; p<0,001), урN (ρ=0,36; p=0,0037) және метастаздалған лимфа түйіндерінің саны (ρ=0,36; p=0,0025) сияқты көрсеткіштермен сенімді байланыс көрсетті. Сақинажасушалы асқазан қатерлі ісігінің жоғары дәрежелену (ρ=0,308; p=0,008) және урТ (ρ=0,324; p=0,007) көрсеткішімен байланысты болды, бірақ TRG-мен байланысты болмады. Бірфакторлы талдауда урN (ρ=–0,24; p=0,048) және метастаздалған лимфа түйіндерінің саны (ρ=–0,28; p=0,021) жалпы өмір сүруге маңызды әсер етті. ӨСҰ және РӨСҰ медианаларына қол жеткен жоқ. Каплан–Майер әдісі бойынша жақсы жауап берген науқастарда (TRG1–2) өмір сүру ұзақтығы айтарлықтай жоғары болды (log-rank χ^2=7,9; p=0,005 және χ^2=10,86; p=0,001).

Қорытындылар: FLOT схемасы бойынша НАХТ-тан кейінгі айқын патоморфологиялық жауап өмір сүру болжамының жақсаруы-мен байланысты, алайда негізгі болжаушы фактор ретінде қалдық лимфогенді метастаз (урN және зақымданған лимфа түйіндерінің саны) қала береді. TRG көрсеткішін лимфа түйіндерінің жағдайын ескере отырып бағалаған жөн. TRG-ның тәуелсіз болжау мәнін растау үшін морфологиялық үйлестірілген бағалау және көпорталықты проспективті зерттеулер қажет.

Түйінді сөздер: *ісіктің патоморфологиялық регрессиясы, асқазан қатерлі ісігі, неоадъювантты химиотерапия*

Дәйексөз үшін:

Болсынбекова С.О., Тулеубаева А.А., Ганиева Е.Д., Урезкова М.М., Гоголев А.Б., Пак Л.А. Асқазан ырығына неоадювантты химитерапиядан кейін патоморфологиялық ісіктердің регрессінің даму перекшілері: ұлттық зерттеу онкология орталығының тәжірибесі // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 21-28. *doi 10.34689/SH.2025.27.4.003*

Introduction

Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, despite a general decline in overall incidence over recent decades. According to GLOBOCAN 2022 data, GC ranks fifth in incidence and fourth in mortality, claiming approximately one million lives annually [1]. The majority of patients are diagnosed at advanced stages, when radical treatment is associated with a high risk of recurrence and metastasis, necessitating the implementation of comprehensive therapeutic approaches.

Neoadjuvant (perioperative) polychemotherapy (NAPCT) has become an essential component in the treatment of locally advanced gastric cancer. The results of the MAGIC trial demonstrated that the addition of the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil) to surgical treatment significantly improved five-year survival (36% vs. 23%) compared to surgery alone [2]. The subsequent FLOT4 study showed the superiority of the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) over ECF/ECX both in terms of R0 resection rates (85% vs. 74%) and median overall survival (50 months vs. 35 months), establishing it as the new standard of care [3, 4, 5, 6].

An important parameter for assessing the effectiveness of neoadjuvant therapy is pathological tumor regression (Tumor Regression Grade, TRG), which reflects the amount of residual tumor mass [7]. In the studies by Becker et al. [8] and Wang et al. [9], TRG demonstrated a significant correlation with overall survival and several clinicopathological parameters (tumor stage, lymph node involvement, vascular invasion), and was identified as an independent prognostic factor [4, 10, 11, 12].

Considering the accumulating evidence supporting the prognostic significance of TRG and the effectiveness of contemporary chemotherapy regimens, further clarification of predictive markers remains essential for optimizing individualized treatment strategies.

This study seeks to evaluate the association between the extent of pathological tumor regression, clinicopathological features, and survival outcomes in patients with locally advanced gastric cancer treated with neoadjuvant chemotherapy.

Materials and methods

Patient Selection

A single-center retrospective cohort study was conducted. The inclusion criteria were as follows: patients aged 18 to 80 years; patients who received neoadjuvant polychemotherapy (NAPCT) followed by surgical resection; histologically confirmed stage II–III gastric adenocarcinoma; availability of pathological tumor regression grade (TRG) assessment, complete clinicopathological data, and follow-up information. Exclusion criteria included: patients with concurrent or metastatic malignancies of other origins; those with unresectable or metastatic gastric cancer; and patients with severe hepatic or renal impairment or other significant comorbidities. A total of 74 patients who underwent NAPCT and curative surgery between 2020 and 2024 at the National Cancer Research Center were included in the study. All patients received the FLOT regimen as neoadjuvant therapy. The investigated parameters and overall characteristics of the study cohort are presented in Table 1.

Table 1.

General characteristics of the sample.

Parameter		Abs. (%), n=74 / Me (25, 75%)
Sex	Male Female	53 (71,6) 21 (28,4)
Age, year		58,5 (52, 64)
BMI, kg/m²		25,95 (22,8, 28,3)
cT	2 3 4	3 (4) 59 (79,7) 12 (16,3)
cN0	0 1	16 (21,7) 58 (78,3)
Clinical stage	II III	14 (19) 60 (81)
Histological grade	1 2 3	1 (1,3) 15 (20,7) 58 (78,3)
Tumor localization	Upper third Middle third Lower third	35 (47,2) 25 (34,8) 14 (18,9)
Completion of NACT courses (4 courses)	Yes No	64 (86,5) 10 (13,5)
Type of surgery	Total gastrectomy Distal gastrectomy Extended volume Liver biopsy Peritoneal biopsy Gastrostomy Gastroenteroanastomosis	55 (74,4) 11 (14,9) 3 (4,1) 2 (3,7) 1 (1,3) 1 (1,3) 1 (1,3)
Postoperative complications (Clavien–Dindo)	I-II III-IV	2 (2,7) 4 (5,4)
Duration of the postoperative period, days		11 (9, 12)
Surgical margin status	R0 R+	61 (82,4) 8 (10,8)
TRG according to Mandard	1 2 3 4 5 No data	9 (12) 2 (3,5) 23 (31) 10 (13,2) 26 (35) 4 (5,3)
Presence of response to NACT (TRG 1-2)	Yes No No data	5 (6,9) 58 (78,4) 11 (14,6)
ypT	0 1 2 3 4 No data	3 (4) 6 (8,1) 11 (14,5) 33 (44,6) 16 (21,7) 5 (7,1)
ypN	0 1 2 3 No data	28 (37,8) 14 (18,9) 14 (18,9) 13 (17,3) 5 (7,1)
Number of lymph nodes examined		15 (11, 19)

Pathological Tumor Regression Grade Assessment

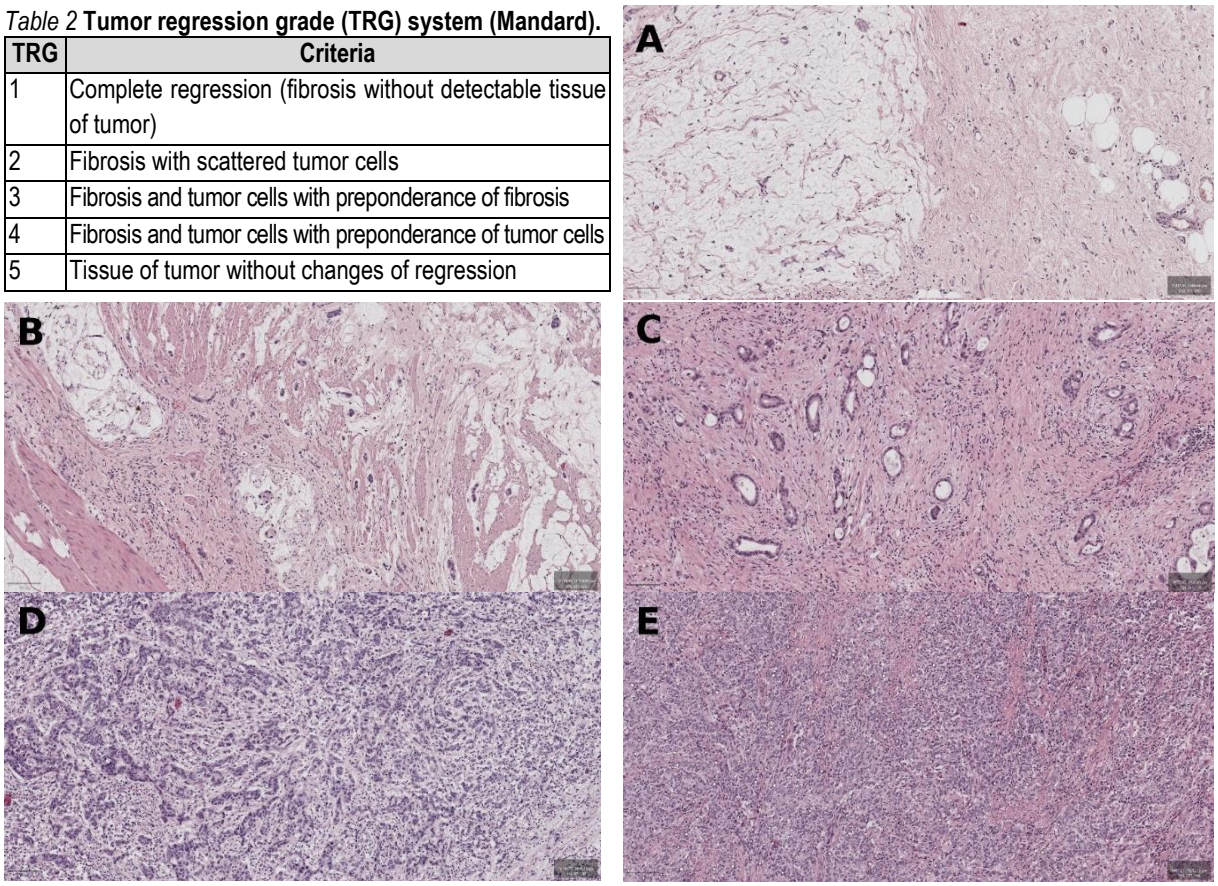
Gastric resection specimens were processed in accordance with the protocols of the College of American Pathologists. During gross examination, all macroscopically identifiable tumor tissue or tumor bed was measured, serially sectioned at 0.5 cm intervals, and embedded in paraffin blocks. Tissue sections were stained with hematoxylin and eosin. Tumor staging (TNM classification) was performed according to the guidelines of the Union for International Cancer Control (UICC, 2019). Pathological tumor regression grade (TRG) following NAPCT was assessed using the Mandard scoring system, which is widely applied to gastrointestinal malignancies, including gastric cancer. This system classifies tumor response into five grades based on the ratio of residual tumor cells to fibrotic tissue in the post-treatment specimen. The criteria for TRG according to the Mandard system are presented in Table 2 and Figure 1.

Statistical Analysis

Associations between TRG and pathological features were evaluated using the chi-square test or Fisher's exact test where appropriate. Survival analysis was performed using the Kaplan–Meier method, log-rank tests, and Cox proportional hazards regression. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using Statistica 14 software (TIBCO Software).

Table 2 **Tumor regression grade (TRG) system (Mandard).**

TRG	Criteria
1	Complete regression (fibrosis without detectable tissue of tumor)
2	Fibrosis with scattered tumor cells
3	Fibrosis and tumor cells with preponderance of fibrosis
4	Fibrosis and tumor cells with preponderance of tumor cells
5	Tissue of tumor without changes of regression



Picture 1. Examples of pathomorphological regression of gastric tumors according to the Mandard system. Hematoxylin and eosin staining, magnification 100x. A – TRG 1, B – TRG 2, C – TRG 3, D – TRG 4, E – TRG 5.

Results

Assessment of Pathological Tumor Regression Grade

A total of 70 surgical specimens from patients with gastric cancer were evaluated using the Mandard tumor regression grading system. Pathological regression grade 1 was observed in 9 patients, grade 2 in 2 patients, grade 3 in 23 patients, grade 4 in 10 patients, and grade 5 in 26 patients. The majority of patients (n = 59) did not achieve a clinically significant pathological tumor response.

Statistical analysis revealed the following associations:

- There was a moderate positive correlation between the Mandard tumor regression grade and residual T stage (ypT) ($\rho = 0.51$; $p < 0.001$). A higher residual T stage following neoadjuvant therapy was associated with a poorer pathological response.

- A weak but statistically significant positive correlation was found between tumor regression grade and residual nodal status (ypN) ($\rho = 0.36$; $p = 0.0037$), indicating that a poorer pathological response was associated with a higher likelihood of metastatic lymph node involvement.

- Tumor regression grade also significantly correlated with the number of metastatic lymph nodes ($\rho = 0.36$; $p = 0.0025$); patients with poorer tumor regression had a greater number of affected lymph nodes.

- No statistically significant correlations were found between tumor regression grade and other clinical or

pathological variables (e.g., age, BMI, laboratory parameters, total number of lymph nodes removed) ($p > 0.05$).

Correlation Analysis Involving Signet Ring Cells

Additional correlation analyses were performed to assess the relationship between the presence of signet ring cells and various clinicopathological characteristics:

- A moderate positive correlation was observed between tumor histological grade and the presence of signet ring cells ($\rho = 0.308$; $p = 0.008$).
- No statistically significant correlation was found between the presence of signet ring cells and the tumor regression grade according to Mandard ($\rho = –0.097$; $p = 0.426$).
- A moderate positive correlation was identified between the presence of signet ring cells and residual T stage (ypT) ($\rho = 0.324$; $p = 0.007$), indicating a larger residual tumor size in tumors containing signet ring cells.
- No correlation was found between the presence of signet ring cells and resection margin status (R status) ($\rho = –0.009$; $p = 0.942$).

Survival Analysis

Overall Survival (OS)

In the univariate Spearman correlation analysis, the following variables demonstrated a statistically significant inverse association with overall survival duration:

- Residual nodal status (ypN): $\rho = –0.24$; $p = 0.048$
- Number of metastatic lymph nodes:
$\rho = –0.28$;
$p = 0.021$

No significant correlations were observed between overall survival and either the Mandard tumor regression grade or residual T stage (ypT) ($p > 0.05$).

In the Kaplan–Meier survival analysis stratified by pathological tumor regression grade (TRG) according to the Mandard system, patients in the regression group (TRG 1–2; n = 11) had significantly better overall survival compared to those without significant regression (TRG 3–5; n = 59). The log-rank test revealed a significant difference between survival curves ($\chi^2 = 7.9$; $p = 0.005$) (Figure 2). The median OS was not reached in either group during the observation period; however, the probability of survival at 60 months remained higher in the TRG 1–2 group than in the TRG 3–5 group. These findings support the prognostic value of a marked pathological response to NAPCT.

Relapse-Free Survival (RFS)

In the Kaplan–Meier analysis of relapse-free survival stratified by TRG (Mandard), patients in the regression group (TRG 1–2; n = 11) also demonstrated significantly better RFS compared to those without regression (TRG 3–5; n = 59). The log-rank test confirmed a significant difference between the survival curves ($\chi^2 = 10.86$; $p = 0.001$) (Figure 2). The median RFS was not reached in either group; the 75th percentile for the entire cohort was approximately 13 months. These results underscore the prognostic importance of a pronounced pathological response in terms of disease control.

None of the assessed variables (ypT, ypN, number of metastatic lymph nodes) showed a statistically significant correlation with RFS duration ($p > 0.05$).

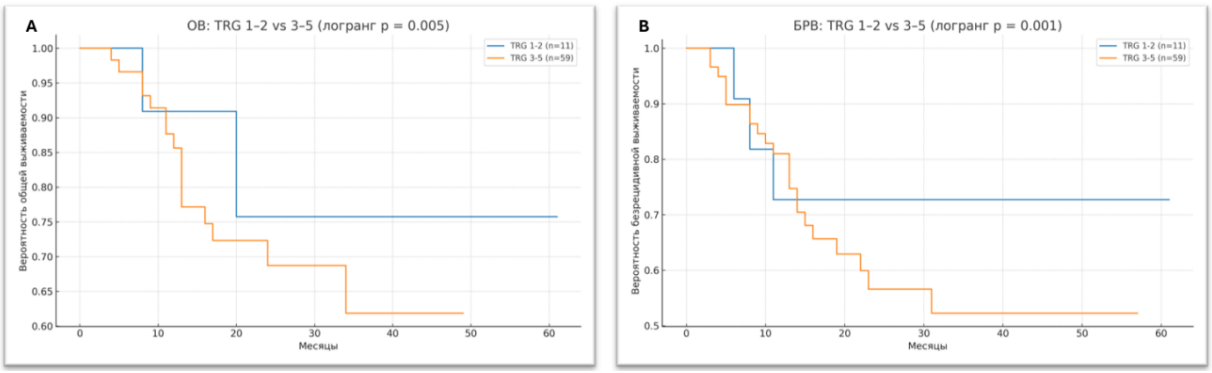


Figure 2. Kaplan-Meier curves for OS (A) and RFS (B) for groups of patients with TRG 1-2 and TRG 3-5.

Discussion

A combined approach incorporating perioperative neoadjuvant polychemotherapy (NAPCT)—in our study, exclusively the FLOT regimen—is currently recognized as the standard of care for locally advanced gastric cancer. Its primary objective is to reduce tumor burden, increase the rate of R0 resections, and thereby improve long-term outcomes. However, the question of which morphological and clinicopathological parameters truly reflect treatment efficacy and prognosis remains a matter of ongoing debate.

In our cohort, a clinically significant pathological response (TRG 1–2 according to Mandard) was achieved in only 16% of patients, which is consistent with data from major studies such as FLOT4, where the proportion of major responses did not exceed one-third of cases [3]. Nevertheless, Kaplan–Meier curves stratified by regression status (TRG 1–2 vs. TRG 3–5) demonstrated statistically significant differences in both overall and relapse-free survival (log-rank $p = 0.005$ and $p = 0.001$, respectively), supporting the clinical relevance of a pronounced pathological response.

The moderate-to-weak but statistically significant collinearity of TRG with ypT and ypN observed in our analysis aligns with the literature, where inclusion of these variables in multivariate models has been shown to attenuate the prognostic value of TRG [13]. In several studies [9, 14], both TRG and ypT lost significance in multivariate analysis, whereas in others, both remained independent predictors [15]; some reports found only one of these variables significant [16]. Such discrepancies are likely due to differences in study design, sample size,

follow-up duration, and variability in pathological assessment protocols.

Our data confirms the predominant prognostic value of lymphatic metastasis: residual nodal status (ypN) and the absolute number of metastatic lymph nodes were strongly associated with overall survival, whereas TRG and ypT, when assessed in isolation, were not. This finding is in line with numerous publications identifying nodal status as a principal risk factor for poor outcomes following NAPCT and surgery [4].

Regarding histological phenotype, the presence of signet ring cells was associated with higher tumor grade and greater residual T stage but showed no correlation with TRG. The literature presents conflicting results on the prognostic implications of signet ring cell carcinoma: some authors associate it with poorer chemotherapy response [17, 18], while others report no such correlation [7]. Our findings support the interpretation that this phenotype is linked to more aggressive tumor behavior but does not necessarily indicate chemoresistance.

Limitations. The retrospective design, single-center setting, and relatively small sample size limit the statistical power of our study, particularly in subgroup analyses of TRG 1–2. Additionally, short follow-up duration for a subset of patients and a limited number of outcome events precluded the calculation of median survival, potentially reducing the sensitivity for detecting prognostic associations. Finally, the subjectivity of TRG assessment and preanalytical variability in specimen processing may affect the reproducibility of the results [19].

Clinical Implications. Our data highlights the need for a comprehensive interpretation of pathological tumor response: although TRG is important, its prognostic impact is modulated by residual nodal status. In the context of postoperative management and surveillance, greater emphasis should be placed on ypN and the number of metastatic lymph nodes, which should be incorporated into multifactorial prognostic models. Looking forward, there is a need to develop integrated scoring systems combining TRG, ypT/ypN, lymphovascular invasion, and molecular markers.

Future Directions. Prospective multicenter studies with standardized protocols for pathological assessment and adequate follow-up are required to validate our findings. The inclusion of quantitative morphometric and digital image analysis techniques (including AI-based tools) may reduce the subjectivity of TRG evaluation and improve the reproducibility of prognostic models.

Conclusion

In patients with locally advanced gastric cancer treated with FLOT-based NAPCT, a marked pathological response (TRG 1–2) is associated with improved overall and relapse-free survival. However, residual lymphatic metastasis (ypN and the number of metastatic lymph nodes) remains the most decisive prognostic factor. TRG correlates with ypT and ypN but does not demonstrate independent prognostic value in isolation; the same applies to tumor grade and signet ring cell phenotype. Accurate risk stratification requires multifactorial models that incorporate nodal status. Prospective multicenter trials with standardized pathological evaluation are needed to confirm the independent prognostic value of TRG and to refine the definition of clinically meaningful tumor regression.

Disclosure: *There are no conflicts of interest among all authors.*

Acknowledgments: *None.*

Funding: *This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan grant number BR24992950 ("Creation and Implementation of Innovative Treatment Methods for Oncological Diseases") and the APC was funded by the same grant.*

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Received: 29 May 2025 / Accepted: 14 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.004

UDC 616.12-009

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TP53 GENE POLYMORPHISM AND BREAST CANCER RISK IN RADIATION-EXPOSED KAZAKH WOMEN

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Abstract

Background. TP53 rs1042522 (Arg72Pro) is a functionally significant polymorphism that alters the apoptotic activity of the p53 protein and is potentially associated with cancer susceptibility. Its contribution to cancer risk in radiation-exposed populations remains insufficiently explored. This study aimed to analyze the frequency of this polymorphism in women with breast cancer residing near the former Semipalatinsk nuclear test site, considering both hereditary and environmental risk factors.

Materials and methods. A case-control study was conducted involving 250 Kazakh women aged 40 to 79 years. Participants were categorized into groups based on cancer diagnosis, family history, and radiation exposure. Genotyping of the TP53 rs1042522 polymorphism was performed using real-time PCR. Statistical analysis included calculation of odds ratios (OR) with 95% confidence intervals (CIs), with Bonferroni correction applied where necessary.

Results. The frequency of GC/CC genotypes was significantly higher among breast cancer patients with both a family history and documented radiation exposure (OR = 6.91; 95% CI: 1.89–25.21; p = 0.0020). A meaningful association was also observed in sporadic breast cancer cases – women with no known familial or radiation-related predisposition (OR = 4.30; 95% CI: 1.15–16.09; p = 0.0269). Genotype distribution in the control group was consistent with Hardy-Weinberg equilibrium, supporting the validity of sampling and genotyping procedures.

Conclusion. The findings of this study suggest that the TP53 rs1042522 polymorphism may contribute to increased susceptibility to breast cancer in women exposed to ionizing radiation. These results highlight the importance of an integrated approach to cancer risk assessment that includes both genetic and environmental factors, and emphasize the need for further investigation of TP53 as a potential biomarker in vulnerable populations.

Keywords: *TP53, Arg72Pro, breast cancer, Semipalatinsk, polymorphism, radiation exposure, Kazakhstan, gene-environment interaction.*

For citation:

Tanatarov S., Atantayeva B., Kurmangaliyev T., Apsalikov B. TP53 gene polymorphism and breast cancer risk in radiation-exposed kazakh women // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 29-35. *doi 10.34689/SH.2025.27.4.004*

Резюме

ПОЛИМОРФИЗМ ГЕНА *TP53* И РИСК РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН КАЗАХСКОЙ НАЦИОНАЛЬНОСТИ, ПОДВЕРГШИХСЯ РАДИАЦИОННОМУ ВОЗДЕЙСТВИЮ

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Введение. TP53 rs1042522 (Arg72Pro) – функционально значимый полиморфизм, изменяющий апоптотическую активность белка p53 и потенциально ассоциированный с онкологической предрасположенностью. Влияние данного варианта на риск развития рака в условиях хронического радиационного воздействия остается недостаточно изученным. Настоящее исследование направлено на анализ частоты данного полиморфизма у женщин с раком молочной железы, проживающих вблизи бывшего Семипалатинского испытательного полигона, с учетом семейного анамнеза и истории радиационного воздействия.

Материалы и методы. Исследование случай-контроль, включившее 250 женщин казахской национальности в возрасте от 40 до 79 лет. Участницы были разделены на группы в зависимости от диагноза, семейного анамнеза и

радиационного воздействия. Генотипирование *TP53* rs1042522 проводилось методом ПЦР в режиме реального времени. Статистический анализ включал расчет отношений шансов (OR) с 95% доверительными интервалами (CI) и поправку Бонферрони.

Результаты. Частота генотипов GC/CC была достоверно выше среди женщин с раком молочной железы, имеющих как семейную отягощенность, так и историю радиационного воздействия (OR = 6,91; 95% CI: 1,89–25,21; p = 0,0020). Существенная ассоциация также наблюдалась в группе спорадических случаев – у пациенток без наследственной и радиационной предрасположенности (OR = 4,30; 95% CI: 1,15–16,09; p = 0,0269). В контрольной группе распределение генотипов соответствовало равновесию Харди-Вайнберга, что подтверждает корректность выборки и генотипирования.

Выводы. Результаты исследования позволяют предположить участие полиморфизма *TP53* rs1042522 в повышении чувствительности к раку молочной железы у женщин, подвергшихся радиационному воздействию. Это подчеркивает актуальность комплексного подхода к оценке онкогенного риска, включающего как генетические, так и экологические параметры, а также необходимость дальнейшего изучения TP53 как потенциального биомаркера.

Ключевые слова: *TP53, Arg72Pro, рак молочной железы, Семипалатинск, полиморфизм, радиационное воздействие, Казахстан, взаимодействие гена и среды.*

Для цитирования:

Танатаров С., Атантаева Б., Курмангалиев Т., Апсаликов Б. Полиморфизм гена TP53 и риск рака молочной железы у женщин казахской национальности, подвергшихся радиационному воздействию // Наука и Здравоохранение. 2025. Vol.27 (4), С.29-35. *doi 10.34689/SH.2025.27.4.004*

Түйіндеме

TP53 ГЕНІНІҢ ПОЛИМОРФИЗМІ ЖӘНЕ РАДИАЦИЯЛЫҚ ӘСЕРГЕ ҰШЫРАҒАН ҚАЗАҚ ӘЙЕЛДЕРІНДЕГІ СҮТ БЕЗІ ОБЫРЫНЫҢ ДАМУ ҚАУПІ

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Кіріспе. TP53 rs1042522 (Arg72Pro) – p53 ақуызының апоптоздық белсенділігіне әсер ететін функционалды маңызды полиморфизм және онкологиялық бейімділікпен ықтимал байланысты генетикалық маркер. Бұл варианттың радиациялық әсерге ұшыраған адамдарда қатерлі ісік қаупіне әсері жеткілікті зерттелмеген. Осы зерттеудің мақсаты – бұрынғы Семей ядролық полигонына жақын аймақтарда тұратын, сүт безі обыры бар әйелдер арасында осы полиморфизм жиілігін, сондай-ақ олардың отбасылық анамнезі мен радиациялық әсер тарихын ескере отырып талдау.

Материалдар мен әдістер. Бұл зерттеу 40-79 жас аралығындағы 250 қазақ ұлтының әйелдері арасында жүргізілген жағдай–бақылау типіндегі зерттеу болды. Қатысушылар сүт безі обыры диагнозы, отбасылық анамнез және радиациялық әсер деректері бойынша топтарға бөлінді. TP53 rs1042522 полиморфизмін генотиптеу нақты уақыттағы ПТР әдісімен жүргізілді. Статистикалық талдау 95% сенімділік интервалдары (CI) бар ықтималдық коэффициенттерін (OR) есептеуді қамтыды, қажет болған жағдайда Бонферрони түзетуі қолданылды.

Нәтижелер. GC/CC генотиптерінің жиілігі отбасылық анамнезі мен радиациялық әсері бар сүт безі обырымен ауырған әйелдер арасында едәуір жоғары болды (OR = 6.91; 95% CI: 1.89–25.21; p = 0.0020). Мұндай байланысты отбасылық және радиациялық тәуекел факторлары жоқ, спорадиялық сүт безі обыры жағдайларынан да байқауға болады (OR = 4.30; 95% CI: 1.15–16.09; p = 0.0269). Бақылау тобындағы генотиптердің таралуы Харди–Вайнберг тепе-теңдігіне сәйкес келді, бұл іріктеу мен генотиптеу сенімділігін көрсетеді.

Қорытынды. Бұл зерттеудің нәтижелері *TP53* rs1042522 полиморфизмінің радиациялық әсерге ұшыраған әйелдерде сүт безі обырына бейімділікті арттыруы мүмкін екенін көрсетеді. Бұл онкологиялық қауіп-қатерді бағалауда генетикалық және экологиялық факторларды біріктіретін кешенді тәсілдің маңыздылығын атап көрсетеді, сондай-ақ TP53 генін болашағы бар биомаркер ретінде әрі қарай зерттеу қажеттілігін көрсетеді.

Түйінді сөздер: *TP53, Arg72Pro, сүт безі обыры, Семей, полиморфизм, радиациялық әсер, Қазақстан, ген-орта әрекеттестігі.*

Дәйексөз үшін:

Танатаров С., Атантаева Б., Курмангалиев Т., Апсаликов Б. TP53 генінің полиморфизмі және радиациялық әсерге ұшыраған қазақ әйелдеріндегі сүт безі обырының даму қаупі // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 29-35. *doi 10.34689/SH.2025.27.4.004*

Introduction

Breast cancer remains the most frequently diagnosed malignancy and one of the leading causes of cancer-related death among women globally. According to GLOBOCAN 2022, approximately 2.3 million new cases and 670,000 deaths were reported worldwide in that year [15]. The etiology of breast cancer is multifactorial, involving both inherited genetic predispositions and environmental exposures [18]. These disparities may reflect differences in screening practices, lifestyle factors, and genetic background.

The global variation in breast cancer incidence is illustrated in Figure 1, which presents age-standardized rates across selected countries. The highest incidence is observed in the United States and Germany, while rates remain comparatively lower in China and Kazakhstan.

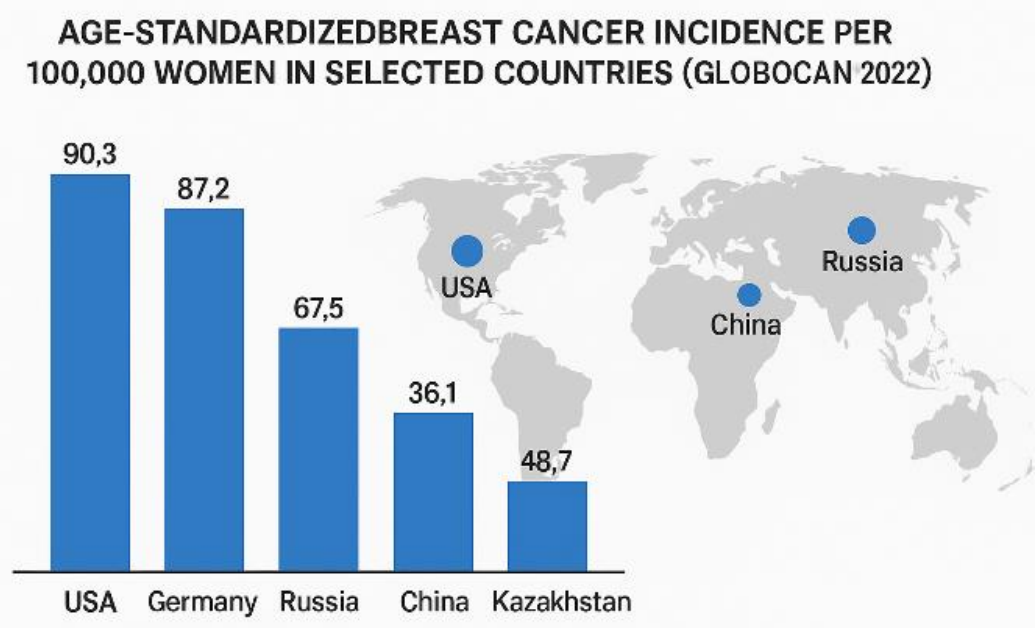


Figure 1. Global distribution of age-standardized breast cancer incidence (per 100,000 women).

In regions affected by long-term radioactive contamination, such as the Semipalatinsk Test Site in Kazakhstan, chronic exposure to ionizing radiation has raised major concerns regarding transgenerational health risks, including carcinogenesis [1,9]. Ionizing radiation is a well-established mutagen that induces DNA damage and genomic instability, which may synergize with inherited mutations to elevate cancer susceptibility [12].

Among the critical tumor suppressor genes involved in genome surveillance is TP53, which encodes the p53 protein. This protein plays a central role in regulating DNA repair, cell cycle arrest, and apoptosis in response to genotoxic stress [11]. A widely studied polymorphism of TP53, rs1042522 (Arg72Pro), results in an amino acid substitution that affects the apoptotic efficiency of the protein. This polymorphism has been associated with variable cancer risk, including breast cancer [17,19]. Although its role has been extensively evaluated in multiple populations, the prevalence and functional significance of this variant remain insufficiently investigated in radiation-exposed populations.

The aim of this study was to assess the frequency of the TP53 rs1042522 polymorphism in breast cancer patients with or without a family history of cancer and radiation exposure in the Semipalatinsk region. We hypothesized that women with both a familial predisposition and a history of radiation exposure would exhibit a significantly higher prevalence of this polymorphism compared to non-exposed healthy controls.

Materials and Methods

This cross-sectional case-control study included a total of 250 women of Kazakh nationality aged 40 to 79 years, recruited between 2015 and 2017 from Semey Oncology Center and local medical facilities in the East Kazakhstan region. All participants provided written informed consent. The study protocol was approved by the institutional ethics committee and adhered to the principles outlined in the Declaration of Helsinki.

Inclusion Criteria: women aged between 40 and 79 years; Kazakh ethnicity confirmed through official documentation (national ID and birth certificates of the participant and both parents); histologically confirmed diagnosis of breast cancer (for cases); no history of any malignancy (for controls); availability of reliable data on family cancer history and residential/radiation exposure history.

Exclusion Criteria: participants were excluded if they were of non-Kazakh ethnicity or had at least one parent of non-Kazakh origin, in order to minimize population stratification and genetic heterogeneity; had other malignancies apart from breast cancer; were older than 80 years (due to potential survivorship bias); had insufficient DNA quality for genotyping; had incomplete clinical or exposure data.

Participants were categorized into four analytical subgroups based on diagnosis and exposure history:

Group A – Women with breast cancer, family history of breast cancer, and documented radiation exposure (either direct or parental exposure due to residence near the Semipalatinsk Test Site).

Group B – Women with breast cancer and family history but without radiation exposure.

Group C – Women with breast cancer without family or radiation history.

Control Group – Healthy women without breast cancer, family history, or radiation exposure.

Age subgroups were created (≥60 years and <60 years) to distinguish between potentially directly irradiated individuals and descendants.

The demographic and clinical characteristics of each group are presented in Table 1.

Table 1.

Distribution of study participants by clinical and exposure characteristics.

Group	Subgroup	Description	N	% within group	Mean Age (± SD)
Group A (Breast cancer + family history + radiation exposure)	A1	Directly exposed women (≥60 years)	25	41.7%	66.2 ± 2.4
	A2	Descendants of exposed (<60 years)	35	58.3%	61.8 ± 2.6
Group B (Breast cancer + family history, no radiation)	B1	Age ≥60 years	30	46.2%	65.1 ± 2.5
	B2	Age <60 years	35	53.8%	62.3 ± 2.2
Group C (Breast cancer, no family history, no radiation)	C1	Age ≥60 years	35	53.8%	66.5 ± 2.3
	C2	Age <60 years	30	46.2%	63.0 ± 2.4
Control Group (No breast cancer, no family history, no radiation)	D1	Age ≥60 years	30	50.0%	69.3 ± 2.1
	D2	Age <60 years	30	50.0%	65.7 ± 2.7
Total	-	-	250	100%	-

Notes:
Subgrouping based on age (<60 and ≥60) was used to approximate directly irradiated women vs. descendants.
No statistically significant age differences were observed between the main groups ($p > 0.05$).
Mean ages calculated separately per subgroup to account for exposure history and age-related risk.

Sample Size and Power Calculation

A sample size of 250 participants (190 cases and 60 controls) was calculated based on a two-sided Fisher's exact test with a significance level of $\alpha = 0.05$ and power $(1–\beta) = 0.80$. Based on prior literature [1], an estimated difference in TP53 rs1042522 polymorphism frequency between exposed cases and unexposed controls of at least 20% was expected. The calculated power was sufficient to detect odds ratios >2.0 with confidence intervals of ±10%.

Genotyping Procedure

Peripheral blood samples (5 mL) were collected in EDTA-coated tubes. Genomic DNA was extracted using the "Standard-NC" kit (DNA-Technology, Moscow, Russia) according to the manufacturer's protocol. DNA quality and concentration were assessed using the NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, USA). Samples were stored at −20°C until analysis.

Genotyping of the TP53 rs1042522 polymorphism was performed using Real-Time PCR with TaqMan Genotyping Assays (Applied Biosystems) on a 7500 Fast Real-Time PCR System. Each reaction included 50 ng of genomic DNA. PCR cycling conditions were: 95°C for 10 minutes (initial denaturation), followed by 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. All genotyping reactions were performed in duplicate to ensure reproducibility and accuracy.

Statistical Analysis

Allele and genotype frequencies were compared using Fisher's exact test. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. Correction for multiple testing (Bonferroni method) was applied where appropriate. All statistical analyses were performed using SPSS Statistics v25.0 (IBM Corp, USA). HWE was assessed for the control group using the chi-square test.

Results

To assess the strength of association between the TP53 rs1042522 polymorphism and breast cancer risk, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each case group in comparison to the control group.

Women with a positive family history and radiation exposure (Group A) demonstrated the highest risk of carrying the GC or CC genotype, with an OR of 6.91 (95% CI: 1.89–25.21; $p = 0.0020$). Group C (sporadic breast cancer) also showed a statistically significant association: OR = 4.30 (95% CI: 1.15–16.09; $p = 0.0269$). Group B (familial history only) demonstrated a non-significant trend (OR = 3.45; $p = 0.0788$).

Figure 2 illustrates the frequency of individuals carrying the GC or CC genotypes (combined) across all study groups, including 95% confidence intervals.

Hardy-Weinberg Equilibrium (HWE) analysis in the control group revealed allele frequencies of G = 91.7% and C = 8.3%. Observed genotype counts were GG = 51, GC = 8, and CC = 1; expected counts under HWE were GG = 50.4, GC = 9.2, and CC = 0.4. The chi-square test yielded $\chi^2 = 0.97$, $p = 0.324$, indicating no significant deviation from HWE.

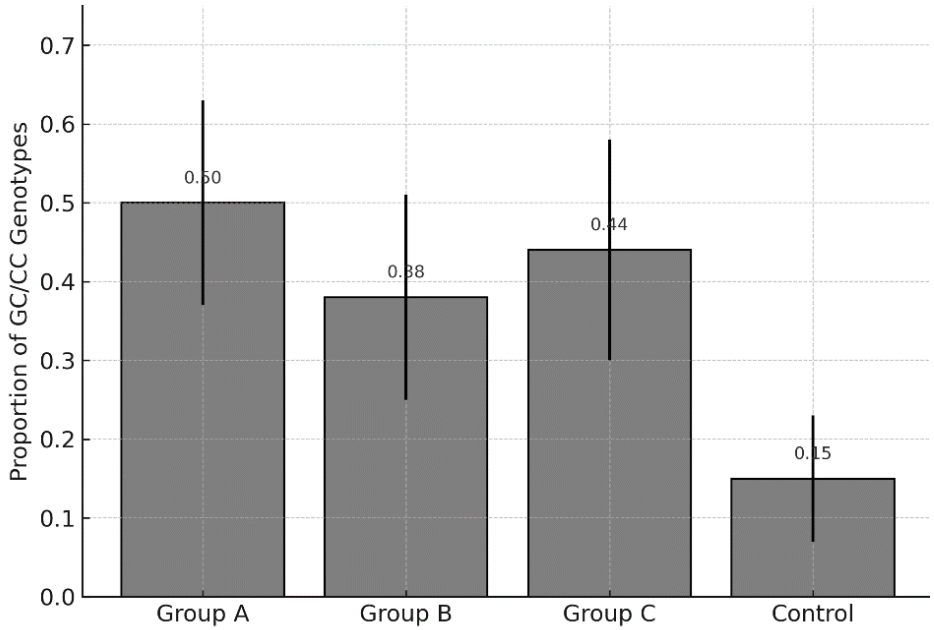


Figure 2. Frequency of TP53 rs1042522 GC/CC genotypes by group. Error bars indicate 95% confidence intervals.

Figure 3 shows the proportional distribution of genotypes (GG, GC, CC) in each group, highlighting structural differences in genotype composition.

Corresponding genotype frequencies in absolute values and percentages are summarized in Table 2.

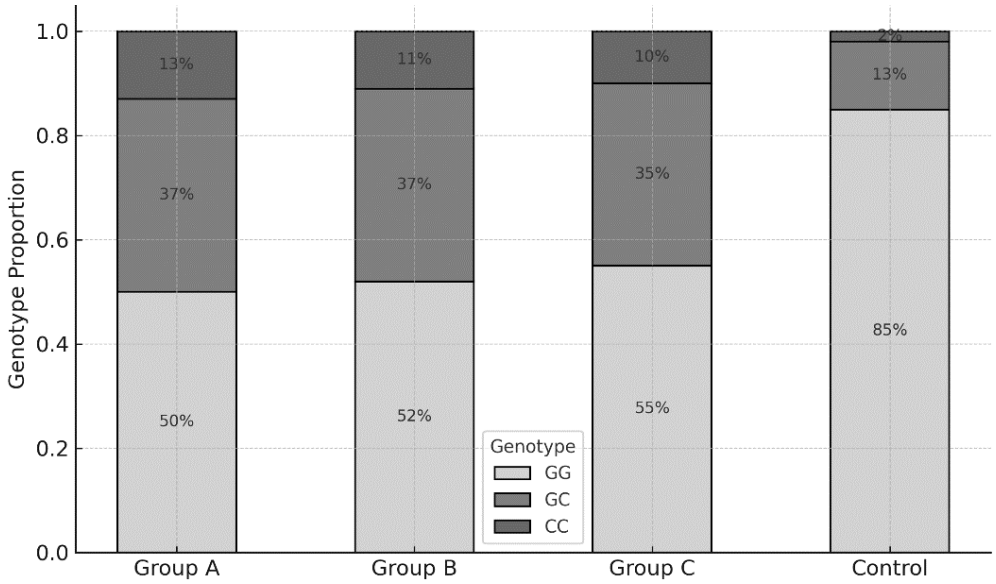


Figure 3 – Relative distribution of TP53 rs1042522 genotypes across study groups. Each bar represents 100% of participants in the group, subdivided by genotype.

Table 2

Distribution of TP53 rs1042522 (Arg72Pro) genotypes across study groups (n and %).

Group	GG (Arg/Arg)	GC (Arg/Pro)	CC (Pro/Pro)	Total
BC + FamHist + RadHist	30 (50.0%)	22 (36.7%)	8 (13.3%)	60
BC + FamHist	34 (52.3%)	24 (36.9%)	7 (10.8%)	65
BC only	36 (55.4%)	23 (35.4%)	6 (9.2%)	65
Healthy controls	51 (85.0%)	8 (13.3%)	1 (1.7%)	60

Taken together, the results demonstrate a significantly higher prevalence of the TP53 rs1042522 GC/CC genotypes among breast cancer patients with both familial and radiation exposure histories. The genotype distribution was consistent with Hardy-Weinberg Equilibrium in the control group, supporting the validity of the genetic data.

These findings suggest a potential gene-environment interaction contributing to breast cancer susceptibility in the Semipalatinsk-exposed population.

Discussion

This study provides new insights into the distribution of the TP53 rs1042522 (Arg72Pro) polymorphism among breast cancer patients residing in a historically radiation-exposed region. The findings suggest that individuals with both a family history of breast cancer and radiation exposure (Group A) exhibit the highest frequency of GC/CC genotypes, supporting the hypothesis of a gene–environment interaction in breast cancer susceptibility.

The Arg72Pro polymorphism affects the pro-apoptotic capacity of the p53 protein. The Pro variant has been reported to be less efficient in inducing apoptosis, potentially allowing survival of genetically damaged cells and contributing to tumor development [4]. Our observation that the GC/CC genotype was significantly more common among women with dual risk factors is consistent with the functional impact of this variant and the biological plausibility of interaction with radiation-induced DNA damage.

Several previous studies have identified the TP53 rs1042522 polymorphism as a low-penetrance genetic factor associated with breast cancer risk, particularly in East Asian and Slavic populations [7,20]. A meta-analysis by Zhang et al. and other regional reviews confirmed that the Pro allele may increase breast cancer risk modestly, especially under recessive and dominant models [3,7,20].

Our results support the relevance of this variant in Central Asian populations and extend observations made in South Asian [7], Middle Eastern [5], and Latin American [14] cohorts. For example, in a study conducted in Egypt, the GC/CC genotypes were significantly more frequent among breast cancer patients than controls, with an OR similar to that observed in our study [5]. Likewise, a Brazilian study reported higher prevalence of the Pro allele among young women with breast cancer [14]. These findings collectively suggest that while the absolute frequencies of genotypes may differ between populations, the risk association remains biologically consistent.

Ionizing radiation is a well-established carcinogen that induces DNA double-strand breaks and genomic instability, creating a permissive background for the emergence and clonal expansion of premalignant cells [16]. In individuals carrying the Pro variant of p53, impaired apoptosis may hinder the elimination of such damaged cells, increasing the likelihood of oncogenic transformation. The observed increase in GC/CC genotypes among exposed individuals and their descendants suggests that radiation may act not only as a direct mutagen but also as a modifier of genotype penetrance. These findings align with studies on atomic bomb survivors and their offspring, which have reported persistent epigenetic and genetic changes across generations [6].

It is worth noting that some population studies, such as those conducted in Turkey and Lithuania, have also demonstrated significant associations between the Pro allele and early-onset or aggressive breast cancer phenotypes [2,8]. Conversely, a few European studies report a lack of association or even suggest a protective role for the Arg allele in certain contexts, emphasizing the importance of environmental modifiers and ethnic-specific genetic backgrounds [13].

Importantly, the genotype distribution in the control group was in Hardy–Weinberg Equilibrium, supporting the validity of genotyping and reducing the likelihood of population stratification or selection bias. The higher prevalence of GC/CC genotypes in Group C (sporadic cases) compared to controls, albeit less significant, suggests that the TP53 polymorphism may confer risk independently of known environmental or familial factors. This aligns with studies showing that even low-risk variants can contribute meaningfully in polygenic models of cancer susceptibility [10].

Despite the novelty of our findings, the study has several limitations. The sample size, while sufficient for primary associations, may not provide adequate power for detecting subtle gene–environment interactions or differences within age subgroups. The classification of radiation exposure relied on registry data and residential history, which may be subject to misclassification. Furthermore, only one polymorphism in TP53 was analyzed, while the gene harbors numerous other functional variants and haplotypes [13].

Conclusion and Perspectives

This study demonstrates a significant association between the TP53 rs1042522 (Arg72Pro) polymorphism and breast cancer risk in women from a radiation-exposed region, particularly among those with both familial and environmental risk factors. The findings support the hypothesis that gene–environment interactions contribute meaningfully to breast cancer susceptibility in historically irradiated populations.

The increased prevalence of GC/CC genotypes among breast cancer patients-especially those with combined risk profiles-suggests that genetic screening for TP53 variants may hold clinical relevance for risk stratification in exposed populations. Moreover, the study reinforces the need to consider environmental history, such as chronic radiation exposure, in genetic association studies and risk models.

Future research should aim to expand the genetic scope beyond single polymorphisms by incorporating additional loci involved in DNA repair, apoptosis, and hormonal pathways. Larger, multiethnic cohorts and longitudinal designs may further clarify the temporal dynamics and biological mechanisms underlying the interaction between inherited susceptibility and radiation exposure.

Funding

The authors declare that no external funding was received for this research.

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Received: 11 May 2025 / Accepted: 20 July 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.005

UDC 618.19-089.87-168.1

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COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF TRADITIONAL POSTOPERATIVE ANALGESIA AND ESP BLOCK IN RADICAL BILATERAL MASTECTOMY

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Abstract

Introduction: According to the Global Cancer Observatory, breast cancer occupies a leading position in the world. According to the Bureau of National Statistics, in the structure of oncological morbidity, breast cancer ranks first (13.2%); lung cancer (10.0%) ranks second, colorectal cancer (9.3%) ranks third, and stomach cancer (7.4%) ranks fourth. Numerous studies and meta-analyses provide valuable data on the frequency, nature and risk factors of pain syndrome after mastectomy. According to studies, the frequency of occurrence of POPS after mastectomy varies from 20% to 68%, depending on the criteria for assessing the study and the nature of pain. In this regard, we, within the framework of the project "Creation and implementation of innovative methods for treating oncological diseases" conduct a comparative prospective study in patients with radical mastectomy. We present the intermediate results of the data obtained.

Aim: to conduct a comparative analysis of the effectiveness of traditional postoperative analgesia and erector spinae plane (ESP) block in radical mastectomy.

Materials and methods: the study was conducted at NROC in Astana. The study involved 40 patients after radical bilateral mastectomy

Results: Both groups included patients who underwent bilateral radical mastectomy. In both groups, general endotracheal anesthesia was performed using inhalation anesthesia. Thus, the first registration of pain in the control group occurred after 57.7±16.3 minutes, while in the main group the first intense pain according to VAS more than 5 points was registered after 713.8±129.8 minutes (($p<0.05$).

Conclusion. Thus, the results obtained in our study show the high and reliable effectiveness of the ESP block in the early postoperative period in patients with radical mastectomy. Publications of peerreviewed journals also emphasize the high importance of regional anesthesia in the prevention of postoperative complications during mastectomy. Moreover, these are not single effects, but a complex improving patient outcomes after radical bilateral mastectomy.

Keywords: *Radical mastectomy, postoperative analgesia, ESP block, postoperative pain syndrome*

For citation:

Zhumabayev M.B., Batyrbekova N.A., Anapiya B.B., Umbetzhanov E.U., Sadvakassova A.K., Burkitbayev Zh., Manatova A.M., Kuanysh Zh., Zhumabayev R.B., Irimbetov S.B. Comparative analysis of the effectiveness of traditional postoperative analgesia and ESP block in radical bilateral mastectomy // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 36-43. *doi 10.34689/SH.2025.27.4.005*

Резюме

СРАВНИТЕЛЬНЫЙ АНАЛИЗ ЭФФЕКТИВНОСТИ ТРАДИЦИОННОГО ПОСЛЕОПЕРАЦИОННОГО ОБЕЗБОЛИВАНИЯ И ESP БЛОКА ПРИ РАДИКАЛЬНОЙ ДВУСТОРОННЕЙ МАСТЭКТОМИИ

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Введение. Рак молочной железы по данным глобальной обсерватории рака занимает лидирующую позицию в мире. По данным бюро национальной статистики в структуре онкологической заболеваемости на первом месте находится рак молочной железы (13,2%); на втором – рак легкого (10,0 %), на третьем – колоректальный рак (9,3 %), на четвертом – рак желудка (7,4 %). Многочисленные исследования и мета-анализы, проведенные в различных странах, предоставляют ценные данные о частоте, характере и факторах риска болевого синдрома после мастэктомии. Согласно исследованиям, частота появления ПОБС после мастэктомии варьирует от 20% до 68%, в зависимости от критериев оценки исследования и характера болевых ощущений. В этой связи, нами, в рамках проекта «Создание и внедрение инновационных методик лечения онкологических заболеваний» проводится сравнительное проспективное исследование у пациенток при радикальной мастэктомии. Мы представляем промежуточные результаты полученных данных.

Цель: провести сравнительный анализ эффективности традиционного послеоперационного обезболивания и erector spinae plane (ESP) блока при радикальной мастэктомии.

Материалы и методы: исследование проведено в Национальном научном онкологическом центре г. Астана. В исследовании приняли участие 40 пациенток после радикальной двусторонней мастэктомии.

Результаты: В обеих группах участвовали пациентки, которым выполнялась двусторонняя радикальная мастэктомия. В обеих группах проводилась общая эндотрахеальная анестезия с применением ингаляционной анестезии. В после операционном периоде в контрольной группе отмечалось скорое развитие болевого синдрома, в отличии от основной группы. Так первая регистрация боли в контрольной группе наступала через 57,7±16,3 минут, в тоже время в основной группе первая интенсивная боль по ВАШ более 5 баллов регистрировалась через 713,8±129,8 минут ((p<0,05). Интенсивности болевого синдрома, в группах также имело выраженное отличие.

Заключение. Таким образом полученные в нашем исследовании результаты показывают высокую и достоверную эффективность ESP блока в раннем послеоперационном периоде у пациенток при радикальной мастэктомии. В публикациях рецензируемых журналов так же подчеркивается высокая значимость регионарного обезболивания в профилактике послеоперационных осложнений при мастэктомии. При чем это не единичные эффекты, а комплексное улучшение исходов у пациентов при радикальной двусторонней мастэктомии.

Ключевые слова: *Радикальная мастэктомия, послеоперационное обезболивание, ESP блок, послеоперационный болевой синдром.*

Для цитирования:

Жумабаев М.Б., Батырбекова Н.А., Әнапия Б.Б., Умбетжанов Е.У., Садвакасова А.К., Буркитбаев Ж., Манатова А.М., Куаныш Ж., Жумабаев Р.Б., Иримбетов С.Б. Сравнительный анализ эффективности традиционного послеоперационного обезболивания и ESP блока при радикальной двусторонней мастэктомии // Наука и Здравоохранение. 2025. Vol.27 (4), С. 36-43. *doi 10.34689/SH.2025.27.4.005*

Түйіндеме

РАДИКАЛДЫ ЕКІ ЖАҚТЫ МАСТЭКТОМИЯДАҒЫ ДӘСТҮРЛІ ОПЕРАЦИЯДАН КЕЙІНГІ АНАЛЬГЕЗИЯ МЕН ESP БЛОКАДАСЫНЫҢ ТИІМДІЛІГІН САЛЫСТЫРМАЛЫ ТАЛДАУ

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Кіріспе: ғаламдық қатерлі ісік обсерваториясының мәліметтері бойынша сүт безі қатерлі ісігі әлемде жетекші орын алады. Ұлттық статистика бюросының мәліметі бойынша онкологиялық сырқаттанушылық құрылымында сүт безі обыры бірінші орында (13,2%); екінші орында өкпе обыры (10,0%), тоқ ішек обыры (9,3%) үшінші, асқазан обыры (7,4%) төртінші орында. Бұл факт, соның салдары ретінде, онкомаммологиядағы жоғары хирургиялық белсенділікті анықтайды. Бұл алаңдатарлық өсу тиімді емдеу стратегияларын және операциядан кейінгі салдарға, соның ішінде мастэктомиядан кейінгі ауырсыну синдромына назар аударуды талап етеді. Зерттеулерге сәйкес, мастэктомиядан кейін POPS пайда болу жиілігі зерттеуді бағалау критерийлеріне және ауырсыну сипатына байланысты 20% -дан 68% -ға дейін өзгереді. Осыған байланысты біз «Онкологиялық ауруларды емдеудің инновациялық әдістерін құру және енгізу» жобасы аясында радикалды мастэктомиямен ауыратын науқастарға салыстырмалы перспективалық зерттеу жүргіземіз. Алынған мәліметтердің аралық нәтижелерін ұсынамыз.

Зерттеудің мақсаты: радикалды мастэктомиядағы дәстүрлі операциядан кейінгі ауырсынуды басу және ESP блокадасының тиімділігіне салыстырмалы талдау жүргізу.

Материалдар мен әдістер: зерттеу Астана қаласындағы Ұлттық ғылыми онкология орталығында жүргізілді. Зерттеуге радикалды екі жақты мастэктомиядан кейін 40 пациент қатысты.

Нәтижелері: Екі топқа екі жақты радикалды мастэктомия жасалған науқастар кірді. Екі топта да севофлуранмен ингаляциялық анестезияны қолдану арқылы жалпы эндотрахеальді анестезия, фентанилмен анальгезия, бұлшықет релаксациясына деполяризациялаушы (полсуксан) және деполяризацияланбайтын (ромеран) бұлшықет босаңсытқыштарын біріктіру арқылы қол жеткізілді. Операциядан кейінгі кезеңде бақылау тобы негізгі топқа қарағанда ауырсыну синдромының қарқынды дамуын атап өтті. Осылайша, бақылау тобындағы ауырсынудың бірінші тіркелуі 57,7±16,3 минуттан кейін орын алса, негізгі топта 5 баллдан жоғары ҚҚС бойынша бірінші интенсивті ауырсыну 713,8±129,8 минуттан кейін тіркелді ((p<0,05).

Қорытынды. Осылайша, біздің зерттеуімізде алынған нәтижелер радикалды мастэктомиясы бар науқастарда операциядан кейінгі ерте кезеңде ESP блокадасының жоғары және сенімді тиімділігін көрсетеді. Рецензияланған журналдардың жарияланымдарында мастэктомия кезінде операциядан кейінгі асқынулардың алдын алуда аймақтық анестезияның жоғары маңыздылығы да атап өтіледі. Сонымен қатар, бұл жалғыз әсерлер емес, екі жақты радикалды мастэктомиядан кейінгі пациенттің нәтижелерін жақсартатын күрделі.

***Түйін сөздер**: Радикалды мастэктомия, операциядан кейінгі ауырсынуды басу, ESP блокадасы, операциядан кейінгі ауырсыну синдромы.*

Дәйексөз үшін:

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Introduction

Breast cancer takes the leading position in the world, according to the Global Cancer Observatory (Fig. 1).

According to the Bureau of National Statistics of the Republic of Kazakhstan, lung cancer consistently ranks the first by the mortality (16.3%), followed by stomach cancer (12.0%), colorectal cancer (10.6%) and breast cancer (8.1%). By the oncological morbidity, breast cancer ranks the first (13.2%); lung cancer ranks the second (10.0%), colorectal cancer ranks the third (9.3%) and stomach cancer ranks the fourth (7.4%) (Fig. 2).

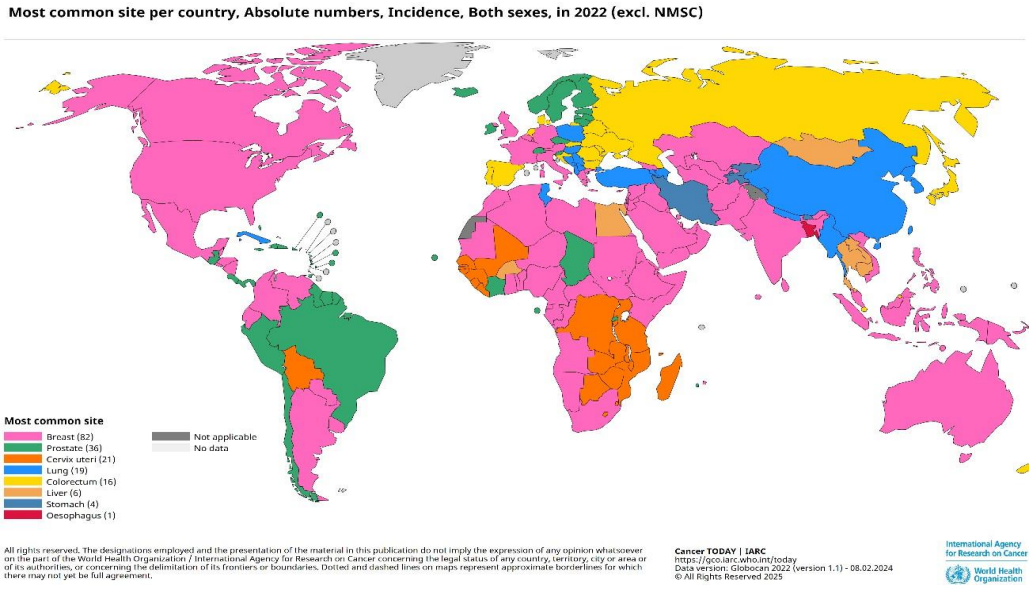


Figure 1. Cancer prevalence by country in 2022 [1].

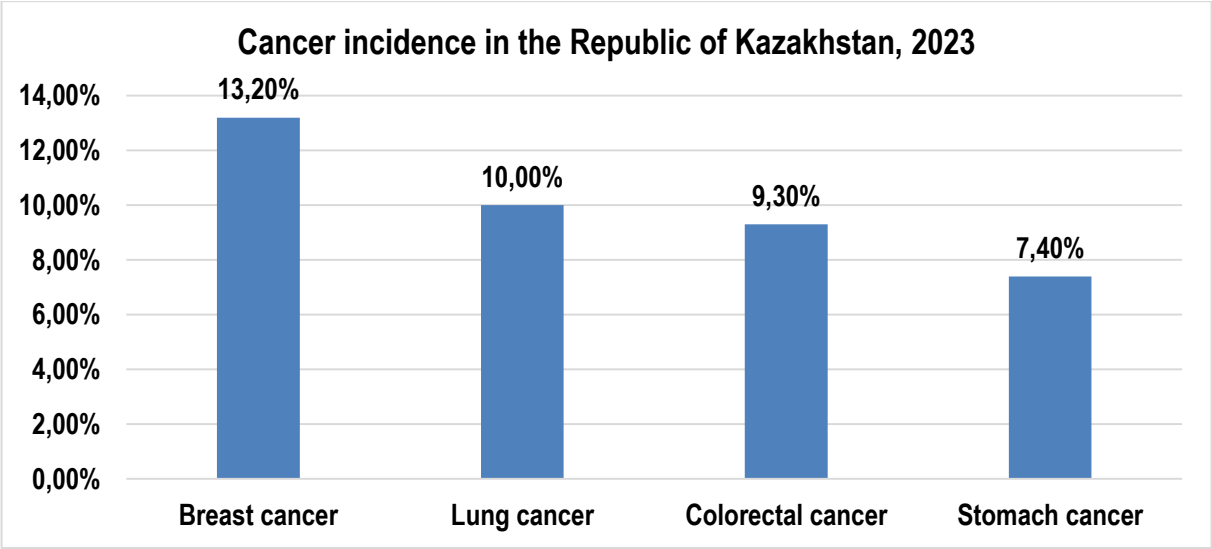


Figure 2. Cancer incidence in the Republic of Kazakhstan, 2023.

Relevant data, as a consequence, leads to high surgical activity in oncomammology. This alarming increase requires effective treatment strategies and attention to postoperative complications, including pain after mastectomy. Growing awareness of the importance of patient quality of life: modern healthcare trends increasingly focus not only on treatment effectiveness but also on quality of life after surgery. More than 60% of patients who have undergone mastectomy express concern about possible postoperative complications, including pain syndrome [3]. This highlights the need for integrated approaches to pain management and improving the quality of life of patients after surgery. Economic implications: post-mastectomy pain also has a significant economic impact. The average annual cost of treating patients with chronic post-mastectomy pain is over $5,000 per patient [4]. Given the increasing incidence of breast cancer, effective pain management is essential for reducing the economic burden on healthcare.

Numerous studies and meta-analyses conducted in various countries provide valuable data on the incidence, nature and risk factors of postmastectomy pain. According to researches, the incidence of postmastectomy pain varies from 20% to 68%, depending on the study assessment criteria and the nature of the pain (5). Some patients experience transient pain, that gradually resolves within a few months after surgery, while others, it may become chronic and last for years. Studies also emphasize the importance of proper postmastectomy pain management. A multimodal approach, including pharmacological therapy, physical rehabilitation, and psychological support, may be most effective in reducing pain and improving patients' quality of life (6).

In this regard, as part of the "Creation and Implementation of Innovative Cancer Treatment Methods" project, we are conducting a comparative prospective study of patients undergoing radical mastectomy. We present the interim results of the data obtained.

Aim: To carry out a comparative analysis of the effectiveness of traditional postoperative analgesia and erector spinae plane (ESP) block in radical mastectomy.

Materials and Methods: The study was conducted at the National Research Oncology Center in Astana. Forty patients underwent radical bilateral mastectomy. The study group consisted of 20 patients who received postoperative pain relief using an erector spinae plane (ESP) block. The control group consisted of 20 patients who received traditional postoperative pain relief using narcotic and non-narcotic analgesics.

Inclusion criteria:

- Patients over 18 years of age and under 75 years of age;
- Patients undergoing bilateral radical mastectomy;
- Patients who signed informed consent to participate in the study
- ECOG=1-2 points
- ASA=1-3

Exclusion criteria:

- Severe thoracic injuries
- Allergic reactions to the drug
- Refusal to participate
- ECOG = 3 and more points
- ASA = 4 and more points
- Neurodegenerative diseases Limitations:
- no randomization,
- the study demonstrates interim results of the research.

All patients received intravenous anesthesia + endotracheal inhalation anesthesia.

Conventional pain management was performed in the control group using opioid analgesics and/or non-narcotic analgesics. Promedol 2% (1 ml) was used as a narcotic analgesic for pain greater than 6 points on the visual analogue scale. It was administered intramuscularly at intervals of 4-6 hours, 3-4 times, until the pain decreased to 3 points or less. Ketoprofen 100 mg intramuscularly was used as a non-narcotic analgesic for pain greater than 4 points on the visual analogue scale.

Erector Spinae Plane (ESP) block was used for postoperative pain relief in the study group. ESP block was

performed under ultrasound guidance using 30 ml of 0.75% Ropivacaine solution at the T5 and T6 levels.

Taking into account the nature and location of the surgical intervention, functional tests included the following movements:

- 2 deep breaths
- Taking a sitting position in bed with legs lowered
- Raising arms in front of yourself

The performance of functional tests was assessed twice: after 12 and 24 hours.

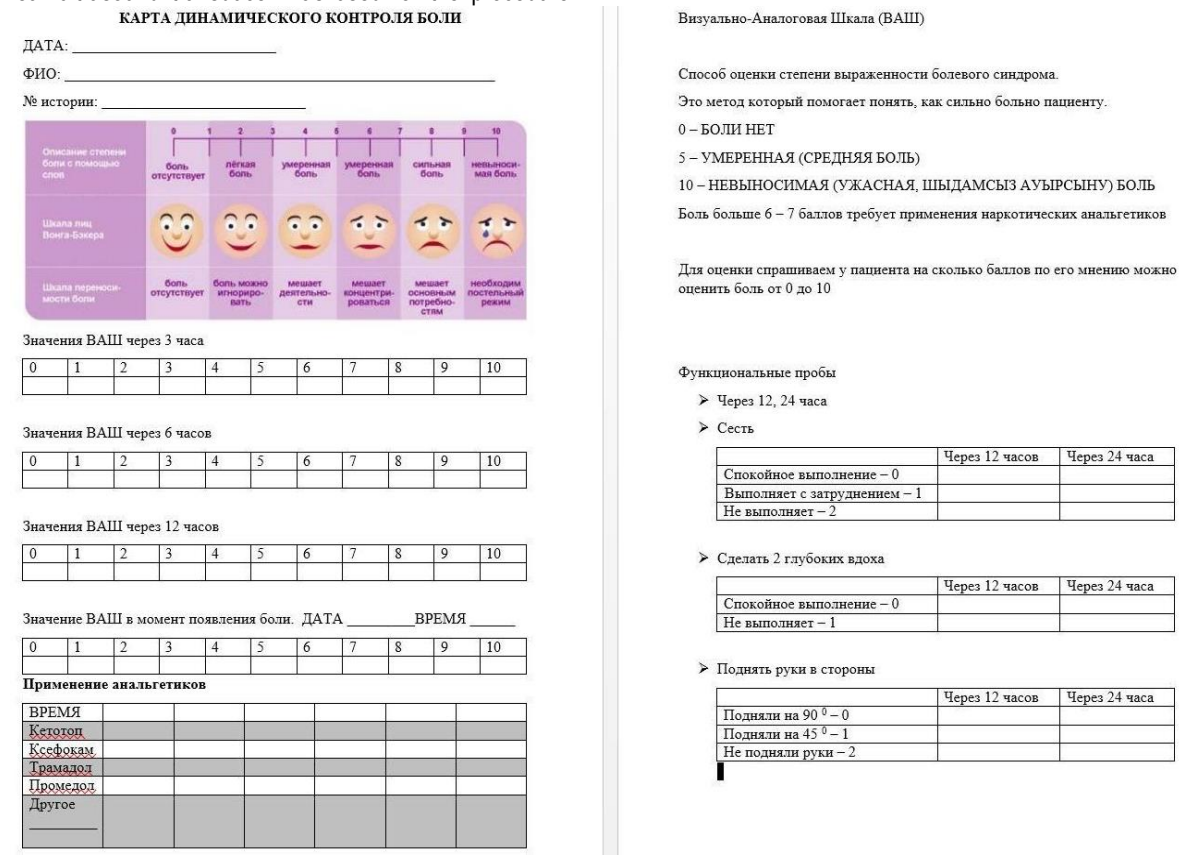
Assessment of pain syndrome and functional status were combined in a dynamic pain control chart (Fig. 3).

In the early postoperative period (0-24 hours after surgery), medical personnel assess both pain syndrome and functional state.

Erector Spinae Plane block is a blockade of the erector spinae muscle, creating a broad sensory block extending over 5-7 segments. This regional anesthesia technique, performed under ultrasound guidance, involves injecting a local anesthetic into the interfascial space between the transverse processes of the vertebrae and the erector spinae muscle, blocking the spinal nerves and, consequently, anesthetizing the area innervated by them. A linear ultrasound transducer was used for the procedure. ESP block was performed before inducing general anesthesia. Given the bilateral mastectomy, the block was performed on both sides.

For statistical analysis of the data, the obtained research results were entered into a database prepared in Microsoft Excel XP, and statistical processing was performed using SPSS version 26. The data processing system included automated quality control of information preparation (excluding values that did not correspond to the numerical series according to the Smirnov criterion), processing of survey results, and data grouping according to specified criteria. Parametric and nonparametric methods were used in the analysis. Continuous values are presented as arithmetic means and standard errors (M ± m). Comparison of quantitative characteristics was performed using the Student's t-test. If the numerical series did not meet the boundary criteria for the applicability of the Student's t-test (lack of a normal distribution of values or equality of variances according to the Kolmogorov-Smirnov criterion), a nonparametric method was used (Mann-Whitney in independent groups or Wilcoxon for the dynamics of indicators in one group).

The threshold for statistical significance was $p<0.05$.



КАРТА ДИНАМИЧЕСКОГО КОНТРОЛЯ БОЛИ

ДАТА: _____

ФИО: _____

№ истории: _____

Описание степени боли с помощью слов	0 боль отсутствует	1 2 3 лёгкая боль	4 5 6 умеренная боль	7 8 сильная боль	9 10 невыносимая боль
Шкала лиц Вонга-Бэкера					
Шкала переносимости боли	боль отсутствует	боль можно игнорировать	мешает деятельности	мешает концентрироваться	мешает основным потребностям	необходим постельный режим

Значения ВАШ через 3 часа

0	1	2	3	4	5	6	7	8	9	10

Значения ВАШ через 6 часов

0	1	2	3	4	5	6	7	8	9	10

Значения ВАШ через 12 часов

0	1	2	3	4	5	6	7	8	9	10

Значение ВАШ в момент появления боли. ДАТА _____ВРЕМЯ _____

0	1	2	3	4	5	6	7	8	9	10

Применение анальгетиков

ВРЕМЯ						
Кетотоп						
Ксефокам						
Трамадол						
Промедол						
Другое _____						

Визуально-Аналоговая Шкала (ВАШ)

Способ оценки степени выраженности болевого синдрома.

Это метод который помогает понять, как сильно больно пациенту.

0 – БОЛИ НЕТ

5 – УМЕРЕННАЯ (СРЕДНЯЯ БОЛЬ)

10 – НЕВЫНОСИМАЯ (УЖАСНАЯ, ШЫДАМСЫЗ АУЫРСЫНУ) БОЛЬ

Боль больше 6 – 7 баллов требует применения наркотических анальгетиков

Для оценки спрашиваем у пациента на сколько баллов по его мнению можно оценить боль от 0 до 10

Функциональные пробы

- Через 12, 24 часа
- Сесть

	Через 12 часов	Через 24 часа
Спокойное выполнение – 0		
Выполняет с затруднением – 1		
Не выполняет – 2		

- Сделать 2 глубоких вдоха

	Через 12 часов	Через 24 часа
Спокойное выполнение – 0		
Не выполняет – 1		

- Поднять руки в стороны

	Через 12 часов	Через 24 часа
Подняли на 90^0 – 0		
Подняли на 45^0 – 1		
Не подняли руки – 2		

Figure 3. A dynamic pain control chart.

Results

Both groups included patients undergoing bilateral radical mastectomy. General endotracheal anesthesia was administered in both groups, including inhalational sevoflurane and fentanyl analgesia. Muscle relaxation was achieved with a combination of depolarizing (polsuxan) and non-depolarizing (romeran) muscle relaxants. The patients' medical history included a diagnosis of breast cancer, no metastatic lesions, and previous chemotherapy courses. The surgical technique involved bilateral mastectomy. The characteristics of the groups are described in Table 1.

Table 1.

Characteristics of groups.

Indicator	Control group, n=20	Study group, n=20	Statistical significance indicator, p
Age, years	48,3±2,5	47,7±3,2	p>0,05
BMI, kg/m²	24,9±3,5	25,3±4,1	p>0,05
Duration of surgical intervention, min	183 ±44,1	173 ±56,1	p>0,05
Duration of IVF, min	231±44,1	257±26,3	p>0,05

In the postoperative period, the control group experienced a more rapid onset of pain than the study group. The first pain in the control group occurred after 57.7±16.3 minutes, while in the study group, the first intense pain (VAS score >5) was recorded after 713.8±129.8 minutes (p<0.05).

A significant difference in the duration of analgesia between these groups is also observed. In the study group, pain relief lasted more than 16 hours, while in the traditional postoperative pain relief group, it did not exceed 5 hours (Fig. 4).

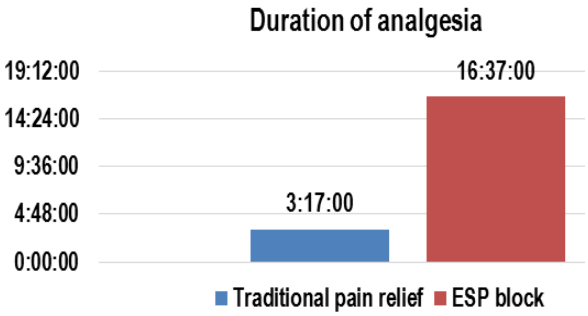


Figure 4. Duration of analgesia in groups, hours

Regarding pain intensity, there were also significant differences between the groups. VAS assessments were conducted after 3, 6, and 12 hours. The results are shown in Figure 5.

We assessed the quality of life in the early postoperative period by analyzing the effectiveness of functional tests performed by patients (Fig. 6).

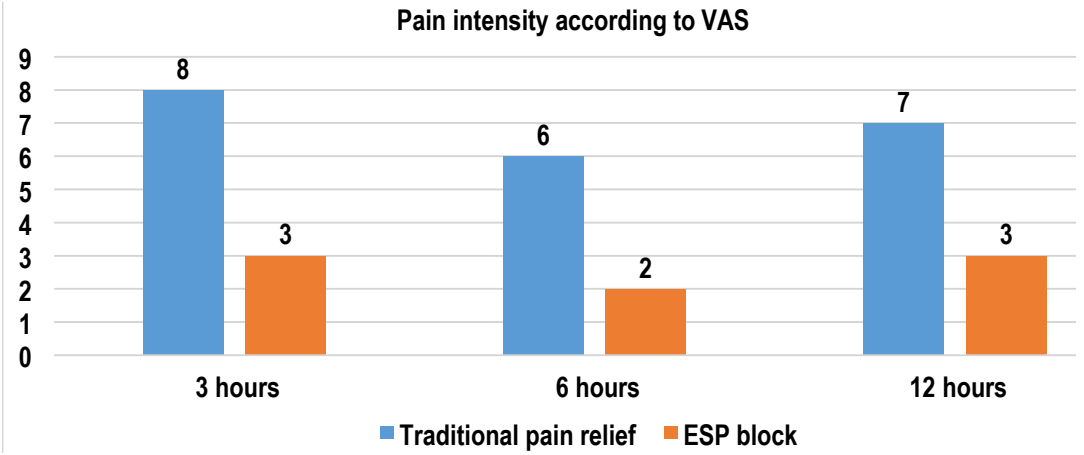


Figure 5. Intensity of pain syndrome in groups, points.

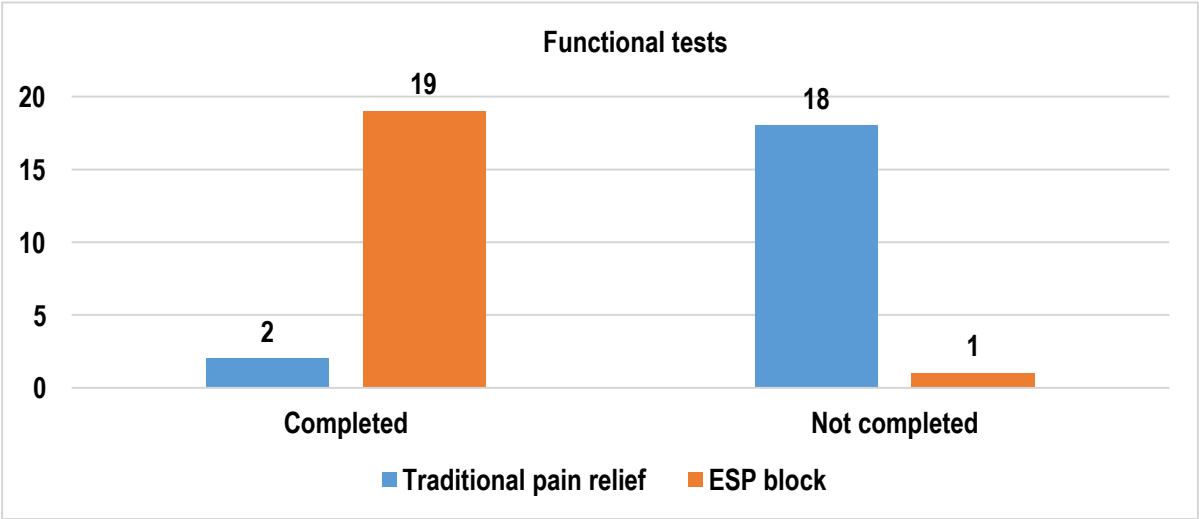


Figure 6. Results of functional tests performed by patients.

Discussion

The results of our study show quite optimistic and convincing evidence for the use of the ESP block for postoperative pain relief, which is confirmed, among other things, by publications and studies from major centers involved in oncomammology.

We reviewed 11 mixed-design studies: a systematic review and meta-analysis, addressing postoperative pain relief in breast oncology. It should be noted that regional pain relief techniques were primarily considered by researchers from Southeast Asia, while the use of pharmacological pain relief was examined by European authors. Seven of the 11 publications focused on regional postoperative analgesia, and four of the 11 focused on the use of pharmacological pain relief techniques.

These studies highlight the high importance and need for effective postoperative analgesia in breast oncology. There are over 8,200 patients undergoing breast surgery in the abovementioned researches.

Ying Zhang et al. [7] mentioned that the ESP block not only provides high levels of pain relief but also reduces opioid analgesic consumption. Compared with the general analgesic group, the observational group showed a significant reduction in morphine consumption during the first 24 hours after surgery, with a mean difference (MD) of -7.67 mg [95% confidence interval (CI) 10.35 to -5.00] ($P < 0.01$). Furthermore, the ESP block group demonstrated lower pain scores than the control group at four time points (1, 6, 12, and 24 hours after surgery). The results of our study, despite its small sample size, confirm the findings of our colleagues.

Grape S. et al. [8,9] found that the use of regional postoperative analgesia reduces the incidence of postoperative nausea and vomiting. This finding was confirmed in our study, although this was not the objective of our study.

One of the key findings of our study was the initial request for analgesia after awakening. Similar results were obtained in the study by Qianchuang *Sun Q. et al.* [10]. Compared to traditional methods of postoperative anesthesia using opioid analgesics, the duration of this period was four times longer. In our study, this period reached up to 20 hours, with a median of 16 hours 37 minutes.

Speaking of postoperative pain relief, it's important to highlight other methods for overcoming this formidable obstacle in the postoperative period. *Ehsan Motaghi et al., Ajit S. Rai et al., and Yaodan Bi et al.* [11, 12, 13] thoroughly examined the use of gabapentin, ketamine, and dexamethasone as adjunctive measures to overcome postoperative pain and neuropathy in patients undergoing mastectomy. Their results demonstrated relatively high efficacy rates; however, they lacked the versatility, accessibility, and safety of regional postoperative pain relief methods.

Another important parameter, which we also documented, was in the studies of *Sheng Huan et al., N Byager et al., and B Versyck et al.:* a reduction in the intensity of postoperative pain syndrome with the use of regional anesthesia [14, 15, 16]. Pain intensity, as measured by VAS, which we also used, was significantly lower in the groups receiving regional anesthesia. Our study also assessed patient function in the early postoperative period. These tests demonstrate the effectiveness of regional anesthesia in the postoperative period, allowing patients to transition to rehabilitation and reducing the risk of hypodynamic complications.

Conclusion

Therefore, the results obtained in our study demonstrate the high and reliable effectiveness of the ESP block in the early postoperative period in patients undergoing radical mastectomy. Peerreviewed journal publications also emphasize the significant role of regional anesthesia in preventing postoperative complications after mastectomy. These are not isolated effects, but rather a comprehensive improvement in patient outcomes after bilateral radical mastectomy. This has broad positive implications not only for the patient but also for the entire healthcare system, including significant pharmacoeconomic benefits, reduced hospital stays, and improved surgical outcomes.

Conflict of interest: *The authors have no conflicts of interest.*

IRB: *protocol #27 of 24.04.2024*

Funding: *This publication was published within the framework of program-targeted funding by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan, IRN: BR24992950.*

Author contributions: *conceptualization – Zh.M.B., M.A.; methodology - A.B.B., Zh.M.B., Zh.K.; review- I.S.B., A.B.B.; analysis - Zh.R.B., U.E.U, Zh.K..; writing (original rough draft) – B.N.A., S.A.K., B.Zh., A.B.B.; writing (review and editing)- B.N.A., Zh.M.B., I.S.B. ; translation - S.A.K., Zh.R.B.*

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Received: 02 June 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.006

UDC 616.441-006-053.2:623.454.832(521.16)

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CURRENT STATUS OF PEDIATRIC THYROID CANCER 14 YEARS AFTER THE FUKUSHIMA NUCLEAR ACCIDENT

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Following the Fukushima Daiichi nuclear power plant accident associated with the Great East Japan Earthquake in 2011, thyroid cancers were detected through population-based ultrasound screening. We herein describe the clinicopathological features of these thyroid cancers.

The mean age at the time of the accident was 17.8 years, with a male-to-female ratio of 1:1.8. Lymph node metastasis was detected in 22.4% of cases preoperatively, but this increased to 77.6% in postoperative pathological examinations, predominantly involving peritracheal nodes. Extrathyroidal extension was observed in 39% of cases, and distant metastasis (M1) was found in 2.4%. The surgical procedures performed included total thyroidectomy in 8.8% and lobectomy in 91.2%, with lymph node dissection performed in all cases.

Histopathology revealed that 98% of cases were papillary carcinoma. Genetic analysis demonstrated BRAF mutations in 69% of cases, whereas RET/PTC3 rearrangements were rare, showing a distinct pattern compared with Chernobyl.

In summary, thyroid cancers detected in Fukushima differed significantly from those after the Chernobyl accident. Except for sex distribution, the clinical features were similar to those of both adult and pediatric sporadic thyroid cancers.

Key words: *Fukushima; thyroid cancer; radiation-induced malignancy; BRAF mutation; RET/PTC rearrangement.*

For citation:

Noso Yoshihiro Current Status of Pediatric Thyroid Cancer 14 Years After the Fukushima Nuclear Accident // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 44-48. *doi 10.34689/SH.2025.27.4.006*

Резюме

ТЕКУЩЕЕ СОСТОЯНИЕ РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ У ДЕТЕЙ ЧЕРЕЗ 14 ЛЕТ ПОСЛЕ ЯДЕРНОЙ АВАРИИ НА ФУКУСИМЕ

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После аварии на атомной электростанции «Фукусима-1», связанной с Великим восточно-японским землетрясением 2011 года случаи рака щитовидной железы были выявлены с помощью ультразвукового скрининга среди населения. В данной статье мы описываем клинико-патологические особенности этих случаев рака щитовидной железы.

Средний возраст на момент аварии составлял 17,8 года, соотношение мужчин и женщин было 1:1,8. Лимфоузловые метастазы были обнаружены в 22,4% случаев до операции, но их количество увеличилось до 77,6% при послеоперационных патологических исследованиях, преимущественно затрагивая перитрахеальные узлы. В 39 % случаев наблюдалось внещитовидное распространение, а в 2,4 % — отдаленные метастазы (M1). Хирургические процедуры включали тотальную тиреоидэктомию в 8,8 % случаев и лобэктомию в 91,2 % случаев, при этом во всех случаях проводилась лимфодиссекция.

Гистопатологическое исследование показало, что в 98% случаев речь шла о папиллярной карциноме. Генетический анализ выявил мутации BRAF в 69% случаев, тогда как перестройки RET/PTC3 были редкими, что свидетельствует о наличии четкой закономерности по сравнению с Чернобылем.

Таким образом, рак щитовидной железы, выявленный в Фукусиме, значительно отличался от рака, выявленного после аварии в Чернобыле. За исключением распределения по полу, клинические особенности были схожи с особенностями спорадического рака щитовидной железы, как у взрослых, так и у детей.

Ключевые слова: Фукусима; Рак щитовидной железы; Опухоли, вызванные радиацией; BRAF мутация; RET/PTC перестройка

Для цитирования:

Носо Йошихиро Текущее состояние рака щитовидной железы у детей через 14 лет после ядерной аварии на Фукусиме // Наука и Здравоохранение. 2025. Vol.27 (4), С.44-48. *doi 10.34689/SH.2025.27.4.006*

Түйіндеме

ФУКУСИМА ЯДРОЛЫҚ АПАТЫНАН 14 ЖЫЛ ӨТКЕННЕН КЕЙІНГІ БАЛАЛАРДАҒЫ ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІНІҢ ҚАЗІРГІ ЖАҒДАЙЫ

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2011 жылғы Ұлы Шығыс жапон жер сілкінісіне байланысты "Фукусима-1" атом электр станциясындағы апаттан кейін қалқанша безінің қатерлі ісігі аурулары халық арасында ультрадыбыстық скрининг арқылы анықталды. Бұл мақалада біз қалқанша безінің қатерлі ісігінің клиникалық және патологиялық ерекшеліктерін сипаттаймыз. Апат кезіндегі орташа жас 17,8 жасты құрады, ерлер мен әйелдердің арақатынасы 1:1,8 болды. Лимфа түйіндерінің метастаздары операцияға дейінгі жағдайлардың 22,4% - анықталды, бірақ операциядан кейінгі патологиялық зерттеулерде олардың саны 77,6% -ға дейін өсті, негізінен перитрахеальды түйіндерге әсер етті. 39% жағдайда қалқанша безден тыс таралу байқалды, ал 2,4 % - да алыс метастаздар (M1) байқалды. Хирургиялық процедураларға 8,8% жағдайда жалпы тиреоидэктомия және 91,2% жағдайда лобэктомия кірді, барлық жағдайларда лимфодиссекция жасалды. Гистопатологиялық талдау нәтижесінде 98%жағдайда папиллярлы карцинома анықталды. Генетикалық зерттеу науқастардың 69%-ында BRAF мутациясын, ал RET/PTC3 қайта құрылымдары сирек кездесетінін көрсетті. Бұл Чернобыльдегі жағдайлармен салыстырғанда айтарлықтай айырмашылықтарды көрсетеді.

Осылайша, Фукусимада анықталған қалқанша безінің қатерлі ісігі Чернобыль апатынан кейін анықталған қатерлі ісіктен айтарлықтай ерекшеленді. Жыныстық арақатынастан басқа, клиникалық ерекшеліктері ересектер мен балалар арасындағы спорадиялық қалқанша безі обырына ұқсас болды.

Түйінді сөздер: *Фукусима; Қалқанша безі обыры; радиация әсерінен туындайтын ісіктер; BRAF мутациясы; RET/PTC қайта құрылуы*

Дәйексөз үшін:

Носо Йошихиро Фукусима ядролық апатынан 14 жыл өткеннен кейінгі балалардағы қалқанша безінің қатерлі ісігінің қазіргі жағдайы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 44-48. *doi 10.34689/SH.2025.27.4.006*

Introduction

On March 11, 2011, the Great East Japan Earthquake triggered a massive tsunami that caused a catastrophic accident at the Fukushima Daiichi Nuclear Power Plant. Large amounts of radioactive materials were released into the atmosphere, raising concerns about radiation-related health effects, particularly in Fukushima Prefecture.

In response, the national and prefectural governments launched the Fukushima Health Management Survey, which included thyroid ultrasound screening for all residents of Fukushima Prefecture who were aged 18 years or younger at the time of the accident.

This paper describes the findings from these thyroid examinations and provides an overview of the clinical outcomes observed up to the present.

Methods

Thyroid ultrasound screening of children and adolescents was initiated at the request of Fukushima Prefecture approximately eight months after the nuclear accident in 2011. The target population included about 360,000 residents who were 18 years of age or younger at the time of the accident. Follow-up examinations continued in 2015 and thereafter.

As shown in Figure 1, by three years after the accident, many high school students had moved outside Fukushima Prefecture for higher education or employment, leading to a decline in the number of examinees. Approximately 10 years after the accident, the number of participants had decreased by nearly half.

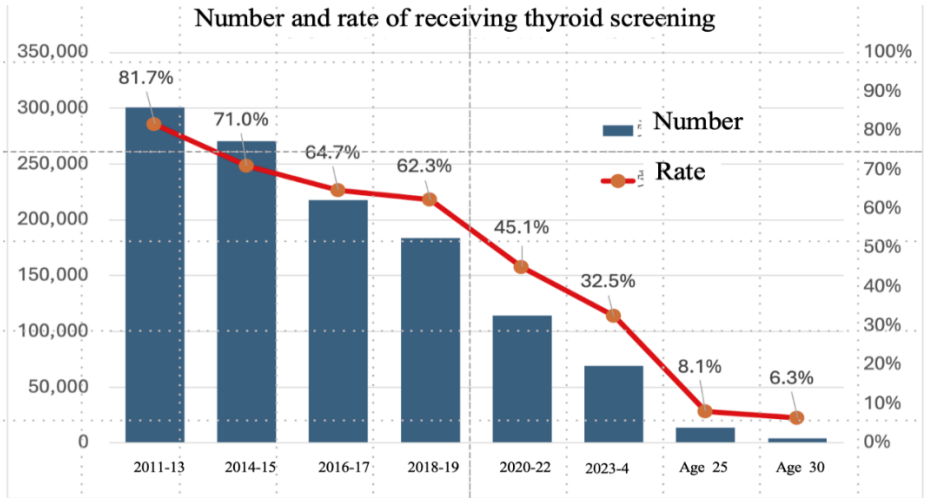


Figure 1. Number and rate of receiving thyroid screening

As summarized in Table 1, the detection of pediatric thyroid cancer gradually decreased over time, and unlike the Chernobyl nuclear accident, there was no phenomenon of a marked increase in cases beginning about three years after the event.

At the first ultrasound examination, nodules ≥5.1 mm or cysts ≥20.1 mm were referred for secondary evaluation. Secondary examinations included blood tests, urinary iodine measurement, and follow-up using established criteria [1,2]. Fine-needle aspiration cytology (FNAC) was performed when indicated, and patients were managed with either surveillance or surgery. All surgical cases underwent pathological review by an expert committee [3].

Table 1.

Trends in Detection of Pediatric Thyroid Cancer After the Fukushima Nuclear Accident.

		1st screening	2nd screening	3rd screening	4th screening	5th screening	6th screening	Screening at age 25	Screening at age 30	Total
Screening year		2011-13	2014-15	2016-17	2018-19	2020-22	2023-24	2017～	2022～	
Screened population		367,637	381,237	336,667	294,228	252,936	211,929	169,956	66,542	–
Malignant/Suspicious		116	71	31	39	50	15	26	9	357
Surgery		102	56	29	34	46	12	19	4	302
Pathology	Papillary ca.	100	55	29	34	45	12	18	4	297
	Por. diff. ca.	1	0	0	0	0	0	0	0	1
	Others	0	1	0	0	1	0	1	0	3

Between the start of the survey in 2011 and March 2021, 260 cases were diagnosed as malignant or suspected malignant, of which 219 underwent surgery. Among them, 218 cases were papillary carcinoma and 1 case was benign.

From 2011 to July 2025 (a 14-year period), 404 cases were diagnosed as malignant or suspected malignant, and 348 patients underwent surgery.

Results

Surgical Indications

In adults, treatment guidelines for thyroid carcinoma are well established. In children and adolescents, the same criteria were applied for low-risk and high-risk cases as in adults. For intermediate-risk cases, whenever possible, lobectomy with peritracheal lymph node dissection was performed, and total thyroidectomy was avoided. Postoperative outcomes were favorable in pediatric patients, and radioactive iodine (RAI) therapy was not recommended except for high-risk cases. The use of RAI in young patients was limited due to concerns from both clinicians and parents, and lifelong thyroid hormone replacement therapy after total thyroidectomy was often met with anxiety, making its implementation difficult.

Patient Characteristics

In the first detailed analysis of 125 cases, the mean age at the time of the nuclear accident was 14.8 years (range, 5–18), and the mean age at diagnosis was 17.8 years (range, 9–23).

The male-to-female ratio was 1:1.8, smaller than that observed in adult thyroid cancer [4,8].

Surgical Procedures

Total thyroidectomy was performed in 8.8% of patients, while lobectomy was performed in 91.8%.

All patients underwent lymph node dissection, with peritracheal dissection in 82.4% and lateral neck dissection in 17.6% [4,8].

Stage and TNM Classification

Stage distribution was as follows: Stage I, 97.6%; Stage II, 2.4%.

Postoperative TNM classification was pT1a 34.4%, pT1b 24.8%, pT2 1.6%, pT3 39.2%, and pT4 0%.

Lymph node status was pN0 22.4%, pN1a 60.8%, and pN1b 16.8%.

Extrathyroidal extension was observed in 39.2% (Ex1), while 60.0% had no extension.

Overall, lymph node metastasis was found in 77.6% of cases, most frequently in the central compartment (N1a, 60.8%). Microscopic extrathyroidal invasion (Ex1, corresponding to T3) was present in 39.2% of cases, which was relatively frequent.

Histopathology

The vast majority of cases were papillary carcinoma.

Among 125 reported cases, papillary carcinoma accounted for 123 cases (98.4%). Rare variants included poorly differentiated carcinoma in 1 case (0.8%), follicular variant in 4 cases (3.2%), diffuse sclerosing variant in 3 cases (2.4%), and solid variant in 2 cases (1.6%). All papillary microcarcinomas (≤10 mm) demonstrated capsular invasion.

Genetic Findings

In Chernobyl-related pediatric thyroid cancers, RET/PTC3 rearrangements were commonly observed and regarded as radiation-induced alterations. However, subsequent studies showed that such rearrangements were also frequent in non-exposed pediatric thyroid cancers, suggesting they represent a general feature of childhood thyroid carcinoma.

In Fukushima, genetic analysis was performed in 68 cases, and BRAF V600E mutations were detected in 68.3%. RET and NTRK fusions were identified in 18.5%, whereas no RAS mutations were found.

In an expanded cohort of 138 cases, BRAF V600E mutations were again common (69.6%), while RET/PTC3 was identified in only one case [11].

Table 2.

Genetic Findings

	Study 1[9], 2[10]		Study3[11]	
Mutated gene	No. of cases	%	No. of cases	%
BRAFV600E	43	68.3	96	69.6
RAS	0	0	0	0
RET/PTC1	6	8.8	8	5.8
ETV6/NTRK3	4	6.3	6	4.3
STRN/ALK	1	1.6	2	1.4
RET/PTC3	1	1.6	1	0.7
AFAP1L2/RET	1	1.6	1	0.7
PPFIBP2/RET	1	1.6	1	0.7
KIAA1217/RET	0	0	1	0.7
ΔRFP/RET	0	0	1	0.7
SQSTM1/NTRK3	1	1.6	1	0.7
TPR/NTRAK1	1	1.6	1	0.7
unknown	9*	13.2	19	13.8
Total	68	100	138	100

Thus, the genetic profile of Fukushima thyroid cancers was markedly different from the Chernobyl radiation-induced cases.

Comparison with Chernobyl

In Chernobyl, total thyroidectomy was frequently performed, followed by postoperative radioactive iodine (RAI) therapy in many cases.

Both Chernobyl and Fukushima introduced ultrasound screening programs. The distribution of tumor size was similar: T1a tumors accounted for 36.9% in Chernobyl and 35.2% in Fukushima [8,16]. In Fukushima, however, T1b tumors were more common (45.6%), likely reflecting the impact of early detection through ultrasound screening.

Regarding sex distribution, adult thyroid carcinoma in Japan occurs overwhelmingly in women [13,14]. By contrast, in Fukushima the female-to-male ratio was 1.8, and in Chernobyl it was 1.6—both considerably smaller than that seen in adult thyroid cancer.

The mean tumor diameter was 14 mm (range, 5–53 mm) in Fukushima and 15 mm (range, 2–60 mm) in Chernobyl, showing no significant difference [8,16].

Rates of clinical lymph node metastasis (cN) and extrathyroidal extension (cEx) were also similar between the two cohorts.

Distant metastasis (M1) was uncommon in Fukushima but relatively frequent in Chernobyl, where it was observed in approximately 18% of cases [13–16].

Future Perspectives

The number of thyroid cancer surgeries in Fukushima has now exceeded 300 cases. Since the accident, revisions of the Japanese guidelines for the management of thyroid cancer have complicated data interpretation to some extent.

Furthermore, many individuals who were under 18 years old at the time of the accident have since moved outside Fukushima Prefecture for university or employment. Consequently, an increasing number of patients are over 20 years of age at the time of surgery, and their treatment often diverges from the strategies originally established for younger patients. Regular postoperative surveillance has also become difficult for those living outside the prefecture, and cases of recurrence have been observed. Recurrences have been noted mainly in the contralateral thyroid lobe or in lateral lymph nodes after lobectomy, while no recurrences have been reported following total thyroidectomy. Although precise data are lacking, the recurrence rate in Fukushima is estimated to be approximately 6–7%, which is substantially lower than the previously reported rate of 20–50% [17]. In contrast, in Chernobyl, despite widespread use of total thyroidectomy and RAI therapy, recurrence was reported in 27.6% of cases, with more than half involving distant metastases [16].

In Japan, the initial treatment strategy for young patients after the accident was to avoid RAI whenever possible. However, more than a decade has now passed, and an increasing number of patients are over 20 years of age at the time of initial or recurrent disease. As a result, the number of total thyroidectomies and completion thyroidectomies performed with the intent of subsequent RAI therapy may increase in the future.

For recurrent cases with NTRK or RET gene alterations, which are often resistant to RAI, molecular targeted therapies are expected to play a key role.

Moreover, psychological care is becoming an important issue throughout the process from screening to surgery, highlighting the need for comprehensive patient support.

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Received: 07 January 2025 / Accepted: 14 April 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.007

***UDC* 616-007-053.1(574.1)**

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ANALYSIS OF THE PREVALENCE OF CONGENITAL DEVELOPMENTAL DEFECTS IN NEWBORNS IN MANGISTAU REGION

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Abstract

Relevance of the study: Congenital malformations (CM) rank among the primary contributors to infant death, perinatal complications, and long-term disability in childhood. According to the World Health Organization, about 6% of babies worldwide are born each year with congenital anomalies, making it a significant issue for healthcare systems and society at large. The relevance of this study is due not only to the high frequency of CM but also to their significant impact on the life expectancy and quality of life of affected children, as well as the financial burden on healthcare systems. Studying CM in environmentally disadvantaged regions such as Mangystau Region of the Republic of Kazakhstan is especially important, where industrial and ecological factors may contribute to the growing prevalence of congenital anomalies.

Aim: To assess the prevalence and structure of congenital malformations among newborns in the Mangystau Region from 2020 to 2024.

Materials and Methods: A retrospective analysis of statistical data on CM was conducted based on reports from regional medical institutions. Trends were assessed by year, by antenatal screening stages, and by organ systems. Standard descriptive statistical methods were used. No personal data were analyzed.

Results: A rise in registered cases of CM was observed from 86 in 2020 to 214 in 2024. Analysis by antenatal screening stages revealed a marked increase in CM detection during the second and third trimesters, particularly in the second screening where 100 cases were recorded in 2024 compared to 58 in 2020. This may reflect advances in prenatal monitoring technologies and increased physician awareness of potential fetal anomalies. By organ system, the highest number of cases in 2024 was reported in the nervous system (39), cardiovascular system (41), and multiple anomalies (47 cases).

Conclusion: The findings highlight the need to strengthen preventive programs, improve the accessibility and quality of prenatal screening, and conduct further research into the impact of environmental factors on CM prevalence in the region.

Keywords: *congenital malformations, newborns, screening, prevalence, Mangystau Region.*

For citation:

Seitmagambetova I.R., Mukasheva G.D., Kurmangali Zh.K., Shabdarbayeva D.M., Smailova Zh.K., Maukayeva S.B., Kudaibergenova N.K., Kairkhanov Ye.K., Kozhanova S.K., Mukanova D.A., *Zhunuspekova A.S.* Analysis of the prevalence of congenital developmental defects in newborns in Mangistau region // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 49-57. *doi 10.34689/SH.2025.27.4.007*

Резюме

АНАЛИЗ РАСПРОСТРАНЕННОСТИ ВРОЖДЕННЫХ ПОРОКОВ РАЗВИТИЯ У НОВОРОЖДЕННЫХ В МАНГИСТАУСКОЙ ОБЛАСТИ

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Актуальность исследования: Врожденные пороки развития (ВПР) являются одной из ведущих причин младенческой смертности, перинатальной заболеваемости и инвалидности детей. По данным ВОЗ, ежегодно в мире регистрируется около 6% случаев рождения детей с врождёнными аномалиями, что составляет существенную медико-социальную проблему. Актуальность исследования обусловлена не только высокой частотой ВПР, но и значительным влиянием этих патологий на продолжительность и качество жизни детей, а также на затраты системы здравоохранения. Особое значение приобретает изучение ВПР в экологически неблагоприятных регионах, таких как Мангистауская область Республики Казахстан, где воздействие промышленных и экологических факторов может способствовать росту распространенности врождённых аномалий.

Цель: Оценить распространенность и структуру врожденных пороков развития среди новорождённых в Мангистауской области за период с 2020 по 2024 годы.

Материалы и методы: Проведен ретроспективный анализ статистических данных о ВПР, полученных из медицинских учреждений региона. Оценивалась динамика по годам, по этапам антенатального скрининга, а также по системам органов. Использовались стандартные методы описательной статистики. Персональные данные не анализировались.

Результаты: Отмечен рост зарегистрированных случаев ВПР с 86 в 2020 году до 214 в 2024 году. Анализ по этапам антенатального скрининга показал значительное увеличение выявляемости ВПР на II и III триместрах, особенно во втором скрининге, где в 2024 году зафиксировано 100 случаев против 58 в 2020 году. Это может указывать на совершенствование технологий пренатального мониторинга и повышение настороженности врачей к потенциальным аномалиям развития плода. В разрезе органных систем наибольшее количество ВПР было зарегистрировано в 2024 году в нервной системе (39 случаев), сердечно-сосудистой системе (41 случай) и в категории множественных ВПР (47 случаев).

Выводы: Результаты свидетельствуют о необходимости усиления профилактических программ, повышения доступности и качества пренатального скрининга, а также проведения дополнительных исследований влияния экологических факторов на частоту ВПР в регионе.

Ключевые слова: *врожденные пороки развития, новорождённые, скрининг, распространенность, Мангистауская область.*

Для цитирования:

Сейтмаганбетова И.Р., Мукашева Г.Д., Курмангали Ж.К., Шабдарбаева Д.М., Смаилова Ж.К., Маукаева С.Б., Кудайбергенова Н.К., Каирханов Е.К., Кожанова С.К., Муканова Д.А., Жунуспекова А.С. Анализ распространенности врожденных пороков развития у новорожденных в Мангистауской области // Наука и Здравоохранение. 2025. Vol.27 (4), С. 49-57. *doi 10.34689/SH.2025.27.4.007*

Түйіндеме

МАҢҒЫСТАУ ОБЛЫСЫНДА ЖАҢА ТУҒАН НӘРЕСТЕЛЕРДЕ ТУА БІТКЕН ДАМУ АҚАУЛАРЫНЫҢ ТАРАЛУЫН ТАЛДАУ

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Зерттеудің өзектілігі: Туа біткен даму ақаулары (ТБА) нәрестелер арасындағы өлім-жітімнің, перинаталдық сырқаттанушылықтың және бала жастағы мүгедектіктің негізгі себептерінің бірі болып табылады. ДДСҰ деректеріне сәйкес, жыл сайын дүниежүзінде шамамен 6% нәресте туа біткен ақаулармен дүниеге келеді, бұл маңызды медициналық-әлеуметтік мәселе болып отыр. Зерттеудің өзектілігі тек ТБА жиілігінің жоғары болуына ғана емес, сонымен қатар бұл патологиялардың балалардың өмір сүру ұзақтығы мен сапасына, сондай-ақ денсаулық сақтау жүйесіне түсетін салмаққа айтарлықтай әсер етуімен де байланысты. Әсіресе, Маңғыстау облысы сияқты экологиялық жағынан қолайсыз аймақтарда ТБА-ны зерттеу өзекті, себебі өнеркәсіптік және қоршаған орта факторлары бұл патологиялардың таралуына ықпал етуі мүмкін.

Зерттеудің мақсаты: 2020–2024 жылдар аралығында Маңғыстау облысында жаңа туған нәрестелер арасындағы туа біткен даму ақауларының таралуы мен құрылымын бағалау.

Материалдар мен әдістер: Аймақтың медициналық мекемелерінен алынған ТБА-ға қатысты статистикалық деректерге ретроспективті талдау жүргізілді. Жылдар бойынша, антенаталдық скрининг кезеңдері мен ағза жүйелері бойынша динамика бағаланды. Сипаттамалық статистиканың стандартты әдістері қолданылды. Жеке деректер қарастырылған жоқ.

Нәтижелер: 2020 жылы тіркелген 86 жағдайдан 2024 жылы 214 жағдайға дейін ТБА санының өскені байқалды. Антенаталдық скрининг кезеңдеріне жасалған талдау екінші және үшінші триместрлерде ТБА-ны анықтаудың едәуір артқанын көрсетті, әсіресе 2024 жылы екінші скринингте 100 жағдай тіркелген (2020 жылы – 58 жағдай). Бұл пренаталдық бақылау технологияларының жетілдірілуіне және дәрігерлердің ұрықтың даму ақауларына деген қырағылығының артуына байланысты болуы мүмкін. Орган жүйелері бойынша 2024 жылы жүйке жүйесі (39 жағдай), жүрек-қантамыр жүйесі (41 жағдай) және көп мүшелі ТБА (47 жағдай) ең жиі тіркелген.

Қорытынды: Зерттеу нәтижелері профилактикалық бағдарламаларды күшейтудің, пренаталдық скринингтің қолжетімділігі мен сапасын арттырудың, сондай-ақ экологиялық факторлардың ТБА жиілігіне әсерін зерттеудің маңыздылығын көрсетеді.

Түйінді сөздер: *туа біткен даму ақаулары, жаңа туған нәрестелер, скрининг, таралуы, Маңғыстау облысы.*

Дәйексөз үшін:

Сейтмаганбетова И.Р., Мукашева Г.Д., Курмангали Ж.К., Шабдарбаева Д.М., Смаилова Ж.К., Маукаева С.Б., Кудайбергенова Н.К., Каирханов Е.К., Кожанова С.К., Муканова Д.А., Жунуспекова А.С. Маңғыстау облысында жаңа туған нәрестелерде туа біткен даму ақауларының таралуын талдау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 49-57. *doi 10.34689/SH.2025.27.4.007*

Introduction

Congenital malformations (CMs) are structural or functional abnormalities that develop during the prenatal period and have a significant impact on a child's health. These defects can affect various organs and systems, leading to serious developmental challenges and often requiring long-term medical intervention [2]. The causes of CMs are diverse and can be either genetic or environmental. Environmental factors include harmful exposures such as infections, poor nutrition (especially folic acid deficiency), and other external influences [10]. Genetic factors include gene mutations and chromosomal abnormalities such as Down syndrome [2,10].

The prevalence of CMs varies by region, ranging from 2% to 6% of newborns [23]. In developed countries, this rate is usually lower due to better access to high-quality prenatal care and diagnostics. In the United States, congenital anomalies are diagnosed in roughly 3% of newborns, whereas in certain Latin American countries, this figure can rise to 5% [8]. In lower-income regions, such as parts of Africa and South Asia, the prevalence is often even higher. This is mainly due to limited access to quality healthcare, poor folic acid intake, and adverse environmental conditions [14]. Congenital malformations also have serious social and economic implications, placing considerable strain on both healthcare systems and social services.

Genetic and chromosomal abnormalities are among the leading causes of congenital malformations. However, environmental factors also play a significant role, including maternal infections during pregnancy (such as rubella, toxoplasmosis, and cytomegalovirus), exposure to harmful substances like alcohol, drugs, or certain medications, and chronic health conditions in the mother, such as diabetes and hypertension [16,19].

Importantly, a lack of folic acid during pregnancy is strongly associated with an increased risk of neural tube defects in the developing fetus [13]. Some of the most commonly observed congenital anomalies include heart defects, cleft lip and palate, neural tube defects, and limb abnormalities [13,16].

In countries with advanced healthcare systems, preventing congenital anomalies remains a public health priority, as they continue to be a major cause of infant mortality and long-term disability. Modern diagnostic and treatment methods can help detect and manage many anomalies, but the mortality rate remains high in regions with less developed healthcare infrastructure [8,14]. Genetic counseling is one of the most effective preventive tools, helping identify at-risk groups and reduce the birth of children with severe abnormalities [15]. Screening programs and health promotion also play a vital role in reducing CM rates [19].

According to official statistics, CM rates vary depending on region and population health. For example, in the Moscow region, the rate is about 3% of all births, while in some parts of Russia such as Krasnodar Krai, an increase in CM cases has been reported, likely linked to worsening environmental conditions [3]. In countries like Kazakhstan,

the CM rate is 22.9 per 1,000 live births, with regional variation from 13.3 to 44.4 per 1,000 [11]. These figures confirm that environmental conditions and healthcare quality directly influence CM prevalence. In Kazakhstan, the highest rates are found in the South Kazakhstan and Pavlodar regions, associated with poor environmental conditions and greater healthcare system strain [4].

Mangystau Region is one of Kazakhstan's industrial areas and has a high rate of congenital malformations. Research shows a significant prevalence of congenital ear defects in the region, which may be linked to environmental pollution and industrial exposure. In cities like Aktau and other populated areas, one in every ten registered CMs involves malformations of the ear [5].

Congenital anomalies affecting hearing and vision are particularly common, which may be due to a combination of genetic and environmental factors [4].

Thus, the aim of this study is to assess the prevalence of congenital malformations among newborns in the Mangystau Region and to identify the most common types of CMs.

Materials and Methods

This study is based on a retrospective analysis of data on CMs in newborns from 2020 to 2024. Data Collection

The data were sourced from official statistical reports provided by medical institutions that documented cases of congenital malformations (CMs) across various organ systems, including the nervous, cardiovascular, respiratory, and others. Data collection followed a standardized protocol and was conducted at all levels of primary healthcare.

The analysis included both annual and categorical frequency data for different types of CMs. No personal information was used in the study, as all data were aggregated and anonymized.

Ethical Considerations

Since the study relied exclusively on anonymized data, informed consent was not required. Ethical approval was obtained from the Ethics Committee of Semey Medical University. The research was conducted in full compliance with the ethical principles set out in the Declaration of Helsinki.

Statistical Analysis

Descriptive and trend analyses were carried out using Microsoft Excel and SPSS software. These tools were used to calculate CM incidence rates and examine patterns over the five-year study period. The results are presented in tables and charts that show how the rates have changed over time.

Results

Figure 1 shows how the number of congenital malformation (CM) cases changed from 2020 to 2024. Overall, there's a clear upward trend, which could be due to several reasons — better diagnostic tools, wider use of screening, or shifts in the general health and environmental situation.

In 2020, there were 86 recorded cases, the lowest over the five-year period. By 2021, the number jumped to 148, possibly because more people were accessing healthcare and screening methods had improved. The increase continued in 2022, reaching 175 cases. In 2023, there was a slight dip to 152, which might reflect changes in how data were collected or reported, or temporary shifts in screening efforts. Then in 2024, the number rose sharply to 214 cases.

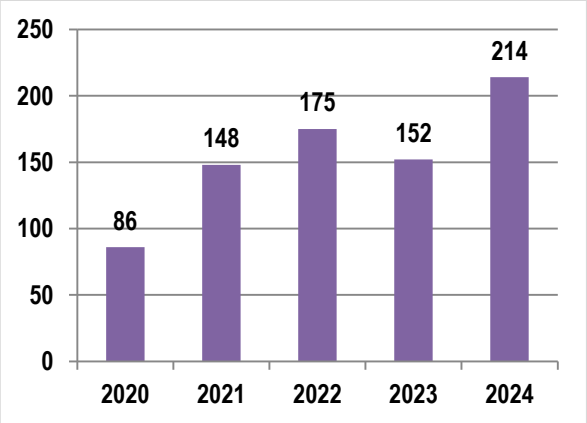


Figure 1. Dynamics of the detection of CM by year (2020–2024).

Figure 2 presents data on the number of both terminated and completed pregnancies from 2020 to 2024. Over this five-year period, the number of terminated pregnancies gradually rose from 68 cases in 2020 to 117 in 2024. At the same time, the number of continued pregnancies (resulting in a live birth) also increased, particularly in 2024, when it reached 97 cases, significantly higher than the 18 cases recorded in 2020.

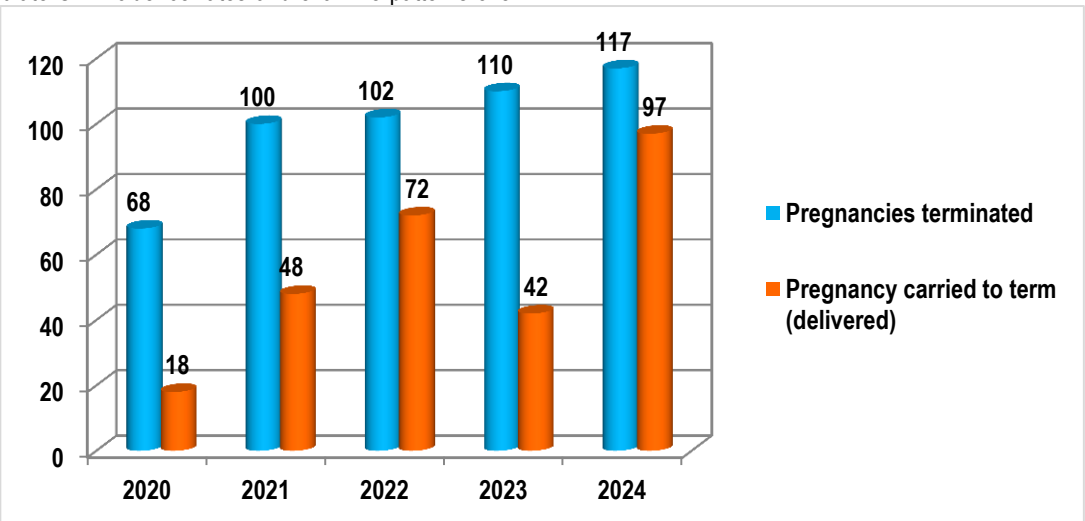


Figure 2. Dynamics of pregnancy termination and continuation by year (2020–2024).

For example, in 2021 there were 100 recorded pregnancy terminations and 48 continued pregnancies, reflecting a general rise in medical interventions during pregnancy. However, in 2023, a slight decrease in continued pregnancies was observed (42 cases), alongside an increase in terminations (110 cases).

Figure 3 illustrates the number of congenital malformations (CMs) identified at various stages of prenatal screening (first, second, and third) from 2020 to 2024. In 2020, 23 cases were detected during the first screening, 58 during the second, and 5 during the third. In 2021, detection rates increased across all stages, with a particularly sharp rise during the second screening, which identified 89 cases — a significant jump compared to the previous year.

By 2022, most cases (128) were identified during the first screening, while the second screening saw a notable decrease, detecting only 24 cases. In 2023, more cases were picked up at the third screening, 52 in total, suggesting better detection of issues later in pregnancy. Then in 2024, the number of cases found at the first screening dropped to 66, but the second screening saw a big rise to 100.

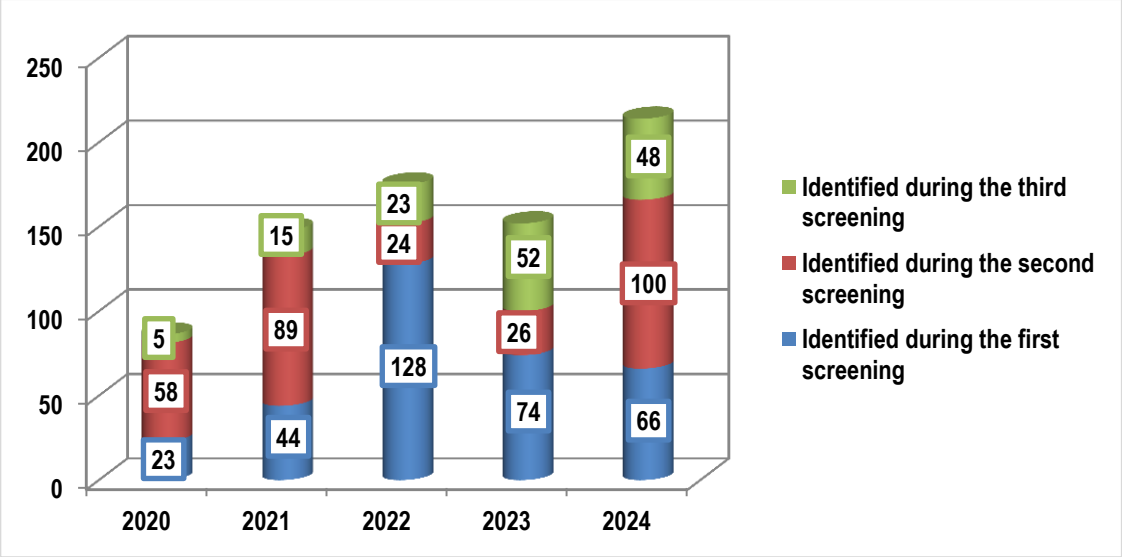


Figure 3. Dynamics of the detection of congenital malformations at different screening stages by year (2020–2024).

Table 1 presents the number of congenital malformation (CM) cases detected in newborns between 2020 and 2024, categorized by affected organ systems. Across the five-year period, nervous system anomalies remained the most frequently reported, showing minor year-to-year variations. The highest number of such cases was recorded in 2024, reaching 39, up from 28 cases in 2020. A significant increase was observed in cardiovascular defects, rising from 11 cases in 2020 to 41 in 2024. A similar trend was noted in genitourinary system anomalies, with cases increasing from 2 to 19 over the same period.

Particular attention is drawn to the rise in multiple congenital anomalies. Starting from 12 cases in 2020, the number nearly quadrupled to 47 by 2024. This may indicate both a true increase in prevalence and improvements in diagnostic accuracy. The category “Other CMs”, which includes congenital anomalies not classified under the main groups, also shows a growth trend, from 8 cases in 2020–2021 to a peak of 41 in 2023, and 34 in 2024.

Table 1.

Detection Trends of Congenital Malformations by Organ System (2020–2024).

Type of Malformation	2020	2021	2022	2023	2024
Nervous system	28	37	35	34	39
Cardiovascular system	11	15	30	27	41
Bronchopulmonary system	3	4	4	4	2
Facial structures	3	13	6	3	6
Gastrointestinal tract (GIT)	5	7	3	1	4
Genitourinary system	2	8	9	5	19
Musculoskeletal system	8	23	5	2	13
Diaphragm	3	4	0	0	1
Anterior abdominal wall	3	5	8	3	8
Multiple congenital anomalies	12	24	45	32	47
Other CMs	8	8	30	41	34

Discussion

CMs result from a combination of genetic and environmental factors. Inherited conditions, gene mutations, and chromosomal abnormalities like Down syndrome can lead to developmental issues [2,10]. Genetic predisposition is often linked to common defects such as heart malformations and cleft lip and palate.

In addition, exogenous factors such infections, environmental toxins, and exposure to teratogens during pregnancy also significantly increase the risk of CMs.

Infections such as rubella, toxoplasmosis, and cytomegalovirus can interfere with fetal development, leading to conditions like neural tube defects, heart abnormalities, and cleft lip or cleft palate [16,19]. Environmental pollution, including emissions of harmful substances into the air and contamination of water resources, has a negative impact on the health of pregnant women and fetal development. or instance, research shows that regions with higher levels of environmental pollution, such as East Kazakhstan, tend to report more cases of congenital anomalies, especially heart defects and malformations of the central nervous system [9,17].

Particular attention should be paid to cardiovascular malformations, which rank among the most prevalent types of CMs. According to statistical data, congenital heart defects are diagnosed in 0.7% to 1.7% of newborns in Kazakhstan, indicating a relatively high prevalence. These types of defects are a major contributor to infant mortality, making up about 47.5% to 47.8% of all deaths caused by congenital anomalies. This underscores the urgent need to prioritize the issue in pediatric healthcare [6]. Early diagnosis and timely treatment are crucial for reducing both infant mortality and the risk of long-term disability.

In addition, external factors such as folic acid deficiency during pregnancy — play a major role in the development of neural tube defects. Numerous studies have confirmed that insufficient folic acid significantly raises the risk of conditions like spina bifida and anencephaly [13]. This underscores the importance of maintaining a balanced diet and ensuring adequate folic acid intake during the preconception period [13].

Another key factor influencing the prevalence of congenital malformations (CMs) is access to medical care. In many low-resource settings, particularly in parts of Africa and South Asia, limited access to quality healthcare often results in late diagnoses. This delay contributes to higher rates of disability and infant mortality associated with congenital anomalies. On the other hand, countries with well-developed healthcare systems like the United States and the United Kingdom tend to have much lower rates of such outcomes, thanks to advanced diagnostic technologies and better medical care [19].

In Kazakhstan, despite ongoing efforts to improve early detection, including initiatives under the “Densaulyk” program aimed at prevention at multiple stages, significant challenges remain. One of the key components of effective prevention is medical and genetic counseling, which plays an important role in identifying at-risk groups and reducing the likelihood of severe congenital conditions. This is particularly important in countries with high CM prevalence, such as Kazakhstan, where environmental and social factors significantly influence the distribution of these conditions [19].

Studies from various regions around the world have identified several factors influencing the prevalence of congenital malformations. For example, a study by *Abdolahi H. et al.* found that in rural areas of Tabriz, nervous system anomalies were the most frequently observed congenital defects. These were largely associated with environmental exposure, particularly in regions located near industrial facilities such as petrochemical plants and thermal power stations [20].

Similarly, in the Republic of Tatarstan, research by *Ginter E.K. et al.* demonstrated significant differences in the prevalence of monogenic hereditary diseases were linked to varying levels of inbreeding across different districts, highlighting the role of genetic factors in disease distribution. These findings may also be relevant to understanding the genetic aspects of congenital anomaly prevalence in the Mangystau region, where unique genetic characteristics of the population may be present [21].

Additionally, research conducted in Gorno-Altaysk and other regions of Russia (Krikunova N.I. et al., 2004) demonstrates that both environmental and genetic predispositions can influence the prevalence of developmental defects. For instance, the high frequency of limb deformities observed in some areas of the Altai Republic may be related to environmental conditions similar to those in the ecologically disadvantaged regions of Mangystau [7].

In Kazakhstan, a similar study (*Sadykova A. et al.,* 2021) shows that despite an overall decline in the incidence of congenital anomalies in recent years, high rates of morbidity persist in southern regions, including areas with increased environmental risk. Studies conducted in the Pre-Aral region (*Nadeev* A.P. *et al.,* 2018) also confirm the influence of environmental factors on newborn health, with a higher frequency of congenital malformations observed in areas with polluted environments [12, 22].

A study in the East Kazakhstan region (*Abylgazinova* A.Zh. *et al*., 2016) showed that although the incidence of congenital anomalies decreased after the closure of the Semipalatinsk nuclear testing site, higher morbidity rates remained in areas close to the former testing zones. This highlights the urgent need for more in-depth research into the long-term ecological impacts of nuclear contamination and its potential effects on newborn health in affected areas [1].

Limitations:

This study has some limitations. Data quality may differ between regions due to varying diagnostic and reporting standards. It also didn’t explore genetic and environmental factors in depth, limiting our understanding of their separate roles. Being based on retrospective data, the study may include gaps or biases. Finally, the results might not apply to regions with different socio-economic or environmental backgrounds. More comprehensive, standardized research is needed.

Conclusions:

The findings stress the need for a broad, integrated approach to understanding congenital malformations. In areas like Mangystau, both environmental and genetic factors, along with healthcare access and diagnostic capacity, must be considered. Addressing these conditions effectively requires early detection, better healthcare access, and reducing environmental risks.

Generative AI Statement

The author(s) declare that generative AI was used in the creation of this manuscript. AI was used to edit the text in the revised version.

Competing interests: *None declared.*
Acknowledgements: *None.*
Funding: *No funding was provided.*

Authors' contributions: I.S., G.M., Zh.K. *conceived the study,* I.S., G.M., Zh.K. *acquired the data.* S.M., S.K., D.M., *A.Zh. contributed to data analysis,* I.S., G.M., Zh.K., N.K.*A drafted the manuscript.* D.Sh., Zh.S., Ye.K. *contributed to critical evaluation and revisions of the manuscript. All authors read and approved the final version of the paper.*

All authors have read, agreed to the final version of the manuscript, and signed the copyright transfer form.

Ethical Standards

Ethical approval was obtained from the Ethics Committee of Semey Medical University. The research was conducted in full compliance with the ethical principles set out in the Declaration of Helsinki.

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Received: 25 May 2025 / Accepted: 15 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.008

UDC 57.084+615.038

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CREATION OF THE PREGNANCY MICE MODEL TO STUDY THE EFFECT OF GLP-1/GIP AGONISTS

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Abstract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists represent a novel class of antidiabetic and anti-obesity agents. Despite their growing clinical relevance, little is known about their safety and potential effects during pregnancy. Here we describe the development of a pregnancy mouse model to study the impact of GLP-1/GIP dual agonists, with a focus on maternal metabolic changes, embryonic development, and organ-specific outcomes.

Introduction. The use of GLP-1 and GIP receptor agonists has expanded significantly due to their efficacy in improving glycemic control and reducing body weight. Tirzepatide, a dual GLP-1/GIP agonist, has shown remarkable clinical outcomes in type 2 diabetes and obesity. However, its safety profile during pregnancy remains poorly understood. Pregnancy is a unique physiological state characterized by altered glucose homeostasis, increased insulin resistance, and complex hormonal regulation. Drug exposure during this period can impact both maternal health and fetal development. Current clinical guidelines recommend discontinuing GLP-1 receptor agonists during pregnancy, but preclinical data are limited.

Aim. This work aims to establish a reproducible mouse pregnancy model to evaluate the effects of GLP-1/GIP agonists, such as Tirzepatide, on maternal physiology and embryonic outcomes.

Materials and Methods. Animals: C57BL/6 female mice, aged 8–10 weeks, were used. Females were mated overnight, and pregnancy was confirmed by vaginal plug observation (defined as embryonic day 0.5, E0.5). Experimental Groups: Control group – intraperitoneal injections of PBS, GLP-1/GIP agonist group – intraperitoneal injections of Tirzepatide. Treatment Protocol: Injections were administered daily starting from E13.5 until E17.5. On embryonic day 17.5, pregnant mice were sacrificed, and maternal organs, placenta, and embryos were collected for further analysis. Endpoints: Maternal body weight and food intake; Fetal number, size, and weight; Placental weight and morphology; Maternal organ collection for histological and molecular studies.

Results. A reproducible mouse pregnancy model to evaluate the effects of GLP-1/GIP agonists (Tirzepatide) on maternal physiology and embryonic outcomes was created. Pregnant mice were successfully treated with PBS, Tirzepatide according to the protocol. On E17.5, animals were sacrificed, and maternal/fetal samples were collected. Data analysis, including weight measurement, morphological assessment, and molecular profiling, is ongoing.

Conclusion. We established a pregnancy mouse model suitable for studying the impact of GLP-1/GIP dual agonists. This approach will generate critical preclinical data to evaluate maternal-fetal safety and mechanistic insights.

Keywords. *Pregnancy model, mice, GLP-1, GIP, dual agonist, tirzepatide, embryonic development, maternal metabolism*

For citation:

Akylzhanova G., Bakenova O., Abetov D., Umarov A., Musaeva Zh., Akilzhanova G., Sarbassov D., Akilzhanova A. Creation of the Pregnancy Mice Model to Study the Effect of GLP-1/GIP Agonists // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 58-64. *doi 10.34689/SH.2025.27.4.008*

Резюме

СОЗДАНИЕ МОДЕЛИ У БЕРЕМЕННЫХ МЫШЕЙ ДЛЯ ИЗУЧЕНИЯ ВЛИЯНИЯ АГОНИСТОВ GLP-1/GIP

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Агонисты рецепторов глюкагоноподобного пептида-1 (GLP-1) и глюкозозависимого инсулинотропного полипептида (GIP) представляют собой новый класс противодиабетических препаратов. Несмотря на растущее клиническое значение, их безопасность и возможные эффекты во время беременности изучены недостаточно. В данной работе описывается разработка модели беременности на мышах для изучения воздействия двойных агонистов GLP-1/GIP с акцентом на изменения материнского метаболизма, эмбриональное развитие и органоспецифические эффекты.

Введение. Применение агонистов рецепторов GLP-1 и GIP значительно расширилось благодаря их эффективности в улучшении гликемического контроля и снижении массы тела. Тирзепатид, двойной агонист GLP-1/GIP, продемонстрировал выдающиеся клинические результаты при лечении сахарного диабета 2 типа и ожирения. Однако его профиль безопасности во время беременности остаётся малоизученным. Беременность представляет собой уникальное физиологическое состояние, характеризующееся изменением гомеостаза глюкозы, повышенной инсулинорезистентностью и сложной гормональной регуляцией. Воздействие лекарственных средств в этот период может повлиять как на здоровье матери, так и на развитие плода. Согласно действующим клиническим рекомендациям, при беременности рекомендуется прекращать приём агонистов GLP-1, однако доклинических данных крайне мало.

Цель данной работы — создать воспроизводимую модель беременности на мышах для оценки влияния агонистов GLP-1/GIP, таких как тирзепатид, на физиологию матери и эмбриональные показатели.

Материалы и методы. Животные: Использовали самок мышей линии C57BL/6 в возрасте 8–10 недель. Самок подсаживали к самцам на ночь, беременность подтверждали по наличию вагинальной пробки (обозначено как эмбриональный день 0,5 — E0.5). Экспериментальные группы. Контрольная группа — внутрибрюшинные инъекции PBS. Группа GLP-1/GIP агониста — внутрибрюшинные инъекции тирзепатида. Протокол лечения. Инъекции проводились ежедневно, начиная с E13.5 и до E17.5. На 17,5-й день беременности (E17.5) беременные мыши подвергались эвтаназии, после чего собирались органы матери, плаценты и эмбрионы для дальнейшего анализа. Конечные точки. Масса тела матери и потребление пищи. Количество, размер и вес плодов. Масса и морфология плаценты. Сбор органов матери для гистологических и молекулярных исследований.

Результаты. Была создана воспроизводимая модель беременности на мышах для оценки влияния агонистов GLP-1/GIP (тирзепатида) на физиологию матери и эмбриональные исходы. Беременные мыши успешно получали PBS или тирзепатид в соответствии с протоколом. На E17.5 животные были эвтаназированы, и были собраны образцы от матерей и плодов. В настоящее время проводится анализ данных, включающий измерение массы, морфологическую оценку и молекулярное профилирование.

Заключение. Нами создана модель беременности у мышей, подходящая для изучения воздействия двойных агонистов GLP-1/GIP. Данный подход позволит получить важные доклинические данные для оценки материнско-плодной безопасности и механистических аспектов их действия.

***Ключевые слова**. Модель беременности, мыши, GLP-1, GIP, двойной агонист, тирзепатид, эмбриональное развитие, материнский метаболизм*

Для цитирования:
Акильжанова Г., Бакенова О., Абетов Д., Умаров А., Мусаева Ж., Акильжанова Г., Сарбасов Д., Акильжанова А. Создание модели у беременных мышей для изучения влияния агонистов GLP-1/GIP // Наука и Здравоохранение. 2025. Vol.27 (4), С. 58-64. *doi 10.34689/SH.2025.27.4.008*

Түйіндеме

GLP-1/GIP АГОНИСТЕРІНІҢ ӘСЕРІН ЗЕРТТЕУ ҮШІН ЖҮКТІ ТЫШҚАН МОДЕЛІН ҚҰРУ

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Глюкагонға ұқсас пептид-1 (GLP-1) және глюкозаға тәуелді инсулинотропты полипептид (GIP) рецепторларының агонисттері қант диабетіне және артық салмаққа қарсы жаңа дәрілер класына жатады. Олардың клиникалық маңызы артып келе жатқанына қарамастан, жүктілік кезеңіндегі қауіпсіздігі мен ықтимал әсерлері жеткілікті зерттелмеген. Бұл жұмыста GLP-1/GIP қос агонисттерінің жүктілік кезіндегі әсерін зерттеу үшін тышқандардың жүктілік моделін құру сипатталады. Зерттеу ананың метаболикалық өзгерістеріне, эмбрион дамуына және ағзаларға әсеріне бағытталған.

Кіріспе. GLP-1 және GIP рецепторларының агонисттерін қолдану соңғы жылдары айтарлықтай кеңейді, себебі олар гликемиялық бақылауды жақсартуда және артық дене салмағын азайтуда тиімді. GLP-1/GIP қос агонисті болып табылатын тирзепатид 2 типті қант диабеті мен артық салмақты азайтуда жоғары клиникалық нәтижелер көрсетті. Алайда, оның жүктілік кезіндегі қауіпсіздігі аз зерттелген. Жүктілік – глюкоза гомеостазының өзгеруімен, инсулинге төзімділіктің артуымен және күрделі гормондық реттелумен сипатталатын ерекше физиологиялық жағдай. Осы кезеңде дәрі-дәрмек қабылдау ананың денсаулығына да, ұрықтың дамуына да ықпал етуі мүмкін. Қазіргі клиникалық нұсқаулықтар жүктілік кезінде GLP-1 агонисттерін тоқтатуды ұсынады, бірақ доклиникалық деректер шектеулі.

Бұл жұмыстың мақсаты — ананың физиологиясына және эмбриондық көрсеткіштеріне GLP-1/GIP агонисттерінің, мысалы тирзепатидтің әсерін бағалау үшін қайталанбалы тышқан жүктілік моделін жасау.

Материалдар мен әдістер. Жануарлар. 8–10 апталық C57BL/6 ұрғашы тышқандар қолданылды. Ұрғашыларды түнде аталықтармен шағылыстырды, жүктілік вагинальды тығын арқылы расталды (эмбрионалды күн 0,5 — E0.5 деп белгіленді). Эксперименттік топтар. Бақылау тобы — PBS иньекциясы. GLP-1/GIP агонист тобы — тирзепатид иньекциясы. Емдеу протоколы. Инъекциялар E13.5-тен бастап E17.5-ке дейін күнге дейін жүргізілді. E17.5 күні жүкті тышқандар эвтаназия жасалып, аналықтар, плацента және эмбриондар кейінгі талдауға алынды. Соңғы нүктелер. Аналықтың дене салмағы мен тамақ қабылдауы. Ұрық саны, өлшемі және салмағы. Плацентаның салмағы мен морфологиясы. Аналық ағзаларын гистологиялық және молекулалық зерттеулерге жинау.

Нәтижелер. GLP-1/GIP агонистінің (тирзепатид) ана физиологиясы мен ұрықтың нәтижелеріне әсерін бағалау үшін тінтуірдің жүктілігінің қайталанатын үлгісі құрылды. Жүкті тышқандарға PBS және тирзепатидпен емдеу протоколына сәйкес жүргізілуде. E17.5 күні жануарларға эвтаназия жасалып, аналық және ұрық үлгілері жиналды. Мәліметтерді талдау (салмақ өлшеу, морфологиялық бағалау және молекулалық зерттеу) жалғасуда.

Қорытынды. Біз GLP-1/GIP қос агонисттерінің әсерін зерттеуге мүмкіндік беретін жүктілік моделі құрдық. Бұл тәсіл аналық-плацентарлық-ұрық жүйесінің қауіпсіздігін және әсер ету механизмдерін бағалауға қажетті маңызды доклиникалық деректер береді.

***Негізгі сөздер**. Жүктілік моделі, тышқан, GLP-1, GIP, қос агонист, тирзепатид, эмбрион дамуы, аналық метаболизмі*

Дәйексөз үшін:

Ақылжанова Ғ., Бакенова Ө., Абетов Д., Умаров А., Мұсаева Ж., Ақылжанова Г., Сарбасов Д., Акильжанова А. GLP-1/GIP агонистерінің әсерін зерттеу үшін жүкті тышқан моделін құру // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 58-64. *doi 10.34689/SH.2025.27.4.008*

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists, as well as dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, have emerged as highly effective therapies for type 2 diabetes and obesity. Among them, Tirzepatide, a first-in-class dual GLP-1/GIP agonist, has demonstrated remarkable improvements in glycemic control, weight reduction, and metabolic regulation in clinical trials [1,2]. However, despite their therapeutic promise, the safety and potential consequences of GLP-1/GIP agonists during pregnancy remain poorly understood.

Pregnancy represents a unique physiological state characterized by profound metabolic adaptations, including increased insulin resistance, altered glucose homeostasis, and complex hormonal changes [3,4]. These adaptations are essential for ensuring proper fetal growth and development, but they may also interact with pharmacological agents in unpredictable ways. Since GLP-1 receptor agonists cross the maternal circulation and can influence metabolic and hormonal pathways, there is a critical need to evaluate their potential impact on both maternal health and embryonic development [5].

Current clinical recommendations advise discontinuation of GLP-1 receptor agonists during pregnancy, largely due to the lack of sufficient preclinical and clinical data [6]. To address this knowledge gap, the development of robust animal models is essential. Mouse models, particularly the C57BL/6 strain, provide a well-established system for studying pregnancy-related physiology and drug effects [7].

The present study aims to establish a pregnancy mouse model to investigate the effects of GLP-1/GIP agonists, with a focus on maternal metabolic outcomes, fetal development, and placental function. This model will serve as a preclinical platform to generate critical insights into the safety and mechanisms of these agents during gestation.

Materials and Methods

Animals and Housing

C57BL/6 female mice (8–10 weeks old, average body weight 18–22 g) were obtained from the animal facility of National Laboratory Astana. Mice were housed in groups of 3–5 per cage under specific pathogen-free (SPF) conditions with a controlled 12 h light/dark cycle, temperature of 22 ± 2 °C, and relative humidity of 50–60%. Standard rodent chow and water were provided *ad libitum*. All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Nazarbayev University, in accordance with the ARRIVE guidelines and the European Directive 2010/63/EU for animal experiments.

Mating Procedure and Establishment of Pregnancy Model

Females were paired overnight with proven fertile C57BL/6 males (1:1 ratio). The presence of a vaginal plug was checked the next morning and recorded as embryonic day 0.5 (E0.5). Pregnancy progression was monitored by weight gain and abdominal palpation.

Experimental Groups and Drug Administration

Pregnant mice were randomly assigned to two groups:

Control group (PBS) – received intraperitoneal (IP) injections of sterile phosphate-buffered saline once daily.

GLP-1/GIP agonist group – received IP injections of Tirzepatide (4 mg/kg), prepared freshly each day in PBS, once daily. Treatment began on embryonic day 13.5 (E13.5), corresponding to late organogenesis, and continued until E17.5. Injections were performed at the same time each day to minimize circadian variability. The number of mice per group was n = 3.

Monitoring of Pregnancy and Body Weight

Maternal body weight was measured at baseline (E0.5) and then on E7.5, E10.5, E14.5, and E17.5 to assess pregnancy progression and treatment effects. Any abnormal behaviors, pregnancy loss, or maternal mortality were recorded.

Sample Collection and Processing

On E17.5, pregnant females were euthanized by CO_2 inhalation followed by cervical dislocation. The uterine horns were dissected under sterile conditions. The number of implantation sites, resorptions, and live fetuses was recorded.

Fetal measurements: body weight and crown-rump length were measured for each fetus.

Placental analysis: placentas were weighed and macroscopically examined.

Tissue collection: maternal tissues (liver, heart, brain, pancreas) and fetal tissues (liver, heart, brain, placenta) were collected. Samples were divided for:

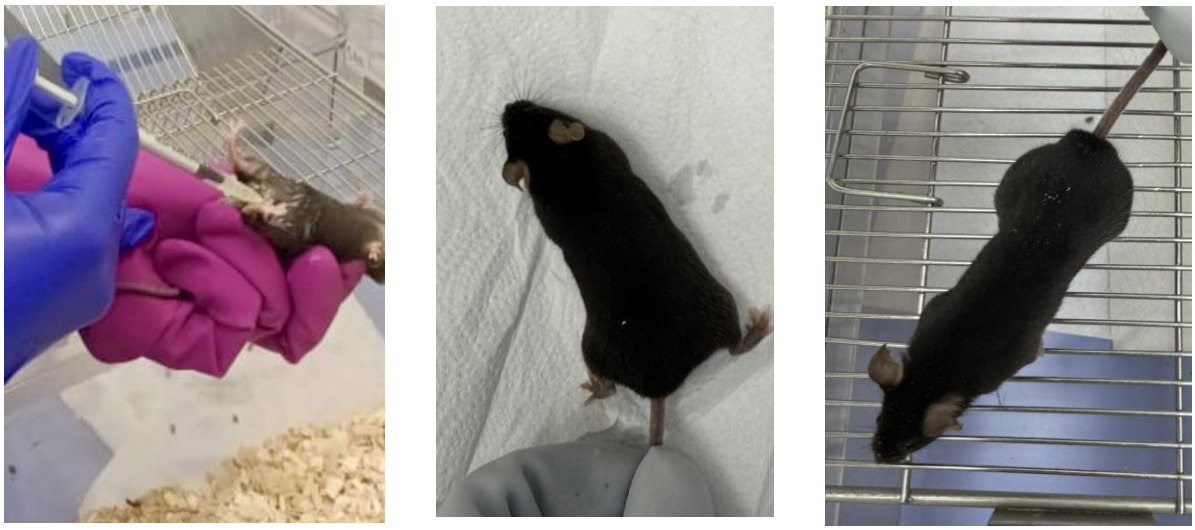
Fixation in 4% paraformaldehyde, followed by paraffin embedding for histological analysis (H&E staining, immunohistochemistry).

Snap-freezing in liquid nitrogen and storage at –80 °C for subsequent molecular studies (RNA, protein, or metabolite extraction).

Results

Preliminary observations from our pregnancy mouse model treated with Tirzepatide demonstrated notable changes compared to the control group. Pregnant mice receiving Tirzepatide exhibited a reduction in maternal body weight during gestation. In addition, the embryos collected at gestational day 17 were smaller in size compared to those from the PBS-treated control group.

Although these findings suggest a potential effect of Tirzepatide on maternal physiology and embryonic development, the study is still ongoing. Further analyses are currently in progress, including histological evaluation of collected tissues and RNA-based molecular studies, which will provide deeper insights into the mechanisms underlying these observed phenotypic change.



A B C

Fig.1 Mouse treated with Tirzepatide. A) Start injection (body weight 27.5 g. B) During pregnancy 32.7 g. C) Before sacrifice (body weight 26.1 g)

Left: tirzepatide treatment; Right: vehicle treatment



A B

Fig.2 Embryos collected from pregnant mice after dissection A) Tirzepatide 17.5 day B)Control 17.5 day

Although our data remain preliminary, they highlight the necessity of cautious consideration when translating incretin-based therapies to pregnant populations. The smaller embryonic size observed in the Tirzepatide-treated group may indicate potential risks to fetal development, warranting further systematic investigation. Our study is currently progressing toward histological assessment of maternal and embryonic tissues, as well as RNA-based analyses, to uncover molecular and cellular pathways that might underlie these phenotypic changes.

Future directions will include expanding the sample size, performing detailed histopathological examinations of placental and embryonic tissues, and integrating molecular assays such as qPCR or RNA-seq to identify alterations in gene expression associated with maternal treatment. Such data will provide more definitive insights into whether GLP-1/GIP agonists may interfere with fetal growth, and could help inform clinical decision-making regarding their use in women of reproductive age.

So, our initial findings support the feasibility of the established pregnancy mouse model and suggest that tirzepatide exposure during pregnancy has measurable effects on maternal and fetal outcomes. Continued analyses will be essential to clarify the mechanisms involved and to evaluate the translational significance of these findings for human health.

Discussion

The present study describes the establishment of a pregnancy mouse model to evaluate the effects of the dual GLP-1/GIP receptor agonist Tirzepatide during gestation. Preliminary findings revealed that maternal administration of Tirzepatide in late pregnancy was associated with reduced maternal weight gain and smaller fetal size compared with control animals. These results suggest that modulation of incretin signaling during pregnancy may influence maternal–fetal metabolic interactions and potentially alter fetal growth trajectories.

The observed reduction in maternal body weight is consistent with the known pharmacological actions of GLP-1 and GIP receptor agonists, which reduce appetite, delay gastric emptying, and enhance insulin sensitivity [1,2]. While these effects are therapeutically beneficial in obesity and type 2 diabetes, during pregnancy they may lead to relative maternal undernutrition or altered nutrient allocation

to the fetus. Reduced nutrient availability or placental transport efficiency could, in turn, contribute to the smaller fetal size observed in the Tirzepatide-treated group. It is also possible that direct effects of GLP-1/GIP signaling on placental tissues modulate trophoblast differentiation, angiogenesis, or nutrient transporter expression, thereby influencing fetal growth. Previous studies have shown that GLP-1 receptors are expressed in placental and decidual tissues, supporting the hypothesis that incretin agonists may act locally within the maternal–fetal interface [8,9].

Another potential mechanism underlying the observed phenotype involves altered maternal insulin and lipid metabolism. GLP-1 and GIP agonists enhance glucose-stimulated insulin secretion and promote lipid oxidation, which may shift the maternal metabolic profile toward a catabolic state. During late gestation, however, normal pregnancy requires increased insulin resistance to ensure adequate glucose supply to the fetus [3,4]. Interference with this adaptive mechanism might disturb the balance between maternal and fetal energy demands, leading to growth restriction or other developmental consequences. Future biochemical and molecular analyses—including insulin and leptin measurements, placental transporter gene expression, and histological assessment of placental morphology—will be necessary to delineate these pathways.

Although few studies have explored the safety of GLP-1 receptor agonists in pregnancy, available preclinical evidence raises concerns. For example, liraglutide and semaglutide have been associated with reduced fetal weight and delayed ossification in animal studies [10,11]. Human data remain limited, as clinical use of GLP-1 analogs is contraindicated during pregnancy. Our findings with Tirzepatide, a more potent dual agonist, align with these preclinical observations and emphasize the need for comprehensive evaluation of incretin-based therapies in reproductive contexts.

Limitations

This study has several limitations that must be acknowledged. First, the data presented are preliminary and based on a limited number of animals. The small sample size restricts the statistical power of our observations and prevents definitive conclusions at this stage. Second, the current analysis is largely descriptive, focusing on gross morphological changes such as maternal weight loss and reduced embryonic size. Without quantitative histological data or molecular analyses, it is not yet possible to determine the specific biological mechanisms underlying these changes.

Additionally, the duration of the experiment was limited to gestational day 17, and long-term effects on embryonic development, viability, or postnatal outcomes were not assessed. Earlier or prolonged exposure may yield different outcomes, particularly regarding implantation or early embryonic development. In addition, quantitative molecular and histological analyses are ongoing, which will provide more definitive evidence of the pathways involved. Since our model currently excludes postnatal follow-up, potential implications for offspring survival and metabolic health remain unexplored. Furthermore, only one dose and regimen of tirzepatide were tested, which may not fully reflect dose-dependent or time-dependent effects.

Finally, while mice provide a valuable model for investigating mechanisms of drug action, species differences in metabolism and placental physiology must be considered when extrapolating these findings to humans. Thus, caution is required before making translational inferences regarding the safety of GLP-1/GIP agonists during pregnancy.

Despite these limitations, the model successfully demonstrates that Tirzepatide exerts measurable physiological effects on pregnant mice and their fetuses, validating its utility for future mechanistic investigations.

Conclusion

This study presents the development of a pregnancy mouse model to investigate the impact of Tirzepatide during gestation. Our preliminary data suggest that GLP-1/GIP receptor activation during pregnancy may alter maternal metabolism and fetal growth. These findings highlight the importance of careful risk–benefit assessment when considering incretin-based therapies in women of reproductive age and underscore the need for further mechanistic and developmental studies. The established mouse model offers a valuable platform for future work aimed at elucidating the molecular and placental mechanisms underlying the maternal and fetal effects of GLP-1/GIP agonists during gestation.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

Funding: *This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (BR24993023, AP19677442; AP23490249; BR24992841) and Nazarbayev University funding CRP grant* 211123CRP1608 (Ainur Akilzhanova).

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Received: 30 January 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.009

UDC 616.89-008.454+616.89-008.44:612.3

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THE INFLUENCE OF THE GUT MICROBIOME ON SYMPTOMS OF ANXIETY AND DEPRESSION

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Abstract

Background. The idea has evolved into what is known as the brain–gut–microbiota system—a more comprehensive framework that reflects the intricate interactions between the central nervous system, the endocrine signaling pathways, the immune system, gut microbes, metabolic processes, and the barrier functions of both the brain and the gut. The coordinated function of these systems is essential for maintaining overall health. When this balance is disrupted, it can contribute to a range of health issues, including mental health disorders such as depression.

Materials and methods. A total of 100 patients were selected. Inclusion and exclusion criteria were defined. The main group received a probiotic, the comparison group did not receive it. Non-parametric Mann–Whitney U tests were used for between-group analyses. The qualitative analysis was conducted by groups, anxiety and depression indicators were assessed in both groups, and frequencies were compared using the Pearson chi-square test.

Results. The results of the study confirm the fact of the influence of gut microbiota on mental health, specifically on the levels of anxiety and depression. The lack of correlation between the BAI and BDI scales and the GAD-7 and PHQ-9 require further research, probably the PHQ-9 and GAD-7 scales are more concise and less detailed than the BDI and BAI scales.

Conclusion. Extensive research has highlighted disturbances in intestinal microbiota and metabolites in depression. The potential benefits of probiotics, prebiotics, and psychobiotics in influencing brain function are indicated by both preclinical and clinical research.

Keywords: *gut microbiome, intestinal microbiota, brain–gut–microbiota axis, probiotics, prebiotics, psychobiotics, gut–brain interaction, mental health, anxiety, depression, mood disorders, gut dysbiosis.*

For citation:

Kushugulova A.R., Bekbosynova M.S., Sakhipova A.G., Sailybaeva A.I., Taukelova A.T. The Influence of the gut Microbiome on symptoms of Anxiety and Depression // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 65-71. *doi 10.34689/SH.2025.27.4.009*

Резюме

ВЛИЯНИЕ КИШЕЧНОГО МИКРОБИОМА НА СИМПТОМЫ ТРЕВОЖНОСТИ И ДЕПРЕССИИ

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Введение. Концепция «мозг-кишечник-микробиота» представляет собой целостную модель, учитывающую сложные взаимодействия между центральной нервной системой, эндокринной и иммунной системами, кишечной микробиотой, метаболическими процессами и барьерными функциями мозга и кишечника. Согласованная работа этих систем необходима для поддержания здоровья; её нарушение может способствовать развитию различных состояний, в том числе депрессивных расстройств.

Материалы и методы. В исследование было включено 100 пациентов. Были сформулированы критерии включения и исключения. Основная группа получала пробиотик; контрольная группа его не принимала. Для межгруппового анализа применялись непараметрические тесты Ман-Уитни (Mann–Whitney U). Качественный анализ проводился по группам, индикаторы тревоги и депрессии оценивались в обеих группах, частоты сравнивались с помощью критерия Пирсона (χ^2).

Результаты. Результаты исследования подтверждают факт влияния кишечной микробиоты на психическое здоровье, в частности на уровни тревоги и депрессии. Отсутствие корреляции между шкалами BAI и BDI и шкалами GAD-7 и PHQ-9 требует дальнейших исследований. Вероятно, шкалы PHQ-9 и GAD-7 являются более лаконичными и менее детализированными по сравнению с BDI и BAI.

Заключение. Обширные исследования подчеркивают нарушения кишечной микробиоты и метаболитов при депрессии. Применение пробиотиков, пребиотиков и психобиотиков потенциально может влиять на функции мозга, что доказано как доклиническими, так и клиническими исследованиями.

Ключевые слова: *Кишечный микробиом, кишечная микробиота, ось «мозг–кишечник–микробиота», пробиотики, пребиотики, психобиотики, взаимодействие кишечника и мозга, психическое здоровье, тревожность, депрессия, аффективные расстройства, дисбиоз кишечника.*

Для цитирования:

Кушугулова А.Р., Бекбосынова М.С., Сахипова А.Г., Сайлыбаева А.И., Таукелова А.Т. Влияние кишечного микробиома на симптомы тревожности и депрессии // Наука и Здравоохранение. 2025. Vol.27 (4), С. 65-71. *doi 10.34689/SH.2025.27.4.009*

Түйіндеме

ІШЕК МИКРОБИОМЫНЫҢ ҮРЕЙ ЖӘНЕ ДЕПРЕССИЯ БЕЛГІЛЕРІНЕ ӘСКРІ

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Кіріспе. «Ми–ішек–микробиота» тұжырымдамасы орталық жүйке жүйесі, эндокриндік және иммундық жүйелер, ішек микробиотасы, метаболикалық үдерістер мен ми және ішек тосқауылдық функциялары арасындағы күрделі өзара байланыстарды қамтитын тұтас модельді білдіреді. Бұл жүйелердің үйлесімді қызметі денсаулықты сақтауда маңызды рөл атқарады. Оның бұзылуы әртүрлі патологиялардың, соның ішінде депрессиялық бұзылыстардың дамуына ықпал етуі мүмкін.

Материалдар мен әдістер. Зерттеу барлығы 100 пациентті қамтыды. Қосылу және алынып тастау критерийлері анықталды. Негізгі топ пробиотик қабылдады, ал бақылау тобы қабылдамады. Топтар арасындағы айырмашылықтарды бағалау үшін Манн–Уитни (Mann–Whitney U) параметрлік емес тесттері қолданылды. Сапалық талдау топтар бойынша жүргізілді, мазасыздық пен депрессия көрсеткіштері екі топта да бағаланды, жиіліктер Пирсон (χ^2) критерийімен салыстырылды.

Нәтижелері. Зерттеу нәтижелері ішек микробиотасының психикалық денсаулыққа, атап айтқанда үрей мен депрессия деңгейлеріне әсер ететінін растайды. BAI және BDI шкалалары мен GAD-7 және PHQ-9 шкалалары арасындағы корреляцияның болмауы қосымша зерттеуді талап етеді. PHQ-9 және GAD-7 шкалалары BDI мен BAI-ға қарағанда қысқа және аз егжей-тегжейлі болып келуі мүмкін.

Қорытынды. Көптеген зерттеулерде депрессия кезінде ішек микробиотасы мен оның метаболиттерінің бұзылуы анықталған. Пребиотиктер, пробиотиктер және психобиотиктердің ми функциясына әсер ету және психикалық жағдайды жақсарту мүмкіндігі клиникаға дейінгі және клиникалық зерттеулерде дәлелденген.

Түйінді сөздер: *ішек микробиомы, ішек микробиотасы, «ми–ішек–микробиота» осі, пробиотиктер, пребиотиктер, психобиотиктер, ішек пен ми арасындағы өзара әрекеттесу, психикалық денсаулық, үрей, депрессия, аффективті бұзылыстар, ішек дисбиозы.*

Дәйексөз үшін:

Кушугулова А.Р., Бекбосынова М.С., Сахипова А.Г., Сайлыбаева А.И., Таукелова А.Т. Ішек микробиомының үрей және депрессия белгілеріне әскрі // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 65-71. *doi 10.34689/SH.2025.27.4.009*

Introduction

The concept of the gut–brain axis was first introduced in 1980, following unexpected research findings that revealed how hormones produced by the gastrointestinal endocrine system could influence neurons and brain cells. In the decades since, this concept has been significantly expanded to include the role of the gut microbiome in the communication between the gut and the brain.

Today, the idea has evolved into what is known as the brain–gut–microbiota system—a more comprehensive framework that reflects the intricate interactions between the central nervous system (CNS), the endocrine signaling

pathways, the immune system, gut microbes, metabolic processes, and the barrier functions of both the brain and the gut.

The coordinated function of these systems is essential for maintaining overall health. When this balance is disrupted, it can contribute to a range of health issues, including mental health disorders such as depression [1,2,8].

Neural signal networks in the brain–gut–microbiota system are important and fast response routes, including the **enteric nervous system** (ENS), vagus nerves and spinal nerves. The ENS, which is also known as the "brain in the gut" or "second brain," controls the gut's external and internal environment. The complex regulation of the ENS serves a multifaceted role in modulating microbial composition, microbiota-related metabolites, **neurotransmitter** and immune signaling, and protection of the **intestinal barrier**. Thus, bidirectional communication between the CNS and ENS, as well as other signals, forms part of the network for the brain–gut–microbiota axis. The vagal pathway has been repeatedly identified as the most direct link for microflora signals to reach the brain. The vagus nerve plays a dual role in the body. On one hand, it helps regulate metabolic homeostasis and feeding behavior, including controlling gastrointestinal motility and secretion. On the other hand, it is actively involved in the body's inflammatory responses, linking the brain, gut, and other organs. Through its afferent and efferent pathways, the vagus nerve detects inflammatory cytokines via pattern recognition receptors such as toll-like receptors. The afferent signals carry this information to the brain, where it is processed. In response, the efferent arm of the vagus nerve regulates immune activity by suppressing the release of pro-inflammatory cytokines from the gut and other organs. This bidirectional communication forms the basis of the inflammatory reflex, a key mechanism in maintaining immune balance. In addition, acetylcholine receptors/ligands mediating the **cholinergic** anti-inflammatory pathway via the vagus nerve have also been proposed as an important immune modulator in the gut microbiota that communicates with the brain [1, 2, 8, 9].

Depression is described as a common mental disorder state, characterized by a continuous feeling of sadness and apathy lasting at least two weeks, as a result of interactions covering social, psychological, and biological factors, for example, significant changes in life, family matters, chronic health problems, or addiction. It is also a common cause of disability and a cause of suicide death. According to WHO, approximately 280 million people worldwide suffer from major depressive disorder (MDD) every year, and more than 700,000 people die from committing suicide. The data described many factors that link this mental disorder with the components of the intestinal microbiota, which was confirmed by *Naseribafrouei et al.* They have shown that the level of the Alistipes genus associated with inflammation and Oscillibacter, which has valeric acid involved in is associated with depression, was elevated in patients with MDD [4].

Zhang et al. [12] showed, using a mouse model, that microbiota dysbiosis was associated with greater intestinal permeability and systemic inflammation. As a result of endogenous melatonin reduction (EMR), the composition of the mice microbiota changed and consisted of a decrease in the relative abundance of Bacteroidetes, an alteration of the Firmicutes/Bacteroidetes ratio, and growth of the relative abundance of Lactobacillus. The study also revealed improved gut permeability (leaky gut) and systemic inflammation in EMR mice [4,6].

The determination of short chain fatty acids (SCFAs) content could be helpful in the analysis of the microbiota composition by patients with MDD. The study concerning the SCAFs profile conducted by *Skonieczna-Żydecka et al.* on a group of 116 women aged 52.0 (±4.7) years, in which 40.52% of them recognized depression, revealed a lower level of propionic acid and a higher content of isocaproic acid compared to healthy subjects [12]. However, because of the small sample size, it is not possible to definitively conclude that SCAFs contribute to the depressive phenotype. Research using animal models has demonstrated a link between the composition of the intestinal microbiota and behaviors or traits such as anxiety and depression. *Gan et al.* showed changes in the behavior of shy personalities of Mongolian gerbils (Meriones unguiculates) after transplantation of the gut microbiota of bold individuals. Shy gerbils often exhibited bold behavior after "bold fecal microbiota" transplantation, suggesting the association between the gut microbiota and the host's personality [4,6].

Communication between the gut and the brain occurs in both directions and utilizes multiple pathways, including neural, endocrine, and immune systems. The microbiota and their metabolites play a crucial role as modulators in this gut-brain communication, giving rise to the concept of the microbiota-gut-brain (MGB) axis. The role of the routes involved in the MGB axis in depression has been well delineated. The microbial composition and metabolites change in MDD patients results in a disrupted homeostasis of the gut microenvironment, affecting the function of the gut epithelium and causing intestinal barrier dysfunction and inflammatory responses. The increased systemic translocation of gut metabolites, microbial cell components, or even the microbiota via the damaged intestinal barrier (the "leaky gut") heightens systemic inflammatory responses (e.g., Th17/regulatory T cell (Th17/Treg) imbalance, interleukin [IL]-6, IL-1β, and tumor necrosis factor-alpha) that have been implicated in the pathogenesis of depression. The ENS, referred to as the "second brain", has been reported to be involved in the development of brain disorders. Abnormal ENS activity arising from intestinal pathology aggravates depression-related pathological changes by altering gut secretion, immune defenses, motility, and permeability. Besides the ENS, the vagus nerve also plays an important role in transmitting microbial signals from the gut to the brain in depression. Preclinical studies have verified that subdiaphragmatic vagotomy blocked the development of depression-like behaviors in rodents after lipopolysaccharide (LPS) injection or fecal microbiota transplantation from Chrna7 knock-out mice with depression-like behaviors. In clinical, vagus nerve stimulation has long been approved for treatment-resistant depression. The microbial cell components, e.g., LPS produced by gram-negative bacteria, and peripheral inflammatory signals reach the brain by crossing the blood–brain barrier resulting in neuroinflammation, subsequently induce neuropathological changes through chronic

activating specific cells, including synaptic defects, demyelination, abnormal neurogenesis and neurotransmitters release, that are involved in the pathogenesis of depression. Microbial signals, pathological neurobiological changes, and depressive emotions can activate the hypothalamic-pituitary-adrenal axis, increasing the synthesis and release of cortisol. As a part of the brain-gut axis, excessive levels of cortisol promote gut pathology by modulating intestinal barrier function and inflammatory responses, resulting in a leaky gut; this process is a key component of the MGB axis in depression. Beyond these routes, various signal transduction systems and metabolic pathways are also implicated in the MGB-based pathogenesis of depression, such as the endocannabinoid system, CAMKII-CREB and MAPK signaling, and glycerophospholipid metabolism. Moreover, mitochondria are reported to be potential key mediators of the gut microbiota dysbiosis and depression relationship. The various pathways involved in gut-brain bidirectional communication create a complex network of mechanisms, and their interactions make it challenging to study how gut microbiota regulate depression [6,7,12].

In Kazakhstan, the association between gut microbiota and heart failure, insulin resistance and cognitive functions, including the association gut dysbiosis with Alzheimer's disease, were investigated. However, researches related to the influence of microbiota on anxiety and depression were not covered. This issue is relevant throughout the world, especially in Kazakhstan, because the Republic of Kazakhstan has great potential for the development of such investigations, taking into account the characteristics of the national diet with the consumption of dairy products.

Materials and methods

A total of 100 patients were selected. Inclusion criteria: Age over 18 years; Diagnosis of heart failure in accordance with internationally recognized guidelines and class I-IV according to NYHA, stage A-C according to the ACC/AHA heart failure classification. Clinically stable condition and optimally selected; drug therapy for CHF at least 4 weeks ago in accordance with current recommendations; Consent to participate in the study. Exclusion criteria: Age under 18 years; Refusal to undergo diagnostic procedures defined by the study protocol; Terminal stage of CHF (stage D according to ANA/ACC); Coronary or peripheral revascularization procedures, valve procedures or any major surgical procedure within 3 months prior to inclusion in the study; Use of antibiotics, cytostatic therapy and pro- or prebiotics less than 1 month before the baseline visit; Oncological and autoimmune diseases (diseases of connective tissue, intestines, skin, etc.). Any acute illness or active infection; Individual intolerance to the nutrients taken (probiotics); The presence of other anatomical or concomitant diseases, or other medical, social or psychological conditions that, in the opinion of the investigator, may limit the ability of the subject to participate in the clinical trial or to comply with the requirements of follow-up, or affect the scientific validity of the results of the clinical trial. Patients in both groups underwent a complete ultrasound examination of the heart.

The main group received a probiotic, the comparison group did not receive it. The multicomponent probiotic contains strains of live lyophilized bifido- and lactobacilli identical to human microflora, with high viability: resistant to gastric juice, digestive enzymes and bile acids. These strains are characterized by a high ability to adhere and colonize on the intestinal mucosa, which creates optimal conditions for the growth of normal microflora. Patients took the probiotic in a sachet for three months before the survey, one sachet twice a day before meals. The laboratory tests were performed but not applicable in this study.

Patients were interviewed on four questionnaires. Anxiety level was assessed on two tests: Beck Anxiety Inventory (BAI) – this scale is a self-report measure of anxiety and General Anxiety Disorder-7 (GAD-7) – this initial screening tool for generalized anxiety disorder. The level of depression was also assessed by two tests: Beck Depression Inventory (BDI) – this self-report rating inventory that measures characteristic attitudes and symptoms of depression and Patient Health Questionnaire (PHQ-9) – this depression symptom scale. All questionnaires are validated and widely used in medicine.

Ethics statement

This study was approved by the Local Ethics Committee No. 2023/01-009.

Statistical analysis

As almost all were not normally distributed, non-parametric Mann–Whitney U tests were used for between-group analyses. The qualitative analysis was conducted by two groups, anxiety and depression indicators were assessed in both groups, and frequencies were compared using the chi-square tests: Pearson chi-square, likelihood ratio, linear-by-linear association and number of valid cases.

Results

Comparisons of groups were performed in both tables using the Mann-Whitney test. As we can see in Table 1, both groups are comparable according to the main criteria: age, body mass index, ejection fraction, valve sizes.

Table 1.

Comparability of groups, comparisons of groups using the Mann-Whitney test.

	Control group M±SD n=44	Study group M±SD n=97	p
age	57,48±14,76	58,24±12,09	0,815
BMI (kg/m2)	28,76±5,24	30,42±5,43	0,124
EF, %	54,17±8,61	46,62±11,06	0,001
MV	0,90±0,84	1,03±0,96	0,553
TV	1,19±0,94	0,81±0,91	0,012
Vmax TR	2,35±0,21	1,92±0,79	0,315
PASP (mm.Hg)	33,51±15,34	29,17±8,40	0,353
AV	0,27±0,40	0,25±0,50	0,317
PV	0,13±0,27	0,05±0,22	0,021

BMI - Body Mass Index, EF - ejection fraction, MV- mitral valve, TV- tricuspid valve, Vmax TR - maximum velocity of the blood flow during tricuspid regurgitation, PASP-pulmonary artery systolic pressure, AV - aortic valve, PV- pulmonary valve.

In table 2 comparisons of groups using the Mann-Whitney test, with median-quartiles, the distribution differs from the normal one due to the asymmetry, especially at the expense of the last columns.

Table 2.

Comparisons of groups using the Mann-Whitney test, with median-quartiles.

	Control group Me(Q1-Q3) n=44	Study group Me(Q1-Q3) n=97	p
EDV (ml)	81,00 (66,50-96,08)	116,00 (87,00-152,00)	<0,001
Index. EDV (ml)	46,44 (39,64-51,60)	59,64 (46,51-78,89)	<0,001
ESV (ml)	35,65 (25,70-43,35)	63,00 (36,30-94,10)	<0,001
Index. ESV (ml)	20,25 (14,42-23,29)	34,75 (19,96-47,82)	<0,001
EDD (cm)	4,50 (4,03-4,98)	5,20 (4,60-5,70)	<0,001
Index. EDD (cm)	2,54 (2,19-2,82)	2,69 (2,41-3,02)	0,024
ESD (cm)	3,15 (2,60-3,50)	4,10 (3,30-4,70)	<0,001
Index. ESD (cm)	1,75 (1,42-1,99)	2,06 (1,74-2,46)	0,001
LA V (ml)	55,55 (43,25-75,48)	74,00 (58,00-102,00)	<0,001
Index. LA V (ml)	31,22 (25,00-39,43)	38,08 (29,87-53,62)	0,003
BAI	11,00 (6,00-22,00)	7,00 (3,00-12,00)	0,001
BDI	8,00 (4,00-13,50)	2,50 (0,00-8,00)	<0,001
GAD-7	4,00 (0,00-6,00)	3,00 (0,00-6,00)	0,481
PHQ-9	6,00 (4,00-8,75)	6,00 (4,00-8,00)	0,869

Table 3.

Qualitative analysis of the results of the BAI.

		Control group		Study group	
		Абс.	%	Абс.	%
BAI	,0			6	6%
	1,0	1	2%	3	3%
	2,0	1	2%	8	8%
	3,0	3	7%	14	14%
	4,0	2	5%	5	5%
	5,0	2	5%	5	5%
	6,0	3	7%	7	7%
	7,0	3	7%	7	7%
	8,0			3	3%
	9,0	2	5%	8	8%
	10,0	1	2%	2	2%
	11,0	4	9%	3	3%
	12,0	1	2%	3	3%
	13,0	2	5%	3	3%
	14,0	1	2%	1	1%
	15,0	1	2%	3	3%
	16,0	1	2%	2	2%
	17,0	2	5%	3	3%
	18,0	1	2%	3	3%
	19,0			1	1%
	20,0			1	1%
	21,0	1	2%		
	22,0	2	5%		
	23,0	4	9%	2	2%
	26,0			2	2%
	27,0			1	1%
	29,0	1	2%		
	30,0	1	2%		
	32,0	1	2%		
	33,0	1	2%		
	35,0			1	1%
	51,0	1	2%		

BAI - Beck Anxiety Inventory.

EDV - end-diastolic volume, Index. EDV – index end-diastolic volume, ESV - end-systolic volume, Index. ESV – index end-systolic volume, EDD - end-diastolic diameter, Index. EDD – index End-diastolic diameter, ESD - end systolic diameter, Index. ESD – index end systolic diameter, LA V - left atrial volume, Index. LA V – index left atrial volume, BAI - Beck Anxiety Inventory, BDI - Beck Depression Inventory, GAD-7 - Generalized Anxiety Disorder and PHQ-9 Patient Health Questionnaire-9.

As a result of statistical analysis, we obtained a statistical difference in the following parameters: end-diastolic volume, index end-diastolic volume, end-systolic volume, index end-systolic volume, end-diastolic diameter, index End-diastolic diameter, end systolic diameter, index end systolic diameter, left atrial volume, index left atrial volume, BAI, BDI. There was no statistical difference between the studied groups on the PHQ-9 and GAD-7 scales.

A qualitative analysis was conducted, where the results of depression and anxiety tests were selected as the analyzed features. Tables 3,5,7,9 provide a qualitative analysis of the analyzed features. The tables 4,6,8,10 show several chi-square tests of the analyzed features respectively.

Table 4.

Chi-Square tests for BAI.

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	35,221[a]	31	0,275
Likelihood Ratio	40,321	31	0,122
Linear-by-Linear Association	13,160	1	0,000
N of Valid Cases	140		

df - Degrees of Freedom, Asymp. Sig. (2-sided) - Asymptotic Significance (2-sided). a - in this table have expected count less than 5, and the minimum expected count is 0,31.

There is a statistical difference between the studied groups on the scale BAI.

Table 5. **Qualitative analysis of the results of the BDI.**

		Control group		Study group	
		Абс.	%	Абс.	%
BDI	,0	2	5%	29	30%
	1,0	2	5%	7	7%
	2,0	2	5%	12	13%
	3,0	2	5%	8	8%
	4,0	5	12%	3	3%
	5,0	3	7%	3	3%
	6,0			3	3%
	7,0	2	5%	5	5%
	8,0	3	7%	6	6%
	9,0	1	2%	3	3%
	10,0	1	2%	3	3%
	11,0	3	7%	1	1%
	12,0	2	5%	1	1%
	13,0	3	7%		
	14,0	1	2%	2	2%
	15,0	2	5%	3	3%
	16,0	1	2%	2	2%
	17,0	1	2%	1	1%
	18,0			1	1%
	19,0	2	5%	1	1%
	20,0			1	1%
	22,0			1	1%
	24,0	1	2%		
	26,0	1	2%		
	29,0	1	2%		

BDI – Beck Depression Inventory.

Table 6. **Chi-Square tests for BDI.**

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	40,861[a]	24	0,017
Likelihood Ratio	44,339	24	0,007
Linear-by-Linear Association	15,703	1	0,000
N of Valid Cases	137		

df - Degrees of Freedom, Asymp. Sig. (2-sided) - Asymptotic Significance (2-sided). a – in this table have expected count less than 5, and the minimum expected count is 0,30.

There is a statistical difference between the studied groups on the scale BDI.

Table 7. **Qualitative analysis of the results of the GAD – 7.**

		Control group		Study group	
		Абс.	%	Абс.	%
GAD-7	,0	12	27%	26	27%
	1,0	3	7%	7	7%
	2,0	4	9%	13	13%
	3,0	1	2%	6	6%
	4,0	3	7%	10	10%
	5,0	6	14%	7	7%
	6,0	5	11%	11	11%
	7,0	2	5%	7	7%
	8,0	1	2%	2	2%
	9,0	3	7%	2	2%
	10,0	1	2%	2	2%
	11,0	1	2%	1	1%
	12,0			2	2%
	13,0	1	2%		
	16,0	1	2%		
	18,0			1	1%

GAD-7 **–** General Anxiety Disorder Questionnaire – 7.

Table 8. **Chi-Square tests for GAD-7.**

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1,544[a]	5	,713
Likelihood Ratio	2,600	5	,633
Linear-by-Linear Association	,871		,351
N of Valid Cases	41		

df - Degrees of Freedom, Asymp. Sig. (2-sided) - Asymptotic Significance (2-sided). a - in this table have expected count less than 5, and the minimum expected count is 0,31.

According to the results of the calculations of the GAD-7 scale, there is no statistical difference in the groups.

Table 9. **Qualitative analysis of the results of the PHQ–9.**

		Control group		Study group	
		Абс.	%	Абс.	%
PHQ-9	,0			2	2%
	1,0	1	2%	2	2%
	2,0	3	7%	9	9%
	3,0	5	11%	4	4%
	4,0	7	16%	8	8%
	5,0	4	9%	14	15%
	6,0	8	18%	15	16%
	7,0	2	5%	16	17%
	8,0	3	7%	11	11%
	9,0	5	11%	8	8%
	10,0	2	5%	2	2%
	11,0	2	5%		
	12,0			1	1%
	13,0	1	2%	1	1%
	14,0			1	1%
	15,0			1	1%
	17,0	1	2%		
	18,0			1	1%

PHQ-9 – Patient Health Questionnaire-9.

Table 10. **Chi-Square tests for PHQ-9.**

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	19,762[a]	17	0,287
Likelihood Ratio	22,351	17	0,172
Linear-by-Linear Association	0,020	1	0,888
N of Valid Cases	140		

df - Degrees of Freedom, Asymp. Sig. (2-sided) - Asymptotic Significance (2-sided). a - in this table have expected count less than 5, and the minimum expected count is 0,31.

According to the results of the calculations of the PHQ-9 scale, there is no statistical difference in the groups.

From the tables above we can judge the statistically significant difference between the anxiety and depression levels in the probiotic groups and the control group. The p-value is less than 0,05 when comparing the groups between themselves on the scales: BAI, BDI, GAD-7. The result of comparison on the PHQ-9 scale is very different, because there is no statistical difference**.**

Discussion

In this research, both groups were studied, selected according to the inclusion and exclusion criteria, which were

comparable in terms of the main indicators. A survey was conducted on anxiety and depression scales, ultrasound examination of the heart. According to the results of the study, a statistically significant difference was revealed in some indicators of ultrasound examination of the heart and the results of the BAI and BDI. An unexpected result was the absence of a statistical difference in the GAD-7 and PHQ-9 scales. The results of statistical analysis according to the Mann-Whitney and chi-square criteria were correlated with each other.

The results of the study confirm the fact of the influence of gut microbiota on mental health, specifically on the levels of anxiety and depression. The lack of correlation between the BAI and BDI scales and the GAD-7 and PHQ-9 require further research, probably the PHQ-9 and GAD-7 scales are more concise and less detailed than the BDI and BAI scales. The identified difference in some indicators of ultrasound of the heart also requires further research in the direction of the influence of gut microbiota on heart failure. In general, the study conducted on the Kazakhstani population is quite ambiguous in its results and deserves the attention of the scientific community.

Extensive research has highlighted disturbances in intestinal microbiota and metabolites in depression [3,11]. Traditional treatments targeting neurotransmitter reuptake have demonstrated limited efficacy, prompting the exploration of novel mechanisms focusing on the gut-brain axis. One study provides compelling evidence for a mechanism of depression involving altered gut microbiota leading to depleted catecholamine neurotransmitter metabolites. The substrates of HVA were tyrosinecontaining compounds, and tyrosine-rich foods such as lean meat, fish, dairy products, and nuts had the mood-regulating effects [12].

The purpose of this work was to enhance our understanding of the role of microbiota and nutrition in the communication between the intestine and the brain. The vast array of microbes residing in and on the human body appears to influence mental health and disease by affecting this communication pathway [5,10]. Clinical studies suggest that the diversity and richness of microbiota contribute to resilience, helping to maintain a balanced microbial composition that may facilitate effective interactions between the gut and the brain. Additionally, the potential benefits of probiotics, prebiotics, and psychobiotics in influencing brain function are indicated by both preclinical and clinical research. Nutrition may play a role in supporting microbial balance and influencing the gut-brain axis as it relates to mood and cognition. However, establishing direct correlations between these observations remains challenging due to the complex nature of psychiatric disorders and the variability of individual microbial profiles. Future extensive clinical trials in humans could provide valuable insights into the potential for microbiota-based approaches in the treatment and prevention of psychiatric disorders, possibly offering alternatives to traditional pharmacological methods [3].

Dietary interventions targeting the gut microbiota to alleviate depression and improve mental health offer promising therapeutic avenues. Further clinical studies are needed to confirm the therapeutic effect of dietary interventions targeting the gut microbiota. And the development of reliable, individualized treatment strategies for mental disorders is also needed [3].

Disclosure: *There are no conflicts of interest among all authors.*

Acknowledgments: *None.*

Funding: *This study was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (IRN BR21882152). Sponsors played no role in the design of the study, data collection and analysis, decision to publish, or preparation of the manuscript.*

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Received: 15 May 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.010

UDC 616.43

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SATISFACTION WITH THE QUALITY OF PRIMARY CARE FOR PATIENTS WITH HYPERTENSION

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Abstract

Introduction. Hypertension is one of the most common diseases, the occurrence of which is associated with a significant increase in the risk of cardiovascular complications and mortality. Satisfaction with the quality of outpatient care for patients with hypertension is becoming increasingly important in healthcare. Although there are many effective methods for managing hypertension, studies show that the treatment of arterial hypertension is unsuccessful mainly due to a lack of cooperation between patients and doctors in terms of lifestyle changes and adherence to prescribed therapy.

Objective: To assess patient satisfaction with the quality of outpatient care for hypertension using a social questionnaire.

Materials and methods: The study design was a single-moment cross-sectional study. The social survey was conducted among patients with hypertension between September 2023 and December 2023 in cardiologists' offices, involving 50 patients from four polyclinics in Astana. The study included patients with arterial hypertension who were registered with a general practitioner, were over 18 years of age, and were receiving treatment under a disease management program.

Results: The study included 200 patients with arterial hypertension, of whom 41% were men and 59% were women. The survey results showed that 72.5% of respondents knew how to measure their own blood pressure, with 67.0% having a blood pressure monitor at their disposal. Satisfaction with the organization of the Disease Management Program was demonstrated by 47.9% of participants. Only 29.7% of respondents attended the hypertension school, which indicates insufficient involvement in the educational aspects of the program. Only 46.5% of patients expressed a willingness to recommend participation in the disease management program to their friends, which may indicate the need to improve the motivational and informational components of this program.

Conclusion. Thus, in order to increase patient satisfaction and improve the effectiveness of the Disease Management Program, it is necessary to intensify the work of health schools, ensure that patients are taught the principles of self-monitoring and the development of individual treatment plans, and strengthen the participation of primary health care specialists in patient support. This will not only improve clinical outcomes but also increase patients' responsibility for their own health.

Keywords: *arterial hypertension, disease management program, patient satisfaction, health schools.*

For citation:

Markabayeva A.M., Kerimkulova A.S., Ospanova A.S., Umbetzhanova A.T, Zhakupbekova M.O. Satisfaction with the quality of primary care for patients with hypertension // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 72-78. *doi 10.34689/SH.2025.27.4.010*

Резюме

УДОВЛЕТВОРЕННОСТЬ КАЧЕСТВОМ ОКАЗАНИЯ АМБУЛАТОРНОЙ МЕДИЦИНСКОЙ ПОМОЩИ ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Введение. Артериальная гипертония является одним из самых распространенных заболеваний, возникновение которого сопряжено со значительным увеличением риска развития сердечно-сосудистых осложнений и смертности.

Удовлетворенность качеством оказания медицинской помощи пациентов с артериальной гипертензией на амбулаторном уровне приобретает важное значение в здравоохранении. Несмотря на множество эффективных методов управления гипертонией, исследования показывают, что лечение артериальной гипертензии безуспешно в основном из-за отсутствия сотрудничества между пациентами и врачами относительно изменения образа жизни и соблюдения предписанной терапии.

Цель: оценить удовлетворенность качеством оказания амбулаторной медицинской помощи пациентов с артериальной гипертензии с помощью социального анкетирования.

Материалы и методы: Дизайн исследования - одномоментное поперечное исследование. Социальный опрос проводился среди пациентов с артериальной гипертензией в период с сентября 2023 года по декабрь 2023 года в кабинетах кардиолога по 50 пациентов из 4 поликлиник г. Астана. В исследование включены пациенты с артериальной гипертензией, состоящие на диспансерном учете у врача общей практики в возрасте старше 18 лет, и получающие лечение по Программе управления заболеванием.

Результаты: В исследование включены 200 пациентов с артериальной гипертензией, среди которых 41% составили мужчины и 59% — женщины. По результатам анкетирования установлено, что 72,5% респондентов владеют навыками самостоятельного измерения артериального давления, при этом 67,0% имеют в распоряжении тонометр. Удовлетворённость организацией Программы управления заболеваниями продемонстрировали 47,9% участников. Школу артериальной гипертензии посещали лишь 29,7% опрошенных, что указывает на недостаточную вовлечённость в образовательные аспекты программы. Готовность рекомендовать участие в Программе управления заболеваниями своим знакомым выразили только 46,5% пациентов, что может свидетельствовать о необходимости повышения мотивационной и информационной составляющей данной программы.

Заключение. Таким образом, для повышения удовлетворенности пациентов и улучшения эффективности Программы управления заболеваниями необходимо активизировать работу школ здоровья, обеспечить обучение пациентов принципам самоконтроля и разработку индивидуальных планов лечения, а также усилить участие специалистов первичной медико-санитарной помощи в сопровождении пациентов. Это позволит не только улучшить клинические исходы, но и повысить уровень ответственности пациентов за собственное здоровье.

Ключевые слова: *артериальная гипертензия, программа управления заболеваниями, удовлетворенность пациентов, школы здоровья.*

Для цитирования:

Маркабаева А.М., Керимкулова А.С., Оспанова А.С., Умбетжанова А.Т., Жакупбекова М.О. Удовлетворенность качеством оказания амбулаторной медицинской помощи пациентов с артериальной гипертензией // Наука и Здравоохранение. 2025. Vol.27 (4), С. 72-78. *doi 10.34689/SH.2025.27.4.010*

Түйіндеме

АРТЕРИЯЛЫҚ ГИПЕРТЕНЗИЯМЕН СЫРҚАТТАРДЫҢ АМБУЛАТОРИЯЛЫҚ МЕДИЦИНАЛЫҚ КӨМЕКТІҢ САПАСЫНА ҚАНАҒАТТАНУШЫЛЫҒЫ

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Кіріспе. Артериялық гипертензия – кең таралған аурулардың бірі, оның пайда болуы жүрек-қан тамырлары асқынулары мен өлім-жітім қаупінің едәуір артуымен байланысты. Артериялық гипертензиясы бар науқастарға амбулаториялық деңгейде медициналық көмектің сапасына қанағаттануын бағалау қазіргі денсаулық сақтау жүйесінде маңызды орын алады. Гипертензияны басқарудың тиімді әдістері болғанымен, зерттеулер көрсеткендей, артериялық гипертензияны емдеу көбінесе өмір салтын өзгерту мен дәрігер белгілеген емдеу шараларын орындау бойынша науқас пен дәрігер арасындағы серіктестіктің болмауы себебінен тиімсіз болады.

Мақсаты: Артериялық гипертензиямен ауыратын науқастардың амбулаториялық медициналық көмектің сапасына қанағаттану деңгейін әлеуметтік сауалнама арқылы бағалау.

Материалдар мен әдістер: Зерттеу дизайны – бірмезгілдік көлденең зерттеу. Әлеуметтік сауалнама 2023 жылдың қыркүйек-желтоқсан айлары аралығында Астана қаласындағы 4 қалалық емханаларында кардиолог кабинеттерінде (әрқайсысынан 50 пациент) жүргізілді. Зерттеуге жалпы тәжірибе дәрігерінің диспансерлік есебінде

тұрған, ауруларды басқару бағдарламасы бойынша ем қабылдайтын, 18 жастан асқан артериялық гипертензиясы бар пациенттер енгізілді.

Нәтижелер: Зерттеуге артериялық гипертензиясы бар 200 пациент қатысты, олардың 41%-ын ер адамдар және 59%-ын әйел адамдар құрады. Сауалнама нәтижесі бойынша, респонденттердің 72,5%-ы артериялық қысымды өздігінен өлшеу дағдысына ие, ал 67,0%-ында тонометр бар. Ауруларды басқару бағдарламасының ұйымдастырылуына 47,9% қатысушы қанағаттанғанын көрсетті. Респонденттердің тек 29,7%-ы ғана артериялық гипертензия мектебіне қатысқан, бұл бағдарламаның білім беру компоненттеріне пациенттердің тартылу деңгейінің төмендігін көрсетеді. Сонымен қатар, пациенттердің тек 46,5%-ы ғана аталған бағдарламаға қатысуды өз таныстарына ұсынуға дайын екендерін білдірді, бұл ауруды басқару бағдарламасы бойынша ақпараттық және мотивациялық жұмыстың әлсіздігін көрсетеді.

Қорытынды. Осылайша, пациенттердің қанағаттану деңгейін арттыру және Ауруларды басқару бағдарламасының тиімділігін жақсарту үшін денсаулық мектептерінің жұмысын жандандырып, пациенттерді өзін-өзі бақылау қағидаттарына оқыту, жеке емдеу жоспарларын әзірлеуді қамтамасыз ету, сондай-ақ бастапқы медициналық-санитариялық көмек мамандарының пациенттерді үздіксіз бақылауға қатысуын күшейту қажет. Бұл тек клиникалық нәтижелерді жақсартып қана қоймай, сонымен қатар пациенттердің өз денсаулығына деген жауапкершілік деңгейін арттырады.

Түйінді сөздер: *артериялық гипертензия, ауруларды басқару бағдарламасы, пациенттердің қанағаттануы, денсаулық мектептері.*

Дәйексөз үшін:

Маркабаева А.М., Керимкулова А.С., Оспанова А.С., Умбетжанова А.Т., Жакупбекова М.О. Артериялық гипертензиямен сырқаттардың амбулаториялық медициналық көмектің сапасына қанағаттанушылығы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 72-78. *doi 10.34689/SH.2025.27.4.010*

Introduction.

Arterial hypertension (AH) is one of the main risk factors for cardiovascular disease [10, 11]. It is associated with a 4–6-fold increase in the risk of ischemic stroke, a 2–3-fold increase in the risk of coronary heart disease (CHD), and contributes to the progression of atherosclerosis and the development of heart failure [12, 14].

According to the World Health Organization (WHO), approximately 1.28 billion adults aged 30 to 79 worldwide suffer from hypertension [9], and more than 80% of them do not control their blood pressure [4,15,18]. According to official statistics of the Republic of Kazakhstan, the prevalence of AH among the adult population is 24.3% [20], and the incidence of hypertension among the population increased from 1,296.5 per 100,000 in 2018 to a peak in 2021 [11].

The problem of organizing and improving the quality of medical care for patients with AH is particularly important in light of the need to improve the effectiveness of the primary health care system [2, 15]. Effective monitoring and timely correction of therapy in patients with AH have a direct impact on disease prognosis and patients' quality of life of [7,8,22]. In this regard, the identification and analysis of factors that hinder the provision of effective medical care to this category of patients is an important step in the development of comprehensive measures aimed at optimizing the treatment and diagnostic process and improving the quality of medical services in outpatient practice [3,5].

Currently, as part of the Republic of Kazakhstan's State Health Development Program, systematic measures are being implemented at the primary health care level aimed at reducing morbidity, complication rates, and mortality associated with chronic noncommunicable diseases (CNCDs). Particular attention is paid to the implementation of disease management programs (DMPs) [1] based on the principles of evidence-based medicine [13]. A key component of such programs is the development of self-management and self-help skills in patients, aimed at increasing their participation in monitoring their health and adhering to treatment recommendations [9]. These initiatives contribute to improving the management of patients with chronic diseases, increasing adherence to treatment, and improving clinical outcomes, in accordance with international recommendations [16, 24].

Patient satisfaction with the quality of outpatient care for hypertension is considered an important indicator of healthcare effectiveness. Despite the availability of effective treatment methods, scientific research indicates that the main reasons for unsatisfactory treatment outcomes are poor doctor-patient communication, non-compliance with recommendations, and insufficient motivation to change their lifestyle.

Given the high prevalence of hypertension in our country and its role in the development of complications, it is important to study the organization of medical care for patients with hypertension, including after the introduction of a disease management program, as one of the tools for improving the quality and effectiveness of outpatient healthcare.

Objective: to assess patient satisfaction with the quality of outpatient care for arterial hypertension using a social survey.

Materials and methods: The study design was cross-sectional. Four polyclinics in Astana were included in the study. Medical organizations were selected using random sampling.

The social survey was conducted among patients with arterial hypertension between September and December 2023 in cardiologists' offices. A total of 200 patients with arterial hypertension were surveyed, 50 patients from each of the four polyclinics. The study included patients with

arterial hypertension who were registered with a general practitioner, were over 18 years of age, and were receiving treatment according to the DMP. Exclusion criteria were patients with secondary hypertension, severe diseases that could distort the results, recently diagnosed individuals who had not yet stabilized on treatment, those unwilling to participate in the study, and those unable to independently sign an informed consent form.

A specially designed questionnaire for patients with arterial hypertension participating in the DMP was used to conduct the survey.

The research protocol "Comprehensive Assessment and Improvement of the Organization of Outpatient Care for Patients with Arterial Hypertension" was approved by the independent local ethics committee of the Astana Medical University (No. 2, dated November 10, 2022).

Microsoft Excel was used to compile the database, and SPSS (Statistical Package for the Social Sciences) version 23.0 for Windows (Astana Medical University) was used to process the data. The X^2 criterion was used to compare the frequency of selected responses in each group. The p-value was used to determine the statistical significance of the differences.

Results:

As part of the study, a questionnaire was conducted in Kazakh and Russian among 200 patients participating in the Hypertension Management Program at four city clinics in Astana. All respondents (100%) confirmed their participation in the program and the existence of a signed informed consent form. The socio-demographic characteristics of the participants are presented in Table №1.

Table 1.

Socio-demographic characteristics of patients who participated in the survey.

Indicator	Category	n(200)	%
Gender	Men	82	41,0
	Women	118	59,0
Age	30–39 years old	5	2,4
	40–49 years old	45	22,3
	50–59 years old	69	34,5
	60–69 years old	72	36,1
	70 years old and older	9	4,7
Education	Higher education	117	58,3
	Specialized secondary education	39	19,7
	Secondary education	44	22,0
Social status	Pensioners	92	46,0
	Workers	24	11,8
	Employees	51	25,7
	Unemployed	9	4,6
	Housewives	10	5,1
	Private entrepreneurs	14	6,8
Marital status	Married	169	84,5
	Widows/widowers	13	6,4
	Divorced	18	9,1

Women predominated among respondents, accounting for 59.0% (n = 118), while men accounted for 41.0% (n = 82). The most represented age group was patients aged 60–69 (36.1%), followed by the 50–59 (34.5%) and 40–49 (22.3%) age groups. The proportion of patients under 40 and over 70 was relatively low, at 2.4% and 4.7%, respectively.

In terms of education, most patients had a higher education degree (58.3%, n = 117). Secondary vocational and secondary general education were obtained by 19.7% (n = 39) and 22.0% (n = 44), respectively. Analysis of social status showed that nearly half of the respondents were pensioners — 46.0% (n = 92). A significant proportion were also employees — 25.7% (n = 51). The proportion of workers was 11.8%, the unemployed — 4.6%, housewives — 5.1%, and private entrepreneurs — 6.8%. In terms of marital status, 84.5% (n = 169) of patients were legally married. 6.4% were widowed, and 9.1% were divorced.

The main part of the questionnaire was aimed at identifying the degree of satisfaction with the organization of PHC and the level of patient involvement in managing their own disease. According to the data obtained, 47.9% of respondents expressed satisfaction with the organization of PHC (see Figure 1). However, this indicator also indicates that the organization of this program in the post-COVID period is assessed by patients as insufficiently effective and requires further improvement in the coordination of actions between medical staff and patients.

As part of the implementation of the DMP, special attention is paid to developing self-management skills in patients through training in health schools, where information about the disease is provided and individual disease management plans are developed. However, the survey results showed that only 29.7% of respondents attended the "school of arterial hypertension" indicating low patient involvement in the educational components of the program.

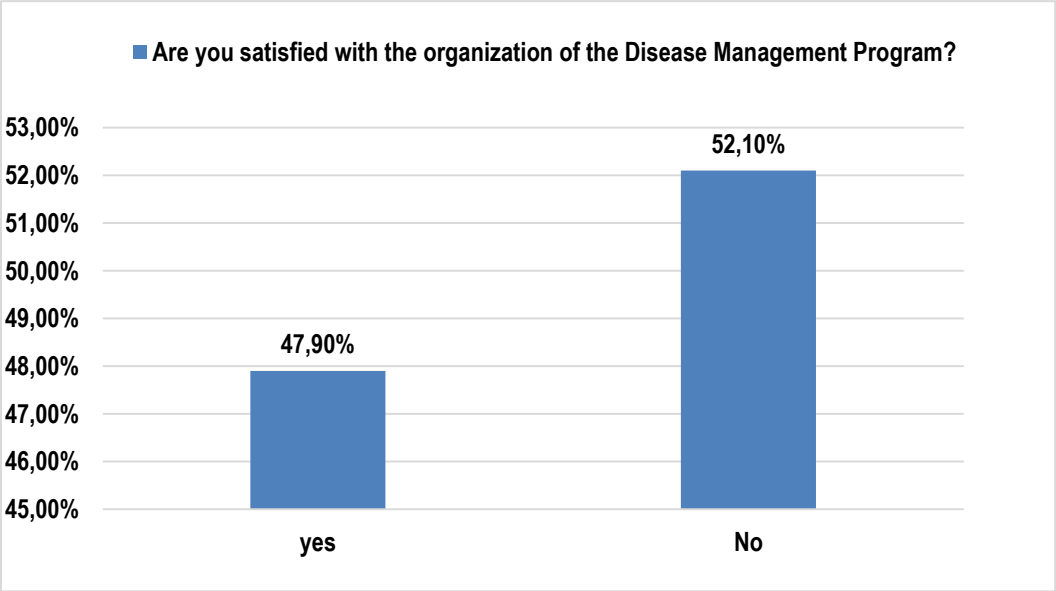


Figure 1. Level of satisfaction of survey participants with the organization of the Disease Management Program.

As part of the DMP, each patient is recommended to develop an individual action plan covering the correction of physical activity, nutrition, lifestyle, and the abandonment of harmful habits. In addition, patients are required to keep a self-monitoring diary and have a personalized plan for medication and non-medication therapy. This study found that 42.6% of participants had individual disease management plans, while 60.3% of respondents did not keep a self-monitoring diary. The data obtained indicate the need to strengthen the role of primary health care specialists in supporting this group of patients, especially in terms of motivation, monitoring adherence, and maintaining chronic disease self-management skills.

When asked about the components of effective disease management, 59.7% of respondents pointed to the importance of regular physical activity, 65% pointed to the importance of following the principles of proper nutrition, 91.2% pointed to the need for timely medication, and 70.2% considered daily blood pressure monitoring to be an integral part of self-management of hypertension (Figure 2).

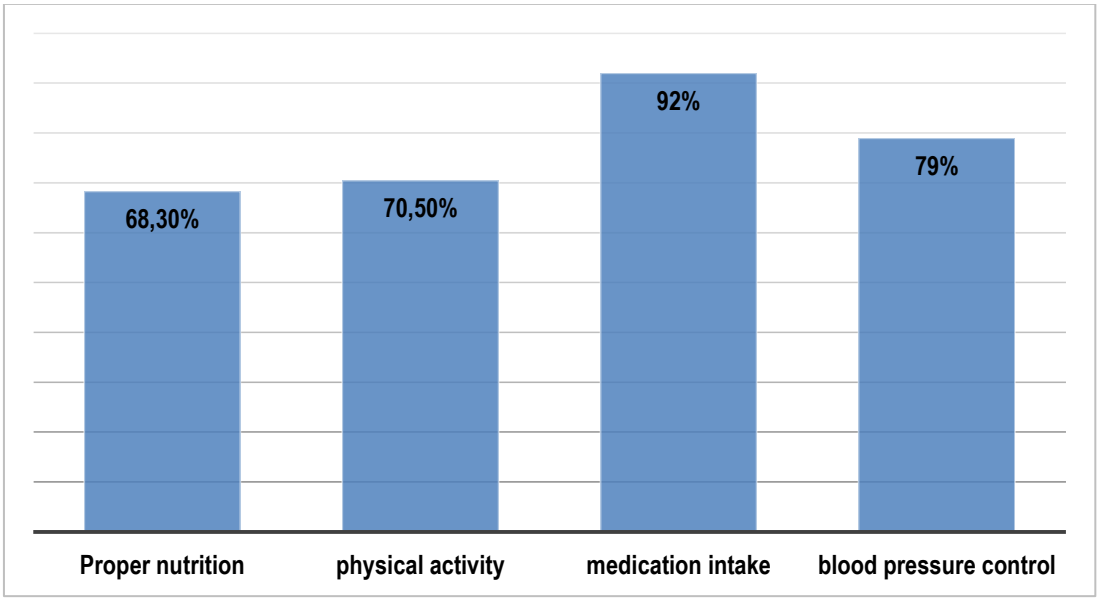


Figure 2. Opinions of patients participating in the Disease Management Program on the components of self-management of their disease.

Patients with hypertension should be able to measure their blood pressure independently at home. According to the survey results, 72.5% of patients indicated that they know how to measure their blood pressure independently. In addition, 67.0% of program participants have a blood pressure monitor to take these measurements.

In 79.3% of the study participants, blood pressure stabilized, while weight loss was observed in only 26.5% of respondents. The low rate of weight loss indicates the need for patients to develop an individual plan that includes increasing physical activity, following a proper diet, and forming a healthy lifestyle.

One indicator of the effectiveness of the DMP is the frequency of hospitalizations among patients participating in the program. According to the survey results, this indicator was only 4.7%. Only 41.8% of respondents expressed willingness to recommend participation in the program to their friends, which reflects a limited level of trust or insufficient awareness of its benefits. Although all DMP participants reported having information about the program, it was found that most of them did not fully understand the differences between the program and traditional approaches to treatment.

The survey revealed low patient participation in "hypertension schools," which may limit the acquisition of knowledge about the characteristics of the disease and reduce the effectiveness of self-management. In addition, most respondents associate disease management exclusively with drug treatment pointing to gaps in educational preparation.

Discussion.

The results of this study demonstrate important aspects of patients' perceptions of the quality of outpatient care for hypertension in the context of the introduction of the DMP. Despite the fact that all surveyed patients (100%) were included in the DMP and signed an informed consent form, less than half (47.9%) were satisfied with the organization of the program. This finding underscores the need for enhanced program implementation in medical institutions.

Low attendance at hypertension schools indicates insufficient involvement in the educational components of the program, which play a key role in developing self-control and increasing adherence to treatment. This may be due to low patient motivation, lack of time, particularly among working individuals, as well as limited availability and organization of such schools in outpatient facilities.

At the same time, 72.5% of respondents reported that they know how to measure their blood pressure independently, and 67.0% have a blood pressure monitor at home, which can be considered positive indicators of self-care and disease control. However, only 46.5% of respondents expressed a willingness to recommend DMP to their friends. This suggests that, despite certain positive changes, patients may not perceive the program as particularly effective or beneficial, which may be due to poor communication with medical staff, insufficient support, and the lack of visible clinical improvements in the short term.

The observed discrepancy between formal participation in the program and low involvement in its key components (diary keeping, individual planning, and attending school) highlights the need to review approaches to the implementation of DMP in outpatient practice. In particular, there is a need to strengthen the educational, motivational, and supportive work of primary care professionals. The results obtained are consistent with international data, according to which the success of programs for the control of chronic diseases, including hypertension, largely depends on the level of patient involvement, access to information, regular monitoring, and close interaction with medical personnel.

Conclusion.

Thus, the presented data emphasize the need to further strengthen the educational component of PHC, in particular, by enhancing the role and availability of health schools. This will increase patients' knowledge, improve self-management skills, and form a sustainable motivation to participate in managing their own health.

Authors' contributions

Markabaeva Akbayan *— conceptualization, methodology, data collection, validation, formal analysis, writing of the original draft, reviewing and editing, and securing funding.*

Kerimkulova A.S., Ospanova A.S., Umbetzhanova A.T., Zhakupbekova M.O. *— writing, reviewing, and editing.*

Conflict of interest

No conflicts of interest declared.

Funding

This work was performed under grant No. AP19176476 commissioned by the Ministry of Science and Higher Education of the Republic of Kazakhstan, "Comprehensive assessment and improvement of the organization of outpatient and polyclinic care for patients with arterial hypertension."

Publication information

This article has not been previously published and is not being considered for publication in other publications.

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Received: 12 May 2025 / Accepted: 19 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.011

UDC 616.728.48:617.586:616.72-002.77-073.756.8

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ANKLE AND FOOT LESIONS IN RHEUMATOID ARTHRITIS – A COMPARATIVE STUDY OF TRIPLE PHASE ^{99m}Tc-MDP BONE SCINTIGRAPHY WITH SPECT/CT, MRI AND USG IMAGING

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Abstract

Introduction. Rheumatoid arthritis [RA] is a chronic inflammatory disease of unknown etiology. It marked by a symmetrical, peripheral polyarthritis with many extra articular manifestations. It is a form of chronic inflammatory arthritis which leads to joint damage and physical disability with extra articular manifestations. Evaluation of antibodies, anti-CCPs and rheumatoid factors are routinely used a marker of diagnostic and prognostic significance. The incidence of RA increases between 25 and 55 years of age. Recently imaging modalities like ultrasonography, MRI, bone scintigraphy and PET/CT have been used to provide information about joint inflammation and damage for clinical assessment of RA.

Aims: 1) To evaluate the frequency of ankle/foot joint involvement in RA patients, 2) To compare triple phase ^{99m}Tc-MDP bone scintigraphy with SPECT/CT, MRI & USG imaging.

Materials and method: Study include 50 patients of RA, underwent 99mTc- MDP scan for affected joints. 30 patients further underwent MRI followed by USG.

Result: In 50 patients who underwent triple phase bone scan, clearly demonstrated 786 joints involvement. Out of which 280 (~36%) were large joints and 506 (~64%) were small joints. In this 30 patients further underwent MRI. When compared, it suggested fair to moderate agreement between two imaging tools. In our study MRI scan clearly demonstrated the synovial changes as well as bone errosion and marrow edema. Planar and SPECT/CT images are also demonstrated increasing activity at correponding site. Also showed if disease involvement present in clinically silent joints. All three imaging modalities showed some extent of disease present before symptoms of RA become clinically evident.

Conclusion: Triple phase ^{99m}Tc- MDP bone scintigraphy is an excellent imaging modality for evaluation of all small and large joints in single study. It provides valuable information about the disease activity, number and location of joint involvement. 99m-Tc MDP triple phase bone scan and MRI showed fair to moderate agreement to elicit the disease burden in MTP joints. USG help to detect the syn.

Key words: Rheumatoid Arthritis of ankle joints, ^{99m}Tc - Triple phase bone scan, SPECT/CT, MRI ankle joint, USG ankle joint.

For citation:

Saini Vivek Kumar, Arya Amitabh, Agarwal Vikas, Mohindra Namita, Thulasi Sunitha Deepa; Ankle and foot lesions in rheumatoid arthritis - a comparative study of triple phase ^{99m}Tc-MDP Bone scintigraphy with SPECT/CT, MRI and USG imaging // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 79-90 *doi 10.34689/SH.2025.27.4.011*

Резюме

ПОВРЕЖДЕНИЯ ГОЛЕНОСТОПНОГО СУСТАВА И СТОПЫ ПРИ РЕВМАТОИДНОМ АРТРИТЕ – СРАВНИТЕЛЬНОЕ ИССЛЕДОВАНИЕ ТРЕХФАЗНОЙ СЦИНТИГРАФИИ КОСТЕЙ С ИСПОЛЬЗОВАНИЕМ ^{99m}Tc-MDP С ПОМОЩЬЮ SPECT/КТ, МРТ И УЗИ

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Актуальность. Ревматоидный артрит (РА) — хроническое воспалительное заболевание неизвестной этиологии. Оно характеризуется симметричным периферическим полиартритом с множеством внесуставных проявлений. Это форма хронического воспалительного артрита, приводящая к повреждению суставов и физической инвалидности с внесуставными проявлениями. Оценка антител, анти-ЦЦП и ревматоидных факторов обычно используется в качестве маркера диагностического и прогностического значения. Заболеваемость РА увеличивается в возрасте от 25 до 55 лет. В последнее время для получения информации о воспалении и повреждении суставов с целью клинической оценки РА используются такие методы визуализации, как ультрасонография, МРТ, костная сцинтиграфия и ПЭТ/КТ.

Цели: 1) Оценить частоту поражения голеностопного сустава/стопы у пациентов с РА. 2) Сравнить трехфазную костную сцинтиграфию с ^{99m}Tc-MDP с визуализацией SPECT/CT, МРТ и УЗИ.

Материалы и методы: В исследование включены 50 пациентов с РА, которым было проведено сканирование пораженных суставов с помощью ^{99m}Tc-MDP. 30 пациентов дополнительно прошли МРТ, а затем УЗИ.

Результаты: У 50 пациентов, прошедших трехфазное сканирование костей, было четко продемонстрировано поражение 786 суставов. Из них 280 (~36%) были крупными суставами, а 506 (~64%) — мелкими суставами. Эти 30 пациентов дополнительно прошли МРТ. Сравнение показало, что между двумя методами визуализации наблюдается хорошее или умеренное согласие. В нашем исследовании МРТ-сканирование четко продемонстрировало синовиальные изменения, а также эрозию кости и отек костного мозга. Плоские и SPECT/CT-изображения также продемонстрировали повышенную активность в соответствующих участках. Также было показано, присутствует ли поражение заболеванием в клинически бессимптомных суставах. Все три метода визуализации продемонстрировали некоторую степень заболевания до того, как симптомы РА стали клинически очевидными.

Заключение: Трехфазная ^{99m}Tc-MDP-сцинтиграфия костей является отличным методом визуализации для оценки всех мелких и крупных суставов в рамках одного исследования. Она предоставляет ценную информацию об активности заболевания, количестве и расположении пораженных суставов. Трёхфазная сцинтиграфия с ^{99m}Tc-MDP и МРТ показали умеренное соответствие в оценке выраженности поражения суставов плюснефаланговой области (МТР-соединения). УЗИ помогает выявлять синовиальные изменения.

Ключевые слова: *Ревматоидный артрит голеностопного сустава, 99mTC - трехфазное сканирование кости, SPECT/КТ, МРТ голеностопного сустава, УЗИ голеностопного сустава.*

Для цитирования:

Сайни Вивек Кумар, Арья Амитабх, Агарвал Викас, Мохиндра Намита, Туласи Сунита Дипа; Повреждения голеностопного сустава и стопы при ревматоидном артрите – сравнительное исследование трехфазной сцинтиграфии костей с использованием ^{99m}Tc-MDP с помощью SPECT/КТ, МРТ и УЗИ // Наука и Здравоохранение. 2025. Vol.27 (4), С.79-90. *doi 10.34689/SH.2025.27.4.011*

Түйіндеме

РЕВМАТОИДТЫ АРТРИТ КЕЗІНДЕГІ ТОБЫҚ ЖӘНЕ ТАБАН БУЫНДАРЫНЫҢ ЗАҚЫМДАНУЫ – ^{99m}Tc-MDP ҚОЛДАНЫП ЖҮРГІЗІЛГЕН ҮШ ФАЗАЛЫ СҮЙЕК СЦИНТИГРАФИЯСЫН SPECT/КТ, МРТ ЖӘНЕ УДЗ ӘДІСТЕРІМЕН САЛЫСТЫРМАЛЫ ЗЕРТТЕУ

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Кіріспе. Ревматоидты артрит (РА) — этиологиясы белгісіз созылмалы қабыну ауруы. Ауру симметриялы шеткері көпбуынды артритпен және буыннан тыс көптеген көріністермен сипатталады. Бұл — буындарды зақымдап, физикалық мүгедектікке әкелетін, буыннан тыс көріністері бар созылмалы қабыну артритінің бір түрі. Антиденелерді, анти-ЦЦП және ревматоидты факторларды бағалау әдетте диагностикалық және болжамдық маңызы бар маркерлер ретінде қолданылады. РА ауруы көбінесе 25–55 жас аралығында жиі кездеседі. Соңғы жылдары клиникалық бағалау мақсатында қабыну мен буын зақымдануы туралы ақпарат алу үшін ультрадыбыстық зерттеу (УДЗ), магнитті-резонанстық томография (МРТ), сүйек сцинтиграфиясы және ПЭТ/КТ сияқты бейнелеу әдістері қолданылуда.

Мақсаттар: Ревматоидты артритпен (РА) ауыратын науқастардағы тобық және табан буындарының зақымдану жиілігін бағалау. ^{99m}Tc-MDP қолданылған үш фазалы сүйек сцинтиграфиясын SPECT/КТ, МРТ және УДЗ әдістерімен салыстыру.

Материалдар мен әдістер: Зерттеуге РА диагнозы қойылған 50 науқас қатыстырылды, оларға зақымданған буындарды ^{99m}Tc-MDP көмегімен сканерлеу жүргізілді. Оның ішінде 30 науқасқа қосымша МРТ және кейіннен УДЗ жасалды.

Нәтижелер: Үш фазалы сүйек сцинтиграфиясынан өткен 50 науқастың 786 буынында патологиялық өзгерістер анықталды. Оның ішінде 280 буын (~36%) ірі буындар, ал 506 буын (~64%) ұсақ буындар болды. Осы 30 науқасқа қосымша МРТ жасалды. Салыстыру нәтижесінде бейнелеу әдістері арасында жақсы немесе орташа деңгейдегі үйлесімділік бары анықталды. Зерттеу барысында МРТ синовиалды өзгерістерді, сүйек эрозиясын және сүйек кемігіндегі ісінуді нақты көрсетті. Планарлы және SPECT/КТ кескіндері де сәйкес аймақтардағы белсенділіктің артқанын көрсетті. Сонымен қатар, клиникалық белгілері жоқ буындарда да аурудың бар-жоғын анықтауға мүмкіндік берді. Үш бейнелеу әдісі де РА клиникалық түрде білінбей тұрып, аурудың белгілі бір дәрежеде басталып кеткенін көрсетті.

Қорытынды: ^{99m}Tc-MDP қолданылатын үш фазалы сүйек сцинтиграфиясы — ұсақ және ірі буындарды бір зерттеудің аясында бағалауға арналған үздік бейнелеу әдісі. Бұл әдіс аурудың белсенділігі, буындардың зақымдану саны мен орналасуы туралы құнды ақпарат береді. ^{99m}Tc-MDP сүйек сцинтиграфиясы мен МРТ метатарсофалангеалды (МТР) буындардағы зақымдану дәрежесін бағалауда орташа деңгейде сәйкестік көрсетті. Ультрадыбыстық зерттеу синовиалды өзгерістерді анықтауға көмектеседі.

Түйінді сөздер: Тобық және табан буындарының ревматоидты артрит, 99mtc-үш фазалы сүйекті сканерлеу, SPECT / КТ, Тобық және табан буындарының МРТ, Тобық және табан буындарының УДЗ

Дәйексөз үшін:

Сайни Вивек Кумар, Арья Амитабх, Агарвал Викас, Мохиндра Намита, Туласи Сунита Дипа; Ревматоидты артрит кезіндегі тобық және табан буындарының зақымдануы – ^{99m}Tc-MDP қолданып жүргізілген үш фазалы сүйек сцинтиграфиясын SPECT/КТ, МРТ және УДЗ әдістерімен салыстырмалы зерттеу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 79-90. *doi 10.34689/SH.2025.27.4.011*

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease of unknown origin that primarily affects symmetric joints. It is most common between 25 and 55 years of age [1], though it can occur at any age. It leads to joint damage, disability, and various extra-articular manifestations. These include subcutaneous nodules, fatigue, pulmonary abnormalities, peripheral neuropathy, and hematologic issues such as anemia.

RA tends to affect small joints of the hands and feet first, often causing morning stiffness lasting over an hour, which improves with activity. In advanced stages, joints like the wrists, MCP, PIP may be most affected, while the DIP joints are typically spared (indicative of coexisting osteoarthritis if involved). Joint deformities such as swan neck, boutonnière, and Z-line deformities can develop, along with tendon issues like tenosynovitis and reduced grip strength.

Involvement of larger joints such as the knee, shoulder, and ankle is common in established disease, while atlantoaxial subluxation (C1-C2 spinal involvement) can cause compressive myelopathy, potentially leading to neurological dysfunction.

Extra-Articular Manifestations:

Subcutaneous nodules occur in 30-40% of patients. Pulmonary involvement, including pulmonary nodules, interstitial lung disease, and pleural effusions, is common. Cardiovascular issues such as coronary artery disease and heart failure are prevalent due to chronic inflammation, making cardiovascular health a priority. Anemia is common, along with other hematologic abnormalities like neutropenia and splenomegaly. Sjogren's syndrome (~10% of RA patients) can occur, causing dry eyes and mouth.The risk of developing lymphoma (especially diffuse large B-cell lymphoma) is 2-4 times higher than in the general population, especially in patients with high disease activity or Felty's syndrome (splenomegaly and neutropenia).

RA can also involve ocular issues like keratoconjunctivitis sicca (dry eyes) and episcleritis, oral manifestations such as xerostomia (dry mouth), and neurological manifestations like cervical myelopathy [1].

Pathophysiology of RA:

RA primarily affects the synovial tissue in joints, leading to synovial inflammation, pannus formation (a growth of inflamed tissue), and bone erosion. Fibroblast-like synoviocytes play a critical role in the destruction of cartilage and bone by secreting matrix-degrading enzymes. The infiltrating immune cells, primarily T-cells and B-cells, secrete proinflammatory cytokines such as TNF-α and IL-1, which cause joint inflammation and damage. Over time, this results in pannus formation that invades both cartilage and bone [2].

The disease is thought to be influenced by genetic factors, environmental triggers (e.g., smoking), and hormonal factors (with estrogen playing a role in disease pathogenesis). RA is more common in women (2-3:1 ratio) [2].

NEW 2010 ACR-EULAR
[American College of Rheumatology -European League Against Rheumatism]

Joint involvement	**Score**
1 - large joint [shoulder, elbow, hip, knee, ankle]	0
2- 10 large joints	1
1 -3 small joints [MCP, PIP, thumb, Ip, MTP, wrists]	2
4- 10 small	3
> 10 joints [at least 1 small joint]	5
Serology	
Negative RF and negative ACPA	0
Low- positive RF or low- positive anti-CCP antibodies [<3 times ULN]	2
High -positive RF or high positive anti-CCp antibodies [>3 times ULN]	3
Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or Abnormal ESR	1
Duration of symptoms	
<6 weeks	0
>6 weeks	1

A score of >6 fulfills requirements for definite RA.

Investigations:

Blood tests:

ESR and CRP are markers of inflammation and correlate with disease activity.

CBC often shows anemia of chronic disease, and thrombocytosis (elevated platelets) is common.

Rheumatoid factor (RF) is present in 60-80% of RA patients but is not specific to RA and can be found in other conditions [3].

Anti-CCP antibodies have high specificity for RA and can predict more erosive disease.

Imaging:

Radiography is the primary method for assessing joint damage, though it is more useful for monitoring disease progression than for early diagnosis.

MRI and ultrasonography are more sensitive for detecting early inflammation and soft tissue involvement (e.g., tendon sheath inflammation and synovitis). Ultrasonography of joints is gaining increased widespread acceptance in clinical practice; however, its use in RA is not yet the standard of care [4].

CT and PET scans are used in specialized cases for better assessment of damage and inflammation.

Treatment:

Early intervention with Disease-modifying antirheumatic drugs (DMARDs) is crucial to slow disease progression and prevent joint damage [5] [6].

Nonbiologic DMARDs (e.g., Methotrexate (MTX), Hydroxychloroquine, Sulfasalazine, Leflunomide) remain the cornerstone of treatment.

Biologic DMARDs (e.g., TNF inhibitors such as Adalimumab, Etanercept, Infliximab) target inflammatory cytokines and are effective in patients not responding to nonbiologic DMARDs.

Corticosteroids and NSAIDs are used for symptom relief but are not disease-modifying agents.

Surgical options may be considered in severe cases where joint deformities impair function or cause pain. This includes:

Synovectomy (removal of inflamed synovium).

Arthroplasty (joint replacement) or arthrodesis (joint fusion).

Vaccinations are recommended for patients on immunosuppressive therapies (e.g., pneumococcal, influenza, hepatitis, and HPV vaccines) to reduce the risk of infections.

Early DMARD therapy (within 6 months of symptom onset) is associated with better outcomes, including fewer joint erosions and a higher likelihood of remission.

Prognosis:

With timely diagnosis and effective treatment, most patients can achieve disease control and prevent further joint damage. However, untreated RA can lead to significant disability and reduced quality of life. The disease can be progressive and may require long-term management with a combination of medications, lifestyle modifications, and monitoring for comorbidities such as cardiovascular disease and osteoporosis.

Aims and Objective:

To evaluate frequency of ankle/foot joint involvement in RA patients.

To compare Triple phase ^{99m}Tc-MDP bone scintigraphy with SPECT/CT, MRI and USG imaging in picking up the Ankle/feet lesions in RA

Methods and Materials

Study Location & Population:

Conducted at:

Department of Nuclear Medicine in association with Radiodiagnosis and Clinical Immunology, SGPGIMS, Lucknow.

Participants:

50 patients diagnosed with Rheumatoid Arthritis (RA) based on the 2010 ACR-EULAR criteria, recruited from the Clinical Immunology OPD.

Consent:

Informed consent was obtained from all participants.

Main focus:

Assessment of left foot MTP (metatarsophalangeal) and PIP (proximal interphalangeal) joints, as they are commonly affected in RA.

Inclusion Criteria: Patients meeting 2010 ACR-EULAR criteria for RA.

Exclusion Criteria: Non-consenting or uncooperative patients.

Age <7 years

Patients with deformed feet

Pregnant or lactating women

Imaging Procedures:

1. Triple Phase Bone Scintigraphy (Bone Scan):

Radiotracer:

15–20 mCi of 99mTc-MDP prepared from a molybdenum-99/technetium-99m generator.

Procedure:

No fasting; patients remained hydrated.

Dynamic flow, blood pool, and delayed images (after 3 hours) were acquired.

Imaging done using Infinia Hawkeye 4 SPECT/CT, focused on feet (planter view) and whole body.

Interpretation:

Two blinded nuclear medicine physicians independently assessed joint involvement based on abnormal tracer uptake in MTP/IP joints.

2. MRI of the Left Foot:

Scanner: 3T Siemens MRI

Protocol: Included sequences like T2W, PD, T1 (pre- and post-contrast), and 3D SPACE.

Focus: Detection of synovitis, bone erosion, and bone marrow edema using the RAMRIS (OMERACT) scoring system.

Assessment:

Done independently by two blinded radiologists.

3. Ultrasonography (USG) of Left Foot:

Machine: ESAOTE with 18 MHz linear probe

Joints assessed: Only MTP joints (150 joints in total); PIP joints excluded due to variability.

Scoring:

Done using OMERACT-based grayscale and Power Doppler scoring.

Interpretation:

Conducted by two trained immunologists independently.

Other Data Collection:

Clinical examination and hematological parameters were documented and correlated with imaging results.

Both small joints (MCP, PIP, thumb IP, MTP, wrist) and large joints (shoulder, elbow, hip, knee, ankle) were evaluated for involvement.

Result

Patient characteristics -

This study group included 50 patients (Mean age 42.9 years, Range 20-64 years. It was observed that 12 patients (24 %) were in the age group of 20-31 years followed by 12 patients (24 %) in the age group of 32-43 years16 patients (32 %) in the age group of 44-55 years and rest 10 patients (20 %) were in the age group of 57-68 years.

In our study out of 50 patients, 6 (12%) patient were male and 44 (88 %) were female.

Out of 50 patients only 4 (8%) patients had ESR less than 20 mm/hours. 28 (56%) patients had ESR between 20-40 mm/hours. 8 (16%) patients had ESR between 41 -60 mm/hour. 1 (2%) patients had ESR between 61-80 mm/hour and 9 (18%) patient had ESR either 81 -100 or more. This study showed maximum patients were in the 20-40 mm/hour group which considered raised as per the reference laboratory value. (< 20 mm/hour).

In our study 15 (30%) patients had anti-CCP antibody level between 0-30 units/ml. 11 (22%) patients had anti-CCP antibody level between 31-300 units/ml and 24 (48%) patients had anti-CCP antibody more than 300 units/ml.

In our study we observed 19 (38%) patient had C-reactive protein less than 0.6 mg/dl. Rest 31 (62%) had CRP level more than reference laboratory value. (< 0.6 mg/dl). It showed more ongoing inflammatory processes and disease activity.

In this study 35 (70 %) patients had rheumatoid factor more than 15 IU/ml that is considered more than reference laboratory value. (< 0-15 IU/ml).

Total disease activity index was less than 2.8 in 10 (20%) patients and it was more than 2.8 in the rest 40 (80%) patients. It showed active phase.

In our study 50 bone scan showed total number of joints involved were 786, 506 (~64%) were the small joints and 280 (~ 36%) were the large joints. Average number of total joints involvement was ~16 per patient.

- ❖ Large joints -Shoulder, Elbow, Hip, knee, Ankle joints.
- ❖ Small joints - MCP, PIP, Thumb, Proximal IP, MTP, wrists joints.

All fifty patients underwent bone scan examination, fifteen (30%) patients were clinically pain free, however scan reveals eleven (22 %) patients had abnormal tracer uptake in the left foot joints. On the other hand, thirty five (70%) patient who clinically had foot pain, thirty one patients showed abnormal tracer uptake in the left foot joints suggested for disease involvement but four patients didn't show any abnormal tracer uptake in the left foot joints.

Above mentioned table showed that clinically silent sites may have abnormal tracer uptake that suggestive of disease activity.

Thirty patients underwent MRI examination, ten (~33%) patients were clinically pain free, however five had left foot joints involvement. On the other hand, twenty patients who clinically had pain, eleven patients showed MRI feature suggested of disease activity in the joints but nine patients didn't show MRI feature suggested of disease activity.

Fifty patients included in our study, thirty further underwent of MRI examination as well. So total 300 joints (5 left MTP and 5 left PIP joints of 30 patients) were evaluated by both examinations.

Bone scan picked up disease activity in total 51 joints and MRI picked up disease activity in 49 joints of left foot. In these total involved joints 42 were MTP & 9 were PIP joints picked up by bone scan and 41 were MTP & 8 were PIP picked up by MRI scan.

Out of 300 joints (5 MTP and 5 PIP joints of 30 patients) that have been examined by both examination, results were concordant in the 258 joints (i.e either positive or either negative in both) and were discordant in 42 joints.

Individual joints assessment by Bone scan and MRI scan

1) First left MTP joints by bone scan and MRI

Thirty 1st MTP joints assisted by bone scan and MRI, ten same joints showed no involvement in the disease in both scans. 10 same joints showed disease involvement in the both scans. In the rest ten discordant 1st Left MTP joints bone scan was positive in all case and MRI was negative in all case. Statistically result showing a fair agreement in both test (kappa coefficient 0.40 with P value -.006).

BMTP1 * MMTP1 Cross tabulation

Count		MMTP1		Total
		N	Y	
BMTP1	N	10	0	10
	Y	10	10	20
Total		20	10	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.400	.124	2.739	.006
N of Valid Cases		30			

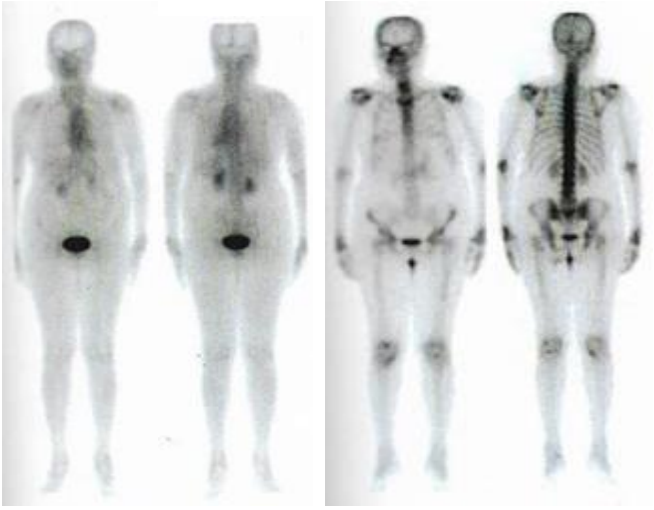
a. Not assuming the null hypothesis. *b. Using the asymptotic standard error assuming the null hypothesis.*



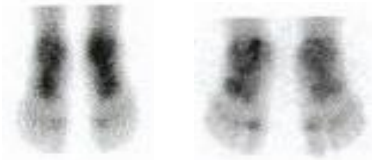
a) Blood pool imags both feet anterior and posterior view.



b) Blood pool images of upper limb anterior and posterior view.



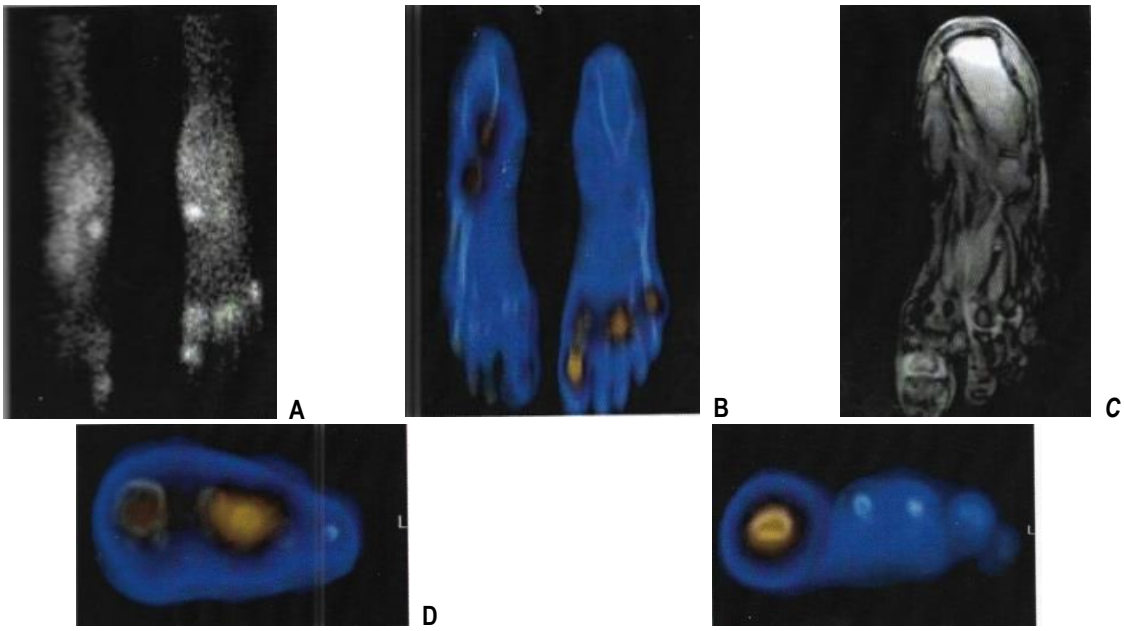
c) Blood pool images whole body anterior and posterior view **d) Delayed imageswhole body anterior and posterior view**



e) Delayed Images anterior and posterior view



***f*: SPECT/CT images of left foot**



Case 1: A 26 year old lady presented with pain in both feet joints. Image (A) delayed planar view of foot showing abnormal tracer uptake inleft 1st IP and Left 2nd IP, 3rd and 5th MTP joint region. Image (B), (D) and (E) SPECT/CT of corresponding site suggestive of abnormal tracer uptake in left 1st IP and 2nd, 3rd and 5th MTP joints. Images (C) MRI showing abnormal contrast enhancement at left 1st IP and 2nd and 3rd MTP joints.

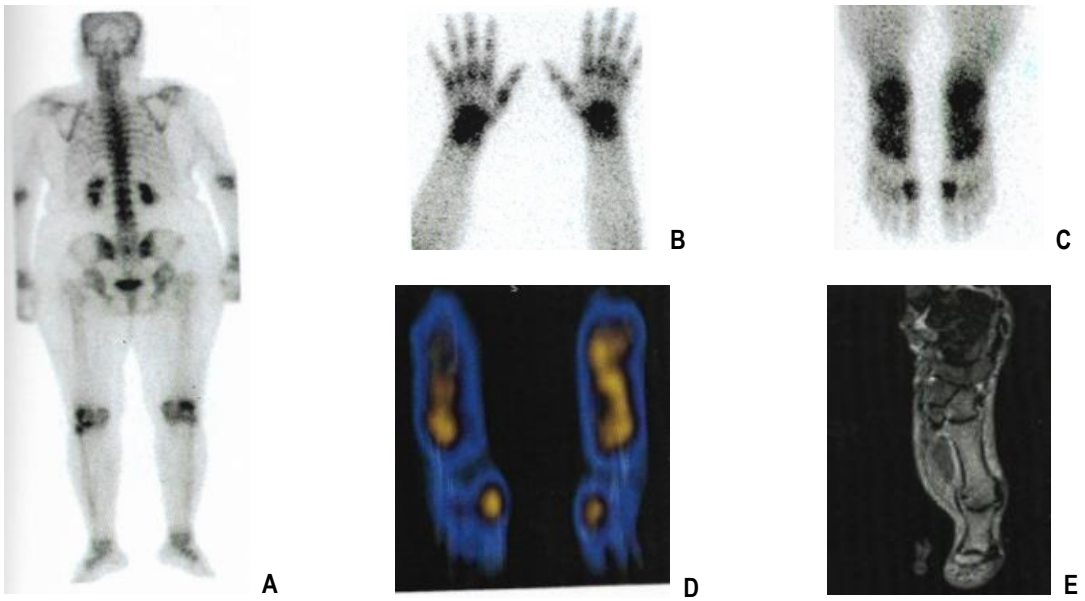


Figure: Image (A) whole body delayed image posterior view. Image (B) spot view of bilateral hand joints posterior view showing multiple small joints abnormal tracer uptake. Image (C) Delayed spot view of bilateral feet in the plantar position with abnormal tracer uptake in the 1st MTP joints. Image (D) SPECT/CT image of corresponding site showing increased tracer uptake in bilateral 1st MTP joints. Image (E) corresponding MRI images of left foot showing bony erosion at 1st tarsal bone.

2) 2nd left MTP joints assessment by bone scan and MRI scan

Thirty 2nd MTP joints assessed by both scans, twenty-one same joints showed no disease involvement. Four same joints showed disease involvement. In the rest 5 discordant 2nd Left MTP joints, bone scan was positive in 1 case and MRI was positive in four case. Statistically result showing a moderate agreement in both test (kappa coefficient 0.516 with P value -.003).

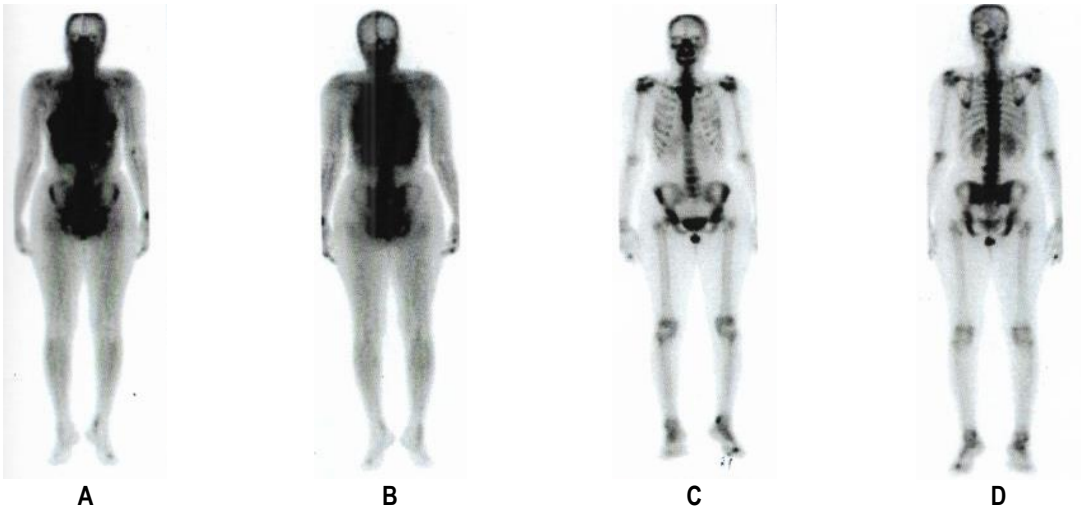
BMTP2 * MMTP2 Cross tabulation

Count		MMTP2		Total
		N	Y	
BMTP2	N	21	4	25
	Y	1	4	5
Total		22	8	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.516	.183	2.954	.003
N of Valid Cases		30			

a. Not assuming the null hypothesis. *b. Using the asymptotic standard error assuming the null hypothesis.*



Case 2: 21 year old female presented with multiple joints pain. Image (A) whole body pool image anterior view Image (B) whole body pool images Posterior view. Image (C) delayed image anterior view. Image (D) delayed image posterior view.

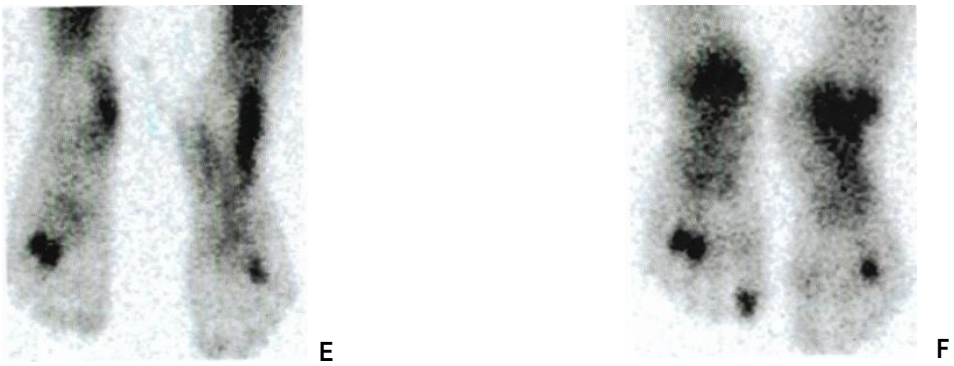


Figure: Image (E) & (F) increased tracer uptake in multiple foot joints.

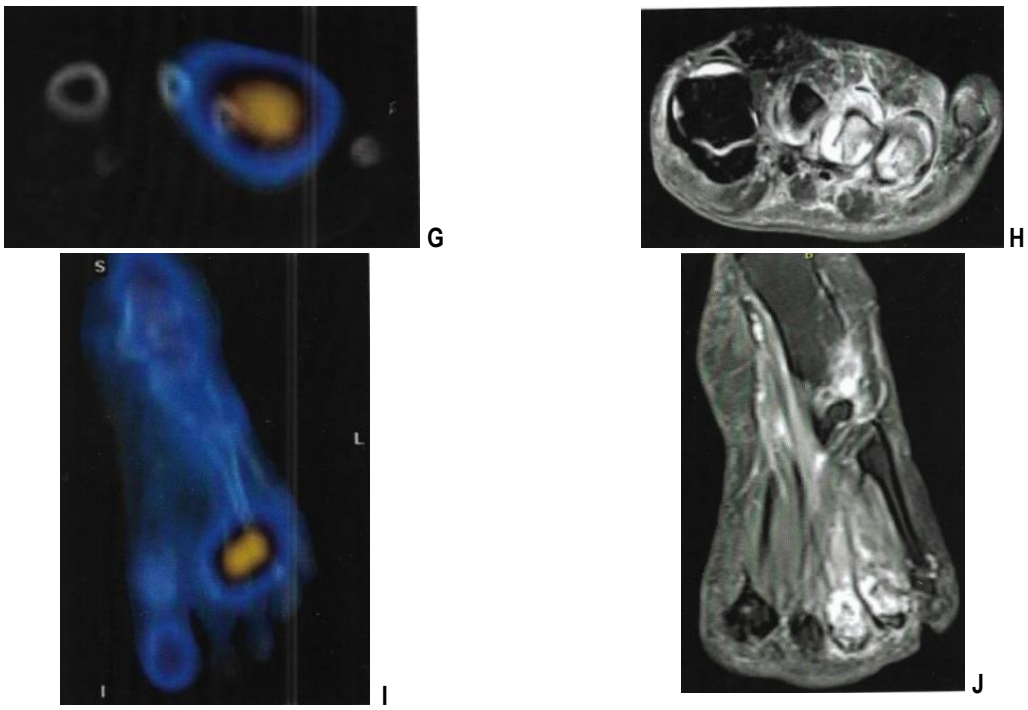


Figure: In the above mentioned case Image (G), (I) SPECT/CT showing abnormal tracer uptake in the Left 3rd and 4th MTP joints. Corresponding images (H), (J) of MRI also showing the contrast enhancement of the 3rd and 4th Left MTP joints.

3) **3rd MTP joint assessment by Bone scan and MRI**

Thirty 3rd MTP joints assessed by both scan, nineteen same joints showed no disease involvement. Six same joints showed disease involvement in the both scans. In the rest five discordant 3rd Left MTP joints bone scan was positive in 1 case and MRI was positive in four case. Statistically result showing a moderate agreement in both test (kappa coefficient 0.59 with P value -.001).

BMTP3 * MMTP3 Crosstabulation

Count		MMTP3		Total
		N	Y	
BMTP3	N	19	4	23
	Y	1	6	7
Total		20	10	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.595	.159	3.358	.001
N of Valid Cases		30			

a Not assuming the null hypothesis. b. Using the asymptotic standard error assuming the null hypothesis.

4) **4th MTP joints assessment by bone scan and MRI**

Thirty 4th MTP joints assessed by both scans, nineteen same joints showed no disease involvement. 04 same joints showing disease involvement. In the rest seven discordant 4th Left MTP joints bone scan was positive in two case & MRI was positive in 5 case. Statistically result showing a fair agreement in both test (kappa coefficient 0.38 with P value -.028).

BMTP4 * MMTP4 Cross tabulation

Count		MMTP4		Total
		N	Y	
BMTP4	N	19	5	24
	Y	2	4	6
Total		21	9	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.386	.186	2.191	.028
N of Valid Cases		30			

a. Not assuming the null hypothesis. b. Using the asymptotic standard error assuming the null hypothesis.

5) **5th MTP joints assessment by bone scan and MRI**

Thirty 5th MTP joints assessed by both scan, twenty four same joints showed no disease involvement. Two same joints showed disease involvement. In the rest four discordant 5th Left MTP joints bone scan was positive in two case & MRI was positive in two case. Statistically result showing a moderate agreement in both test (kappa coefficient 0.42 with P value -0.020).

BMTP5 * MMTP5 Cross tabulation

Count		MMTP5		Total
		N	Y	
BMTP5	N	24	2	26
	Y	2	2	4
Total		26	4	30

a. Not assuming the null hypothesis. b. Using the asymptotic standard error assuming the null hypothesis.

Individual proximal interphalangeal joint assessment by bone scan and MRI

1) 1st PIP joints assessment by bone scan and MRI.

Thirty 1st left IP joints assisted by both scan, nineteen same joints showed no disease involvement, three same joints showed disease involvement. In the rest 8 discordant 1st left IP joints bone scan was positive in six case and MRI was positive in two case. Statistically result showed a slight agreement in both test (kappa coefficient 0.27 with P value -.109).

BIP1 * MIP1 Cross tabulation

Count		MIP1		Total
		N	Y	
BIP1	N	19	2	21
	Y	6	3	9
Total		25	5	30

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.273	.187	1.604	.109
N of Valid Cases		30			

a Not assuming the null hypothesis. b Using the asymptotic standard error assuming the null hypothesis.

2) **2nd left IP joint assessment by bone scan and MRI**

Thirty 2nd left IP joints assessed by both scans, twenty-nine same joints showed no disease involvement. Rest one discordant 2nd left IP joints was positive in MRI. No positive finding was noted in the bone scan. Statistically no agreement was noted in the both scans.

BIP2 * MIP2 Cross tabulation

Count		MIP2		Total
		N	Y	
BIP2	N	29	1	30
Total		29	1	30

Symmetric Measures

		Value	Asymp. Std. Error[b]	Approx. T[c]
Measure of Agreement	Kappa	.000[a]	.	.
N of Valid Cases		30		

a. No statistics are computed because BIP2 is a constant.
b. Not assuming the null hypothesis.
c. Using the asymptotic standard error assuming the null hypothesis.

3) **3rd left IP joint assessment by bone scan and MRI.**

Thirty 3rd left IP joints assessed by both scans, twenty-nine same joints showed disease involvement. Rest one discordant 3rd left IP joints was positive in MRI. No positive finding was noted in the bone scan. Statistically no agreement is noted in the both scans.

BIP3 * MIP3 Cross tabulation

Count		MIP3		Total
		N	Y	
BIP3	N	29	1	30
Total		29	1	30

Symmetric Measures

		Value	Asymp. Std. Error[b]	Approx. T[c]
Measure of Agreement	Kappa	.000[a]	.	.
N of Valid Cases		30		

a. No statistics are computed because BIP3 is a constant.
b. Not assuming the null hypothesis.
c. Using the asymptotic standard error assuming the null hypothesis.

4) **4th left IP joint assessment by bone scan and MRI**

Thirty 4th left IP joints assessed by both scan total 30 were negative on both scans.

BIP4 * MIP4 Cross tabulation

Count		MIP4	Total
		N	
BIP4	N	30	30
Total		30	30

Symmetric Measures

		Value
Measure of Agreement	Kappa	.[a]
N of Valid Cases		30

a. No statistics are computed because BIP4 and MIP4 are constants.

5) **5th left IP joint assessment by bone scan and MRI.**

Thirty 5th left IP joints assessed by both scan, twenty nine same joints showed no disease involvement. Rest one discordant 5th left IP joints was positive in MRI. No positive findings were noted in the bone scan. Statistically no agreement is noted in the both scans.

So finally, study conclude that for the evaluation of left MTP joints both scan showing fair to moderate agreement, but this agreement is not seen in the PIP joints, its largely likely due to less involvement of PIP joints in the rheumatoid arthritis.

Discordant 42 joints result.

MRI Scan	20 positives
Bone Scan	22 positives

Out of forty-two discordant joints twenty joints were positive on MRI and twenty two joints were positive on bone scan.

All patients after triple phase bone scan and MRI examination underwent Outcome measures in Rheumatology (OMERACT) Rheumatoid Arthritis (RA) ultrasound-based scoring of left MTP joints only was done. Total one hundred fifty joints were evaluated out of which one hundred joints were involved in RA according to USG scoring system.

This scoring is based on synovitis according to the usual practice of different sonographers, using both grey-scale (GS) (synovial hypertrophy (SH) and effusion) and power Doppler (PD). Results Baseline reliability was highly variable but better for static than dynamic images that were directly acquired and immediately scored. Using static images, intrareader and inter-reader reliability for scoring PD were excellent for both binary and semiquantitative (SQ) grading but GS showed greater variability for both scoring systems. So false positive results may be high.

Clinical history and USG scan result of (n-30).

Clinical history	N-30	USG positive	USG negative
Pain in the left feet	20	18	02
No pain in the left feet	10	10	00

Thirty patients underwent USG examination, ten patients didn't had history of pain in the left foot however its result suggested that all patients had left foot joint involvement. On the other hand, twenty patient who clinically had pain, eighteen patients showing disease involvement but two patients didn't show any abnormality in the joints.

Discussion

As we know Rheumatoid arthritis is a chronic autoimmune disease that characterized by persistent inflammation of synovial membrane, increased capillary permeability with formation of new blood vessels, synovial changes, exudate collection in synovial stroma with infiltration of cellular elements cause synovial changes leading to progressive joints destruction and disability which causes pain, swelling of joints. In the clinical environment, final diagnosis of RA is made on the basis of typical clinical symptoms and signs, detailed physical examination, supporting biochemical findings and radiographic imaging. Recently, imaging modalities such as ultrasonography, MRI, bone scintigraphy and PET/CT in addition to plain radiography have been used to provide information about joint inflammation and damage in the clinical assessment of RA [7].

Several previous studies have underestimated the diagnostic efficacy of bone scintigraphy compared with other imaging modalities because the majority of these studies involved late phase bone scintigraphy without perfusion or blood pool phase. In recent years, many studies demonstrated that angiogenesis is an essential event in maintaining inflammatory and immune responses, as well as supporting pannus growth and development of RA New vessel formation and inflammation may increase the perfusion or blood pool phase. Therefore, comparable or even higher diagnostic efficacy to the other imaging modalities would be expected. [8] [9].

In our study abnormal increased tracer uptake was also based on blood pool and delayed images and for better image interpretation and localization we also performed SPECT/CT of bilateral feet joints. In fifty patients who underwent for triple phase bone scintigraphy, bone clearly demonstrated 786 joints involvement. Out of which 280 (~36%) were large joints and 506 (~64%) joints were small. This data showed head to toe evaluation of disease burden in RA can be clearly demonstrated with a single investigational tool.

Apart from this bone scintigraphy has many advantages over these other imaging modalities for evaluating multiple joint problems because of its high sensitivity, low cost, good availability, and the possibility of whole-body imaging [10].

In our study thirty patients underwent both MRI & triple phase bone scintigraphy. When compared both imaging modalities it suggested fair to moderate agreement between two imaging tools. Out of 300-foot joints evaluated by both scan, 258 (86 %) results were concordant either positive or negative. Only in 42 (14%) joints results showed discordant results.

As MRI concerned it recognized as the imaging technology of choice for visualization of the inflamed synovial membrane and bone edema. A part from this MRI has been shown to be a sensitive, non-invasive imaging modality for early detection and quantification of bone erosions. Erosions may be visible on MRI years before they are visible on radiographs. MRI can give us a better anatomical detail as bone marrow edema, bone erosion and synovitis of a specific joint or region. In MRI increased vascularity reflected by contrast enhancement.

In our study MRI scan clearly demonstrated the synovial changes as well as bone erosion and marrow edema. Planar and SPECT/CT images are also demonstrating the increased tracer activity at the corresponding site.

MRI picked up total forty-nine joints of left foot and bone scan picked up fifty joints of left foot. MRI reveals better anatomical detail as well as disease activity that reflected by contrast enhancement at the joint involved. However, in few joints effusion was noted without any contrast enhancement.

The major drawbacks of routine MRI usage are the time and expense of the procedure. It may be uncomfortable for some people because it can produce claustrophobia. MRI cost is significantly higher than the bone scan. From an economical point of view, the triple phase bone scan is still cheaper than performing multiple different scan.

Various studies showed high-frequency US and MRI are both effective in detecting bone erosion, tendinitis and tendon sheath edema in patients with early RA. MRI was demonstrated to be superior in the evaluation of bone marrow edema, while high-frequency US demonstrated an increased sensitivity for detecting early joint effusion and synovial proliferation in comparison with MRI. As further evidence becomes available, US and MRI will become increasingly important in the diagnosis and management of early RA. High-frequency US may be considered as a valuable modality for the detection of early RA, particularly when MRI is not accessible. The decision of which tool should be used in a given trial should rely on the clinical output requirement in order to minimize patient discomfort [11].

Us has been shown to be more sensitive than clinical examination in determining synovitis [12]. Studies showed that RA patients to be in remission had significant evidence of active inflammation on USG. This ongoing subclinical inflammation can lead to radiographic progression [13]. The accurate evaluation of disease status may improve RA management by providing a more timely and accurate diagnosis, improving treatment decisions and more accurately assessing remission. In our study 10 patients didn't had pain clinically however USG picked up disease in all joints. one hundred fifty joints evaluated by USG, one hundred (~66.66%) joints had synovial changes. Study suggest ultrasonography is non-inferior to other imaging modality to detect the joints detail expect bone edema.

Our study demonstrated that disease involvement may be present in clinically silent joints. All three imaging modalities showed that some extent of disease may present before symptoms of RA become evident. So disease, if detected in clinically silent joints these imaging modalities may help in better evaluation of disease extent.

Conclusion

❖ Triple phase ^{99m}Tc-MDP bone scintigraphy is an excellent imaging modality for evaluation of all small and large joints in single study. It provides valuable information about the disease activity, number and location of joints involvement.

❖ Bone edema, erosions, synovitis and contrast enhancement are MRI findings of joint involvement in RA. These MRI findings, if detected in clinically silent joints it help in better evaluation of disease extent.

❖ Both imaging modalities (^{99m}Tc-MDP triple phase bone scan and MRI) showed fair to moderate agreement to elicit the disease burden in the MTP joints.

❖ Ultrasonography is non-inferior imaging modality to detect the synovial changes in the early RA disease, although inter-observer variability may affect its efficiency.

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Received: 22 February 2025 / Accepted: 10 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.012

UDC 616.13-089

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RESULTS OF SURGICAL TREATMENT OF PATIENTS WITH CRITICAL ISCHAEMIA OF THE LOWER EXTREMITIES USING BIFURCATION SELECTIVE PROFUNDOPLASTY WITH REVERSED AUTOVENOUS GRAFTING

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Abstract

This article discusses the problems of surgical tactics in critical ischaemia of the lower extremities and its complications, both in the early postoperative period and in the long term. High limb amputation rates are prompting surgeons to search for the optimal surgical treatment method to achieve the best results. Amputation below the knee joint is considered preferable, as preserving the knee joint significantly improves functional outcomes, in particular the possibility of successful prosthetics and restoration of limb support. However, stump survival, the risk of postoperative complications, and the potential for prosthetics depend to a large extent on adequate blood supply in the amputation area.

Aim: To improve the results of surgical treatment of patients with critical lower limb ischaemia using bifurcation selective profundoplasty with reversed autovenous grafting.

Materials and Methods: This study involved 63 patients who underwent surgery between 2022 and 2024 in the city of Semey, Abai region. The study examined the general characteristics of surgical interventions performed on patients with critical lower limb ischaemia using the treatment methods we proposed to improve the final results.

Results: The analysis showed that patients who underwent lower leg amputation combined with bifurcation profundoplasty had better postoperative outcomes compared to the group that underwent isolated amputation. In the second group, complications from the stump were significantly less common, the ability to undergo prosthetic replacement was higher (71.9% vs. 45.2%, $p < 0.05$), and patency of the deep femoral artery was maintained in 81.3% of cases during 12 months of follow-up.

Conclusions: The data obtained confirm that preservation of the knee joint during amputation, combined with optimisation of collateral blood flow through profundoplasty, contributes to better functional outcomes and improved quality of life for patients. The proposed combined approach can be considered an effective alternative to isolated amputation in patients with severe vascular pathology and limited possibilities for direct revascularisation.

Keywords: *Critical limb ischaemia, atherosclerosis, amputation, profundoplasty.*

For citation:

Kozhakhmetov Zh.O., Sabitov Y.T., Toleutayev T.A., Toleutayeva D.M., Kazymov Ye.M., Imanbaev M.N. Results of surgical treatment of patients with critical ischaemia of the lower extremities using bifurcation selective profundoplasty with reversed autovenous grafting // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 91-97. *doi 10.34689/SH.2025.27.4.012*

Резюме

РЕЗУЛЬТАТЫ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ БОЛЬНЫХ С КРИТИЧЕСКОЙ ИШЕМИЕЙ НИЖНИХ КОНЕЧНОСТЕЙ С ПРИМЕНЕНИЕМ БИФУРКАЦИОННОЙ СЕЛЕКТИВНОЙ ПРОФУНДОПЛАСТИКИ С РЕВЕРСИРОВАННОЙ АУТОВЕНОЙ

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В данной статье рассматриваются проблемы хирургической тактики при критической ишемии нижних конечностей и ее осложнениях, как в раннем послеоперационном периоде, так и в отдаленном периоде. Высокие показатели ампутации конечности подталкивают хирургов на поиски оптимального метода хирургического лечения для получения лучших результатов. Уровень ампутации ниже коленного сустава считается предпочтительным, так как при сохранении коленного сустава значительно улучшаются функциональные результаты, в частности — возможность успешного протезирования и восстановления опороспособности конечности. Однако выживаемость культи, риск послеоперационных осложнений и потенциал для протезирования в значительной степени зависят от адекватного кровоснабжения в зоне ампутации.

Цель исследования: Улучшить результаты хирургического лечения больных с критической ишемией нижних конечностей с применением бифуркационной селективной профундопластики с реверсированной аутовеной.

Материалы и методы: В данном исследовании приняли участие 63 пациента, которым проведено хирургическое вмешательство с 2022 по 2024 года в городе Семей, области Абай. В исследовании были изучены общие характеристики хирургических вмешательств, выполненных больным с критической ишемией нижней конечности с использованием предложенными нами методов лечения для улучшения конечных результатов.

Результаты: Проведённый анализ показал, что у пациентов, перенёсших ампутацию голени в сочетании с бифуркационной профундопластикой, отмечались лучшие послеоперационные исходы по сравнению с группой, где выполнялась изолированная ампутация. Во второй группе достоверно реже встречались осложнения со стороны культи, выше была способность к протезированию (71,9% против 45,2%, $p < 0,05$), а также сохранялась проходимость глубокой бедренной артерии в 81,3% случаев в течение 12 месяцев наблюдения.

Выводы: Полученные данные подтверждают, что сохранение коленного сустава при ампутации в сочетании с оптимизацией коллатерального кровотока за счёт профундопластики способствует лучшим функциональным исходам и повышению качества жизни пациентов. Предлагаемый комбинированный подход может рассматриваться как эффективная альтернатива изолированной ампутации у пациентов с выраженной сосудистой патологией и ограниченными возможностями к прямой реваскуляризации.

Ключевые слова: *Критическая ишемия конечности, атеросклероз, ампутация, профундопластика.*

Для цитирования:
Кожахметов Ж.О., Сабитов Е.Т., Толеутаев Т.А., Толеутаева Д.М., Казымов Е.М., Иманбаев М.Н. Результаты хирургического лечения больных с критической ишемией нижних конечностей с применением бифуркационной селективной профундопластики с реверсированной аутовеной // Наука и Здравоохранение. 2025. Vol.27 (1), С.91-97. *doi 10.34689/SH.2025.27.4.012*

Түйіндеме

РЕВЕРСИЯЛАНҒАН КӨКТАМЫРМЕН СЕЛЕКТИВТІ БИФУРКАЦИЯЛЫҚ ПРОФУНДОПЛАСТИКА ӘДІСІН ҚОЛДАНА ОТЫРЫП, АЯҚТЫҢ КРИТИКАЛЫҚ ИШЕМИЯСЫ БАР НАУҚАСТАРҒА ЖАСАЛҒАН ХИРУРГИЯЛЫҚ ЕМДЕУДІҢ НӘТИЖЕЛЕРІ

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Бұл мақалада аяқтың критикалық ишемиясы кезіндегі хирургиялық тактика мен оның асқынулары, ерте және кеш отадан кейінгі кезеңдердегі ерекшеліктері қарастырылған. Аяқты ампутациялау көрсеткіштерінің жоғарылығы хирургтарды жақсы нәтижелерге қол жеткізу үшін тиімді әдістерді іздеуге итермелейді. Тізеден төмен деңгейде ампутация жасау қолайлы болып саналады, себебі тізе буынының сақталуы функционалды нәтижелерді едәуір

жақсартады, атап айтқанда – сәтті протездеу мүмкіндігін және аяқтың тірек қабілетін қалпына келтіруді қамтамасыз етеді. Алайда, тұқылдың (культяның) тез жазылуы, операциядан кейінгі асқынулар қаупі және протездеу ампутация аймағындағы қанмен қамтамасыз етілу деңгейіне айтарлықтай байланысты.

Зерттеудің мақсаты: Реверсияланған көктамырмен орындалатын бифуркациялық селективті профундопластика қолдану арқылы аяқтың критикалық ишемиясы бар науқастарды хирургиялық емдеу нәтижелерін жақсарту.

Материалдар мен әдістер: Зерттеуге 2022–2024 жылдар аралығында Абай облысының Семей қаласында ота жасалған 63 науқас қатысты. Зерттеу барысында аяқтың критикалық ишемиясы бар науқастарға қолданылған хирургиялық емдеу әдістерінің жалпы сипаттамалары мен соңғы нәтижелері талданды.

Нәтижелер: Талдау көрсеткендей, сирақ ампутациясын бифуркациялық профундопластикамен бірге өткізген науқастарда, оқшауланған ампутация жасалған топпен салыстырғанда, операциядан кейінгі нәтижелер жақсы болды. Екінші топта тұқылдың (культя) асқынулар сенімді түрде аз кездесті, протездеу мүмкіндігі жоғары болды (71,9% қарсы 45,2%, $p < 0,05$), сондай-ақ терең жамбас артериясының өткізгіштігі 12 айлық бақылау кезеңінде 81,3% жағдайда сақталды.

Қорытынды: Алынған деректер тізе буынын сақтау және профундопластика арқылы коллатералды қан айналымын жақсарту функционалды нәтижелерді күшейтіп, науқастардың өмір сапасын арттыратынын дәлелдейді. Ұсынылған кешенді тәсіл айқын тамырлық патологиясы бар әрі тікелей реваскуляризация жасау мүмкіндігі шектеулі науқастарда оқшауланған ампутацияға тиімді альтернативі ретінде қарастырылуы мүмкін.

Түйінді сөздер: Аяқтың критикалық ишемиясы, атеросклероз, ампутация, профундопластика.

Дәйексөз үшін:

Кожахметов Ж.О., Сабитов Е.Т., Толеутаев Т.А., Толеутаева Д.М., Казымов Е.М., Иманбаев М.Н., Реверсияланған көктамырмен селективті бифуркациялық профундопластика әдісін қолдана отырып, аяқтың критикалық ишемиясы бар науқастарға жасалған хирургиялық емдеудің нәтижелері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 91-97. *doi 10.34689/SH.2025.27.4.012*

Introduction

Every 30 seconds, a non-traumatic lower limb amputation occurs worldwide, amounting to more than 2,500 cases daily. According to various data, the annual incidence of major amputations ranges from 120 to 500 per million inhabitants [7]. This represents not only a medical but also a significant socio-economic problem, directly impacting patients' quality of life, work capacity, and life expectancy. Contemporary epidemiological data show that up to 90% of all non-traumatic amputations are associated with vascular diseases, primarily chronic critical limb ischemia (CLI) caused by progressive atherosclerosis of the lower extremity arteries.

Despite the severe detrimental effects of CLI on health, public awareness remains low. In many cases, patients seek medical help only at advanced stages characterized by significant trophic disturbances - gangrene or ischemic ulcers - which limits the possibilities for effective revascularization and increases the risk of amputation. Early detection and timely intervention are essential for successful treatment outcomes.

The most common anatomical localization of atherosclerotic lesions is the femoropopliteal segment. Isolated lesions in this area account for up to 65% of all recorded cases of lower limb arterial disease [9]. In cases of superficial femoral artery (SFA) occlusion, the deep femoral artery (DFA), which does not directly continue into the popliteal artery, plays a key role as a source of collateral blood flow. The extensive branching of the DFA allows for the formation of collaterals that partially compensate for blood supply to the distal parts of the limb. However, the presence of hemodynamically significant stenosis of the DFA markedly reduces the efficiency of this compensatory mechanism, which may lead to progression of ischemia, tissue necrosis in the foot and lower leg, and the necessity of amputation [4, 8].

Given the role of the DFA in collateral circulation, its functional status is critically important in patients with CLI. In some cases, reconstruction of the deep femoral artery (profundoplasty) improves perfusion in distal limb segments, even when full revascularization of more distal arteries is not feasible. Recent studies confirm that open reconstruction of the DFA not only promotes ulcer healing and amputation prevention but also increases the likelihood of successful prosthetic fitting after below-knee amputation.

Currently, two main approaches are used to restore blood flow in chronic femoropopliteal occlusions: open surgical interventions (including bypass surgery and profundoplasty) and endovascular methods - percutaneous transluminal angioplasty and stenting. Endovascular treatment is considered the first-line strategy for lesions of the superficial femoral and popliteal arteries [10]. However, in cases involving the common femoral artery (CFA) and the ostium of the deep femoral artery, open endarterectomy with patch angioplasty remains the gold standard [1].

In cases where revascularization is impossible or ineffective, amputation is performed. However, even in these situations, the condition of the DFA remains clinically significant: adequate blood flow to the stump is critical for wound healing, prevention of infectious complications, and successful prosthetic rehabilitation. Therefore, assessment of the status and reconstructive options of the DFA should be an integral part of preoperative planning in patients with severe limb ischemia.

The aim of the study is to improve the results of surgical treatment of patients with critical ischaemia of the lower extremities using bifurcation selective profundoplasty with reversed autovenous grafting.

Materials and methods

The study included 63 patients with critical lower limb ischaemia (CLLI) stage IV according to the Rutherford classification, who were scheduled for lower limb amputation at the shin level. All patients were treated in the cardiovascular surgery department of the University Hospital NCJSC 'SMU' from 2022 to 2024. The average age of the patients was 65.2 years (range 57 to 73 years). Of the total number of patients examined, 47 (74.6%) were men and 16 (25.4%) were women.

Inclusion criteria: patients with critical lower limb ischaemia who are indicated for limb amputation with significant stenosis of the deep femoral artery on the affected side.

Exclusion criteria: patients with critical ischaemia without indications for lower limb amputation, absence of significant stenosis of the deep femoral artery in patients.

The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the State Medical University of Semey (Protocol 5 dated January 25, 2022, y).

Patients were divided into two groups:

• Group 1 (n = 31): Lower leg amputation without reconstructive surgery;

• Group 2 (n = 32): Lower leg amputation combined with bifurcation selective profundoplasty using a reversed autovenous graft.

Table 1.

Distribution of patients by groups and demographic characteristics.

Indicator	Group 1 (n=31)	Group 2 (n=32)	Total (n=63)
Average age (years)	64,8 ± 4,2	65,6 ± 3,9	65,2 ± 4,0
Age range (years)	57–73	58–72	57–73
Men, n (%)	24 (77,4%)	23 (71,9%)	47 (74,6%)
Women, n (%)	7 (22,6%)	9 (28,1%)	16 (25,4%)

Pre- and postoperative assessment included:

• Clinical examination (pain syndrome, viability of stump tissues);

• Ultrasound with Doppler imaging;

• In some cases – CT angiography;

• Assessment of suture integrity and wound healing quality;

• Deep femoral artery patency (in the second group);

• Prosthetic potential (stump bearing capacity).

The duration of observation was 12 months. Follow-up examinations were conducted at 1, 3, 6, and 12 months.

Statistical analysis

Intergroup comparison of quantitative characteristics was performed using the Mann-Whitney U test. Comparison of frequency indicators in independent samples was performed using Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

Results

A comprehensive analysis of 63 patients was conducted. The comorbidities of both groups are presented below (Table 2).

Table 2.

Prevalence of comorbidities in patients in both groups.

Associated disease	Group 1 (n=31)	Group 2 (n=32)	Total (n=63)	*p-value*
History of acute cerebrovascular accident	9 (29,0%)	7 (21,9%)	16 (25,4%)	0,48
Arterial hypertension	25 (80,6%)	26 (81,3%)	51 (81,0%)	0,94
Ischemic heart disease	18 (58,1%)	16 (50,0%)	34 (54,0%)	0,51
Chronic kidney disease (CKD)	11 (35,5%)	8 (25,0%)	19 (30,2%)	0,38
Obliterating atherosclerosis of the BCA	9 (29,0%)	7 (21,9%)	16 (25,4%)	0,48
Chronic heart failure	10 (32,3%)	9 (28,1%)	19 (30,2%)	0,72
Obesity (BMI ≥ 30 kg/m²)	6 (19,4%)	5 (15,6%)	11 (17,5%)	0,66

A high incidence of concomitant chronic diseases was observed among the patients examined. Arterial hypertension was detected in the majority of patients (81.0%), ischaemic heart disease in 54.0%, and chronic kidney disease in 30.2%. A history of acute cerebrovascular accident was present in 25.4% of patients, and obesity (BMI ≥ 30 kg/m²) in 17.5%. The distribution of concomitant pathology between the groups was comparable, with no statistically significant differences recorded ($p > 0.05$ for all indicators). The combination of severe vascular pathology with somatic diseases forms a high-risk group, which requires special attention when choosing treatment tactics and in postoperative observation.

Surgical procedure:

In the first group, standard amputation of the lower leg at the mid-third level was performed using the generally accepted technique. In the second group, a combined procedure was performed: amputation of the lower leg at the mid-third level combined with bifurcation selective profundoplasty. The indication for profundoplasty was stenosis of the deep femoral artery (DFA) with unaffected inflow pathways and surface occlusion. When performing isolated profundoplasty, we used regional (epidural or spinal) anaesthesia. A reversed great saphenous vein borrowed from the contralateral or ipsilateral limb was used for reconstruction. Surgical access was achieved through a medial femoral incision. Revision of the common, superficial, and deep femoral arteries was performed. Anastomoses were performed between the venous shunt and the main branches of the deep femoral artery, ensuring improved collateral blood flow to the stump (Figure 1).

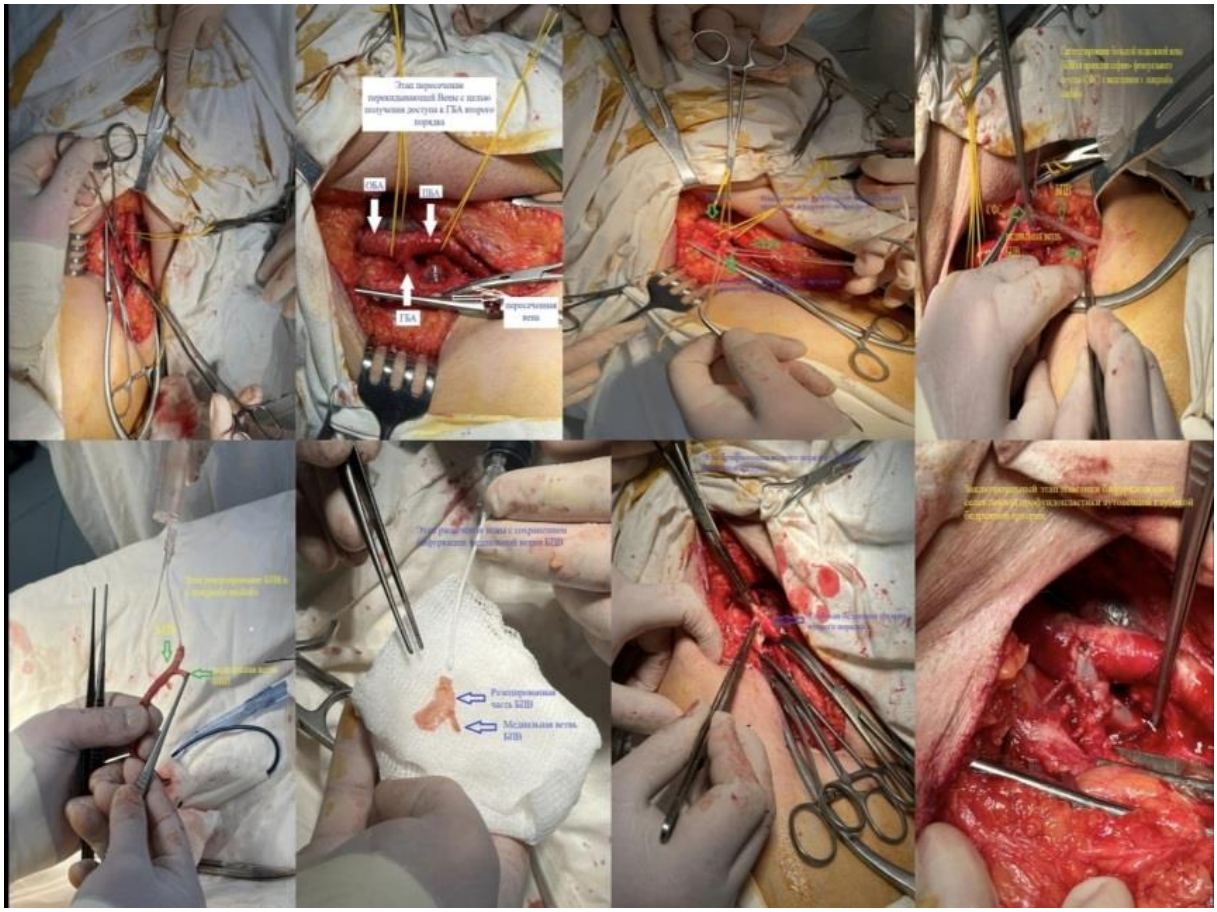


Figure 1. 1. Isolation of the common, deep and superficial femoral arteries. 2. Crossing of the perforating vein. 3. Isolation of the second-order DFA. 4. Harvesting of the GSV with the medial branch. 5. Reversal of the GSV with the medial branch. 6. Incision of the vein with preservation of the bifurcation of the medial branch. 7. Arteriotomy of the second-order DFA. 8. General view after selective bifurcation plasty of the second-order DFA.

This surgical treatment method has been granted patent No. 36887 by the Republic of Kazakhstan in 2023.

Patients in the second group showed more favourable indicators of stump tissue viability and wound healing quality in the postoperative period. Delayed complications (stump necrosis, wound infection, suture dehiscence) were statistically significantly less frequent in the second group compared to the first ($p < 0.05$). The ability to undergo prosthetic replacement after 12 months of observation was significantly higher in the second group: 71.9% of patients ($n = 23$) successfully underwent primary prosthetic replacement and achieved satisfactory stump bearing capacity, while in the first group the corresponding figure was 45.2% ($n = 14$) ($p = 0.03$) .

Discussion

Below-knee amputation in cases of critical limb ischemia (CLI) remains a relevant and sometimes the only feasible surgical treatment for patients with severe, irreversible arterial circulation disorders. However, the success of such surgery is determined not only by patient survival but also by functional outcomes, particularly the load-bearing capacity of the stump and the potential for prosthetic rehabilitation. At the same time, inadequate blood supply in the amputation area significantly increases the risk of postoperative complications such as tissue necrosis, infection, wound dehiscence, and formation of an unstable stump requiring revision surgery [2].

The study demonstrated that the use of selective profundoplasty at the bifurcation in patients with isolated stenosis of the profunda femoris artery and occlusion of the superficial femoral artery significantly improved the outcomes of below-knee amputation. In the second group, where this technique was applied, there was a significant reduction in the incidence of local complications and an increase in the proportion of patients eligible for prosthetic rehabilitation compared to the group that underwent isolated amputation [3, 5].

Given that in some CLI patients the profunda femoris artery remains the only source of collateral blood supply to the distal limb, its reconstruction becomes especially important. The performed profundoplasty contributed to improved tissue perfusion in the stump area, which, in turn, positively affected wound healing and final functional outcomes. The authors also emphasize that the diameter of the profunda femoris artery is a critical factor in achieving favorable results [6]. Furthermore, it is important to note that the combined procedure did not increase hospital mortality or the rate of serious systemic complications, indicating its safety when appropriate preoperative patient selection is applied. Additionally, the use of an autogenous venous graft

(reversed great saphenous vein) provided high graft patency over a 12-month follow-up period.

Moreover, the reconstruction of the profunda femoris artery as part of a comprehensive approach to CLI treatment not only improves immediate surgical outcomes but also enhances patients' quality of life in the postoperative period. A more stable stump and the potential for early prosthetic fitting significantly increase the chances of social and domestic reintegration, especially in elderly patients with multiple comorbidities. This is particularly relevant considering the disabling nature of lower-limb amputations and the need for rapid functional recovery.

The reduced incidence of local postoperative complications—such as soft tissue necrosis, wound dehiscence, and secondary infection—also contributes to shorter hospital stays and less frequent need for reoperations, which has both clinical and economic significance. These benefits are especially valuable in resource-limited healthcare settings, where achieving maximum treatment efficiency is essential.

Comparison with other studies also supports the rationale for using profundoplasty. Several authors [3, 8] have previously emphasized the importance of maintaining or restoring blood flow through the profunda femoris artery in patients with superficial femoral artery occlusion. Our findings confirm these conclusions and demonstrate their practical feasibility even in cases where only an amputation was initially planned.

Nevertheless, it is essential to highlight that the success of this intervention largely depends on proper patient selection. Key criteria include the anatomical patency and adequate diameter of the profunda femoris artery, availability of suitable autologous vein grafts, and the patient's overall condition. Therefore, individualized treatment planning and involvement of a multidisciplinary team (including a vascular surgeon, anesthesiologist, and rehabilitation specialist) are crucial factors in decision-making and optimizing clinical outcomes.

In conclusion, the results confirm that below-knee amputation combined with profunda femoris artery reconstruction can be an effective and justified approach in patients with severe ischemia, where revascularization via the superficial femoral artery or below is not possible or ineffective. However, despite the encouraging results, the limited sample size and retrospective nature of the study must be taken into account. Future randomized prospective studies with larger patient cohorts and longer follow-up periods are warranted to more accurately assess the efficacy of this technique and define its place in clinical guidelines.

Conclusions

The results of the study demonstrate the clinical feasibility and effectiveness of bifurcation selective profundoplasty combined with lower leg amputation in patients with stage IV critical lower limb ischaemia in the presence of deep femoral artery stenosis. Performing reconstructive surgery in the context of amputation improves blood supply to the stump, reduces the frequency of postoperative complications, increases tissue viability, and significantly increases the proportion of patients who are eligible for prosthetics and restoration of limb function. The data obtained confirm that preservation of the knee joint during amputation, combined with optimisation of collateral blood flow through profundoplasty, contributes to better functional outcomes and improved quality of life for patients. The proposed combined approach can be considered an effective alternative to isolated amputation in patients with severe vascular pathology and limited possibilities for direct revascularisation.

All authors contributed equally to the research and writing of this article. Sabitov E.T., and Imanbaev M.N. supervised the scientific research and made adjustments. Kozhakhmetov Zh.O., Sabitov E.T., Toleutaev T.A., Kazymov E.M., Imanbaev M.N., carried out a search of literature data and their processing. Kozhakhmetov Zh.O., Sabitov E.T., Toleutaev T.A., Kazymov E.M., Imanbaev M.N., carried out a sample of patients and their surgical treatment, and also took part in developing the outline of the article, editing the text and approving the final version of the article. Sabitov E.T., and Imanbaev M.N. edited and designed the text of the article. No conflicts of interest declared.

The authors declare that this material has not been previously submitted for publication in other publications.

There was no funding from third-party organizations or medical agencies in carrying out this work.

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Received: 02 December 2024 / Accepted: 30 June 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.013

UDC 616.13-089.87

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ASSESSMENT OF QUALITY OF LIFE OF PATIENTS AFTER ABOVE AND BELOW KNEE AMPUTATION WITH LOWER LIMB ARTERY OCCLUSION WITH CRITICAL ISCHEMIA

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Abstract

Introduction: Lower limb arterial occlusion often leads to critical ischemia requiring amputation. The level of amputation determines not only the patient's functional capabilities but also their quality of life, which makes it important to study the effect of knee preservation on rehabilitation and subjective perception of health.

Objective: to determine and compare the quality of life of patients after above-knee amputation (AKA) and below-knee amputation (BKA) performed for occlusive disease of the lower limb arteries with critical ischemia.

Research methods: A prospective study of 63 patients (33 BKA, 30 AKA) was conducted. Quality of life was assessed using the SF-36 questionnaire at 1, 6, and 12 months after surgery. The analysis included eight SF-36 scales, as well as comorbidities. Statistical analysis was performed using the χ^2 test and Student's t-test, significance level $p < 0.05$.

Results: BKA patients had higher scores on physical functioning (68.2 ± 12.1 vs. 39.7 ± 10.4 points, $p < 0.001$), role functioning due to physical condition (56.7 ± 11.5 vs. 42.3 ± 9.8, $p < 0.001$), and lower pain severity (63.8 ± 10.9 vs. 49.1 ± 10.2, $p < 0.001$). General health status was also assessed higher in BKA (59.5 ± 9.8 vs. 48.6 ± 8.9, $p < 0.001$). No significant differences were found in the psychoemotional scales, but there was a tendency for better indicators in the BKA group.

Conclusions: The study showed that the level of amputation significantly affects the physical activity and autonomy of patients. Patients with below-knee amputation (BKA) showed higher indicators of physical functioning (68.2 vs. 39.7 points, $p < 0.001$), role activity (56.7 vs. 42.3 points, $p < 0.001$) and less pain severity (63.8 vs. 49.1 points, $p < 0.001$), which positively affected their psychological state and perception of quality of life. Preservation of the knee joint accelerates rehabilitation, while for patients with above-knee amputation (AKA), comprehensive physical and psychological support is especially important.

Key words: *amputation; above- and below-knee amputation; occlusive arterial disease; critical ischemia; lower limbs; quality of life; vascular surgery; rehabilitation; disability; peripheral arterial disease.*

For citation:

Kozhakhmetov Z.O., Dyusupov A.A., Sabitov Y.T., Toleutaev T.A., Kazymov E.M., Salmenbaev E.A., Imanbaev M.N., Masalov A.E., Abdrakhmanov S.T. Assessment of quality of life of patients after above and below knee amputation with lower limb artery occlusion with critical ischemia // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 98-106. *doi 10.34689/SH.2025.27.4.013*

Резюме

ОЦЕНКА КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ ПОСЛЕ АМПУТАЦИИ ВЫШЕ И НИЖЕ КОЛЕННОГО СУСТАВА ПРИ ОККЛЮЗИИ АРТЕРИИ НИЖНИХ КОНЕЧНОСТЕЙ С КРИТИЧЕСКОЙ ИШЕМИЕЙ

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Введение: Окклюзия артерий нижних конечностей нередко приводит к критической ишемии, требующей ампутации. Уровень ампутации определяет не только функциональные возможности пациента, но и его качество жизни, что делает важным изучение влияния сохранения коленного сустава на реабилитацию и субъективное восприятие здоровья.

Цель: определить и сравнить качество жизни пациентов после ампутации выше (above-knee amputation, AKA) и ниже коленного сустава (below-knee amputation, BKA), выполненной по поводу облитилирующие заболеваний артерий нижних конечностей с критической ишемией.

Методы исследования: Проведено проспективное исследование 63 пациентов (33 — BKA, 30 — AKA). Оценка качества жизни выполнялась с помощью опросника SF-36 через 1, 6 и 12 месяцев после операции. Анализ включал восемь шкал SF-36, а также сопутствующую патологию. Статистическая обработка проводилась с использованием χ^2-теста и t-теста Стьюдента, уровень значимости $p < 0,05$.

Результаты: Пациенты BKA имели более высокие показатели физического функционирования (68,2 ± 12,1 против 39,7 ± 10,4 балла, $p < 0,001$), ролевого функционирования, обусловленного физическим состоянием (56,7 ± 11,5 против 42,3 ± 9,8, $p < 0,001$), и меньшую выраженность боли (63,8 ± 10,9 против 49,1 ± 10,2, $p < 0,001$). Общее состояние здоровья также оценивалось выше у BKA (59,5 ± 9,8 против 48,6 ± 8,9, $p < 0,001$). Существенных различий по психоэмоциональным шкалам не выявлено, однако отмечалась тенденция к лучшим показателям в группе BKA.

Выводы: Проведённое исследование показало, что уровень ампутации существенно влияет на физическую активность и автономность пациентов. У больных с ампутацией ниже коленного сустава (BKA) отмечены более высокие показатели физического функционирования (68,2 против 39,7 балла, $p < 0,001$), ролевой активности (56,7 против 42,3 балла, $p < 0,001$) и меньшая выраженность боли (63,8 против 49,1 балла, $p < 0,001$), что положительно сказывается на их психологическом состоянии и восприятии качества жизни. Сохранение коленного сустава ускоряет реабилитацию, тогда как для пациентов с ампутацией выше колена (AKA) особенно важна комплексная физическая и психологическая поддержка.

Ключевые слова: *ампутация; выше- и нижеколенная ампутация; облитерирующие заболевания артерий; критическая ишемия; нижние конечности; качество жизни; сосудистая хирургия; реабилитация; инвалидизация; периферическая артериальная болезнь.*

Для цитирования:

Кожахметов Ж.О., Дюсупов А.А., Сабитов Е.Т., Толеутаев Т.А., Казымов Е.М., Сальменбаев Е.А., Иманбаев М.Н., Масалов А.Е., Абдрахманов С.Т. Оценка качества жизни пациентов после ампутации выше и ниже коленного сустава при окклюзии артерии нижних конечностей с критической ишемией // Наука и Здравоохранение. 2025. Vol.27 (4), С.98-106. *doi 10.34689/SH.2025.27.4.013*

Түйіндеме

ТӨМЕНГІ АРТЕРИЯ ОККЛЮЗИЯСЫНДАҒЫ ТІЗЕ БУЫНЫНАН ЖОҒАРЫ ЖӘНЕ ТӨМЕН АМПУТАЦИЯДАН КЕЙІНГІ НАУҚАСТАРДЫҢ ӨМІР СҮРУ САПАСЫН БАҒАЛАУЖӘНЕ КРИТИКАЛЫҚ ИШЕМИЯМЕН

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Кіріспе: төменгі аяқ артерияларының окклюзиясы жиі ампутацияны қажет ететін сыни ишемияға әкеледі. Ампутация деңгейі пациенттің функционалдығын ғана емес, сонымен қатар оның өмір сүру сапасын да анықтайды, бұл тізе буынының сақталуының оңалтуға және денсаулықты субъективті қабылдауға әсерін зерттеуді маңызды етеді.

Мақсаты: жоғарыда (above-knee amputation, AKA) және тізе буынынан төмен (below-knee amputation, BKA) ампутациядан кейінгі пациенттердің өмір сүру сапасын анықтау және салыстыру.төменгі аяқтың артериялық ауруларын сыни ишемиямен облитиляциялау.

Зерттеу әдістері: 63 пациентке перспективалық зерттеу жүргізілді (33 — BKA, 30 — AKA). Өмір сапасын бағалау операциядан кейін 1, 6 және 12 айдан кейін SF-36 сауалнамасы арқылы жүргізілді. Талдау сегіз SF-36 шкаласын, сондай-ақ ілеспе патологияны қамтыды. Статистикалық өңдеу β2-тест пен студенттің t-тестін қолдану арқылы жүргізілді, $p < 0,05$ маңыздылық деңгейі.

Нәтижелер: BKA пациенттерінде физикалық жұмыс көрсеткіштері жоғары болды (68,2 ± 12,1 қарсы 39,7 ± 10,4 балл, $p < 0,001$), физикалық жағдайға байланысты рөлдік жұмыс (56,7 ± 11,5 қарсы 42,3 ± 9,8, $p < 0,001$) және ауырсыну ауырлығы төмен (63,8 ± 10,9 қарсы 49,1 ± 10,2, $p < 0,001$). Жалпы денсаулық BKA-да жоғары бағаланды (59,5 ± 9,8 қарсы 48,6 ± 8,9, $p < 0,001$). Психоэмоционалды шкалалар бойынша айтарлықтай айырмашылықтар анықталған жоқ, бірақ BKA тобындағы ең жақсы көрсеткіштерге бейімділік байқалды.

Қорытындылар: жүргізілген зерттеу ампутация деңгейі пациенттердің физикалық белсенділігі мен автономиясына айтарлықтай әсер ететінін көрсетті. Тізе буынынан төмен ампутациясы бар науқастарда (BKA) физикалық жұмыс көрсеткіштері жоғары (68,2 қарсы 39,7 балл, $p < 0,001$), рөлдік белсенділік (56,7 қарсы 42,3 балл, $p < 0,001$) және ауырсынудың ауырлығы төмен (63,8 қарсы 49,1 балл, $p < 0,001$), бұл олардың психологиялық жұмысына оң әсер етеді өмір сапасын қабылдау және қабылдау. Тізе буынын сақтау оңалтуды тездетеді, ал тізеден жоғары ампутациясы (AKA) бар науқастар үшін кешенді физикалық және психологиялық қолдау әсіресе маңызды.

Түйінді сөздер: *ампутация; жоғары және төменгі тізе ампутациясы; артериялардың облитиляциялық аурулары; критикалық ишемия; төменгі аяқтар; өмір сапасы; тамырлы хирургия; оңалту; мүгедектік; перифериялық артериялық ауру.*

Дәйексөз үшін:

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Introduction

Lower limb amputation is a radical surgical intervention that belongs to the category of highly traumatic operations, accompanied by significant anatomical, functional, psycho-emotional and social-adaptive changes in the patient's condition. According to clinical practice, two main types of such interventions are most often performed: upper-knee amputation (AKA) and lower-knee amputation (BKA) [1].

A pressing task of modern vascular surgery and rehabilitation remains the study of the influence of the level of amputation on key indicators of treatment outcomes - quality of life, functional capacity, the possibility of returning to independent movement and the success of prosthetics.

Preservation of the knee joint in case of lower leg amputation (BKA) ensures a more biomechanically rational gait pattern, reduces metabolic costs during locomotion and increases the likelihood of full adaptation of the prosthetic-orthotic device. In contrast, amputation of the femur (AKA) is more often performed in case of widespread ischemic and necrotic lesions, which initially predetermines a more complex course of the recovery period and potentially worse functional results.

Despite the introduction of high-tech prosthetic systems that allow partial compensation for lost functions of the musculoskeletal system, the height of amputation continues to be considered as one of the leading prognostic factors determining the effectiveness of rehabilitation measures and the degree of restoration of the patient's quality of life.

Modern areas of vascular surgery and rehabilitation are aimed at a detailed study of the influence of the level of lower limb amputation on clinical outcomes and social adaptation indicators. There is convincing evidence that patients who have undergone below-knee amputation (BKA) demonstrate a higher level of autonomous mobility and adapt to prosthetics more successfully compared to patients after above-knee amputation (AKA) [2–4].

Occlusion of the arteries of the lower extremities complicated by the development of critical limb ischemia (CLI) is the terminal stage of chronic arterial insufficiency, in which a pronounced deficit in the blood supply to the tissues of the distal parts of the limb is formed. The clinical picture of this condition is characterized by the appearance of intense ischemic pain at rest, the formation of trophic ulcers, necrotic changes in soft tissues and an extremely high probability of loss of the affected limb [5]. In those clinical situations when reconstructive or endovascular interventions to restore adequate blood flow are impossible or ineffective, surgical amputation is considered a forced measure aimed at preventing the spread of necrosis and saving the patient's life. However, this operation is associated with serious consequences affecting not only physical health, but also the psychoemotional state, as well as the social adaptation of the patient [6].

According to the World Health Organization, the prevalence of peripheral arterial disease (PAD) globally reaches approximately 202 million people. At the same time, according to experts, about 10-11% of patients have severe clinical forms of the disease, in which the restoration of blood flow requires surgical or endovascular interventions [7].

European statistics show that between 150,000 and 200,000 lower limb amputations are performed on the continent every year, with atherosclerotic occlusion of the main arteries being the main etiological factor in 50–70% of cases [8].

The prognosis for critical limb ischemia remains extremely poor: up to 30% of patients undergo amputation within the first year of diagnosis, and the five-year mortality rate after such surgery exceeds 50% [9]. These data highlight the need for early diagnosis and comprehensive treatment of peripheral arterial disease to reduce the number of amputations and improve long-term outcomes.

The height (level) of amputation has a direct and multifactorial effect on the subsequent functional state of the patient, including physical activity indicators, the amount of energy expenditure when walking, the pace and success of mastering the prosthetic and orthopedic device, as well as the degree of social and everyday adaptation. According to clinical studies, preserving the knee joint during amputation at the level of the lower leg (below-knee amputation, BKA) is associated with higher values of quality of life according to the validated SF-36 scales. In addition, this group shows better results of prosthetics - success reaches up to 88% of cases, while with hip amputation (above-knee amputation, AKA) this figure does not exceed 63% [10, 11].

However, the choice of the optimal level of amputation in clinical practice is often determined by the severity of ischemic disorders and the volume of necrotic damage to soft tissues, which in some cases objectively limits the possibility of preserving the knee joint.

Aim: To determine and compare the quality of life of patients after above-knee amputation (AKA) and below-knee amputation (BKA) performed for lower limb arterial occlusion with critical ischemia.

Materials and Methods: A study was conducted to assess the quality of life of patients after lower limb amputation at different levels due to occlusion of lower limb arteries. Two groups were compared: The main group (BKA) - amputation below the knee joint. The control group (AKA) - amputation above the knee joint. The duration of observation of patients was 12 months after surgery.

The diagnosis of lower extremity artery occlusion in all patients was confirmed using a comprehensive clinical and instrumental examination in accordance with current international and national clinical guidelines. Clinical examination - assessment of the skin condition, the presence of trophic disorders, ulcerative defects, skin color, limb temperature, as well as palpation of the pulse on the main arteries of the lower extremities. Instrumental methods - ultrasound Dopplerography (USDG) and duplex scanning of the arteries of the lower extremities to determine the degree of stenosis and localization of occlusion; if necessary, contrast angiography or CT angiography was performed to clarify the extent of the lesion and the state of collateral blood flow. Laboratory tests — determination of lipid profile (total cholesterol, LDL, HDL, triglycerides), fasting blood glucose level, glycosylated hemoglobin (HbA1c) in patients with suspected or existing diabetes mellitus, as well as inflammation markers (C-reactive protein). Evaluation of ischemia severity - was carried out based on the Fontaine and Rutherford classifications, taking into account the severity of pain syndrome, pain-free walking distance and the presence of necrotic changes.

All surgical interventions were performed according to uniform standards, taking into account the principles of atraumaticity and formation of an optimal stump for subsequent prosthetics. Below-knee amputation (BKA) was performed with preservation of a functional knee joint and sufficient length of the tibia for prosthetics. When forming the stump, adequate myoplasty and myodesis were ensured to increase stability and reduce the risk of pain. Above-knee amputation (AKA) was performed at the level of the middle third of the thigh with preservation of the maximum length of the femur, allowing the use of modern prostheses. Particular attention was paid to the formation of a conical stump with smooth skin and optimal distribution of soft tissues. Anesthesia - in most cases, spinal or epidural anesthesia was used; in case of contraindications - general endotracheal anesthesia. Postoperative care included prevention of infectious complications, deep vein thrombosis, correction of pain syndrome and early initiation of rehabilitation measures. Early rehabilitation began on the first day after surgery and included breathing exercises, isometric exercises to maintain muscle mass, teaching patients self-care skills, and subsequently preparing the stump for prosthetics.

Inclusion criteria: diagnosis of occlusive disease of the arteries of the lower extremities with critical ischemia (CLI), confirmed by clinical and instrumental methods; amputation performed at the level of the thigh or lower leg; period after surgery ≥ 6 months; age ≥ 18 years; consent to participate.

Exclusion criteria included amputation due to trauma, tumor or infection; bilateral amputation, patients who did not agree to participate in the study for any reason, and incompetent patients.

The study included 63 patients: 33 (52.4%) - BKA and 30 (47.6%) - AKA, treated in the Vascular Surgery Department of the UG NCJSC «SMU» in the period from January 2021 to December 2024.

The mean age of all participants was 62.4 ± 8.9 years (range 41–81 years). In the BKA group, the mean age was 61.3 ± 8.7 years, in the AKA group, 63.6 ± 9.1 years (p = 0.12).

In terms of gender composition, BKA is 12 men (36.4%) and 21 women (63.6%); AKA is 11 men (36.7%) and 19 women (63.3%).

To assess the quality of life of patients, the Short Form-36 Health Survey (SF-36) questionnaire was used, which is an internationally recognized instrument that has undergone a procedure of cultural adaptation and validation in Russian. This questionnaire allows for a comprehensive assessment of the patient's physical, psychological and social well-being, as well as subjective perception of health. SF-36 consists of 36 questions, combined into eight scales:

1. PF (Physical Functioning) — physical functioning, reflects the degree of limitations in performing physical activities.
2. RP (Role-Physical) — role functioning associated with the physical condition.
3. BP (Bodily Pain) — the intensity of the pain syndrome and its impact on activity.
4. GH (General Health) — general perception of health.
5. VT (Vitality) — vitality and energy level.
6. SF (Social Functioning) — social activity and quality of interaction with others.
7. RE (Role-Emotional) — role functioning caused by the emotional state.
8. MH (Mental Health) — mental health, including mood, anxiety and depression levels.

Each scale is rated on a scale from 0 to 100, with higher scores indicating better health or lesser limitations.

Survey procedure: The first stage is 1 month after amputation, in a hospital or outpatient setting. The second stage is 6 months after surgery. The third stage is 12 months after surgery.

The questionnaire was conducted in the form of a personal interview with the patient or independent completion of the questionnaire, depending on the cognitive and motor capabilities of the subject. In case of difficulties, patients received assistance from the researcher, but the wording of the questions and the order of their presentation were strictly preserved, which excluded the influence of external factors on the answers.

Ethical approval.

Before the study, a meeting of the Ethics Committee of the Non-Profit Joint-Stock Company Semey Medical University (NCJSC SMU), Semey, Kazakhstan, "Protocol No. 5" dated January 25, 2022, was held, at which the study protocol, informed consent forms, start and end dates of the scientific study were approved and approval of the Ethics Committee was obtained. The study was conducted in accordance with the institutional guidelines for human research and the principles of the Declaration of Helsinki. The study protocols were approved by the Ethics Committee of NCJSC SMU, Semey and the University Hospital of the Non-Profit Joint-Stock Company Semey Medical University, Semey, Kazakhstan. All patients participating in the study were familiarized with the informed consent. They also signed consent to participate in the scientific work and the patients were given information on full confidentiality and anonymity of the data.

Statistical analysis

Homogeneity between groups was assessed using the chi-square test for categorical variables and independent Student's t-tests for continuous variables. Continuous data were presented as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages (%). A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 20.0.

Results

The study included 63 patients with critical lower limb ischemia due to vascular occlusion, who underwent limb amputation at different levels. The main group (BKA) - 33 people (52.4%) and the control group (AKA) - 30 people (47.6%).

The average age of the entire sample was 62.4 ± 8.9 years (from 41 to 81 years). In the BKA group - 61.3 ± 8.7 years, in the AKA group - 63.6 ± 9.1 years (p = 0.12).

By gender: BKA - 12 men (36.4%) and 21 women (63.6%), AKA - 11 men (36.7%) and 19 women (63.3%). The differences in gender are statistically insignificant (p = 0.74).

Table 1.

Concomitant pathology in patients of two groups.

Concomitant disease	BKA (n=33)	AKA (n=30)	p-value
Arterial hypertension	24 (72,7 %)	22 (73,3 %)	0,69
Coronary heart disease	19 (57,6 %)	18 (60,0 %)	0,78
Chronic heart failure	9 (27,3 %)	9 (30,0 %)	0,73
COPD	4 (12,1 %)	3 (10,0 %)	0,82
Chronic renal failure	2 (6,1 %)	2 (6,7 %)	0,94

An analysis of the structure of concomitant diseases in the study sample showed that the largest proportion is made up of chronic non-infectious diseases of the cardiovascular system.

Arterial hypertension was the most common pathology: it was detected in 72.7% of patients in the BKA group and in 73.3% of the AKA group. This indicator reflects the high frequency of hypertension in patients with occlusion of lower extremity vessels and confirms its role as a leading risk factor for the progression of cardiovascular pathology.

Coronary artery disease (CAD) was found in 57.6% of patients in the BKA group and 60.0% in the AKA group. This demonstrates a close relationship between the systemic atherosclerotic process and peripheral arterial disease: patients with occlusion of the lower extremity vessels, as a rule, have severe coronary artery disease.

Chronic heart failure (CHF) was recorded in 27.3% of BKA patients and in 30.0% of AKA patients. The high frequency of CHF is explained by the combination of arterial hypertension and ischemic heart disease, which together form a long-term myocardial overload.

Chronic obstructive pulmonary disease (COPD) was found in 12.1% of BKA patients and 10.0% of AKA patients. This figure is probably related to the age of the patients and the high prevalence of smoking among patients with vascular diseases.

Chronic renal failure (CRF) was observed in 6.1% of patients in the BKA group and 6.7% in the AKA group. This figure reflects a relatively low but stable incidence of this pathology, which often accompanies severe systemic vascular disorders.

In general, the structure of comorbidity indicates that patients with occlusion of lower extremity vessels represent a population with pronounced multifactorial comorbidity, where cardiovascular diseases predominate.

Analysis of data obtained using the SF-36 questionnaire revealed significant differences between patients who had undergone below-knee amputation (BKA) and patients who had undergone above-knee amputation (AKA), primarily in scales reflecting physical status.

Table 2.

SF-36 scale Mean scores in comparison of two groups.

SF-36 scale	BKA (n=33)	AKA (n=30)	p-value
PF — physical functioning	68,2 ± 12,1	39,7 ± 10,4	<0,001
RP — role functioning (physical)	56,7 ± 11,5	42,3 ± 9,8	<0,001
BP — pain intensity	63,8 ± 10,9	49,1 ± 10,2	<0,001
GH — general health	59,5 ± 9,8	48,6 ± 8,9	<0,001
VT — vitality	56,8 ± 9,5	50,1 ± 8,7	0,07
SF — social functioning	65,7 ± 8,9	57,9 ± 8,3	0,08
RE — role functioning (emotional)	62,4 ± 8,7	56,2 ± 7,9	0,09
MH — mental health	61,3 ± 7,8	57,4 ± 8,2	0,10

Physical Functioning (PF): BKA patients had significantly higher physical function scores (68.2 points vs. 39.7 points in AKA, $p < 0.001$). This reflects that preserving the knee joint provides a more rational gait pattern, lower energy expenditure during ambulation, and faster recovery of motor skills.

Role functioning related to physical condition (RP). Role limitations were significantly lower in BKA patients (56.7 points vs. 42.3 points in AKA, $p < 0.001$). This indicates that patients with below-knee amputations are less likely to experience difficulties in performing every day and professional duties.

Pain intensity (BP). BKA patients have lower pain intensity (63.8 vs. 49.1, $p < 0.001$). This is due to the lower trauma of the surgery, preservation of most of the muscle mass and joint complex, and more favorable conditions for prosthetics.

General health (GH). Patients with BKA rate their health higher (59.5 vs. 48.6, $p < 0.001$). This indicator integrally reflects general well-being, level of autonomy and subjective perception of their condition.

Vitality (VT): Although the differences did not reach statistical significance, BKA patients had higher vitality and energy scores (56.8 vs. 50.1, $p = 0.07$).

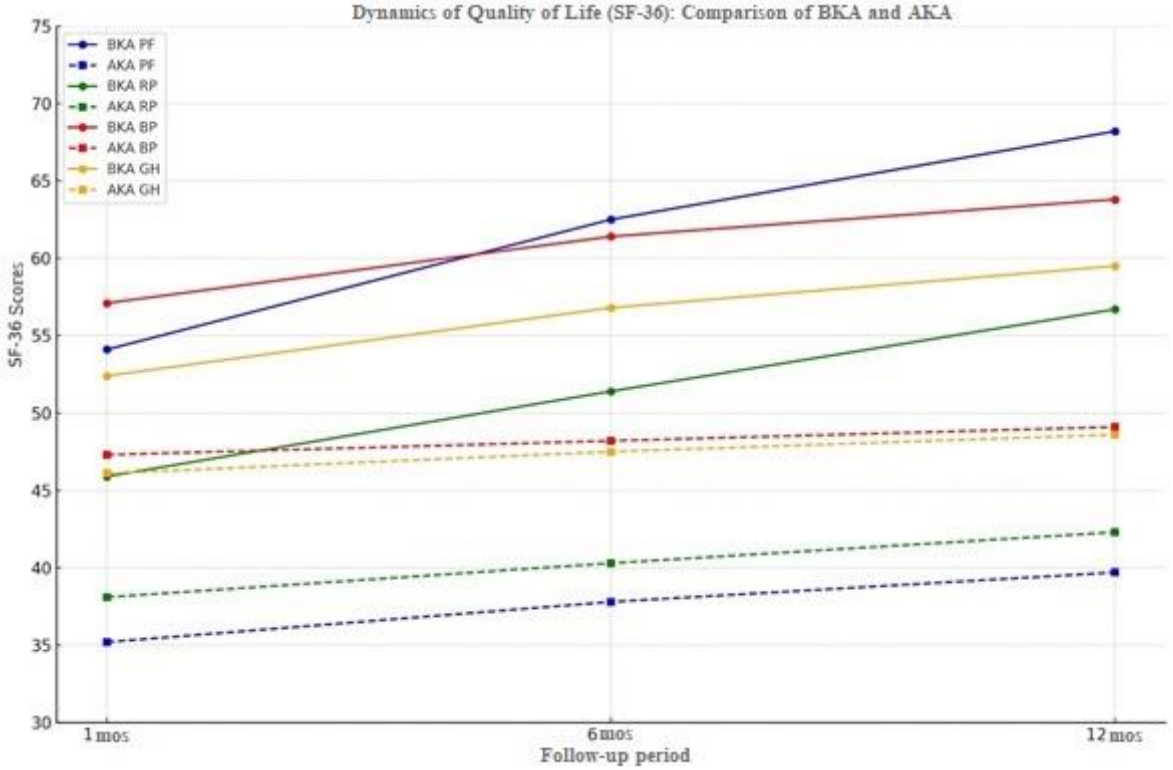
Social functioning (SF): BKA patients demonstrated higher levels of social functioning (65.7 vs. 57.9, $p=0.08$), which may be associated with better mobility and greater independence in daily living.

Role functioning related to the emotional state (RE): BKA patients tended to have better results (62.4 vs. 56.2, $p = 0.09$). This reflects a lower level of emotional limitations related to the disease.

Mental health (MH). Mental health scores were also higher in BKA (61.3 vs. 57.4, $p=0.10$), although the differences did not reach statistical significance. This indicates that preserving the knee joint also has a positive effect on psychological adaptation, but this effect is less pronounced than the physical benefits.

Overall, the results of the table show that the key differences between the groups concern the physical component of quality of life (PF, RP, BP, GH), where the advantages are reliably on the side of BKA. Psychoemotional indicators (VT, SF, RE, MH) demonstrate only a tendency towards better values in the BKA group, but did not reach statistical significance.

The analysis of the dynamics of the quality of life of patients who underwent amputation at different levels was carried out at three time points: 1 month after surgery - early rehabilitation stage. 6 months after surgery - active recovery period. 12 months after surgery - late stage of rehabilitation with maximum stabilization of the condition.



Physical functioning (PF). BKA patients showed a significant increase in the parameters: from 54.1 ± 11.2 at 1 month to 62.5 ± 10.8 at 6 months (+8.4; $p < 0.01$) and to 68.2 ± 12.1 at 12 months (+14.1 from the outcome; $p < 0.001$). In the AKA group, the increase was minimal: from 35.2 ± 8.7 at 1 month to 37.8 ± 9.3 at 6 months (+2.6; $p = 0.11$) and to 39.7 ± 10.4 at 12 months (+4.5; $p = 0.09$). The rate of PF recovery in BKA was 3.1 times higher than in AKA.

Role functioning related to physical condition (RP). In the BKA group, the indices increased from 45.9 ± 9.4 after 1 month to 51.4 ± 10.2 after 6 months (+5.5; $p < 0.05$) and 56.7 ± 11.5 after 12 months (+10.8; $p < 0.01$). In the AKA group, the dynamics were significantly weaker: from 38.1 ± 8.9 to 40.3 ± 9.1 (+2.2; $p = 0.18$) and to 42.3 ± 9.8 (+4.2; $p = 0.12$).

Pain intensity (BP). In BKA patients, the intensity of pain syndrome decreased more significantly: 57.1 ± 10.2 after 1 month, 61.4 ± 9.8 after 6 months (+4.3; $p < 0.05$) and 63.8 ± 10.9 after 12 months (+6.7; $p < 0.01$). In the AKA group, the increase was minimal: from 47.3 ± 9.6 to 48.2 ± 10.1 (+0.9; $p = 0.44$) and 49.1 ± 10.2 (+1.8; $p = 0.31$). Thus, BKA provided an almost two-fold reduction in pain syndrome compared to AKA.

General health status (GH). GH values in BKA increased from 52.4 ± 9.7 at 1 month to 56.8 ± 9.1 at 6 months (+4.4; $p < 0.05$) and 59.5 ± 9.8 at 12 months (+7.1; $p < 0.01$). In AKA patients, changes were minimal: from 46.1 ± 8.6 to 47.5 ± 8.8 (+1.4; $p = 0.21$) and 48.6 ± 8.9 (+2.5; $p = 0.16$).

Vital activity (VT). In BKA, the values increased from 51.7 ± 8.9 to 54.9 ± 9.1 (+3.2; $p = 0.07$) and 56.8 ± 9.5 (+5.1; $p = 0.06$). In AKA, the dynamics were weakly expressed: from 48.3 ± 8.4 to 49.4 ± 8.6 (+1.1; $p = 0.32$) and 50.1 ± 8.7 (+1.8; $p = 0.27$).

Social functioning (SF). In BKA patients, the scores increased from 59.3 ± 8.1 to 63.5 ± 8.7 (+4.2; $p < 0.05$) and 65.7 ± 8.9 (+6.4; $p < 0.01$). In AKA patients, they increased from 54.6 ± 7.9 to 56.8 ± 8.2 (+2.2; $p = 0.12$) and 57.9 ± 8.3 (+3.3; $p = 0.10$).

Role functioning due to the emotional state (RE). In BKA, the increase was from 56.8 ± 8.3 to 59.4 ± 8.5 (+2.6; $p = 0.09$) and 62.4 ± 8.7 (+5.6; $p = 0.07$). In AKA, the indicators increased only from 53.7 ± 7.8 to 55.1 ± 7.9 (+1.4; $p = 0.18$) and 56.2 ± 7.9 (+2.5; $p = 0.15$).

Mental health (MH). The dynamics in the BKA group were moderate: from 58.4 ± 7.6 to 60.2 ± 7.7 (+1.8; $p = 0.21$) and 61.3 ± 7.8 (+2.9; $p = 0.19$). In the AKA group, the changes were insignificant: from 56.1 ± 7.9 to 56.9 ± 8.1 (+0.8; $p = 0.34$) and 57.4 ± 8.2 (+1.3; $p = 0.28$).

BKA patients demonstrated stable positive dynamics in all physical scales (PF, RP, BP, GH) with an increase from 6.7 to 14.1 points over 12 months. In the AKA group, statistically significant improvements were not noted in most scales, indicating limited possibilities for physical rehabilitation in above-knee amputations. The greatest

difference between the groups remained in the PF scale (28.5 points by the end of the follow-up).

Analysis of the frequency and structure of complications in the postoperative period showed that they occurred in both groups, but their frequency and severity depended on the level of amputation. In patients with above-the-knee amputation (AKA), complications were observed more often (26.7%) compared to the BKA group (18.2%). Although the differences did not reach statistical significance (p = 0.18), the trend indicates a more favorable course of the postoperative period in patients with a preserved knee joint.

Table 3.

Structure of complications depending on the level of amputation.

Type of complication	BKA (n=33)	AKA (n=30)	p-value
Stump infection	2 (6,1 %)	3 (10,0 %)	0,21
Wound edge necrosis	1 (3,0 %)	2 (6,7 %)	0,29
Delayed healing (> 30 days)	1 (3,0 %)	2 (6,7 %)	0,21
Formation of a rough scar	0 (0 %)	1 (3,3 %)	0,28
Stump pain syndrome (chronic)	2 (6,1 %)	3 (10,0 %)	0,23
Total patients with complications	6 (18,2 %)	8 (26,7 %)	0,18

Stump infection was the most common complication in both groups: 6.1% in the BKA group and 10.0% in the AKA group. A higher risk of infection in AKA patients is associated with greater trauma of the intervention, a larger wound surface volume and a longer healing period. Wound edge necrosis was diagnosed in 3.0% of BKA patients and 6.7% of AKA patients. A more frequent development of necrotic changes in patients with femoral amputation is due to severe circulatory disorders and a more aggressive nature of the ischemic process. Delayed wound healing was noted in 3.0% of BKA patients and 6.7% of AKA patients. This indicator was also more common in patients with femoral amputation, which is associated with a larger volume of surgical trauma and concomitant comorbidity. Rough scar formation was observed in only 1 patient in the AKA group (3.3%). This complication was not recorded in BKA patients. Severe scarring may complicate subsequent prosthetic replacement, especially in the case of hip amputation. Stump pain syndrome (chronic) was observed in 6.1% of BKA patients and 10.0% of AKA patients. The higher incidence of pain syndrome in hip amputation is explained by greater damage to nerve trunks and a high probability of phantom pain formation.

Discussion

The results of this study demonstrate that patients with below-knee amputation (BKA) have significantly higher quality of life according to most SF-36 scales than patients with above-knee amputation (AKA). Particularly pronounced differences were noted in physical functioning (PF), role functioning (RP), pain intensity (BP) and general health (GH). These data are consistent with the results of a number of studies, according to which the level of amputation is one of the key predictors of physical and social rehabilitation after surgery.

The revealed difference of 28.5% on the PF scale in favor of BKA is explained by the preservation of the knee joint, which ensures a more physiological and energy-efficient walking pattern. Patients with BKA master the prosthesis faster and use the prosthesis more often in everyday life. According to the literature, preserving the knee joint reduces energy costs during walking by 25-40% compared to AKA, which directly correlates with PF indicators.

In our study, the average adaptation period to the prosthesis was 4.8 months for BKA and 7.3 months for AKA. These periods are comparable with data from foreign studies, which report an average duration of primary rehabilitation of 4–6 months for BKA and 6–9 months for AKA.

According to the BP scale, BKA patients had an average of 14.7% lower pain severity. This is due to a shorter surgical trauma length, less damage to nerve trunks, and better stump stability. In the AKA group, high-intensity phantom pain was more common.

General health (GH) was also higher in BKA patients. Their subjective perception of health improved faster, which was associated with greater autonomy, better exercise tolerance, and less dependence on outside help.

Although no statistically significant differences were found in the scales of vitality (VT), social functioning (SF), role functioning (emotional) (RE) and mental health (MH), a tendency towards higher values was observed in the BKA group. This can be explained by the fact that the level of physical autonomy directly affects social involvement and psychological well-being.

The results of the study are consistent with the findings of large meta-analyses, in which knee joint preservation was associated with higher quality of life, lower incidence of stump complications, and higher rates of rehabilitation.

Conclusions: The study showed that the level of amputation significantly affects the physical activity and autonomy of patients. Patients with below-knee amputation (BKA) showed higher physical functioning (68.2 vs. 39.7 points, $p < 0.001$), role activity (56.7 vs. 42.3 points, $p < 0.001$) and less pain (63.8 vs. 49.1 points, $p < 0.001$), which positively affects their psychological state and perception of quality of life. Preservation of the knee joint accelerates rehabilitation, while for patients with above-knee amputation (AKA), comprehensive physical and psychological support is especially important.

All authors contributed equally to the research and writing of this article. Dyusupov A.A., Sabitov E.T., and Imanbaev M.N. supervised the scientific research and made adjustments. Kozhakhmetov Zh.O., Dyusupov A.A., Sabitov E.T., Toleutaev T.A., Kazymov E.M., Salmenbaev E.A., Imanbaev M.N., Masalov A.E., Abdrakhmanov S.T. carried out a search of literature data and their processing. Kozhakhmetov Zh.O., Sabitov E.T., Toleutaev T.A., Kazymov E.M., Salmenbaev E.A., Imanbaev M.N., carried out a sample of patients and their surgical treatment, and also took part in developing the outline of the article, editing the

text and approving the final version of the article. Masalov A.E., Abdrakhmanov S.T. edited and designed the text of the article. No conflicts of interest declared.

The authors declare that this material has not been previously submitted for publication in other publications.

There was no funding from third-party organizations or medical agencies in carrying out this work.

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Received: 12 May 2025 / Accepted: 19 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.014

UDC 616.831-008.918:004.8

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EVALUATION OF READABILITY INDICES OF CHATGPT-4 AND GOOGLE GEMINI IN PATIENT EDUCATION ABOUT INTRACRANIAL HEMORRHAGES

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Abstract

Aim. Subarachnoid haemorrhage (SAH) and intracranial aneurysms are critical neurological conditions with significant implications for patient morbidity and mortality. The intersection of readability indices and artificial intelligence (AI) is an emerging field that aims to improve the accessibility and understanding of written material in different areas. Readability indices, such as the Automated Readability Index (ARI) and the Flesch–Kincaid grade level, provide quantitative measures of text complexity that are crucial for tailoring content to specific audiences . Therefore, in this study, we aimed to examine the answers given to questions asked by patients with intracranial haemorrhage using readability indices.

Materials and Methods. In this study, questions directly posed by patients and their relatives concerning subarachnoid haemorrhage and intracranial aneurysms were compiled. The collated questions were then divided into subcategories, including definition, diagnosis, treatment options, surgical procedures, complications, and impact on daily life. Flesch Reading Ease (FRE) Formula, Fog Scale (Gunning FOG Formula), SMOG Index, Automated Readability Index (ARI),

Coleman-Liau Index, Linsear Write Formula, Dale-Chall Readability Score, Spache Readability Formula. AI technologies were compared across groups.

Results. The results indicate that for most readability indices, there is no statistically significant difference between the two models, with one notable exception; Coleman-Liau Readability Index: Gemini: 10.59 ± 0.98 vs. ChatGPT: 11.80 ± 1.64; p-Value: 0.014 The only exception is the Coleman-Liau Readability Index, where a statistically significant difference was found, with ChatGPT showing a slightly higher score, implying potentially greater complexity according to that specific measure.

Conclusion. Our article provides valuable quantitative data on the readability of texts from ChatGPT and Gemini, its scope is narrow. A more comprehensive study would ideally include qualitative assessments, a broader range of text types, and detailed information on the methodology and model versions to provide a more holistic understanding of the models' performance.

Keywords: *Subarachnoid haemorrhage, intracranial aneurysms, Coleman-Liau Readability.*

For citation:

Mutlucan U.O., Bedel C., Zortuk Ö., Selvi F. Evaluation of readability indices of ChatGPT-4 and Google Gemini in patient education about intracranial hemorrhages // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 107-112. *doi 10.34689/SH.2025.27.4.014*

Резюме

ОЦЕНКА ПОКАЗАТЕЛЕЙ ЧИТАЕМОСТИ CHATGPT-4 И GOOGLE GEMINI В ОБУЧЕНИИ ПАЦИЕНТОВ ПО ВОПРОСАМ ВНУТРИЧЕРЕПНЫХ КРОВОИЗЛИЯНИЙ

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Актуальность. Субарахноидальное кровоизлияние (САК) и внутричерепные аневризмы являются критическими неврологическими состояниями, имеющими значительные последствия для заболеваемости и смертности пациентов. Пересечение индексов читаемости и искусственного интеллекта (ИИ) является новой областью, направленной на улучшение доступности и понимания письменных материалов в различных областях. Индексы читаемости, такие как автоматический индекс читаемости (ARI) и уровень сложности текста по шкале Флеша-Кинкейда, предоставляют количественные показатели сложности текста, которые имеют решающее значение для адаптации контента к конкретной аудитории. Поэтому в данном исследовании мы поставили **цель** проанализировать ответы на вопросы, заданные пациентами с внутричерепным кровоизлиянием, с использованием индексов читаемости.

Материалы и методы. В данном исследовании были собраны вопросы, непосредственно заданные пациентами и их родственниками, касающиеся субарахноидального кровоизлияния и внутричерепных аневризм. Затем собранные вопросы были разделены на подкатегории, включая определение, диагностику, варианты лечения, хирургические процедуры, осложнения и влияние на повседневную жизнь. Формула читабельности Флеша (FRE), шкала Fog (формула Gunning FOG), индекс SMOG, автоматический индекс читабельности (ARI), индекс Коулмана-Ляу, формула Линсеара, шкала читабельности Дейла-Чалла, формула читабельности Спаче. Технологии искусственного интеллекта были сравнены между группами.

Результаты. Результаты показывают, что для большинства индексов читаемости нет статистически значимой разницы между двумя моделями, за одним заметным исключением; Индекс читаемости Коулмана-Лиау: Gemini: 10,59 ± 0,98 против ChatGPT: 11,80 ± 1,64; p-значение: 0,014 Единственным исключением является индекс читаемости Коулмана-Лиау, где была обнаружена статистически значимая разница: ChatGPT показал немного более высокий балл, что означает потенциально большую уровень сложности по этому конкретному показателю.

Заключение. Наша статья предоставляет ценные количественные данные о читаемости текстов ChatGPT и Gemini, однако ее область применения ограничен. Более комплексное исследование в идеале должно включать качественную оценку, более широкий спектр типов текстов и подробную информацию о методологии и версиях моделей, чтобы обеспечить более целостное понимание производительности моделей.

Ключевые слова: *субарахноидальное кровоизлияние, внутричерепные аневризмы, индекс читаемости Коулмана-Ляу.*

Для цитирования:

Мутлукан У.О., Бедел Дж., Зортук О., Сельви Ф. Оценка показателей читаемости CHATGPT-4 и Google Gemini в обучении пациентов по вопросам внутричерепных кровоизлияний // Наука и Здравоохранение. 2025. Vol.27 (4), С.107-112. *doi 10.34689/SH.2025.27.4.014*

Түйіндеме

ПАЦИЕНТТЕРДІҢ БАС СҮЙЕК ІШІНЕ ҚАН ҚҰЙЫЛУ БОЙЫНША БІЛІМ АЛУЫНДА CHATGPT-4 ЖӘНЕ GOOGLE GEMINI ОҚУ КӨРСЕТКІШТЕРІН БАҒАЛАУ

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Мақсаты. Субарахноидты қан кету (SAH) және бас сүйек іші аневризмалары пациенттердің аурушаңдығы мен өліміне айтарлықтай әсер ететін маңызды неврологиялық жағдайлар болып табылады. Оқу және жасанды интеллект (AI) индекстерінің тоғысуы әртүрлі салалардағы жазбаша материалдардың қолжетімділігі мен түсінігін жақсартуға бағытталған жаңа сала болып табылады. Автоматты оқылым индексі (ARI) және Флэш-Кинкейд шкаласы бойынша мәтіннің күрделілік деңгейі сияқты оқылым индекстері мазмұнды белгілі бір аудиторияға бейімдеу үшін маңызды мәтіннің күрделілігінің сандық көрсеткіштерін ұсынады. Сондықтан, осы зерттеуде біз бас сүйек ішіне қан құйылумен ауыратын науқастардың оқылым индекстерін қолдана отырып қойған сұрақтарына жауаптарды талдауды мақсат етіп қойдық.

Материалдар мен әдістер. бұл зерттеуде пациенттер мен олардың туыстары субарахноидты қан кетуге және бас сүйек іші аневризмасына қатысты тікелей қойған сұрақтары жинақталды. Содан кейін жинақталған сұрақтар анықтау, диагностика, емдеу нұсқалары, хирургиялық процедуралар, асқынулар және күнделікті өмірге әсер ету сияқты кіші санаттарға бөлінді. Флештің оқылым формуласы (FRE), Fog шкаласы (Gunning FOG формуласы), SMOG индексі, Автоматты оқылым индексі (ARI), Коулман-Ляу индексі, Линсеар формуласы, Дейл-Чаллдың оқылым шкаласы, Спаче оқылым формуласы. Жасанды интеллект технологиялары топтар арасында салыстырылды

Нәтижелер. Нәтижелер көптеген оқылым индекстері үшін екі модель арасында статистикалық маңызды айырмашылық жоқ екенін көрсетеді, тек бір ерекше жағдайды қоспағанда; Коулман-Лиаудың оқылу индексі: Gemini: 10,59 ± 0,98 керісінше ChatGPT: 11,80 ± 1,64; p-мәні: 0,014 жалғыз ерекшелік-Коулман-Лиаудың оқылу индексі, онда статистикалық маңызды айырмашылық: ChatGPT сәл жоғары балл көрсетті, бұл нақты көрсеткіш бойынша күрделіліктің ықтималдылығының жоғары деңгейін білдіреді.

Қорытынды. Біздің мақалада ChatGPT және Gemini мәтіндерінің оқылуы туралы құнды сандық мәліметтер келтірілген, бірақ оның қолдану аясы шектеулі. Неғұрлым жан-жақты зерттеу модельдердің өнімділігі туралы біртұтас түсінік беру үшін сапалы бағалауды, мәтін түрлерінің кең спектрін және модельдердің әдістемесі мен нұсқалары туралы егжей-тегжейлі ақпаратты қамту керек.

***Түйін сөздер**: субарахноидты қан кету, бас сүйек іші аневризмалары, Коулман-Ляу оқу индексі.*

Дәйексөз үшін:

Мутлукан У.О., Бедел Дж., Зортук О., Сельви Ф. Пациенттердің бас сүйек ішіне қан құйылу бойынша білім алуында CHATGPT-4 және Google Gemini оқу көрсеткіштерін бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 107-112. *doi 10.34689/SH.2025.27.4.014*

Introduction

Subarachnoid haemorrhage (SAH) and intracranial aneurysms are critical neurological conditions with significant implications for patient morbidity and mortality. SAH is primarily caused by the rupture of an aneurysm in the brain, leading to bleeding in the subarachnoid space [1]. This condition is associated with high mortality and disability rates, particularly in younger populations. Managing and treating SAH and intracranial aneurysms involves making complex clinical decisions and often requires a multidisciplinary approach [2]. Although SAH accounts for only a small percentage of all strokes, it has a disproportionate impact due to its high morbidity and mortality rates, particularly in younger individuals, with an average age of onset of 50–55 years [3].

Artificial intelligence (AI) has emerged as a transformative tool in the detection and management of these conditions. Early detection and intervention are critical for these conditions due to their high morbidity and mortality rates [4,5]. AI has been integrated into clinical workflows to support decision-making in the management of SAH. This includes predicting complications, optimising treatment strategies and reducing the time to intervention, all of which are crucial for improving survival rates [6]. The intersection of readability indices and artificial intelligence (AI) is an emerging field that aims to improve the accessibility and understanding of written material in different areas. Readability indices, such as the Automated Readability Index (ARI) and the Flesch–Kincaid grade level, provide quantitative measures of text complexity that are crucial for tailoring content to specific audiences [7].

Therefore, in this study, we aimed to examine the answers given to questions asked by patients with intracranial haemorrhage using readability indices.

Metods. The present study did not require ethics committee approval as it did not involve any human or animal models.

Data Collection and Preparation

In this study, questions directly posed by patients and their relatives concerning subarachnoid haemorrhage and intracranial aneurysms were compiled. The questions presented herein were collated from a variety of online forums, neurosurgical websites, and the websites of relevant associations, hospitals and organisations.

The collated questions were then divided into subcategories, including definition, diagnosis, treatment options, surgical procedures, complications, and impact on daily life. From each category, the twenty most frequently asked questions were selected for analysis. Prior to analysis, these selected questions were reviewed and corrected for grammatical and semantic accuracy.

Response Generation by AI Models

The prepared questions were submitted to the ChatGPT-5 and Gemini-2.5 Pro artificial intelligence models to generate responses. Prior to the formulation of the inquiries, both AI models were instructed to formulate their responses in a language appropriate for a general audience with no prior medical knowledge on the subject. The responses generated by the models were recorded.

Readability Analysis and Statistical Evaluation

The readability levels of the responses generated by the AI models were measured using the nine different standard formulas listed below:

- ***Flesch Reading Ease (FRE) Formula:*** This formula calculates readability on a 100-point scale using sentence length and word syllables, where a higher score means the text is easier to understand [8].
- ***Flesch-Kincaid Grade Level (FKGL):*** This formula estimates the U.S. grade level required to comprehend a text by analyzing the average sentence length and syllables per word [9].
- ***Fog Scale (Gunning FOG Formula):*** The Gunning FOG Index estimates the years of formal education a person needs to understand a piece of writing upon first reading [10].
- ***SMOG Index:*** The SMOG Index determines the required years of education to understand a text by counting the number of words with three or more syllables [11].
- ***Automated Readability Index (ARI):*** The Automated Readability Index calculates the U.S. grade level of a text using character, word, and sentence counts, making it ideal for computer processing [12].
- ***Coleman-Liau Index:*** This computer-friendly formula estimates the U.S. grade level by measuring the average number of letters and sentences per 100 words [13].
- ***Linsear Write Formula:*** The Linsear Write Formula calculates a U.S. grade level, primarily for technical documents, by assigning different weights to "easy" and "hard" words within sentences [14].

• ***Dale-Chall Readability Score:*** This score determines a text's grade level based on its percentage of "difficult" words, which are defined as words not found on a specific list of 3,000 common words [15].

• ***Spache Readability Formula:*** The Spache Readability Formula is specifically designed to assess the reading level of texts for young children in early elementary grades 1-3 [16]

The scores obtained from all readability formulas were compiled. These scores were then subjected to a comparative and analytical statistical process using SPSS software.

The readability of neurosurgical educational materials is a critical factor in ensuring effective patient education. A plethora of extant resources have been found to be incongruent with the recommended readability levels. This has the potential to impede patient comprehension and engagement. This issue assumes particular pertinence within the domain of neurosurgery, wherein the communication of intricate medical information necessitates effective accessibility. The integration of readability indices and advanced technologies, such as AI, has the potential to significantly enhance the quality of neurosurgical education materials.

Statistical Analysis

In our study, we analysed data from artificial intelligence models using SPSS version 27 (IBM Corp., USA). The data were classified according to type. Categorical data were defined as percentages and frequencies. The chi-squared test was used to compare these. Distribution analysis was used to describe numerical data. Data conforming to a normal distribution were expressed as the mean ± standard deviation and a t-test was applied. Data that did not conform to a normal distribution were expressed as the median, minimum and maximum, and non-parametric tests were applied to them. Data with a p-value below 0.05 were considered significant.

Results

Our study presents a comparison of readability scores between ChatGPT and Gemini, utilizing various readability formulas. The results indicate that for most readability indices, there is no statistically significant difference between the two models, with one notable exception ARI (Automated Readability Index) Gemini: 10.05 ± 1.16 vs ChatGPT: 10.43 ± 1.81, p-Value: 0.327; Flesch Reading Ease: Gemini: 56.81 ± 7.13 vs. ChatGPT: 50.31 ± 14.04, p-Value: 0.114 Fog Scale (Gunning FOG Formula) Gemini: 0.76 ± 1.10 vs. ChatGPT: 10.95 ± 2.32, p-Value: 0.947; Flesch-Kincaid Grade Level Geini: 9.36 ± 1.16 vs. ChatGPT: 9.59 ± 1.68, p-Value: 0.718; Coleman-Liau Readability Index: Gemini: 10.59 ± 0.98 vs. ChatGPT: 11.80 ± 1.64; p-Value: 0.014 In summary, the results indicate that for most readability metrics, there is no significant difference in the readability of texts generated by Gemini and ChatGPT. The only exception is the Coleman-Liau Readability Index, where a statistically significant difference was found, with ChatGPT showing a slightly higher score, implying potentially greater complexity according to that specific measure.

Discussion

It is evident that the levels of readability are elevated. Research has indicated that a significant proportion of neurosurgical educational materials are written at a level that exceeds the recommended reading grade level for the general public [17]. For instance, the American Society of Neuroradiology's resources are written at an average grade level of 13.9, far above the range of 3 to 7 recommended by the National Institutes of Health and the American Medical Association [18]. Moreover, online patient education materials concerning neurointerventional procedures frequently exhibit a comprehension level commensurate with that of 10th to 11th-grade students, with some necessitating college-level cognitive abilities [19]. Complexity of Content: The complexity of neurosurgical procedures and conditions contributes to the high readability scores. For instance, the American Association of Neurological Surgeons (AANS) and other prominent organisations have materials that are frequently at a postgraduate readability level [20]. This inherent complexity can act as an impediment to the effective dissemination of patient education information, as many patients may lack the requisite literacy skills to comprehend the material in its entirety [21].

AI-Generated Summaries: The utilisation of artificial intelligence (AI), exemplified by ChatGPT, has demonstrated potential in the generation of more accessible summaries of neurosurgical literature. Research has indicated that AI-generated summaries exhibit considerably diminished readability scores in comparison to original abstracts, thereby rendering them more accessible to non-specialists. To illustrate this point, one may consider the finding that GPT-4-generated summaries have a Flesch-Kincaid reading grade of 7.70, in comparison to 12.55 for original abstracts [22]. This finding indicates that artificial intelligence (AI) has the potential to enhance the clarity and accessibility of neurosurgical educational materials [23]. The following indices of readability are employed: A variety of readability indices, including the Flesch-Kincaid Grade Level, Gunning Fog Index, and Simple Measure of Gobbledygook (SMOG) index, are employed to evaluate the readability of educational materials. These indices provide a quantitative measure of the reading difficulty, which can guide the development of more accessible content .The utilization of these indices by organisations facilitates the alignment of materials with recommended readability levels [24].

The readability indices frequently employed in the field are predicated on mathematical formulae that incorporate linguistic features such as word and sentence length. For instance, the Automated Readability Index (ARI) employs the calculation of average word length and sentence length to derive readability scores, which demonstrate a high degree of correlation with other indices [25]. The Flesch Reading Ease (FRE) scale is a widely utilized metric for assessing the readability of texts. Higher scores on this scale are indicative of texts that are more easily readable. The utilization of this approach has been demonstrated to be effective in a variety of contexts, including the design of prompts for oral proficiency assessments [26].

It is evident that certain indices, such as the one proposed by *Matricciani,* take into account cognitive aspects such as short-term memory capacity, an aspect which is often overlooked by traditional indices [27]. In the context of educational settings, readability indices have been shown to facilitate the alignment of written materials with students' reading abilities, thereby ensuring that the materials do not present an excessively facile or overly challenging level of

difficulty. This is of critical importance for the development of language and comprehension [28]. In the domain of health communication, the term "readability indices" is employed to denote the instruments utilized for the assessment of the clarity of online health-related information. For instance, during the course of the pandemic, it was demonstrated that a significant proportion of online resources were found to exceed the recommended sixth-grade reading level, which may have hindered public understanding [16-20]. Notwithstanding their practical applications, readability indices are subject to certain constraints. It is evident that these models frequently neglect to consider the semantic and contextual subtleties inherent within a text, a factor which has the potential to compromise comprehension [29]. It is important to note that the indices may not fully capture the complexity of texts in different languages or cultural contexts. To illustrate, a system developed for the purpose of Italian readability assessment offers a more intuitive understanding by comparing text difficulty to educational levels [11-14]. In summary, the results indicate that for most readability metrics, there is no significant difference in the readability of texts generated by Gemini and ChatGPT. The only exception is the Coleman-Liau Readability Index, where a statistically significant difference was found, with ChatGPT showing a slightly higher score, implying potentially greater complexity according to that specific measure. The provided document primarily focuses on presenting the comparative readability scores between ChatGPT and Gemini. It does not explicitly detail the limitations of the study. However, based on the information presented, several potential limitations can be inferred:

The study relies entirely on quantitative readability metrics. A qualitative assessment, involving human evaluators, could provide deeper insights into how understandable, engaging, or natural the texts generated by each model truly are, which might not be fully captured by formulaic scores. While the table indicates n=40 for both Gemini and ChatGPT, the paper does not specify how these samples were generated (e.g., what prompts were used, what topics were covered, or the length of the texts). A limited or homogenous sample of generated texts might not fully represent the models' capabilities across a wide range of applications or user queries. M Readability formulas, by their nature, are statistical approximations based on word and sentence characteristics (e.g., syllable count, word length, sentence length). They do not account for semantic complexity, context, or prior knowledge of the reader, which can significantly impact actual comprehension. Therefore, relying solely on these formulas might not provide a complete picture of true readability. The specific versions of ChatGPT and Gemini used for the study are not mentioned. Large language models are constantly evolving, and results obtained from older versions might not be representative of their current capabilities.

In conclusion, while the paper provides valuable quantitative data on the readability of texts from ChatGPT and Gemini, its scope is narrow. A more comprehensive study would ideally include qualitative assessments, a broader range of text types, and detailed information on the methodology and model versions to provide a more holistic understanding of the models' performance.

Table 1.

Comparison of CHATGPT vs GEMINI in terms of readability scores.

	GEMINI	CHAT –GPT	p-Value
ARI	10.05±1.16	10.43±1.81	0.327
Flesch Reading Ease	56.81±7.13	50.31±14.04	0.114
Fog Scale (Gunning FOG Formula)	10.76 ±1.10	10.95±2.32	0.947
Flesch-Kincaid Grade Level	9.36±1.16	9.59±1.68	0.718
Coleman-Liau Readability Index	10.59±0.98	11.80± 1.64	**0.014**
The SMOG Index	9.11±0.99	8.81±1.63	0.547
Linsear Write Formula	71.68±3.32	7016±3.36	0.446
Dale-Chall Readability Score	8.28±0.58	8.24±0.84	0.925
Spache Readability Formula	6.37±0.46	6.37±0.49	0.738

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Received: 29 January 2025 / Accepted: 14 July 2025 / Published online: 30 August 2025

DOI 10.34689/SH.2025.27.4.015

UDC 615.03:614.2(574)

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RATIONALE USE OF MEDICINES IN OUTPATIENT PRACTICE IN KAZAKHSTAN: ASSESSMENT OF WORLD HEALTH ORGANIZATION INDICATORS

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Abstract

Introduction: Rational use of medicines (RUM) is the cornerstone of safe, effective, and affordable outpatient care. We assessed how practices in Shymkent polyclinics align with WHO indicators.

Objective: To evaluate WHO indicators for prescribing and patient care in the outpatient setting and to identify variability requiring targeted improvements.

Materials and methods: A cross-sectional study based on WHO methodology (December 2024–April 2025) was conducted in 13 polyclinics. A total of 390 outpatient visits of patients were analyzed for patient-care indicators and 1300 prescriptions for prescribing indicators. Descriptive statistics, Welch's ANOVA, and permutation χ^2-tests were applied. Composite performance indices were constructed for benchmarking.

Results: The mean consultation duration was 13.5±6.2 minutes (range 3–35 across centers; $p<0.001$). Dispensing time averaged 205±139 seconds (45–960; $p<0.001$). On average, 94.4% of prescribed medicines were dispensed; 86.4% of patients correctly knew their dosages, both showing significant inter-center variation. An average of 1.8±0.9 medicines was prescribed per visit; 100% by INN and from the EML. Antibiotics were prescribed in 3.4% of visits (0–8% across centers; $p=0.01$). Injections were used in 24.5% of visits (low variability; $p=0.992$). Composite indices identified center 9 as best-performing in patient care and center 7 in prescribing; centers 2, 6, and 13 consistently lagged (e.g., in center 6 only 77% of medicines were dispensed, and dosage knowledge reached just 60%).

Conclusions: Outpatient care in Shymkent demonstrates strengths - low polypharmacy, universal INN prescribing, alignment with essential medicines, and relatively low antibiotic use. However, key challenges remain: wide variability in consultation and dispensing times, insufficient patient counseling, stock-outs of medicines in some centers, and persistently high injection prescribing. Priority measures: Standardization of consultation and dispensing processes, reduction of unnecessary injections through clinical protocols and provider training, strengthening of pharmaceutical counseling and patient education, and ensuring equitable medicine availability - especially in underperforming centers.

Keywords: *Rational use of medicines; World Health Organization indicators; Outpatient care; Kazakhstan polyclinics; Prescribing and dispensing.*

For citation:

Amirkhanova G.N., Yermukhanova Ly.S., Mussina A.Z., Dzhusupov K.O., Kimatova K.N., Nurbakyt A.N., Assylbekov N.A. Rationale use of medicines in outpatient practice in Kazakhstan: assessment of World Health Organization indicators // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 113-122. *doi 10.34689/SH.2025.27.4.015*

Резюме

РАЦИОНАЛЬНОЕ ИСПОЛЬЗОВАНИЕ ЛЕКАРСТВЕННЫХ СРЕДСТВ В АМБУЛАТОРНОЙ ПРАКТИКЕ КАЗАХСТАНА: ОЦЕНКА ИНДИКАТОРОВ ВСЕМИРНОЙ ОРГАНИЗАЦИИ ЗДРАВООХРАНЕНИЯ

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Введение: Рациональное использование лекарственных средств (ЛС) - ключ к безопасной, эффективной и доступной амбулаторной помощи. Мы оценили, насколько практика в поликлиниках г. Шымкент соответствует индикаторам ВОЗ.

Цель: Оценить индикаторы ВОЗ по назначению и обслуживанию пациентов в амбулаторном звене и выявить вариабельность, требующую целевых улучшений.

Методы и методы: Поперечное исследование по методике ВОЗ (декабрь 2024 – апрель 2025) в 13 поликлиниках. Проанализированы 390 амбулаторных визитов пациентов для индикаторов обслуживания и 1300 рецептов для индикаторов назначения. Использованы описательная статистика, ANOVA Уэлча и перестановочные χ^2-тесты. Сформированы интегральные показатели (performance indices) для бенчмаркинга.

Результаты: Средняя длительность консультации - 13,5±6,2 мин (по центрам 3–35; p<0,001). Время отпуска ЛС - 205±139 сек (45–960; p<0,001). В среднем отпущено 94,4% назначенных ЛС; доля пациентов, знающих правильные дозы, — 86,4%; оба показателя существенно варьировали между центрами. В одном визите назначали 1,8±0,9 препарата; 100% назначений - по МНН и из перечня ЖНВЛП/EML. Антибиотики назначались в 3,4% визитов (0–8% по центрам; p=0,01). Инъекции - в 24,5% визитов (вариация мала; p=0,992). Интегральные индексы показали лучшую работу по обслуживанию в центре 9 и по назначению - в центре 7; центры 2, 6 и 13 последовательно отставали (например, в центре 6 отпущено лишь 77% ЛС, знание доз - 60%).

Выводы: Амбулаторная помощь в Шымкенте имеет сильные стороны - низкая полипрагмазия, 100% назначений по МНН и из перечня основных ЛС, относительно низкая частота назначения антибиотиков. Вместе с тем выявлены проблемные зоны: широкая вариабельность времени консультаций и отпуска, недостаточное информирование пациентов, дефициты ЛС в отдельных центрах и устойчиво высокий уровень назначений инъекций. Приоритетные меры: стандартизация длительности визитов и процессов отпуска, снижение необоснованных инъекций через клинические протоколы и обучение врачей, усиление фармацевтического консультирования и образовательной работы с пациентами, выравнивание доступности ЛС - прежде всего в центрах-аутсайдерах.

Ключевые слова: *Рациональное использование лекарственных средств; Индикаторы ВОЗ; Амбулаторная помощь; Поликлиники Казахстана; Назначение и отпуск лекарств.*

Для цитирования:

Амирханова Г.Н., Ермуханова Л.С., Мусина А.З., Джусупов К.О., Киматова К.Н., Нурбакыт А.Н., Асылбеков Н.А. Рациональное использование лекарственных средств в амбулаторной практике Казахстана: оценка индикаторов Всемирной Организации Здравоохранения // Наука и Здравоохранение. 2025. Vol.27 (4), С.113-122. *doi 10.34689/SH.2025.27.4.015*

Түйіндеме

ҚАЗАҚСТАНДАҒЫ АМБУЛАТОРЛЫҚ ТӘЖІРИБЕДЕ ДӘРІЛІК ЗАТТАРДЫ ҰТЫМДЫ ПАЙДАЛАНУ: ДҮНИЕЖҮЗІЛІК ДЕНСАУЛЫҚ САҚТАУ ҰЙЫМЫНЫҢ КӨРСЕТКІШТЕРІН БАҒАЛАУ

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Кіріспе: Дәрілік заттарды (ДЗ) ұтымды пайдалану - қауіпсіз, тиімді және қолжетімді амбулаторлық көмектің кілті. Біз Шымкент қаласының емханаларындағы тәжірибенің Дүниежүзілік денсаулық сақтау ұйымының (ДДСҰ) индикаторларына қаншалықты сәйкес келетінін бағаладық.

Мақсат: Амбулаторлық буында ДДСҰ индикаторларын (дәрі жазу және пациенттерді қамтамасыз ету) бағалау және мақсатты жетілдіруді талап ететін вариабельділікті анықтау.

Материалдар мен Әдістер: ДДСҰ әдістемесі бойынша көлденең зерттеу (2024 ж. желтоқсан - 2025 ж. сәуір) 13 емханада жүргізілді. Қызмет көрсету индикаторлары үшін 390 амбулаторлық қабылдау және дәрі жазу индикаторлары үшін 1300 рецепт талданды. Сипаттамалық статистика, Уэлч ANOVA және перестановкалы χ^2-тесттер қолданылды. Бенчмаркинг үшін интегралдық көрсеткіштер (performance indices) қалыптастырылды.

Нәтижелер: Консультацияның орташа ұзақтығы - 13,5±6,2 мин (орталықтар бойынша 3–35; p<0,001). ДЗ беру уақыты – 205±139 сек (45–960; p<0,001). Орта есеппен тағайындалған ДЗ-ның 94,4%-ы берілген; дұрыс дозаны білетін пациенттердің үлесі – 86,4%; екі көрсеткіш те орталықтар арасында айтарлықтай ерекшеленді. Бір қабылдауда орта есеппен 1,8±0,9 дәрі тағайындалған; 100% тағайындау Халықаралық патенттелмеген атаулар бойынша және Өмірлік маңызы бар дәрілер тізімінен жасалған. Антибиотиктер 3,4% қабылдауда тағайындалды (орталықтар бойынша 0–8%; p=0,01). Инъекциялар - 24,5% қабылдауда (вариация аз; p=0,992). Интегралдық индекстер қызмет көрсетуде 9-орталықтың, ал дәрі жазуда 7-орталықтың үздік жұмысын көрсетті; 2, 6 және 13-орталықтар жүйелі түрде артта қалды (мысалы, 6-орталықта ДЗ тек 77% берілген, дозаны білу деңгейі – 60%).

Қорытындылар: Шымкенттегі амбулаторлық көмек мықты жақтарға ие - төмен полипрагмазия, 100% МНН бойынша және негізгі ДЗ тізімінен тағайындаулар, антибиотиктердің салыстырмалы түрде төмен деңгейде тағайындалуы. Сонымен бірге, проблемалы аймақтар анықталды: консультация мен ДЗ беру уақытының едәуір вариабельділігі, пациенттерді жеткіліксіз ақпараттандыру, жекелеген орталықтардағы ДЗ тапшылығы және инъекциялардың тұрақты жоғары деңгейі. Басым шаралар: қабылдау ұзақтығы мен дәрі беру процесін стандарттау, негізсіз инъекцияларды клиникалық хаттамалар мен дәрігерлерді оқыту арқылы азайту, фармацевтикалық кеңес беру мен пациенттерге білім беруді күшейту, ДЗ қолжетімділігін теңестіру - ең алдымен артта қалып отырған орталықтарда.

Түйінді сөздер: *Дәрілік заттарды ұтымды пайдалану; Дүниежүзілік денсаулық сақтау ұйымының индикаторлары; Амбулаторлық көмек; Қазақстан емханалары; Дәрі жазу және беру.*

Дәйексөз үшін:

Амирханова Г.Н., Ермуханова Л.С., Мусина А.З., Жүсіпов К.О., Киматова К.Н., Нурбакыт А.Н., Әсілбеков Н.А. Қазақстандағы амбулаторлық тәжірибеде дәрілік заттарды ұтымды пайдалану: Дүниежүзілік денсаулық сақтау ұйымының көрсеткіштерін бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 113-122. *doi 10.34689/SH.2025.27.4.015*

Relevance

Rational use of medicines is considered one of the key elements of the healthcare system. It implies that the patient receives the necessary drugs strictly according to clinical indications, in dosages corresponding to the individual characteristics of the body, for an adequate period of time, and at an affordable cost [4,13,19]. Such use of medicines should be not only safe but also economically justified, which is directly related to the effectiveness of the entire healthcare system [20]. To achieve this goal, coordinated work is required at different levels of healthcare: starting from proper prescribing of drugs, their correct dispensing, and ending with responsible adherence to the treatment regimen by the patients themselves. Violations of these principles lead to irrational use of medicines, which today is of a global nature, especially in resource-limited countries.

According to the World Health Organization (WHO), up to half of all prescriptions worldwide are carried out improperly, and a significant proportion of patient's misuse prescribed medicines. In resource-limited settings, this leads to additional costs, increased drug resistance, and deterioration in the quality of healthcare. For Kazakhstan, as well as for other countries in the region, this issue is particularly relevant due to the need to improve the efficiency of the outpatient sector, which is the first and most common level of contact between the population and the healthcare system.

In the Republic of Kazakhstan, the issues of rational use of medicines are regulated normatively. In accordance with the order of the Ministry of Health dated November 3, 2020, No. ҚР ДСМ-179/2020, the assessment of rationality in the use of medicines is carried out both within medical organizations and during external inspections in the framework of accreditation [6]. This approach ensures control over the compliance of the care provided with established standards.

Despite the active implementation of international standards and national formularies in the country, empirical data on how much prescribing and dispensing of medicines correspond to WHO recommendations remain extremely limited. Existing studies are fragmented and rarely include a comprehensive assessment of both the clinical and organizational components of the process [22,21,3]. **The aim of this study** was to evaluate WHO indicators for prescribing and patient care in the outpatient setting and to identify variability requiring targeted improvements. In this regard, conducting a systematic analysis using the standardized WHO methodology in outpatient settings of Shymkent has become a necessary step to identify current problems, assess differences between medical organizations, and determine priority areas for optimizing the practice of prescribing and using medicines.

Materials and methods

In the conducted study, the main tool used was a standardized WHO questionnaire, which allows for a comprehensive assessment of factors influencing the rational use of medicines in outpatient practice. The study covered three key areas: analysis of the quality of drug prescribing, examination of the specifics of patient care, and assessment of the organizational conditions under which drug provision is carried out.

At the first stage, attention was focused on how exactly doctors prescribe drugs. The average number of medicines prescribed per visit, the frequency of prescribing drugs by international nonproprietary names, the frequency of prescribing antibiotics and injectable forms, as well as the compliance of prescriptions with the national drug formulary were evaluated. This block of indicators made it possible to understand how well prescriptions meet clinical recommendations and standards.

Next, the emphasis was placed on the interaction of the patient with the healthcare system. The duration of consultations, the time spent on dispensing medicines, the completeness of drug provision according to prescriptions, the awareness of patients about prescribed medicines, and the correctness of their labeling were studied. These parameters reflected the quality of communication between healthcare workers and patients, as well as the availability of information about treatment.

The third area was the assessment of the working conditions of medical organizations. Here, the availability of an up-to-date drug formulary, the provision of essential medicines, and their availability according to nosology's were taken into account.

The sample was formed in accordance with WHO methodological recommendations. To ensure the representativeness of the data, 13 polyclinics of Shymkent were selected from December to April 2024, in each of which 30 patients were randomly surveyed, making a total of 390 respondents. The study included patients over 18 years' old who were on dispensary observation and received free medicines at the outpatient level. Cases related to highly specialized medical care, such as immunization, psychiatry, or dentistry, were excluded.

Data collection covered all prescriptions issued to patients with chronic and acute diseases who met the inclusion criteria. This made it possible to obtain diverse material for analysis.

Thus, the research methodology was based on a comprehensive assessment of various aspects of the rational use of medicines and made it possible to obtain reliable data reflecting both the clinical and organizational side of the drug provision process at the outpatient level.

Statistical analysis. Statistical analysis and visualization of the obtained data were carried out using the statistical computing environment R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics are presented as absolute and relative frequencies for categorical variables, mean (± standard deviation), median (1st; 3rd quartiles), as well as minimum and maximum values for quantitative variables.

To assess the heterogeneity of the studied centers with respect to patient age, the Kruskal–Wallis test was used; to assess the heterogeneity of the studied centers with respect to gender composition and education level, a permutation χ^2 test was applied.

To assess the heterogeneity of the studied centers with respect to quantitative indicators, a one-way analysis of variance with Welch's correction was used; to assess heterogeneity with respect to binomial proportions, a permutation χ^2 test was applied.

Participant characteristics

The study included 390 patients for the calculation of patient care indicators and 1,300 prescriptions for the analysis of drug prescribing indicators (Table 1). The mean age of participants in both samples was similar - 59.4 ± 12.7 and 60.1 ± 14.1 years, respectively. However, inter-center differences were statistically significant ($p<0.001$ for the care sample; $p=0.031$ for the prescribing sample): in some centers the mean patient age was substantially lower (e.g., center 4 - 48.9 years) or higher (centers 2 and 5 – 65-68 years), reflecting the heterogeneity of the populations served. The age range was wide (from 13 to 92 years), indicating coverage of both young adults and elderly patients, including the oldest age groups.

Gender distribution in the overall sample was balanced: 58.5% women and 41.5% men, with no significant inter-center differences ($p=0.191$). However, in some polyclinics (e.g., 2, 3, and 5) women predominated (up to 70-73%), whereas in polyclinics 7 and 8 the proportion of men exceeded 50%. These differences may reflect both demographic features of the local population and the specific patterns of healthcare utilization.

Particular attention is drawn to the level of education. More than half of respondents had higher education (56.9%), meaning that the majority of study participants were highly educated. At the same time, differences between polyclinics were statistically significant ($p=0.004$): in polyclinics 6 and 7 the share of patients with higher education reached 73%, while in polyclinics 3 and 13 this figure did not exceed 40%. The presence of a small proportion of participants with only school education (2.3%) also deserves attention, since this group may be at greater risk of non-adherence to treatment and medication errors [18,15,11,9].

In terms of diagnostic profile, distribution was relatively uniform across the main groups of diagnoses (11-15% for each of categories 1-7). However, significant inter-center fluctuations were observed for rare conditions. For example, diagnosis 9 occurred in 2.6% of cases in the overall sample but ranged from isolated cases to 7% in some centers ($p=0.027$). Similarly, diagnoses 11 and 13, although rare (<1% overall), demonstrated significant differences between polyclinics ($p=0.049$ and $p<0.001$, respectively). This may indicate localized clusters of pathology or particularities of patient referral pathways in the studied institutions.

Patient-care indicators

Table 2 presents the results of the analysis of patient-care indicators in the studied polyclinics. Consultation time ranged from 3 to 35 minutes, with an average consultation time of 13.5 (±6.2) minutes, and statistically significant variability was observed between centers ($p<0.001$). Dispensing time ranged from 45 to 960 seconds, with an average dispensing time of 205.2 (±138.7) seconds, and statistically significant variability of this indicator was also observed between polyclinics ($p<0.001$). Center 10 stood out in particular, where the median time reached 480 seconds (8 minutes), which was more than four times higher than the figures of most other centers. In contrast, in centers 3, 4, and 7 the average time did not exceed 2 minutes. These differences may reflect both the specific organization of the pharmaceutical service and differences in the completeness of patient counseling.

The proportion of medicines dispensed ranged from 77% to 98%, with an average of 94.4% (±5.5), which corresponds to international standards of drug availability at the outpatient level. However, in center 6 this indicator was

Table 1. **Characteristics of patients.**

Characteristics	Overall	Center													p
		1	2	3	4	5	6	7	8	9	10	11	12	13	
Sample for patient-care indicators calculations															
n	390	30	30	30	30	30	30	30	30	30	30	30	30	30	
Age (years)															
Mean (±SD)	59.4 (±12.7)	57.3 (±8.2)	65.6 (±11)	55.2 (±8.1)	48.9 (±14.4)	65.7 (±11.4)	58 (±9.6)	62.9 (±10.3)	61.4 (±11.3)	61.1 (±13.2)	61.4 (±14.1)	53 (±12.7)	58.3 (±13.8)	62.8 (±14.7)	
Median (Q_1; Q_3)	59 (53; 64.5)	66.5 (59; 71)	56 (49; 61)	54 (36.5; 59)	68.5 (65; 71)	58 (52; 65)	63 (57.5; 69)	62 (53; 69)	64 (56.5; 68)	63 (57; 70)	56 (47; 59)	63 (49; 70)	65.5 (51; 73)	59 (53; 64.5)	**<0.001**
Min; max	18; 88	39; 70	47; 88	43; 72	18; 72	35; 81	35; 78	31; 87	37; 82	21; 82	18; 83	19; 80	30; 85	36; 85	
Gender															
female	228 (58.5%)	15 (50%)	21 (70%)	22 (73.3%)	17 (56.7%)	21 (70%)	21 (70%)	13 (43.3%)	14 (46.7%)	19 (63.3%)	14 (46.7%)	15 (50%)	19 (63.3%)	17 (56.7%)	0.191
male	162 (41.5%)	15 (50%)	9 (30%)	8 (26.7%)	13 (43.3%)	9 (30%)	9 (30%)	17 (56.7%)	16 (53.3%)	11 (36.7%)	16 (53.3%)	15 (50%)	11 (36.7%)	13 (43.3%)	
Education															
school	9 (2.3%)	0 (0%)	0 (0%)	4 (13.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6.7%)	0 (0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	
secondary specialized	159 (40.8%)	17 (56.7%)	11 (36.7%)	14 (46.7%)	12 (40%)	19 (63.3%)	8 (26.7%)	8 (26.7%)	7 (23.3%)	13 (43.3%)	15 (50%)	6 (20%)	12 (40%)	17 (56.7%)	**0.004**
higher	222 (56.9%)	13 (43.3%)	19 (63.3%)	12 (40%)	18 (60%)	11 (36.7%)	22 (73.3%)	22 (73.3%)	23 (76.7%)	15 (50%)	15 (50%)	23 (76.7%)	17 (56.7%)	12 (40%)	
Sample for prescribing indicators calculations															
n	1300	100	100	100	100	100	100	100	100	100	100	100	100	100	
Age (years)															
Mean (±SD)	60.1 (±14.1)	62.4 (±15.2)	61.1 (±15.8)	57.4 (±14.5)	61.7 (±15.4)	60.6 (±13.4)	57.1 (±13.3)	61.4 (±14.2)	60.9 (±12.5)	60.9 (±12.7)	59.9 (±12.8)	57.8 (±13.7)	61.3 (±12.8)	58.5 (±15.3)	
Median (Q_1; Q_3)	61 (53; 70)	65 (54; 72)	63.5 (55; 71)	59 (49; 68)	63 (53.8; 72)	61.5 (55; 69)	58 (49; 67.5)	64.5 (55; 71.2)	62 (52.5; 69)	61 (55; 68)	59.5 (54; 70)	58.5 (51; 67)	60 (53; 71)	62 (50; 70)	**0.031**
Min; max	13; 92	18; 88	13; 92	17; 91	20; 90	19; 89	18; 81	18; 83	29; 91	26; 84	23; 87	18; 83	23; 85	22; 86	
Diagnosis															
1	197 (15.2%)	23 (23%)	18 (18%)	16 (16%)	17 (17%)	14 (14%)	13 (13%)	16 (16%)	15 (15%)	12 (12%)	12 (12%)	14 (14%)	14 (14%)	13 (13%)	0.775
2	159 (12.2%)	9 (9%)	11 (11%)	13 (13%)	11 (11%)	14 (14%)	12 (12%)	11 (11%)	13 (13%)	15 (15%)	13 (13%)	13 (13%)	12 (12%)	12 (12%)	>0.999
3	153 (11.8%)	9 (9%)	12 (12%)	12 (12%)	11 (11%)	12 (12%)	13 (13%)	14 (14%)	12 (12%)	12 (12%)	11 (11%)	12 (12%)	13 (13%)	10 (10%)	>0.999
4	174 (13.4%)	16 (16%)	15 (15%)	14 (14%)	14 (14%)	13 (13%)	12 (12%)	13 (13%)	13 (13%)	14 (14%)	13 (13%)	13 (13%)	12 (12%)	12 (12%)	>0.999
5	144 (11.1%)	4 (4%)	9 (9%)	12 (12%)	11 (11%)	11 (11%)	11 (11%)	12 (12%)	13 (13%)	13 (13%)	11 (11%)	12 (12%)	12 (12%)	13 (13%)	0.874
6	154 (11.8%)	11 (11%)	12 (12%)	12 (12%)	13 (13%)	10 (10%)	12 (12%)	14 (14%)	12 (12%)	12 (12%)	12 (12%)	12 (12%)	12 (12%)	10 (10%)	>0.999
7	148 (11.4%)	7 (7%)	13 (13%)	12 (12%)	11 (11%)	14 (14%)	12 (12%)	12 (12%)	10 (10%)	11 (11%)	13 (13%)	9 (9%)	12 (12%)	12 (12%)	0.983
8	112 (8.6%)	3 (3%)	8 (8%)	6 (6%)	8 (8%)	7 (7%)	8 (8%)	7 (7%)	9 (9%)	11 (11%)	10 (10%)	12 (12%)	12 (12%)	11 (11%)	0.601
9	34 (2.6%)	1 (1%)	2 (2%)	2 (2%)	1 (1%)	5 (5%)	5 (5%)	1 (1%)	1 (1%)	0 (0%)	5 (5%)	3 (3%)	1 (1%)	7 (7%)	**0.027**
10	9 (0.7%)	3 (3%)	0 (0%)	1 (1%)	3 (3%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.064
11	5 (0.4%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0.049**
12	2 (0.2%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.09
13	6 (0.5%)	6 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**<0.001**
14	1 (0.1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999
15	1 (0.1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999
16	1 (0.1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999

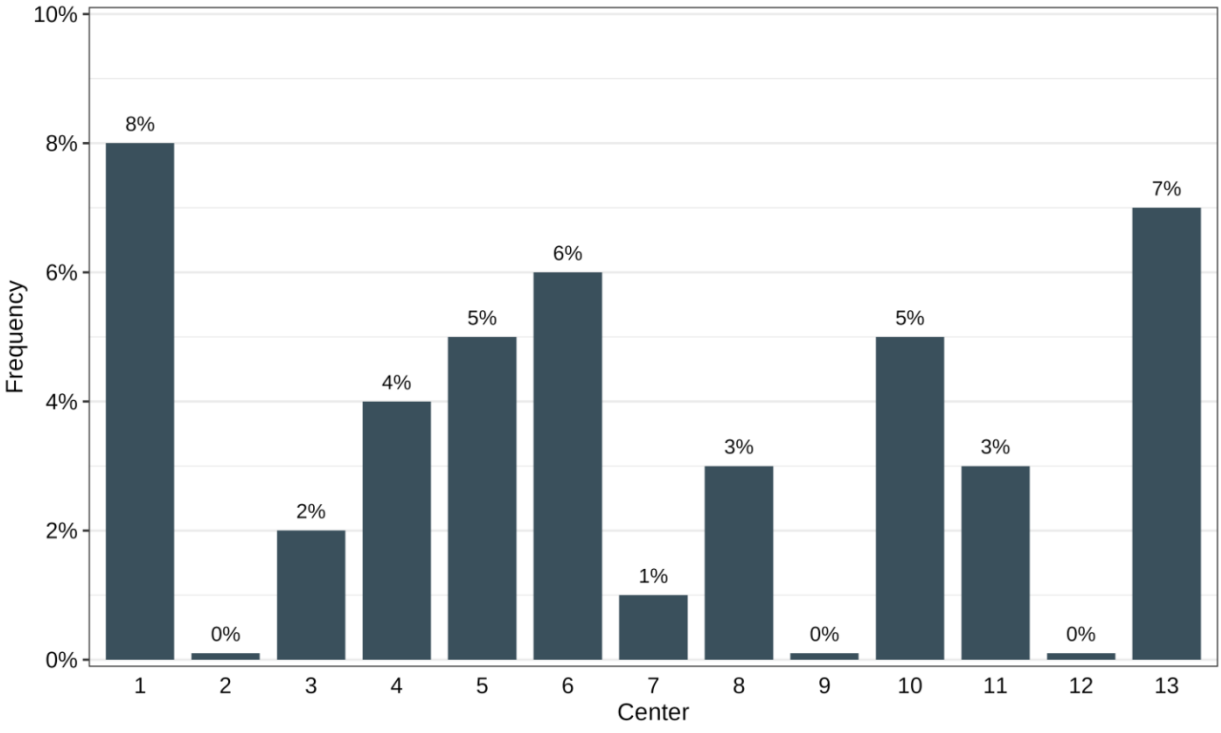
noticeably lower (77%), indicating problems with medicine supply in certain institutions (p<0.001). All dispensed medicines were adequately labeled. The proportion of patients informed about the correct dosage ranged from 60% to 93.3%, with an average of 86.4% (±10.1); statistically significant heterogeneity between the studied polyclinics was also established for this indicator (p=0.002).

Patient knowledge of the correct dosage of medicines averaged 86.4 ± 10.1%. In most centers this figure exceeded 90%, indicating a sufficient level of awareness. However, in center 6 it was minimal - only 60% of patients correctly reproduced the treatment regimen (p=0.002). This may indicate a lack of communication between healthcare workers and patients, as well as the need for additional educational interventions.

Table 2.

Indicators of patient care.

Center	Consultation time (minutes)	Dispensing time (seconds)	Dispensing time (seconds)	Percent medicines adequately labeled	Percent patients with knowledge of correct doses
1	7.1 (±2.6)	150.6 (±90.3)	94.1	100	93.3
2	7.6 (±2.2)	256.3 (±126.7)	98	100	90
3	15.1 (±4.5)	121.8 (±57.7)	92.2	100	93.3
4	19.1 (±5.9)	202 (±60)	95.9	100	90
5	20 (±2.6)	175 (±32.6)	97.4	100	86.7
6	7.8 (±2.2)	114.9 (±69.9)	77	100	60
7	13.9 (±4.5)	241.3 (±101.8)	96.7	100	93.3
8	17.4 (±5.1)	286 (±66.3)	97.3	100	93.3
9	14.5 (±2.5)	512 (±219.9)	93.8	100	70
10	16 (±5.6)	208.3 (±76.7)	96.5	100	90
11	15.8 (±5.7)	155 (±35.9)	96.9	100	83.3
12	15.7 (±4.9)	126.2 (±73)	94.6	100	90
13	5.7 (±1.7)	118.5 (±29.4)	96.7	100	90
Overall	13.5 (±6.2)	205.2 (±138.7)	94.4 (±5.5)	–	86.4 (±10.1)
p	<0.001	<0.001	<0.001	–	0.002



Picture 1. Percent encounters with an antibiotic prescribed.

Prescribing indicators

Table 3 presents the results of the analysis of prescribing indicators in the studied centers. On average, 1.8 (±0.9) medicines were prescribed per outpatient visit. However, statistically significant variability was observed between centers (p=0.002). In particular, in center 2 the average number of medicines was higher (2.2), whereas in centers 6 and 7 it was the lowest (1.6). Despite this, the median value in all centers remained equal to two medicines per visit, which corresponds to the optimal values recommended by WHO for the outpatient level.

Table 3.

Prescribing indicators

Center	Number of medicines prescribed per patient encounter	Percent medicines prescribed by generic name	Percent encounters with an antibiotic prescribed	Percent encounters with an injection prescribed	Percent medicines prescribed from essential medicines list
1	1.8 (±0.9)	100	8	18	100
2	2.2 (±1.1)	100	0	27	100
3	1.8 (±0.8)	100	2	26	100
4	1.8 (±0.8)	100	4	26	100
5	1.6 (±0.7)	100	5	24	100
6	1.6 (±0.8)	100	6	24	100
7	1.7 (±0.8)	100	1	22	100
8	1.7 (±0.9)	100	3	25	100
9	1.8 (±0.8)	100	0	26	100
10	1.8 (±0.8)	100	5	26	100
11	1.7 (±0.7)	100	3	26	100
12	1.7 (±0.7)	100	0	25	100
13	1.9 (±1)	100	7	23	100
Overall	1.8 (±0.9)	–	3.4 (±2.7)	24.5 (±2.4)	–
p	0.002	–	0.01	0.992	–

Table 4.

Performance indicators.

Performance indicators	Center												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Patient-Care Indicators													
Consultation time index	0.71	0.76	1.51	1.91	2	0.78	1.39	1.74	1.45	1.6	1.58	1.57	0.57
Dispensing time index	1.67	2.85	1.35	2.24	1.94	1.28	2.68	3.18	5.69	2.31	1.72	1.4	1.32
Dispensed drugs index	0.94	0.98	0.92	0.96	0.97	0.77	0.97	0.97	0.94	0.96	0.97	0.95	0.97
Labeled drugs index	1	1	1	1	1	1	1	1	1	1	1	1	1
Patients' knowledge index	0.93	0.9	0.93	0.9	0.87	0.6	0.93	0.93	0.7	0.9	0.83	0.9	0.9
IRPCDU	5.26	6.49	5.72	7.02	6.78	4.43	6.97	7.83	9.78	6.78	6.11	5.81	4.76
Rank	11	7	10	3	5	13	4	2	1	6	8	9	12
Prescribing Indicator													
Non-polypharmacy index	0.98	0.81	1.02	1	1.15	1.14	1.07	1.07	1.03	1.02	1.07	1.06	0.96
Generic name index	1	1	1	1	1	1	1	1	1	1	1	1	1
Rational antibiotic index	3.35	–	13.4	6.7	5.36	4.47	26.8	8.93	–	5.36	8.93	–	3.83
Injection safety index	1.34	0.89	0.93	0.93	1	1	1.1	0.96	0.93	0.93	0.93	0.96	1.05
Essential drugs list index	1	1	1	1	1	1	1	1	1	1	1	1	1
IRDP	7.67	3.71	17.34	10.63	9.51	8.61	30.96	12.96	3.96	9.31	12.93	4.02	7.84
Rank	10	13	2	5	6	8	1	3	12	7	4	11	9

The frequency of antibiotic prescribing was relatively low - 3.4% (±2.7%), which is below the thresholds reported in most developing countries. Inter-center differences were statistically significant (p=0.01): for example, in center 1 antibiotics were prescribed in 8% of visits, while in centers 2, 9, and 12 they were not prescribed at all Picture 1. This indicator reflects a relatively rational practice of prescribing antibacterial drugs, although the identified inter-center variations require further analysis of the underlying causes (e.g., differences in disease profiles or patient management strategies). In contrast, the frequency of prescribing injectable forms was high - 24.5% (±2.4%), and the differences between centers were not statistically significant (p=0.992). This level exceeds the optimal WHO reference values (<10%) and may reflect both the persistent practice of preferring parenteral forms and patient expectations. It should be noted that injections were prescribed in every fourth outpatient consultation, indicating the presence of a systemic trend that requires targeted interventions in the field of clinical guidelines and educational programs.

The analysis of summary indices showed considerable inter-center variability in the effectiveness of outpatient care delivery.

Patient-care quality indices

The consultation time index ranged from 0.57 (center 13) to 2.0 (center 5), reflecting differences in the availability and depth of physician - patient contact (see Table 4). The dispensing time index varied even more: the lowest values were observed in center 6 (1.28), whereas in center 9 it reached 5.69, indicating substantial differences in the organization of the pharmaceutical service. The index of medicines actually dispensed was consistently high across all centers (0.92–0.98), except for center 6 (0.77), pointing to problems with medicine supply in this facility. The patient knowledge index showed critical disparities: in center 6 it was only 0.6, while in most centers it exceeded 0.9. The overall integrated indicator of rational patient care (IRPCDU) was highest in center 9 (9.78) and lowest in center 6 (4.43), which made it possible to identify centers with the best and worst practices.

Drug prescribing quality indices

The non-polypharmacy index in all centers was close to the optimal values (0.96–1.15), indicating a relatively rational level of prescribed medicines (Table 4). The international nonproprietary name (INN) prescribing index was equal to 1 in all centers, reflecting a high degree of compliance with WHO standards. However, the most pronounced differences were identified in the rational antibiotic prescribing index: values ranged from no prescriptions (centers 2, 9, and 12) to 26.8 (center 7), indicating heterogeneity in antimicrobial therapy practices. The injection safety index was generally consistently high (0.89 - 1.34), and the essential drugs list (EDL) compliance index was maximal (1.0 in all centers). The overall integrated indicator of rational prescribing (IRDP) ranged from 3.71 (center 2) to 30.96 (center 7), showing a pronounced gap between leading and lagging centers.

Comprehensive assessment

The integration of care and prescribing data made it possible to identify two polar examples: center 9, which demonstrated the highest values for care (IRPCDU=9.78), and center 7, which showed the highest results for prescribing (IRDP=30.96). In contrast, centers 2, 6, and 13 were characterized by the lowest values in both blocks of indicators, requiring a targeted analysis of organizational and clinical factors.

Discussion

The results of the study demonstrated both the strengths of the outpatient medicine supply system in Shymkent and critical areas of risk. Among the positive findings is the high proportion of prescriptions written by international nonproprietary names (100%), which indicates compliance with the national medicines policy. Also noteworthy is the relatively low frequency of antibiotic prescribing, which favorably distinguishes Kazakhstan from a number of countries with high levels of antibiotic resistance.

At the same time, significant problems were identified. First, consultation duration and dispensing time varied several-fold between centers, indicating insufficient standardization of clinical processes. Second, the high frequency of prescribing injectable forms (a quarter of all visits) represents a persistent practice that contradicts international recommendations and may reflect the continued “cultural preference” for parenteral medicines. Third, in certain centers (especially in center 6) a critically low level of medicine availability (77%) and extremely low patient awareness of dosages (60%) were identified, creating risks of inappropriate medicine use and reduced treatment effectiveness [14, 5].

A strength of the study is the use of standardized WHO methodology and statistical methods, which allow for objective comparison across different centers. However, the limitations include the cross-sectional design (which makes it impossible to assess changes over time), as well as the potential influence of disease profiles on prescribing indicators [7–8].

Taken together, the data indicate the need for targeted organizational interventions -standardization of consultation duration, strengthening of pharmaceutical support, improving the availability of medicines, and the implementation of patient education programs. Particular attention should be given to the underperforming centers (2, 6, 13), where the indicators lag significantly behind the average values.

Our study, based on the standardized methodology of the WHO, revealed a multifaceted picture of the rational use of medicines in the outpatient sector of Shymkent.

First, the sociodemographic profile of participants demonstrated considerable heterogeneity between centers. Although the mean age of patients was about 60 years, some facilities were dominated by younger patients, while others by older adults. More than half of the participants had higher education, but the differences between centers indicate potential inequalities in the level of health literacy.

Second, the analysis of “patient-care indicators” showed significant differences in consultation duration and dispensing time. In some centers, consultations lasted more than 15–20 minutes, while in others they were limited to 5-7 minutes. Dispensing time also varied from less than 2 minutes to more than 8 minutes. Despite overall high medicine availability (>94%), one center reported a critical shortage (77%). A similar situation was observed with patient knowledge: in most facilities patients knew their

dosages, yet in one center this indicator was only 60%, creating risks of poor adherence. The study by Jimmy and colleagues showed that more than 60% of patients were unable to correctly recall instructions immediately after the visit, including dosage and frequency, which is very close to our scenario with "the center where knowledge was only 60%." In another study in Saudi Arabia, only 70% of knowledge indicators were satisfactory, which also confirms that in different facilities patient awareness may not reach even 70%, let alone 100% [12, 2].

Third, the "drug prescribing indicators" revealed both strengths and weaknesses. On average, 1.8 medicines (± 0.83) were prescribed per visit, which corresponds to WHO standards (1.6–1.8) and indicates a low level of polypharmacy, as shown in the study by GG Hailesilase et al. (2024) [10]. All prescriptions were made by international nonproprietary names, reflecting compliance with national medicines policy. At the same time, two serious problems remain: the frequency of antibiotic prescribing varied from 0 to 8% of visits, demonstrating heterogeneity of clinical practice, and injectable forms were prescribed in 24.5% of cases, which significantly exceeds the WHO reference values (<10%) and indicates a persistent practice of preferring parenteral medicines. Such variability reflects not only differences in clinical approaches between facilities but also the need to strengthen control over the rationality of prescribing. The high frequency of injection use, despite the availability of oral alternatives, may indicate persistent stereotypes among physicians and patients, which in the long term increases the risks of complications and unnecessary costs. These results underscore the relevance of implementing educational and regulatory measures aimed at reducing the excessive use of antibiotics and parenteral dosage forms [20, 6, 17].

Finally, the integrated "performance indicators" made it possible to identify both leading and underperforming centers. Thus, centers 7 and 9 demonstrated the best practices in prescribing and quality of care, respectively. At the same time, centers 2, 6, and 13 consistently showed low results across a number of parameters - from medicine availability to patient knowledge. This points to systemic differences within a single city healthcare network, likely related to organizational and managerial factors.

Among the strengths of the study is the use of validated WHO methodology, which ensures international comparability of data and provides a comprehensive analysis - from clinical practices to organizational conditions. The sample size and coverage of 13 polyclinics made it possible to identify both general patterns and local problems.

The limitations include the cross-sectional design, which does not allow for the assessment of changes over time, as well as the possible influence of the disease structure on prescribing indicators across different centers.

Conclusion

Our study was the first comprehensive assessment of the rational use of medicines in outpatient practice in Shymkent using WHO methodology. The results showed that, despite certain achievements - such as a low level of polypharmacy and 100% use of international nonproprietary names - serious challenges remain. Among them are: excessive prescribing of injectable forms, pronounced differences in consultation duration and dispensing time, insufficient patient awareness, and uneven medicine availability across centers.

To improve the situation, targeted interventions are needed, including: standardization of consultation duration and dispensing practices; reducing the frequency of injection prescribing through the implementation of clinical protocols and educational programs for physicians; strengthening pharmaceutical support and patient counseling, especially in underperforming centers; and ensuring equal availability of medicines across all healthcare facilities.

Thus, the rational use of medicines in outpatient practice is not only a matter of individual prescriptions but also an indicator of the effectiveness of the entire organizational model of healthcare.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

Funding: *The research was not funded. This work was carried out as part of the doctoral dissertation.*

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Received: 04 February 2025 / Accepted: 13 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.016

UDC 616.43

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STAFFING OF THE DENTAL SERVICE IN THE REGIONS OF KAZAKHSTAN: A 2014-2024 ANALYSIS

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Abstract

Background: Dental staffing plays a key role in the quality and accessibility of dental care. In Kazakhstan, the number and distribution of dentists, their qualifications, and their level of training remain pressing issues for the healthcare system.

This study **aims** to analyze the staffing of the dental service in Kazakhstan from 2014 to 2024, identifying issues in the distribution and training of dental specialists.

Materials and methods*:* Official statistical data from the Ministry of Health of the Republic of Kazakhstan were examined. Indicators of dentist provision per 10,000 populations were extracted for 2014–2024 across all administrative regions, including newly established areas, with separate analysis of urban and rural populations. Descriptive and comparative statistical methods were applied to identify trends, disparities, and structural changes.

Results: The total number of dentists increased from 4812 in 2014 to 5213 in 2024, showing a moderate upward trend. However, significant interregional and settlement-based disparities persist. Large cities such as Astana, Almaty, and Shymkent demonstrated growth and relatively high staffing levels, whereas rural territories remained critically underserved. In 2024, urban areas had on average 3.5 dentists per 10,000 populations, compared to only 1.0 in rural areas. Regions such as Aktobe and Zhambyl showed steady improvement, while Karagandy, East Kazakhstan, and Akmola experienced a pronounced decline. Newly established regions, including Abai, Zhetysu, and Ulytau, revealed unstable dynamics, reflecting structural and organizational challenges.

Conclusion: Significant regional differences, insufficient renewal of the material and technical base in peripheral regions, and problems with the distribution of human resources require the development and implementation of targeted state programs and strategies.

Keywords: Dental workforce, staffing, provision, Kazakhstan, healthcare accessibility, human resources in dentistry.

For citation:

Syzdykova Az., Syzdykova Ai., Bekkazinova D., Seiduanova L., Ruzuddinov T., Qumar A.B. Staffing of the dental service in the regions of Kazakhstan: a 2014–2024 analysis // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 123-129. *doi 10.34689/SH.2025.27.4.016*

Резюме

КАДРОВОЕ ОБЕСПЕЧЕНИЕ СТОМАТОЛОГИЧЕСКОЙ СЛУЖБЫ В РЕГИОНАХ КАЗАХСТАНА: АНАЛИЗ ЗА 2014-2024 ГОДЫ

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Введение: Кадровое обеспечение стоматологической службы играет ключевую роль в качестве и доступности стоматологической помощи. В Казахстане актуальными вопросами для системы здравоохранения остаются численность и распределение врачей-стоматологов, их квалификация и уровень подготовки.

Целью данного исследования является анализ кадрового обеспечения стоматологической службы в Казахстане с 2014 по 2023 год, выявление проблем в распределении и подготовке стоматологических специалистов.

Материалы и методы: Были изучены официальные статистические данные Министерства здравоохранения Республики Казахстан. Показатели обеспеченности стоматологической помощью на 10 000 населения были получены за 2014–2024 годы по всем административным регионам, включая вновь образованные районы, с раздельным анализом городского и сельского населения. Для выявления тенденций, различий и структурных изменений применялись методы описательной и сравнительной статистики.

Результаты: Общее количество врачей-стоматологов увеличилось с 4812 в 2014 году до 5213 в 2024 году, демонстрируя умеренную тенденцию к росту. Тем не менее, сохраняются значительные межрегиональные и поселенческие различия. Крупные города, такие как Астана, Алматы и Шымкент, продемонстрировали рост и относительно высокий уровень кадрового обеспечения, в то время как сельские территории оставались критически недообеспеченными. В 2024 году в городах в среднем на 10 000 населения приходилось 3,5 врача-стоматолога, по сравнению с 1,0 в сельской местности. Такие регионы, как Актюбинская и Жамбылская, продемонстрировали устойчивое улучшение, в то время как Карагандинская, Восточно-Казахстанская и Акмолинская области столкнулись с выраженным спадом. Вновь созданные регионы, включая Абайскую, Жетысускую и Улытаускую, продемонстрировали нестабильную динамику, что отражает структурные и организационные проблемы.

Заключение: Значительные региональные различия, недостаточное обновление материально-технической базы в периферийных регионах, проблемы с распределением кадровых ресурсов требуют разработки и реализации целевых государственных программ и стратегий.

Ключевые слова: *Стоматологические кадры, кадровое обеспечение, обеспеченность, Казахстан, доступность здравоохранения, кадровые ресурсы в стоматологии.*

Для цитирования:

Сыздыкова А., Сыздыкова А., Бекказинова Д., Сейдуанова Л., Рузуддинов Т.Б., Кумар А.Б. Кадровое обеспечение стоматологической службы в регионах Казахстана: анализ за 2014-2024 гг. // Наука и Здравоохранение. 2025. Vol.27 (4), С.123-129. *doi 10.34689/SH.2025.27.4.016*

Түйіндеме

ҚАЗАҚСТАН АЙМАҚТАРЫНДАҒЫ СТОМАТОЛОГИЯЛЫҚ ҚЫЗМЕТТІҢ КАДРЛЫҚ ҚҰРАМЫ: 2014-2024 ЖЫЛДАРҒА ТАЛДАУ

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Кіріспе. Стоматологиялық кадрлармен қамтамасыз ету стоматологиялық көмектің сапасы мен қолжетімділігінде шешуші рөл атқарады. Қазақстанда тіс дәрігерлерінің саны мен таралуы, олардың біліктілігі мен дайындық деңгейі денсаулық сақтау жүйесі үшін өзекті мәселелер болып қала береді.

Бұл зерттеудің **мақсаты** – 2014-2023 жылдар аралығындағы Қазақстандағы стоматологиялық қызметтің кадрлық қамтамасыз етілуіне талдау жасау, стоматологиялық мамандарды бөлу мен оқытудағы проблемаларды анықтау.

Материалдар мен әдістер: Қазақстан Республикасы Денсаулық сақтау министрлігінің ресми статистикалық мәліметтері зерттелді. 2014-2024 жылдарға 10 000 тұрғынға шаққандағы стоматологпен қамтамасыз ету көрсеткіштері қала және ауыл тұрғындарын бөлек талдау арқылы жаңадан құрылған аудандарды қоса алғанда, барлық әкімшілік аймақтар бойынша алынды. Трендтерді, диспропорцияларды және құрылымдық өзгерістерді анықтау үшін сипаттамалық және салыстырмалы статистикалық әдістер қолданылды.

Нәтижелер: Тіс дәрігерлерінің жалпы саны 2014 жылы 4812-ден 2024 жылы 5213-ке дейін өсті, бұл қалыпты өсу үрдісін көрсетті. Дегенмен, аймақаралық және елді мекендерге негізделген елеулі айырмашылықтар сақталуда. Астана, Алматы және Шымкент сияқты ірі қалалар өсу мен салыстырмалы түрде жоғары кадрлық деңгейлерді көрсетті, ал ауылдық аумақтар өте төмен қызмет көрсету деңгейінде қалды. 2024 жылы қалалық жерлерде 10 000 халыққа орташа есеппен 3,5 тіс дәрігері болса, ауылдық жерлерде 1,0 ғана болды. Ақтөбе және Жамбыл сияқты

облыстарда тұрақты жақсару байқалса, Қарағанды, Шығыс Қазақстан және Ақмолада айтарлықтай құлдырау байқалды. Жаңадан құрылған аймақтар, соның ішінде Абай, Жетісу және Ұлытауда құрылымдық және ұйымдастырушылық қиындықтарды көрсететін тұрақсыз динамика анықталды.

Қорытынды: Елеулі өңірлік айырмашылықтар, шеткері аймақтардағы материалдық-техникалық базаның жеткіліксіз жаңартылуы, адам ресурстарын бөлу проблемалары мемлекеттік мақсатты бағдарламалар мен стратегияларды әзірлеуді және іске асыруды талап етеді.

Түйін сөздер: *Стоматологиялық персонал, кадрлық қамтамасыз ету, қауіпсіздік, Қазақстан, денсаулық сақтаудың қолжетімділігі, стоматологиядағы адам ресурстары.*

Дәйексөз үшін:

Сыздыкова А., Сыздыкова А., Бекказинова Д., Сейдуанова Л., Рузуддинов Т.Б., Құмар А.Б. Қазақстан аймақтарындағы стоматологиялық қызметтің кадрлық құрамы: 2014-2024 жылдарға талдау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 123-129. *doi 10.34689/SH.2025.27.4.016*

Introduction

Dental service staffing is a key factor in determining the quality and accessibility of dental care for the population [15]. The optimal number of specialists, their professional training, and rational distribution across regions ensure the timeliness and effectiveness of dental services [2, 5].

Experiences from overseas highlight key challenges in ensuring equitable access to dental services, particularly in rural and remote areas [18]. Australian federal programs addressing inequalities have encountered low uptake rates and inefficiencies, suggesting that financial support alone is insufficient to improve access [16]. These further highlights systemic issues in workforce distribution and health infrastructure.

In all cases, dentists' care is targeted to communities and populations that experience inequalities in dental care and have historically had difficulty accessing treatment [1].

The dental workforce in developed countries is diverse and these roles support preventive and comprehensive care [4]. However, gaps in service provision, particularly for children and underserved populations, persist [17]. These findings highlight the importance of strategic workforce planning and policy adjustments to ensure equitable distribution of dental professionals across regions [7].

In Kazakhstan, issues of dental service staffing remain relevant, as there are significant differences in the number of dentists per capita across different regions and heterogeneity in their professional qualifications. Despite efforts to improve the medical education system, including regular professional development and revisions to accreditation standards, problems persist, such as disparities in workforce allocation, a shortage of medical staff in rural regions, and the outflow of professionals to the private sector.

In addition, the introduction of innovative treatment methods, driven by the development of digital technologies and the growing need for an integrated approach to dental care, requires adapting personnel training systems and revising resource management strategies in the industry [3]. In this regard, an urgent task is to assess the current state of staffing of the dental service in Kazakhstan, identify key problems and develop recommendations for their solution.

This study aims to analyze the staffing of the dental service in Kazakhstan from 2014 to 2023, identifying issues in the distribution and training of dental specialists.

Materials and methods.

We used bibliographic, information-analytical, and statistical research methods. The primary source of information was the official statistical data published by the Ministry of Health of the Republic of Kazakhstan in the annual statistical compendia “Health of the Population of the Republic of Kazakhstan and the Activities of Healthcare Organizations” [9-14]. We extracted indicators of the provision of dentists to the population for 2014-2023 for each region and for rural-urban differences. The study encompassed the entire population of the Republic of Kazakhstan, focusing on the provision of dental services by dentists at the national, regional, and local (urban vs. rural) levels. The unit of analysis was the number of practicing dentists per 10,000 population.

A descriptive statistical analysis was performed to identify dynamics and trends in the provision of dental services from 2014 to 2023. Comparative analysis was conducted to reveal differences across regions and between urban and rural populations. Time-series analysis was applied to assess changes over the 10 years and to detect anomalies or abrupt shifts in the data (e.g., sudden decreases that may be associated with administrative or methodological modifications). Data consistency and reliability were cross-checked with demographic indicators of the national population, using information from the Bureau of National Statistics of the Republic of Kazakhstan.

The study relied exclusively on publicly available aggregated statistical data. No personal or sensitive information was collected. Therefore, ethical approval was not required.

Results

Regional differences in dentist provision.

However, despite the overall growth, the distribution of dentists across the country remains heterogeneous, with significant interregional and urban-rural disparities (Table 1).

The analysis of regional data reveals several distinct patterns. Some territories are characterized by consistent growth and relatively favorable dynamics. For instance, in the Aktobe Region, the number of dentists rose from 280 in 2014 to 418 in 2024, making it one of the leading regions in terms of workforce expansion. Similar positive dynamics were observed in the Zhambyl Region, where provision increased from 175 to 266 over the same period, and in the Kyzylorda Region, which more than doubled its capacity (62 to 130 dentists). The Turkestan Region, where statistics are available only from 2020, showed continuous growth, reaching 343 dentists by 2024. Major urban centers also demonstrated a gradual increase: in

Astana, the number of dentists rose from 509 in 2014 to 539 in 2024, while in Shymkent it grew from 297 in 2018 to 389 in 2024. These trends likely reflect the attractiveness of larger cities and developing regions for medical professionals due to better infrastructure, professional opportunities, and higher demand for dental services.

In contrast, several regions demonstrate declining or unstable trajectories. The Karagandy Region experienced a steady decrease, from 588 dentists in 2014 to 403 in 2024, reflecting either migration of specialists to other regions or insufficient replacement of retiring professionals. A similar downward trend is evident in the East Kazakhstan Region, where the number of dentists dropped from 445 in 2014 to 288 in 2024. Particularly critical is the situation in the Akmola Region, where after relatively stable values in 2014–2018 (around 118–139 dentists), the indicator plummeted to 28 in 2019. Although a minor recovery occurred by 2024 (39 dentists), the provision remains extremely low. The Almaty Region demonstrated instability, with a peak of 477 dentists in 2017, followed by a dramatic decline to 165 in 2024.

Table 1

Provision of the population with dentists for 2014-2024.

Regions	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Kazakhstan Republic	4812	4717	5528	4993	5089	4799	5081	4963	4911	4 957	5 213
Abai Region	-	-	-	-	-	-	-	0	118	96	107
Akmola	124	118	118	139	139	28	29	26	24	33	39
Aktobe	280	252	239	247	322	316	325	340	348	398	418
Almaty	277	293	401	477	430	430	422	382	152	161	165
Atyrau	110	110	103	97	96	98	103	96	86	96	94
West Kazakhstan	85	91	95	89	102	112	128	126	140	136	142
Zhambyl	175	176	194	195	212	198	203	195	236	245	266
Zhetysu Region	-	-	-	-	-	-	-	0	206	142	110
Karagandy	588	559	545	534	525	509	512	490	407	405	403
Kostanay	213	215	207	256	236	237	221	204	190	192	193
Kyzylorda	62	70	81	87	72	92	73	91	97	112	130
Mangistau	99	157	162	199	227	260	270	233	236	114	181
Pavlodar	220	211	221	199	195	199	203	200	189	200	252
North Kazakhstan	118	119	123	114	121	124	118	110	103	111	114
South Kazakhstan	624	464	504	518	174	191	-	-	-	-	
Turkestan	-	-	-	-	-	-	211	217	248	300	343
Ulytau Region	-	-	-	-	-	-	-	-	53	65	72
East Kazakhstan	445	472	471	454	465	397	419	382	270	282	288
Astana City	509	514	449	456	550	532	526	487	531	537	539
Almaty City	883	896	1615	932	926	782	960	940	937	987	968
Shymkent City	-	-	-	-	297	294	358	444	340	345	389

In Almaty City, the dynamics were marked by an anomalous spike in 2016 (1615 dentists), which most likely resulted from changes in reporting methodology rather than real growth; since then, the number has stabilized around 968 in 2024. These regions highlight the systemic challenges of uneven workforce retention and redistribution.

The newly established administrative units also reveal mixed trends. In the Abai Region, the number of dentists increased slightly from 96 in 2023 to 107 in 2024, indicating a positive trajectory despite the relatively low starting point. The Zhetysu Region, however, showed a significant decline from 206 dentists in 2022 to 110 in 2024, suggesting structural instability or possible migration of specialists. The Ulytau Region recorded modest but positive growth from 53 in 2022 to 72 in 2024, while the Mangistau Region demonstrated recovery after a sharp reduction in 2023 (114 dentists) to 181 in 2024.

Overall, these findings underscore a persistent imbalance in the distribution of dentists across Kazakhstan. Regions with strong urbanization and better-developed healthcare systems continue to accumulate human resources, whereas peripheral, rural, and newly established regions face difficulties in maintaining stable staffing levels. This uneven distribution not only reflects demographic and economic differences but also highlights the need for targeted national policies to strengthen the dental workforce in underserved areas.

Urban-rural disparities.

The comparative analysis of urban and rural indicators highlights the persistence of disproportions in the

accessibility of dental care. In 2024, urban areas had on average 3.5 dentists per 10 000 population, whereas in rural areas the provision was only 1.0 per 10 000 (Figure 1). This threefold gap emphasizes the unequal distribution of human resources in dentistry, which continues to be one of the most acute problems in Kazakhstan's healthcare system.

The highest levels of staffing in urban settings were observed in the Aktobe Region (5.8), West Kazakhstan Region (5.4), Almaty City (4.3), and Astana (3.9). These regions and cities are characterized by relatively high levels of urbanization, a concentration of medical universities and training centers, and a more developed private sector, which attracts dental professionals with better working conditions and higher income opportunities. In contrast, the lowest urban indicators were recorded in the Akmola Region (0.5), Atyrau Region (1.9), Abai Region (2.2), and Turkestan Region (2.3), reflecting the challenges of professional outmigration, insufficient incentives for work in peripheral territories, and underdeveloped healthcare infrastructure.

The situation in rural areas is even more critical. The Ulytau Region (0.2), Aktobe Region (0.3), and Akmola Region (0.4) demonstrated extremely low provision, suggesting that dental care is practically inaccessible in remote settlements. By comparison, relatively better indicators were observed in the Zhambyl Region (1.6) and the East Kazakhstan Region (1.1), which may be associated with the presence of public dental offices and state-supported facilities in rural localities. Nevertheless, even these values remain below the threshold considered sufficient for ensuring adequate population coverage.

The imbalance between urban and rural provision reflects broader socio-economic and demographic trends. Larger metropolitan areas not only accumulate dental professionals but also offer opportunities for continuing education, specialization, and integration into modern private practices. In contrast, rural areas remain less attractive due to lower wages, limited professional growth prospects, and insufficiently developed social and medical infrastructure. The absence of targeted state programs to retain and redistribute specialists exacerbates this imbalance.

Overall, despite the increase in the absolute number of dentists in Kazakhstan by 2024, the territorial disproportions in their distribution remain pronounced. Large metropolitan areas such as Almaty, Astana, and Shymkent continue to concentrate the majority of the dental workforce, while peripheral, rural, and newly established regions remain underserved. This structural inequality creates a persistent challenge for ensuring equitable access to dental care across the country. It highlights the need for comprehensive policy interventions, including incentive programs for rural practice, development of mobile dental teams, and integration of teledentistry to bridge the urban-rural gap.

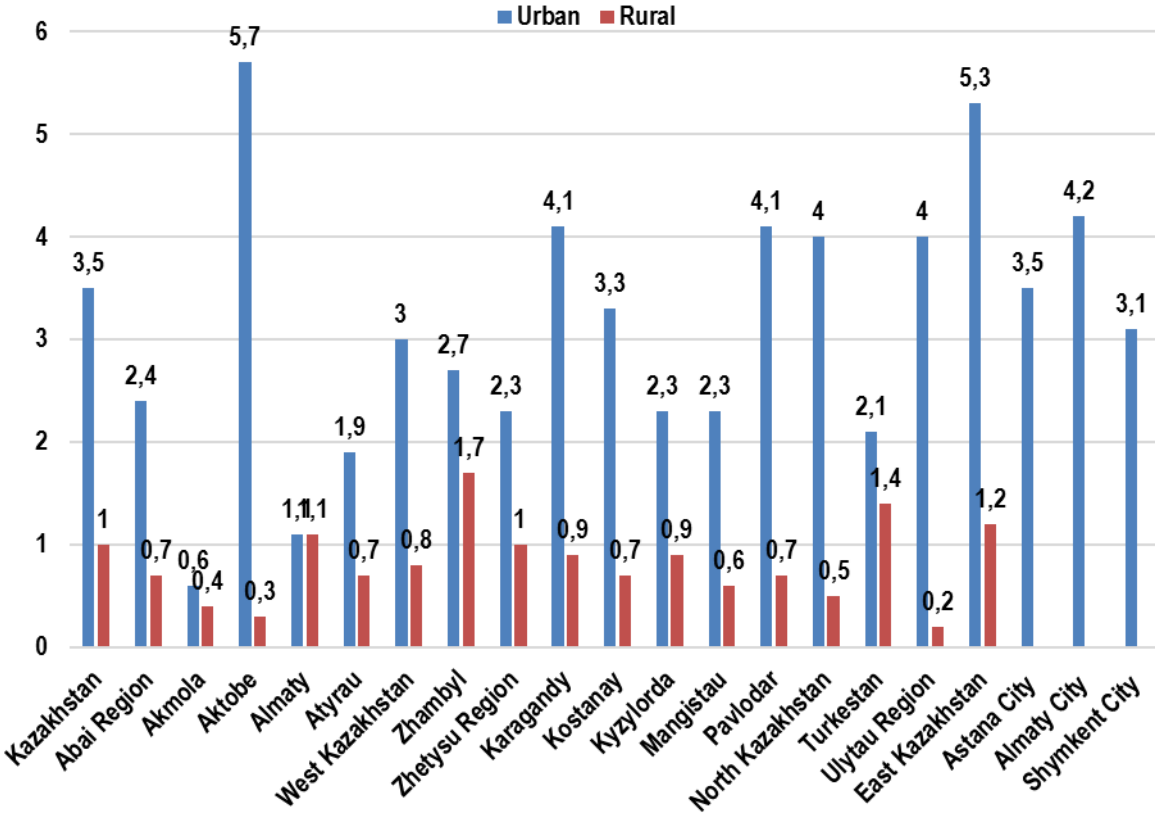


Figure 1. Dentist provision per 10,000 people.

Discussion

An analysis of the data on the number of dentists in Kazakhstan from 2014 to 2024 revealed significant regional differences in the provision of specialists to the population. In some regions, the number of dentists is growing, while in others, their numbers are declining or unstable. These differences may be due to various factors, including demographic changes, economic development, healthcare reforms, and specialist migration.

The growth in the number of dentists in regions such as Aktobe (from 280 in 2014 to 418 in 2024) and Zhambyl (from 175 to 266) indicates positive changes in staffing.

These trends may be associated with an increase in the number of medical graduates, improved working conditions, and the growth of the private dental services sector.

However, instability is observed in Almaty, where a sharp increase in indicators was recorded in 2016 (1615 dentists), which is likely due to a change in the accounting methodology or temporary changes in the staffing. In subsequent years, the figure stabilized at around 987 specialists. Similar fluctuations are observed in the Mangystau region, where the number of dentists reached 270 in 2020, but then dropped to 114 in 2023, which may indicate changes in the regional healthcare system.

The decline in dentists in the Karagandy and East Kazakhstan regions warrants a more in-depth investigation into its underlying causes. Potential factors may include the migration of specialists to other regions or abroad, shifting healthcare system priorities, or a reduced appeal of the dental profession. A particularly steep drop is seen in the Akmola region, where the number of dentists fell dramatically from 139 in 2018 to just 39 in 2024. This fact may indicate a reorganization of the healthcare system, changes in reporting, or other structural processes.

Another important aspect is the difference in the provision of dentists between the urban and rural populations. The average rate in Kazakhstan is 3.4 dentists per 10,000 people in urban areas and only 0.9 in rural areas. This indicates significant imbalances in access to dental care, especially in remote and rural areas. The largest differences are observed in Aktobe (5.6 vs. 0.3) and West Kazakhstan (5.3 vs. 0.8) regions. The shortage of personnel in rural areas may be due to the low attractiveness of work in remote areas, a lack of incentives, and limited infrastructure.

Thus, the results of the study highlight the need to develop strategies to equalize territorial disparities in the provision of dentists. This may include introducing programs to support young professionals, improving working conditions, incentivizing the private sector, and developing mobile dental teams for rural areas [4]. Future research should prioritize identifying the factors that affect the distribution of dentists and evaluating the effectiveness of current strategies aimed at strengthening the human resources capacity for dental services in Kazakhstan. Analysis of the diagram confirms the existence of significant regional differences in the provision of dental services, which necessitates comprehensive solutions at the healthcare level in Kazakhstan.

The shortage of dentists in rural areas necessitates the development of programs to attract and retain doctors in these areas, including benefits, salary increases, and housing support. It is essential to develop telemedicine and mobile dental teams, particularly in regions experiencing a critical personnel shortage, such as the Ulytau, Aktobe, and West Kazakhstan regions. It is necessary to strengthen educational programs and target the distribution of medical university graduates to areas with low availability of dentists [3]. It is essential to develop private dentistry in underdeveloped regions, possibly through the creation of conditions that facilitate business and public-private partnerships.

The analysis identified the main problems and factors affecting the effectiveness of dental care in the Republic of Kazakhstan. Compared to other post-Soviet and OECD countries, Kazakhstan lags in the equitable distribution of dental professionals. For example, countries like Estonia and Lithuania have successfully implemented incentive programs to attract dental professionals to rural areas, including student loan forgiveness, higher rural salaries, and improved professional infrastructure [18]. Similarly, government-led public-private partnerships have expanded access to care in underserved communities in Poland and Hungary. At the same time, Scandinavian countries have leveraged mobile clinics and tele-dentistry to bridge geographic gaps [6,7,8].

Kazakhstan can benefit from adopting similar strategies — enhancing digital infrastructure, introducing regional incentive packages, and expanding postgraduate training tailored to the needs of underserved areas. Comparative analysis highlights the potential effectiveness of such measures in reducing territorial imbalances and improving the overall efficiency of dental service delivery.

The strength of this study lies in its comprehensive approach to analyzing the staffing situation in Kazakhstan's dental service. The work utilizes official statistics, as well as the results of surveys and interviews with practicing dentists, which enabled a deeper examination of the factors affecting staffing.

However, the study has several limitations. First, the analysis is based on available statistics, which may not account for dentists' informal employment in the private sector. Second, the study does not include a detailed analysis of dentists' satisfaction with working conditions, which could provide a more complete picture of the causes of staffing imbalances.

In the future, it is advisable to expand the study by including a comparative analysis with other Central Asian countries and an assessment of the impact of government incentive programs on attracting specialists to sparsely populated regions. Additionally, it is crucial to examine the impact of digital technologies and telemedicine on enhancing the efficiency of dental services.

Thus, the presented study not only identifies existing staffing problems in dentistry in Kazakhstan but also suggests possible directions for their solution, which can serve as the basis for further reforms in the healthcare sector.

Conclusion

The current state of dental care in the Republic of Kazakhstan is characterized by significant success in modernizing infrastructure and introducing new technologies in large cities, which contributes to a high level of service provision. However, substantial regional differences, insufficient updating of the material and technical base in peripheral regions and problems with the distribution of human resources require the development and implementation of targeted state programs and strategies. A comprehensive approach that includes investment in infrastructure, continuous professional development of specialists, and organizational reforms is essential for ensuring consistent quality in dental care and enhancing the population's overall health.

Authors contribution:

Syzdykova Azhar initiated the study. Syzdykova Aiman and Bekkazinova D. collected data and Ruzuddinov T. contributed statistical analysis. Seiduanova L. and Qumar A.B. designed the

study and wrote the manuscript. All authors read and approved the final manuscript.

Competing interests: *The authors declare that they have no competing interests.*

Funding: *No.*

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Received: 23 May 2025 / Accepted: 04 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.017

***UDC* 616.31-08-039.71-057.875**

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AWARENESS OF STUDENTS OF SEMEY MEDICAL UNIVERSITY ABOUT THE PREVENTION OF ORAL CANDIDIASIS

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Abstract

Background: Oral candidiasis is a common fungal infection with an increasing prevalence. Key risk factors include weakened immunity, prolonged antibiotic therapy, and dysbiosis. However, students' awareness of preventive measures remains low.

Purpose: To assess the awareness of oral candidiasis, its risk factors, and prevention among NCJSC «Semey Medical University» students and to determine the influence of age, gender, and year of study on their knowledge.

Materials and Methods: Study design: cross-sectional study. An anonymous online survey was conducted among 109 students. Pearson's chi-square test was used for statistical analysis.

Results: Most students lacked knowledge about oral candidiasis prevention. Age and year of study were statistically significant factors influencing awareness ($p < 0.05$), while no gender differences were observed ($p > 0.05$). Students aged 25–30 were more knowledgeable than younger age groups (16–18 years).

Conclusion: Increasing students' awareness of oral candidiasis prevention is essential. It is important to promote educational initiatives, encourage the rational use of antibiotics, and prevent dysbiosis.

Keywords: *oral candidiasis, Candida albicans, students, antibiotics, prevention.*

For citation:

Mukasheva G.D., Kurmasheva M.O., Seitzhanova A.B., Shabdarbayeva D.M., Smailova Zh.K., Maukayeva S.B., Kudaibergenova N.K., Kairkhanov Ye.K., Kozhanova S.K., Mukanova D.A., Zhunuspekova A.S. Awareness of students of Semey Medical University about the prevention of oral candidiasis // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 130-137. *doi 10.34689/SH.2025.27.4.017*

Резюме

ОСВЕДОМЛЕННОСТЬ ОБУЧАЮЩИХСЯ МЕДИЦИНСКОГО УНИВЕРСИТЕТА СЕМЕЙ О ПРОФИЛАКТИКЕ КАНДИДОЗА ПОЛОСТИ РТА

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Введение: Кандидоз полости рта – распространенная грибковая инфекция, частота которой растет. Основными факторами риска являются снижение иммунитета, длительная антибиотикотерапия и дисбактериоз. Однако среди студентов уровень осведомленности о мерах профилактики кандидоза остается низким.

Цель: Оценить уровень осведомленности студентов НАО МУС о кандидозе полости рта, его факторах риска и профилактике, а также выявить влияние возраста, пола и курса обучения на знания респондентов.

Материалы и методы: Дизайн исследования: одномоментное поперечное исследование. Проведено анонимное онлайн-анкетирование 109 студентов. Для статистического анализа использовался критерий хи-квадрат Пирсона.

Результаты: Большинство студентов не осведомлены о профилактике кандидоза полости рта. Было выявлено, что возраст и курс обучения оказывают статистически значимое влияние на уровень знаний ($p<0,05$), в то время как гендерных различий не обнаружено ($p>0,05$). Студенты 25–30 лет демонстрировали более высокий уровень осведомленности, чем младшие возрастные группы (16–18 лет).

Заключение: Необходима просветительская работа среди студентов для повышения знаний о кандидозе полости рта. Важно рациональное использование антибиотиков, профилактика дисбактериоза и контроль факторов риска.

Ключевые слова: *кандидоз полости рта, Candida albicans, студенты, антибиотики, профилактика.*

Для цитирования:

Мукашева Г.Д., Курмашева М.Ө., Сейтжанова А.Б., Шабдарбаева Д.М., Смаилова Ж.К., Маукаева С.Б., Кудайбергенова Н.К., Каирханов Е.К., Кожанова С.К., Муканова Д.А., Жунуспекова А.С. Осведомленность обучающихся Медицинского университета Семей о профилактике кандидоза полости рта // Наука и Здравоохранение. 2025. Vol.27 (4), С.130-137. *doi 10.34689/SH.2025.27.4.017*

Түйіндеме

СЕМЕЙ МЕДИЦИНА УНИВЕРСИТЕТІ СТУДЕНТТЕРІНІҢ АУЫЗ ҚУЫСЫ КАНДИДОЗЫНЫҢ АЛДЫН АЛУ ТУРАЛЫ ХАБАРДАРЛЫҒЫ

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Кіріспе: Ауыз қуысының кандидозы – жиі кездесетін саңырауқұлақ инфекциясы, оның таралуы соңғы жылдары артып келеді. Бұл аурудың дамуына иммунитеттің төмендеуі, ұзақ мерзімді антибиотикотерапия және дисбактериоз ықпал етеді. Алайда студенттер арасында бұл инфекцияның алдын алу шаралары туралы хабардарлық деңгейі төмен болып отыр.

Мақсат: «СМУ» КеАҚ студенттерінің ауыз қуысының кандидозы, оның қауіп факторлары және алдын алу шаралары туралы хабардарлығын бағалау және жас, жыныс пен оқу курсының әсерін анықтау.

Материалдар мен әдістер: Зерттеу дизайны: бірсәтті көлденең зерттеу.Зерттеу 109 студенттің қатысуымен анонимді онлайн-сауалнама түрінде жүргізілді. Статистикалық талдау үшін хи-квадрат Пирсон критерийі қолданылды.

Нәтижелер: Студенттердің көбісі ауыз қуысының кандидозы және оның алдын алу шаралары туралы жеткілікті ақпаратқа ие емес. Жас ерекшелігі мен оқу курсы хабардарлық деңгейіне әсер ететіні анықталды ($p < 0.05$), ал

жыныстық айырмашылықтар байқалмады (p > 0.05). 25–30 жас аралығындағы студенттер инфекция туралы жақсы хабардар болғанымен, 16–18 жас тобында білім деңгейі айтарлықтай төмен болды.

Қорытынды: Ауыз қуысының кандидозының алдын алу бойынша студенттердің білімін арттыру қажет. Инфекцияның даму қаупін төмендету үшін ақпараттық іс-шараларды күшейту, антибиотиктерді ұтымды пайдалану, және пробиотиктерді қоса қолдану маңызды.

Түйінді сөздер: *ауыз қуысының кандидозы, Candida albicans, студенттер, антибиотикотерапия, алдын алу.*

Дәйексөз үшін:

Мукашева Г.Д., Курмашева М.Ө., Сейтжанова А.Б., Шабдарбаева Д.М., Смаилова Ж.К., Маукаева С.Б., Кудайбергенова Н.К., Каирханов Е.К., Кожанова С.К., Муканова Д.А., Жунуспекова А.С. Семей медицина университеті студенттерінің ауыз қуысы кандидозының алдын алу туралы хабардарлығы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 130-137. *doi 10.34689/SH.2025.27.4.017*

Introduction

Oral candidiasis is one of the pressing issues in modern dentistry, with its prevalence showing an increasing trend. According to WHO data, up to 20% of the population experience various forms of candidiasis during their lifetime [5].

The primary cause of candidiasis development is immune suppression influenced by both exogenous and endogenous factors, which promote the transition of Candida fungi to a pathogenic state [11].

Currently, more than 150 species of Candida fungi are known; however, in 90% of cases, oral candidiasis is caused by *Candida albicans*, which is part of the normal oral microflora in 30–50% of people [17]. The disease is characterized by the appearance of a curd-like coating on the mucous membranes, burning sensations, and dryness in the mouth, making it a common reason for dental visits [4].

The fungal flora is activated and acquires pathogenic properties when the natural balance of microorganisms is disrupted. One key cause is prolonged use of antibiotics, especially without concurrent antifungal therapy and probiotics. Drugs that contribute to candidiasis development include corticosteroids, cytostatics, antiprotozoal agents, and oral contraceptives [2].

The risk of candidiasis is especially high in patients with infectious diseases who receive long-term antibiotic treatment, leading to dysbiosis and active multiplication of Candida fungi [3].

Dysbiosis is a pathological condition characterized by an imbalance in the normal intestinal microflora, with decreased bifidobacteria and lactobacilli and predominance of pathogenic microorganisms [1]. This creates favorable conditions for the excessive growth of Candida fungi, which may lead to their active spread in the oral cavity.

Patients with oral candidiasis often complain of dryness and burning of the mucous membrane. On examination, a white coating is detected, which may be accompanied by discomfort and pain [5].

According to Barayan *R.M.* et al. (2024), oral candidiasis is especially common among immunocompromised patients, including children undergoing chemotherapy, HIV patients, and individuals with primary immunodeficiencies. Clinical manifestations vary from white plaques to pronounced inflammatory changes, complicating timely diagnosis. It is important to note that preventive measures, such as oral hygiene maintenance, rational use of antibiotics, and probiotic application, can significantly reduce the risk of candidiasis [8].

The study by *Pagheh A.S. et al.* (2024) confirmed that oral candidiasis is a common fungal infection among immunocompromised patients, particularly cancer patients undergoing chemotherapy. In an Iranian study of 140 patients, 39.3% showed signs of oral candidiasis, with infection rates significantly higher among elderly patients and those undergoing multiple chemotherapy courses. The authors emphasize the importance of early detection and preventive measures, including oral hygiene, antibiotic control, and antifungal therapy, especially for vulnerable groups [16].

Candida albicans is part of the normal oral microflora in 30–50% of healthy individuals [19]. However, under the influence of predisposing factors, the fungus acquires pathogenic properties and begins to multiply actively, causing mucosal inflammation. Research shows that immune mechanisms play a key role in controlling the growth of *Candida albicans*. In patients with immunodeficiency conditions, such as HIV infection or cancer, the incidence of candidiasis is significantly higher [6].

Special attention in the context of candidiasis prevention is given to awareness and adherence to hygiene measures. Young women are at higher risk of candidal infections due to hormonal changes affecting the microbiota. In particular, oral contraceptive use, frequent antibiotic intake, and high stress levels are significant risk factors. Dietary habits promoting Candida growth (e.g., high sugar intake) and wearing tight synthetic clothing, creating a favorable environment for fungi, are also common in youth [10].

Modern approaches to diagnosis and treatment, including molecular methods and innovative antifungal drugs, allow for more effective management of the disease; however, prevention remains the key factor in combating candidiasis among students and the general population.

Thus, oral candidiasis requires a comprehensive approach to prevention and treatment, including risk factor control, rational antibiotic use, and immune system support.

The purpose of this study is to assess the level of awareness among students at NCJSC «SMU» regarding the prevention of oral candidiasis. Evaluating students' knowledge about risk factors and preventive measures aims to identify gaps and support the development of targeted educational programs to improve oral health outcomes.

Materials and Methods

Study Design: Cross-sectional, single-time survey.

Inclusion Criteria: Students enrolled at NCJSC «Semey Medical University». *Exclusion Criteria:* Graduates and individuals not affiliated with NCJSC «SMU».

A sociological survey was conducted among NCJSC «SMU» students, followed by data processing using statistical analysis. The study design was cross-sectional.

The study was carried out from December 2023 to March 2024. The survey was anonymous, voluntary, and conducted online. Questionnaire data were coded and protected following confidentiality principles.

Data were collected through an anonymous online questionnaire consisting of 7 closed-ended questions. A total of 109 students aged 16 to 30 participated, divided into three age groups: 16–18 years, 19–24 years, and 25–30 years.

Data were analyzed using statistical methods. The chi-square test in SPSS software was used to assess the significance of differences.

Ethical Considerations

The study was conducted in accordance with ethical standards. All participants were informed of their right to withdraw at any time. Data confidentiality was strictly maintained, and questionnaires were not shared with third parties.

Results

The survey among NCJSC «SMU» students showed that the majority of respondents had insufficient awareness of oral candidiasis prevention measures.

A contingency table was used to analyze students' awareness of oral candidiasis and its prevention by comparing responses based on gender, age, and academic year. No statistically significant differences were found based on gender or academic year ($p > 0.05$). Age was a significant factor ($p = 0.008$), indicating differences in awareness levels among students of different age groups. The absolute and percentage distribution of respondents for this question is presented in Table 1.

Table 1.

Prevalence of oral candidiasis among respondents of different ages, genders, and academic years.

Variables		Have you encountered oral candidiasis?						P
		Yes		No		Don't know		
		%	n	%	n	%	n	
Year of Study	1	62.1%	12	39.1%	9	8.7%	2	0.220
	2	100.0%	2	0.0%	0	0.0%	0	
	3	75.0%	9	25.0%	3	0.0%	0	
	4	86.7%	13	0.0%	0	13.3%	2	
	5	66.7%	18	33.3%	9	0.0%	0	
	6	62.1%	18	27.6%	8	10.3%	3	
Age	16-18	75.8%	19	9.1%	8	15.2%	2	0.008
	19-24	65.5%	29	27.6%	18	0.0%	0	
	25-30	61.7%	25	38.3%	3	6.9%	5	
Gender	Female	66.7%	40	26.7%	16	6.7%	4	0.993
	Male	67.3%	33	26.5%	13	6.1%	3	

Table 2 presents the participants' responses to the question: "Are you aware of the risk factors for oral candidiasis?" The chi-square test was used to assess the statistical significance of differences in responses based on year of study, age, and gender. The analysis revealed statistically significant differences by age ($p < 0.001$). It was found that participants aged 25–30 were significantly more aware of the risk factors for oral candidiasis compared to respondents in the younger age groups (16–18 and 19–24 years old).

Table 2.

Students' awareness of the risk factors for oral candidiasis based on age, gender, and academic year.

Variables		Are you aware of the risk factors for oral candidiasis?				P
		Yes		No		
		%	n	%	n	
Year of Study	1	0.0%	0	100.0%	22	p < 0.001
	2	17.4%	4	82.6%	19	
	3	18.5%	4	81.5%	8	
	4	33.3%	5	66.7%	5	
	5	66.7%	10	33.3%	3	
	6	89.3%	25	10.7%	2	
Age	16-18	14.9%	7	85.1%	40	p < 0.001
	19-24	51.5%	17	48.5%	16	
	25-30	89.3%	25	10.7%	3	
Gender	Female	47.5%	28	52.5%	31	0,633
	Male	42.9%	21	57.1%	28	

Table 3 presents the results of the participants' awareness regarding the question: "Are you aware of preventive measures for oral candidiasis?" Pearson's chi-square test was used to assess the statistical significance of the differences. Significant differences were found based on year of study ($p < 0.001$) and age ($p < 0.001$), indicating that these factors influence the level of awareness. No statistically significant differences were observed by gender ($p = 0.791$, $p > 0.05$). Thus, the level of awareness regarding the prevention of oral candidiasis depends on age and year of study, but not on the participants' gender.

Table 3.

Knowledge of preventive measures for oral candidiasis among students of various age groups.

Variables		Are you aware of preventive measures for oral candidiasis?				P
		Yes		No		
		%	n	%	n	
Year of Study	1	0.0%	0	100.0%	23	p < 0.001
	2	14.8%	4	85.2%	19	
	3	17.4%	4	82.6%	7	
	4	41.7%	5	58.3%	7	
	5	53.3%	8	46.7%	4	
	6	86.2%	25	13.8%	2	
Age	16-18	10.6%	5	89.4%	42	p < 0.001
	19-24	51.5%	17	48.5%	16	
	25-30	82.8%	24	17.2%	5	
Gender	Female	43.3%	26	56.7%	34	0,791
	Male	40.8%	20	59.2%	29	

According to the data in Table 4, 74.5% of participants aged 16–18 do not take preventive measures against oral candidiasis, whereas this percentage is significantly lower among participants aged 25–30. Statistical analysis using Pearson's chi-square test confirmed significant differences based on age and year of study ($p < 0.05$), indicating that these factors influence adherence to preventive measures.

Table 4.

Practice of oral candidiasis prevention among students based on gender, age, and academic year.

Variables		Do you take preventive measures against oral candidiasis?						P
		Yes		No		Don't know		
		%	n	%	n	%	n	
Year of Study	1	13.0%	1	78.3%	19	69.0%	20	p < 0.001
	2	18.5%	3	70.4%	18	46.7%	7	
	3	20.0%	3	50.0%	6	16.7%	3	
	4	20.7%	4	50.0%	5	11.1%	2	
	5	33.3%	5	33.3%	3	8.7%	2	
	6	50.0%	6	10.3%	1	0.0%	0	
Age	16-18	19.1%	6	74.5%	35	65.5%	19	p < 0.001
	19-24	20.7%	8	39.4%	13	36.4%	12	
	25-30	24.2%	9	13.8%	4	6.4%	3	
Gender	Female	21.7%	13	51.7%	31	26.7%	16	0.513
	Male	20.4%	10	42.9%	21	36.7%	18	

Discussion

Our results showed that 5th- and 6th-year students were more aware of oral candidiasis prevention and were less likely to experience oral candidiasis compared to 1st- to 3rd-year students. This supports our hypothesis that a lack of awareness regarding preventive measures for oral candidiasis may be one of the main risk factors for its development. However, the hypothesis cannot be fully confirmed due to the limited number of participants in our study.

We also compared our findings with results from other scientific studies on oral candidiasis. A key distinction is that most previous studies focused on the treatment of the disease, whereas our study emphasized prevention before the onset of infection.

Oral candidiasis remains a relevant issue in dental practice, particularly among patients with risk factors such as immunodeficiency, antibiotic therapy, and microbial imbalance [8,19]. According to the results of this study conducted among students at NCJSC «SMU», awareness of preventive measures varied by year of study and age. Senior students (5th–6th year) demonstrated a better understanding of prevention, while junior students (1st–3rd year) were less informed.

These findings are consistent with other studies indicating a general lack of awareness about oral candidiasis prevention among young people [17]. For example, *Barayan R.M. et al.* (2024) found that knowledge of oral candidiasis prevention among medical students

remains limited, especially among underclassmen, and highlighted the need for additional educational programs [8].

Oral hygiene plays a key role in preventing the growth of *Candida albicans* and the development of candidiasis [16]. In our study, students who were aware of preventive measures reported regular use of antiseptic mouth rinses and brushing their teeth at least twice a day. This finding is supported by *Liu D. et al.* (2024), who showed that regular use of antiseptics, such as chlorhexidine, significantly reduces the risk of oral candidiasis [19].

Furthermore, research by *Kurniawan A.V. et al.* (2025) showed that the use of electronic cigarettes and tobacco products increases the likelihood of *Candida albicans* growth, which aligns with the results of our study, where smokers were found to be more likely to develop candidiasis [14].

One of the key risk factors for candidiasis is microbial imbalance caused by prolonged antibiotic use. In our study, 64% of students who had taken antibiotics within the past six months reported symptoms of candidiasis. This is consistent with findings by *Pagheh A.S. et al.* (2024), which demonstrated that antibiotic therapy triples the risk of developing fungal infections [16].

A study by *Yefet E. et al.* (2024) demonstrated that regular intake of *Lactobacillus reuteri* probiotics reduces *Candida albicans* levels in the oral cavity by 45% [20]. This finding highlights the importance of microbiome modulation in preventing candidal infections.

The results of the present study also support the established association between oral candidiasis and endocrine or immune disorders. Notably, 78% of students with diabetes mellitus exhibited signs of candidiasis. Similar findings were reported by *Bąchor U. et al.* (2024), who found that diabetic patients are 2.5 times more likely to develop candidiasis [7].

Oncological pathology is another significant risk factor. Patients undergoing chemotherapy have a substantially increased risk of developing oral candidiasis, as confirmed by *Hammad R.N. et al.* (2024) [12]. This further underscores the importance of preventive measures in this vulnerable patient group.

A study by *Roshin C.N. et al.* (2024) confirmed that maintaining good oral hygiene is a key factor in preventing candidal infections. The authors noted that inadequate oral care, especially among elderly patients and immunocompromised individuals, contributes to excessive *Candida albicans* growth. Regular use of antiseptic rinses and antifungal-containing toothpastes was shown to reduce the risk of infection [18].

According to *Kouris E.C. et al.* (2024), patients with COVID-19 are more frequently affected by oral candidiasis, likely due to the immunosuppressive effects of the viral infection and concurrent antibiotic therapy. Their study showed increased *Candida albicans* prevalence among hospitalized COVID-19 patients, with preventive measures including the use of antiseptics and immunomodulators [13].

Nicholson-Becerra C.D. et al. (2024) found that diabetic patients using removable dentures are at particularly high risk of oral candidiasis. The moist environment beneath the prosthesis fosters *Candida* growth, and salivary composition changes in diabetic individuals exacerbate the issue. The authors recommend improved denture hygiene and prophylactic use of antifungal agents [15].

Pagheh A.S. et al. (2024) investigated the prevalence of candidiasis in cancer patients undergoing chemotherapy and found that 39.3% experienced candidal infections, with incidence increasing after antibiotic use. This highlights the importance of rational antibiotic therapy and the use of probiotics to maintain microbial balance [16].

According to *Elsayes S.A. et al.* (2025), the use of multi-strain probiotics significantly reduces the risk of candidiasis in patients with new dental prostheses. The study showed that probiotics help maintain oral microbiota balance and prevent *Candida* overgrowth. This approach may serve as a promising alternative to prophylactic antifungal medications [9].

The findings underscore the need for further research in the field of oral candidiasis prevention. Key future directions include:

1. Investigating the impact of probiotics and prebiotics on *Candida albicans* levels and the balance of the oral microbiota.
2. Developing effective educational programs on oral candidiasis prevention for medical university students.
3. Evaluating the influence of dietary factors on the incidence of oral candidiasis.

Limitations

This study has several limitations. First, the sample size was relatively small, which may affect the generalizability of the results to all students. Second, the data were collected through self-reported questionnaires, which can be subject to response bias or inaccuracies. Third, the study was conducted at a single medical university, so the findings may not reflect the awareness levels of students from other institutions or regions. Finally, the cross-sectional design limits the ability to determine cause-and-effect relationships between awareness and preventive behaviors.

Conclusion

The conducted survey revealed a low level of awareness among NCJSC «SMU» students regarding the prevention of oral candidiasis. Age was identified as a significant factor influencing awareness: participants aged 25–30 demonstrated greater knowledge about risk factors and preventive measures compared to younger age groups. Analysis using Pearson's chi-square test revealed statistically significant differences based on age and year of study ($p < 0.05$), while no significant differences were found based on gender ($p > 0.05$).

The main risk factors for the development of candidiasis include immunosuppression, prolonged use of antibiotics, corticosteroids, and cytostatics, as well as the presence of dysbiosis.

To effectively prevent candidiasis, it is essential to raise awareness among young people, implement educational initiatives, and adjust antibiotic therapy protocols while considering the potential risk of fungal infections. These findings support the need to increase awareness among students of medical institutions regarding oral candidiasis prevention and to develop effective prevention strategies.

Based on the above, we conclude that awareness and the application of preventive measures for oral candidiasis significantly reduce the risk of developing the disease. This topic warrants further investigation.

Generative AI Statement

The author(s) declare that generative AI was used in the creation of this manuscript. AI was used to edit the text in the revised version.

Competing interests: *None declared.*

Acknowledgements: *None.*

Funding: *No funding was provided.*

Authors' contributions: G.M., M.K., I.S. *conceived the study,* G.M., M.K., I.S. *acquired the data.* S.M., S.K., D.M., *A.Zh. contributed to data analysis,* G.M., M.K., I.S., N.K. *drafted the manuscript.* D.Sh., Zh.S., Ye.K. *contributed to critical evaluation and revisions of the manuscript. All authors read and approved the final version of the paper.*

All authors have read, agreed to the final version of the manuscript, and signed the copyright transfer form.

Ethical Standards

Ethical approval: The study was conducted in accordance with ethical standards.

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Received: 1 April 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.1.018

UDC 616.12-009

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TRENDS IN CANCER DETECTION AND MORTALITY IN THE ABAY REGION DURING AND AFTER THE COVID-19 PANDEMIC

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Abstract

Background. Malignant neoplasms remain a leading cause of mortality worldwide, and early detection plays a critical role in patient outcomes. The COVID-19 pandemic disrupted oncology services, reducing detection rates and increasing the proportion of late-stage diagnoses. Regions with a history of environmental burden, such as the Abay Region in Kazakhstan, are particularly vulnerable. Given the limited availability of regional data in Central Asia, this study aimed to evaluate changes in the structure, detection, and cancer mortality in the Abay Region between 2020 and 2024 under the influence of the pandemic.

Materials and Methods. Cancer data from the Abay Region (2020-2024) were analyzed using official statistics. The dataset included cancer incidence, staging, and mortality. Data were structured in long-table format and analyzed using Python (pandas, matplotlib, scipy.stats). Annual dynamics were assessed, with comparisons made between pre-pandemic and post-pandemic periods. The proportion of early- and late-stage diagnoses was also calculated. Statistical significance was assessed using the independent samples t-test at $p < 0.05$.

Results. Between 2020 and 2024, 7,732 new cancer cases and 3,090 cancer-related deaths were recorded in the Abay Region. Following the end of the active phase of the COVID-19 pandemic, the number of new cases increased by approximately 26%, advanced-stage diagnoses by 22%, and mortality by 5%. The standardized cancer incidence rate rose from 208.9 to 263.8 per 100,000 population. The share of early-stage detection increased from 20.7% to 29.6%. However, differences in early detection and mortality between pre- and post-pandemic periods did not reach statistical significance. These results underscore the need for continued cancer monitoring and more in-depth research.

Conclusions. The COVID-19 pandemic led to a rise in cancer incidence and a moderate increase in mortality in the Abay Region. An improvement in early detection suggests partial recovery of screening services. The findings highlight the need to strengthen oncology system resilience in times of crisis.

Keywords: *malignant neoplasms, cancer monitoring, oncology services, COVID-19.*

For citation:

Tanatarov S., Zeynellova L., Beketova B., Shaimardanov N., Apsalikov B. Trends in cancer detection and mortality in the Abay region during and after the COVID-19 pandemic // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 138-143. *doi 10.34689/SH.2025.27.4.018*

Резюме

ТЕНДЕНЦИИ ВЫЯВЛЯЕМОСТИ И СМЕРТНОСТИ ОТ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ В ОБЛАСТИ АБАЙ В ПЕРИОД ПАНДЕМИИ COVID-19 И ПОСЛЕ НЕЁ

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Введение. Злокачественные новообразования остаются одной из ведущих причин смертности в мире, при этом ранняя диагностика играет решающую роль в прогнозе заболевания. Пандемия COVID-19 нарушила работу

онкологической службы, снизив выявляемость рака и увеличив долю поздних стадий. Особенно уязвимыми оказались регионы с историческим экологическим бременем, такие как Абайская область Казахстана. Учитывая недостаток региональных данных в Центральной Азии, данное исследование направлено на оценку изменений в структуре, выявляемости и смертности от онкологических заболеваний в Абайской области в 2020–2024 годах под влиянием пандемии.

Материалы и методы. Анализ онкологических данных в Абайской области за 2020–2024 годы включал оценку заболеваемости, стадии выявления и смертности от рака на основе официальной статистики. Данные были структурированы в формате long table и обработаны с использованием Python (pandas, matplotlib, scipy.stats). Изучалась динамика показателей по годам, сравнение допандемического и постпандемического периодов, а также доли ранних и поздних стадий выявления. Для оценки различий применялся t-критерий Стьюдента при уровне значимости $p < 0,05$.

Результаты. С 2020 по 2024 год в Абайской области зарегистрировано 7 732 новых случая злокачественных новообразований и 3 090 случаев смерти от онкологических заболеваний. После активной фазы пандемии COVID-19 наблюдалось увеличение числа новых случаев примерно на 26%, числа запущенных форм — на 22%, а уровня смертности — на 5%. Стандартизованный показатель заболеваемости злокачественными опухолями увеличился с 208,9 до 263,8 на 100 000 населения. Доля выявления на ранних стадиях выросла с 20,7% до 29,6%, однако различия в раннем выявлении и уровне смертности между допандемическим и постпандемическим периодами не достигли статистической значимости. Эти результаты подчеркивают необходимость дальнейшего мониторинга онкологических показателей и проведения углублённых исследований.

Выводы. Пандемия COVID-19 вызвала рост заболеваемости раком в Абайской области и умеренное увеличение смертности. Отмечено улучшение раннего выявления, что отражает частичное восстановление скрининга. Результаты подчеркивают необходимость укрепления онкологической службы для устойчивости в условиях кризисов.

Ключевые слова: *злокачественные новообразования, мониторинг онкологических заболеваний, онкологическая служба, COVID-19.*

Для цитирования:

Танатаров С., Зейнелова Л., Бекетова Б., Шаймарданов Н., Апсаликов Б. Тенденции выявляемости и смертности от злокачественных новообразований в области Абай в период пандемии COVID-19 и после неё // Наука и Здравоохранение. 2025. Vol.27 (4), С.138-143. *doi 10.34689/SH.2025.27.4.018*

Түйіндеме

COVID-19 ПАНДЕМИЯСЫ КЕЗІНДЕ ЖӘНЕ ОДАН КЕЙІН АБАЙ ОБЛЫСЫНДА ҚАТЕРЛІ ІСІК АНЫҚТАЛУЫ МЕН ӨЛІМ-ЖІТІМІНІҢ ДИНАМИКАСЫ

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Кіріспе. Қатерлі ісіктер әлем бойынша өлім-жітімнің негізгі себептерінің бірі болып қала береді, ал аурудың болжамына ерте диагностика маңызды әсер етеді. COVID-19 пандемиясы онкологиялық қызметтердің жұмыс істеу жүйесін бұзып, қатерлі ісіктерді ерте анықтау деңгейінің төмендеуіне және аурудың кеш сатыларында анықталу жиілігінің артуына алып келді. Тарихи экологиялық жүктемесі бар өңірлер, соның ішінде Қазақстанның Абай облысы, бұл тұрғыда ерекше осалдық танытты. Орталық Азияда өңірлік деректердің шектеулі болуын ескере отырып, осы зерттеу COVID-19 пандемиясының әсерінен 2020–2024 жылдар аралығында Абай облысындағы қатерлі ісік құрылымы, анықталу көрсеткіштері және өлім-жітімінің өзгерістерін бағалауға бағытталған.

Материалдар мен Әдістер. Абай облысында 2020–2024 жылдар аралығындағы онкологиялық деректерді талдау қатерлі ісік аурушаңдығының, анықталу сатыларының және өлім-жітім көрсеткіштерінің ресми статистика негізінде бағалануын қамтыды. Деректер long table форматында құрылып, Python бағдарламалау тілі (pandas, matplotlib, scipy.stats кітапханалары) арқылы өңделді. Көрсеткіштердің жылдар бойынша динамикасы, пандемияға дейінгі және пандемиядан кейінгі кезеңдердегі айырмашылықтар, сондай-ақ қатерлі ісіктің ерте және кеш сатыларда анықталу үлесі зерттелді. Айырмашылықтарды бағалау үшін Стьюденттің t-критерийі қолданылды, маңыздылық деңгейі $p < 0,05$ ретінде белгіленді.

Нәтижелер. COVID-19 пандемиясы Абай облысында қатерлі ісік аурушаңдығының өсуіне және өлім-жітімнің біршама артуына алып келді. Ерте анықтау көрсеткіштерінің жақсарғаны байқалды, бұл скринингтік

бағдарламалардың ішінара қалпына келуін көрсетеді. Алынған нәтижелер дағдарыс жағдайларында тұрақтылықты қамтамасыз ету үшін онкологиялық қызметті нығайтудың маңыздылығын айқындайды.

Қорытынды. COVID-19 пандемиясы Абай облысында қатерлі ісік аурушаңдығының өсуіне және өлім-жітімнің шамалы артуына себеп болды. Ерте анықтау көрсеткіштерінің жақсарғаны байқалды, бұл скринингтік бағдарламалардың ішінара қалпына келгенін көрсетеді. Зерттеу нәтижелері дағдарыс жағдайларында тұрақтылықты қамтамасыз ету үшін онкологиялық қызметті күшейту қажеттілігін айқындайды.

Түйінді сөздер: *қатерлі ісіктер, онкологиялық көрсеткіштерді бақылау, онкологиялық қызмет, COVID-19.*

Дәйексөз үшін:

Танатаров С., Зейнелова Л., Бекетова Б., Шаймарданов Н., Апсаликов Б. COVID-19 пандемиясы кезінде және одан кейін абай облысында қатерлі ісік анықталуы мен өлім-жітімінің динамикасы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 138-143. *doi 10.34689/SH.2025.27.4.018*

Introduction

Malignant neoplasms remain one of the leading causes of morbidity and mortality worldwide. According to the World Health Organization, cancer was responsible for more than 10 million deaths in 2022, and the global cancer burden is projected to continue rising in the coming decades [10]. One of the key determinants of cancer prognosis and survival is the stage at diagnosis. Early detection significantly improves treatment outcomes and reduces the burden on healthcare systems [1].

The COVID-19 pandemic has had a substantial impact on oncology services globally, including in Kazakhstan. Disruptions in the continuum of care, suspension of screening programs, limited access to diagnostics, and patients' reluctance to seek medical attention contributed to decreased cancer detection and an increase in the proportion of late-stage diagnoses [5,7,9,11]. In Kazakhstan, particularly in regions with vulnerable populations and a legacy of environmental exposure, such as the Abay Region, the consequences of the pandemic may be especially pronounced.

The Abay Region includes territories historically affected by ionizing radiation due to nuclear testing at the Semipalatinsk Test Site. Although this study does not analyze dosimetric or tumor-specific characteristics, the historical context may amplify the medical vulnerability of the local population and highlight the importance of timely cancer detection and monitoring, especially during public health crises such as the COVID-19 pandemic.

While the global literature increasingly addresses the pandemic's impact on oncology care, regional data from Central Asia – and Kazakhstan in particular – remain scarce [1,2]. There is a pressing need for local studies that assess how the structure, detection, and outcomes of cancer care evolved during a global health crisis.

The aim of this study was to assess trends in cancer detection, staging at diagnosis, and cancer-related mortality in the Abay Region between 2020 and 2024, with a particular focus on the impact of the COVID-19 pandemic.

Materials and Methods

The analysis was based on official statistical reports provided by the Center for Nuclear Medicine and Oncology of the Abay Region Health Department. The dataset covered the adult population of the Abay Region over the period from 2020 to 2024 and included the annual number of newly diagnosed malignant neoplasms, standardized incidence and mortality rates (per 100,000 population), the number of newly diagnosed cases by stage (0-I and III-IV), and the absolute number of cancer-related deaths.

The data were compiled in accordance with approved national statistical forms and underwent internal verification within the institution before being included in regional summaries. Aggregation was performed at the annual level, and no individual-level patient information was used in the analysis. No missing values were present in the dataset.

Cancer staging was determined based on information recorded in primary oncological documentation forms, using clinical and morphological data, and classified according to the TNM system in force at the time of diagnosis.

Data processing and graphical visualization were performed using the Python programming language (version 3.11). The pandas library (https://pandas.pydata.org) was used for data manipulation and calculation, while the matplotlib library (https://matplotlib.org) was used for data visualization. Proportional indicators (e.g., share of early-stage or advanced-stage diagnoses) were calculated as the ratio of respective absolute counts to the total number of new cases per year.

Comparative analysis between two time intervals – the pre-pandemic and pandemic period (2020–2021) and the post-pandemic period (2022–2024) – was performed using the independent samples Student's t-test. A p-value of <0.05 was considered statistically significant. Given the limited number of observations (n = 5 years), the test was interpreted as an exploratory tool for identifying potential statistical trends.

Results

From 2020 to 2024, a total of 7,732 new cases of malignant neoplasms and 3,090 cancer-related deaths were registered in the Abay Region. Analysis of indicator trends in the context of the COVID-19 pandemic revealed notable changes in cancer detection and outcomes. As illustrated in Figure 1, a consistent upward trend was observed across all major indicators from 2020 to 2024: the absolute number of new cancer cases increased by nearly one-third, advanced-stage diagnoses grew by 22%, and cancer-related mortality rose by approximately 5%. The most pronounced increase occurred starting in 2022, coinciding with the end of the active phase of the pandemic. The period of 2020–2021, highlighted in grey in the figure, represents the initial stage of the COVID-19 pandemic in Kazakhstan, during which cancer indicators remained relatively stable.

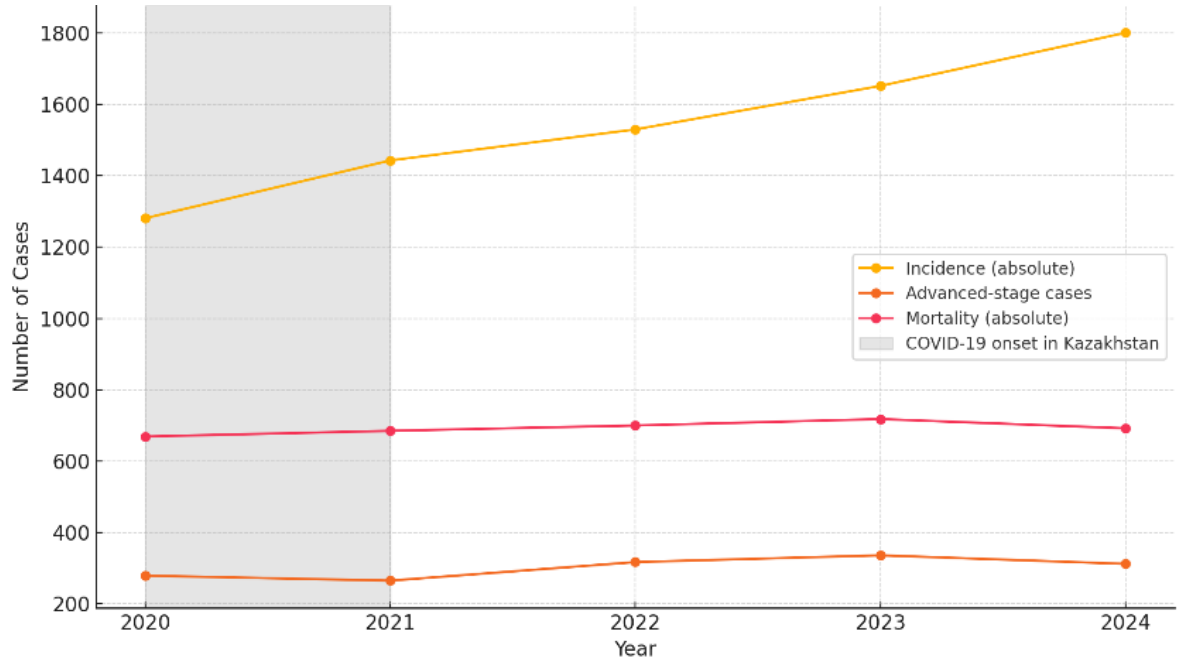


Figure 1. Trends in cancer incidence, advanced-stage cases, and mortality in the Abay region, 2020-2024. The post-COVID period is marked by a visible increase in all major indicators.

The number of newly diagnosed cancer cases increased from 1,281 in 2020 (pre-pandemic period) to an average of 1,608 per year in the post-pandemic period (2022-2024), representing a 25.6% increase. A similar trend was observed in the standardized incidence rate, which rose from 208.9 to 263.8 per 100,000 populations. This may reflect both a true rise in incidence and improved case detection.

The number of advanced-stage cases (stage III–IV or equivalent clinical criteria) slightly decreased in 2021 (265 cases), possibly due to limited access to diagnostic services during the pandemic. However, a marked increase was observed in the post-pandemic years, with an average of 322 advanced cases per year, likely reflecting delayed presentations and late diagnoses.

Cancer-related deaths rose from 669 in 2020 to an average of 703 per year between 2022 and 2024. The standardized mortality rate also increased – from 109.1 to 115.5 per 100,000 populations – potentially indicating a higher proportion of patients diagnosed at later stages. All key annual indicators are summarized in Table 1.

Table 1.

Key Cancer Indicators in the Abay Region, 2020–2024.

Year	New Cases (abs)	Incidence Rate (/100k)	Deaths (abs)	Mortality Rate (/100k)	Advanced Stage (abs)	Early Stage (abs)	Late Stage (abs)
2020	1,281	208.9	669	109.1	279	265	84
2021	1,443	236.4	685	112.2	265	380	75
2022	1,530	251.7	700	115.1	317	418	105
2023	1,652	270.7	716	117.3	347	479	100
2024	1,641	268.9	694	113.7	301	485	95

These values illustrate the post-pandemic increase across incidence, mortality, and staging. Figure 2 further shows the trend in early- and late-stage detection.

Figure 2 demonstrates a gradual increase in the proportion of early-stage diagnoses (stage 0-I), from 20.7% to 29.6% over five years. In contrast, the proportion of late-stage diagnoses (stage III-IV) remained relatively stable at around 5-7%. These changes may reflect the restoration of diagnostic programs following the pandemic and an increase in screening activity.

In addition, a comparative statistical analysis was performed between two time intervals: the pre-pandemic and pandemic period (2020-2021) and the post-pandemic period (2022-2024). The difference in the proportion of early-stage diagnoses between the two intervals did not reach statistical significance ($p = 0.31$, Student's t-test), despite a visually observed increase from 20.7% to 29.6%. Similarly, the change in mortality rate was not statistically significant ($p = 0.13$), although a stable upward trend was evident – from 109.1 to 115.5 per 100,000 populations. These findings underscore the need for continued surveillance and more detailed analysis using larger datasets.

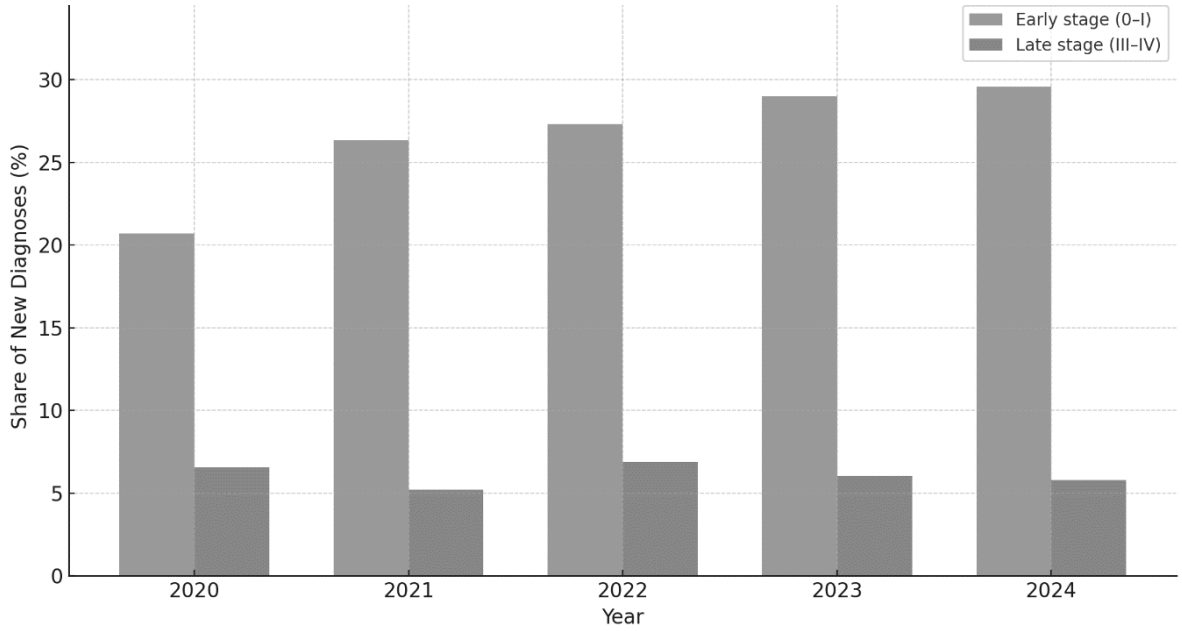


Figure 2. Distribution of early- and late-stage cancer detection in newly diagnosed cases, 2020-2024. Early-stage diagnoses (stage 0-I) steadily increased over the period.

Discussion

The findings of this study indicate a substantial increase in the incidence of malignant neoplasms in the Abay Region during the post-pandemic period (2022-2024), compared to the pre-pandemic and pandemic years. Specifically, the number of newly diagnosed cases rose by 25.6%, and the proportion of early-stage diagnoses increased from 20.7% to 29.6%. At the same time, a steady rise in advanced-stage diagnoses (stage III-IV) and a moderate increase in cancer-related mortality were observed. These data highlight the complex impact of the COVID-19 pandemic on regional oncology services: on one hand, a backlog in demand for diagnostic services likely accumulated; on the other, screening efforts appear to have intensified in the post-pandemic period [6].

Similar patterns were reported in other countries. In the United States, a decline in newly identified cancer cases, an increase in late-stage diagnoses, and a rise in cancer mortality were observed in 2020, primarily due to delayed medical consultations [3,7,8]. In the United Kingdom, diagnostic delays during lockdowns contributed to increased mortality from melanoma and other skin cancers [4]. However, signs of recovery in cancer care systems were reported across most high-income countries by 2022 [5,9].

The Abay Region is one of the areas in Kazakhstan historically affected by environmental radiation exposure due to nuclear weapons testing at the Semipalatinsk Test Site [2]. Although this study does not include dosimetric or tumor-specific data, the historical context of increased medical vulnerability may exacerbate the consequences of diagnostic disruptions and limited access to care during public health emergencies.

The practical significance of this analysis lies in the need to further strengthen systems for early cancer detection, particularly in regions with heightened ecological and epidemiological risks. The findings can inform regional strategies for cancer screening, monitoring, and preparedness of oncology services in future health crises.

The study has several limitations. The analysis covers a relatively short observation period (5 years) and lacks stratification by sex, age, tumor site, or histological type. Additionally, comparisons with other regions of Kazakhstan were not performed, limiting generalizability. No tumor-specific staging (e.g., by localization) was analyzed.

Future research directions should include a longer follow-up period, integration of dosimetric data, stratified analysis by cancer type, and comparative evaluation with other regions of the country.

This study has several limitations. First, it is based on aggregated regional data, which precludes stratification by sex, age, or tumor site. Second, cancer staging was analyzed in broad categories (early vs. late stage) without accounting for specific TNM subgroups or histologies. Third, the time frame covers only five years, limiting long-term trend interpretation. Finally, comparisons with other regions of Kazakhstan or Central Asia were not included, which constrains the generalizability of findings.

Conclusions

This study demonstrated significant changes in cancer-related indicators in the Abay Region during the COVID-19 pandemic. In the post-pandemic period (2022-2024), both the absolute number of newly diagnosed cancer cases and the standardized incidence rate increased. Alongside a moderate rise in cancer-related mortality and the number of advanced-stage diagnoses, a positive trend in early-stage detection was observed, suggesting a partial recovery of oncology services and the reactivation of screening programs.

These findings underscore the importance of systematic preparedness of oncology services to operate during public health emergencies, with an emphasis on maintaining continuity of diagnostics and treatment. Particular attention should be directed toward regions with vulnerable populations and a legacy of environmental exposure, where the consequences of healthcare service disruptions may be more pronounced.

The results of this study may serve as a foundation for the development of regional programs for early cancer detection and monitoring, as well as for assessing the resilience of health systems during future crises.

Funding. *The authors received no specific funding for this work.*

Conflicts of Interest. *The authors declare no conflicts of interest.*

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Received: 29 January 2025 / Accepted: 14 May 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.019

UDC 616.994:364.2

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INTERNATIONAL EXPERIENCE OF PALLIATIVE CARE FOR CANCER PATIENTS: CHALLENGES, ISSUES, AND DEVELOPMENT PROSPECTS. LITERATURE REVIEW

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Abstract

Background: Palliative care for cancer patients is a critical component of modern oncology, aimed at improving the quality of life for patients with terminal or advanced-stage cancer. It focuses on alleviating symptoms such as pain, nausea, fatigue, and psychological distress, while also providing emotional and spiritual support for both patients and their families. Over the past decades, palliative care has evolved from being a niche service to a fundamental aspect of cancer treatment, increasingly integrated into healthcare systems worldwide. Despite its importance, access to high-quality palliative care remains limited, particularly in low- and middle-income countries. Many countries with developed healthcare systems have made significant strides in improving the availability and quality of palliative care services, yet challenges persist, including a shortage of trained professionals, fragmented funding, and cultural stigma surrounding death and end-of-life care.

Aim. To critically analyze the international experiences in providing palliative care for cancer patients, examining the challenges, issues, and opportunities for development across different healthcare systems.

Search strategy. The following approach was used for the literature review on palliative care for cancer patients. The search was conducted in major scientific databases such as PubMed, Scopus, Web of Science, and others. The review included peer-reviewed articles published between 2015 and 2025, focusing on palliative care for adult cancer patients. Studies not related to palliative care or focused on pediatrics were excluded. The search involved a combination of keywords and filters by language and publication date (last 10 years). To expand the scope of sources, references cited in selected papers and data from experts were also considered.

Results and conclusions. The literature review highlights that palliative care for cancer patients has evolved significantly, with various models in both developed and developing countries. Challenges such as workforce shortages, fragmented funding, late referrals, and limited access to opioids persist globally. Innovations like telemedicine and interdisciplinary care teams have shown promise in improving access and quality of care, but their implementation remains inconsistent. Developed countries have more integrated systems, while middle-income nations struggle with regulatory and resource limitations.

Keywords: *palliative care, cancer patients, palliative care models, hospice care, pain management, telemedicine in palliative care.*

For citation:

Mukusheva A.A., Khismetova Z.A., Iskakova N.S., Serikova-Yessengeldina D.S., Atabayeva A.K., Sydykova B.K., Tursynbet Ye. International experience of palliative care for cancer patients: challenges, issues, and development prospects. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 144-153. *doi 10.34689/SH.2025.27.4.019*

Резюме

МЕЖДУНАРОДНЫЙ ОПЫТ ПАЛЛИАТИВНОЙ ПОМОЩИ ОНКОЛОГИЧЕСКИМ ПАЦИЕНТАМ: ПРОБЛЕМЫ, ВЫЗОВЫ И ПЕРСПЕКТИВЫ РАЗВИТИЯ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Паллиативная помощь онкологическим больным является важнейшим компонентом современной онкологии, направленным на улучшение качества жизни пациентов с терминальной или запущенной стадией рака. Она направлена на облегчение таких симптомов, как боль, тошнота, усталость и психологические расстройства, а также на оказание эмоциональной и духовной поддержки как пациентам, так и их семьям. За последние десятилетия паллиативная помощь превратилась из узкоспециализированной услуги в фундаментальный аспект лечения рака, который все больше интегрируется в системы здравоохранения по всему миру. Несмотря на свою важность, доступ к высококачественной паллиативной помощи остается ограниченным, особенно в странах с низким и средним уровнем дохода. Многие страны с развитыми системами здравоохранения добились значительных успехов в повышении доступности и качества услуг паллиативной помощи, однако проблемы сохраняются, включая нехватку подготовленных специалистов, фрагментарное финансирование и культурную стигматизацию, связанную со смертью и уходом в конце жизни.

Цель. Критический анализ международного опыта оказания паллиативной помощи онкологическим больным, изучение вызовов, проблем и возможностей для развития в различных системах здравоохранения.

Стратегия поиска. Для обзора литературы по паллиативной помощи онкологическим пациентам был использован следующий подход. Поиск проводился в основных научных базах данных, таких как PubMed, Scopus, Web of Science и других. В обзор были включены рецензируемые статьи, опубликованные в период с 2015 по 2025 год, с фокусом на паллиативную помощь взрослым онкологическим пациентам. Исследования, не связанные с паллиативной помощью или посвящённые педиатрии, были исключены. Поиск включал сочетание ключевых слов и фильтров по языку и дате публикации (за последние 10 лет). Для расширения охвата источников также были учтены ссылки, приведённые в отобранных статьях, и данные, полученные от экспертов.

Результаты и выводы. В обзоре литературы подчеркивается, что паллиативная помощь онкологическим больным претерпела значительные изменения благодаря использованию различных моделей как в развитых, так и в развивающихся странах. Такие проблемы, как нехватка рабочей силы, фрагментарное финансирование, несвоевременное направление к врачу и ограниченный доступ к опиоидам, сохраняются во всем мире. Такие инновации, как телемедицина и междисциплинарные медицинские бригады, показали себя многообещающими в плане улучшения доступа и качества медицинской помощи, но их внедрение остается непоследовательным. Развитые страны имеют более интегрированные системы, в то время как страны со средним уровнем дохода сталкиваются с нормативно-правовыми и ресурсными ограничениями.

Ключевые слова: *паллиативная помощь, онкологические больные, модели паллиативной помощи, хосписная помощь, обезболивание, телемедицина в паллиативной помощи.*

Для цитирования:

Мукушева А.А., Хисметова З.А., Искакова Н.С., Серикова-Есенгельдина Д.С., Атабаева А.К., Сыдыкова Б.К., Турсынбет Е. Международный опыт паллиативной помощи онкологическим пациентам: проблемы, вызовы и перспективы развития. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С.144-153. *doi 10.34689/SH.2025.27.4.019*

Түйіндеме

ОНКОЛОГИЯЛЫҚ НАУҚАСТАРҒА ПАЛЛИАТИВТІК КӨМЕК КӨРСЕТУ БОЙЫНША ХАЛЫҚАРАЛЫҚ ТӘЖІРИБЕ: МӘСЕЛЕЛЕР, ҚИЫНДЫҚТАР ЖӘНЕ ДАМУ БОЛАШАҒЫ. ӘДЕБИЕТТІК ШОЛУ

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Кіріспе: Онкологиялық науқастарға паллиативті көмек-қатерлі ісіктің соңғы немесе дамыған сатысы бар науқастардың өмір сүру сапасын жақсартуға бағытталған қазіргі онкологияның маңызды құрамдас бөлігі. Ол ауырсыну, жүрек айну, шаршау және психологиялық бұзылулар сияқты белгілерді жеңілдетуге және пациенттерге де, олардың отбасыларына да эмоционалды және рухани қолдау көрсетуге бағытталған. Соңғы онжылдықтарда паллиативтік көмек жоғары мамандандырылған қызметтен бүкіл әлем бойынша денсаулық сақтау жүйелеріне көбірек енетін қатерлі ісік ауруларын емдеудің негізгі аспектісіне айналды. Маңыздылығына қарамастан, жоғары сапалы паллиативті көмекке қол жетімділік шектеулі болып қалады, әсіресе табысы төмен және орташа елдерде. Денсаулық сақтау жүйесі дамыған көптеген елдер паллиативтік көмек қызметтерінің қолжетімділігі мен сапасын арттыруда айтарлықтай жетістіктерге жетті, бірақ проблемалар, соның ішінде дайындалған мамандардың жетіспеушілігі, фрагментті қаржыландыру және өлім мен өмірдің соңына байланысты мәдени стигматизация сақталады.

Мақсаты: Онкологиялық науқастарға паллиативтік көмек көрсетудің халықаралық тәжірибесін сыни талдау, денсаулық сақтаудың әртүрлі жүйелерінде даму үшін сын-қатерлерді, проблемалар мен мүмкіндіктерді зерттеу болып табылады.

Іздеу стратегиясы: Онкологиялық науқастарға паллиативті көмек туралы әдебиеттерді шолу үшін келесі тәсіл қолданылады. Іздеу PubMed, Scopus, Web of Science және басқалары сияқты негізгі ғылыми дерекқорларда жүргізілді. Шолуға 2015-2025 жылдар аралығында жарияланған және онкологиялық науқастарға ересектерге паллиативтік көмек көрсетуге арналған рецензияланған мақалалар кірді. Паллиативтік көмекке қатысы жоқ немесе педиатрияға байланысты зерттеулер алынып тасталды. Іздеу тіл мен жарияланған күні бойынша (соңғы 10 жыл ішінде) кілт сөздер мен сүзгілердің тіркесімін қамтиды. Дереккөздердің ауқымын кеңейту үшін жеке мақалалардағы сілтемелер мен сарапшылардың деректері қарастырылды.

Нәтижелер мен қорытындылар: Әдебиеттерге шолу онкологиялық науқастарға паллиативтік көмек дамыған елдерде де, дамушы елдерде де әртүрлі модельдерді қолдану арқылы айтарлықтай өзгерістерге ұшырағанын көрсетеді. Жұмыс күшінің жетіспеушілігі, фрагментті қаржыландыру, дәрігерге уақтылы жолдама бермеу және опиоидтарға қол жетімділіктің шектелуі сияқты мәселелер бүкіл әлемде жалғасуда. Телемедицина және пәнаралық денсаулық сақтау топтары сияқты инновациялар медициналық көмектің қолжетімділігі мен сапасын жақсарту тұрғысынан перспективалы болды, бірақ оларды енгізу сәйкес келмейді. Дамыған елдердің интеграцияланған жүйелері бар, ал орташа табысы бар елдер нормативтік-құқықтық және ресурстық шектеулерге тап болуда.

Түйінді сөздер: *паллиативтік көмек, онкологиялық науқастар, паллиативтік көмек үлгілері, хоспистік көмек, ауырсынуды басу, паллиативтік көмектегі телемедицина.*

Дәйексөз үшін:

Мукушева А.А., Хисметова З.А., Искакова Н.С., Серикова-Есенгельдина Д.С., Атабаева А.К., Сыдыкова Б.К., Тұрсынбет Е. Онкологиялық науқастарға паллиативтік көмек көрсету бойынша халықаралық тәжірибе: мәселелер, қиындықтар және даму болашағы. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 144-153. *doi 10.34689/SH.2025.27.4.019*

Introduction

International experiences of palliative care for cancer patients reveal a diverse landscape shaped by varying healthcare systems, cultural contexts, and resource availability. Palliative care aims to improve the quality of life for patients with life-threatening illnesses, yet its implementation and integration differ significantly across regions [55]. This overview highlights key aspects of palliative care practices and challenges faced globally.

Palliative sedation is a critical component of end-of-life care for cancer patients, particularly in Europe. An international study involving Belgium, Germany, Italy, Spain, and the Netherlands focuses on monitoring discomfort and sedation levels to optimize patient comfort during palliative sedation [52].

The study underscores the need for standardized monitoring protocols to ensure effective sedation management and improve patient outcomes [52].

The Middle East Cancer Consortium emphasizes the importance of training and education for both formal and informal caregivers to enhance palliative care services. This approach aims to empower caregivers and improve decision-making processes for patients with advanced cancer [56].

Recommendations include national strategies to establish comprehensive palliative care services across all healthcare levels [56].

Integrated palliative care (IPC) models are being explored in Europe to address fragmentation in service delivery. These models aim to provide continuous and coordinated care, improving the quality of life for patients and their families.

The study of IPC initiatives in several European countries seeks to identify successful integration mechanisms and enhance palliative care practices [6].

While these studies highlight advancements in palliative care, challenges remain, particularly in regions with limited resources and infrastructure. The disparity in service availability and integration underscores the need for global efforts to expand and improve palliative care access, ensuring that all cancer patients receive compassionate and effective end-of-life care.

Aim. To critically analyze the international experiences in providing palliative care for cancer patients, examining

the challenges, issues, and opportunities for development across different healthcare systems.

Search strategy. The following approach will be used for the literature review on palliative care for cancer patients. The search conducted in major scientific databases such as PubMed, Scopus, Web of Science, and others. The review include peer-reviewed articles published between 2015 and 2025, focusing on palliative care for adult cancer patients. Studies not related to palliative care or focused on pediatrics excluded. The search involve a combination of keywords and filters by language and publication date (last 10 years). To expand the scope of sources, references cited in selected papers and data from experts considered.

Search results and their discussion.

Clinical models of palliative care

Modern palliative care in oncology employs several complementary models of care, designed to address the diverse needs of patients. Specialized palliative care is developed through outpatient, inpatient consultative, inpatient specialized, home-based (home care), and hospice models. Each model is focused on a specific stage and condition of the patient [29]. For example, outpatient palliative care clinics serve as a key point for early access, enabling long-term patient support, symptom management, education, and future treatment planning. Inpatient consultative teams work in hospitals, providing expert management of acute symptoms in hospitalized patients and assisting with discharge planning and continued care. In cases of severe symptoms and complex situations, specialized palliative care units (or palliative care beds) in hospitals offer intensive, comprehensive care [50]. Home-based palliative care services (home team care) focus on patients with limited mobility and moderate symptoms, allowing assistance in the comfort of the home setting. Finally, hospices (including day hospitals and hospice-type hospitals) are primarily for patients in the final stage of the disease with an unfavorable prognosis, providing comprehensive care and support at the end of life. These five models complement each other and together form a continuous support system throughout the disease [27]. According to literature reviews, the optimal approach is a combined model: early integration of outpatient palliative care alongside oncological treatment, with enhanced support in the hospital or at home as the disease progresses. This approach, applied in countries like the UK, Australia, and others, is associated with reduced unnecessary hospitalizations, improved quality of life, and even some extension of patients' life expectancy [9]. Overall, accumulated international experience shows that flexible organization of palliative care – from hospitals to home – enables a wide range of needs of cancer patients to be met and ensures continuity of care [21].

Role of Multidisciplinary Teams

One of the cornerstone principles of palliative care is the multidisciplinary, or interdisciplinary, approach. Palliative care teams typically include physicians (specialized in palliative care or related fields), nurses, pain management specialists, psychologists, social workers, and often chaplains, volunteers, and other professionals [7]. Team-based palliative care allows specialists from various disciplines to jointly and comprehensively address the multidimensional needs of patients and their families—ranging from physical symptoms to psychological, social, and spiritual support [26]. Numerous studies confirm that the involvement of such a team can significantly improve pain and symptom control, reduce levels of anxiety and depression in patients, increase satisfaction with care, and enhance the overall quality of life [32]. For example, a meta-analysis showed that multidisciplinary palliative care significantly improves the quality of life of cancer patients and reduces their levels of depression and anxiety compared to standard approaches [37]. In clinical practice in developed countries, the team-based approach has become the standard: for instance, the American Society of Clinical Oncology (ASCO) officially recommends the involvement of a specialized interdisciplinary palliative care team for all patients with advanced cancers and high symptom management needs [53]. Similarly, in the United Kingdom, palliative care has historically been built on the collaboration between general practitioners, hospice specialists, and social services, ensuring a holistic approach to alleviating patient suffering. Multidisciplinary teams not only address diverse issues (pain, shortness of breath, nausea, emotional distress, family and spiritual matters) but also assist in making complex decisions, planning the next stages of care, and connecting patients with necessary resources [54]. Ultimately, the interdisciplinary approach enhances the effectiveness of palliative care and its ability to adapt to the unique needs of each patient. This approach is recognized globally as a key factor in the success of palliative programs [26].

Legislative Regulation and Healthcare Strategies

Legislative and regulatory measures over the past decade have played a crucial role in the development of palliative care, solidifying it as an integral part of healthcare systems. An international benchmark was set by the WHO Resolution 67.19, adopted in 2014, which called for all countries to strengthen palliative care as part of universal health coverage throughout life [43]. The resolution included recommendations for developing national policies, funding, workforce training, improving access to opioid analgesics, and integrating palliative care at all levels of healthcare delivery [23].

In response to this call, many countries have taken steps toward institutionalizing palliative care. In developed healthcare systems, palliative care was already largely integrated, but the last 10 years have seen new legislative initiatives and strategies. In the UK, the first national End-of-Life Care Strategy was adopted in 2008, outlining goals to expand hospice and palliative care within the NHS. Subsequent programs like "Ambitions for Palliative and End-of-Life Care" (2015–2020) have aimed to ensure equal access to end-of-life care. Although there is no separate law specifically for palliative care in the UK, regulatory support is provided through its inclusion in the guaranteed NHS package and government support for hospices. At the institutional level, the National Council for Palliative Care oversees policy, and clinical guidelines are developed by entities such as the National Institute for Health and Care Excellence (NICE) [57].

In Germany, a significant step was the adoption of the Federal Hospice and Palliative Care Act (HPG) in December 2015. This legislation officially included palliative

care as part of standard services covered by mandatory health insurance, strengthening support for hospices and home care services. The law requires insurance funds to cover 95% of hospice costs (previously around 90%) and introduced mechanisms for quicker contract agreements between funds and home-based palliative care providers. Additionally, nursing homes are now required to collaborate with hospice services, and inpatient palliative care units are entitled to special reimbursement rates for treatment [40].

In Canada, the passage of the "Framework on Palliative Care in Canada Act" (2017) led to the publication of a comprehensive National Palliative Care Framework in 2018. This framework defined palliative care, established workforce training commitments, and addressed service development across settings (hospital, hospice, home, long-term care) [1]. In subsequent years, Canada's government implemented the Palliative Care Action Plan (2019), investing in hospice expansion, workforce education through Pallium Canada, and access monitoring systems [1].

In Australia, the government developed the National Palliative Care Strategy 2018, a unified plan coordinated between the federal government and states aimed at ensuring all Australians have access to quality palliative care for life-limiting illnesses. This strategy enshrines palliative care as a fundamental part of universal healthcare and sets goals for the next five years, including a monitoring system for implementation [20].

In the United States, although there is no single law guaranteeing palliative care for all citizens, regulatory measures have been introduced to promote its development. A key component is the Medicare hospice benefit, introduced in the 1980s, which covers hospice care for terminal patients over 65. In the last decade, several versions of the PCHETA (Palliative Care and Hospice Education and Training Act) have been presented to Congress, advocating for funding specialist training and research in palliative care. Furthermore, many states have enacted regulations requiring hospitals to inform patients about palliative care options or establish palliative care consultative services in large hospitals [53]. As a result of these policies, by 2019, 72% of U.S. hospitals with 50 or more beds had their own palliative care teams, a significant increase from approximately 53% in 2008 [63].

Overall, the experience of developed countries shows that governmental support and clear policies significantly accelerate the integration of palliative care into healthcare systems. National strategies or legislation (such as those in Germany and Canada) ensure funding, coordination of efforts, and the removal of barriers (e.g., access to opioid analgesics) [34]. However, even wealthy countries continue to face challenges—such as the mismatch between high end-of-life treatment costs and the average quality of palliative care in the U.S.—which highlights the importance of not only funding but also focusing the system on the needs of dying patients [63].

Funding of Palliative Care

The financial and economic models of palliative care organization significantly impact the accessibility and quality of services. International comparative analysis shows that in most countries, palliative care funding is mixed, combining resources from public (or insurance) systems, charitable organizations, and personal funds from patients [62]. Non-governmental sources continue to play a significant role – historically, hospices and palliative care services in many countries originated as initiatives by non-profit organizations and philanthropists and are still partially supported by charitable funds in many places. Meanwhile, government funding is gradually expanding but is rarely strictly tied to objective epidemiological needs, resulting in unevenness and gaps in the financing system [19].

For example, in the UK, considered one of the leaders in palliative care, the state covers about 83% of the costs for palliative consultations in hospitals, approximately 59% of the costs for home-based (domiciliary) care, around 30% of the expenses related to inpatient stays, and only about 23% of the costs for day hospice services. The rest of the financial burden is covered by charitable funds and donations, reflecting the historically established partnership between the NHS and the non-governmental sector in this field [21] .

In Germany, following the 2015 law, almost all basic hospice and palliative care services are financed by mandatory health insurance (statutory Krankenkassen). Insurance funds now reimburse 95% of the costs of inpatient hospices for adults (previously about 90%); additionally, they are required to cover not only personnel costs but also medications and materials for home hospice services. Special palliative care (SAPV) services at home are billed separately, encouraging outpatient providers to enter into contracts with insurance funds [40].

In Canada, funding for palliative care is a shared responsibility between provincial authorities and the federal government, with services for patients generally being free of charge under the universal healthcare system. However, until recently, the volume and quality of services varied significantly across provinces. The implementation of the 2018 National Palliative Care Framework implies federal funding for the development of home care services, training, and research initiatives [1].

In the United States, the funding model differs: hospice care for elderly patients is funded by the government through the Medicare program (fixed daily rates for patients with a life expectancy of six months or less), while palliative care teams for non-terminal patients are funded through regular sources such as insurance companies or directly by hospitals [42] . This has led to the wide development of hospices in the U.S. (in 2018, about 1.55 million patients received hospice services), while outpatient palliative care clinics and hospital-based consultative teams are funded differently, often through hospital budgets, charitable grants, or consultation fees [24]. Recently, new payment models have been developed in the U.S., aimed at promoting early palliative care – for example, pilot projects for simultaneous (concurrent) provision of palliative support alongside oncology treatment with separate payments. However, funding remains fragmented [60].

Australia and New Zealand primarily finance palliative care from public sources within their public health systems, but private charitable organizations (e.g., the Silver Chain Foundation in Australia) also contribute, particularly in the development of home services and hospices [25]. Overall, a common feature of palliative care funding in developed countries is the combination of government guarantees with

support from the third sector. Experts note that payment mechanisms often do not reflect the actual workload of care and patients' needs. For example, funding may be based on fixed rates (per diem in hospices or DRG in hospitals) that do not differentiate patients by the complexity of their cases [49]. Modern studies call for improvements in funding models – introducing payment for the volume of care provided (e.g., by team activity or by needs indicators), avoiding incentives that lead to patient segregation or undesirable administrative decisions [19].

Innovative Technologies and Approaches

In recent years, there has been active implementation of technological and organizational innovations in palliative care, partially accelerated by the COVID-19 pandemic. One of the key trends has been the use of telemedicine in palliative care [4]. The emergence and widespread adoption of modern telecommunications have opened new opportunities for supporting patients who are at home or in remote areas [59]. Studies show that telehealth applications help expand the reach and effectiveness of palliative services, providing consultations and monitoring from a distance [28]. Telemedicine is used for video consultations between patients and palliative care doctors and nurses, remote symptom assessments, psychological support, as well as organizing teleconsultations among specialists (e.g., between oncologists and palliative care experts) [22]. A separate development is telepharmacy, which involves remote monitoring of prescription management and medication intake, particularly relevant for pain management and symptom therapy [39].

A comprehensive 2024 review notes several advantages of telepalliative care: it increases patient access to experts (especially in rural and hard-to-reach areas), reduces the need for exhausting trips for seriously ill patients to clinics, and allows for prompt responses to changes in the patient's condition [35]. At the same time, challenges arise, including the need to train elderly patients in using video communication, ensuring confidentiality and quality of communication, and maintaining the "human" aspect of care when contact is mediated remotely [28].

The COVID-19 pandemic in 2020–2021 dramatically accelerated the adoption of telemedicine: in many hospitals and hospices around the world, the forced shift to remote consultations (due to lockdowns and the risk of infection) proved the viability of this format. After the pandemic, many elements of telecare remained part of routine practice, becoming an important complement to in-person visits [38]. For instance, in the UK and Canada, protocols for remote symptom monitoring for cancer patients receiving palliative care have been developed, while in the USA, the Palliative Care Quality Collaborative (CAPC) issued recommendations on organizing telepalliative visits [15].

In addition to telemedicine, other innovations are emerging in palliative care. The use of mobile applications and wearable devices to track symptoms and medication intake is growing, providing real-time data on patient condition [36]. Some centers (e.g., in Australia) have introduced electronic alert systems to notify palliative care teams about patients admitted to the hospital with an exacerbation of cancer, allowing timely consultation. Automated prescribing systems (triggers) based on electronic health records are being used for the timely referral of patients to palliative care services when certain criteria are met (e.g., repeated hospitalizations, tumor progression) [41]. It is also worth mentioning the development of online educational platforms and resources for caregivers – in recent years, numerous websites and courses have emerged, teaching caregivers palliative care skills at home, psychological support, and legal aspects (such as guardianship, wills, etc.) [44]. These resources are actively developing in Canada and Australia with government support. Finally, experiments with artificial intelligence technologies are beginning to penetrate the field of palliative care, such as using AI for predicting patient needs or identifying hidden symptoms based on voice and video data, although this is still in the research phase [58].

Thus, innovative technologies complement traditional palliative care models, enhancing accessibility, flexibility, and personalization. The key task for the coming years is to develop an evidence base and standards for the application of these technologies (especially telemedicine) in palliative care to maximize their benefits and minimize potential risks. The development of policies and protocols in this area will determine the further trajectory of innovation implementation in palliative care practices [28].

Features of Developed and Developing Countries: Comparison and Trends

Countries with highly developed healthcare systems have accumulated extensive experience in organizing palliative care, which can serve as a benchmark for the rest of the world. For example, the United Kingdom is traditionally recognized as one of the leaders: in 1967, the first modern hospice (St. Christopher's Hospice) opened there, and today the UK ranks first in the world in terms of quality end-of-life care. The British model is characterized by a wide network of hospices (many of which are charitable but receive significant support from the National Health Service), as well as the integration of palliative care teams into hospitals and clinics nationwide. High standards of training, the presence of clinical guidelines (such as those by NICE), and public support for the hospice movement have helped the UK secure its leadership position [16].

Australia and New Zealand are also consistently among the countries with the best palliative care; in the 2021 global ranking, Australia received the highest grade (Grade A), ranking 4th out of 81 countries evaluated. This reflects the success of national strategies, a strong primary care system (where general practitioners participate in palliative care), and attention to rural regions through telemedicine and home care services [10].

Germany has significantly expanded access to palliative care over the past decade. Legislation guarantees funding, and the country has dozens of hospices and specialized units within hospitals. The SAPV (Specialized Outpatient Palliative Care) system ensures the management of seriously ill patients at home across all federal states.

The United States demonstrates a combination of advanced experience and certain shortcomings: on the one hand, many large cancer centers (e.g., MD Anderson, Memorial Sloan Kettering) have exemplary palliative care integration programs, and numerous studies and innovations come from the U.S.; on the other hand, access to services across the country is uneven, and due to

funding peculiarities, there is often an emphasis on expensive treatment until the very end, which impacts the average quality of dying (the U.S. ranks in the middle of global rankings) [12].

Canada's approach is similar to that of the UK, although regional differences exist due to its geographical and federal structure. Overall, all of the mentioned developed countries have national policies, specialized training for doctors and nurses, a wide range of care models (hospital, outpatient, home, hospice), and a focus on early palliative care for cancer patients. Their experience confirms the effectiveness of integrated palliative care: for example, in the UK, there has been a decrease in the proportion of cancer patients dying in hospitals, with an increase in the number of those who can spend their final days at home or in a hospice, which aligns with many patients' preferences. In Germany, the 2015 legislative changes led to an increase in home care services and better coordination between hospitals and hospices [51].

In the U.S., from 2015 to 2019, the coverage of hospitals with palliative care teams increased from 67% to 72%, and the number of hospitalizations accompanied by palliative consultations also increased significantly, linked to efforts by associations to implement quality standards. In Canada, after the launch of the national framework in 2018, there has been increased access to hospices and expanded home care programs, particularly in Indigenous communities and remote areas [31].

Australia reports the implementation of national palliative care standards and the development of outcome measurement systems (e.g., national palliative care indicators monitored by the Australian Institute of Health and Welfare). Thus, developed countries demonstrate that political will and investment in palliative care lead to tangible improvements in clinical practice and patient satisfaction [64].

Progress in palliative care also exists in middle-income countries, but it is more fragmented. According to estimates by WHO and the World Hospice Alliance, 80% of the global need for palliative care is in low- and middle-income countries, but only about 4% of that need is met there. In other words, the overwhelming majority of patients in these countries still do not receive adequate pain relief and other symptom management. While affluent countries meet about half of the needs of the seriously ill (50% of the need), in less wealthy regions, palliative care is often still in its infancy [61].

In countries such as Iran, India, and some African states, palliative care is not yet systematically integrated: services are provided sporadically, covering a narrow circle of patients, and are not effectively incorporated into national healthcare systems [48]. National programs or policies in this area are often absent, access to opioid analgesics is limited due to regulatory barriers, and the training of medical staff is sparse [8], [18].

Nevertheless, the last decade has seen positive shifts. Several middle-income countries have become pioneers at the regional level. For example, Malaysia has incorporated palliative care into its healthcare strategy, developing it at oncology centers, which has enabled services to be provided in some areas of the country. South Africa, one of the leading African countries, has established several hospice care centers, partially relying on NGOs and international support [47]. In Eastern Europe, countries such as Poland, Romania, and Russia have increased the number of hospices and home care teams in recent years, largely due to the enthusiasm of individual organizations and support from churches or philanthropists.

Latin America is also showing progress: in Chile, palliative care for cancer patients was recognized as a patient right in 2020 and included in the guaranteed health coverage package, while Colombia and Argentina are developing national training programs for palliative medicine doctors [14]. Many middle-income countries are adopting WHO's 2014 recommendations, adapting the public health model in the development of palliative care, which includes six key components: political support, funding, workforce training, access to medications, service delivery systems, and monitoring/research [2].

However, significant challenges remain. According to international estimates, there is a shortage of at least 2 million trained specialists globally, with this shortage most acutely felt in middle- and low-income countries [17]. The issue of access to opioid analgesics also remains problematic: despite the easing of some international regulations, in several countries, strict control and concerns over prescribing morphine have led to a decrease in average morphine consumption – from 6 mg per person in 2014 to about 4.5 mg in 2021 (per capita in the hypothetical patient). This indicates insufficient removal of barriers to pain relief [46].

Nonetheless, there is a growing understanding that palliative care is an essential component of the healthcare system, even with limited resources. WHO urges countries to include palliative care in universal health coverage programs and train primary care physicians in basic palliative care skills (the concept of primary palliative care in clinics) [5].

In middle-income countries, the most realistic and sustainable strategy is to develop palliative care at the primary care level – trained general practitioners and nurses can provide basic care, bringing in specialists for more complex cases. This model has been successfully tested in certain provinces of South Africa and India (Kerala state) [45], [11]. On a global scale, ten years after the WHO resolution, experts express disappointment at the pace of progress: according to the World Hospice Alliance, only about 14% of the estimated 60 million people who need palliative care annually receive it [30].

Nonetheless, positive shifts are undeniable – palliative care has firmly entered the global health agenda as a crucial area related to human rights and the right to a dignified life until the end. Accelerating the development of palliative care in middle- and low-income countries is possible with the activation of political will, international support, and the removal of key barriers (regulatory, educational, financial) [13].

Promising trends include expanding social and volunteer support, involving communities and family members in care, creating national palliative care plans (as Kenya and Bangladesh have done in recent years), and integrating palliative care into existing structures, such as oncology clinics and chronic disease services [3].

Conclusion

The international experience of the last decade convincingly demonstrates that palliative care for adult

cancer patients is an essential component of modern oncology and healthcare in general. Developed countries have formed comprehensive clinical models that cover patients at all stages – from outpatient management right after the diagnosis of terminal cancer to home and hospice care in the final stages. Multidisciplinary teams have become the gold standard, providing a holistic approach to patients and their families, improving symptom control, and reducing the burden on the system (more rational use of hospitalizations, preventing crisis situations) [33].

The development of palliative care heavily depends on effective government policies and funding: where palliative care is recognized as a priority (either legislatively or strategically) and is adequately funded, there is a significant increase in services and improved end-of-life quality indicators. On the other hand, gaps in funding and policy absence lead to fragmentation and inequity in access.

Innovations – from telemedicine to new organizational approaches – open new horizons, making palliative care more accessible and convenient for patients, especially in the era of digitization and the lessons learned from the pandemic. The main challenge of the new decade is to spread the successes of palliative care worldwide, overcoming the gap between rich and poor countries. Despite serious challenges (workforce, financial, infrastructure), there is a clear understanding of the way forward: integrating palliative care into healthcare systems, training every doctor in the basics of palliative care, ensuring access to key medications (morphine must stop being a luxury), and engaging society in supporting vulnerable patients. Palliative care, which originated as a humanitarian initiative, has today become an integral part of evidence-based medicine and human rights. The international review shows that with political will, proper planning, and compassion, the suffering of millions of cancer patients can be significantly alleviated, giving them and their families dignity, comfort, and support during the most difficult time of life.

Conflicts of interest

There are no conflicts of interest.

Financial support and sponsorship

No sponsorship or financial support was provided for this study.

Ethical Standards

Ethical approval: Not applicable.

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Received: 15 April 2025 / Accepted: 29 July 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.020

UDC 616.69

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REPRODUCTIVE HEALTH ISSUES AMONG ADOLESCENT AND YOUNG MALE POPULATIONS. PART I

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Abstract

Introduction: Male reproductive health is a critical component of demographic stability and public well-being. Contemporary epidemiological studies indicate a decline in male fertility, with adolescence and early adulthood representing a particularly vulnerable period for the development of reproductive potential. Insufficient awareness, social barriers, and limited access to specialized care exacerbate the risks to male health.

Objective: To identify key factors influencing the reproductive health of adolescent and young males, with a focus on prevention and early correction of disorders.

Search strategy: Following the identification of core keywords and their synonyms, a comprehensive literature search was conducted using international (PubMed, Google Scholar, Embase) and national (Cyberleninka, e-Library) scientific databases, covering publications from the past ten years. Selected sources were evaluated for citation frequency, and abstracts were assessed for thematic relevance. Full texts of studies meeting the inclusion criteria were retrieved for detailed analytical review. Inclusion criteria comprised thematic relevance, publication language (English or Russian), year of publication (from 2015 onward), and coverage of various study types — including original research, reviews, systematic reviews, meta-analyses, clinical guidelines, monographs, and conference proceedings.

Results and Conclusion: In recent decades, Kazakhstan has seen a steady increase in the prevalence of male reproductive disorders, including erectile dysfunction, infertility, and hormonal imbalances. According to a national screening of 25,000 men, ED was identified in 56.3%, reproductive disorders in 30.4%, and STIs in 42.4% of cases. Among adolescents, urological pathologies were detected in 90.3% of cases, emphasizing the importance of early diagnosis. National studies further revealed that over 50% of men in both urban and rural areas experience symptoms of androgen deficiency and sexual dysfunction. Despite the implementation of the state program "Men and Reproductive Health," population coverage remains fragmented, and the need for systematic andrological care continues to grow.

Keywords: *reproductive health, adolescents, male gender, male fertility, erectile dysfunction*

For citation:

Mukhamejan M.B., Alchinbayev M.K., Tabynbaev N.B., Kussainova A.A., Kassym L.T. Reproductive health issues among adolescent and young male populations. Part I // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 154-165. *doi 10.34689/SH.2025.27.4.020*

Резюме

ВОПРОСЫ РЕПРОДУКТИВНОГО ЗДОРОВЬЯ СРЕДИ ПОДРОСТКОВ И МОЛОДЫХ МУЖЧИН. ЧАСТЬ I

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Введение: Репродуктивное здоровье мужчин является важнейшей составляющей демографической стабильности и общественного благополучия. Современные эпидемиологические исследования фиксируют снижение мужской фертильности, при этом подростковый и юношеский возраст представляют собой критически уязвимый период для формирования репродуктивного потенциала. Недостаточная осведомлённость, социальные барьеры и ограниченный доступ к специализированной помощи усугубляют риски для мужского здоровья.

Цель: Оценить ключевые факторы, влияющие на репродуктивное здоровье подростков и молодых мужчин, с акцентом на профилактику и раннюю коррекцию нарушений.

Стратегия поиска: После составления перечня ключевых терминов и их синонимических вариантов был осуществлён комплексный библиографический поиск в международных (PubMed, Google Scholar, Embase) и отечественных (Cyberleninka, e-Library) научных базах данных, охватывающий публикации последних десяти лет. Отобранные источники подверглись оценке по частоте цитирования, а аннотации были проанализированы на предмет соответствия тематике исследования. Полные версии работ, соответствующих установленным критериям, были включены в углублённый аналитический обзор. В критерии отбора входили: тематическая релевантность, язык публикации (английский или русский), дата выпуска не ранее 2015 года, а также охват различных типов исследований — от оригинальных и обзорных статей до систематических обзоров, метаанализов, клинических рекомендаций, научных монографий и сборников тезисов.

Результаты и Заключение: В последние десятилетия в Казахстане наблюдается устойчивый рост распространённости мужских репродуктивных расстройств, включая эректильную дисфункцию, бесплодие и гормональные нарушения. Так, по результатам массового скрининга 25 000 мужчин, ЭД была выявлена у 56,3%, расстройства репродуктивной функции - у 30,4%, а ИППП - у 42,4% обследованных. Среди подростков урологические патологии фиксировались у 90,3% случаев, что подчёркивает важность ранней диагностики. Национальные исследования также показали, что более 50% мужчин в городах и сельской местности сталкиваются с симптомами андрогенного дефицита и сексуальных нарушений. Несмотря на реализацию государственной программы «Мужчины и репродуктивное здоровье», охват населения остаётся фрагментированным, а потребность в системной андрологической помощи продолжает расти.

Ключевые слова: *репродуктивное здоровье, подростки, мужской пол, мужская фертильность, эректильная дисфункция*.

Для цитирования:

Мухамеджан М.Б., Алчинбаев М.К., Табынбаев Н.Б., Кусаинова А.А., Касым Л.Т. Вопросы репродуктивного здоровья среди подростков и молодых мужчин. Часть I // Наука и Здравоохранение. 2025. Vol.27 (4), С. 154-165. *doi 10.34689/SH.2025.27.4.020*

Түйіндеме

ЖАСӨСПІРІМДЕР МЕН ЖАС ЕРЛЕР АРАСЫНДА РЕПРОДУКТИВТІК ДЕНСАУЛЫҚ МӘСЕЛЕЛЕРІ. І-БӨЛІМ

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Кіріспе: Ерлердің репродуктивтік денсаулығы — демографиялық тұрақтылық пен қоғамдық игіліктің маңызды құрамдас бөлігі. Қазіргі эпидемиологиялық зерттеулер ерлердің құнарлылығының төмендеуі үрдісін көрсетіп отыр, ал жасөспірімдік және жастық кезең репродуктивтік әлеуеттің қалыптасуы үшін аса осал кезең болып табылады. Ақпараттың жеткіліксіздігі, әлеуметтік кедергілер мен мамандандырылған медициналық көмектің шектеулі болуы ерлер денсаулығына төнетін қауіптерді күшейтеді.

Мақсат: Жасөспірімдер мен жас ерлердің репродуктивтік денсаулығына әсер ететін негізгі факторларды бағалау, алдын алу және бұзылыстарды ерте түзету шараларына басымдық беру.

Іздеу стратегиясы: Негізгі терминдер мен олардың синонимдерін анықтағаннан кейін соңғы он жылды қамтитын халықаралық (PubMed, Google Scholar, Embase) және отандық (Cyberleninka, e-Library) ғылыми дерекқорларында кешенді әдеби шолу жүргізілді. Таңдап алынған дереккөздер дәйексөз жиілігі бойынша бағаланып, аннотациялары зерттеу тақырыбына сәйкестігі тұрғысынан талданды. Іріктеу талаптарына сәйкес келетін зерттеулердің толық мәтіндері терең аналитикалық шолуға енгізілді. Іріктеу критерийлеріне тақырыптық сәйкестік, жарияланым тілі (ағылшын немесе орыс), 2015 жылдан бастап жарияланған болуы, сондай-ақ зерттеу түрлерінің кең спектрі — түпнұсқа және шолу мақалалар, жүйелі шолулар, метаанализдер, клиникалық ұсынымдар, монографиялар және конференция материалдары кірді.

Нәтижелер мен қорытынды: Соңғы онжылдықтарда Қазақстанда ерлердің репродуктивтік бұзылыстарының, соның ішінде эректильді дисфункцияның, бедеуліктің және гормондық теңгерімсіздіктің таралуының тұрақты өсуі байқалуда. 25 000 ер адамды қамтыған ұлттық скрининг нәтижесінде ЭД 56,3%, репродуктивтік функция бұзылыстары 30,4%, ал ЖЖБИ 42,4% жағдайында анықталған. Жасөспірімдердің арасында урологиялық патология 90,3% жағдайда тіркелген, бұл ерте диагностиканың маңыздылығын көрсетеді. Ұлттық зерттеулер қала мен ауыл

тұрғындарының 50%-дан астамында андроген тапшылығы мен жыныстық дисфункция белгілері бар екенін көрсетті. «Ерлер және репродуктивтік денсаулық» мемлекеттік бағдарламасы жүзеге асырылғанына қарамастан, халықты қамту әлі де бытыраңқы сипатта қалып отыр, ал андрологиялық көмектің жүйелі түрде көрсетілуіне деген қажеттілік өсіп келеді.

Түйінді сөздер*: репродуктивтік денсаулық, жасөспірімдер, ер жынысы, ерлердің құнарлылығы, эректильді дисфункция*.

Дәйексөз үшін:

Мухамеджан М.Б., Алчинбаев М.К., Табынбаев Н.Б., Кусаинова А.А., Касым Л.Т. Жасөспірімдер мен жас ерлер арасында репродуктивтік денсаулық мәселелері. I-Бөлім // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 154-165. *doi 10.34689/SH.2025.27.4.020*

Background

Male reproductive health constitutes an essential dimension of overall population well-being and plays a pivotal role in maintaining demographic sustainability. While maternal health and female reproductive care have long received significant attention in global medical and scientific discourse, male fertility has often remained underrepresented in both research and clinical priorities [69, 7]. Recent epidemiological evidence indicates a concerning global decline in both the quality and quantity of male reproductive function, with far-reaching implications for fertility rates and the health of future generations [46].

According to the World Health Organization (WHO), one in six men worldwide experiences infertility-related issues, and male factors contribute to 40–50% of all cases of childlessness in couples [5]. In Kazakhstan, healthcare records show a growing number of consultations related to sexual dysfunction, varicocele, genitourinary infections, and other conditions that directly or indirectly impair reproductive capacity [2]. Urological disorders during adolescence are frequently overlooked, particularly in rural regions where access to specialized care is limited [32].

Puberty and the development of the reproductive system mark a critical stage in the male life course [8]. It is during adolescence and early adulthood that foundational aspects of fertility are established, hormonal regulation is shaped, and sexual and reproductive behaviors begin to form [4]. However, this period is characterized by high vulnerability to multiple risk factors — including socioeconomic hardship, insufficient sexual education, harmful habits, and early sexual debut [29, 11]. Research shows that adolescents and young men often lack adequate knowledge of reproductive hygiene, STI prevention strategies, and the risks associated with self-treatment [10, 14, 15, 50]. These factors underscore the need for an integrated approach to understanding and addressing threats to male reproductive health, particularly during the early stages of development.

Objective: To identify key factors influencing the reproductive health of adolescent and young males, with a focus on prevention and early correction of disorders.

Search strategy. After formulating the primary search terms along with their synonymous expressions, a comprehensive literature review was carried out using international databases (PubMed, Google Scholar, Embase) and regional Russian-language platforms (Cyberleninka and eLibrary). The search was limited to publications released within the last ten years to ensure the inclusion of up-to-date and relevant data. The selected articles were subjected to bibliographic cross-referencing, including both references cited in the publications and subsequent studies that had cited them. Abstracts were then assessed to determine thematic relevance and compliance with the research focus. Based on clearly defined eligibility parameters, the remaining literature was categorized, and full-text versions were obtained for in-depth analysis. Only validated and methodologically sound studies were included in the final synthesis, as outlined in the search strategy (see Figure 1).

Inclusion criteria encompassed the following: (1) conceptual alignment with the scope of the review; (2) availability in English or Russian languages; (3) publication date from 2015 onward; and (4) coverage of both primary and secondary sources, including systematic reviews, meta-analyses, clinical recommendations, scholarly monographs, and conference proceedings.

Exclusion criteria involved omission of any publications that did not conform to the above inclusion standards.

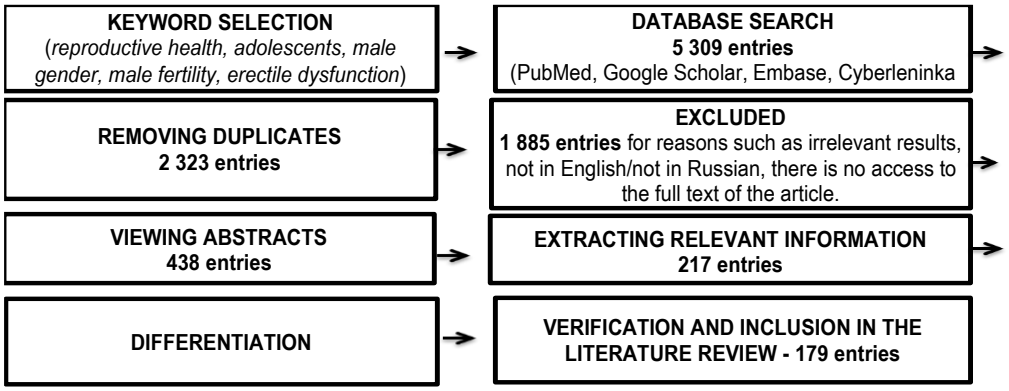


Fig. 1 Search strategy.

The main part

The role of adolescence and early adulthood in shaping male reproductive potential

The concept of reproductive health emerged in international medical and scientific discourse during the 1980s as a response to the growing need for an integrated approach to fertility, sexual well-being, and parental health protection [16]. According to the WHO 1994 definition, reproductive health refers not merely to the absence of disease, but to a state of complete physical, mental, and social well-being in relation to the reproductive system and its functions and processes [6]. However, in the context of ongoing global health challenges, the application of the term “reproductive health” to children and adolescents may be considered insufficiently precise. A more accurate and biologically grounded framework is the notion of “reproductive potential”, which reflects the somatic and psycho-emotional maturity required for future fertility upon reaching biological and social adulthood [9].

Understanding the developmental stages of puberty is essential, especially in light of the updated age classifications proposed by WHO in 2022. This revised categorization defines "adolescents" as individuals aged 10–19, "young people" as those aged 10–24, and "youth" as those aged 15–24 [3]. These categories, developed through broad scientific consensus and aligned with data from international bodies such as the United Nations Population Fund (UNFPA), allow for more precise consideration of biological and psychosocial characteristics across age groups. This framework is particularly relevant for designing reproductive and sexual health programs tailored to developmental needs.

In the context of male reproductive development, adolescence plays a pivotal role [68]. During this stage, the testes begin to function as endocrine and germinative organs. Their internal structure - comprising Sertoli cells, Leydig cells, and peritubular myoid cells - ensures the coordinated progression of spermatogenesis. Sertoli cells, which maintain the internal milieu of seminiferous tubules, are key regulators of spermatogenesis and are responsible for forming the blood–testis barrier that protects germ cells from autoimmune attack [34]. Spermatogenesis is a complex process involving mitosis, meiosis, and spermiogenesis. Concurrently, Leydig cells initiate robust testosterone synthesis, which supports the emergence of secondary sexual characteristics and the hormonal environment necessary for gametogenesis [51].

This maturation process is governed by the hypothalamic–pituitary–gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH), secreted by the hypothalamus, stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH activates Leydig cells to produce testosterone and insulin-like peptide 3 (INSL3), while FSH binds to receptors on Sertoli cells, driving spermatogenic progression [67].

The action of testosterone is mediated through androgen receptors (AR) and operates via genomic and non-genomic mechanisms. In the genomic pathway, the AR–testosterone complex translocates to the nucleus to modulate gene transcription. The non-genomic pathway, activated by low androgen concentrations, involves membrane-associated ARs and downstream signaling cascades such as ERK1/2 and CREB, which influence Sertoli cell function, blood–testis barrier integrity, and germ cell survival [25].

FSH activates intracellular signaling through the cAMP/PKA pathway as well as PI3K/Akt and MAPK cascades. These mechanisms enhance proliferation and differentiation of Sertoli cells, prevent apoptosis, and stimulate the synthesis of growth factors such as GDNF, FGF2, SCF, and BMP4, which are vital for maintaining the spermatogonial stem cell pool. FSH also regulates meiosis and facilitates galectin-3 expression, reducing spermatocyte loss [30].

At the local level, inhibin B and activin A play critical regulatory roles. Inhibin B, produced by Sertoli cells, exerts negative feedback on FSH secretion and serves as a marker of Sertoli cell activity and spermatogenic efficiency [43]. In contrast, activin A promotes FSH synthesis and supports gonocyte proliferation and epididymal development [21]. Dysregulation of these pathways is implicated in reproductive disorders.

Anti-Müllerian hormone (AMH), secreted by immature Sertoli cells, is necessary for Müllerian duct regression during fetal development. Its serum concentration serves as a diagnostic marker of Sertoli cell maturity and is utilized in conditions such as cryptorchidism and anorchia [33].

INSL3, synthesized by Leydig cells, is essential for testicular descent during embryogenesis and protects germ cells from apoptosis. INSL3 levels correlate with Leydig cell functionality and may be used as a biomarker for spermatogenic preservation in the context of hormonal therapy [42].

Although estrogens are traditionally associated with female physiology, their role in male reproductive regulation is increasingly recognized. The enzyme aromatase (CYP19A1), expressed in testicular tissue, converts androgens to estrogens, which are essential for ductal maturation, fluid absorption, and meiotic control. Estrogen imbalance can result in testicular atrophy, germ cell apoptosis, and reduced fertility [39].

Prolactin modulates Leydig cell sensitivity to LH and regulates gonadotropin secretion. Hyperprolactinemia has been linked to impaired spermatogenesis and sexual dysfunction. Although prolactin’s role in male fertility remains under investigation, experimental evidence supports its regulatory importance [59].

Oxytocin, produced by the posterior pituitary, is also found in male reproductive tissues. It contributes to spermiation, enhances contractility of the seminiferous tubules, and stimulates testosterone synthesis. Oxytocin has been shown to increase the expression of proliferative and anti-apoptotic proteins in Sertoli cells [71].

In summary, male fertility is regulated by a complex network of hormonal interactions involving androgens, gonadotropins, inhibins, activins, prolactin, oxytocin, and estrogens. These hormonal factors act in concert to ensure the proper development and function of the male reproductive system. An overview of the key reproductive hormones involved in this regulatory network is provided in Table 1.

Epidemiological assessment of male reproductive disorders: global and Kazakhstani perspectives

Over the past several decades, numerous countries—including Kazakhstan—have reported a progressive deterioration in male reproductive health indicators. The prevalence of conditions such as impaired spermatogenesis, erectile dysfunction (ED), and hormonal imbalance has been steadily increasing. This trend is attributed to a wide range of

contributing factors, including population aging, lifestyle modifications, environmental exposure, and socio-economic challenges. According to the Global Burden of Disease (GBD) study, between 1990 and 2019, the global number of men diagnosed with infertility rose by nearly 77%, reaching approximately 56.5 million. The age-standardized incidence rate climbed to 1402.98 per 100,000 males—19% higher than in 1990. Infertility was most prevalent in regions such as Eastern Europe, East Asia, and Western Sub-Saharan Africa, with the highest rates observed in men aged 30–34 and in countries with moderate to high levels of sociodemographic development [40]

Table 1.

Hormones involved in the regulation of the male reproductive system

Hormone	Secretory regions	Function during puberty	Related diseases
GnRH	Hypothalamus	Stimulates the production of LH and FSH by the pituitary gland, triggers puberty	Hypogonadism, and delayed sexual development [76]
LH	Adenohypophysis (anterior pituitary gland)	Stimulates Leydig cells to produce testosterone	Hypogonadism, infertility [60]
FSH	Adenohypophysis	Stimulates spermatogenesis in the seminal tubules	Oligospermia, azoospermia [25]
Testosterone	Leydig cells (testicles)	Development of secondary sexual characteristics, muscle growth, voice, libido	Hypogonadism, infertility, erectile dysfunction [36]
AMH	Sertoli cells (testicles)	Inhibits the development of the Muller ducts (female reproductive system)	Persistent Muller ducts, intersex conditions [33]
Inhibin B	Sertoli cell (testicles)	Inhibits FSH secretion, participates in regulation of spermatogenesis	Fertility disorders, decreased spermatogenesis [47]
Estrogen	Peripheral aromatization of testosterone	Involved in sperm maturation, maintaining bone density	Gynecomastia, and impaired fertility [39]
Prolactin	Pituitary gland (anterior lobe)	Indirectly affects gonadal functions, modulates testosterone levels	Hyperprolactinemia, decreased libido, infertility [59]
Oxytocin	Hypothalamus, released from the posterior pituitary gland	Promotes orgasm, affects social behavior	Social dysfunction, affective disorders [71]
INSL3	Leydig cell	Regulates testicular prolapse, supports the function of Leydig cells	Cryptorchidism, Leydig cell dysfunction [20]

A systematic review conducted by *Irfan M. et al.* (2020) compared the prevalence and risk factors of male sexual disorders in European and Asian populations. The findings indicated that ED (95.0% vs. 88.8%) and hypoactive sexual desire disorder (HSDD) (81.4% vs. 65.5%) were more frequently reported among Asian men, whereas anorgasmia and premature ejaculation (PE) were more common among European men [41].

In post-Soviet countries, including the Russian Federation, there remains a substantial deficit in public awareness—especially among adolescents - regarding sexual education, family planning, STI prevention, and modern contraceptive methods. This lack of knowledge directly affects the reproductive health outcomes of younger populations. For example, a regional survey conducted in Irkutsk among boys and adolescents aged 7–17 found that 34.2% of respondents exhibited various forms of reproductive pathology. Specifically, delayed puberty, characterized by underdevelopment of secondary sexual characteristics, was diagnosed in 18–32% of adolescents. Among those with hypothalamic syndrome and obesity, 18–32% demonstrated pubertal delay, while 7–12.7% showed signs of pathological gynecomastia, and 2–3.6% were diagnosed with atypical sexual development. Furthermore, around one-third of participants exhibited false testicular retention, wherein testicular descent into the scrotum had not occurred appropriately [9].

An epidemiological study conducted in Kazakhstan in 2007 used standardized questionnaires - namely, the International Index of Erectile Function (IIEF) and the Aging Male Symptoms (AMS) scale—to assess the prevalence of sexual disorders in men. The survey included 2,203 men aged 18 to 74, with 70.4% residing in urban and 29.6% in rural areas. The findings revealed that signs of ED were present in 50.8% of urban and 55.6% of rural respondents, while symptoms suggestive of androgen deficiency were reported by 29.3% and 30.3% of the respective groups [45].

According to a national screening conducted by *Alchinbayev M.* and colleagues (2014), involving 25,000 adult males across Kazakhstan, sexual and reproductive disorders were highly prevalent: ED was identified in 56.3% of participants, reproductive dysfunction in 30.4%, and STIs in 42.4%. A targeted assessment of 26,000 industrial workers showed that reproductive health disorders were present in 63.5% of oil industry employees and 53.2% of those working in the non-ferrous metallurgy sector. Among 3,563 men who underwent comprehensive urological evaluation, 82.3% were diagnosed with at least one condition affecting the reproductive system. The most common diagnoses included chronic prostatitis (33.9%) and benign prostatic hyperplasia (20.1%). Low free testosterone levels were detected in 37.3% of the men. The highest prevalence of chronic prostatitis was recorded in the cities of Aktau (54%), Ust-Kamenogorsk (45%), Taraz (44%), and Astana (42%). During the national “Men’s Health Days” campaign, 458 adolescents were examined, and urological pathologies were identified in 90.3% of them [1].

Collectively, these data illustrate a consistent upward trend in the prevalence of male reproductive dysfunctions, particularly among men aged 30–50 years.

Clinical and non-clinical approaches to diagnosing male reproductive disorders

Organizational aspects of andrological assessment in adolescent and young males

Andrology is a medical discipline that should provide comprehensive monitoring and support for male reproductive health across the entire life span—ideally beginning from the prenatal period and continuing through senescence. This necessity is underscored by the fact that many reproductive, hormonal, genitourinary, sexual, oncological, and psychosocial disorders diagnosed in adult men often have developmental origins in childhood or adolescence, and in some cases, can be traced back to intrauterine or neonatal periods [22]. Without timely diagnosis and routine andrological screening, such conditions may remain undetected and manifest at various stages - before, during, or after puberty - requiring age-specific clinical approaches based on developmental physiology.

Despite this, the coverage of basic urological and andrological services for children, adolescents, and young men remains insufficient. A retrospective study by *Olana S. et al.* (2018) examined male adolescent referrals (ages 10–19) to the andrology department at the Sapienza University Hospital in Rome. Among the 2,855 first-time male patients assessed, only 197 (6.9%) were adolescents. Notably, in 11.7% of these cases, the initial reason for referral was revised following examination—particularly in patients over 15 years old. For 15% of adolescents presenting with sexual complaints, basic education and reassurance were sufficient to alleviate anxiety. Physical examinations proved highly effective, with clinical abnormalities identified in over 60% of adolescent patients, highlighting the importance of routine andrological assessments in this age group [52].

A separate investigation by *Zampieri N.* and *Camoglio F.* (2020), conducted between 2009 and 2019 at a pediatric urology clinic in Italy, emphasized the role of coordinated outpatient services. Their findings pointed to the importance of interdisciplinary collaboration between primary care providers and specialists during both surgical and non-surgical consultations. Within the study period, the clinic managed 1,436 cases of varicocele, 132 cases of webbed penis, 89 cases of penile curvature, 18 cases of gynecomastia, 39 post-hypospadias repair complications, 14 instances of ED, and 47 cases involving obesity and semen abnormalities. The authors stress the significance of specialized andrology clinics staffed by experienced professionals capable of diagnosing and managing conditions that often emerge during adolescence [77].

Particular attention is warranted for boys and young men with chronic somatic illnesses. Delayed puberty, hypogonadism, infertility, and sexual dysfunction are frequently observed in this group, often resulting from the primary disease, its complications, or long-term pharmacotherapy. Hemoglobinopathies, endocrine disorders, gastrointestinal diseases, and renal pathologies are among the most common contributors to compromised reproductive health. Despite being sexually active and concerned about future fertility, this population is frequently overlooked by healthcare providers when it comes to reproductive counseling. Adolescents and young men with long-standing or severe chronic conditions should be referred to multidisciplinary care teams - comprising endocrinologists, andrologists, geneticists, psychologists, and specialized nurses. Emphasis must be placed on education related to contraception, pregnancy, STIs, and infertility, as well as on organizing a structured and patient-centered transition from pediatric to adult healthcare services [31].

In Kazakhstan, the scope and frequency of diagnostic evaluations for urogenital conditions in children and adolescents are regulated by the Order of the Minister of Health of the Republic of Kazakhstan No. ҚР ДСМ-264/2020, dated December 15, 2020. This order outlines the rules, scope, and timing of preventive medical examinations for key population groups, including children in preschool, school, and vocational or higher education institutions. The initial stage of assessment—conducted by pediatricians, general practitioners, or internists—involves genital examinations and assessment of pubertal development using Tanner staging or puberty charts, with classification into normal, advanced, or delayed development. The specialized phase of screening is performed by surgeons (for cryptorchidism), urologists (for urinary and genital abnormalities), and endocrinologists (for pubertal and hormonal disorders). These examinations are conducted in children and adolescents aged 0–18 years, primarily in school or preschool healthcare settings [12].

Among young men of conscription age, military medical commissions serve as a key mechanism for assessing genitourinary health. The surgeon's evaluation includes palpation of the testes and epididymis, assessment of the spermatic cord and prostate, and screening for conditions such as cryptorchidism, hydrocele, testicular tumors, stones, and prostatitis [13].

It is important to recognize that school-based health screenings and military medical evaluations have the potential to identify andrological problems at early stages. However, their effectiveness is often limited by the restricted scope of examinations, shortage of trained specialists, insufficient focus on sexual and reproductive health, and lack of continuity of care through follow-up monitoring and referrals.

Core diagnostic approaches to evaluating male reproductive function

In contemporary andrological practice, diagnostic procedures are most commonly applied in cases involving reproductive dysfunction, erectile and ejaculatory disorders, oncological conditions (e.g., prior to sperm cryopreservation), and endocrine or inflammatory diseases. The standard assessment protocol typically includes a detailed collection of personal and family medical history, a thorough physical examination, and the use of supplemental imaging techniques such as testicular ultrasound, transrectal ultrasonography (TRUS), or Doppler sonography of the reproductive tract. Hormonal profiling is also an essential component of this evaluation, while semen analysis (spermogram) remains the gold standard in laboratory diagnostics of male fertility potential [38].

Although the rise of telemedicine has shifted clinical priorities toward laboratory and imaging-based assessments, in-person consultations involving clinical history and physical examination remain critical. Physical examination plays a particularly vital role in detecting palpable abnormalities in the testes, epididymis, and spermatic cord, as well as identifying clinical varicocele [66].

In young patients, imaging is frequently employed to assess the prostate and scrotal contents. According to *Vespasiani G. et al.* (1991), ultrasonography is an effective diagnostic tool for identifying acute inflammatory conditions in young men and assists in determining appropriate treatment strategies—whether surgical or conservative [74]. However, the indications for ultrasonographic evaluation extend well beyond

inflammatory disease. Transrectal ultrasound (TRUS) is used to: (1) assess prostate volume for diagnostic or preoperative planning; (2) guide prostate biopsies; (3) identify congenital anomalies; (4) investigate infertility; (5) monitor post-surgical outcomes; and (6) conduct follow-up after treatment of prostate tumors. Scrotal ultrasonography is applied to evaluate: (1) testicular trauma or torsion; (2) inguinal or scrotal masses; (3) scrotal asymmetry or swelling; (4) hernias; and (5–6) clinical or subclinical varicocele [49].

Hormonal assessment and therapeutic intervention are essential in the diagnosis and management of andrological disorders in young men. Evaluating the hypothalamic–pituitary–gonadal (HPG) axis through measurement of testosterone and gonadotropins is especially important in cases of suspected hypogonadism [24]. Early identification of hormonal abnormalities can guide timely intervention and enhance fertility outcomes [23]. A typical hormonal panel includes follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, inhibin B, and serum prolactin. These biomarkers, when interpreted alongside clinical findings, aid in differentiating among various endocrine pathologies, such as age-related androgen deficiency, hypogonadotropic or hypergonadotropic hypogonadism (e.g., Kallmann or Klinefelter syndromes), and prolactinomas [26].

Semen analysis is an integral part of the diagnostic process, encompassing evaluation of ejaculate volume, morphology, motility, and biochemical parameters [63]. It is a fundamental method for assessing reproductive potential and identifying subclinical andrological conditions. Research has shown that many young men without overt symptoms may still exhibit semen abnormalities such as teratozoospermia, asthenozoospermia, or oligozoospermia [57]. Furthermore, semen parameters vary with age: adolescents are more likely to present with normozoospermia compared to older men [56]. However, *Tarnovska A.* and *Heneha A.* (2024) emphasize that differences in sperm quality are more closely linked to the presence and combination of risk factors than to chronological age alone [70].

A comprehensive uroandrological screening—consisting of semen analysis, physical examination, and blood tests—can enable early detection of a wide range of pathologies, including hypogonadism, varicocele, and even testicular neoplasms [57]. These findings highlight the importance of an integrated andrological evaluation in young men to ensure timely diagnosis and treatment of reproductive disorders.

Use of questionnaires and surveys in the assessment of male reproductive health and sexual behavior

Structured questionnaires and survey tools serve as critical instruments in systematically assessing male reproductive and sexual health. These tools facilitate the collection of standardized and comparable data concerning individuals' knowledge, attitudes, and practices (KAP), while also identifying psychosocial and behavioral determinants that influence male health outcomes. Their importance is especially pronounced in settings with limited access to healthcare services and where topics related to sexuality remain stigmatized [66]. The insights gained from such assessments provide a foundational basis for the development of targeted educational, preventive, and clinical intervention programs.

Modern andrological research has introduced a range of validated instruments for diagnosing reproductive dysfunction, evaluating risk factors, and monitoring sexual health. One such tool is the Brief Male Sexual Function Inventory (BSFI), which was initially developed to provide normative data on the sexual function of middle-aged men in the United States. The psychometric properties of the BSFI have been thoroughly examined to ensure its reliability and validity, and the tool assesses domains such as libido, erectile capacity, ejaculation, and overall sexual satisfaction [53].

The BSFI has also been used in studies involving men with diverse clinical conditions. For instance, in a study by *Ozumba D. et al.* (2003), 51 men who had previously sustained pelvic fractures completed the questionnaire two years post-injury. Their responses were compared to those of 53 individuals who had experienced ankle fractures. The pelvic trauma group exhibited significantly lower scores across all sexual function domains—libido, erection, ejaculation, and satisfaction—highlighting sexual dysfunction as a frequent and multifaceted consequence of pelvic injury [54].

Subsequently, the BSFI has been translated and culturally adapted for use in various populations and healthcare contexts across multiple countries. Researchers have consistently noted its ease of application and cross-cultural utility in both clinical and research settings [28, 61, 72]. In 2024, Italian researchers extended its application even further by validating the instrument for use among female respondents, thus demonstrating its versatility across sexes and enhancing its relevance in broader sexual health assessments [55].

In the context of adolescent and young male populations, examining literacy, knowledge, attitudes, and behavioral patterns is particularly important for identifying risk factors and designing preventive strategies. Recognizing this, the United Nations' Programme on Human Reproduction launched a multi-country research initiative between 1998 and 1999, aiming to explore sexual and reproductive health issues among adolescents in developing countries. The goal was to generate actionable evidence to inform interventions capable of improving health outcomes. From 1999 to 2001, 38 projects were funded under this initiative, covering themes ranging from sexual safety and autonomy to gender norms, health-seeking behavior, and the perceived quality of care.

As a result, a toolkit entitled *"Asking Young People About Sexual and Reproductive Behaviours: Illustrative Core Instruments"* was developed. This set included standardized survey templates, focus group guides, and in-depth interview protocols designed for adaptation to specific cultural and research contexts. Researchers emphasized the importance of localizing these tools and conducting rigorous pretesting, especially when instruments are translated into new languages [19].

Fergus S. et al. (2007) reported that the peak of risky sexual behavior occurs during adolescence, particularly around ninth grade in the U.S. school system [35]. In India, a large-scale survey involving 1,140 adolescents and young adults in the southern region revealed that 17.6% (n=201) reported risky sexual practices, while 8.7% (n=99) had experienced sexually transmitted infections (STIs), and only 8% demonstrated adequate knowledge of proper condom use [48]. Other Indian studies confirm the rising prevalence of poor sexual health literacy and risky behavior among male youth [64]. Early initiation of sexual activity without sufficient understanding of protection methods significantly increases the likelihood of contracting STIs, including HIV, and raises the risk of unintended pregnancies and sexual violence. Social taboos

and limited access to reliable information further exacerbate these challenges.

Comprehensive behavioral research plays a vital role in identifying knowledge gaps, cultural influences, and behavioral patterns that shape young men's sexual decision-making. Such data are essential for guiding the design of effective, culturally sensitive interventions and health education campaigns [73, 75].

Comprehensive programs and initiatives for the promotion and protection of male reproductive health

In recent decades, the issue of male reproductive health has increasingly gained prominence in both scientific discourse and public health policy discussions. Nonetheless, at the global level, most healthcare and preventive strategies continue to prioritize women, while the reproductive, sexual, and hormonal health needs of men remain largely underrepresented. Various barriers—including persistent social stigma, limited access to specialized services, and insufficient awareness—impede men's engagement with reproductive health services.

A number of countries have launched targeted initiatives to address these gaps. For instance, the U.S. Department of Health and Human Services began promoting male-focused clinical and educational programs in the mid-1990s, emphasizing family planning, prevention of sexually transmitted infections (STIs), and treatment of sexual dysfunctions [27]. A noteworthy example is a male health clinic in New York designed to serve ethnically diverse youth aged 13 to 30, offering services in STI testing, reproductive health education, and psychosocial support [18]. Another significant initiative, "Man2Man" in Philadelphia, fosters responsibility and sexual health awareness among young men through mentorship and peer-led education [65]. In Canada, the "Men's Sheds" movement—originally designed to promote men's mental well-being—has expanded its scope to include STI prevention and sexual health awareness by creating inclusive spaces for social interaction, screening, counseling, and health education [44]. Australia's public health system has adopted a more institutionalized approach through its National Male Health Policy, which promotes holistic programs targeting infertility, hormonal imbalances, erectile dysfunction, and mental health as a determinant of sexual wellness. One of the central pillars of this strategy is ensuring men's active participation at all levels of health promotion, from guideline development to service delivery integration in primary care settings [62].

At the international level, organizations such as the World Health Organization (WHO) have advocated for life-course and interdisciplinary approaches to male reproductive health. According to WHO's Global Reproductive Health Strategy (2022), health systems must guarantee access not only to basic services but also to advanced diagnostics, hormonal treatment, STI management, and fatherhood counseling [37]. For example, in Iran, culturally adapted mobile clinics and awareness campaigns were implemented to integrate men into family planning services [58].

Kazakhstan has also undertaken national-level initiatives to incorporate male reproductive health into its public health framework. The National Health Development Plan of the Republic of Kazakhstan (2020–2025) highlights the importance of andrological care and the prevention of male infertility [12]. A pioneering example is the nationwide initiative Men and Reproductive Health, introduced by Professor M. Alchinbaev. It remains the first and only comprehensive program in Kazakhstan addressing male reproductive diagnostics, prevention, and social-medical support. Based on extensive scientific research, the program led to the establishment of Male Health and Family Longevity Centers (MHFLCs) across the country within primary healthcare institutions. Legal authorization for these centers was granted on January 8, 2014, under Order No. 3 of the Ministry of Health, which mandated the inclusion of urology and andrology specialists in the primary care workforce. Concurrently, a Comprehensive Plan for the Development of Uroandrological Services (2014–2019) was implemented to enhance diagnostics, treatment, and rehabilitation for male patients. Evaluation data from 2013 showed that out of 5,648 men examined, 4,928 were placed under dispensary observation and received treatment. The average age of patients was 42.5 ± 8.4 years. The most successful centers operated in Kyzylorda and Zhambyl regions due to full staff capacity and ongoing public awareness campaigns. Conversely, areas such as Akmola, Almaty, East Kazakhstan, and Mangystau regions experienced lower service utilization due to late program rollouts and limited population awareness [1]. The absence of a sustained follow-up or similar programs in subsequent years underscores the urgent need for a strategic overhaul of male reproductive health policy, with attention to regional disparities in service access and public awareness.

Promising directions include expanding digital tools such as online consultations for men's health, implementing self-testing platforms for STIs, and introducing reproductive health education for boys within school health systems. Crucially, the long-term viability of such programs depends on the meaningful involvement of men as partners, fathers, and citizens in shaping culturally sensitive and gender-inclusive healthcare models.

In summary, the development of holistic, evidence-based programs to support male reproductive health requires cross-sector collaboration, political commitment, and sustained public engagement. A systems-level approach—blending prevention, care, and education—is essential to ensure optimal reproductive well-being for men in Kazakhstan and globally.

Conclusion

Male reproductive health is increasingly recognized as a critical component of public health, yet epidemiological evidence reveals a steady rise in reproductive disorders, including infertility, erectile dysfunction, and hormonal imbalance, both globally and in Kazakhstan. Early-life factors, particularly during adolescence and young adulthood, play a decisive role in shaping long-term reproductive potential, highlighting the importance of age-specific screening and preventive strategies. Despite national efforts, such as screening programs and clinical guidelines in Kazakhstan, access to specialized andrological care remains limited, especially in rural areas and among adolescents. Diagnostic approaches - combining hormonal profiling, physical examination, imaging, semen analysis, and standardized questionnaires - are essential for early detection and intervention. Addressing knowledge gaps and integrating multidisciplinary, youth-focused reproductive health services are key priorities for improving male reproductive outcomes.

Conflict of Interest. *The authors declare that they have no conflict of interest.*

Contribution of authors. *All authors were equally involved in the writing of this article.*

Funding: *No funding was provided.*

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Received: 28 February 2025 / Accepted: 14 July 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.021

UDC 616-008:618.11

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METABOLIC SYNDROME AND ITS ASSOCIATION WITH OVARIAN DYSFUNCTION. LITERATURE REVIEW

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Abstract

Introduction. Metabolic syndrome (MS) – a cluster of conditions like central obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia – increases the risk of cardiovascular disease and type 2 diabetes in women of reproductive age. Its prevalence is rising globally due to poor diets and reduced physical activity. Additionally, ovarian dysfunction conditions such as PCOS, diminished ovarian reserve (DOR), and premature ovarian insufficiency (POI) are increasingly linked to metabolic disturbances. Understanding the connection between MS and ovarian dysfunction is critical to improving reproductive outcomes and reducing long-term health risks.

Aim. This review aims to summarize and critically analyze the current understanding (2020–2025) of the relationship between MS and ovarian dysfunction, emphasizing shared mechanisms, clinical implications, and future research directions.

Material's and method. A targeted literature review was performed using PubMed, ScienceDirect, and PMC databases. Studies published between January 2020 and June 2025, peer-reviewed, and focused on MS and ovarian dysfunction (PCOS, DOR, POI) were included.

Results and Conclusions. Recent research reveals that MS and ovarian dysfunction share common pathophysiological mechanisms, including hyperinsulinemia, adipokine imbalance, chronic inflammation, oxidative stress, and altered hepatic metabolism. Insulin resistance is present even in lean PCOS phenotypes. Mendelian randomization studies suggest a bidirectional causal link between MS and ovarian dysfunction. The coexistence of these conditions impairs fertility, increases pregnancy complications, and elevates long-term cardiometabolic risk. Interventions like lifestyle changes, insulin-sensitizing drugs, and integrated reproductive-metabolic care show promise.

Key words: *metabolic syndrome, polycystic ovary syndrome, diminished ovarian reserve, premature ovarian insufficiency, insulin resistance*

For citation:

Serikbayeva A.T., Khamidullina Z.G. Metabolic syndrome and its association with ovarian dysfunction. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 166-173. *doi 10.34689/SH.2025.27.4.021*

Резюме

МЕТАБОЛИЧЕСКИЙ СИНДРОМ И ЕГО ВЗАИМОСВЯЗЬ С НАРУШЕНИЕМ ФУНКЦИИ ЯИЧНИКОВ. ОБЗОР ЛИТЕРАТУРЫ

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Введение. Метаболический синдром (МС) — сочетание таких состояний, как центральное ожирение, инсулинорезистентность, гипертония, дислипидемия и гипергликемия — повышает риск сердечно-сосудистых заболеваний и диабета 2 типа у женщин репродуктивного возраста. Его распространенность растет в мире из-за неправильного питания и снижения физической активности. Кроме того, состояния овариальной дисфункции, такие как синдром поликистозных яичников (СПЯ), сниженный овариальный резерв (СОР) и преждевременная овариальная недостаточность (ПНЯ), все чаще связаны с метаболическими нарушениями. Понимание связи между МС и овариальной дисфункцией крайне важно для улучшения репродуктивных исходов и снижения долгосрочных рисков для здоровья.

Цель исслендования. Целью данного обзора является обобщение и критический анализ современного понимания (2020–2025) связи между МС и овариальной дисфункцией, с акцентом на общие механизмы, клинические последствия и направления будущих исследований.

Методы. Был проведен целенаправленный обзор литературы с использованием баз данных PubMed, ScienceDirect и PMC. Включены исследования, опубликованные с января 2020 года по июнь 2025 года, рецензируемые и фокусирующиеся на МС и овариальной дисфункции (СПЯ, СОР, ПНЯ).

Результаты и выводы. Последние исследования показывают, что МС и овариальная дисфункция имеют общие патофизиологические механизмы, включая гиперинсулинемию, дисбаланс адипокинов, хроническое воспаление, оксидативный стресс и нарушенный метаболизм в печени. Инсулинорезистентность наблюдается даже у женщин с "тонкими" фенотипами СПКЯ. Исследования Менделевской рандомизации предполагают двустороннюю причинно-следственную связь между МС и овариальной дисфункцией. Совместное существование этих состояний ухудшает

фертильность, увеличивает количество осложнений при беременности и повышает долгосрочные кардиометаболические риски. Обещающие методы вмешательства включают изменение образа жизни, препараты, повышающие чувствительность к инсулину, а также интегрированное репродуктивно-метаболическое лечение.

Ключевые слова: *метаболический синдром, синдром поликистозных яичников, сниженный овариальный резерв, преждевременная овариальная недостаточность, инсулинорезистентность.*

Для цитирования:

Серикбаева А.Т., Хамидуллина З.Г. Метаболический синдром и его взаимосвязь с нарушением функции яичников. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С. 166-173. *doi 10.34689/SH.2025.27.4.021*

Түйіндеме

МЕТАБОЛИКАЛЫҚ СИНДРОМ ЖӘНЕ ОНЫҢ ОВАРИАЛДЫ ДИСФУНКЦИЯМЕН БАЙЛАНЫСЫ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Метаболикалық синдром (МС) - орталық семіздік, инсулинге төзімділік, гипертензия, дислипидемия және гипергликемия сияқты жағдайлардың жиынтығы - репродуктивті жастағы әйелдерде жүрек-қан тамырлары аурулары мен 2 типті қант диабетінің даму қаупін арттырады. Оның таралуы әлемде дұрыс тамақтанбау мен физикалық белсенділіктің азаюына байланысты өсіп келеді. Сонымен қатар, овариальды дисфункция жағдайлары, мысалы, аналық безінің поликситоздылық синдромы (АПС), аналық без резервінің төмендеуі (АРТ) және ерте аналық без жеткіліксіздігі (ЕАЖ) метаболикалық бұзылыстармен жиі байланысты. МС және овариальды дисфункция арасындағы байланысты түсіну репродуктивті нәтижелерді жақсарту және ұзақ мерзімді денсаулық қаупін азайту үшін маңызды.

Зерттеу мақсаты. Бұл шолу мақсаты МС пен овариальды дисфункция арасындағы байланыс туралы қазіргі түсініктерді (2020–2025) жинақтап, сыни түрде талдау жасау, жалпы механизмдер, клиникалық салдарлар және болашақ зерттеулердің бағыттарына назар аудару.

Әдістер. PubMed, ScienceDirect және PMC дерекқорларын пайдаланып мақсатты әдебиет шолуы жүргізілді. 2020 жылдың қаңтарынан 2025 жылдың маусымына дейін жарияланған, рецензияланған және МС пен овариальды дисфункцияға (аналық бездің поликистозды синдромы, аналық бездің резистенттілік синдромы, аналық бәзінің біріншілік жетіспеушілігі) бағытталған зерттеулер енгізілді.

Нәтижелер мен қорытындылар. Соңғы зерттеулер МС пен овариальды дисфункцияның ортақ патофизиологиялық механизмдері бар екенін көрсетеді, оған гиперинсулинемия, адипокиндер дисбалансы, созылмалы қабыну, оксидативті стресс және бауыр метаболизмінің бұзылуы кіреді. Инсулинге төзімділік тіпті «жіңішке» поликистозды аналық без синдромы фенотиптері бар әйелдерде де байқалады. Менделевтік рандомизация зерттеулері МС мен овариальды дисфункция арасындағы өзара байланыстың болатынын көрсетеді. Бұл жағдайлардың бірлесіп болуы ұрпақ өрбіту қабілетіне зиян келтіреді, жүктілік кезіндегі асқынуларды арттырады және ұзақ мерзімді кардиометаболикалық қауіптерді жоғарылатады. Өмір салтын өзгерту, инсулинге сезімталдықты арттыруға арналған дәрілер және интеграцияланған репродуктивті-метаболикалық емдеу сияқты араласу әдістері болашағы бар.

Түйінді сөздер: *метаболикалық синдром, поликистозды аналық бездер синдромы, аналық бездердің төмен резерві, ерте аналық без жеткіліксіздігі, инсулинге төзімділік*

Дәйексөз үшін:

Серикбаева А.Т., Хамидуллина З.Г. Метаболикалық синдром және оның овариалды дисфункциямен байланысы. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 166-173. *doi 10.34689/SH.2025.27.4.021*

Introduction

The global prevalence of metabolic syndrome (MS) is estimated at 20–30% and continues to rise, particularly in low- and middle-income countries, where changing lifestyles contribute to increasing rates of obesity, insulin resistance (IR), and other metabolic disturbances. Among women of reproductive age, this growing metabolic burden is mirrored by a higher incidence of ovarian dysfunction, most notably polycystic ovary syndrome (PCOS), which affects 5–21% of women worldwide. While PCOS has long been recognized as a key reproductive manifestation of MS, emerging evidence highlights important links between MS and other forms of ovarian pathology, including diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI) [1]. This intersection underscores the need for integrated approaches that address both metabolic health and reproductive function, as metabolic management strategies may represent an underutilized opportunity to protect ovarian reserve, extend reproductive lifespan, and improve overall health outcomes in affected women [2].

MS is considered a combination of disorders, the complex of which is associated with an increased risk of cardiovascular disease and diabetes mellitus [3]. Currently, several definitions of MS are used by specialists, including the World Health Organization (WHO), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP

III), and the International Diabetes Federation (IDF). Although there are slight variations between these definitions, they share common components.

By NCEP ATP III criteria (2001, updated 2005) metabolic syndrome is diagnosed when three or more of the following risk factors are present:

- Waist circumference: >102 cm (40 in) in men; >88 cm (35 in) in women (population-specific cutoffs may apply)
- Triglycerides (TG): ≥150 mg/dL (1.7 mmol/L) or on treatment for elevated TG
- HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women or on treatment for low HDL
- Blood pressure: ≥130/85 mmHg or on antihypertensive treatment
- Fasting plasma glucose: ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes [4].

According to IDF, central obesity (defined by waist circumference with ethnicity-specific values) is a required criterion plus any two of the following:

- Triglycerides: ≥150 mg/dL (1.7 mmol/L) or specific treatment
- HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.29 mmol/L) in women or specific treatment
- Blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg or treatment of previously diagnosed hypertension
- Fasting plasma glucose: ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes [5].

The WHO criteria (1999) place greater emphasis on insulin resistance, requiring evidence of insulin resistance (e.g., impaired glucose tolerance, impaired fasting glucose, type 2 diabetes, or elevated insulin levels) plus at least two of the following: obesity (BMI >30 kg/m² or high waist-hip ratio), dyslipidemia, hypertension, or microalbuminuria [6].

Despite slight differences among criteria, the core components of MS remain consistent: abdominal obesity, dyslipidemia, elevated blood pressure, and impaired glucose metabolism [7]. Early identification using standardized diagnostic criteria allows timely lifestyle and pharmacological interventions to reduce the risk of future cardiovascular and metabolic disease [8].

Ovarian Dysfunction

PCOS is the most prevalent cause of anovulatory infertility and metabolic disturbances in women of reproductive age [9]. According to the Rotterdam criteria (2003), PCOS is diagnosed when at least two of the following three features are present, after exclusion of other etiologies (such as thyroid disease, hyperprolactinemia, or congenital adrenal hyperplasia):

- Oligo- or anovulation: Infrequent or absent ovulation, typically manifesting as irregular menstrual cycles.
- Clinical and/or biochemical signs of hyperandrogenism: This includes hirsutism, acne, alopecia, and/or elevated serum androgen levels.
- Polycystic ovarian morphology on ultrasound: Presence of ≥12 antral follicles (2–9 mm) in each ovary and/or increased ovarian volume (>10 mL) [10].

PCOS is a heterogeneous condition, with phenotypes that may or may not exhibit all features, making thorough clinical and laboratory assessment critical [11].

DOR refers to a reduction in the quantity and often quality of oocytes available in the ovaries, leading to reduced fertility potential. Diagnostic markers include low levels of Anti-Müllerian hormone (AMH), elevated levels of Follicle-stimulating hormone (FSH) and low Antral follicle count (AFC) on transvaginal ultrasound (typically <5–7 follicles in total) which are indicative of a decreased follicular pool. DOR may be age-related or occur prematurely due to genetic factors, surgery, chemotherapy, or autoimmune conditions [12].

POI is characterized by early loss of ovarian function before the age of 40, leading to hypoestrogenism and infertility. Diagnostic criteria include elevated gonadotropins (FSH ≥25–40 IU/L on at least two occasions, typically 4 weeks apart), low estradiol levels reflecting ovarian failure to produce estrogen, and amenorrhea or oligomenorrhea (absence of menstruation or irregular cycles for at least 4–6 months). POI may have genetic, autoimmune, or idiopathic causes, and is distinct from natural menopause in its earlier onset and potential for intermittent ovarian activity [13]. PCOS, DOR, and POI represent key forms of ovarian dysfunction, each with unique diagnostic features and clinical implications [14]. Early and accurate diagnosis using validated criteria is crucial for personalized management aimed at preserving fertility, preventing long-term complications, and improving quality of life [15].

Pathophysiological Mechanisms

Insulin resistance, a core feature in up to 80% of PCOS cases, affects both obese and lean women [16]. Compensatory hyperinsulinemia stimulates ovarian theca cells to produce excess androgens and suppresses Sex Hormone-Binding Globulin (SHBG) synthesis, leading to hyperandrogenism and disrupted folliculogenesis [17]. Insulin resistance is defined as the diminished ability of cells in peripheral tissues - such as skeletal muscle, liver, and adipose tissue - to respond effectively to insulin. This leads to compensatory hyperinsulinemia as pancreatic β-cells increase insulin secretion to maintain normoglycemia [18]. In women with MS, IR is not only a driver of hyperglycemia and dyslipidemia, but also a critical factor in disrupting ovarian function. Even in the absence of overt obesity, IR is prevalent among women with PCOS and contributes to the characteristic features of the syndrome [16].

Hyperinsulinemia exerts direct and indirect effects on ovarian steroidogenesis by synergizing with LH on theca cells to stimulate excessive androgen production via upregulation of androgen biosynthesis enzymes, suppressing hepatic SHBG synthesis and thereby increasing free androgens, and impairing granulosa cell function and follicular maturation, which leads to anovulation and accumulation of small antral follicles characteristic of PCOS [19].

While the role of IR is well established in PCOS, emerging evidence suggests its involvement in DOR and POI. Chronic hyperinsulinemia and metabolic stress contribute to oxidative stress and low-grade inflammation, accelerating follicular atresia. Disrupted intraovarian insulin signaling may impair oocyte quality and the survival of primordial follicles, potentially shortening reproductive lifespan. Additionally, IR-associated endothelial dysfunction can impair ovarian blood flow, further compromising follicular health. Although further research is needed, IR

and its metabolic consequences are increasingly recognized as significant factors in early ovarian aging [20].

The coexistence of insulin resistance, hyperinsulinemia, and ovarian dysfunction places women at risk for infertility, pregnancy complications (e.g., gestational diabetes, preeclampsia), and long-term cardiometabolic disease. Early detection and management of insulin resistance are crucial [21, 22].

Interventions targeting insulin sensitivity, including lifestyle modification (weight loss, dietary changes, physical activity) and pharmacotherapy (e.g., metformin), have shown efficacy in improving ovulatory function, reducing androgen levels, and enhancing fertility outcomes, particularly in PCOS [20].

Insulin resistance and compensatory hyperinsulinemia are key pathophysiological mechanisms linking metabolic syndrome and ovarian dysfunction. Understanding these mechanisms is essential for developing effective strategies to preserve reproductive function and prevent long-term metabolic complications in women.

Adipokines play a critical role in the pathophysiology of ovarian dysfunction associated with metabolic syndrome. Leptin, secreted by adipocytes, regulates energy balance and reproductive function, but in obesity and MS, hyperleptinemia and leptin resistance impair the hypothalamic-pituitary-gonadal axis, disrupt granulosa cell steroidogenesis, and reduce oocyte quality [23]. Adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, is reduced in MS, contributing to systemic and ovarian insulin resistance, androgen excess, and anovulation in PCOS. Elevated resistin and visfatin levels in obesity further promote insulin resistance, inflammation, and disrupted ovarian steroidogenesis, while the precise role of visfatin in follicular development remains under study. Additionally, pro-inflammatory cytokines like TNF-α and IL-6 produced by adipose tissue impair insulin signaling, contribute to ovarian stromal fibrosis, and disturb the follicular microenvironment and endometrial receptivity, exacerbating reproductive dysfunction [24].

Studies show that even modest weight loss (5–10% of body weight) in overweight or obese women with PCOS improves menstrual regularity, ovulation, and fertility potential. Adiposity and altered adipokine secretion form a critical mechanistic link between metabolic syndrome and ovarian dysfunction. Recognizing the endocrine role of adipose tissue highlights the importance of comprehensive metabolic management in women with reproductive disorders to optimize both reproductive and long-term health outcomes [25].

Abnormal lipid profiles in MS increase oxidative stress and endothelial dysfunction, potentially reducing ovarian blood flow and follicular health. Additionally, dysregulated liver metabolism - notably nonalcoholic fatty liver disease - is prevalent in PCOS and may exacerbate systemic metabolic disturbances [26]. Dyslipidemia is a common feature of MS, typically characterized by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. **This abnormal lipid profile contributes to:**

- **Lipotoxicity**, where excessive circulating free fatty acids accumulate in non-adipose tissues, including the ovaries, leading to cellular dysfunction and apoptosis.
- **Disruption of steroidogenesis**, as altered lipid availability impairs the synthesis of sex steroids essential for normal follicular development.
- **Endothelial dysfunction**, reducing ovarian blood flow and impairing the follicular environment, further compromising oocyte quality and ovulation [27].

Dyslipidemia, a common component of metabolic syndrome, is typically characterized by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol, and it plays a significant role in ovarian dysfunction. The abnormal lipid profile contributes to lipotoxicity, where excess free fatty acids accumulate in the ovaries, leading to cellular dysfunction and apoptosis. It also disrupts steroidogenesis by impairing the synthesis of sex steroids necessary for normal follicular development, and causes endothelial dysfunction, which reduces ovarian blood flow and compromises the follicular environment, ultimately impairing oocyte quality and ovulation [28].

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. Women with MS exhibit elevated oxidative stress due to chronic inflammation, hyperglycemia, and dyslipidemia.

Key consequences for ovarian function include:

- **Damage to oocytes and granulosa cells**, leading to impaired folliculogenesis and anovulation.
- **Acceleration of follicular atresia**, contributing to diminished ovarian reserve and potentially earlier onset of POI.
- **Altered endometrial receptivity**, reducing fertility potential even if ovulation occurs [29].

Studies in women with PCOS have consistently shown increased markers of oxidative stress, which correlate with hyperandrogenism and insulin resistance, further perpetuating ovarian dysfunction [30].

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is elevated in women with metabolic syndrome due to chronic inflammation, hyperglycemia, and dyslipidemia, and it has significant consequences for ovarian function. This stress damages oocytes and granulosa cells, impairing folliculogenesis and leading to anovulation, accelerates follicular atresia, contributing to diminished ovarian reserve and potentially earlier onset of premature ovarian insufficiency (POI), and alters endometrial receptivity, thereby reducing fertility potential even when ovulation occurs. Studies in women with PCOS consistently demonstrate increased oxidative stress markers that correlate with hyperandrogenism and insulin resistance, creating a vicious cycle that exacerbates ovarian dysfunction [31].

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of MS and is frequently observed in women with PCOS and other forms of ovarian dysfunction.

- **Altered hepatic metabolism of sex hormones:** The liver is essential for the clearance and binding of sex steroids. NAFLD is associated with reduced SHBG production, increasing free androgens and exacerbating hyperandrogenic states in PCOS.
- **Contribution to systemic insulin resistance:** Liver dysfunction aggravates insulin resistance, further impacting ovarian function.

- **Pro-inflammatory cytokine production:** The fatty liver contributes to systemic low-grade inflammation, amplifying oxidative stress and ovarian damage [32].

Non-alcoholic fatty liver disease (NAFLD), often considered the hepatic manifestation of metabolic syndrome, is frequently observed in women with PCOS and other forms of ovarian dysfunction and contributes to reproductive disturbances through several mechanisms. Altered hepatic metabolism of sex hormones in NAFLD leads to reduced production of sex hormone-binding globulin (SHBG), increasing levels of free androgens and worsening hyperandrogenic states characteristic of PCOS. Additionally, liver dysfunction exacerbates systemic insulin resistance, further impairing ovarian function, while the fatty liver's production of pro-inflammatory cytokines amplifies low-grade inflammation, oxidative stress, and subsequent ovarian damage [33].

The interplay of dyslipidemia, oxidative stress, and liver dysfunction not only contributes to infertility through impaired oocyte development and ovulatory dysfunction but also increases the risk of pregnancy complications (e.g., gestational diabetes, preeclampsia) and long-term cardiovascular disease [34]. Management strategies targeting lipid abnormalities, reducing oxidative stress through antioxidant supplementation, and improving liver health (via lifestyle change or pharmacotherapy) have shown promise in improving reproductive outcomes in affected women [35].

Dyslipidemia, oxidative stress, and liver dysfunction are central components linking MS to ovarian dysfunction. Their combined effects disrupt steroidogenesis, folliculogenesis, and oocyte quality, highlighting the need for integrated metabolic and reproductive care in women at risk [36]. Early intervention targeting these mechanisms is essential for preserving fertility and preventing long-term complications.

MS associates with elevated pro-inflammatory cytokines (e.g., CRP, IL-6, TNF-α, CXCL12, MIF, Serpin E1) that disrupt insulin signaling and ovarian steroidogenesis [37].

MS is characterized by a state of persistent low-grade systemic inflammation. Adipose tissue, especially visceral fat, plays a key role in this process by:

- Producing pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1).
- Recruiting and activating immune cells (e.g., macrophages) that amplify inflammatory signaling.
- Promoting oxidative stress and endothelial dysfunction, contributing to metabolic and vascular complications [38].

This inflammatory milieu is closely tied to the progression of insulin resistance and other metabolic abnormalities characteristic of MS.

Chronic inflammation adversely affects ovarian physiology through multiple mechanisms:

- **Disruption of folliculogenesis:** Pro-inflammatory cytokines impair granulosa and theca cell function, inhibiting normal follicular development and promoting atresia.
- **Promotion of hyperandrogenism:** TNF-α and IL-6 can enhance androgen production by theca cells, contributing to the hyperandrogenic state observed in PCOS.
- **Oocyte damage:** Elevated levels of inflammatory mediators and associated oxidative stress compromise oocyte quality, leading to reduced fertility potential.
- **Endometrial effects:** Systemic inflammation alters endometrial receptivity, increasing the risk of implantation failure and pregnancy loss [39].

Chronic inflammation adversely affects ovarian physiology by disrupting folliculogenesis through impaired granulosa and theca cell function [40], promoting hyperandrogenism via increased androgen production by theca cells [41], compromising oocyte quality through elevated inflammatory mediators and oxidative stress [42], and altering endometrial receptivity, which increases the risk of implantation failure and pregnancy loss [43].

In women with PCOS, markers of chronic inflammation—including elevated C-reactive protein (CRP), TNF-α, and IL-6—are consistently reported and correlate with disease severity, insulin resistance, and hyperandrogenism [44].

Role in DOR and POI

Emerging evidence suggests that chronic inflammation may contribute to the accelerated loss of ovarian follicles, leading to diminished ovarian reserve and premature ovarian insufficiency [45].

- Persistent low-grade inflammation can damage ovarian stromal and follicular tissue, accelerating follicular apoptosis [46].
- Autoimmune mechanisms, often linked to inflammatory pathways, are implicated in some cases of POI [47].

Although the exact causal relationships require further study, inflammation appears to be a common thread connecting metabolic dysfunction and early ovarian aging [46].

Emerging evidence suggests that chronic inflammation plays a role in the accelerated loss of ovarian follicles, contributing to diminished ovarian reserve (DOR) and premature ovarian insufficiency (POI). Persistent low-grade inflammation can damage ovarian stromal and follicular tissue, promoting follicular apoptosis and reducing the ovarian follicular pool, while autoimmune mechanisms linked to inflammatory pathways are implicated in certain cases of POI [1]. Although the precise causal relationships remain to be fully clarified, inflammation appears to be a unifying factor that connects metabolic dysfunction with early ovarian aging.

Genetic and Epigenetic Factors

Bidirectional Mendelian randomization studies (2024) support a causal interplay between MS components- waist circumference, triglycerides, HDL, insulin resistance-and ovarian dysfunction [48]. Epigenetic changes in glucose transporters (e.g., GLUT4) and steroidogenic enzymes further link systemic metabolism to ovarian pathology [1].

Genetic susceptibility underlies both metabolic and reproductive traits, and certain genes appear to influence both MS and ovarian dysfunction [49].

- **PCOS and MS shared loci:** Genome-wide association studies (GWAS) have identified genetic variants in loci such as DENND1A, THADA, FSHR, and INSR that are implicated in both PCOS and metabolic traits, including insulin resistance and obesity [50].
- **Genes regulating insulin signaling:** Mutations and polymorphisms in genes involved in insulin receptor function and post-receptor pathways (e.g., INSR, IRS-1, IRS-2) are linked to both MS and ovarian hyperandrogenism [51].
- **Lipid metabolism genes:** Variants in genes involved in lipid handling (e.g., APOE, CETP) may contribute to the

dyslipidemia seen in MS and its association with ovarian dysfunction [1].

While genetic factors do not act in isolation, they set the foundation upon which environmental influences exert their effects, shaping individual susceptibility to both metabolic and reproductive disorders [53].

Genetic factors play a significant role in linking metabolic syndrome (MS) and ovarian dysfunction, as certain genes influence both metabolic and reproductive traits. Genome-wide association studies (GWAS) have identified shared genetic loci such as DENND1A, THADA, FSHR, and INSR, which are implicated in both PCOS and metabolic abnormalities like insulin resistance and obesity. Mutations in genes regulating insulin signaling (e.g., INSR, IRS-1, IRS-2) contribute to both MS and ovarian hyperandrogenism, while variants in lipid metabolism genes (e.g., APOE, CETP) may underlie dyslipidemia and its reproductive consequences [54]. Although these genetic predispositions do not act alone, they provide the basis upon which environmental factors influence individual susceptibility to both metabolic and ovarian dysfunction [55].

Women with DOR exhibit higher rates of hypertension, dyslipidemia, elevated TyG index, and serum homocysteine compared to those with normal reserve. Narrative reviews also highlight adipose dysfunction in POI, including hyperlipidemia and insulin resistance, and underline the potentiating effect of DNA repair gene variants (e.g., BRCA1, MCM8/9) in reproductive age [54].

Ovarian reserve refers to the quantity and quality of a woman's remaining follicles and oocytes, which determine reproductive potential. Key biomarkers of ovarian reserve include serum levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and the antral follicle count (AFC) assessed via ultrasound [55]. In women with MS, these markers are increasingly being studied, with evidence suggesting that metabolic dysfunction may accelerate ovarian aging and deplete the follicular pool [54].

Ovarian reserve, reflecting the quantity and quality of a woman's remaining follicles, is increasingly recognized as vulnerable to the effects of MS, with studies showing that women with MS often have lower AMH levels, higher FSH, and reduced antral follicle count independent of age and BMI [56]. MS contributes to diminished ovarian reserve through insulin resistance and hyperinsulinemia that disrupt folliculogenesis and promote early atresia, chronic inflammation and oxidative stress that damage ovarian tissue, dyslipidemia causing lipotoxicity and mitochondrial dysfunction, and adipokine imbalances that impair oocyte competence [1]. These same mechanisms, along with endothelial dysfunction and epigenetic alterations, may accelerate ovarian aging and contribute to POI, while women with POI often display features of MS, suggesting a bidirectional link. Clinically, these associations underscore the need for early metabolic screening and lifestyle interventions in women with menstrual irregularities or subfertility to protect ovarian reserve and delay ovarian aging. An integrated approach addressing both reproductive and metabolic health is essential to optimize long-term outcomes in this population [57].

Conclusion

Advances in biomarker development, including genetic, epigenetic, metabolomic, proteomic, and imaging markers, offer great potential for early identification and monitoring of metabolic syndrome (MS)-associated ovarian dysfunction, enabling personalized risk assessment and more precise diagnostics. There is an urgent need for large longitudinal and interventional studies to elucidate the natural history of MS-related reproductive disorders and to evaluate the long-term impact of lifestyle, pharmacologic, and reproductive therapies on both fertility and cardiometabolic outcomes. Mechanistic and genetic research focusing on insulin signaling, oxidative stress, adipokines, and androgen pathways, as well as Mendelian randomization and polygenic risk analyses, will help clarify causal links and inform targeted prevention. Finally, integrated care models - combining multidisciplinary teams, digital health tools, and personalized management strategies—are essential to address the complex interplay between reproductive and metabolic health and to optimize outcomes for affected women.

Future progress in addressing MS-associated ovarian dysfunction requires integration of biomarker discovery, rigorous clinical research, and innovative care delivery models. Such strategies will enable earlier detection, better prevention, and more effective treatment of this complex intersection of reproductive and metabolic health.

The evidence points to a robust, bidirectional relationship between metabolic syndrome and ovarian dysfunction, spanning PCOS, DOR, and POI. Underlying mechanisms include insulin resistance, adipokine dysregulation, inflammation, oxidative stress, liver metabolism, and genetic/epigenetic drivers. Clinically, this interplay exacerbates infertility and long-term metabolic risk. Effective care requires integrated metabolic and reproductive strategies emphasizing lifestyle change, targeted pharmacotherapy, fertility monitoring, and cardiovascular risk management. Future discovery hinges on refined biomarkers, targeted interventions, and integrated clinical care pathways.

Contributors. *All the authors equally participated in the selection, assessment, and analysis of the selected studies. All of them have approved the final article.*

Conflict of interest. *The authors declared no potential conflicts of interest with respect to the authorship, research, and publication of this article.*

Funding. *The authors received no financial support for the authorship, research, and publication of this article*

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Received: 02 April 2025 / Accepted: 29 July 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.022

UDC 616.24

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PATHOLOGICAL CHANGES IN LUNG TISSUE UNDER THE INFLUENCE OF ELECTRONIC CIGARETTES. LITERATURE REVIEW.

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Abstract

Background: Electronic cigarettes (e-cigarettes) have gained substantial popularity worldwide, particularly among adolescents and young adults. Their aerosols contain nicotine, flavoring agents, propylene glycol, glycerol, and thermal degradation by-products capable of reaching the distal airways and inducing inflammatory, fibrotic, and potentially precancerous alterations. Coordinated public health measures are necessary to mitigate the global burden of e-cigarette–related respiratory disease.

Aim: To synthesize current evidence on morphological changes in lung tissue following exposure to e-cigarette aerosols.

Search strategy: A literature review was conducted using PubMed, Scopus, Google Scholar, and e-Library databases for studies published between from 2015 to March 2025. Search terms included “electronic nicotine delivery systems,” “vaping,” “lungs,” “morphology,” and “oxidative stress.” Eligible publications comprised systematic reviews and original research in English and Russian.

Results: Data analysis revealed a marked increase in e-cigarette use over the last decade. Given the direct inhalation route, pathological changes predominantly occur in lung tissue, including acute epithelial injury, chronic inflammation, and fibrotic remodeling.

Conclusions: E-cigarette aerosols exert deleterious effects on the respiratory system, with potential mechanisms involving oxidative stress, pro-inflammatory cytokine activation, and suppression of DNA repair. Further morphological and immunohistochemical studies are warranted to elucidate long-term pulmonary consequences.

Keywords: *electronic nicotine delivery systems; vaping; lung pathology; inflammation; fibrosis; oxidative stress.*

For citation:

Tatykayeva U.B., Abdullayeva A.A., Sadykova K.Zh., Apbassova S.A., Apbassova M., Nuskabaeva G.O., Nurdinov N.S. Pathological changes in lung tissue under the influence of electronic cigarettes. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 174-182. *doi 10.34689/SH.2025.27.4.022*

Резюме

ПАТОМОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ЛЁГОЧНОЙ ТКАНИ ПРИ ВОЗДЕЙСТВИИ ЭЛЕКТРОННЫХ СИГАРЕТ. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. В современном мире электронные сигареты, или вейпы, стали очень популярными, особенно среди лиц молодого возраста. Аэрозоль электронных сигарет содержит никотин, ароматизаторы, пропиленгликоль, глицерин и продукты термического разложения, способные проникать в глубокие отделы легких и способны вызывать воспалительные и даже предраковые изменения. Международные и национальные усилия по профилактике курения электронных сигарет необходимы для снижения заболеваемости и смертности от болезней дыхательной системы во всем мире.

Цель исследования: Обобщить данные о морфологических изменениях в легочной ткани, выявленных при воздействии аэрозоля электронных сигарет

Стратегия поиска: Мы проанализировали систематические обзоры и оригинальные исследования с использованием международных англо- и русскоязычных баз данных, включая PubMed, Scopus, Google Scholar и eLibrary. Поиск охватывал публикации с 2015 по март 2025 года и проводился с использованием ключевых слов: «электронные системы доставки никотина», «вейпинг», «лёгкие», «морфология», и «оксидативный стресс».

Результаты: Анализ литературы позволил сделать выводы о значительном росте употребления электронных сигарет за последнее десятилетие. Учитывая что аэрозоли электронных сигарет попадают сначала в дыхательную систему, основные повреждения наблюдаются в легочной ткани.

Выводы: Проведенный нами обзор научной литературы указывает на негативное влияние употребления электронных сигарет на дыхательную систему, включая острые повреждения, хронические воспалительные и фиброзные изменения в легких. Возможными молекулярными механизмами повреждения являются оксидативный стресс, активация провоспалительных цитокинов, подавление репарации ДНК. Подчеркивается необходимость дальнейших морфологических и иммуногистохимических исследований для оценки долгосрочных последствий использования электронных сигарет.

Ключевые слова: *электронные системы доставки никотина, вейпинг, лёгкие, морфология, воспаление, фиброз, оксидативный стресс.*

Для цитирования:

Татыкаева У.Б., Абдуллаева А.А., Садыкова К.Ж., Апбасова С.А., Апбасова М., Нускабаева Г.О., Нұрдинов Н.С. Патоморфологические изменения лёгочной ткани при воздействии электронных сигарет. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С.174-182. *doi 10.34689/SH.2025.27.4.022*

Түйіндеме

ЭЛЕКТРОНДЫҚ ТЕМЕКІЛЕРДІҢ ӘСЕРІНЕН ӨКПЕ ТІНІНДЕГІ ПАТОМОРФОЛОГИЯЛЫҚ ӨЗГЕРІСТЕР. ӘДЕБИЕТТІК ШОЛУ.

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Өзектілігі. Қазіргі уақытта электрондық темекілер немесе вейптер, әсіресе жастар арасында, кеңінен таралған. Электрондық темекінің аэрозолі никотинді, хош иістендіргіштерді, пропиленгликольді, глицеринді және жылулық ыдырау өнімдерін қамтиды, олар өкпенің терең бөлімдеріне еніп, қабыну және тіпті обырға дейінгі өзгерістер тудыруы мүмкін. Дүниежүзілік деңгейде тыныс алу жүйесі ауруларының сырқаттанушылығын және өлім-жітімін төмендету үшін электрондық темекі шегудің алдын алуға бағытталған халықаралық және ұлттық шаралар қажет.

Зерттеу мақсаты: Электрондық темекі аэрозолінің әсерінен анықталған өкпе тініндегі морфологиялық өзгерістер жөніндегі мәліметтерді жинақтау.

Іздеу стратегиясы: PubMed, Scopus, Google Scholar және eLibrary сияқты халықаралық ағылшын- және орыс тіліндегі деректер базасын пайдалана отырып, жүйелі шолулар мен түпнұсқа зерттеулер талданды. Іздеу 2015 жылдан 2025 жылдың март айына дейінгі жарияланымдарды қамтыды және келесі кілт сөздер қолданылды: «никотинді жеткізуге арналған электрондық жүйелер», «вейпинг», «өкпе», «морфология», «оксидативтік стресс».

Нәтижелер: Әдебиеттерді талдау соңғы он жылдықта электрондық темекіні қолданудың айтарлықтай өскенін көрсетті. Электрондық темекі аэрозолі алдымен тыныс алу жүйесіне түсетіндіктен, негізгі зақымданулар өкпе тінінде байқалады.

Қорытындылар: Ғылыми әдебиеттерге жүргізілген шолу электрондық темекі қолданудың тыныс алу жүйесіне теріс әсерін көрсетеді, оған жедел зақымданулар, созылмалы қабыну және өкпедегі фиброздық өзгерістер жатады.

Зақымданудың ықтимал молекулалық механизмдері — оксидативтік стресс, қабынуға қарсы цитокиндердің белсенуі, ДНҚ репарациясының тежелуі. Электрондық темекіні қолданудың ұзақ мерзімді салдарын бағалау үшін морфологиялық және иммуногистохимиялық зерттеулерді жалғастыру қажеттілігі атап өтіледі.

Түйінді сөздер: *никотинді жеткізуге арналған электрондық жүйелер, вейпинг, өкпе, морфология, қабыну, фиброз, оксидативтік стресс.*

Дәйексөз үшін:

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Introduction

In the modern world, the frequent use of electronic cigarettes (e-cigarettes) and vaping devices has become commonplace, especially among adolescents and young adults. In 2011, there were approximately 7 million users worldwide; however, this number steadily increased to 68 million in 2020, and by 2021 it had already reached 82 million adult users [1; 16].

Survey data on e-cigarette users were available for 49 countries, covering 2.8 billion adults, but were unavailable for another 2.9 billion. Given that information on vaping was provided for only half of the world's population, it can be assumed that the actual number of e-cigarette users is significantly higher. Moreover, the pronounced annual growth rate raises concerns regarding their adverse effects on the respiratory system and other organ systems [1; 16].

Key reasons for the active spread of vaping among young people include the perception of e-cigarettes as fashionable, high-tech accessories, as well as the widespread belief that they are less harmful than traditional tobacco products. Additionally, such devices are often used as a means of reducing dependence on conventional cigarettes during smoking cessation attempts [14].

Search strategy: A comprehensive literature review was conducted using international English- and Russian-language databases, including PubMed, Scopus, Google Scholar, and eLibrary. The search strategy covered publications from 2015 to March 2025, using the keywords "electronic nicotine delivery systems," "vaping," "lungs," "morphology," and "oxidative stress." Articles were systematically analyzed, and 42 studies meeting predefined criteria were selected for in-depth analysis from the PubMed database (Figure 1).

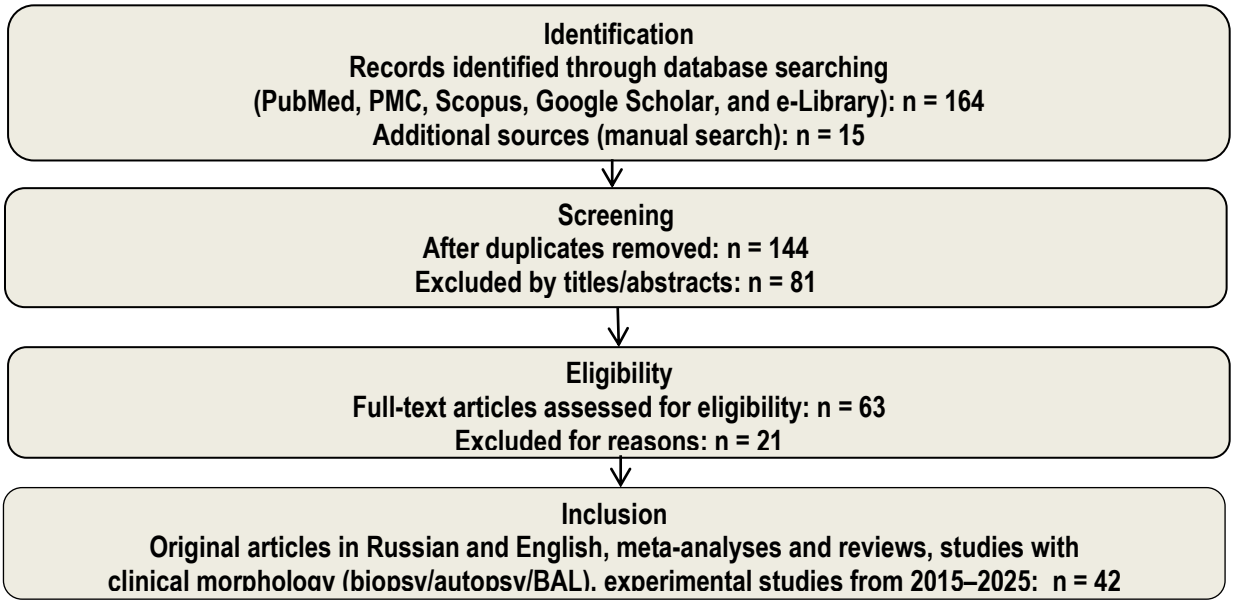


Figure 1. Selection table of articles included in the analysis.

Inclusion criteria: original articles in Russian and English, meta-analyses, and reviews; both clinical morphological studies and experimental animal research assessing morphological changes in lung tissue.

Exclusion criteria: articles without full text, duplicate publications, or studies lacking relevant abstracts; articles exclusively focused on conventional smoking.

The number of publications directly related to the topic under study is relatively limited. In preparing this review we have only included sources from international databases, which explains the relatively small number of sources. During the preparation of this review, we focused on relevant publications from recent years in order to provide a current understanding of issue. Despite this limited literature, our analysis has allowed us to identify key trends and gaps in existing knowledge.

Discussion

Global and Regional Trends in E-Cigarette Use

In recent years, the use of e-cigarettes and vaping among the general population has been growing rapidly.

According to the Global Youth Tobacco Survey (GYTS), conducted in 68 countries from 2012 to 2019, the average

prevalence of e-cigarette use in the past 30 days among adolescents aged 12–16 years was 9.2%, with the lowest rate recorded in Kazakhstan (1.9%) and the highest in Guam (33.2%) (Figure 2) [32].

The latest GYTS data for Kazakhstan (2018) report that approximately 3.1% of adolescents aged 11–15 had used e-cigarettes in the past month, with 4.6% among boys and 1.6% among girls. Additionally, 9.4% had tried e-cigarettes at least once [17].

In Europe, according to a review encompassing data from 75 countries, the average prevalence of e-cigarette use among adolescents aged 13–15 years was 10.9%, while 20.2% had tried them at least once [31]. Rates varied widely, from 5.5% in Serbia to 41.4% in Monaco [2]. In England, up to 30% of 15-year-old girls had used e-cigarettes, compared with an EU average of approximately 21% [41].

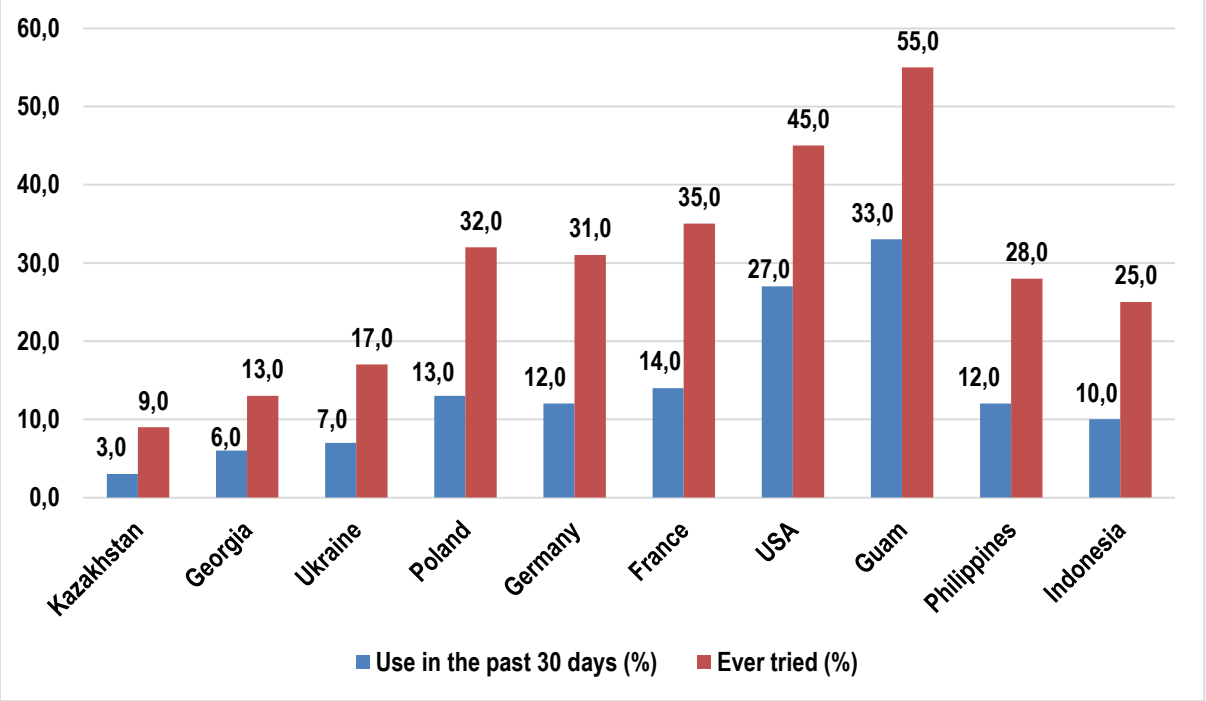


Figure 2. Prevalence of e-cigarette use among adolescents (GYTS) [32].

In the United States, the 2024 National Youth Tobacco Survey (NYTS) reported that 5.9% of middle and high school students had used e-cigarettes in the past 30 days. Of these, 38.4% used the device on ≥20 days per month, and 26.3% used them daily [34]. Among older cohorts, the rates were even higher: among high school students who had ever tried vaping, 49.5% had used e-cigarettes in the past 30 days, and 22.8% used them regularly (≥20 days) [29].

Thus, despite regional differences, e-cigarettes are currently one of the most common forms of nicotine products among adolescents. These trends require special attention, as vaping is associated with the risk of developing a range of pathological changes in the respiratory system, including acute and chronic lung injury.

Composition of E-Cigarette Aerosols

E-cigarettes are portable devices that heat and vaporize liquids, allowing the user to inhale aerosols [12]. The liquid typically consists of propylene glycol, glycerol, flavorings, and—most often—nicotine [19]. In some cases, the liquid may contain tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis.

When heated, the liquid produces an inhalable aerosol. Studies have shown that e-cigarette aerosols contain heavy metals and volatile organic compounds, which may originate from both the liquid and the metallic heating elements of the device. Notably, except for cadmium, metal levels in e-cigarettes often exceed those in conventional tobacco products.

Toxic substances identified in aerosols include acenaphthylene, acetone, benzene, formaldehyde, nitrosonornicotine, and specific tobacco-specific nitrosamines. The long-term effects of these components on human health remain incompletely understood and are the subject of ongoing research [8; 24].

The composition of aerosols varies considerably depending on the manufacturer, device brand, and liquid source. This is especially relevant for homemade mixtures or products purchased on the illicit market, including online sources. E-cigarettes are also frequently used to inhale psychoactive substances, most commonly THC and cannabidiol (CBD) oils, but sometimes also hazardous narcotic compounds such as synthetic cathinones, cocaine (benzoylmethylecgonine), GHB (gamma-hydroxybutyric acid), heroin, fentanyl, MDA, MDMA, and methamphetamine [4; 28].

Acute Lung Injury (Clinical Studies)

Since the early 2010s, e-cigarettes and vaping devices have been actively promoted as a less harmful alternative to conventional smoking. However, as early as 2014, experts from the World Health Organization (WHO) warned that the level of scientific evidence regarding their safety and their effectiveness in combating nicotine addiction remained insufficient. The WHO officially stated that electronic devices cannot be considered a safe replacement for conventional cigarettes [40].

As these devices gained popularity, studies began to emerge that questioned their relative harmlessness. For

example, in May 2019, results from an in vitro laboratory experiment showed that exposure to aerosols from smokeless devices (such as IQOS) exerted a negative impact on lung epithelial cells, comparable to the harm caused by tobacco smoke [30].

Particular concern arose with a sharp increase in cases of acute respiratory illness recorded in the summer of 2019 in the United States. At that time, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) reported the first cases of severe lung injury in e-cigarette and vaping users. This condition was later given the official name **EVALI** (E-cigarette or Vaping product use-Associated Lung Injury), marking the beginning of a new area of clinicopathological research [26].

According to CDC data, by December 2019, there had been 2,409 confirmed cases of EVALI (also known as VAPI — Vaping-Associated Pulmonary Injury) in the United States. A significant proportion of these cases exhibited severe disease, and in 52.2% a fatal outcome was recorded. The epidemic encompassed a broad spectrum of vaping-related lung pathologies, prompting active study of both clinical manifestations and mechanisms of lung injury associated with e-cigarette use [9].

In most cases, morphological and imaging findings in vaping-associated lung injury indicate the development of organizing pneumonia and diffuse alveolar damage [10;11;18]. The morphological pattern varies depending on the stage of the disease at the time of biopsy. In addition to these common patterns, other less frequent types of injury have been described in the literature, such as acute eosinophilic pneumonia and diffuse alveolar hemorrhage [11;18].

Reagan-Steiner S. et al. (2020) examined autopsy material (n = 13) and biopsy specimens (n = 10) from individuals with a history of e-cigarette or vaping use. Of these, 21 cases met the criteria for EVALI, while the remaining two were considered clinically suspected EVALI. Histological examination revealed that all lung biopsies and 9 of the 13 autopsies demonstrated patterns of acute and subacute lung injury, including diffuse alveolar damage or organizing pneumonia [27].

In 2020, *Mukhopadhyay S. et al.* analyzed lung biopsies from 8 patients with vaping-related lung disease. Histological features were characterized by acute lung injury patterns, such as diffuse alveolar damage and organizing pneumonia, evidenced by fibrinous exudates, hyaline membranes, fibroblastic plugs, type II pneumocyte hyperplasia, and interstitial organization. Notably, there were no signs typical of exogenous lipoid pneumonia. In isolated cases, a mild interstitial chronic inflammatory infiltrate was observed [22].

In patients with chronic obstructive pulmonary disease (COPD), e-cigarettes stimulate neutrophilic inflammation and lung injury, accelerating disease progression [3; 23].

According to a 2019 study conducted in Wisconsin and Illinois, bronchoalveolar lavage (BAL) from 43 patients revealed lipid-laden macrophages (endogenous lipoid pneumonia). However, this finding is nonspecific, as it can also be observed in other conditions such as lung cancer, pulmonary tuberculosis, and fungal pneumonia. Histological examination of biopsy material showed mild nonspecific inflammation, organizing pneumonia, bronchiolitis with organizing pneumonia, acute diffuse alveolar damage, foamy macrophages, and interstitial and peribronchiolar granulomatous pneumonitis [20].

Most cases of lung injury were associated with products containing THC or other cannabinoids. Biopsies revealed nonspecific signs of acute lung injury with accumulation of foamy macrophages, predominantly in the small airways. Lipid-laden macrophages are often present in BAL but are nonspecific and should not be used for definitive diagnosis. There are no specific morphological markers for EVALI; diagnosis requires clinicopathological correlation and exclusion of other etiologies [5].

Thus, EVALI is diagnosed by exclusion: there must be a documented history of e-cigarette use within the past 90 days, no alternative cause of lung injury (including infectious, toxic, and autoimmune diseases), and pathological changes on chest CT [10; 11; 18].

Pathomorphological variants of lung changes associated with e-cigarette use, according to histological studies, are presented in Table 1 [11;26].

Table 1.

Pathomorphological changes in the lungs of patients with vaping-associated lung injury [11, 26].

BAL cytological findings	Histological findings (transbronchial biopsy)	Histological findings (surgical biopsy)
• Lipid-laden alveolar macrophages • Foamy macrophages • Predominant neutrophils • Predominant eosinophils • Hemorrhagic secretions / hemorrhagic exudate	• Acute alveolitis with intra-alveolar fibrosis • Diffuse alveolar damage (DAD) • Organizing pneumonia (OP)	• Organizing pneumonia (OP) • Respiratory bronchiolitis–associated interstitial pneumonitis (RB-associated pneumonitis) • Desquamative interstitial pneumonia (DIP) • Diffuse alveolar damage (DAD) • Lipoid pneumonia

Experimental Animal Studies

According to experimental research, e-cigarettes lead to infiltration of lung tissue by eosinophils, erythrocytes, and mononuclear cells, thickening of interalveolar septa, and hyperemia. Collagen deposition - is also observed within interalveolar septa and in the peribronchial region. It is most likely that exposure to nicotine in the form of e-cigarettes induces degeneration of lung tissue, collagen deposition, activation of eosinophils and myofibroblasts, and angiogenesis. These architectural changes impair gas exchange in specific areas [37].

Exposure to nicotine-free e-cigarette liquid composed of glycerol and propylene glycol may result in areas of emphysematous alveolar enlargement, thickening of interalveolar septa, and the phenomenon of plasma imbibition, leading to consolidation of lung tissue [35].

Pikalyuk V.S. et al. (2016) studied the lung structure of Wistar rats exposed to aerosol from nicotine-free e-cigarette liquid in acute (7 days), subacute (30 days), and chronic (60 days) periods. In the acute stage, lung tissue exhibited signs of atelectasis, pronounced inflammatory changes in the bronchi, swelling of interalveolar septa, and accumulation of serous fluid in alveolar spaces. In the subacute stage, an increase in emphysematous transformation of alveoli was noted, along with persistent septal edema and inflammatory response from the bronchial tree. In the chronic stage, morphological changes were dominated by emphysema: thinning of interalveolar septa and expansion of terminal and respiratory bronchioles [25].

In a mouse study, inflammatory cytokine levels and morphological changes in lung tissue were analyzed after three weeks of exposure to e-cigarette aerosol (ECA) and cigarette smoke (CS) separately. Both ECA and CS exposure led to an increase in BAL cellularity; however, pronounced morphological changes—such as infiltration and thickening of interalveolar septa—were more pronounced with CS exposure. In addition, the authors recorded an increase in fibrotic changes in lung tissue, which potentially worsens the course of chronic obstructive pulmonary disease (COPD) due to a decrease in its elasticity and deterioration of external respiratory function. Overall, both exposures caused inflammation and morphological deterioration of the lungs, but the degree of negative change was less pronounced with ECA compared to CS [7].

Research has shown that in COPD, e-cigarette aerosol exacerbates inflammation and promotes pulmonary fibrosis [13].

One-month exposure to e-cigarettes resulted in dystrophic changes in epithelial and endothelial cells, accompanied by reduced collagen and elastin fibers in the extracellular matrix. With prolonged exposure (three months), marked structural alterations were observed: the alveolar membrane became anucleate, endothelial cells were absent, indicating destruction of the extracellular framework. Alveolar spaces were dilated and filled with edematous exudate, and alveolar walls lost their integrity. These changes caused stretching and deformation of interalveolar septa [42].

Molecular and immune mechanisms

In a mouse study, levels of inflammatory cytokines and morphological changes in lung tissue were analyzed after three weeks of exposure to e-cigarette aerosol and to cigarette smoke. Both exposures produced increases in IL-6 and TNF-α in bronchoalveolar lavage fluid (BALF), as well as increased IL-6 in serum; a significant rise in serum TNF-α was observed predominantly in the CS group [7].

Studies indicate that in chronic obstructive pulmonary disease (COPD) models, e-cigarette aerosol modulates pulmonary immune responses and cytokine production. In mice with COPD, exposure to e-cigarette aerosol was associated with elevated levels of several anti-inflammatory cytokines and an increased number of macrophages of the M2 phenotype, which are linked to inflammation regulation. Increased production of multiple cytokines—including M-CSF, IL-1 receptor antagonist (IL-1rα), IL-10 and TGF-β1—was detected in BALF of mice exposed to e-cigarette aerosol, suggesting a shift toward an anti-inflammatory/regulatory microenvironment under certain exposure conditions [13].

Rats exposed to e-cigarette vapor for six weeks showed significantly higher serum concentrations of inflammatory markers (including IL-2, IL-6, IL-9, IL-22, GM-CSF and TNF-α) compared with animals exposed to tobacco smoke or with controls. These findings indicate differences in systemic immune responses that may be important for understanding mechanistic distinctions between vaping and conventional smoking in terms of pulmonary and systemic inflammation [38].

Lee H.W. et al. reported that chronic exposure to e-cigarette aerosol can reduce DNA repair activity and the expression of DNA repair proteins XPC and OGG1/2 in lung tissue, which may have implications for genomic stability and carcinogenesis risk [21].

Acute exposure to e-cigarette aerosol induces oxidative stress in the lung without necessarily producing immediate structural alterations or a marked inflammatory infiltrate. Redox-proteomic analyses have revealed site-specific oxidation of protein thiols caused by acute e-cigarette exposure [36].

Ween M.P. et al., using cultured bronchial epithelial cells, found evidence of airway epithelial cell death, apoptosis, and macrophage efferocytosis mediated by alterations in receptor expression [39].

In an in vitro model of small-airway epithelium exposed to aerosols from capsule-type ENDS (electronic nicotine delivery systems), prolonged device use or device aging was associated with increased oxidative stress, cellular senescence, and DNA damage—likely related to heightened exposure to hazardous aerosols and metal particulates [15].

The principal data on exposure doses and durations and corresponding morphological changes are summarized in the following table (Table 2).

Conclusions

Taken together, the results of preclinical and clinical studies indicate that e-cigarette aerosol produces structural and inflammatory alterations in the lungs that are similar to those observed after exposure to tobacco smoke, while also exhibiting distinct features. The presence of oils, flavoring agents and other additives contributes to the development of lipoid pneumonia and to impaired function of alveolar macrophages. It is particularly concerning that even nicotine-free liquids may provoke inflammation and oxidative stress.

Based on the reviewed evidence, it is advisable that adolescents, young adults and pregnant women refrain from using e-cigarettes. This review synthesizes current data on the morphological characteristics of EVALI and underscores the need for further research to clarify pathogenic mechanisms, improve differential diagnosis, and develop therapeutic approaches for this condition.

Table 2.

Morphological changes in the lungs of animals after exposure to e-cigarette aerosols.

No.	Reference (selected)	Animal model	Duration	Dose / aerosol parameters	Main morphological changes
1	Pikalyuk V.S. et al. (2016) [25]	Rats	7 / 30 / 60 days	4 min once/day; 0.005 mL nicotine-free liquid	Alveolar enlargement, macrophage infiltration
2	Lee H.W. et al. (2018) [22]	Mice (FVB/N)	12 weeks	3 h/day; liquid with 10 mg/mL nicotine	DNA damage, reduced repair activity, preneoplastic changes
3	Tang M.S. et al. (2019) [33]	Mice (FVB/N)	54 weeks	4 h/day; 36 mg/mL nicotine, flavored liquid	22.5% lung adenocarcinoma, 57.5% bladder urothelial hyperplasia
4	Wang Q. et al. (2019) [36]	Mice	3 days	3 h/day; PG/VG 50:50, 25 mg/mL nicotine	Foci of inflammatory infiltrates
5	Wawryk-Gawda E. et al. (2020) [37]	Wistar rats	6 weeks	2×10 inhalations/day; 12 mg/mL nicotine; PG/VG 50:50	Chronic inflammation, fibrosis, epithelial destruction, apoptosis
6	Crotty-Alexander L.E. et al. (2021) [6]	Mice	3 and 6 months	1 h/day; PG/VG 50:50, 24 mg/mL nicotine	Barrier dysfunction, multi-organ fibrosis
7	Han H. et al. (2021) [13]	Mice (COPD model)	8 weeks	30 min/day; 50 mg/mL nicotine	Alveolar enlargement, increased mucus production, fibrogenesis
8	Yanina I.Y. et al. (2023) [35]	Rats	5 days	1×10 min/day; 0.6 mL nicotine-free flavored liquid	Emphysematous alveolar enlargement, septal thickening, plasma-imbibition phenomenon
9	Day Y. et al. (2023) [7]	Mice (BALB/c)	3 weeks	30 min, twice/day; nicotine liquid 10 mg/mL	Respiratory dysfunction, inflammatory cell infiltration, septal widening
10	Wiriansya E.P. et al. (2023) [42]	Rats	1 and 3 months	1 h/day; PG/VG 50:50, 3 mg/mL nicotine	Epithelial and endothelial degeneration, septal damage, edema

Generative AI Statement - *The author(s) declare that generative AI was used in the creation of this manuscript. AI was used to edit the text in the revised version.*

Competing interests: *None declared.*

Acknowledgements: *None.*

Funding: *This research is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant № BR24992814)*

Authors' contributions: *UT, AA, KS conceived the study, UT, KS, AA, MA, NN, GN acquired the data. UT, KS, SA, GN, NN contributed to data analysis, AA, UT, KS and MA drafted the manuscript. GN, SA, KS, UT contributed to critical evaluation and revisions of the manuscript. All authors read and approved the final version of the paper.*

All authors have read, agreed to the final version of the manuscript, and signed the copyright transfer form.

Ethical Standards

Ethical approval: Not applicable.

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Received: 02 May 2025 / Accepted: 29 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.023

UDC 616.24-008.4-053.1-083.98

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RESPIRATORY SUPPORT FOR CHRONIC HYPERCAPNIC RESPIRATORY FAILURE IN THE OUTPATIENT SETTINGS. LITERATURE REVIEW.

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Abstract

Chronic respiratory failure (CRF) represents a common outcome of chronic bronchopulmonary diseases and significantly influences hospitalization rates, quality of life, and mortality. Improvement in patient prognosis depends not only on the management of the underlying disease but also on the targeted correction of CRF through various modalities of respiratory support, both during exacerbations and in remission phases. The principal strategies for respiratory support include oxygen therapy and non-invasive ventilation (NIV). The primary indication for long-term non-invasive ventilatory support is chronic hypercapnic respiratory failure. Prolonged use of NIV has been shown to improve pulmonary function, enhance gas exchange, increase exercise tolerance, reduce dyspnea, improve quality of life, decrease the risk of rehospitalization, and ultimately enhance survival. Currently, there is insufficient evidence regarding the initiation of non-invasive respiratory support in the outpatient setting for patients with chronic bronchopulmonary pathology. Only a limited number of studies with small cohorts have investigated home initiation of NIV in patients with hypercapnic CRF due to chronic obstructive pulmonary disease (COPD). These studies have demonstrated comparable efficacy in terms of arterial carbon dioxide levels when compared to in-hospital initiation. There is a clear need to expand research in this area by increasing sample sizes, which would allow for the development of evidence-based guidelines for outpatient NIV initiation. At present, there are no standardized recommendations regarding the timing of NIV initiation, patient selection criteria, or parameters for monitoring the effectiveness of non-invasive respiratory support in the ambulatory setting. Moreover, there is no consensus on evaluating the effectiveness of outpatient management of chronic hypercapnic respiratory failure. Thus, the development of clinical algorithms and evidence-based recommendations for the initiation, monitoring, and long-term management of patients receiving non-invasive ventilatory support in the outpatient setting remains a pressing issue.

Keywords: *chronic respiratory failure, hypercapnia, non-invasive ventilation*

For citation:

Serikova A.S., Mukatova I.Y., Baidurin S.A., Urazalina Zh.M. Respiratory Support for Chronic Hypercapnic Respiratory Failure in the Outpatient Settings. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 183-191. *doi 10.34689/SH.2025.27.4.023*

Резюме

РЕСПИРАТОРНАЯ ПОДДЕРЖКА ПРИ ХРОНИЧЕСКОЙ ГИПЕРКАПНИЧЕСКОЙ ДЫХАТЕЛЬНОЙ НЕДОСТАТОЧНОСТИ В АМБУЛАТОРНЫХ УСЛОВИЯХ. ОБЗОР ЛИТЕРАТУРЫ.

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Хроническая дыхательная недостаточность (ХДН) является исходом хронических бронхолегочных заболеваний и определяет частоту госпитализаций, качество жизни и летальность. Улучшение прогноза пациентов обусловлено не только лечением основного заболевания, но и коррекцией непосредственно ХДН различными вариантами респираторной поддержки, как при обострении, так и в период ремиссии. Основные направления респираторной поддержки включают в себя применение кислородотерапии и неинвазивной вентиляции легких (НИВЛ). Показаниями

для назначения длительной неинвазивной респираторной поддержки является хроническая гиперкапническая дыхательная недостаточность. Долгосрочная НИВЛ может улучшить функцию легких, газообмен, повысить толерантность к физическим нагрузкам, уменьшить одышку, улучшить качество жизни, снизить риск повторной госпитализации и повысить выживаемость. На сегодня, данных об инициации неинвазивной респираторной поддержки амбулаторно у пациентов с бронхолегочными заболеваниями недостаточно. Существуют единичные исследования с небольшим количеством пациентов с гиперкапнической ХДН на фоне ХОБЛ по началу неинвазивной респираторной поддержки в домашних условиях. Эти исследования продемонстрировали равнозначную эффективность с началом терапии в стационаре по уровню углекислого газа в артериальной крови. Необходимо расширение подобных исследований, увеличения группы наблюдения, что позволит создать рекомендации для инициации НИВЛ в амбулаторных условиях. На данный момент нет четких рекомендаций по срокам инициации НИВЛ, критериям отбора пациентов и контроля эффективности амбулаторной неинвазивной респираторной поддержки. Нет единой рекомендации по оценке эффективности хронической гиперкапнической дыхательной недостаточности на амбулаторном этапе. Актуальным является разработка алгоритмов и рекомендаций по инициации, контролю и ведению таких пациентов на амбулаторном этапе.

Ключевые слова: *хроническая дыхательная недостаточность, гиперкапния, неинвазивная вентиляция легких.*

Для цитирования:

Серикова А.С., Мукатова И.Ю., Байдурин С.А., Уразалина Ж.М. Респираторная поддержка при хронической гиперкапнической дыхательной недостаточности в амбулаторных условиях. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С. 183-191. *doi 10.34689/SH.2025.27.4.023*

Түйіндеме

АМБУЛАТОРИЯЛЫҚ ЖАҒДАЙДА СОЗЫЛМАЛЫ ГИПЕРКАПНИЯЛЫҚ ТЫНЫС ЖЕТІСПЕУШІЛІГІ КЕЗІНДЕ ТЫНЫС АЛУДЫ ҚОЛДАУ. ӘДЕБИЕТТІК ШОЛУ.

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Созылмалы тыныс жеткіліксіздігі (СТЖ) созылмалы бронхөкпелік аурулардың ақырғы кезеңі болып табылады және ол ауруханаға жатқызу жиілігін, өмір сапасын және өлім-жітім көрсеткішін айқындайды. Науқас болжамын жақсарту тек негізгі ауруды емдеумен ғана емес, сонымен қатар СТЖ-нің өзін әртүрлі тыныс қолдау әдістері арқылы түзетумен байланысты, бұл шаралар аурудың асқыну кезеңінде де, ремиссия кезеңінде де қолданылады. Тыныстық қолдаудың негізгі бағыттарына оттегі терапиясы мен инвазивті емес өкпенің жасанды желдетілуі (ИЕӨЖ) жатады. Ұзақ мерзімді инвазивті емес тыныс қолдауын тағайындауға көрсеткіш — созылмалы гиперкапниялық тыныс жеткіліксіздігі. Ұзақ уақыт бойы ИЕӨЖ қолдану өкпе қызметін, газ алмасуын жақсартып, физикалық жүктемеге төзімділікті арттыруы, ентігуді азайтуы, өмір сапасын жоғарылатуы, қайта ауруханаға жатқызу қаупін төмендетуі және өміршеңдікті арттыруы мүмкін. Қазіргі уақытта бронхөкпелік аурулары бар науқастарға амбулаториялық жағдайда инвазивті емес тыныс қолдауын бастау туралы мәліметтер жеткіліксіз. Созылмалы обструктивті өкпе ауруы (СӨА) аясында гиперкапниялық СТЖ бар науқастарға үй жағдайында тыныстық қолдауды бастауды зерттеген аздаған шағын зерттеулер бар. Бұл зерттеулер артериялық қандағы көмірқышқыл газы деңгейі бойынша емдеуді стационарда бастаумен салыстырғанда ұқсас тиімділікті көрсетті. Мұндай зерттеулердің ауқымын кеңейту және бақылау топтарын ұлғайту қажет, бұл өз кезегінде амбулаториялық жағдайда ИЕӨЖ бастаудың клиникалық ұсынымдарын әзірлеуге мүмкіндік береді. Қазіргі уақытта ИЕӨЖ-ді бастау мерзімі, науқастарды іріктеу критерийлері және амбулаториялық тыныс қолдаудың тиімділігін бақылау бойынша нақты ұсынымдар жоқ. Созылмалы гиперкапниялық тыныс жеткіліксіздігін амбулаториялық кезеңде бағалауға арналған бірыңғай тәсіл қалыптаспаған. Сондықтан амбулаториялық кезеңде ИЕӨЖ-ді бастау, бақылау және жүргізу бойынша клиникалық алгоритмдер мен ұсынымдарды әзірлеу – өзекті мәселе болып отыр.

Түйінді сөздер: *созылмалы тыныс жетіспеушілігі, гиперкапния, инвазивті емес желдету.*

Дәйексөз үшін:

Серикова А.С., Мукатова И.Ю., Байдурин С.А., Уразалина Ж.М. Амбулаториялық жағдайда созылмалы гиперкапниялық тыныс жетіспеушілігі кезінде тыныс алуды қолдау. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 183-191. *doi 10.34689/SH.2025.27.4.023*

Introduction

In recent years, the number of patients with chronic respiratory failure (CRF) requiring respiratory support has increased. This is due to improved diagnostics, approaches to the treatment of chronic bronchopulmonary diseases with a corresponding increase in life expectancy and the emergence of a pool of patients in need of additional non-drug interventions [53, 20]. Due to the need to correct CRF, select individual patient management schemes, which is usually carried out in specialized departments, the workload on hospitals has increased, leading to an increase in financial costs. There is a need to update the diagnostics and correction of CRF at the outpatient stage to optimize patient management and reduce the socio-economic burden of this condition.

Search strategy

The following full-text and bibliographic databases were used: PubMed, Embase, Web of Science, Scopus, The Cochrane Library, eLIBRARY. Ru, while writing the literature review. The search for primary information sources was carried out at a depth of 5 years (2020-2025) using the following keywords: chronic respiratory failure, chronic obstructive pulmonary disease, congenital bronchopulmonary anomalies, cystic fibrosis, bronchiectasis, idiopathic pulmonary fibrosis, acid-base balance, hypercapnia, respiratory support, oxygen therapy, non-invasive ventilation. In total, 70 publications were included in the review.

Search results

Chronic respiratory failure is the outcome of most chronic bronchopulmonary diseases and determines the frequency of hospitalizations, quality of life and mortality in this category of patients [46, 18]. Improved prognosis and reduced patient mortality are due not only to the treatment of the underlying disease, but also to timely correction of CRF directly with various options for respiratory support, both during exacerbation and during remission. The main directions of respiratory support include the use of oxygen therapy and non-invasive ventilation (NIV) [9].

CRF is divided into two main types: hypoxemic, hypercapnic [46, 31]. The issue of diagnosis and treatment of hypoxemic CRF has been studied quite well [17, 52, 40]. There are recommendations for long-term oxygen therapy in hypoxemic CRF and most specialists are well informed on this issue. Hypercapnic CRF is more difficult to diagnose and correct. Hypercapnic respiratory failure (RF) is associated with more frequent and prolonged hospitalizations, decreased quality of life and increased mortality [64, 5, 6].

A prospective study examined whether hypercapnia could predict hospital and annual mortality in patients with dyspnea or lung diseases [63]. The study included 2710 patients, of whom 588 had hypercapnia on admission. The observation was carried out for 12 months from the moment of hospitalization. The results of the study showed a significant increase in mortality in patients with acute hypercapnia compared to patients with chronic hypercapnia and normocapnia. The mortality rate of hospitalized patients with acute hypercapnia during the next year after discharge reached 32%, significantly exceeding similar data in patients with chronic hypercapnia, in whom the mortality rate was 20. 2%, and in patients with normocapnia, with a mortality rate of 14. 5% [63].

A study from the University of Vermont, USA, studied the risks of rehospitalizations and mortality in patients with hypercapnic RF [37]. The study included 202 patients who met the inclusion criteria: 46% of them were diagnosed with COPD, 10% with bronchial asthma, 24% with obstructive sleep apnea syndrome, and 6% with obesity-hypoventilation syndrome. During hospitalization, 15 patients died, which accounted for 7%. Forty-one patients (23%) were readmitted within 30 days after discharge. Analysis of comorbid conditions showed that peripheral vascular disease (OR 4. 78, CI 1. 45–15. 74) and tachycardia (OR 2. 97, CI 1. 22–7. 26) were associated with an increased risk of readmission. During the next 12 months after discharge, 66 patients (36%) died. When analyzing the deceased, it was found that the risk of death was higher in elderly patients (OR 1. 32, CI 1. 13–1. 54 per 5 years), in patients with peripheral vascular disease (OR 12. 56, CI 2. 35–67. 21), in patients with a higher Charlson comorbidity index (OR 1. 39, CI 1. 09–1. 76). Also, the use of long-term home oxygen therapy (OR 4. 03, CI 1. 89–8. 57) and repeated hospitalizations (OR 3. 07, CI 1. 46–6. 43) were identified as important risk factors for death [37]. This study demonstrates the significant impact of hypercapnic RF against the background of chronic bronchopulmonary diseases, in particular COPD, and an increased risk of mortality in the presence of comorbidity, with the use of long-term oxygen therapy, as well as with repeated hospitalizations during the next few months after discharge.

Hypercapnic respiratory failure is a complex diagnosis in routine clinical practice. It is not always possible to diagnose this type of respiratory failure in a timely manner. This is due to diagnostic difficulties, in particular the need for an invasive study - acid-base balance (ABB), which is not a generally available method in routine practice [68, 2, 48]. The study requires arterial blood sampling, which is usually available only in intensive care units and resuscitation departments. Accordingly, hypercapnic CRF is diagnosed late, usually with a significant increase in the level of partial pressure of carbon dioxide (PaCO2), which leads to the need for hospitalization of the patient in the intensive care unit, often the need for artificial ventilation of the lungs (ALV). Since the advent of NIV more than 30 years ago, the approach to respiratory support in patients with CRF has changed. Initially, NIV was used at the stage of weaning the patient from artificial ventilation and transition to spontaneous breathing. Today, NIV with positive pressure has become more widespread and has been actively used at all levels of medical care [39, 30, 70]. This method of respiratory support is used not only in intensive care units, but also in routine departments and outpatient practice. The most significant historical study is one of the first available for analysis, published back in 1996, which compared NIV and artificial ventilation with endotracheal intubation (EI) in patients with COPD and acute RF. This study showed that early use of NIV prevented EI and was associated with better survival compared to patients who received mechanical ventilation [61].

The beginning of NIV use was usually accompanied by its use in hospital settings against the background of exacerbation of chronic bronchopulmonary diseases. Much later, NIV began to be recommended for longer outpatient use. Long-term NIV is a recognized method of treating patients with terminal COPD suffering from hypercapnic CRF. This is reflected in national and international guidelines [34, 41, 27]. The goal of NIV is both to normalize PaCO2 during direct ventilation and to maintain this effect in the periods between the use of NIV and the patient's comfortable perception of the treatment itself [25, 22, 3].

There is less evidence for the effectiveness of long-term NIV in hypercapnic CRF compared to the improved outcomes of NIV in acute life-threatening hypercapnic HF due to COPD exacerbations [54, 36]. The implementation of NIV in an acute situation in hospitalized patients is fundamentally different from daily NIV at home. In everyday practice, patients with CRF should understand that they will probably need respiratory support for the rest of their lives and should be fully motivated to use NIV every night for at least 5 hours to significantly reduce PaCO2 levels [49, 66]. Therefore, full patient commitment and motivation are necessary to achieve control, especially during the recovery period after acute RF and discharge from hospital [69].

The available publications on the correction of CRF mainly concern patients with COPD. This is due to the fact that there are quite a large number of these patients and there is an opportunity to conduct studies. Accordingly, CRF due to COPD has been the most well studied [42]. In stable patients with COPD and chronic hypercapnia (FEV1/FVC < 0. 70; PaCO2 at rest > 45 mmHg; in stable condition), long-term NIV can improve lung function, gas exchange, increase exercise tolerance, reduce dyspnea, improve quality of life, reduce the risk of rehospitalization and increase survival [34].

Recent large studies have also shown positive results of long-term use of NIV in patients with stable COPD [43, 19, 23]. A meta-analysis including studies from 1995 to 2019, covering a total of 51, 085 patients with COPD and hypercapnia, demonstrated that the use of BiLevel positive airway pressure at home, compared with no respiratory support, was associated with a lower risk of mortality (OR, 0. 66), fewer hospitalizations (OR, 0. 22) and a lower need for intubation (OR, 0. 34) [67].

The most common causes of COPD exacerbations are respiratory infections and progression of CRF. In both situations, acute hypercapnic RF may occur against the background of existing CRF [65, 32]. And then, for the first time, the question of initiating non-invasive respiratory support is raised when a hospitalized patient with a severe exacerbation, progression of RF develops severe hypercapnia. Often these patients undergo a stage of artificial ventilation in the intensive care unit, which increases the risk of hospital infection, prolongs the duration of hospitalization, and increases mortality [56, 1, 33].

One of the general goals in the treatment of patients with COPD is to minimize the number of hospitalizations for severe exacerbations of the disease and to prolong the period until the next exacerbation, especially in patients with a high risk of developing acute hypercapnic RF [16, 26].

With diagnosed hypercapnic CRF, initiation and titration of long-term NIV aimed at reducing PaCO2 is usually carried out in a hospital setting, which in some cases is the main reason for hospitalization, which naturally increases the financial costs associated with hospitalization in general, the risk of hospital complications and is the cause of a worsening prognosis [57].

The study demonstrated that initiation of long-term NIV in patients with COPD in a stable condition can reduce the number of future hospitalizations [29]. In a study involving 195 patients with stable COPD GOLD IV and PaCO2 51. 9 mm Hg. and above and pH more than 7. 35, NIV was started in the main group with the goal of reducing PaCO2 by at least 20% or to achieve PaCO2 less than 48. 1 mm Hg. The observation was carried out for a year. The results of the study demonstrated a decrease in the number of emergency hospitalizations in the group receiving NIV, compared with the control group (2. 2 and 3. 1 exacerbations per patient per year, respectively). Mortality within 12 months was 12% (12 of 102 patients) in the intervention group and 33% (31 of 93 patients) in the control group; hazard ratio 0. 24 (95% CI 0. 11–0. 49; p=0. 0004) [29]. This study demonstrated the feasibility and effectiveness of NIV in patients with stable hypercapnic CRF in terms of reducing future hospitalizations for exacerbation of COPD.

Despite the existing international guidelines for the use of NIV in patients with hypercapnic CRF, numerous studies confirming the effectiveness of NIV in reducing future exacerbations, mortality and improving quality of life in general, the issue of the frequency of prescription and use of NIV at home remains relevant. In one such study, the prevalence of hypercapnic CRF and the use of home NIV was examined among a high-risk group - individuals with a history of at least one hospitalization for COPD [15]. A retrospective analysis of the medical records of patients at the Veterans Affairs Medical Center, Iowa, who had at least one hospitalization for COPD between 2011 and 2017 was conducted. In 186 patients, the overall prevalence of hypercapnic CRF, defined as PaCO2> 45 mmHg at pH = 7. 35–7. 45, was 52. 7%, and the overall prevalence of home NIV was 4. 3%. In patients with one hospitalization for COPD, the prevalence of hypercapnic CRF was 43. 6%, and home NIV was 1. 8%. Among patients with ≥4 hospitalizations for COPD, the prevalence of hypercapnic CRF was 77. 8% (14 of 18), and home NIV was 11. 1% (2 of 18). Thus, approximately half of patients who have had at least one hospitalization for COPD have hypercapnic CRF, but only 8. 2% of them use home NIV [15]. Large multicenter studies are needed to examine the prevalence of CRF and the extent of NIV underuse in this category of patients.

The conducted literature review showed that there is no data on the correction of hypercapnic CRF in the outcome of other chronic bronchopulmonary diseases, among which bronchopulmonary anomalies of various origins, conditions after pulmonary tuberculosis with an outcome in pneumofibrosis, and interstitial lung diseases are quite common. One of the recent studies, which retrospectively analyzed 1281 case histories of patients with CRF of various etiologies who received NIV in the period from 2004 to 2014, was conducted [14]. According to the diseases, patients were divided into nine categories: obstructive airway diseases (COPD, bronchial asthma, bronchiectasis)

(16%); interstitial lung diseases (3%); obesity-hypoventilation syndrome (11%); neuromuscular diseases (10%); chest diseases (4%); obstructive sleep apnea syndrome (26%); malignant neoplasms (2%); others (3%) and acute respiratory failure (8%), which refers to patients who did not meet the criteria for CRF. After the start of NIV, the median overall survival was 4. 5 years (95% CI from 3. 6 to 5. 4) and varied depending on the disease. There are also isolated descriptions of clinical cases on the effectiveness of long-term respiratory support in a patient after pulmonectomy in the outcome of pulmonary tuberculosis with the development of hypercapnic CRF. In the described cases, the effectiveness and safety of outpatient NIV in this category of patients was demonstrated [4, 38].

Since the number of patients with CRF who will be indicated for non-invasive respiratory support increases every year, the issue of increasing the frequency of hospitalizations, respectively, increasing the risks of nosocomial infection, and generally increasing the burden on the healthcare system arises. This fact requires changing approaches to the initiation of non-invasive respiratory support. There are already data on outpatient initiation of NIV, in particular in patients with neuromuscular and restrictive diseases of the chest. In one of such studies, in patients with amyotrophic lateral sclerosis, initiation of NIV at home was equally effective and cost-effective compared to initiating this type of therapy in a hospital setting [62, 50]. A Dutch study showed the same improvement in gas exchange and quality of life, as well as the cost-effectiveness of initiating NIV at home in patients with neuromuscular diseases and chest deformities, compared to initiating NIV in a hospital setting [59]. These data indicate the possibility of starting non-invasive respiratory support at home, without additional hospitalization for the initiation of NIV and require further expansion to develop clearer criteria for the selection of patients who need this type of therapy.

The use of outpatient initiation of NIV in patients with a pulmonary profile can minimize the need for hospitalization, which will reduce the risks of hospital infections and the cost of managing these patients in general [28, 21]. But to date, there is insufficient data on the initiation of NIV on an outpatient basis specifically in patients with bronchopulmonary diseases.

There are isolated studies with a small number of patients with hypercapnic CRF against the background of COPD on the initiation of NIV at home, where equivalent effectiveness of starting therapy both in hospital and outpatient in terms of PaCO2 levels was demonstrated [11]. A study of 67 patients with stable hypercapnic COPD who were initiated with NIV in hospital and at home using telemedicine showed that NIV initiation in the outpatient setting was essentially equivalent to inpatient. Mean PaCO2 in outpatient vs. Inpatient was 0. 04 kPa (95% CI -0. 31 to 0. 38 kPa), with both groups demonstrating a decrease in PaCO2 at 6 months compared to baseline (home: from 7. 3 ± 0. 9 to 6. 4 ± 0. 8 kPa ($p < 0. 001$) and inpatient: from 7. 4 ± 1. 0 to 6. 4 ± 0. 6 kPa ($p < 0. 001$)). Quality of life improved in both groups with no significant difference between groups. In addition, the study results demonstrated that initiation of NIV in the outpatient setting was significantly cheaper (outpatient: median €3, 768 versus hospitalization: median €8, 537; $p<0. 001$). This is the first study to demonstrate that outpatient initiation of long-term NIV in patients with stable hypercapnia and COPD using telemedicine is non-inferior to inpatient initiation, is safe, and reduces costs by more than 50% [11].

Jolly and colleagues from Rouen University, France conducted a cohort study including 250 patients with obesity hypoventilation syndrome (n = 95; 38%), neuromuscular disease (n = 70; 28%), COPD (n = 66; 26%), and chest wall disease (n = 19; 8%) [25]. These patients were treated with NIV at home for 2 years. Quality of life was assessed at baseline and follow-up using the Severe Respiratory Insufficiency (SRI) Questionnaire and five targets had to be met: daily use for more than 4 h/day, improvement in gas exchange, health-related quality of life (HRQL), and sleep quality without adverse effects. Adequate treatment initiation was defined as achieving at least three of the five targets, and successful initiation was defined as achieving all targets. At follow-up, all five targets were achieved in only 141 (56%) patients. NIV initiation was adequate in 96 (68%) patients and successful in 12 (9%) patients. Improvement in PaCO2 did not correlate with improvement in HRQL or sleep quality. Based on this observation, the investigators concluded that successful initiation of home NIV is rarely achieved in real life and that quality of life and tolerability of NIV should be assessed to improve patient-centered outcomes [25].

In addition to the specifics of initiating NIV in an outpatient setting, the question of direct management and observation of these patients always arises [10]. This monitoring can be carried out through the use of modern methods for monitoring the condition of these patients. In particular, one study surveyed patients and caregivers. All patients with hypercapnic CRF received NIV. A survey of NIV users showed that approximately half of them and 60% of their caregivers welcomed telemonitoring for monitoring the patient's condition and adjusting therapy. Telemonitoring provides information through a cloud-based system that allows the transmission of patient data and data on therapy, time of use, and adherence to NIV. Based on the information received, doctors have the opportunity to adjust the settings of the NIV device. Telemedicine is used both at the stage of initiating NIV and for monitoring and titrating treatment [10, 58].

Although initiation of NIV in COPD requires careful titration and monitoring, initiation does not necessarily have to be done in a hospital setting [7, 51]. Therapy can be administered under the supervision of a physician, who can also delegate this task to a respiratory therapist, a specialist nurse or other specially trained health care professional. The presence of a physician is not necessary, provided that appropriate communication channels (telephone, telemonitoring) are available [55, 60, 8]. This approach is feasible, acceptable and can improve clinical symptoms, help physicians in monitoring patients, identifying those who are suitable for home NIV. Telemonitoring can also help with adaptation, titration and adherence to NIV [12].

A multicenter prospective RCT examined the benefits of management using different types of internet communication with patients receiving home NIV compared with traditional management with a personal visit by a

health care professional [24]. The study enrolled 148 patients (age: 72. 7 ± 6. 8 years; male: 85. 8%; FEV1: 0. 7 ± 0. 3 L; PaCO2: 66. 4 ± 12. 0 mmHg) recruited from 11 Chinese hospitals between 2019 and 2021. Patients were randomly assigned to the intervention group (n = 73) and control group (n = 75). After 12 months of follow-up, the mean Severe Respiratory Insufficiency (SRI) Questionnaire score was 56. 5 in the intervention group and 50. 0 in the control group (95% CI, 3. 71–8. 80; P < 0. 001). The risk of rehospitalization within 12 months was 34. 3% in the intervention group compared with 56. 0% in the control group, adjusted hazard ratio 0. 56 (95% CI 0. 34–0. 92; P = 0. 023). The study demonstrated that in stable patients with hypercapnic CRF due to COPD, NIV monitoring using different internet communication options improves health-related quality of life and increases the time to rehospitalization.

A study comparing transcutaneous capnometry-guided and polysomnography-guided NIV initiation included patients with COPD and obstructive sleep apnea syndrome [44]. The results demonstrated that nurse-led nocturnal titration of NIV using transcutaneous capnometry was more effective than polysomnography-guided NIV initiation. The study showed that this telemedicine-based monitoring method is feasible at home.

Another study also confirmed the effectiveness of using telemedicine to assess the effectiveness of NIV and long-term oxygen therapy at home. In patients with chronic hypercapnia COPD on respiratory support, telemonitoring can reduce the frequency of exacerbations and hospitalizations [45, 47].

Thus, the conducted analysis of available literature sources demonstrates the possibilities of conducting positive pressure respiratory support in patients with CRF of various genesis at the outpatient stage. However, all currently available studies are insufficient in terms of the number of patients covered; it is necessary to expand such studies and increase the observation group. At the moment, there are no clear recommendations on the timing of NIV initiation, patient selection criteria and monitoring of the effectiveness of outpatient NIV.

There is also no single recommendation for assessing the effectiveness of hypercapnic CRF at the outpatient stage. The existing criterion for the effectiveness of respiratory support is a decrease in PaCO2, is difficult to implement at the outpatient stage, since this method is not used in routine outpatient practice, but is available only in inpatient settings.

It should also be noted that various healthcare systems require the development of algorithms for the initiation of non-invasive respiratory support, taking into account local characteristics. In particular, regarding Kazakhstan, there are currently no data on the initiation of NIV on an outpatient basis in available sources. It is relevant to create recommendations for the initiation and specific features of NIV in outpatients.

Disclosure: *There are no conflicts of interest among all authors.*

Acknowledgments: *None.*

Funding: *This study was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (IRN BR21882152). Sponsors played no role in the design of the study, data collection and analysis, decision to publish, or preparation of the manuscript.*

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Received: 02 March 2025 / Accepted: 12 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.024

UDC 616-02-092-073.757.7-07-089

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ATRIOVENTRICULAR SEPTAL DEFECT: ETIOLOGY, PATHOGENESIS, CLASSIFICATION, MODERN DIAGNOSTIC METHODS, AND SURGICAL CORRECTION. LITERATURE REVIEW

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Abstract

Atrioventricular septal defect (AVSD) is a complex congenital heart defect characterized by abnormal endocardial cushion formation, leading to atrial and ventricular septal defects and atrioventricular valve anomalies. AVSD accounts for approximately 7% of all congenital heart defects and is frequently associated with Down syndrome. Without surgical intervention, patients with complete AVSD are at high risk of developing pulmonary hypertension and heart failure. Modern imaging techniques allow for precise anatomical assessment and optimization of surgical treatment. This study aims to investigate the etiology, pathogenesis, classification, modern diagnostic methods, and surgical correction techniques for AVSD.A review of publications from electronic databases PubMed, MEDLINE, Web of Science, Google Scholar, and an electronic library was conducted using relevant keywords over the past 10 years. A total of 50 sources were included, while duplicate publications and conference abstracts were excluded. Genetic and epigenetic factors, particularly mutations affecting endocardial cushion development, play a significant role in AVSD formation. Impaired cell migration leads to various AVSD subtypes. Modern radiological diagnostic techniques enable accurate defect evaluation. Surgical correction, including the double-patch and single-patch techniques, remains the primary treatment. In complex cases, palliative surgical approaches are employed. Modern diagnostic and surgical methods significantly improve the prognosis of AVSD patients. Genetic research facilitates early detection, while advanced surgical techniques reduce the risk of complications. A comprehensive approach integrating etiological research, pathogenetic modeling, precise diagnosis, and surgical interventions is key to the effective management of AVSD.

Keywords: *atrioventricular septal defect, etiology, pathogenesis, imaging diagnosis, surgical correction.*

For citation:

Almussina A.K., Rakhimzhanova R.I., Dautov T.B., Abdrakhmanova Zh.S., Ganiyeva A.A., Nurzhanov A.A. Atrioventricular Septal Defect: Etiology, Pathogenesis, Classification, Modern Diagnostic Methods, and Surgical Correction. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 192-201. *doi 10.34689/SH.2025.27.4.024*

Резюме

АТРИОВЕНТРИКУЛЯРНЫЙ СЕПТАЛЬНЫЙ ДЕФЕКТ: ЭТИОЛОГИЯ, ПАТОГЕНЕЗ, КЛАССИФИКАЦИЯ, СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ И ХИРУРГИЧЕСКОЙ КОРРЕКЦИИ. ОБЗОР ЛИТЕРАТУРЫ

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Атриовентрикулярный септальный дефект (AVSD) — сложный врожденный порок сердца, характеризующийся нарушением формирования эндокардиальных валиков, что приводит к дефектам межпредсердной и межжелудочковой перегородок, а также аномалиям атриовентрикулярных клапанов. AVSD составляет 7% всех врожденных пороков сердца и часто встречается при синдроме Дауна. Без хирургического вмешательства пациенты с полной формой AVSD подвержены высокому риску легочной гипертензии и сердечной недостаточности. Современные методы визуализации позволяют точно оценить анатомию порока и оптимизировать хирургическое лечение. Целью исследования является изучение этиологии, патогенеза, классификации, современных методов диагностики и хирургической коррекции атриовентрикулярного септального дефекта. Проанализированы публикации в электронных базах данных PubMed, MEDLINE, Web of Science, Google Scholar и электронной библиотеке с использованием ключевых слов за последние 10 лет. В исследование были включены 50 источник, при этом дублирующиеся публикации и материалы конференций были исключены. В развитии AVSD значительную роль играют генетические и эпигенетические факторы, особенно мутации, влияющие на формирование эндокардиальных валиков. Нарушение миграции клеток приводит к различным формам AVSD. Современные методы лучевой диагностики позволяют точно оценить анатомию дефекта. Хирургическая коррекция, включая технику двойного и одинарного патча, является основным методом лечения. В сложных случаях применяется паллиативная хирургия. Современные диагностические и хирургические методы улучшают прогноз пациентов с AVSD. Генетические исследования способствуют раннему выявлению, а современные хирургические технологии снижают риск осложнений. Комплексный подход является ключевым в эффективном лечении AVSD.

Ключевые слова: *атриовентрикулярный септальный дефект, этиология, патогенез, визуальная диагностика, хирургическая коррекция.*

Для цитирования:
Альмусина А.К., Рахимжанова Р.И., Даутов Т.Б., Абдрахманова Ж.С., Ғаниева А.А., Нуржанов А.А. Атриовентрикулярный септальный дефект: этиология, патогенез, классификация, современные методы диагностики и хирургической коррекции. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С. 192-201. *doi 10.34689/SH.2025.27.4.024*

Түйіндеме

АТРИОВЕНТРИКУЛЯРЛЫҚ СЕПТАЛЬДЫ АҚАУ: ЭТИОЛОГИЯСЫ, ПАТОГЕНЕЗІ, ЖІКТЕЛУІ, ЗАМАНАУИ ДИАГНОСТИКАСЫ ЖӘНЕ ХИРУРГИЯЛЫҚ ТҮЗЕТУ ӘДІСТЕРІ. ӘДЕБИЕТТІК ШОЛУ.

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Атриовентрикулярлық септальды ақау (AVSD) – эндокардиальды жастықшалардың дұрыс қалыптаспауынан жүрек аралық және қарынша аралық перделердің ақаулары мен атриовентрикулярлық қақпақшалардың аномалиялары дамитын күрделі туа біткен жүрек ақауы. AVSD барлық туа біткен жүрек ақауларының 7%-ын құрайды және көбінесе Даун синдромы бар науқастарда кездеседі. Хирургиялық араласусыз толық AVSD бар науқастар өкпе гипертензиясы мен жүрек жеткіліксіздігінің жоғары қаупіне ұшырайды. Заманауи визуализация

әдістері ақаудың анатомиясын дәл бағалауға және хирургиялық емдеуді оңтайландыруға мүмкіндік береді. Бұл зерттеудің мақсаты – AVSD-нің этиологиясын, патогенезін, жіктелуін, заманауи диагностика әдістері мен хирургиялық түзету тәсілдерін зерттеу. PubMed, MEDLINE, Web of Science, Google Scholar электрондық дерекқорларындағы соңғы 10 жылдағы жарияланымдарға шолу жасалды. Жалпы 50 дереккөз қамтылды, қайталанған басылымдар мен конференция материалдары алынып тасталды.

AVSD қалыптасуында генетикалық және эпигенетикалық факторлар, әсіресе эндокардиальды жастықшалардың дамуына әсер ететін мутациялар, маңызды рөл атқарады. Эмбрионалды жасушалардың миграциясының бұзылуы ақаудың әртүрлі түрлерінің дамуына әкеледі. Заманауи радиологиялық диагностика әдістері ақаудың анатомиялық ерекшеліктерін дәл анықтауға мүмкіндік береді. Қос патч және бір патч әдістерін қамтитын хирургиялық түзету – AVSD емдеудің негізгі тәсілі болып табылады. Күрделі жағдайларда паллиативті хирургия қолданылады. Заманауи диагностикалық және хирургиялық әдістер AVSD бар науқастардың болжамын едәуір жақсартады. Генетикалық зерттеулер ақаудың ерте анықталуына ықпал етеді, ал жетілдірілген хирургиялық технологиялар асқыну қаупін төмендетеді. Этиологиялық зерттеу, патогенезді модельдеу, дәл диагностика және хирургиялық араласу әдістерін біріктіретін кешенді көзқарас AVSD басқарудағы негізгі стратегия болып табылады.

Түйінді сөздер: *атриовентрикулярлық септальды ақау, этиология, патогенез, визуалды диагностика, хирургиялық түзету.*

Дәйексөз үшін:

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Introduction

Atrioventricular septal defect (AVSD) is a significant congenital heart anomaly that arises from improper development of the endocardial cushions during embryogenesis. It is characterized by a common atrioventricular junction, defects in the atrial and ventricular septa, and abnormalities in the atrioventricular valves. AVSD is classified into partial, intermediate, and complete forms based on the extent of septal involvement and the structural abnormalities of the valves. This condition represents approximately 7% of all congenital heart defects and has a notably higher prevalence in individuals with Down syndrome, accounting for 40–50% of cases in this population [34, 32, 10, 31, 29, 13].

Clinically, AVSD poses significant challenges due to its impact on hemodynamics. Left-to-right shunting of blood through septal defects, atrioventricular valve regurgitation, and increased pulmonary blood flow contribute to progressive heart failure and pulmonary hypertension if untreated. Moreover, the spectrum of clinical manifestations varies widely, ranging from asymptomatic cases to severe presentations in infancy [32, 25, 43, 13, 16].

Radiological imaging plays a crucial role in diagnosing and evaluating AVSD. Echocardiography remains the first-line modality, providing detailed visualization of the common atrioventricular junction and associated anomalies. However, advances in cardiac computed tomography (CT) have enhanced diagnostic precision, offering high-resolution, three-dimensional reconstructions for complex cases. Notable radiological features, such as the "gooseneck sign," serve as key indicators in imaging studies [24, 43, 19, 3, 7].

Surgical correction is the cornerstone of AVSD management, with early intervention recommended to prevent irreversible pulmonary vascular disease. Techniques such as double-patch and modified single-patch repairs are commonly employed, each with distinct advantages. Recent studies have demonstrated comparable long-term survival and event-free outcomes between these techniques, underscoring the importance of individualized surgical planning [9, 23, 4, 20].

Despite advancements in treatment, challenges persist, including postoperative complications such as atrioventricular valve regurgitation and arrhythmias. The development of minimally invasive approaches and refined imaging technologies continues to improve outcomes and expand treatment options for AVSD [1, 2, 44, 30, 12, 20].

Given the significant clinical burden and evolving management strategies, this review aims to provide a comprehensive synthesis of current knowledge on AVSD. Emphasis is placed on the role of advanced imaging modalities in diagnosis, the outcomes of various surgical techniques, and emerging therapeutic approaches to optimize care for affected individuals.

The purpose of this review was to explore the etiology, pathogenesis, methods for diagnosing atrioventricular septal defect (AVSD), focusing on improving screening sensitivity and diagnostic accuracy, as well as optimizing surgical correction strategies to enhance patient outcomes.

Search strategy. A review of publications from electronic databases PubMed, MEDLINE, Web of Science, Google Scholar, and an electronic library was conducted using relevant keywords over the past 10 years. A total of 51 sources were included, while duplicate publications and conference abstracts were excluded.

Discussion

Epidemiology of Atrioventricular Septal Defect (AVSD)

1. Prevalence of AVSD

AVSD is one of the most common forms of congenital heart defects, accounting for approximately 7% of all congenital heart anomalies. The global prevalence is around 2 per 10,000 live births, emphasizing the

significance of this condition in pediatric cardiology [34, 50, 8, 48, 16, 4]. A particularly high prevalence is observed in patients with Down syndrome, where AVSD is detected in 40–50% of cases, making this defect a key marker in this genetic condition [13].

2. Global Variability

A meta-analysis of data from 1970 to 2017 revealed significant geographic heterogeneity in the prevalence of congenital heart defects, including AVSD. According to studies conducted in various regions, Asia demonstrates the highest incidence rate—9,342 cases per 1,000 live births, surpassing Europe and North America, where diagnostic and registration practices are more comprehensive. In Africa, however, the lowest prevalence rates have been recorded—2,315 cases per 1,000, likely due to limited diagnostic capabilities and restricted access to healthcare services [50, 41, 5, 28, 33].

3. Gender Differences

According to epidemiological studies, AVSD occurs at a similar frequency in males and females, except for certain subtypes of the defect, where minor gender differences have been noted. However, these data require further confirmation in larger study populations [13].

4. Age and Clinical Presentation

AVSD is most commonly diagnosed within the first few months of life due to severe hemodynamic disturbances. In adult patients, the defect is rarely detected, usually in the form of partial AVSD, such as ostium primum defects or isolated valvular abnormalities [37].

Without surgical intervention, children with AVSD face a high risk of developing pulmonary hypertension, heart failure, and early mortality [12, 4].

5. Risk Factors and Associations

● **Genetic Factors**: Down syndrome remains the most significant association with AVSD, increasing the likelihood of this defect by 200 times compared to the general population [34, 50, 24, 15, 13, 4].

● **Teratogenic Factors**: Exposure to teratogens, including maternal diabetes and intrauterine alcohol exposure, has also been linked to an increased risk of AVSD [34, 50, 24, 15, 33].

● **Regional Characteristics**: The availability of medical care and early diagnosis significantly influence the detection rate of the defect, particularly in developing countries [34, 50, 24, 15, 27, 33].

6. Trends in Incidence Over Time

Meta-analysis data indicate an increase in diagnosed cases of AVSD from 1995 to 2017. This trend is attributed to advancements in imaging techniques, such as echocardiography and CT, and the earlier detection of less severe forms of the defect, including partial AVSD [35, 42, 33, 3].

Conversely, the incidence of severe cases, such as left ventricular outflow tract obstructions, has decreased, likely due to improvements in prenatal diagnostics and medical decision-making, including termination of pregnancy in cases of severe fetal anomalies [45, 17, 33, 12].

7. Importance of Epidemiological Studies

Epidemiological data play a crucial role in planning healthcare services and resource allocation for the treatment of AVSD. Improving access to modern diagnostic technologies in developing countries could significantly impact morbidity and mortality rates associated with this defect [34, 50, 24, 15, 33].

Pathogenesis of Atrioventricular Septal Defect (AVSD)

1. Key Mechanisms of Pathogenesis

AVSD develops due to abnormal embryonic formation of endocardial cushions, which play a crucial role in separating the common atrioventricular canal into two distinct atrioventricular orifices. These cushions contribute to the development of the atrioventricular valves, atrial septum, and ventricular septum. Disruptions in this process lead to various anomalies, including:

● The formation of a common atrioventricular junction.

● The presence of atrial and/or ventricular septal defects.

● Valve anomalies, including fusion, cleft formation, or underdevelopment of valve leaflets 15, 31, 29, 13].

2. Role of Endocardial Cushions

Endocardial cushions are mesenchymal structures that form due to the epithelial-mesenchymal transition (EMT) of endocardial cells. These cells migrate, proliferate, and fuse to create the structural framework of the heart. Disruptions at any stage of this process - such as deficient migration or improper differentiation - result in the characteristic malformations observed in AVSD [42, 31, 29].

3. Embryonic Development of the Heart

● **Weeks 4–5**: Formation of the primary heart tube, division of the atria and ventricles, and emergence of endocardial cushions.

● **Weeks 6–7**: Fusion of the endocardial cushions and initiation of atrioventricular septation.

● **Weeks 7–8**: Completion of atrial and ventricular septation and formation of the atrioventricular valves [29, 12].

In AVSD, the fusion of cushions and septation process is impaired, leading to:

● Deficiency of mesenchymal cells.

● Misalignment of valve leaflets.

● Formation of a common valve instead of two distinct mitral and tricuspid valves.

4. Genetic Factors

● Chromosomal Abnormalities: The most significant risk factor for AVSD is trisomy 21 (Down syndrome). Patients with Down syndrome exhibit defects in signaling pathways, such as the Notch pathway, which is crucial for endocardial cushion development [13].

● Genetic Mutations: Mutations in genes such as GATA4, NKX2-5, and CRELD1 contribute to the pathogenesis of AVSD. These genes regulate cell migration, proliferation, and apoptosis during heart development [31, 16].

5. Hemodynamic Abnormalities

● Blood Shunting: In the presence of atrial and/or ventricular septal defects, blood is shunted from the left heart chambers to the right, causing pulmonary overcirculation and increasing the risk of pulmonary hypertension [13, 12].

● Valve Dysfunction: Insufficiency of the common atrioventricular valve leads to regurgitation and volume overload of the ventricles, contributing to the progression of heart failure [37, 20].

6. Role of Radiological Findings in Understanding Pathogenesis

Radiological techniques, such as CT and echocardiography, allow visualization of key pathogenetic features of AVSD, including:

● The common valve and its abnormal orientation.

● Atrial and ventricular septal defects.

● Right heart hypertrophy due to volume overload [3, 7].

7. Influence of Environmental and Epigenetic Factors

● Maternal Factors: Conditions such as maternal diabetes, intrauterine alcohol exposure, and certain medications (e.g., lithium) increase the risk of AVSD.

● Epigenetic Changes: DNA methylation abnormalities and microRNA dysregulation affect the expression of genes involved in endocardial cushion development [33, 12].

8. Future Perspectives in AVSD Pathogenesis Research

Current research is focused on:

● Identifying novel genes and molecular pathways involved in endocardial cushion development.

● Exploring regenerative medicine approaches, such as stem cell therapy, to correct defects at the embryonic development stage 16, 4].

Modern Radiological Methods for Diagnosing Atrioventricular Septal Defect (AVSD)

Radiological diagnosis of atrioventricular septal defect (AVSD) plays a key role in preoperative planning, evaluating the hemodynamic consequences of the defect, and monitoring the patient's postoperative condition. Modern imaging techniques include echocardiography (ECHO), computed tomography (CT), magnetic resonance imaging (MRI), and angiography, each of which offers specific capabilities for detailed assessment of heart anatomy.

Echocardiography in AVSD Diagnosis

Echocardiography remains the primary diagnostic method for AVSD, providing real-time anatomical and hemodynamic information. Modern echocardiographic techniques include two-dimensional (2D), three-dimensional (3D) echocardiography, and prenatal fetal echocardiography.

● Two-dimensional echocardiography (2D-ECHO) helps identify the common atrioventricular valve, assess the size of atrial and ventricular septal defects, and determine the degree of regurgitation. The study by *Singh P. et al.* (2010) demonstrated that 2D-ECHO has high accuracy in visualizing valvular structures, particularly in young children [2, 27, 11, 40, 44, 46].

● Three-dimensional echocardiography (3D-ECHO) provides more detailed volumetric images, which are particularly useful for evaluating the atrioventricular valve and planning surgical intervention. According to Jegatheeswaran A. et al. (2010), 3D-ECHO significantly improves the diagnosis of valve leaflet clefts and residual defects after surgery [26].

● Transthoracic echocardiography (TTE) is the first-line diagnostic tool for AVSD suspicion. *Atik E. et al.* (2019) reported that TTE is effective in detecting primary atrial septal defects, valvular anomalies, and the degree of atrioventricular valve regurgitation [6, 12].

● Transesophageal echocardiography (TEE) allows for a more detailed visualization of valvular anatomy and adjacent structures, especially in complex cases. *Wang G. et al.* (2020) highlighted that 3D-TEE enhances the assessment of valve anatomy and function, which is critical for preoperative planning [12, 20, 47].

● Prenatal echocardiography, particularly the FINE (Fetal Intelligent Navigation Echocardiography) method, has demonstrated high efficacy in detecting AVSD in fetuses. *Veronese P. et al.* (2023) noted that this technique allows for highly accurate automatic visualization of standard cardiac views and congenital defects [46].

Computed Tomography in AVSD Diagnosis

Computed tomography (CT) plays a crucial role in diagnosing complex anatomical variants of AVSD. Unlike echocardiography, CT provides high-resolution three-dimensional images, which are particularly useful for preoperative surgical planning.

● Multislice CT (MSCT) is used for detailed assessment of septal defects, atrioventricular valves, and major vessels. The study by *Yoshitake S. et al.* (2020) confirmed that phase-contrast CT accurately determines the location of the atrioventricular conduction system, reducing the risk of conduction system injury during surgery [1, 36, 40, 49].

● The study by *Balpande N. et al.* (2022) demonstrated that CT can detect the "gooseneck sign" characteristic of AVSD, a feature previously identified only in angiographic studies. This finding underscores the importance of CT imaging in visualizing endocardial cushion defects [1, 2, 3, 7, 9, 23].

● *Nunes M. et al.* (2021) found that modern low-dose CT protocols minimize radiation exposure while maintaining high image quality. The authors emphasized that CT is particularly useful for assessing the anatomy of major vessels, determining defect size, and clarifying valve apparatus status [7, 9,13, 28].

● High-speed dual spiral CT reduces radiation exposure, making it the preferred imaging modality for children. *Goo H.W. et al.* (2018) demonstrated that ECG-synchronized CT enhances the accuracy of coronary vessel imaging and minimizes motion artifacts [22, 36, 38].

Magnetic Resonance Imaging in AVSD Diagnosis

Cardiac MRI is an indispensable diagnostic tool for AVSD, especially when echocardiographic visualization is limited.

● The study by *Elders B. et al.* (2019) demonstrated that 4D flow MRI allows for a detailed assessment of hemodynamic parameters, including wall shear stress of the aorta, which can change in AVSD patients after surgical correction. These findings highlight the importance of MRI in long-term patient monitoring [6, 16, 27, 48].

● *Schumacher K. et al.* (2023) showed that one of the key postoperative complications of AVSD repair is residual atrioventricular valve regurgitation, making MRI the preferred method for long-term monitoring of such patients [27, 38, 49].

● Contrast-enhanced MRI allows for the detection of myocardial fibrosis, which is crucial for prognosis in AVSD patients. Alsoufi B. et al. (2019) also noted that MRI plays a critical role in evaluating residual shunts and valvular dysfunctions following AVSD surgical correction [4, 16, 27].

Angiography and Cardiac Catheterization

Cardiac catheterization and angiography are used in complex anatomical forms of AVSD, particularly when

precise measurements of pulmonary artery pressure and cardiac chamber pressures are required.

● *Nicolay S. et al.* (2015) emphasized that angiography remains the "gold standard" for intracardiac shunt assessment and is crucial for determining pulmonary vascular resistance before surgery [23, 30, 33].

● The study by Deri & English (2018) confirmed that angiography is an essential tool for evaluating pulmonary vascular resistance before surgery, particularly in cases with high pulmonary hypertension risk [30, 18].

● Modern non-invasive techniques, such as CT angiography (CTA), provide high-quality cardiovascular imaging without the need for invasive catheterization. The study by *Chen S.J. et al.* (2017) compared ECG-synchronized CTA with traditional angiography, demonstrating that CTA offers high diagnostic accuracy with reduced radiation exposure [30, 36, 48].

Modern radiological methods significantly enhance the diagnostic accuracy, surgical planning, and postoperative monitoring of AVSD:

● Echocardiography (2D, 3D, TEE, fetal) remains the primary diagnostic tool, offering real-time hemodynamic and structural assessment.

● CT imaging (MSCT, phase-contrast, ECG-synchronized) is crucial for detailed anatomical assessment and preoperative planning.

● MRI is essential for functional evaluation, long-term postoperative monitoring, and fibrosis detection.

● Angiography and cardiac catheterization remain vital in complex cases, particularly for hemodynamic assessment and surgical decision-making.

Advances in imaging techniques have improved AVSD detection rates, reduced the need for invasive procedures, and contributed to better surgical outcomes and long-term patient management.

Table 1.

Comparative analysis of methods.

Method	Advantages	Limitations
Echocardiography (2D, 3D, TEE, fetal)	Accessibility, non-invasiveness, real-time hemodynamic assessment	Limited image quality in obese patients or those with post-surgical changes
Computed Tomography (MSCT, CTA)	High spatial resolution, ability to generate 3D reconstructions	Radiation exposure, need for contrast administration
MRI (4D flow, contrast-enhanced)	High tissue contrast, functional assessment capabilities	Long scan duration, contraindications for patients with metallic implants
Angiography	Gold standard for shunt evaluation, direct hemodynamic measurement possible	Invasiveness, risk of complications

Each radiological diagnostic method for AVSD has its own specific characteristics. The use of modern radiological techniques significantly improves the detection of this pathology, facilitates surgical planning, and ensures postoperative patient monitoring. Echocardiography remains the primary diagnostic method, while CT and MRI play a crucial role in refining anatomical details, functional assessment, and predicting surgical outcomes. Angiography continues to be used in complex cases and prior to surgical intervention. The combination of these methods provides a comprehensive approach to AVSD diagnosis and treatment.

Recent studies (*Jegatheeswaran A. et al., Singh P. et al., Yoshitake S. et al., Schumacher et al.)* confirm that a multidisciplinary approach to radiological AVSD diagnosis significantly increases diagnostic accuracy and improves patient prognosis [18, 49, 22, 26, 46, 40].

Classification of Atrioventricular Septal Defect (AVSD)

Atrioventricular septal defects (AVSD) represent a heterogeneous group of congenital heart defects that vary in anatomical configuration, presence, and severity of septal and valvular abnormalities. Based on anatomical characteristics, AVSD can be classified into complete, partial, and intermediate forms.

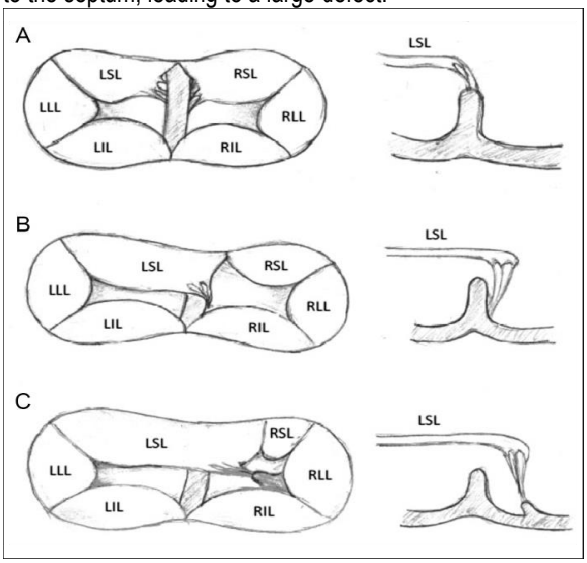
Rastelli Classification

The Rastelli classification is based on the attachment of the superior bridging leaflet to the interventricular septum and distinguishes three types of AVSD:

● Type A – The bridging leaflet attaches to the crest of the interventricular septum, creating a minimal defect.

● Type B – The leaflet extends across the interventricular septum and attaches to an abnormal papillary muscle structure in the right ventricle.

● Type C – The leaflet remains free and does not attach to the septum, leading to a large defect.



This classification was first detailed in the study by *Singh P. et al.* (2010) in the journal *Echocardiography*, highlighting its importance in preoperative planning and patient prognosis [40, 46].

Balanced and Unbalanced Forms of AVSD

AVSD can also be classified based on the balance between the right and left ventricles. This classification is particularly important for determining surgical strategy.

● Balanced AVSD (bAVSD) – The common atrioventricular (AV) valve is positioned to allow relatively equal ventricular filling.

● Unbalanced AVSD (uAVSD) – The septum is shifted toward one ventricle, causing hypoplasia of the affected ventricle and hemodynamic disturbances.

The study by Jegatheeswaran A. et al. (2010) demonstrated that unbalanced forms of AVSD significantly increase the risk of surgical intervention and are associated with higher mortality [26].

Classification Based on Blood Shunting Levels

Another classification method for AVSD is based on the level of pathological blood shunting:

● Atrial-level defect (ostium primum defect) – Blood shunts from the left atrium to the right atrium.

● Ventricular-level defect – Blood shunts through a hole in the interventricular septum.

● Combined defect – Shunting occurs at both the atrial and ventricular levels.

This classification is used to clarify the clinical presentation of AVSD and guide treatment strategies [47].

Anatomical Variations

There are also anatomical subtypes of AVSD that may be associated with other congenital anomalies, such as hypoplastic left heart syndrome, tetralogy of Fallot, and transposition of the great arteries. These features must be considered when selecting a surgical strategy, as highlighted in the study by *Jegatheeswaran A. et al.* (2010).

Thus, the classification of AVSD plays a crucial role in diagnosis, prognosis, and the selection of surgical tactics. Based on echocardiography, CT, and MRI data, the most optimal approach for each patient can be determined.

Clinical Presentation of Atrioventricular Septal Defect

The clinical presentation of atrioventricular septal defect (AVSD) varies depending on the type of defect, degree of blood shunting, functional state of the valves, and presence of associated anomalies. In newborns and young children, AVSD most commonly presents with heart failure symptoms due to significant left-to-right shunting and pulmonary volume overload. According to Rigby M. (2021), these symptoms include tachypnea, poor weight gain, feeding difficulties, and pronounced fatigue with minimal activity [29, 37].

Patients with complete AVSD exhibit more severe symptoms due to substantial volume overload and early development of pulmonary hypertension. Clinicians frequently observe cardiomegaly on physical examination, which is confirmed by chest radiography findings, as reported by *Almarzooq Z. et al.* (2019) [3, 37]. Additionally, auscultation may reveal a systolic murmur caused by regurgitation through the common atrioventricular valve.

In contrast, partial AVSD may remain asymptomatic during childhood and be diagnosed only in adulthood, particularly upon the development of pulmonary hypertension or progressive valvular dysfunction. *Balpande N. et al.* (2022) emphasize that such patients may lack significant symptoms in early stages, but later develop exertional dyspnea, arrhythmias, and signs of right ventricular failure [3, 7].

The clinical course of AVSD is closely linked to the presence of associated syndromes. In patients with Down syndrome, AVSD is detected in 40–50% of cases, and the condition is often complicated by concurrent cardiac and extracardiac anomalies. *Hua Z. et al.* (2020) note that these patients have a higher incidence of progressive pulmonary hypertension, which is attributed to abnormal pulmonary vascular development [47].

Surgical Techniques for the Correction of Atrioventricular Septal Defect

Surgical correction of atrioventricular septal defect (AVSD) is the standard treatment aimed at eliminating anatomical defects, restoring normal hemodynamics, and preventing the progression of pulmonary hypertension. The choice of surgical technique depends on the type of AVSD, the patient's age, defect size, and associated pathologies. The primary approach is biventricular repair, which involves closure of atrial and ventricular septal defects as well as reconstruction of the atrioventricular valve. According to *Fong L.S. et al.* (2019), two main techniques are most commonly used: double patch repair (Double Patch) and modified single patch repair (Modified Single Patch) [4,20].

The double patch technique involves the use of two separate patches to close the atrial and ventricular septal defects, ensuring precise anatomical reconstruction of the septa and valves. This approach is preferred for patients with large defects and complex valve anatomy. The study by *Wang G. et al.* (2020) emphasizes that double patch repair provides long-term structural stability and minimizes the risk of residual defects [20,47].

In contrast, the modified single patch technique involves using one patch to close both the atrial and ventricular septal defects. This method is less invasive and is associated with reduced cardiopulmonary bypass time, making it preferable for infants and high-risk surgical patients. However, as noted by *Alsoufi B. et al.* (2020), the single patch technique may be less effective for large defects and cases with significant valvular insufficiency [4, 16].

For patients with a functionally single ventricle, where complete repair is not feasible, palliative surgical strategies are implemented. These cases require a staged approach, including shunt procedures (e.g., Blalock-Taussig shunt) to improve pulmonary blood flow and the Fontan procedure, which directs venous blood flow to the pulmonary arteries, bypassing the right heart. The study by *Nunes M. et al.* (2021) highlights that staged palliative procedures remain a viable option for patients with severe morphological abnormalities that preclude biventricular repair [7, 13].

Postoperative follow-up is critical for evaluating the effectiveness of surgical repair and detecting complications. The most common postoperative issues include residual septal defects, atrioventricular valve regurgitation, and arrhythmias. These complications often require additional surgical or medical management. According to *Balpande N. et al.* (2022), modern imaging techniques, such as 3D echocardiography and CT, allow for early detection and intervention in postoperative complications [39, 3].

Surgical treatment of AVSD has significantly reduced mortality and improved the quality of life for patients. However, long-term outcomes depend on the accuracy of preoperative diagnostics, the choice of surgical technique, and the effectiveness of postoperative monitoring. Advancements in surgical techniques and anesthetic

management continue to improve the prognosis for patients with this complex congenital heart defect.

Conclusions

Atrioventricular septal defect (AVSD) represents one of the most significant groups of congenital heart defects, characterized by complex anatomy and variability in clinical presentation. Modern data highlight its high prevalence in patients with Down syndrome and its substantial contribution to the overall structure of congenital cardiac anomalies. The diversity of AVSD forms, ranging from partial to complete defects, requires precise diagnosis and an individualized treatment approach. Imaging modalities, including echocardiography, computed tomography, and magnetic resonance imaging, serve as essential tools for assessing the anatomical and functional characteristics of the defect. Echocardiography remains the gold standard for diagnosis, while CT and MRI provide additional data for preoperative planning and postoperative monitoring. The clinical presentation of AVSD varies from an asymptomatic course to severe manifestations of heart failure and pulmonary hypertension. Partial AVSD often remains undetected until adulthood, whereas complete forms present with early symptoms requiring urgent intervention.

Surgical treatment is the primary method of AVSD correction, aiming to restore normal hemodynamics and prevent complications. Modern techniques, such as double and modified single patch repair, have demonstrated high efficacy and safety. In complex cases, including single-ventricle physiology, staged palliative procedures such as shunting and the Fontan procedure are utilized. Long-term treatment outcomes depend on early diagnosis, the selection of an appropriate surgical technique, and meticulous postoperative monitoring. Advanced imaging methods enable the timely detection of complications, such as residual defects and valvular regurgitation, and facilitate appropriate intervention. The importance of a multidisciplinary approach in managing patients with AVSD continues to grow, contributing to improved quality of life and reduced mortality.

This article provides a comprehensive review of the epidemiology, clinical presentation, diagnostic approaches, and surgical treatment methods for AVSD, emphasizing the significance of an individualized approach for each patient. [4, 20, 47, 18, 26]

Contributors. *All the authors equally participated in the selection, assessment, and analysis of the selected studies. All of them have approved the final article.*

Conflict of interest. *The authors declared no potential conflicts of interest with respect to the authorship, research, and publication of this article.*

Funding. *The authors received no financial support for the authorship, research, and publication of this article*

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Received: 28 March 2025 / Accepted: 09 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.025

UDC 616.329-74-018.38-089.843

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MANAGEMENT OF REFRACTORY ANASTOMOTIC STRICTURES FOLLOWING ESOPHAGEAL ATRESIA REPAIR. LITERATURE REVIEW

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Abstract

Background: Refractory anastomotic strictures (AS) following esophageal atresia (EA) repair in children remain a challenging clinical issue, often resistant to standard endoscopic balloon dilatation (EBD). Despite multiple sessions, some patients experience persistent or recurrent symptoms, potentially associated with excessive fibrosis during healing process.

Objective: To evaluate novel, less invasive, and potentially more effective treatment strategies for managing refractory anastomotic strictures after esophageal atresia repair in pediatric patients.

Search strategy: A literature review was conducted using the Web of Science and PubMed databases, covering a 5-year period. The treatment modalities for refractory esophageal anastomotic strictures were categorized into seven groups: (1) intralesional corticosteroid injection (ICI), (2) systemic corticosteroid therapy, (3) topical application of mitomycin C (MMC), (4) endoscopic incisional therapy (EIT), (5) esophageal stenting, (6) cell-based therapies, and (7) magnetic recanalization.

Results: Contemporary treatment options for pediatric refractory esophageal strictures were analyzed. Intralesional corticosteroid injections, particularly triamcinolone, have been associated with reduced dilation frequency in short strictures, though potential complications include adrenal suppression and infectious risks. MMC has shown variable efficacy; some studies reported a reduction in stricture frequency, while others found no significant benefit. EIT has proven effective for short, asymmetric strictures but carries a high risk of esophageal perforation. Both esophageal stenting and systemic corticosteroid therapy remain controversial due to limited supporting evidence. Emerging techniques, including magnetic recanalization and cell-based therapies using autologous grafts or extracellular matrix scaffolds, are still in experimental stages but have shown promising outcomes in select cases.

Conclusion: There is no universally accepted treatment for refractory esophageal strictures. Intralesional corticosteroids and mitomycin C appear promising for short strictures, while novel therapies require further investigation. Prospective, comparative studies involving larger cohorts and long-term follow-up are essential to determine optimal treatment strategies, establish objective efficacy criteria, and confirm the safety of new therapeutic approaches.

Keywords: *esophageal atresia, anastomotic stricture, refractory and recurrent stenosis, adjunctive therapies, esophageal stenting.*

For citation:

Sakuov Zh.N., Lozovoy V.M., Yerekeshov A.A., Bokayeva M.S. Management of Refractory Anastomotic Strictures Following Esophageal Atresia Repair. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 202-210. *doi 10.34689/SH.2025.27.4.025*

Резюме

ЛЕЧЕНИЕ РЕФРАКТЕРНЫХ СУЖЕНИЙ АНАСТОМОЗА ПОСЛЕ КОРРЕКЦИИ АТРЕЗИИ ПИЩЕВОДА. ОБЗОР ЛИТЕРАТУРЫ

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Резюме: Рефрактерные стриктуры анастомоза (СА) после коррекции атрезии пищевода (АП) у детей остаются сложной проблемой, часто устойчивой к стандартной эндоскопической баллонной дилатации (ЭБД). Несмотря на повторные процедуры, у ряда пациентов наблюдается рецидив или стойкое персистирование симптомов, что может быть связано с усиленным фиброгенезом в процессе заживления.

Цель: Изучить новые, менее инвазивные и более эффективные варианты лечения рефрактерных стриктур анастомоза после коррекции атрезии пищевода у детей.

Методы: Обзор литературы был проведен с использованием баз данных Web of Science и PubMed. Глубина поиска составила 5 лет. Методы лечения рефрактерных сужений анастомоза пищевода были разделены на семь групп: (1) внутриочаговая инъекция глюкокортикостероидов (ВИГ), (2) системная терапия глюкокортикостероидами (ГКС), (3) применение митомицина С (ММС), (4) эндоскопическая инцизионная терапия (ЭИТ), (5) стентирование пищевода, (6) клеточная терапия, (7) магнитная реканализация.

Результаты: Рассмотрены современные подходы к лечению рефрактерных анастомотических стриктур пищевода у детей после коррекции атрезии пищевода (АП). Внутриочаговое инъекции глюкокортикостероидов, особенно триамцинолона, показали снижение частоты дилатаций при коротких стриктурах, но сопровождаются рисками, включая супрессию надпочечников и инфекционные осложнения. Митомицин С, применяемый локально, продемонстрировал противоречивые результаты: в некоторых исследованиях отмечено уменьшение частоты стриктур, в других — отсутствие эффекта. Эндоскопическая инцизионная терапия эффективна при коротких и асимметричных стриктурах, но связана с высоким риском перфорации пищевода. Стентирование и системная терапия глюкокортикостероидами остаются спорными методами с ограниченной доказательной базой. Новые технологии, включая магнитную реканализацию и клеточную терапию с использованием аутологичных трансплантатов или внеклеточного матрикса, находятся на экспериментальной стадии, но демонстрируют обнадеживающие результаты в отдельных случаях.

Выводы: Не существует универсального метода лечения рефрактерных стриктур пищевода. Наиболее перспективны внутриочаговое введение глюкокортикостероидов и Митомицина С при коротких стриктурах, тогда как инновационные методы требуют дальнейших исследований. Необходимы последующие проспективные, сравнительные исследования с большим количеством пациентов и долгосрочным наблюдением для определения оптимальных стратегий, разработки объективных критериев оценки эффективности и подтверждения безопасности новых терапевтических подходов.

Ключевые слова: *атрезия пищевода, сужение анастомоза, рефрактерные и рецидивирующие стриктуры, вспомогательные методы лечения, стентирование пищевода*.

Для цитирования:

Сакуов Ж.Н., Лозовой В.М., Ерекешов А.А., Бокаева М.С. Лечение рефрактерных сужений анастомоза после коррекции атрезии пищевода. Обзор литературы // Наука и Здравоохранение. 2025. Vol.27 (4), С.202-210. *doi 10.34689/SH.2025.27.4.025*

Түйіндеме

ӨҢЕШ АТРЕЗИЯСЫН ТҮЗЕТУДЕН КЕЙІНГІ РЕФРАКТЕРЛІ АНАСТОМОЗДЫҚ ТАРЫЛУЛАРДЫ ЕМДЕУ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Өңеш атрезиясын хирургиялық түзетуден кейінгі рефрактерлі анастомоздық стриктуралар (АС) балалар арасында эндоскопиялық баллонды дилатацияға (ЭБД) тұрақты жауап бермейтін күрделі мәселе болып қала береді. Қайталама процедураларға қарамастан, кейбір науқастарда симптомдардың қайта пайда болуы немесе тұрақты сақталуы байқалады, бұл жазылу процесіндегі күшейген фиброгенезбен байланысты болуы мүмкін.

Мақсаты: Өңеш атрезиясын түзеткеннен кейін дамитын рефрактерлі анастомоздық стриктураларды емдеудің тиімді әрі инвазивтілігі төмен жаңа әдістерін зерттеу.

Әдістер: Web of Science және PubMed деректер базасы арқылы соңғы 5 жыл ішіндегі әдебиетке шолу жүргізілді. Өңеш анастомозы стриктураларын емдеу әдістері келесі жеті топқа бөлінді: (1) ошақішілік глюкокортикостероидты инъекция (ГКС), (2) жүйелі глюкокортикостероидты терапия, (3) митомицин С (ММС) қолдану, (4) эндоскопиялық инцизиялық терапия (ЭИТ), (5) өңешті стенттеу, (6) жасушалық терапия, (7) магниттік реканализация.

Нәтижелер: Өңеш атрезиясын түзеткеннен кейінгі рефрактерлі анастомоздық стриктураларды емдеудің қазіргі тәсілдері қарастырылды. Глюкокортикостероидтардың, әсіресе триамцинолонның ошақішілік инъекциялары қысқа стриктураларда дилатация жиілігін төмендеткенімен, бүйрек үсті безі функциясының тежелуі және инфекциялық

асқынулар секілді қауіптермен байланысты. Митомицин С жергілікті қолданылғанда әртүрлі нәтижелер көрсетті: кейбір зерттеулерде стриктура жиілігі азайған, басқаларында әсері болмаған. Эндоскопиялық инцизиялық терапия қысқа және асимметриялық стриктураларда тиімді, бірақ өңештің перфорациясы қаупімен шектеледі. Стенттеу және жүйелі ГКС терапиясы дәлелдеме базасы жеткіліксіз, даулы әдістер болып қалып отыр. Жаңа технологиялар, соның ішінде магниттік реканализация мен аутологиялық трансплантаттар немесе жасушасыз матрикс арқылы жасушалық терапия әлі эксперименттік сатыда, бірақ жекелеген жағдайларда үміт күттіреріік нәтижелер көрсетті.

Қорытынды: Рефрактерлі өңеш стриктураларын емдеудің әмбебап әдісі жоқ. Қысқа стриктураларда ГКС және ММС ошақішілік қолдану ең перспективті тәсілдер болып табылады, ал инновациялық әдістерді кеңірек зерттеу қажет. Емнің қауіпсіздігі мен тиімділігін дәлелдейтін, үлкен популяцияда жүргізілетін болашақ проспективті, салыстырмалы зерттеулер қажет.

Түйінді сөздер: *өңеш атрезиясы, анастомоздық стриктура, рефрактерлі және рецидивті стриктуралар, қосымша емдеу әдістері, өңешті стенттеу.*

Дәйексөз үшін:

Сакуов Ж.Н., Лозовой В.М., Ерекешов А.А., Бокаева М.С. Өңеш атрезиясын түзетуден кейінгі рефрактерлі анастомоздық тарылуларды емдеу. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 202-210. *doi 10.34689/SH.2025.27.4.025*

Introduction

Despite dilation treatment of postoperative esophageal stricture, some patients may experience recurrence or persistent symptoms. The causes of recurrent episodes or persistent anastomotic stenosis (AS) are not fully understood. The development of stricture is influenced by numerous initial conditions, as well as intra- and postoperative risk factors, which can significantly affect the outcome of the disease. The dilation procedure, in turn, may partially contribute to increased fibrogenesis during healing, which is an important factor in repeat interventions. Repeated dilation sessions increase the risk of complications and can have a negative impact on the psychological state of patients, especially children. If the stricture becomes resistant to dilation, it is preferable to adhere to a conservative approach before considering the patient as a candidate for surgical intervention [42]. Despite the lack of specialized controlled studies, various non-surgical methods of adjuvant treatment can be used in clinical practice for refractory and recurrent AS.

Search strategy

A comprehensive literature review was conducted using the PubMed and Web of Science databases, with a cutoff date of December 31, 2024. The search strategy included combinations of the following keywords: “esophageal atresia”, “anastomotic stricture”, “refractory”, “recurrent”, “adjunctive treatment”, and “esophageal stenting”.

Studies published between 2020 and 2024 were screened, with a particular emphasis on refractory or recurrent anastomotic strictures following esophageal atresia repair. Given the limited availability of pediatric data, additional studies were included if they addressed esophageal strictures of other etiologies - such as caustic injuries - that shared similar clinical behavior and treatment challenges.

Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Studies were included if they reported outcomes of adjunctive or alternative therapies for refractory esophageal strictures in pediatric patients. Included interventions were categorized into seven groups: intralesional corticosteroid injection, systemic corticosteroid therapy, topical mitomycin C application, endoscopic incisional therapy, esophageal stenting, cell-based therapies, and magnetic recanalization.

Each treatment modality was evaluated based on its reported effectiveness and safety, the durability of response, the need for repeated dilatations, and the occurrence of complications. In cases where pediatric-specific data were lacking, relevant findings from adult populations were considered to supplement and contextualize the evidence base.

Results

An analysis of contemporary approaches to the treatment of refractory anastomotic strictures following esophageal atresia (EA) repair over the past five years has identified seven main techniques, which are presented below.

Intralesional injection of glucocorticosteroids (GCS)

The administration of GCS into the stricture area, in addition to dilation, was proposed for the prevention of recurrence more than 50 years ago. Despite extensive clinical experience, the mechanism of action remains poorly understood. GCS are effective in hypertrophic scars and keloids, making them potentially useful in recurrent anastomotic strictures. The administration of GCS, such as triamcinolone acetonide (TAC), reduces collagen synthesis, enhances its breakdown, and reduces fibrous healing after dilation, preventing cross-linking of collagen molecules and the formation of contractures in scar tissue, improving long-term treatment outcomes [3,44].

The most commonly used steroid for intralesional injections is triamcinolone acetate or acetonide; betamethasone and dexamethasone preparations are also used [25]. TAC is usually injected using a standard sclerotherapy needle into four quadrants of the esophagus along the proximal edges of the stricture prior to dilation, as described in *Ramage et al.* [38]. In some cases, an additional injection is made directly into the scar tissue if its thickness is uneven. The concentration used varies from 10 to 40 mg/ml according to different sources. The authors prefer 10 mg/ml, as 40 mg/ml is more viscous and requires dilution before use [50]. Steroids can be administered before and after dilation therapy. The optimal number of injections remains controversial, but some experts limit themselves to three procedures, since further administration does not provide any additional effect and is also associated with an increased risk of systemic and local complications [45].

A systematic review and meta-analysis involving more than 3,000 patients demonstrated the efficacy of intrafocal glucocorticosteroid injections (IGI) in the treatment of esophageal anastomotic strictures. On average, patients required 2.1 injections, and the number of dilations decreased from 5.2 to 1.13 after steroid administration [45]. *Gandhi et al.* described a series of 12 patients, 5 of whom underwent correction of esophageal atresia and received IGI in combination with dilation, which resulted in long-term remission of symptoms. [21]. Two retrospective studies have shown that intralesional steroid injections for benign esophageal strictures in children are more effective in short-segment lesions, reducing the frequency of dilations and increasing the intervals between them. No significant improvement was observed in long strictures, indicating that the effectiveness of the method depends on the length of the stricture [11,14].

Potential complications of esophageal steroid injections include adrenal suppression, esophageal perforation, intramural infection, candidal infection, mediastinitis, pleural effusion, and growth retardation [45]. In addition, there is a separate report of spontaneous rupture of the right aortic arch, presumably associated with weakening of the arterial wall under the influence of steroids [28]. *Annefleur et al.* report in a meta-analysis that the overall incidence of adverse effects was moderate at 7.1%, with most adverse effects being local in nature and not requiring additional treatment (approximately 10%), while systemic complications were less common (0.7%) and were associated with adrenal insufficiency, Cushing's syndrome, or growth retardation [45]. Therefore, careful clinical monitoring and assessment of growth curves in patients receiving IGI is necessary.

In conclusion, it should be noted that since studies investigating the efficacy and safety of intralesional steroid therapy are few, uncontrolled, and heterogeneous, it is difficult to draw definitive conclusions about the benefit of steroids in reducing recurrent stricture formation in patients with EA. The guidelines for pediatric gastrointestinal endoscopy do not recommend the routine use of intrafocal steroids for refractory esophageal strictures in children [26,42]. Prospective, comparative studies need to be conducted before intralesional steroid injection is recognized as a safe and effective method.

Systemic therapy with glucocorticosteroids

Systemic GCS therapy is considered a possible alternative treatment for refractory esophageal strictures in cases where standard approaches, such as intralesional steroid injections and dilation, prove ineffective. However, the use of this technique in endoscopic dilation has been described only in isolated clinical cases.

Hishiki et al. reported a patient with esophageal atresia (EA) who developed refractory anastomotic stricture (AS), requiring surgical resection of the stenosed segment followed by anastomotic reconstruction. The secondary AS was resistant to balloon dilation but regressed after two short courses of intravenous dexamethasone (1 mg/kg) [24].

Morikawa et al. described the use of high doses of methylprednisolone in a patient with refractory AS who was scheduled for surgery. The patient underwent a stepwise dose reduction regimen: methylprednisolone was administered intravenously (25, 15, 10, 5, and 2 mg/kg daily for 4 days each) after balloon dilatation with intrafocal steroid injection, and then sequentially replaced with oral prednisolone (2, 1, and 0.5 mg/kg daily for 1 week each). As a result of this therapy, the AS finally regressed [36].

Yokota et al. investigated the efficacy of intravenous pulse therapy with steroids after balloon dilatation for the prevention of restenosis. In their study, none of the patients experienced serious side effects such as adrenal insufficiency, gastrointestinal ulcers, or severe infections, indicating the relative safety of short-term use of systemic GCS [52].

To date, the use of systemic GCS in refractory AS remains limited, as this strategy requires careful assessment of potential risks. The literature reports cases of adrenal suppression even with local administration of steroids, especially in the context of AS treatment after BP correction. In this regard, dynamic monitoring of patients receiving steroid therapy is recommended, with monitoring of adrenal function and replacement therapy if necessary [5].

Mitomycin C

Mitomycin C (MMC) is an antibiotic isolated in 1958 from Streptomyces caespitosus. In addition to its antimicrobial and well-known antineoplastic properties, it has antiproliferative effects, reducing collagen synthesis and scar formation [6]. In this regard, MMC has been proposed as an additional method for treating esophageal strictures.

The method of MMC administration is an important aspect that requires special attention. The drug should act strictly on the stenotic segment without having a potentially dangerous effect on the surrounding healthy mucous membrane. The most common method is the local application of MMC solution using a cotton swab under endoscopic control [42]. To protect the mucosa from contact with the drug, methods using tubes, caps, and ligators for varicose veins of the esophagus have been described. The use of a microporous polytetrafluoroethylene catheter balloon with drug elution, inserted through the stricture under fluoroscopic control, has also been proposed [23]. Alternative methods include direct instillation[55] and MMC injections into the walls of the stenosis after its dilation [56].

MMC is usually prepared immediately before use. According to a recent systematic review, the concentration of the drug ranged from 0.1 to 1 mg/ml, the volume was 1–3 ml, and the number of procedures ranged from 1 to 12, with a median of 1–2 applications. When re-administered, the intervals between procedures ranged from 1 week to 13 months, with a median of 4 weeks [39]. A concentration of 0.4 mg/ml is the most commonly used [8]. However, recent studies have not revealed any significant differences in the effectiveness of MMC depending on the method of application or concentration [29].

The efficacy of MMC in anastomotic strictures remains a subject of debate. One study reported a 71% efficacy rate in patients with esophageal atresia (mainly type C), where success was defined as a reduction in the frequency of endoscopic dilations after administration of the drug [29]. Another study showed that injectable MMC after at least two dilations in patients with recurrent stenosis was highly effective. Factors that increased the success of therapy were short and single stenosis, as well as Esophageal atresia (EA) type C [12]. At the same time, *Divarci et al.* did not find any effect of stricture length on the effectiveness of MMC [15].

Similarly, based on a study involving 31 patients reported in 11 publications (clinical cases and small series of patients), the authors concluded that MMC was effective (defined as clinical improvement) in 68% of patients [6]. An analysis of 24 studies involving both children and adult patients showed that a complete response was achieved in 73% of patients receiving MMC as treatment for refractory strictures of the gastrointestinal tract [39].

Mitomycin C has demonstrated its effectiveness in several prospective studies on post-burn strictures. In a double-blind RCT, El-Asmar et al. showed that 80% of patients with short caustic esophageal strictures experienced complete resolution of strictures, compared with 35% in the placebo group [16]. In a similar study of long caustic strictures, the efficacy reached 85.7% when using 0.5 mg/ml MMC [17].

However, a number of studies have shown low efficacy of MMS. *Chapuy et al.* compared the use of MMS with repeated dilations in patients with severe forms of EA types A and C. Stricture resolution was observed in 73% of patients after 1.9 sessions with MMS, while in the group without MMC, successful treatment was achieved in 90% of children after 3 balloon dilations [12].

Zimmer et al. report a 55% success rate, where the length of the stricture ranged from 2 to 8 mm and successful treatment was defined as endoscopic resolution of the stricture, whereas in many studies the clinical dysphagia score was used. The authors determined that the response rate to mitomycin C was 60% in patients with stenosis less than 4 mm and 50% in children with stenosis greater than 4 mm [32]. *Rosseneu et al.* obtained similar results [55]. In addition, a systematic review and meta-analysis of the efficacy of MMC in post-burn strictures did not reveal statistically significant differences in the total number of dilations between groups with and without the use of the drug [18].

The most dangerous systemic side effects of MMC are changes in heart rate or blood pressure, allergic reactions, and bone marrow suppression[27]. Among local complications, there is an increased risk of iatrogenic perforation. Chapuy et al. suggested that in their study, the appearance of reflux could be associated with subclinical perforation caused by MMC [12]. In another study by this group, perforation was recorded during the procedure, which was treated conservatively [12].

Another complication of MMC injection is the formation of peptic ulcers [22], which makes local application more preferable. However, Wishahy et al. did not record ulcer formation in their study [47].

Since mitomycin C is a cytostatic drug, one of the potential side effects may be dysplasia of healthy tissues after accidental exposure during application. This risk is expected to increase, especially with repeated use. Cases of de novo gastric metaplasia in the anastomosis area after local application of mitomycin C have been reported. Ley et al. found one case of gastric metaplasia in a child with caustic stenosis, but were unable to determine its exact cause - whether it was caused by mitomycin C, cauterization, or dilations [29]. Dysplastic lesions of the upper gastrointestinal tract have not been described in the literature, but the limited number of observations requires long-term endoscopic monitoring with biopsy.

Although the data obtained in the pediatric population are promising, large randomized clinical trials (RCTs) are needed before the administration of mitomycin C becomes the standard of care for children with benign recurrent esophageal stricture.

Endoscopic incisional therapy (EIT)

Endoscopic incisional therapy (EIT) is used for congenital strictures, strictures that have developed as a result of chemical burns, and postoperative complications following correction of esophageal atresia. The method is based on the understanding that many strictures, especially anastomotic ones, have an asymmetrical structure with areas of varying degrees of scar tissue thickness. While balloon dilation can lead to rupture in areas with thinner scar tissue, EIT allows selective treatment of denser fibrous areas, which increases the effectiveness of treatment [50].

The procedure is performed using an electrosurgical needle knife and involves a series of radial incisions parallel to the longitudinal axis of the esophagus in the area of the stricture, followed by endoscopic balloon dilation. All stages of the procedure are performed under direct endoscopic visualization. This method is considered to be most effective for strictures less than 1 cm in length [33].

Tan Y. et al. reported a case of successful treatment of refractory esophageal stricture using a combination of endoscopic incisional therapy (EIT) and esophageal stenting. In a recent retrospective study involving seven pediatric patients, sustained clinical improvement in dysphagia symptoms was observed in 71.4% (5 out of 7) during a follow-up period ranging from 1 to 21 months. Based on the hypothesis that longer strictures are associated with a higher risk of recurrence, three patients with strictures exceeding 1.5 cm received additional esophageal stenting as part of their management strategy [43].

Manfredi et al. reported favorable outcomes following endoscopic incisional therapy (EIT) in a cohort of 42 patients, including 40 with anastomotic strictures. Treatment effectiveness was observed in 78% (32 out of 41 cases) at 6 months and 64.5% (20 out of 31 cases) at 12 months post-intervention. Procedural success was defined as requiring no more than five dilations within six months following EIT, while long-term success was defined as needing no more than six dilations within 12 months. The overall incidence of esophageal perforation associated with the procedure was 4.4% [33].

In another study involving 58 patients, EIT achieved stricture resolution in 76% of patients during 2 years of follow-up. In the subgroup of patients with refractory strictures, the efficacy of the method was 61%, and the incidence of perforations was 2.3% [34].

In a study by *Yasuda et al.,* the incidence of perforations during balloon dilation without EIT in patients with congenital esophageal stenosis was 2.5% (3/118 endoscopies), while the incidence of perforations during endoscopic interventions involving EIT reached 29% (17/58 endoscopies). As expected, the risk of complications was significantly higher in procedures involving EIT [51].

Although the complication rate remains low, its significance requires special attention. It is necessary for the endoscopist to be prepared to repair esophageal perforation using appropriate endoscopic techniques (e.g.,

EVAC or stenting) and to have experience in surgical correction of complications.

Esophageal stenting

Esophageal stenting relies on the same fundamental principle as balloon dilation - applying continuous circumferential radial pressure to mechanically widen the esophageal lumen [28]. Early reports described the use of silicone tubes [13] and polytetrafluoroethylene (PTFE) stents [4,37], which were externally fixed via the nasal passage to maintain positioning. More recent studies have focused on the use of self-expanding stents, which can be placed either endoscopically or under fluoroscopic guidance. Various types of self-expanding stents have been employed in pediatric patients, including plastic [9], metallic [53] and biodegradable stents [46], depending on the specific clinical context and stricture characteristics.

Self-expanding metal stents (SEMS) are cylindrical mesh devices composed of woven, knitted, or laser-cut metallic structures, typically made of nitinol, an alloy of nickel and titanium. These stents are designed to self-expand to a predetermined diameter. To minimize tissue ingrowth through the stent mesh, SEMS may be fully or partially covered with a plastic or silicone membrane [1]. Self-expanding plastic stents (SEPS) consist of a woven polyester framework entirely encased in a silicone membrane. Radiopaque markers located at both ends and the midsection allow for precise fluoroscopic guidance during placement [1]. Biodegradable stents (BDS) are constructed from biodegradable polymers that gradually dissolve in vivo, thereby eliminating the need for endoscopic removal. These stents typically retain their structural integrity and radial force for approximately 6 weeks, with complete degradation occurring within 11 to 12 weeks post-implantation [2]. While all three stent types etallic, plastic, and biodegradable - have been utilized in the management of refractory benign esophageal strictures in adults, only SEPS are currently approved for use in children [41]. Pediatric data on esophageal stenting remain limited and heterogeneous, with reported clinical success rates ranging from 26% to 86% depending on patient selection and procedural technique [7,9,19,35]. Data on stenting specifically in children with esophageal atresia (EA) are even more scarce. *Manfredi et al.* reported outcomes in 23 pediatric patients with EA who underwent 40 esophageal stenting procedures. The reported success rates were 39% at ≥30 days and 26% at ≥90 days following stent removal. Both bare metal stents (used in 14 patients) and fully covered stents (used in 26 patients) were included in the analysis. The mean duration of stent placement was 9.7 days, with a range from 2 to 30 days [35].

In conclusion, esophageal stenting represents a promising therapeutic option for the management of recurrent and refractory anastomotic strictures. Its main advantages include prolonged maintenance of luminal patency and improved oral intake. However, stent tolerance may be suboptimal in pediatric patients, and complications such as stent migration and other adverse events may occur. The long-term efficacy and safety of esophageal stenting in children require further confirmation through prospective clinical studies.

Magnetic recanalization

Magnetic recanalization and magnetic compression anastomosis (MCA) are emerging techniques for the treatment of refractory esophageal strictures in children. The first successful pediatric case of magnetic recanalization for esophageal stenosis was reported by *Bulyhin et al.* in 1993 [54]. These techniques utilize magnetic devices and magnetic force to eliminate scar tissue at the site of the anastomosis without injuring the muscular layer of the gastrointestinal tract [31]. MCA involves positioning magnets on either side of the stricture; once aligned, the magnetic attraction induces localized ischemia, leading to necrosis and sloughing of the fibrotic tissue, thereby re-establishing esophageal patency. Key technical parameters include the orientation, strength, and intermagnetic distance. Increasing the length of the cylindrical magnet array proportionally enhances the magnetic flux density and, consequently, the attractive force. An expert consensus has been established to guide the clinical use of MCA, addressing aspects such as patient selection, magnetic device design, surgical approach, perioperative care, and prevention of complications. Indications for magnetic recanalization include short-segment esophageal stenosis - postoperative, congenital, or caustic in origin - typically measuring less than 2 cm, though limited use in 2–3 cm lesions has been described. Contraindications include the presence of a tracheoesophageal fistula, esophageal perforation, stenotic segments longer than 4 cm, and ectopic tracheal cartilage in cases of congenital stenosis [30].

The literature describes cases of successful use of magnetic compression stricturoplasty in children with refractory strictures after repair of esophageal atresia. A study by *Woo et al.* reports the successful treatment of two patients with refractory strictures using neodymium magnets. Additional interventions, such as balloon dilation and stenting, were required after the procedure, but after 31 months, both patients had sustained esophageal patency without dysphagia[48].

In conclusion, magnetic recanalization and MCA are promising methods for treating refractory esophageal strictures in children. Further research and accumulation of clinical experience will allow this technology to be optimized and its long-term effectiveness to be determined. Knowledge of the fundamental principles of magnetism is crucial for the successful application of magnets in surgery.

Cell therapy

In the search for more effective and less invasive treatment strategies, cell therapy and tissue engineering—particularly those involving somatic stem cells—have emerged as promising areas of investigation. One actively explored approach is the transplantation of cell sheets derived from autologous oral mucosa. This technique is based on the concept of cell sheet engineering, which enables the cultivation and harvesting of intact cellular layers without the use of proteolytic enzymes, thereby preserving the extracellular matrix and facilitating seamless engraftment.

Previous clinical studies in adults with esophageal squamous cell carcinoma have demonstrated the efficacy of autologous oral mucosal cell sheet transplantation in preventing post-procedural esophageal stenosis following extensive endoscopic submucosal dissection. These findings provide a rationale for further investigation into the application of this method in the pediatric population, particularly in cases of refractory or recurrent esophageal strictures [49].

The use of this method in children with refractory postoperative anastomotic stenosis after correction of

esophageal atresia and stenosis was investigated in a clinical trial. In one of the three patients, despite two transplants, the effect was temporary and limited, which ultimately led to the need for surgical resection of the stenosis due to severe fibrosis and thickening of the submucosal layer. The researchers suggest that the high degree of scarring and the large number of previous endoscopic balloon dilations (more than 100 procedures) in this patient may have limited the effectiveness of the therapy. However, in two other patients, cell sheet transplantation was more successful: they did not require endoscopic balloon dilation for at least 48 weeks, and one of them for more than two years, allowing them to return to a normal diet. These results confirm that cell sheet transplantation can be effective in some cases of refractory anastomotic stenosis [20].

Another emerging approach involves tissue engineering using biocompatible scaffolds to reconstruct esophageal defects. A systematic review and meta-analysis of preclinical studies in animal models demonstrated that this strategy holds significant promise for esophageal tissue regeneration, although it remains associated with considerable challenges [40]. The most commonly reported postoperative complications in experimental models included graft stenosis (46%), postoperative dysphagia (15%), and anastomotic leakage (12%).

Various types of scaffolds have been investigated, including non-absorbable materials (e.g., silicone or collagen-based), absorbable polymers (e.g., polyglycolic acid combined with collagen), and decellularized extracellular matrices. Seeding these scaffolds with mesenchymal stem cells (MSCs) appears particularly promising, as MSCs possess multipotent differentiation capacity and may support the regeneration of functional esophageal tissue.

Despite their potential, critical limitations—such as graft stenosis and the lack of peristaltic motility in bioengineered esophageal segments—remain major obstacles and require further investigation in preclinical settings before transitioning to large-scale clinical trials. Nevertheless, a clinical case report has described the successful use of a decellularized extracellular matrix scaffold for treating recurrent esophageal stricture in a child, suggesting potential feasibility in select cases [10].

Overall, cell-based therapies and tissue engineering approaches represent promising strategies for the treatment of refractory esophageal anastomotic strictures. However, these modalities require further refinement and the conduct of well-designed prospective clinical trials to validate their long-term efficacy and safety, as well as to establish the optimal indications and treatment protocols for pediatric patients.

Discussion

The management of refractory anastomotic strictures (AS) in children following esophageal atresia (EA) repair often requires the application of various treatment modalities. Although several adjunctive and experimental techniques have been described, none has yet emerged as a universal standard of care. The lack of controlled and methodologically homogeneous studies makes it difficult to draw definitive conclusions regarding the efficacy and safety of most available interventions.

Further prospective, comparative studies with larger patient cohorts and long-term follow-up are necessary to identify optimal treatment strategies, establish objective criteria for assessing clinical outcomes, and confirm the safety of novel therapeutic approaches.

Conflict of Interest. *The authors declare that they have no conflict of interest.*

Contribution of authors. *All authors were equally involved in the writing of this article.*

Funding: *No funding was provided*

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Received: 09 October 2024 / Accepted: 18 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.026

UDC 616.43

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DIABETIC FOOT SYNDROME: MULTIDISCIPLINARY ASPECTS AND THE ROLE OF NURSES

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Abstract

Background. Diabetic foot ulcers are a common complication of diabetes that can lead to limb amputation. Effective treatment of this condition requires in-depth knowledge of risk factors, regular medical monitoring, and careful prevention.

Aim: to analyze current understanding of the pathogenesis, diagnosis, and prevention of diabetic foot.

Search strategy. We conducted a literature search and included articles published between 2014 and 2024. Search queries were regularly performed in academic databases (PubMed, MEDLINE, CINAHL, Embase). No gender filters were used in the search, only patients over 18 years of age were included by age, observational, experimental, and secondary studies were included by study type. In addition to the main search, references of relevant publications were analyzed, international and national guidelines were analyzed to include current approaches to the diagnosis, treatment, and prevention of diabetic foot.

Results. The analysis showed that the pathogenesis of diabetic foot involves complex processes associated with impaired microcirculation, neuropathy, and infection. Teaching patients proper foot hygiene, nail care, and choosing the right footwear plays a key role in reducing the risk of injury. Diagnostic approaches continue to improve, allowing for early detection of pathology and increased treatment effectiveness. Following a systematic approach to diagnosis and classification improves communication between physicians and specialists, simplifying the treatment of complications. Such a coordinated approach may ultimately lead to a reduction in the number of diabetes-related lower limb amputations.

Conclusions. Foot changes in patients with diabetes have become one of the most common complications and the main reason for hospitalization. Treatment should be comprehensive, including hyperglycemia control, wound care, and infection therapy. Effective care should be multidisciplinary and personalized according to the patient's condition and needs. It is important to provide prevention education, emotional support, and encourage the patient to follow recommendations, including regular foot care and blood glucose monitoring.

Keywords: *type 2 diabetes mellitus, diabetic foot syndrome, primary health care, multidisciplinary team, nurse.*

For citation:

Batarbekova Sh., Zhunussova D., Derbissalina G., Bekbergenova Zh. Diabetic foot syndrome: multidisciplinary aspects and the role of nurses // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 211-221. *doi 10.34689/SH.2025.27.4.026*

Резюме

СИНДРОМ ДИАБЕТИЧЕСКОЙ СТОПЫ: МЕЖДИСЦИПЛИНАРНЫЕ АСПЕКТЫ И РОЛЬ МЕДСЕСТЕР

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Актуальность. Диабетические язвы на стопе – частое осложнение при диабете, которое может привести к ампутации конечности. Эффективное лечение этого состояния требует глубоких знаний о факторах риска, регулярного медицинского наблюдения и тщательной профилактики.

Цель: проанализировать современные представления о патогенезе, диагностике и профилактике синдрома диабетической стопы.

Стратегия поиска. Нами был проведен поиск литературы и в описательный обзор включены статьи, опубликованные в период с 2014 по 2024 год. Поисковые запросы регулярно выполнялись в академических базах данных (PubMed, MEDLINE, CINAHL, Embase). При осуществлении поиска фильтры по полу не применялись, по возрасту включались только пациенты старше 18 лет, по типу исследований включались обсервационные, экспериментальные исследования, а также вторичные исследования. В дополнение к основному поиску был

проведен анализ ссылок релевантных публикаций и анализ международных и национальных рекомендаций с целью включения актуальных подходов к диагностике, лечению и профилактике диабетической стопы.

Результаты. В результате проведённого анализа установлено, что патогенез диабетической стопы включает сложные процессы, связанные с нарушением микроциркуляции, развитием нейропатии и инфекционного процесса. Обучение пациентов правильной гигиене стоп, уходу за ногтями и выбору правильной обуви играет ключевую роль в снижении риска получения травм, которые могут вызвать появление язв. Диагностические подходы продолжают совершенствоваться, что позволяет выявлять патологию на ранних стадиях и повышать эффективность терапии. Следование систематическому подходу к диагностике и классификации способствует улучшению взаимодействия между врачами и специалистами, что упрощает лечение осложнений. Такой согласованный подход в конечном итоге может привести к сокращению числа ампутаций нижних конечностей, связанных с диабетом.

Выводы. Изменения стоп у пациентов с сахарным диабетом 2 типа стали одним из наиболее часто встречающихся осложнений, являются главной причиной госпитализации. Лечение должно быть комплексным, включая контроль гипергликемии, обработку ран, терапию инфекций. Эффективный уход должен быть мультидисциплинарным и персонализированным в соответствии с состоянием и потребностями пациента. Важно проводить обучение по профилактике, обеспечивать эмоциональную поддержку и стимулировать пациента следовать рекомендациям, включая регулярный уход за ногами и контроль уровня глюкозы в крови.

Ключевые слова: *сахарный диабет 2 типа, синдром диабетической стопы, первичная медико-санитарная помощь, мультидисциплинарная команда, медицинская сестра.*

Для цитирования: *Батарбекова Ш., Жунусова Д., Дербисалина Г., Бекбергенова Ж.* Синдром диабетической стопы: мультидисциплинарные аспекты и роль медицинских сестер // Наука и Здравоохранение. 2025. Vol.27 (4), С. 211-221. *doi 10.34689/SH.2025.27.4.026*

Түйіндеме

ДИАБЕТТІК ТАБАН СИНДРОМЫ: МУЛЬТИДИСЦИПЛИНАРЛЫҚ АСПЕКТІЛЕР ЖӘНЕ МЕЙІРГЕРЛЕРДІҢ РӨЛІ

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Өзектілігі. Диабеттік аяқтың жарасы қант диабетінің жиі кездесетін асқынуы болып табылады және ампутацияға әкелуі мүмкін. Бұл жағдайды тиімді емдеу қауіп факторларын терең білуді, тұрақты медициналық бақылауды және мұқият алдын алуды талап етеді.

Мақсаты: диабеттік табан синдромының патогенезі, диагностикасы және алдын алу туралы заманауи идеяларды талдау.

Іздеу стратегиясы. Біз әдебиеттерді іздестірдік және 2014–2024 жылдар аралығында жарияланған мақалаларды әңгіме шолуына қостық. Іздеу жүйелі түрде академиялық деректер қорларында жүргізілді (PubMed, MEDLINE, CINAHL, Embase). Іздестіру кезінде жынысы бойынша сүзгілер пайдаланылмаған, жас бойынша тек 18 жастан асқан емделушілер, ал зерттеу түрі бойынша бақылау, эксперименттік және қайталама зерттеулер енгізілген. Негізгі іздестіруден басқа, диабеттік табан диагностикасына, емдеуге және алдын алуға қазіргі көзқарастарды қамту үшін тиісті басылымдардың сілтемелеріне шолу және халықаралық және ұлттық ұсыныстарды талдау жүргізілді.

Нәтижелер. Талдау нәтижесінде диабеттік табанның патогенезі микроциркуляцияның бұзылуымен, нейропатияның дамуымен және инфекциялық процеспен байланысты күрделі процестерді қамтитыны анықталды. Науқастарды аяқтың дұрыс гигиенасы, тырнақ күтімі және дұрыс аяқ киім туралы үйрету ойық жара тудыруы мүмкін жарақаттар қаупін азайтудың кілті болып табылады. Диагностикалық тәсілдер жетілдірілуде, бұл патологияны ерте кезеңде анықтауға және терапияның тиімділігін арттыруға мүмкіндік береді. Диагностика мен жіктеуге жүйелі көзқарасты ұстану дәрігерлер мен мамандар арасындағы байланысты жақсартады, асқынуларды басқаруды жеңілдетеді. Бұл үйлестірілген тәсіл, сайып келгенде, қант диабетімен байланысты төменгі аяқтардың ампутациясын азайтуға әкелуі мүмкін.

Қорытындылар. 2 типті қант диабеті бар науқастарда аяқтың өзгеруі жиі кездесетін асқынулардың біріне айналды және ауруханаға жатқызудың негізгі себебі болып табылады. Емдеу гипергликемияны бақылауды, жараларды емдеуді және инфекцияларды емдеуді қамтитын кешенді болуы керек. Тиімді күтім науқастың жағдайы мен қажеттіліктеріне сәйкес мультидисциплинарлы және дербестендірілген болуы керек. Профилактикалық білім беру, эмоционалды қолдау көрсету және науқасты ұсыныстарды орындауға ынталандыру, соның ішінде тұрақты аяқ күтімі және қандағы глюкоза деңгейін бақылау маңызды.

Түйін сөздер: *2 типті қант диабеті, диабеттік табан синдромы, алғашқы медициналық көмек, көпсалалы команда, мейіргер.*

Дәйексөз үшін: *Батарбекова Ш., Жунусова Д., Дербисалина Г., Бекбергенова Ж.* Диабеттік табан синдромы: мультидисциплинарлық аспектілер және мейіргерлердің рөлі // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 211-221. *doi 10.34689/SH.2025.27.4.026*

Introduction

Diabetes, a disease of the endocrine system, is defined by abnormally high levels of glucose in the blood and is one of the most common and rapidly developing diseases in the world [79]. The tenth edition of the International Diabetes Federation Atlas notes that type 2 diabetes accounts for more than 90% of all diabetes cases worldwide. Diabetes remains a major public health problem and compared to 2019, the overall incidence of diabetes worldwide has increased by 73.6 million, the number of undiagnosed cases by 7.8 million, and the number of diabetes-related deaths by 2.5 million. The Republic of Kazakhstan ranks 116th out of 214 in terms of diabetes incidence [34]. It is projected to affect 693 million adults worldwide by 2045, more than 50% more than the number of cases in 2017, and by 2050, more than 1.31 billion people are expected to suffer from diabetes [21,28].

The increase in the number of patients with type 2 diabetes directly leads to an increase in the number of patients with diabetic complications. Diabetes affects the heart, kidneys, eyes and nerves, leading to complications such as heart attack, stroke, blindness, renal failure, and amputation of the lower limbs. An unhealthy lifestyle and metabolic dysfunction syndrome lead to an increase in the concentration of triglycerides and non-esterified fatty acids. Excess lipids accumulate in non-adipose tissue, blocking insulin signaling pathways and causing insulin resistance. This leads to an increase in glucose formation in the liver and a decrease in its ability to absorb glucose, which contributes to an increase in blood glucose levels and an increase in basal insulin concentrations [59]. Increased insulin levels promote lipid accumulation, worsening insulin resistance and creating a vicious circle. Elevated glucose and lipid levels cause hyperglycolipotoxicity of islet β-cells, which damages their secretory function and quantitative composition, further increasing glucose levels [44, 26]. Diabetic foot is a chronic destruction of deep tissues caused by neurological dysfunctions, vascular diseases, and bacterial infections. [24, 73]. Patients suffering from diabetic foot syndrome, at the initial stage of development, often experience intense manifestations of sensitivity in the feet, such as a sensation of burning or stabbing pain, tingling, and in the later stages - numbness, paresthesia, impaired walking and the presence of long-term non-healing wound defects.

The objective of the review is to analyze modern concepts of pathogenesis, diagnosis and prevention of diabetic foot syndrome.

Search strategy and data sources

We conducted a literature review including articles published between 2014 and 2024. Academic databases such as PubMed, MEDLINE, CINAHL, and Embase were searched routinely. The main keywords used in the search included "diabetic foot syndrome", "diabetic foot ulcers", "multidisciplinary approach", "nursing role", "nursing education", "nursing care", "nursing interventions," "classification of diabetic foot", "economic impact", "pathogenesis of diabetic foot", и "prevention of diabetic foot". To cover different aspects of the topic, these terms were combined with "clinical guidelines", "management", "interprofessional collaboration". No gender filters were used in the search, and the age criterion was limited to patients over 18 years. Observational, experimental, and secondary studies were included in the study. Studies focusing on the pathogenesis, classification, and prevention of diabetic foot, publications on the role of nurses and multidisciplinary teams, and clinical guidelines on a multidisciplinary approach were considered. Materials without mentioning the role of health care professionals, reports with an insufficient evidence base, articles that were not peer-reviewed, publications in languages other than English, and studies with little statistical information or highly specialized clinical cases were excluded. Guidelines from leading professional associations such as the International Diabetic Foot Working Group, the International Diabetes Federation, and the World Health Organization were analyzed, which provided up-to-date information on the diagnosis, treatment, and prevention of diabetic foot, as well as recommendations on the role of health care professionals in caring for such patients. A search for systematic reviews and meta-analyses on the topic of diabetic foot provided structured and summarized evidence to facilitate the assessment of the outcomes and effectiveness of different treatments, including the role of the multidisciplinary team and nurses.

Mechanisms of diabetic foot formation

There are four main aspects of diabetic foot formation: peripheral arterial disease, peripheral neuropathy, bacterial infection and cellular dysfunction. Hyperglycemia that occurs in diabetes mellitus stimulates non-enzymatic glycation of collagen with amino acids of proteins, mainly with lysine and arginine, which leads to the formation of advanced glycation end products [10]. Hyperglycemia, insulin resistance, excess free fatty acids, and advanced glycation products inhibit the production of nitric oxide synthase and reactive oxygen species, thereby reducing oxidative stress. These products reduce the solubility of the extracellular matrix, which leads to an increase in the number of pro-inflammatory factors. In conditions of intense inflammation, leukocytes adhere to the inner lining of arteries, migrate to the site of inflammation, absorb fatty deposits and turn into foam cells, which contributes to the development of atherosclerosis [22]. Atherosclerosis plays a key role in the pathological processes associated with peripheral vascular disease. Atherosclerotic plaque rupture can trigger thrombus formation in the peripheral arteries, which directly leads to arterial occlusion and ischemia of the lower extremities. The lower knee arteries (posterior tibial artery and anterior tibial artery) are most often affected, while the femoral and lower leg arteries (superficial femoral artery and popliteal artery) are affected less frequently [11]. There is a poor arterial blood supply, making peripheral ischemia one of the main causes of ulceration in 35% of cases. Restriction of blood flow in peripheral vessels leads to poor wound healing. Reduced arterial perfusion leads to weakening of the peripheral pulse, increasing the risk of ulcers, infections and delayed healing, leading to chronic conditions with gangrene and possible amputation [55].

Different types of diabetic neuropathy can be classified according to various criteria: anatomical distribution (proximal, distal, symmetrical, asymmetrical, focal, multifocal, diffuse), clinical course (acute, subacute, chronic), characteristic features (painful, painless, sensory, motor, autonomic) or pathophysiology [2]. Sensory

neuropathy is characterized by decreased or lost proprioception, superficial sensation, pain and temperature sensation. Burning feet syndrome is considered particularly severe, usually occurring at night and accompanied by intense pain. The pain subsequently decreases due to chronic sensory neuropathy. Due to the lack of pain, serious lesions or minor injuries may remain unnoticed, people with diabetes may not feel a sharp object in their shoes, which increases the risk of re-injury and often goes unnoticed for several weeks. Peripheral autonomic neuropathy can lead to vasomotor paresis, promotes the formation of arteriovenous shunts in the subcutaneous vascular network. Neuropathy can cause decreased function of sweat glands, leading to dry and fragile skin prone to cracking, decreased ability to vasoconstriction controlled by the sympathetic nervous system, and impaired regulation of skin microvessels, which contributes to local edema. Motor neuropathy contributes to accelerated depletion of the extensor muscles, manifested in atrophy of the small muscles of the foot. Imbalance between flexors and extensors leads to incorrect positioning of the toes, foot deformities, and an unstable gait. Incorrect distribution of weight on the foot, long periods of stress on the foot when walking, or minor injuries can cause the formation of a callus, which progresses to an ulcer [76, 47, 75, 77, 61].

Foot ulcers caused by inadequate blood sugar levels lead to diabetic foot infections. Infections occur when there are open wounds and begin with a breakdown of the protective layer of skin at the site of injury or ulcer. In diabetics, signs and symptoms of inflammation may be hidden by the presence of peripheral neuropathy, peripheral arterial disease, or immune dysfunction. Because wounds are colonized by microorganisms, infection cannot be determined based on wound culture alone [43, 16]. The infection may manifest as a localized superficial skin lesion or as deeper structural lesions that extend beyond the initial site. Such infections can involve joints, bones, and the circulatory system [57]. In the meta-analysis by *Macdonald K.E.* et al., the most common microorganism was Staphylococcus aureus, of which 18.0% (95% CI 13.8–22.6%; I2 = 93.8% [93.0–94.5%]) were methicillin-resistant Staphylococcus aureus. Common microorganisms included Pseudomonas spp., Escherichia coli, and Enterococcus spp [45]. Diabetics were found to be 4.75% more likely to be colonized with methicillin-resistant Staphylococcus aureus ($p<0.0001$). The data showed that the prevalence of methicillin-resistant Staphylococcus aureus was 16.78% (95% CI, 13.21–20.68%). Among 2147 cases of skin and soft tissue infections not associated with foot infections, the proportion of methicillin-resistant Staphylococcus aureus was 18.03% (95% CI, 6.64–33.41) [71]. It has been proven that methicillin-resistant staphylococcus aureus infection does not increase mortality, is associated with an increased frequency of hospitalizations and an increased risk of limb amputation [63]. In polymicrobial infections, identifying the specific microorganism causing the infection can be difficult because of the presence of multiple pathogens. Synergistic interactions between different microbial species can enhance their virulence or antibiotic resistance, making it difficult to isolate and identify the infectious agent. The composition of microbes in polymicrobial infections can vary from patient to patient and over time within the same patient, making it difficult to identify the main pathogen responsible for the infection. Many microorganisms can form biofilms that protect them from antibiotics and the body's immune responses. Biofilms may include multiple microbial species, making it difficult to identify the dominant pathogen [7].

The wound healing process is a complex process and involves a sequence of interrelated stages, starting with the hemostatic phase, the inflammatory phase, the proliferation phase and the remodeling phase, which results in the formation of a scar [12]. Macrophages play a key role in the wound healing process. In the early stages, they promote inflammation, eliminate pathogens, and remove apoptotic cells. In the later stages of the healing process, they reduce inflammation and produce factors that control the proliferation, differentiation, and migration of keratinocytes, fibroblasts, and endothelial cells, which promotes neovascularization and wound healing. Macrophages in diabetics exhibit changes that affect their ability to engulf pathogens and remove apoptotic cells. This leads to a weakening of the body's ability to fight infections, since the process of efferocytosis is important for the transition of macrophages to the reparative M2 phenotype at the site of injury. Insufficient numbers of M2 macrophages lead to delayed wound healing and, in many cases, to further tissue damage. Another complication is a decrease in the body's ability to fight infection, which increases the likelihood of amputation [1, 80, 60].

Classification is a key factor in determining treatment strategy

To ensure widespread use of a classification system, it is necessary that it be easy to use and not require specialized equipment. For convenience, it is important that the system contains the necessary information for effective categorization of patients and is sufficiently reliable [53]. Classification is usually used for description, while scoring is a numerical indicator that reflects severity. It is difficult to imagine how one classification system can simultaneously serve both functions. The choice between descriptive and numerical classification depends on the clinical situation [27].

The Meggitt-Wagner classification, originally introduced by Meggitt and later expanded by Wagner, is a linear, six-tiered classification system for diabetes. The first three tiers of the system focus on the depth of foot involvement. Despite its limitations, the classification is popular due to its intuitive simplicity and ease of use [27, 78, 50]. Although the validation of the Wagner classification was insufficient and unable to clearly differentiate between different types of ulcers, it became the first widely used classification and continues to classify patients according to the Meggitt-Wagner scale and even provides compelling arguments that such systems can be successfully applied by practitioners regardless of their experience in wound care [18]. A study by *Shah P. et al.* evaluated various diabetic foot lesions according to the Wagner classification. The most common lesion among 50 patients was Wagner grade 2 foot ulcer, which was observed in 42% of cases, grade 3 lesions were found in 34% of patients, and grade 4 lesions in 12% of patients. The study found a strong positive correlation between Wagner grade and age [68].

The University of Texas system is designed to assess the depth of a wound, classify it according to the presence

of infection and ischemia. The system does not consider neuropathy or ulcer areas; it offers grades from 0 to 3 and stages from A to D. Its complexity lies in various degrees and stages, which can make it difficult to memorize and apply in everyday practice [29]. The aim of the study was *Santema T.B. et al.* It consisted of assessing the agreement between observers on two classifications: Meggitt-Wagner and the University of Texas. The consistency of the Meggitt-Wagner classification between the observers was moderate, amounting to 0.415 (95% CI 0.413–0.418). Nurses demonstrated slightly but statistically significantly (p=0.006) a higher level of agreement between observers (0.423; 95% CI 0.420–0.426) compared with doctors (0.404; 95% CI 0.392–0.417). The agreement between the observers according to the University of Texas classification was also moderate, amounting to 0.462 (95% CI: 0.445–0.479) among doctors and 0.451 (95% CI 0.447–0.456) among nurses, with no significant differences between the observer groups (p=0.238). It follows from the results that both classifications cannot be used as a single tool for selecting treatment methods or comparing them with research data. It is recommended to use them together with additional clinical information [64].

The Society for Vascular Surgery of the Lower Extremities Guidelines Committee has introduced WiFi (Wound, Ischemia, and Foot Infection System). The system addresses three key risk factors that can lead to the need for lower extremity amputation [78]. Wounds are classified into four grades, from zero to three, based on size, depth, severity, and prognosis for healing. Zero grade means the patient has no wound. Grade I wounds are characterized by minor tissue loss that can be repaired with simple techniques such as digital amputation or skin grafting. Grade II wounds are more severe but can be treated with multiple digital amputations or a standard transmetatarsal amputation. If there is extensive tissue loss requiring amputation closer to the level of a standard transmetatarsal amputation or the need to use a free flap, or if there is a deep heel ulcer that extends through the entire thickness of the foot, this is considered a grade III wound. Advanced gangrene that does not allow the functional foot to be saved is excluded from the classification [49]. An additional harmonized notation for re-evaluation of WiFi during treatment of a compromised limb is proposed. To correctly assess the increase or decrease in WIfI, the time frame of events and associated interventions must be considered to reflect the actual status of the limb. This division includes four stages: initial presentation, during therapy, recovery, and relapse. When assessing an index ulcer, the clinician should begin with an assessment of the initial presentation that is associated with the risk of severe lower limb ischemia and/or the possibility of revascularization, which will be the preliminary WIfI or "pWIfI" score. During and after treatment, regardless of the type and number of procedures and the follow-up time, the score can be re-evaluated as many times as necessary using the post-treatment WIfI or "tWIfI" score. Re-evaluation remains important since the ischemic component may persist. Therefore, the user should designate the status with "hWIfI" [14].

The S(AD) SAD - Size, (Area, Depth), infection (Sepsis), ischaemia (Arteriopathy) and neuropathy (Denervation) system consists of five main components, each of which is rated on a scale from 0 to 3. Criticisms that the system attracted concerned the lack of detail in key clinical categories and the inclusion of Charcot neuropathy as a degree of neuropathy severity. It was because of these concerns that the system was improved and transformed into the SINBAD system [27].

The SINBAD (Site, Ischemia, Neuropathy, Bacterial infection, Depth) scoring system includes six criteria, each of which is scored as present or absent (0 or 1) during the examination of the ulcer and foot [30]. The classification is easy to use, yet reliable, and provides the required information without the need for specialized equipment, except for routine clinical examinations. The system uses complex parameters with clear criteria, which facilitate rapid and accurate clinical decision-making to prevent lower limb amputation [15].

The PEDIS system (Perfusion (ischemia), Extent (area), Depth, Infection, Sensation (neuropathy)) developed by the International Diabetic Foot Working Group includes five domains. Unlike SINBAD, PEDIS does not take location into account. It differs from the University of Texas system and S(AD) SAD in that it is specifically designed for the selection of participants in prospective studies. PEDIS uses clear definitions for different degrees of peripheral arterial disease and infection, which gives it the character of complexity [27, 19].

Fife C.E. et al. created the Wound Healing Index (WHI) to predict the likelihood of wound healing in patients with diabetic foot disease based on individual characteristics of both the patient and their wound. The WHI is composed of 10 variables: wound area, patient mobility (ability to walk without assistance, with a cane, on crutches, with a walker, in a wheelchair, or confined to bed), hospitalization status (whether the patient was hospitalized on the day of care), wound count (the total number of ulcers or wounds the patient has), infection status (evidence of bacterial contamination in the wound), renal status (whether the patient is on dialysis or has had a transplant), and ulcer grade according to the Wagner scale [25].

The Diabetic Foot Ulcer Assessment Scale (DFUAS) developed by *Arisandi D. et al.* is designed to monitor the progression of diabetic ulcers over time and to assess the effectiveness of interventions. It includes 11 items, with a minimum and maximum score of 0 and 98, with a higher score indicating severe wound disease [8].

The Diabetic Foot Risk Assessment (DIAFORA) tool includes eight variables. The tool is divided into two parts: the first four variables are designed to predict the likelihood of ulcer development, the full version, considering all eight variables, is used to assess the risk of amputation in people with an existing diabetic foot. The scoring system includes points: 4 points for the presence of neuropathy, 1 point for foot deformity, 7 points for peripheral arterial disease, 3 points for a history of diabetic foot ulcer or lower limb amputation, 4 points for multiple ulcers, 4 points for infection, 10 points for gangrene and 7 points for bone damage in diabetic foot. The scale used is less than 15 points - low risk, from 15 to 25 points - average risk, more than 25 points - high risk [51].

Chetpet A. et al. developed a scale to assess the risk of amputation in patients with diabetic foot ulcers. It includes 13 parameters: sensory neuropathy (according to the

Semmes-Weissman test), motor neuropathy (deep tendon reflexes and muscle strength level), ulcer grade according to the Rutherford classification, diabetes duration, age, glycated hemoglobin level, foot deformities, history of previous amputations, ankle-brachial index, ulcer depth, assessment according to the criteria of the Infectious Diseases Society of America, habit of walking barefoot outdoors and the presence of comorbidities. The score ranges from 3 to 41 points, where higher values indicate a worse prognosis [20].

Jun D. et al. developed the DIRECT (Debridement of necrosis, Infection control, Revascularization, Exudate control, Chronicity, and Top surface) coding system as a simple, systematic, and standardized tool for evaluating all types of wounds. The system includes six scoring components, each based on pathophysiological aspects that influence the healing process: debridement of necrosis, infection control, revascularization, exudate control, chronicity, and top surface analysis [40].

The new SHID model (Suriadi, Haryanto, Imran, and Defa) was developed based on the authors' clinical observations of patients with diabetic ulcers in Indonesia. It not only covers the levels from skin tissue to bone, but also includes elements aimed at preventing complications. The first classification describes the superficial layer covering the epidermis and/or dermis, the second considers the occurrence of one or more signs or symptoms of infection and/or inflammation, ischemia, or osteomyelitis. The third class covers injuries involving the lower layers of the dermis (subcutaneous) that extend to tendon but do not reach bone; the fourth class covers injuries to subcutaneous, muscular, fascial, and tendinous tissues with one or more signs of inflammation, infection, ischemia, or osteomyelitis; the fifth class describes injuries to all skin tissue that reach bone, including areas with localized and extensive gangrene; the sixth class is similar to the fifth class but is supplemented by one or more of the following signs: inflammation, infection, ischemia, or osteomyelitis [72, 36].

The authors *Monteiro-Soares M. et al.* [52], *Oe M. et al.* [56] presented a scale for assessing the condition of the diabetic foot, including seven parameters: depth, maceration, inflammation/infection, size, type of tissue in the wound, type of wound edge and tunneling/subcutaneous emphysema. The total score can range from 0 to 34

Despite the existence of classification and grading systems, existing systems suffer from insufficient validation in specific populations, inadequate consideration of regional differences, and incomplete assessment of risk factors and outcomes [4, 6].

Interdisciplinary approach and the role of nurses

Since the disease itself, type 2 diabetes, and consequently its complication, diabetic foot, cannot be completely cured, correct and timely education of patients at the stage of primary care is of paramount importance [70]. Effective and timely treatment of foot lesions require a comprehensive approach, including accurate diagnosis and classification, systematic assessment of risk factors, and appropriate selection of treatment tactics. A diabetic foot care team that takes a comprehensive approach, viewing foot changes as an indicator of a systemic disease, and integrates various related medical fields plays a leading role in care planning, patient management, and delivery of care [67]. According to a systematic review by *Musuuza et al.*, the composition of healthcare teams for diabetic foot care varies widely across the world. A review of studies found that major limb amputations due to diabetic foot care were reduced by 94% when patients in this category were cared for by a multidisciplinary team. Teams should include representatives from medical and surgical specialties, have a clear structure with core and additional members, follow care algorithms to ensure timely and comprehensive care, and address four key tasks: blood glucose control, wound and vascular care, and infection control [54]. According to practical recommendations for the prevention and treatment of diabetic foot diseases, in all countries of the world for optimal work there should be at least three levels of care organization with the participation of interdisciplinary specialists. The first level should include: a general practitioner, an orthopedist and a nurse, the second level - a diabetologist, a surgeon, a vascular specialist, an infectious disease specialist or a clinical microbiologist, an orthopedist or prosthetist and a nurse. The third is a specialized reference center focused on the treatment of foot diseases associated with diabetes, in which several experts from related disciplines work [66]. Wound care specialists play an important role in a multidisciplinary team committed to achieving positive outcomes. Their in-depth knowledge of chronic wound care is based on certification and years of training, giving them the knowledge, skills, and abilities to develop an effective, evidence-based patient care plan [31]. Most often, the multidisciplinary team includes: an endocrinologist, a vascular surgeon, a podiatrist, and nurses, who have a special key role in the team. Due to the long-term care and treatment, nurses interact with the patient longer, determine his primary needs, make a nursing diagnosis using their clinical thinking and combining clinical, social, behavioral and other data, and create long-term and short-term care plans [46]. Nurses provide standard patient education on foot care, proper shoe selection, daily examination, wound care, dressing, and reduction of factors that contribute to decreased quality of life, which can delay the progression of foot ulcers, which is a key primary prevention strategy to reduce the overall disease burden and overall morbidity [69]. Thus, a prospective study analyzed changes in the feet of patients with type 2 diabetes mellitus who attended a nursing appointment lasting from 30 minutes to an hour. During the appointment, during the foot examination, patients were advised to carefully monitor any changes, and were given recommendations on foot care, including the rules for washing and drying feet, cutting nails, and choosing suitable socks and shoes. At the end of each appointment, patients were given written recommendations on prevention, as well as a folder containing data on glucose levels, lipid profile, blood pressure, and weight. After multivariate analysis, it was found that the only factor that reduced the risk of death was the time spent under the supervision of nurses (95% CI 0.66 (0.61–0.71)). Each year of patient supervision by nurses reduced the risk of death by 34% across all classifications of diabetic foot. The study found that patients who had their feet checked regularly by nurses and who attended appointments over many years lived longer due to a reduced risk of complications [65]. The

study by *Mekonen E.G. et al.* showed the following results: patients who had not previously received information about foot care rules had an 88% higher risk of poor foot care than those who had been informed [AOR = 0.12, 95% CI (0.06, 0.24)]. Patients who received good support from family had a 57% lower likelihood of poor foot care than those who faced insufficient support [AOR = 0.57, 95% CI (0.34, 0.94)] [48].

Comprehensive nursing intervention is an integrated and multidisciplinary approach to care that includes health education, nutritional advice, physical activity, medication therapy and other aspects of nursing care. This approach helps improve patients' awareness of diabetic foot disease and their self-management skills, which allows them to manage the disease more effectively, reducing the incidence of diabetic foot disease and amputation rates [81]. A study by *Ren M. et al.* included 185 patients with diabetes at high risk for foot disease. They underwent intensive nurse education, which included individual counseling on diabetes and foot disease, as well as education on foot care. According to the results, toe ulcers were found in 24 cases, which accounted for 48.0% of the total number of ulcers, of which 70.8% were located on the big toe. The incidence of foot ulcers decreased from 41.2% to 11.1% after nurse education, but the location of the ulcers did not change: half of them were still on the toes. [62].

There are a widespread belief that systematic, organized and regular education plays a key role in preventing diabetes-related foot changes, so effective patient education on foot care includes specific, clear and understandable information about their condition to enable patients to be active participants in their own care [3]. Education should be culturally sensitive, gender sensitive, appropriate to health literacy, and personal circumstances. It is important to assess how clear the recommendations are to the patient, family members, or caregivers, how motivated they are to follow the recommendations, and whether the patient has sufficient self-care skills. Traditional didactic education, a classic approach that focuses on imparting knowledge and convincing patients to follow certain rules, often has little impact on their self-care habits. In contrast, modern strategies such as open-ended communication, interview style, and collaborative approach have been shown to be more effective in changing behavior. These new approaches better engage patients in the treatment process and promote intrinsic motivation to change health-related behavior. The study by *Heng M.L. et al.* analyzed modern communication approaches and their impact on improving patient education outcomes. Participants were randomly assigned to either collaborative patient education or traditional didactic education. Participants in the experimental group showed greater improvement in knowledge retention and self-care behaviors compared to the control group. There was a significant increase in scores at post-study compared to baseline ($p<0.001$) [33]. Education about proper diabetic foot care and practicing self-care are key to preventing diabetic foot disease [58]. In a study by *Alrashed F.A. et al.,* it was found that among patients with good knowledge of proper foot care, 44% inspected their feet daily, while only 13% did not. Among patients with diabetes who inspected their shoes before using them (always - 44% and sometimes - 31.6%), 75.6% had good knowledge of proper foot care [5]. In this context, the knowledge and skills of the professionals themselves will be a decisive factor. The medical staff who provide such instructions should undergo regular training to improve their skills in caring for patients [67]. For greater efficiency, it is recommended that medical workers themselves take part in organizing and conducting theoretical and practical training programs without interruption from work, considering the needs for training. As is known, the correct balance between theory and practice not only contributes to an increase in the level of knowledge but also improves skills that will contribute to improving the behavior of patients in caring for themselves and improving their quality of life [41]. A qualitative analysis of participants' perceptions identified four key themes influencing foot care: personal knowledge of people with similar problems had a positive impact on care, while the emotional impact of diabetes and physical, social and everyday limitations made it difficult [39].

Economic Impact

There is a global effort to develop and implement effective treatments that can heal ulcers and prevent serious sequelae. There are many treatments for diabetic foot disease, and access to these treatments remains a challenge, particularly in low- and middle-income countries. Information on ulcer management in health care settings and outcomes related to amputation prevention are widely available. However, information on interventions to prevent diabetic foot disease is rare. With new factors such as the global epidemic of infectious diseases, diabetes outcomes may be even more important and should be considered in planning future public health interventions [23]. It is therefore important to conduct well-designed clinical trials to confirm the effectiveness of new treatments, management, diagnosis and prevention [37]. There is currently significant investment in clinical practice, clinical research and public health interventions, but there is no sign of a slowdown in the growth of chronic diseases [42]. The high frequency and difficulty of treating foot lesions require significant financial resources and increased medical care costs. It is natural that under such conditions there will be a significant financial burden on the country's health care system, which includes direct and indirect costs such as lost wages, disability, and the burden on the few medical personnel [74]. Costs include direct costs such as hospitalization, medical supplies, medications, and surgeries, as well as indirect costs associated with the social and psychological consequences of diabetic foot complications. In a study on the productivity and work capacity of patients with diabetic foot, patients were divided into three groups. The results showed that patients with diabetic foot experienced more difficulties in time management, planning, and performing tasks requiring physical strength, mobility, endurance, coordination, and flexibility. This group also reported limitations in performing cognitive tasks and interacting with colleagues, and a reduced ability to complete work within the established deadlines and to the required volume and quality. Regarding absenteeism, patients reported the greatest number of workdays missed due to health problems [17]. The burden associated with diabetic foot care is difficult to quantify accurately, and cost estimates

vary widely across sources. For example, researchers in New Zealand found that the economic burden was significantly higher than they had expected [38]. In a study by *Barshes N.R. et al.,* the authors found that the costs of treating diabetic foot disease were three times greater than the costs of treating colorectal cancer [13]. The average cost of the United Kingdom National Health Service for wound treatment over 12 months was 7,800 pounds for a diabetic foot ulcer, with 13% of this amount accounted for amputations. Treatment of a non-healing diabetic foot was four times more expensive than that of a healed one (2,140 pounds for a healed one and 8,800 pounds for an unhealed one). The cost of treatment for an amputated limb was 16,900 pounds, not including rehabilitation after amputation [32]. According to the study by Armstrong et al., the overall economic impact of diabetic foot disease is comparable to cancer in all respects, and yet assistive technologies that can predict and prevent the disease could lead to potential savings in health care costs, but only in the short term. An emphasis on early preventive treatment and long-term maintenance therapy for diabetic foot lesions during remission would lead to increased life expectancy and improved health outcomes. And the financial savings from shifting focus from treatment to prevention could be used as investments to find and address the causes of diabetes complications, thereby reducing future suffering [9]. In a study by *Jais S. et al.,* wound care specialists in private hospitals in Indonesia demonstrated greater cost-effectiveness in treating diabetic foot ulcers. Their cost was IDR 2,804,423.3, significantly lower than IDR 6,483,493.4 for nurses in public hospitals. The incremental cost-effectiveness ratio was -165,723.9 [35].

Conclusions

The review analyzes key aspects of diabetic foot syndrome development, its mechanisms, and major risk factors. The results of the analysis indicate that the pathogenesis of diabetic foot includes complex processes associated with impaired microcirculation, development of neuropathy, and infectious diseases. Timely identification of risk factors and implementation of educational programs for patients and their families on self-care and foot care play an important role in prevention, helping to reduce the incidence of complications. Effective care should be individualized according to the patient's condition and needs. It is important to conduct prevention education, provide emotional support, and motivate the patient to follow recommendations, including regular foot care and blood glucose monitoring. Treatment should be comprehensive and include hyperglycemia control, wound care, infection therapy, and arteriopathy correction, since developing tissue necrosis can lead to a reduction in life expectancy due to the need for amputation, deterioration in quality of life, and increased health care costs.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

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Received: 11 June 2025 / Accepted: 12 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.027

UDC 616.981.42-07

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BRUCELLA SPP. ANTIGENS IMPACT IN THE PATHOGENESIS AND DIAGNOSIS OF HUMAN BRUCELLOSIS

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Abstract

Introduction. Brucellosis remains one of the most widespread and underdiagnosed zoonotic infections, with over 500,000 new human cases annually and continued endemic circulation in livestock. *Brucella melitensis, B. abortus, B. suis*, and *B. canis* are the key pathogenic species causing chronic disease with nonspecific clinical symptoms. Brucella antigens are central to the pathogenesis and immune response, yet current diagnostic tests lack sufficient specificity, and no licensed human vaccine is available. This highlights the urgent need for more accurate antigen-based tools for both diagnosis and prevention.

Aim. To review and evaluate the main *Brucella* antigens with proven or potential diagnostic and vaccine value, focusing on their structural features, immunogenicity, and applicability in translational research.

Search strategy: A systematic review was conducted following PRISMA guidelines. Literature searches were performed in PubMed, Scopus, and Web of Science (2018–2025) using predefined keywords related to *Brucella* antigens, diagnostics, and vaccine development. After multi-stage screening of titles, abstracts, and full texts, 106 studies were included in the final analysis, as illustrated in the PRISMA flow diagram.

Results. Outer membrane proteins (Omp16, Omp19, Omp25, Omp31), periplasmic proteins (BP26, Cu/Zn-SOD, L7/L12), heat shock proteins (Hsp60, Hsp70), and Type IV secretion system proteins (VirB) demonstrate distinct immunogenic profiles. Among them, L7/L12, Omp19, and SOD show the highest promise in terms of serological sensitivity and protective immune stimulation. A subset of these antigens is currently being explored as part of recombinant subunit vaccine formulations.

Conclusion. Molecularly defined *Brucella* antigens offer tangible opportunities to improve human brucellosis diagnostics and support the rational development of safer, targeted vaccines. Their documented immunological relevance justifies further preclinical evaluation and standardization in applied immunodiagnostics.

Keywords: *Brucellosis, Brucella spp., outer membrane proteins, antigen, diagnostics, vaccine development, human brucellosis, heat shock proteins, lipopolysaccharides, proteins, type IV secretion system (t4ss) proteins.*

For citation:

Kossylganova A., Atakanova A., Mukhitdenova A., Bitanova E., Zhaparkulova K., Izekenova A. BRUCELLA spp. antigens impact in the pathogenesis and diagnosis of human brucellosis // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 222-236. *doi 10.34689/SH.2025.27.4.027*

Резюме

ВЛИЯНИЕ АНТИГЕНОВ *BRUCELLA* SPP. НА ПАТОГЕНЕЗ И ДИАГНОСТИКУ БРУЦЕЛЛЕЗА У ЧЕЛОВЕКА

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Введение. Бруцеллез остаётся одной из наиболее распространенных и недодиагностируемых зоонозных инфекций, с более чем 500 000 новых случаев среди людей ежегодно и устойчивой энзоотией среди сельскохозяйственных животных. *Brucella melitensis, B. abortus, B. suis* и *B. canis* являются основными патогенными видами, вызывающими хронические заболевания с неспецифическими клиническими проявлениями. Антигены *Brucella* играют ключевую роль в патогенезе и

формировании иммунного ответа, однако существующие методы диагностики недостаточно специфичны, а лицензированной вакцины для человека до сих пор не существует. Это подчёркивает необходимость создания более точных антиген-ориентированных средств диагностики и профилактики.

Цель. Провести обзор и оценку основных антигенов *Brucella* spp., обладающих подтвержденной или потенциальной диагностической и вакцинной значимостью, с акцентом на их структурные особенности, иммуногенность и прикладную ценность.

Стратегия поиска: Систематический обзор проведён в соответствии с рекомендациями PRISMA. Поиск литературы выполнен в базах PubMed, Scopus и Web of Science за период 2018–2025 гг. с использованием заранее определённых ключевых слов, связанных с антигенами *Brucella*, диагностикой и разработкой вакцин. После многоэтапного отбора по заголовкам, аннотациям и полным текстам в итоговый анализ было включено 106 исследований, что отражено на схеме PRISMA.

Результаты. Наружные мембранные белки (Omp16, Omp19, Omp25, Omp31), периплазматические белки (BP26, Cu/Zn-SOD, L7/L12), белки теплового шока (Hsp60, Hsp70) и компоненты системы секреции типа IV (VirB) демонстрируют разную степень иммуногенности. Среди них белки L7/L12, Omp19 и SOD обладают наибольшим потенциалом как серологические маркеры и компоненты вакцинных конструкций. Часть этих антигенов рассматривается в составе рекомбинантных субъединичных вакцин.

Заключение. Молекулярно охарактеризованные антигены Brucella открывают реальные перспективы для совершенствования диагностики и разработки целенаправленных и безопасных вакцин против бруцеллеза человека. Их иммунологическая значимость обосновывает необходимость дальнейшей доклинической оценки и внедрения в прикладную иммунодиагностику.

Ключевые слова: *бруцеллёз, Brucella spp., антигены, наружные мембранные белки, диагностика, вакцинопрофилактика, тепловые шоковые белки, липополисахариды, белки, белки системы секреции типа IV.*

Для цитирования:

Косылганова А., Атаканова А., Мухитденова А., Битанова Э., Жапаркулова К., Изекенова А. Влияние антигенов *Brucella spp.* на патогенез и диагностику бруцеллёза у человека // Наука и Здравоохранение. 2025. Vol.27 (4), С.222-236. *doi 10.34689/SH.2025.27.4.027*

Түйіндеме

BRUCELLA SPP. АНТИГЕНДЕРІНІҢ АДАМ БРУЦЕЛЛЁЗІНІҢ ПАТОГЕНЕЗІ МЕН ДИАГНОСТИКАСЫНА ӘСЕРІ

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Кіріспе. Бруцеллез – жыл сайын 500 000-нан астам адамда тіркелетін, үй жануарлары арасында кеңінен таралған және жиі анықталмайтын зооноздық инфекция. *Brucella melitensis, B. abortus, B. suis* және *B. canis* – аурудың негізгі қоздырғыштары, олар созылмалы және спецификалық емес белгілермен сипатталатын инфекцияларды тудырады. *Brucella* антигендері ауру патогенезінде және иммундық жауапта маңызды рөл атқарады. Алайда қазіргі диагностикалық тесттердің спецификалығы төмен және адамға арналған лицензияланған вакцина әлі жасалмаған. Бұл диагностика мен алдын алуға арналған антигендік негіздегі құралдарды жетілдіру қажеттігін көрсетеді.

Мақсат. *Brucella* spp. антигендерінің құрылымдық сипаттамалары, иммуногендік қасиеттері және қолданбалы әлеуетін бағалай отырып, олардың диагностикалық және вакциналық маңыздылығын талдау.

Іздеу стратегиясы. Жүйелі шолу PRISMA нұсқауларына сәйкес жүргізілді. Әдебиеттерді іздеу PubMed, Scopus және Web of Science деректер базаларында 2018–2025 жылдар аралығында Brucella антигендері, диагностикасы және вакцина әзірлеуіне қатысты алдын ала анықталған кілт сөздер арқылы орындалды. Тақырыптар, аңдатпалар және толық мәтіндер бойынша көпсатылы іріктеуден кейін қорытынды талдауға 106 зерттеу енгізілді, бұл PRISMA диаграммасында көрсетілген.

Нәтижелер. Omp16, Omp19, Omp25, Omp31 секілді сыртқы мембраналық белоктар, BP26, Cu/Zn-SOD, L7/L12 периплазмалық белоктары, Hsp60, Hsp70 жылулық шок белоктары және VirB секреция жүйесінің белоктары әртүрлі иммуногендік белсенділік көрсетті. L7/L12, Omp19 және SOD антигендері серологиялық сезімталдық пен қорғаныштық жауапты индукциялау бойынша ерекше әлеуетке ие. Бұл антигендер рекомбинантты субъединикалық вакциналар құрамында зерттелуде.

Қорытынды. Молекулалық деңгейде сипатталған Brucella антигендері адам бруцеллезін диагностикалау мен мақсатты, қауіпсіз вакциналарды құрастыру бағытында маңызды мүмкіндіктер береді. Олардың иммунологиялық маңыздылығы доклиникалық зерттеулер мен қолданбалы иммунодиагностикада одан әрі зерттеуді қажет етеді.

Түйінді сөздер: *бруцеллез, Brucella spp., антигендер, сыртқы мембраналық белоктар, диагностика, вакцина, жылулық шок белоктары, липополисахаридтер, белоктар, IV типті секреция жүйесінің белоктары*

Дәйексөз үшін:

Қосылғанова А., Атаканова А., Мухитденова А., Битанова Э., Жапаркулова К., Изекенова А. Brucella spp. антигендерінің адам бруцеллезінің патогенезі мен диагностикасына әсері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 222-236. *doi 10.34689/SH.2025.27.4.027*

Introduction

Brucellosis is a globally prevalent zoonotic disease, with the highest endemicity reported in the Mediterranean region, Central Asia, sub-Saharan Africa, and Latin America. The causative agents, Gram-negative facultative intracellular coccobacilli of the genus *Brucella*, affect both public health and livestock productivity by causing reproductive failure in animals and systemic illness in humans [4,39]. Transmission to humans typically occurs via ingestion of raw milk or dairy items, exposure to airborne infectious particles, or physical interaction with livestock carrying the pathogen or their secretions. Occupations involving close animal contact-such as farming, slaughtering, and veterinary work-remain the highest risk [13,93]. The global distribution of brucellosis prevalence, based on epidemiological data published between 2015 and 2024, is illustrated in Figure 1.

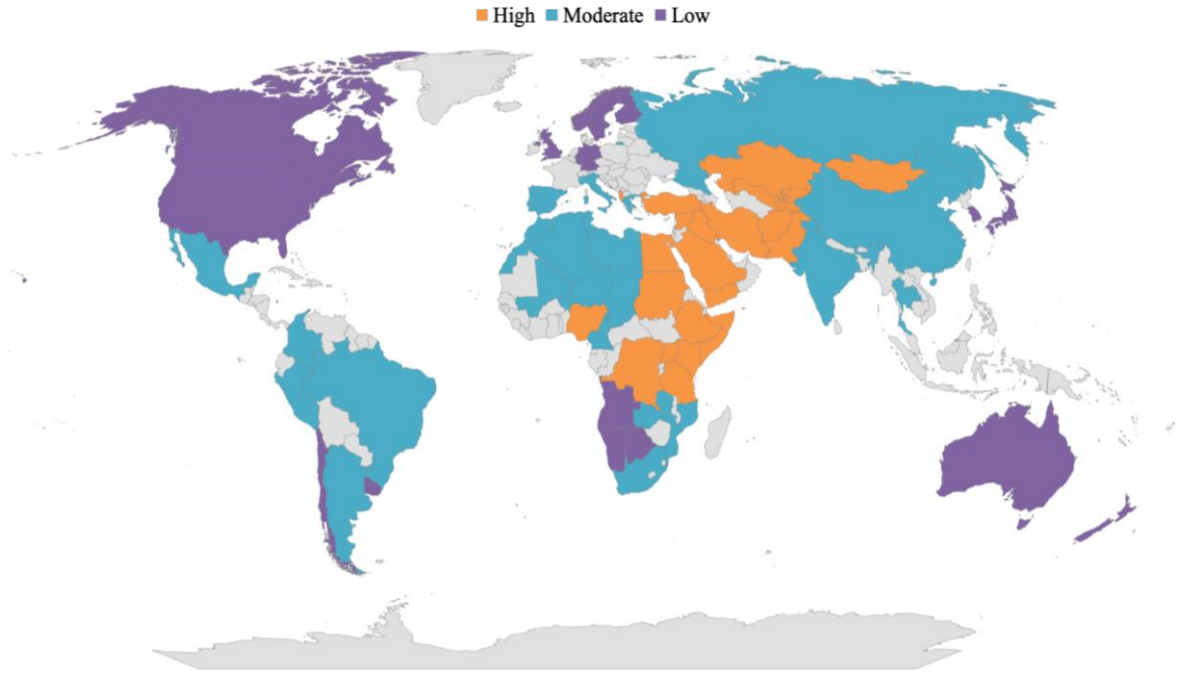


Figure 1. Global distribution of human brucellosis prevalence based on reviewed epidemiological literature (2015–2024). The color scale indicates prevalence levels: high (orange), moderate (blue), and low (purple). Only countries with available data are shown.

Twelve *Brucella* species have been formally identified, with *B. melitensis*, *B. abortus*, *B. suis*, and, to a lesser extent, *B. canis* recognized as the primary human pathogens. *B. melitensis*, commonly found in sheep and goats, is the most virulent and often causes chronic systemic disease [16,76]. The clinical manifestations of brucellosis are non-specific-fever, fatigue, arthralgia-and may resemble various febrile conditions, complicating clinical recognition, especially in chronic or subclinical infections [12].

Bacteriological diagnosis through blood culture remains the gold standard, yet is often limited by low sensitivity in chronic cases and long incubation times. Serological methods such as the Rose Bengal test (RBT), standard agglutination test (SAT), and enzyme-linked immunosorbent assay (ELISA) are widely used but exhibit variable performance depending on disease stage, endemicity, and host immune status [39,92]. The development of antigen-based diagnostic platforms-particularly those incorporating recombinant outer membrane proteins (OMPs) like Omp28 and Omp31-has improved specificity and reproducibility in ELISA assays [3,38]. Additional methods such as fluorescence polarization assays and paper-based ELISAs offer promise for point-of-care testing in field conditions [41].

Despite the availability of effective veterinary vaccines such as *B. abortus* S19 and *B. melitensis* Rev.1, no vaccine is currently licensed for human use. These animal vaccines, although valuable for controlling livestock infections, are unsuitable for human application due to residual virulence, safety concerns in vulnerable populations, and interference with serological diagnostics [59,17]. These challenges underscore the need for safe, well-defined *Brucella* antigens with diagnostic and immunogenic potential.

Among the most relevant immunological targets are outer membrane-associated proteins (OMPs), structural endotoxins like lipopolysaccharides (LPS), stress-inducible proteins such as Hsp60 and Hsp70, antioxidant defense enzymes including Cu/Zn-superoxide dismutase (SOD), and molecular determinants of virulence encoded by the type IV secretion system (T4SS). Each of these antigen classes contributes to different facets of *Brucella* pathogenicity-including immune evasion, intracellular persistence, and inflammation modulation. For example, recombinant Omp19 and Omp31 have demonstrated protective efficacy and strong immunoreactivity in experimental models [29]. LPS and HSPs suppress innate immune signaling and facilitate chronic infection [50], while T4SS proteins are indispensable for intracellular replication and resistance to host clearance mechanisms. Their systematic characterization forms the basis for the development of next-generation serological assays and subunit vaccines [19].

Search strategy

A systematic search of the literature was conducted in PubMed, Scopus, and Web of Science databases for publications between 2018 and 2025. The following combinations of keywords and Medical Subject Headings (MeSH) terms were used: *Brucella* spp., *Brucella melitensis*, *Brucella abortus, Brucella suis*, diagnosis, epidemiology, antigen, outer membrane proteins (Omp16, Omp19, Omp25, Omp31), periplasmic proteins (BP26, L7/L12, SodC), heat shock proteins (Hsp60, Hsp70, DnaK, GroEL), lipopolysaccharides (S-LPS, R-LPS), type IV secretion system (VirB), vaccine candidate, and serodiagnosis.

Selection process

– Initial search retrieved 4,460 records

– Title screening excluded 2,806 studies as duplicates or irrelevant

– Abstract screening excluded 554 additional records due to thematic or methodological mismatch

– Full-text review excluded 138 articles because of methodological overlap or insufficient data

– **Final inclusion:** 106 publications that fulfilled all eligibility criteriaInclusion criteria

– Peer-reviewed articles indexed in PubMed, Scopus, or Web of Science

– Published in English

– Publication period: 2018–2025

– Studies providing data on antigen structure, immunogenicity, pathogenesis, or diagnostic/vaccine potential of *Brucella* spp.

Exclusion criteria

– Duplicate records

– Studies unrelated to *Brucella* antigens or diagnostics

– Reviews without original data (unless of high scientific value)

– Articles with insufficient methodological transparency

Distribution of included studies

– Introduction: 16

– Sections 1.1–1.3 (epidemiology, diagnostics, preventive challenges): 24

– Section 2.1 (Outer membrane proteins): 17

– Section 2.2 (Periplasmic proteins): 16

– Section 2.3 (Heat shock proteins): 12

– Section 2.4 (Lipopolysaccharides): 14

– Section 2.5 (Type IV secretion system proteins): 12

– Section 2.6 (Other antigens): 8

Epidemiological relevance of brucellosis as a persistent zoonotic threat

Brucellosis ranks among the most widespread and economically significant zoonoses, particularly in regions with inadequate veterinary infrastructure. The disease reduces livestock productivity through abortions and infertility, and it continues to pose a substantial risk to human health due to zoonotic spillover [4,93]. Although official data report around 500,000 new human cases annually, modelling studies estimate the true global incidence at over 2 million, reflecting widespread underdiagnosis and underreporting, particularly in Asia and Africa [41]. The global distribution of human brucellosis prevalence is shown in Figure 2, based on data from reviewed epidemiological studies published between 2015 and 2024.

High-income countries have largely controlled brucellosis through systematic test-and-slaughter programs and livestock vaccination.

However, in endemic zones such as Central Asia, East Africa, and parts of Latin America, the disease remains entrenched. Field investigations in Kenya and Uganda have shown a clear epidemiological connection between infected livestock and human brucellosis within the same communities [17,29].

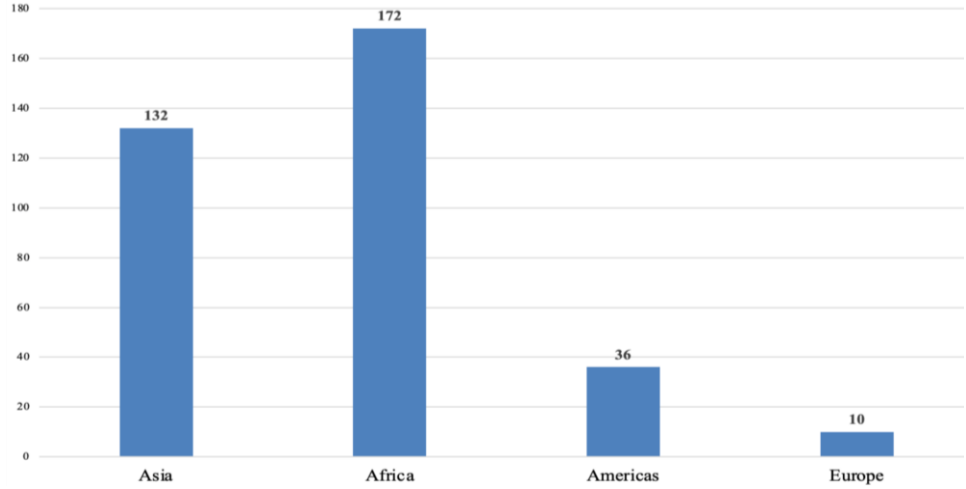


Figure 2. Geographical distribution of brucellosis-related studies included in the review. The majority of studies were conducted in Africa (n=172) and Asia (n=132), followed by the Americas (n=36) and Europe (n=10), reflecting regional research focus and burden.

Medically important Brucella species

Among the twelve identified Brucella species, human brucellosis is primarily attributed to *B. melitensis, B. abortus, B. suis*, and, less frequently, *B. canis*. *B. melitensis*, predominantly found in sheep and goats, is the most pathogenic and commonly identified in endemic regions. Its high bacterial concentration in placental tissues and unpasteurised milk increases the risk of human infection via ingestion or contact [74,50].

B. abortus, associated with cattle, presents a significant occupational risk in areas with insufficient veterinary control. Although generally less aggressive, it accounts for a substantial proportion of human cases [19]. *B. suis*, primarily affecting pigs, causes a more chronic and suppurative form of brucellosis, often involving abscess formation and osteoarticular complications. Human infection occurs mostly in hunters, swine farmers, and abattoir workers [74,17]. *B. canis*, though rare, is occasionally reported in immunocompromised individuals and poses a risk in canine breeding or veterinary settings. Additionally, emerging species such as *B. inopinata* and marine mammal–associated *Brucella* strains have demonstrated zoonotic potential and require surveillance [18].

Challenges in diagnosis and limitations of current vaccines. The diagnosis of brucellosis remains challenging due to the non-specificity of symptoms, low bacterial loads, and overlapping clinical features with other infections. Culture, while definitive, is often impractical in chronic cases due to delayed growth [13,12]. Serological tests (RBT, SAT, ELISA) are widely used but suffer from false-positive results due to cross-reactivity with other Gram-negative bacteria and false negatives following antimicrobial therapy [24,89].

Molecular assays, particularly real-time PCR, have significantly improved the sensitivity and specificity of *Brucella* detection, enabling early diagnosis and species differentiation [60,90]. However, their routine use is limited by high costs, the need for specialised infrastructure, and the lack of standardised protocols across laboratories, which hinders result comparability and widespread implementation [35].

On the prophylactic front, live attenuated veterinary vaccines-such as *B. melitensis* Rev.1 and *B. abortus* S19-have played a central role in controlling brucellosis in livestock. Nevertheless, their use in humans is contraindicated due to the risk of residual virulence, abortion in pregnant individuals, and post-vaccination seroconversion, which can interfere with serological diagnostics [27,40]. These limitations have prompted the search for alternative human vaccine strategies that combine safety with robust protective immunity.

Modern approaches to *Brucella* vaccine development increasingly emphasize recombinant subunit platforms incorporating well-characterized antigens such as Omp16, Omp19, Omp25, Omp31 (outer membrane proteins), stress-response molecules like Hsp60 and Hsp70, and antioxidant enzymes including Cu/Zn-superoxide dismutase (SOD). These components have demonstrated the capacity to activate both humoral and cellular branches of the immune system in experimental settings. To enhance immunogenicity, they are tested in combination with adjuvants or delivered via attenuated vectors such as *Salmonella enterica* or viral platforms, aiming to stimulate mucosal and systemic immunity [37].

Immunological significance of *Brucella* antigens

Brucella antigens are central to the pathogen's intracellular lifestyle, immune modulation, and chronic persistence. OMPs-such as Omp16, Omp19, Omp25, and Omp31—facilitate adhesion, immune evasion, and survival within host phagocytes, making them attractive targets for diagnostics and recombinant vaccines [73,91]. The smooth form of LPS (S-LPS), present in *B. melitensis* and *B. abortus*, reduces TLR4-mediated activation and impairs pro-inflammatory signaling, whereas rough LPS variants, typical of *B. canis*, are less immunosuppressive [44].

Intracellular survival of *Brucella* is facilitated by the type IV secretion apparatus (T4SS), encoded within the virB gene cluster, which disrupts phagolysosomal maturation and enables the establishment of replicative compartments [5]. Antioxidant enzymes like Cu/Zn-SOD allow *Brucella* to neutralize reactive oxygen species within phagocytes, supporting its persistence [25]. Moreover, TIR-domain-containing effector proteins (BtpA, BtpB) mimic host signaling molecules and inhibit IL-12 and IFN-γ responses, suppressing protective Th1 immunity [84].

Transcriptomic analyses of infected human immune cells confirm downregulation of genes involved in inflammation and antigen presentation [55]. In parallel, recent findings show that *Brucella* antigens disrupt dendritic cell function-especially in plasmacytoid DCs-by modulating SLAMF7/8 signaling, thereby impairing interferon responses and T cell activation during chronic infection [106,43].

The main groups of *Brucella* spp. antigens and their characterisation

Outer Membrane Proteins (OMPs)

Outer membrane proteins (OMPs) of *Brucella* spp. are integral components of the bacterial cell envelope and play a central role in pathogenesis, immune evasion, and intracellular survival. These membrane-associated proteins are involved in maintaining structural stability, regulating molecular exchange, and facilitating nutrient uptake. Due to their localization on the bacterial surface and ability to elicit immune responses, they represent valuable candidates for serodiagnostic assays and the design of recombinant vaccines. [28,6].

Structurally, *Brucella* OMPs are grouped by molecular weight into three categories: high molecular weight proteins (88–94 kDa), porins (36–38 kDa), and low to medium-sized immunogenic proteins (25–34 kDa) [28]. Among these, the 25–34 kDa group includes Omp25 and Omp31, which are highly conserved across pathogenic species and have been most extensively studied due to their strong immunogenicity and translational relevance [8,63].

Omp25 plays a multifaceted role in virulence and immune modulation. It downregulates TNF-α secretion in macrophages, facilitating bacterial persistence by dampening host inflammatory responses [49]. Although masked by smooth lipopolysaccharide (S-LPS) during natural infection, recombinant Omp25 has demonstrated strong humoral and cellular immunogenicity in animal models, particularly when used with adjuvants [75].

Omp31 is absent in *B. abortus* but present in *B. melitensis* and *B. suis*. It is involved in iron acquisition and outer membrane permeability, and elicits strong antibody responses-especially in infections caused by rough strains such as *B. ovis* [70]. Its immunodominance and species-specific expression make it a valuable antigen for differential diagnosis and targeted immunoprophylaxis [57].

Porin proteins Omp2a and Omp2b form trimeric β-barrel channels that regulate outer membrane permeability. Despite over 85% sequence identity, species-specific

mutations result in functional divergence. While less immunogenic than Omp25 or Omp31, these porins contribute to resistance against environmental stressors and antimicrobial peptides, and may serve as auxiliary components in multivalent vaccine formulations to enhance protective breadth [87, 23].

Smaller outer membrane lipoproteins such as Omp16 and Omp19 also play significant roles in *Brucella* survival and host interaction. Omp16, homologous to peptidoglycan-associated lipoproteins, is essential for cell viability. Conditional knockdown of Omp16 impairs membrane integrity and triggers elevated pro-inflammatory cytokine responses in host cells [104]. Omp19 acts as a protease inhibitor, aiding survival in hostile environments such as phagosomes and mucosal surfaces. Notably, recombinant *Lactococcus lactis* expressing Omp19 has induced mucosal immunity and protection in oral vaccination models, supporting its utility for needle-free immunization [20].

The diagnostic application of OMPs is well substantiated. Recombinant forms of Omp25, Omp31, Omp16, and Omp19 have been successfully incorporated into ELISA platforms, demonstrating improved specificity and sensitivity over traditional LPS-based tests [7,58]. Their reduced cross-reactivity with other Gram-negative bacteria and suitability for DIVA (Differentiating Infected from Vaccinated Animals) strategies enhance their value in both human and veterinary diagnostics [68,11].

A major advantage of OMP-based antigens is their high sequence conservation across *Brucella* species, enabling the development of cross-protective vaccines. Bioinformatics-driven epitope mapping has facilitated the design of multi-epitope constructs incorporating conserved OMP regions, several of which have shown promising immunogenicity and protection in preclinical studies [97]. Moreover, their recombinant nature and lack of residual virulence make them safer alternatives to whole-cell vaccines, particularly for human use [75,97].

Periplasmic proteins of *Brucella spp.* play essential roles in maintaining cell envelope integrity, evading host immune responses, and surviving intracellular stress conditions. Unlike classical surface-exposed virulence factors, these proteins are often hidden from direct immune detection but exhibit significant immunogenic potential, making them relevant candidates for diagnostic and vaccine development. The most studied include BP26, Cu/Zn-SOD (SodC), DsbA, HtrA, PrpA, BepC, and Omp19.

Also referred to as Omp28, BP26 is a highly conserved protein (~26 kDa) expressed across smooth *Brucella* species [7]. Initially misclassified as an outer membrane protein, it was later localized to the periplasmic space. Structurally, BP26 shares homology with phage channel proteins and has demonstrated interactions with host extracellular matrix components such as collagen and vitronectin, suggesting a potential role in adhesion [58].

Immunologically, BP26 elicits strong antibody responses in both infected and vaccinated hosts. It has been widely applied in indirect ELISA and lateral flow tests with high sensitivity and specificity [7, 58]. Its utility as a DIVA (Differentiating Infected from Vaccinated Animals) marker is supported by data from BP26-deficient vaccine strains (e.g., *B. melitensis* Rev.1 Δbp26) [68]. Recombinant BP26 has also shown the capacity to induce Th1-biased responses and partial protection in murine models [11, 97].

SodC is a periplasmic metalloenzyme that catalyzes the dismutation of superoxide radicals into hydrogen peroxide and molecular oxygen, providing crucial protection against the oxidative burst of phagocytes. It is required for survival of *Brucella* within macrophages, particularly under phagolysosomal stress [78].

Although SodC induces relatively modest humoral responses, it triggers robust T-cell immunity, including IFN-γ production. Immunization with SodC, especially in combination with antigens like L7/L12 and Omp25, enhances protection in murine models [22, 32]. Recombinant vaccines incorporating SodC have shown significant immunogenicity in BALB/c mice and are considered valuable components in multivalent vaccine formulations [83].

DsbA is a periplasmic thiol-disulfide oxidoreductase essential for the folding of exported proteins via disulfide bond formation. Disruption of dsbA expression in *Brucella* leads to compromised stress resistance and severely reduced intracellular survival [61].

Mutants lacking DsbA display defects in outer membrane protein maturation and envelope homeostasis. These properties make DsbA a potential target for rational attenuation of live vaccines, preserving immunogenicity while reducing virulence [66].

HtrA is a periplasmic serine protease upregulated in response to stress stimuli such as heat, oxidative agents, and acidic pH. It degrades misfolded proteins and stabilizes the bacterial envelope under host-imposed stress [105].

Deletion of htrA impairs *Brucella* survival in macrophages and increases sensitivity to antimicrobial peptides. Live attenuated vaccine strains lacking htrA have demonstrated safety and the ability to elicit Th1-skewed immune responses, making HtrA a valuable marker for stress response and vaccine design [33].

PrpA is an immunomodulatory periplasmic enzyme capable of catalyzing the conversion of L-proline to D-proline and inducing polyclonal B-cell activation in a T-cell-independent manner. It promotes hypergammaglobulinemia and upregulates TGF-β, contributing to immune suppression and *Brucella* persistence [48].

Although not protective alone, PrpA enhances cellular immunity when incorporated into multivalent vaccine formulations, helping to reduce bacterial loads [83]. Elevated anti-PrpA antibodies in chronic brucellosis cases suggest potential use in immune profiling.

BepC, a TolC-like outer membrane channel, functions as part of *Brucella's* tripartite efflux systems that expel bile salts, antimicrobial peptides, and antibiotics. Knockout of bepC results in heightened sensitivity to these agents and reduced virulence in murine models [81].

While not strongly immunogenic under natural infection, BepC is currently explored as a DIVA marker and a possible target for efflux pump inhibitors to enhance antibiotic efficacy. Although classified as an outer membrane lipoprotein, Omp19 anchors to the inner leaflet and acts functionally as a periplasmic protease inhibitor. It protects *Brucella* against proteolytic degradation in the gastrointestinal tract and within lysosomes. Omp19-deficient mutants show reduced infectivity after oral administration and impaired intracellular survival [58, 33].

Recombinant unlipidated Omp19 (U-Omp19) has demonstrated adjuvant properties, enhancing mucosal

immunity and antigen presentation. It also serves as a DIVA marker, as Rev.1 Δomp19 mutants do not induce detectable anti-Omp19 antibodies [81].

Heat shock proteins (HSPs) play essential roles in the adaptation, survival, and immune interactions of *Brucella* spp. under host-induced stress. Among the most functionally and immunologically relevant are the chaperone proteins Hsp60 (GroEL), Hsp70 (including DnaK), and the ATP-independent serine protease HtrA. These molecules are not only critical for intracellular proteostasis but also serve as immunodominant antigens with significant implications for serodiagnosis and vaccine development.

GroEL is a 60 kDa chaperonin involved in protein folding, expressed under stress conditions and essential for *Brucella* spp. survival in the intracellular environment. It promotes immune responses, especially in combination with outer membrane proteins (OMPs) such as Omp25 and Omp31. Co-immunization studies have demonstrated enhanced protection in murine models, indicating synergistic effects between GroEL and surface antigens [1]. Transcriptomic analyses of the *Brucella melitensis* Rev.1 vaccine strain revealed downregulation of GroEL under acidic stress, which may correlate with attenuated virulence [71]. Furthermore, GroEL expression is modulated in response to antibiotics such as polymyxin B, highlighting its role in stress adaptation. Post-translational modifications including lysine acylation affect GroEL and other virulence-associated proteins, linking structural regulation with immune evasion and intracellular persistence. Studies also indicate a role for GroEL in subverting autophagic host defenses, particularly via LC3-dependent mechanisms in macrophages [105].

Hsp70 proteins, including DnaK, contribute to protein homeostasis and immune activation. DnaK has been identified in the vaccine strain *Brucella* 104M through proteogenomic profiling, confirming its constitutive expression and immunogenicity [54]. Functionally, DnaK facilitates refolding of misfolded proteins and promotes macrophage activation via NF-κB pathways, leading to pro-inflammatory cytokine production [30, 34, 56]. Its dual role in stress resilience and host immune signaling underscores its potential as a diagnostic and vaccine antigen. Structural modeling of Hsp70 family members, including insights into inhibitor interactions, further highlights their biomedical relevance [98].

Beyond ATP-dependent chaperones, ATP-independent serine proteases such as HtrA also contribute critically to protein homeostasis and virulence. HtrA is a periplasmic protease essential for *Brucella* virulence and protein quality control. It degrades misfolded proteins and modifies outer membrane components, facilitating adaptation to oxidative and thermal stress [30, 51]. Experimental deletion of the *htrA* gene results in reduced virulence and impaired intracellular survival of *Brucella* within macrophages. HtrA regulates multiple virulence-associated functions, including bacterial adhesion, invasion, and biofilm development [52]. It may also interfere with host immune responses by modulating cellular signaling pathways . Given its ability to function without ATP, its induction under cellular stress, and the high degree of structural preservation across *Brucella* strains, HtrA is regarded as a strong candidate for use in both diagnostic strategies and antigen-specific vaccine development [51].

Although less extensively studied, small heat shock proteins (sHSPs) such as Hsp20-like proteins are believed to contribute to immediate bacterial stress responses without requiring ATP. These proteins assist in preventing protein aggregation and stabilizing membrane integrity during infection. Their expression is often upregulated under heat or oxidative stress and may aid *Brucella* spp. in rapid adaptation to intracellular host environments [56]. While their immunogenicity remains less characterized compared to major HSPs, their functional relevance and evolutionary conservation warrant further investigation as potential diagnostic or vaccine adjuncts.

HSPs of *Brucella* spp. function at the intersection of virulence regulation, stress adaptation, and immune interaction. Their expression is modulated by transcriptional regulators such as MucR, further embedding them in broader regulatory networks [71]. The conserved structure and antigenicity of HSPs, particularly GroEL, DnaK, and HtrA, across multiple *Brucella* species including *B. melitensis*, *B. abortus*, and *B. suis*, enhance their relevance for cross-protective vaccine strategies. Diagnostic applications, including lateral flow assays targeting Hsp70, show promise for rapid field detection [56]. In vaccine design, co-formulation of HSPs with OMPs or adjuvants has demonstrated increased efficacy in animal models, offering pathways for subunit vaccine development [1].

In summary, HSPs are multifunctional proteins essential for *Brucella* spp. virulence, intracellular survival, and immune evasion. Their structural conservation and immunogenic potential make them compelling candidates for targeted diagnostics and subunit vaccine platforms against brucellosis.

Lipopolysaccharides (LPS)

Lipopolysaccharide (LPS) is a major surface component of *Brucella* spp. and represents the principal immunodominant antigen in smooth strains. Structurally, *Brucella* LPS consists of three classical domains: lipid A, a non-repeating oligosaccharide core, and an O-polysaccharide, also known as the O-antigen. Unlike enterobacterial LPS, the lipid A of *Brucella* is modified with very long-chain fatty acids and exhibits hypoacylation and hypophosphorylation, leading to low endotoxicity and reduced recognition by Toll-like receptor 4 (TLR4) [72].

The O-polysaccharide is composed exclusively of 4-formamido-4,6-dideoxy-α-D-mannopyranose (N-formylperosamine) residues, primarily linked by α-(1→2) glycosidic bonds. This conserved homopolymer, consisting of approximately 90–100 repeating units, provides serological specificity and supports immune evasion through molecular mimicry [10].

Brucella spp. display two LPS phenotypes: smooth (S-LPS), with a complete O-antigen chain, and rough (R-LPS), lacking or having a truncated surface polysaccharide. Smooth strains, including *B. melitensis*, *B. abortus*, and *B. suis*, exhibit species-specific antigenic profiles: *B. melitensis* primarily expresses M-epitopes, *B. abortus* A-epitopes, while *B. suis* shows a mixed pattern [21]. In contrast, rough strains such as *B. canis* and *B. ovis* produce R-LPS and are generally less virulent in humans [42].

Functionally, the O-antigen plays a central role in immune evasion. It shields outer membrane proteins, interferes with opsonization and complement activation, and reduces neutrophil recruitment. The low immunostimulatory potential of *Brucella* LPS, due to its weak interaction with TLR4, allows intracellular invasion with minimal inflammation [100]. Furthermore, the branched structure of the core

oligosaccharide masks pathogen-associated molecular patterns (PAMPs), enhancing immune concealment [101].

The O-antigen also contributes to intracellular survival. In smooth strains, it impairs phagosome-lysosome fusion and delays phagosomal maturation, facilitating replication within host macrophages [65]. Conversely, R-LPS mutants, which lack this protective barrier, are more susceptible to immune clearance due to increased membrane permeability and exposure of antigenic determinants [53].

Immunologically, the O-antigen elicits the dominant humoral response during natural infection. Specific antibodies, particularly of the IgM and IgG2 subclasses, arise early and form the basis of classical serological assays for example, the Rose Bengal assay, the complement fixation reaction, and enzyme-linked immunosorbent assays (ELISAs) [15]. However, these tests are limited by cross-reactivity among smooth *Brucella* species and with unrelated Gram-negative bacteria. A notable example is *Yersinia enterocolitica* O:9, which expresses an identical terminal saccharide epitope [47].

Vaccination further complicates serodiagnosis. Live attenuated strains such as *B. abortus* S19 and *B. melitensis* Rev.1 generate anti-O-antigen antibodies indistinguishable from those induced by infection, hampering surveillance and eradication programs [26]. To overcome this, the rough strain *B. abortus* RB51 is used in veterinary settings. Its lack of O-antigen prevents interference with serological testing and aligns with DIVA (Differentiating Infected from Vaccinated Animals) principles [62].

Despite its immunodominance, the O-antigen is a thymus-independent antigen and fails to activate T-helper cells or induce lasting immunological memory. Thus, while anti-LPS antibodies can mediate opsonization in vitro, effective protection against brucellosis relies primarily on Th1-driven cellular immunity [64].

From a vaccine perspective, native LPS is suboptimal due to its residual endotoxin-like properties and limited capacity to induce cell-mediated responses. Nevertheless, detoxified LPS preparations and conjugate vaccines—linking the O-antigen to protein carriers such as tetanus toxoid or bovine serum albumin—have demonstrated improved immunogenicity and partial protection in murine models. However, these strategies remain experimental and face ongoing challenges, including cross-reactivity and potential diagnostic interference [36].

Type IV secretion system proteins (VirB)

The type IV secretion apparatus (T4SS), whose genetic components are organized within the virB operon (virB1 to virB12), represents one of the principal virulence mechanisms in *Brucella spp.* and is indispensable for intracellular survival, immune evasion, and chronic persistence in the human host. Structurally and functionally analogous to conjugative systems of Gram-negative bacteria, the T4SS mediates the translocation of effector proteins across the bacterial envelope into host cells, enabling *Brucella* to subvert key cellular processes such as vesicle trafficking, apoptosis, autophagy, and innate immune signaling. Recent studies have also identified novel T4SS effectors, such as RS15060, which contribute to intracellular replication and chronic infection, further underscoring the role of this system in bacterial virulence [94,95].

The *virB* operon was initially characterized in *B. suis* and subsequently found to be highly conserved across *B. melitensis* and *B. abortus*. Its expression is upregulated in response to phagosomal acidification within the *Brucella*-containing vacuole (BCV), typically peaking within the first 4–6 hours post-internalization. The assembled T4SS spans both bacterial membranes and comprises three structural modules: (i) the cytoplasmic ATPase complex (VirB4, VirB11), (ii) the inner membrane platform (VirB3, VirB6, VirB8, and the N-terminal of VirB10), and (iii) the outer membrane core complex (VirB7, VirB9, and the C-terminal of VirB10) [79].

VirB2, the major pilin subunit, is essential for pilus assembly and is involved in effector delivery. VirB4 and VirB11 act as ATPases energizing translocation, while VirB9 and VirB10 are critical for the stability of the secretion channel. Disruption of these genes abolishes secretion function and abrogates intracellular replication in both murine and ruminant models [88]. Other components such as VirB1 (a peptidoglycan hydrolase), VirB7 (lipoprotein), and VirB12 (surface-exposed protein) are not essential for secretion per se but contribute to apparatus stability and host-pathogen interactions [85].

The *Brucella* T4SS delivers several effector proteins that actively reprogram host cell biology. VceC induces endoplasmic reticulum (ER) stress by binding the chaperone BiP/Grp78, promoting membrane remodeling and facilitating BCV maturation and ER association [103]. RicA targets the small GTPase Rab2, disrupting ER-Golgi trafficking and interfering with phagosome maturation [45]. TIR-domain-containing effectors BtpA and BtpB inhibit Toll-like receptor (TLR) signaling by mimicking host adaptor proteins, suppressing NF-κB activation and proinflammatory cytokine production. These activities collectively enable Brucella to persist within macrophages and prevent effective antigen presentation, contributing to the stealthy and chronic nature of human brucellosis [46, 80].

Due to their conserved nature and immunological relevance, several VirB proteins have been investigated as serodiagnostic and vaccine targets. Antibodies against VirB9, VirB10, VirB11, and VirB12 have been consistently detected in sera from naturally infected humans and animals, with recombinant forms used in diagnostic ELISA formats demonstrating sensitivity and specificity above 90% [85,95]. Notably, VirB12, while non-essential for secretion, is surface-exposed and highly immunodominant, making it a promising DIVA (Differentiating Infected from Vaccinated Animals) marker. In parallel, PCR assays targeting VirB genes have proven useful for identifying virulent *Brucella* field isolates and for molecular epidemiology in endemic regions [99].

In the context of vaccine development, VirB proteins offer a rational strategy to disrupt *Brucella* intracellular persistence. Subunit vaccine candidates incorporating VirB9 and VirB11 have shown the ability to induce Th1-skewed cellular responses, which are essential for protection against intracellular pathogens [69]. Additionally, T4SS effectors such as VceC and BtpB have demonstrated immunomodulatory and protective potential in experimental murine models, contributing to reduced bacterial loads and altered cytokine profiles following challenge. Nevertheless, limitations remain concerning antigen delivery systems, adjuvant selection, and cross-protection across *Brucella* species, warranting further research into optimized multivalent vaccine constructs [67,88].

Other Potential Antigens

Beyond the well-characterized antigenic determinants of *Brucella* spp., such as lipopolysaccharides (LPS), outer membrane proteins (OMPs), and type IV secretion system

(T4SS) components, a range of less-studied but immunologically promising proteins have been identified through immunoproteomic approaches and computational epitope prediction. These include cytoplasmic enzymes with atypical surface exposure, ribosomal constituents, periplasmic transporters, and transcriptional regulators. Despite the limited availability of in vivo validation, their evolutionary conservation, stress-induced upregulation, and demonstrated immunogenicity in infected hosts suggest a potential role in both serodiagnostics and rational vaccine design [14].

Among the most notable are cytosolic metabolic enzymes such as noteworthy examples include the cytosolic enzymes enolase, GAPDH (glyceraldehyde-3-phosphate dehydrogenase), and MDH (malate dehydrogenase). These multifunctional or "moonlighting" proteins, despite the absence of conventional secretion motifs, have been identified at the bacterial cell surface, where they engage in interactions with host factors. Enolase, in particular, has been shown to bind plasminogen, potentially promoting degradation of the extracellular matrix and facilitating bacterial dissemination. GAPDH has been implicated in adhesion processes through binding to host fibronectin and other extracellular components. Importantly, MDH has shown selective immunoreactivity with sera from naturally infected, but not vaccinated, animals, indicating its diagnostic value as a marker of early-stage infection [77].

Ribosomal proteins, particularly the L7/L12 ribosomal stalk complex, are evolutionarily conserved antigens that elicit strong Th1-biased immune responses. L7/L12 has been widely investigated as a subunit vaccine component and diagnostic antigen, especially when combined with outer membrane proteins to improve assay specificity [86]. Some ribosomal proteins beyond L7/L12, such as putative 30S subunit components, have been tentatively detected as reactive in proteomic analyses, but their diagnostic relevance is unclear due to limited characterization and high sequence conservation [96].

The *Brucella* cell surface protein 31 (BCSP31), a 31-kDa conserved protein originally described as a transport-related factor, is frequently targeted in PCR-based diagnostics and has demonstrated reliable immunogenicity in serological assays. Its application as a capture antigen in lateral flow devices and ELISA formats has been well documented, although its precise physiological function remains incompletely defined [76].

Additional periplasmic transporter proteins, including OppA (oligopeptide-binding protein), LAO-binding proteins (specific for L-arginine and ornithine), and elements of the Sec-dependent secretion system, have been identified as seroreactive antigens in ruminants naturally infected with *Brucella*. Although not surface-exposed in the classical sense, their elevated periplasmic abundance during infection and consistent recognition by host antibodies support their utility as internal markers in multiplex serodiagnostic platforms [2].

Regulatory proteins, notably the quorum-sensing transcriptional regulator VjbR and the cold-shock protein CspA, display altered expression profiles during intracellular adaptation. VjbR regulates the transcription of multiple virulence-associated genes and is involved in modulating host immune responses, while CspA contributes to bacterial survival under host-induced stress. Both proteins have demonstrated modest T-cell immunogenicity in preliminary experimental models, but their utility as diagnostic or vaccine antigens remains to be validated in comprehensive immunological studies [31].

The invasion-associated protein IalB is a membrane-associated factor essential for *Brucella* adhesion and intracellular survival. Deletion of the ialB gene in *B. suis* leads to reduced virulence, highlighting its role in pathogenesis. While its immunogenicity is moderate, IalB remains a potential target for subunit vaccines or DIVA diagnostics [9].

Discussion

Modern serological diagnostics of brucellosis have progressively transitioned from crude bacterial lysates toward the use of defined, molecular antigens. This refinement addresses the need for improved test specificity, particularly in endemic areas where cross-reactivity with *Yersinia enterocolitica* O:9 remains a major confounder. The adoption of recombinant antigens has not only enhanced specificity but also enabled species-independent detection and improved assay reproducibility across laboratories.

The enzyme-linked immunosorbent assay (ELISA) continues to be the primary platform for brucellosis screening in both humans and animals. Commercially available ELISA kits frequently incorporate recombinant or purified proteins such as Omp31, BP26, ribosomal protein L7/L12, and Cu/Zn superoxide dismutase (SOD), all of which demonstrate consistent immunoreactivity in infected sera. L7/L12 and SOD, in particular, show sustained serological responses throughout the course of infection, making them valuable markers for detecting both acute and chronic brucellosis.

The fluorescence polarization assay (FPA), recommended by the World Organisation for Animal Health, employs fluorescein-labeled O-polysaccharides derived from smooth lipopolysaccharide (S-LPS). While FPA offers rapid and highly sensitive detection, its reliance on high-quality LPS extraction and its inability to distinguish between *Brucella* species limit its broader diagnostic applicability. New approaches incorporating synthetic oligosaccharide analogues or recombinant proteins into FPA formats are currently under investigation to overcome these limitations.

Despite these advances, existing antigen-based assays still fall short in early-stage detection and multi-host application. To address these gaps, multiepitope recombinant constructs combining outer membrane proteins (e.g., Omp16, Omp19) with intracellular proteins such as enolase, malate dehydrogenase (MDH) are being developed. These composite antigens offer higher specificity by minimizing cross-reactivity with non-pathogenic microorganisms and may improve diagnostic accuracy during early infection.

Among the most promising diagnostic antigens, Omp16, Omp19, and Omp31 consistently exhibit strong immunogenicity across various *Brucella* species. Although Cu/Zn-SOD is periplasmic in localization, it elicits both humoral and cellular responses and has shown excellent diagnostic potential. Ribosomal protein L7/L12, which induce early-phase antibody responses particularly in ruminants, are emerging as valuable components of non-LPS diagnostic panels. Additionally, several cytoplasmic metabolic enzymes—such as enolase, MDH, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH)—function as “moonlighting” proteins that become surface-exposed under intracellular stress conditions. Alongside regulatory proteins like VjbR, these antigens broaden the diagnostic landscape and may enhance sensitivity in latent infections.

In parallel, the pursuit of a safe and effective human brucellosis vaccine remains an urgent but unmet objective. Currently available live attenuated veterinary vaccines (e.g., *B. melitensis* Rev.1) are not suitable for human use due to residual virulence and interference with serological surveillance. This has shifted the focus to subunit and DNA-based vaccine strategies utilizing well-characterized, immunogenic proteins.

Promising antigen candidates validated in murine models include Omp16, Omp19, Omp25, Omp31, BP26, Cu/Zn-SOD, and L7/L12. DNA vaccines encoding L7/L12 and Omp16 have demonstrated strong Th1-type responses marked by IFN-γ and TNF-α secretion and a significant reduction in splenic bacterial burden following challenge. Cu/Zn-SOD, in addition to its antioxidant function, has proven highly immunogenic and effective in stimulating cell-mediated responses. Preliminary studies suggest that IalB may contribute to protection in DNA vaccine constructs, although its immunogenicity and protective efficacy remain lower than those of more established *Brucella* antigens.

The rational design of multivalent subunit vaccines rests on the inclusion of structurally and functionally diverse antigens that cover different stages of *Brucella* pathogenesis. Combinations such as Omp25, Omp31, and BP26 have already achieved diagnostic performance exceeding 94% sensitivity and 100% specificity in human ELISA formats. The inclusion of stress-responsive metabolic and regulatory antigens could improve the identification of persistent or subclinical *Brucella* infections, particularly in cases characterized by diminished levels of circulating antibodies.

Nevertheless, several translational challenges remain. Preclinical safety and immunogenicity data must be rigorously validated in relevant animal models. The scalable production of recombinant proteins under GMP conditions, optimization of adjuvants (e.g., CpG-ODNs, monophosphoryl lipid A), and selection of effective delivery platforms (such as viral vectors, mRNA, or nanoparticle systems) are critical next steps. Initial studies on intranasal and oral immunization strategies have already yielded encouraging results, demonstrating both favorable safety profiles and robust mucosal immunity.

In summary, the incorporation of defined *Brucella* antigens into diagnostic assays and vaccine platforms represents a promising path forward. The combined use of outer membrane, periplasmic, and cytoplasmic proteins offers an opportunity to develop highly specific, broadly applicable tools for the detection and prevention of human brucellosis. A comparative overview of immunogenicity levels for the most studied *Brucella* antigens is presented in Figure 3.

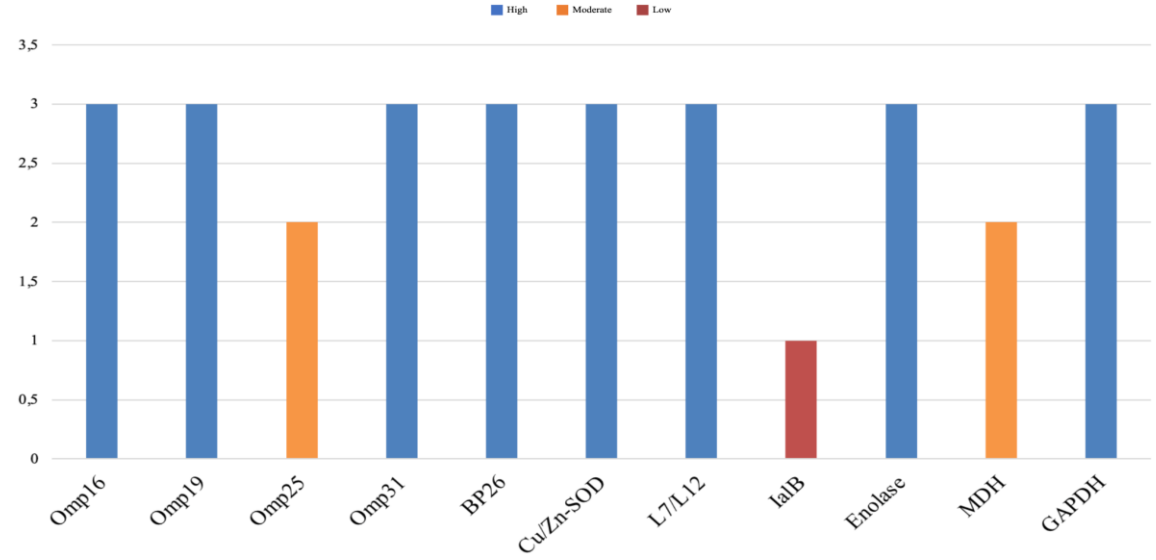


Figure 3. Comparative immunogenicity of *Brucella* antigens. The chart summarizes relative immunogenicity levels based on Th1/Th2 cytokine profiles, antibody responses, and T-cell reactivity data extracted from experimental studies. Only antigens with available and quantifiable immune data are included. Immunogenicity categories: high (blue), moderate (orange), and low (dark red).

Conclusion

Brucellosis remains a significant zoonotic threat that necessitates both the refinement of diagnostic tools and the development of effective preventive strategies. Traditional serological methods often exhibit insufficient sensitivity and specificity, particularly in chronic or latent infections, reinforcing the need for highly specific, antigen-based diagnostic assays.

Simultaneously, the formulation of a subunit vaccine represents a safe and scientifically grounded alternative to live-attenuated vaccines. Based on immunological relevance and accumulated experimental data, a panel of *Brucella* antigens has been identified as promising candidates: ribosomal protein L7/L12, Cu/Zn-SOD, and outer membrane proteins Omp16, Omp19, Omp25, and Omp31. Their combined inclusion ensures broad-spectrum immunogenicity while maintaining a favorable safety profile. This integrated approach may substantially contribute to the global effort to control human brucellosis.

Funding

This research was funded by the Ministry of Healthcare of the Republic of Kazakhstan under the program-targeted financing for 2024–2026 (Grant No. BR25293294).

Acknowledgements

The authors gratefully acknowledge the support of the Research Institute for Biological Safety Problems (RIBSP, Gvardeisky, Otar) for providing essential infrastructure, scientific

expertise, and institutional collaboration that contributed to the implementation of this work.

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Scopus ID: 57200621687

Received: 09 June 2025 / Accepted: 04 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.028

UDC 340.6:611.781

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DIAPHRAGMATIC RELAXATION: CLINICAL MANIFESTATIONS AND FORENSIC CONSIDERATIONS

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Abstract

Diaphragmatic relaxation is a rare but critical condition that can lead to severe respiratory complications. This article presents a clinical case of a 36-year-old female patient who presented with severe respiratory distress due to idiopathic left diaphragmatic relaxation, complicated by compression atelectasis and pulmonary embolism. The case underscores the need for heightened vigilance in diagnosing and managing diaphragmatic disorders, particularly in patients with unexplained respiratory symptoms. The findings highlight the importance of recognizing this condition early and considering surgical options as a treatment pathway. By bridging the gap between clinical practice and forensic analysis, this study seeks to improve the management of patients suffering from diaphragmatic dysfunction.

Keywords: *diaphragmatic relaxation, diaphragm dysfunction, surgical intervention, respiratory distress, idiopathic condition, diagnosis, case study.*

For citation:

Mussabekova S.A., Burkova E.I., Mustapayev M.O., Shavnina N.P., Dusmailov R.M. Diaphragmatic relaxation: Clinical manifestations and forensic considerations // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 237-242. *doi 10.34689/SH.2025.27.4.028*

Резюме

ДИАФРАГМАЛЬНАЯ РЕЛАКСАЦИЯ: КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ И СУДЕБНО-МЕДИЦИНСКИЕ АСПЕКТЫ

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Диафрагмальная релаксация - редкое, но критическое состояние, которое может привести к тяжелым респираторным осложнениям. В этой статье представлен клинический случай 36-летней пациентки с тяжелым респираторным дистрессом из-за идиопатической левой диафрагмальной релаксации, осложненной компрессионным ателектазом и тромбоэмболией легочной артерии. Случай подчеркивает необходимость повышенной бдительности при диагностике и лечении диафрагмальных расстройств, особенно у пациентов с необъяснимыми респираторными симптомами. Результаты подчеркивают важность раннего распознавания этого состояния и рассмотрения хирургических вариантов в качестве пути лечения. Устраняя разрыв между клинической практикой и судебно-медицинским анализом, это исследование стремится улучшить лечение пациентов, страдающих дисфункцией диафрагмы.

Ключевые слова: *диафрагмальная релаксация, дисфункция диафрагмы, хирургическое вмешательство, респираторный дистресс, идиопатическое состояние, диагностика, исследование случая.*

Для цитирования:

Мусабекова С.А., Буркова Е.И., Мустапаев М.О., Шавнина Н.П., Дусмаилов Р.М. Диафрагмальная релаксация: клинические проявления и судебно-медицинские аспекты // Наука и Здравоохранение. 2025. Vol.27 (4), С. 237-242. *doi 10.34689/SH.2025.27.4.028*

Түйіндеме

ДИАФРАГМАЛЫҚ РЕЛАКСАЦИЯ: КЛИНИКАЛЫҚ КӨРІНІСТЕРІ МЕН СОТ-МЕДИЦИНАЛЫҚ АСПЕКТІЛЕРІ

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Диафрагмалық релаксация — сирек, бірақ тыныс алу жүйесінің ауыр асқынуларына әкелуі мүмкін, өте ауыр көрініс беретін жағдай. Бұл мақалада идиопатиялық сол жақ диафрагмалық релаксацияның әсерінен ауыр тыныс алу бұзылысы бар 36 жасар науқастың компрессиялық ателектаз бен өкпе артериясының тромбоэмболиясына асқынған клиникалық жағдайы келтірілген. Бұл жағдай диафрагмалық бұзылыстарды диагностикалау және емдеу кезінде ерекше сақтық танытудың маңыздылығын көрсетеді, әсіресе түсініксіз тыныс алу бұзылыстары бар науқастарда. Зерттеу нәтижелері осы жағдайды ерте анықтаудың және емдеу жолы ретінде хирургиялық тәсілдерді қарастырудың маңызды екенін атап көрсетеді. Клиникалық тәжірибе мен сот-медициналық талдауды байланыстыра отырып, бұл зерттеу диафрагманың дисфункциясымен ауыратын науқастардың емдеу жолын жақсартуды мақсат етеді.

***Түйін сөздер**: диафрагмалық релаксация, диафрагманың дисфункциясы, хирургиялық емдеу, тыныс алу бұзылысы, идиопатиялық жағдай, диагностика, жағдайды зерттеу.*

Дәйексөз үшін:

Мусабекова С.А., Буркова Е.И., Мустапаев М.О., Шавнина Н.П., Дусмаилов Р.М. Диафрагмалық релаксация: клиникалық көріністері мен сот-медициналық аспектілері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 237-242. *doi 10.34689/SH.2025.27.4.028*

Introduction

Diaphragm dysfunction is a respiratory disorder characterized by impaired diaphragm movement, leading to symptoms such as dyspnea, exercise intolerance, and sleep disturbances. It is diagnosed through imaging tests and pulmonary function assessments [9]. A specific form of this dysfunction, diaphragmatic relaxation or elevation, refers to abnormal diaphragm positioning that can cause respiratory distress, particularly during exertion [16]. When the diaphragm is compromised by conditions such as diaphragmatic relaxation, patients may experience paradoxical diaphragm movement, leading to inadequate ventilation and oxygenation [8]. Diaphragmatic relaxation is a critical clinical condition that may result in severe respiratory complications, yet it is frequently underdiagnosed in both acute and chronic contexts. Typically, unilateral paralysis of the diaphragm is asymptomatic and often identified incidentally during X-ray examinations, presenting as dyspnea during significant physical exertion [19]. The etiology of diaphragmatic relaxation is diverse. Traumatic events can lead to diaphragmatic hernias or paralysis due to phrenic nerve injury [1,19]. Congenital conditions, including congenital diaphragmatic hernia, can severely impact respiratory function from birth. Neuromuscular diseases such as Amyotrophic Lateral Sclerosis or Spinal Muscular Atrophy contribute significantly to diaphragmatic dysfunction by weakening the respiratory musculature [7].

The clinical manifestations of diaphragmatic relaxation range from subtle respiratory symptoms to acute respiratory distress syndrome, depending on the severity and cause [14]. Globally, the incidence of diaphragmatic relaxation remains underreported, with few documented cases in the medical literature [2,11]. Recent studies have highlighted the significant impact of diaphragmatic relaxation on overall respiratory health, emphasizing the necessity for early detection and intervention [3]. The lack of awareness among healthcare professionals can delay diagnosis and treatment, exacerbating patient outcomes [4]. In this context, timely identification and intervention are essential to prevent life-threatening complications.

Forensic analysis of diaphragmatic relaxation is critical, as it can provide essential insights into the circumstances surrounding its onset, particularly in cases of trauma. Understanding the mechanisms of injury and the subsequent physiological responses is vital for accurate assessment and management [13].

This article aims to examine the clinical manifestations and forensic implications of diaphragmatic relaxation through a detailed case study, highlighting the importance of timely diagnosis and intervention.

Case Presentation

A 36-year-old female patient was admitted to the emergency department with unstable hemodynamics and complaints of significant weakness and chest pain. Her medical history was notable for episodes of syncope and persistent pallor. The patient described her symptoms as

having intensified over the previous two days, attributing them to a recent episode of physical exertion. In addition, the woman reported that she had been beaten on her abdomen and chest.

Objectively, the patient's general condition was severe due to accompanying abdominal syndrome, pain syndrome, and respiratory failure. The patient appeared severely distressed and assumed a forced posture. Upon examination, the patient exhibited severe dyspnea, with a respiratory rate of 22 breaths per minute and oxygen saturation of 78%. Both sides of the chest moved equally during breathing. The thorax was of normal shape, with no deformities. Auscultation: vesicular respiration, weakened in the lower parts of the left side, no wheezing. Auscultation revealed diminished breath sounds on the left side of her chest. These findings raised suspicion of diaphragmatic dysfunction. Heart rate was 90 per min, and her blood pressure was 110/80 mmHg.

Initial imaging, including chest X-rays and CT scans, revealed left diaphragmatic relaxation accompanied by compression of the left lung and a significant pleural effusion. Computed tomography of the chest and mediastinum showed a high position of the left diaphragm dome (relaxation), compression atelectasis of S7, S8, S9, and S10 segments of the left lung, and signs of pulmonary hypertension. The review radiograph showed an Rg-picture of the high standing of the left dome of the diaphragm, with compression of the lower parts of the left lung. Ultrasonography revealed 80 ml of free fluid in the left pleural cavity.

The next day, the patient experienced a cardiac arrest of the ventricular fibrillation type. After successful resuscitation, the patient underwent laparoscopic diaphragmatic plication. The procedure aimed to restore the diaphragm's normal anatomical position and improve respiratory mechanics. Anesthesia was total intravenous with mechanical ventilation.

Surgical recovery was complicated by acute pulmonary embolism. During the operation, the patient suffered a sudden cardiac arrest. Resuscitation measures were started: cardiopulmonary resuscitation. Against the background of an extremely severe condition, resistant to vasopressor therapy and intensive care measures, she progressed to asystole. There was no effect of resuscitation measures within 30 minutes, and biological death was stated. Final clinical diagnosis were: traumatic relaxation of the dome of the diaphragm on the left (J98.6); acute respiratory failure acute respiratory failure, grade 3 (J96.0); cardiac arrest with successful recovery of cardiac activity (146.0); Obesity 3rd degree (E 66.0); Pulmonary embolism (126.9). Obesity is due to excess energy. Clinical death from XX/XX/2024 successful resuscitation (3 min) TELA.

Following the initial clinical assessment, a forensic examination was conducted to evaluate potential causes of acute respiratory failure.

The external examination revealed no signs of trauma. There were no visible contusions, abrasions, or signs of injection, and the skeletal structure appeared intact with no pathological mobility. The absence of external trauma suggested that the patient's respiratory distress was primarily attributable to diaphragmatic dysfunction rather than external physical injury.

An internal forensic examination revealed several significant findings. The diaphragm exhibited relaxation, characterized by a loss of normal tension and an elevation of the left hemidiaphragm, which was pathologically high (at the level of the third rib). The left diaphragm appeared flabby, stretched, and gathered in folds, with thinning observed (Fig.1). It maintained a normal color, was free from hemorrhages, and exhibited a smooth surface without abnormal formations.

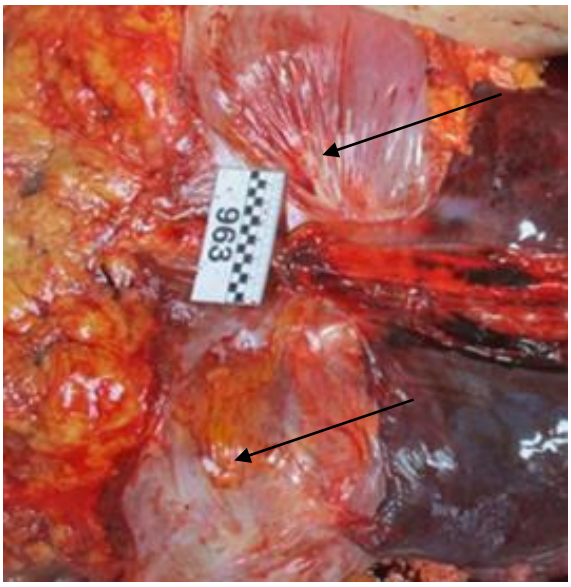


Figure 1. Diaphragm: on the left - flabby, stretched, gathered in folds, thin, of usual color, without hemorrhages, surface smooth, without any formations; on the right side - without features.

A forensic histological examination indicated weakly expressed dystrophic changes in the left diaphragmatic nerve (Fig.2) and focal hemorrhages in the surrounding connective tissue of the diaphragmatic nerve (Fig.3). Additionally, prominent stromal edema (Fig.4) and dystrophic changes in muscle fibers were noted, particularly on the left side of the diaphragm (Fig.5).

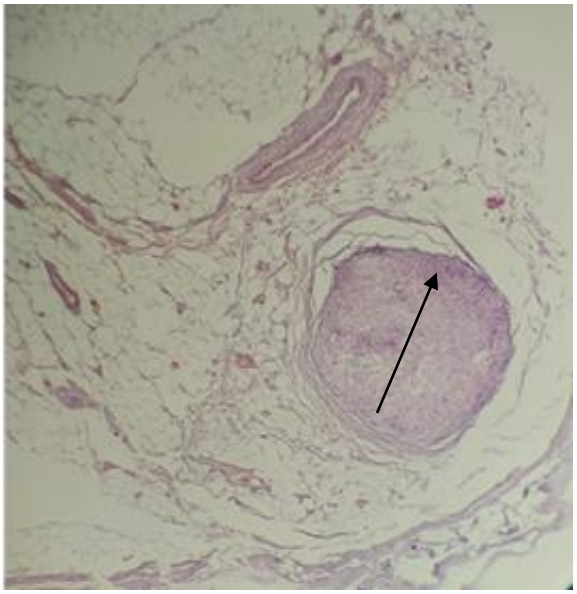


Figure 2. Diaphragmatic nerve (left): Mild dystrophic changes

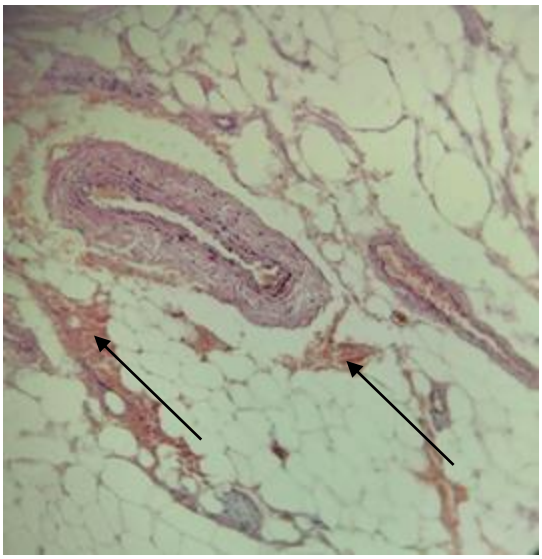


Figure 3. Diaphragmatic nerve (left): Focal hemorrhages in the surrounding fiber of the diaphragmatic nerve

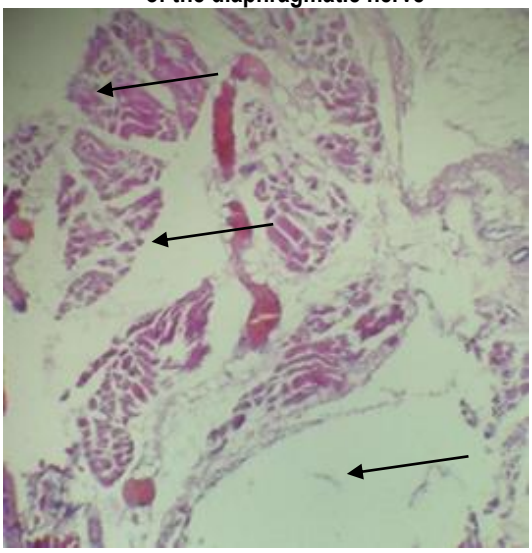


Figure 4. Diaphragm (left): Prominent stromal edema, dystrophic changes in muscle fibers

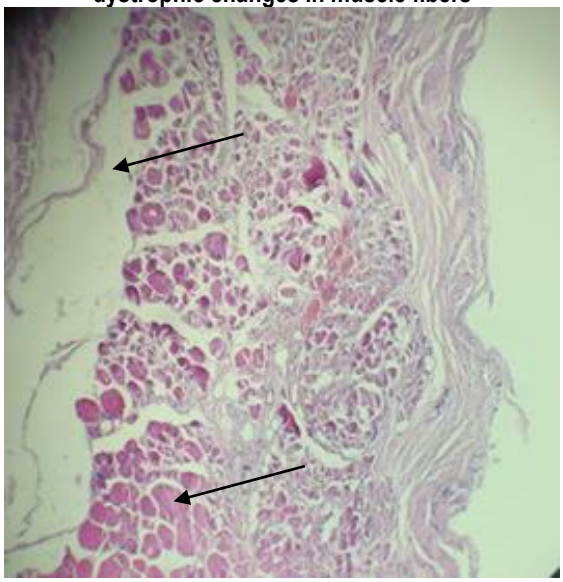


Figure 5. Diaphragm (left): Prominent stromal edema, dystrophic changes, and swelling of diaphragm muscle fibers.

Examination of the lungs revealed a smooth and shiny surface, with the tissue displaying a purplish-red color interspersed with pale pink areas. The right lung is small-air to the touch, featuring multiple greyish-pink foci of acute emphysema slightly elevated above the surrounding pulmonary surface. In contrast, the left lung was sharply collapsed, demonstrating a doughy consistency, with similar greyish-pink foci of acute emphysema.

Microscopic examination of lung tissue samples from the left side indicated areas of compression atelectasis, characterized by collapsed alveoli and significant inflammatory changes (Fig.6). The alveolar walls were thickened, and there was an increase in interstitial fluid, suggestive of pulmonary edema.

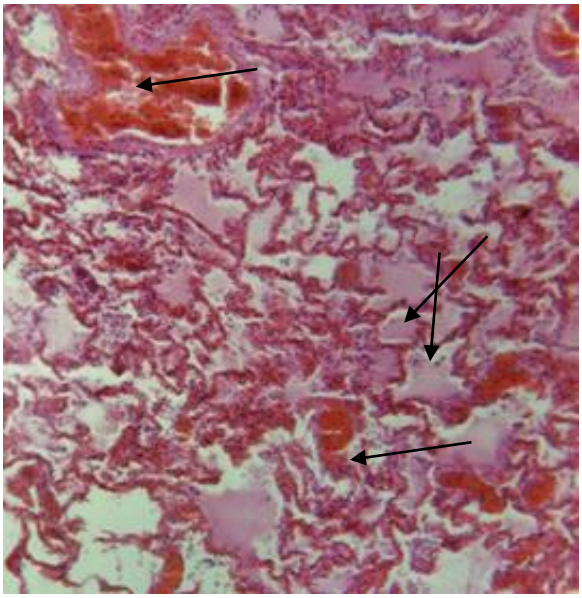


Figure 6. Lung (left): Multiple obturating erythrocyte thrombi in the lumen of pulmonary artery vessels of different caliber and capillaries of interalveolar septa. Large focal extra-alveolar and intra-alveolar hemorrhages of saturated red color. Foci of acute alveolar emphysema of various degrees of severity and spread, with thinning and defects of several interalveolar septa, which alternate with areas of collapsed alveoli. Alveolar edema.

The examination of the heart and vascular system revealed signs of strain consistent with acute respiratory distress and potential hypoxic injury. The right ventricle showed signs of hypertrophy, likely due to increased pulmonary artery pressure resulting from the compromised left lung. Histological analysis of the adrenal glands indicated nodular hyperplasia, which may have contributed to the patient's overall instability. The presence of edema in the lungs, alongside the noted pleural effusion, reinforced the diagnosis of acute respiratory failure. Forensic diagnosis: «Idiopathic (of unknown genesis) relaxation of the diaphragm on the left: distended, flabby diaphragm on the left, high pathological standing of the diaphragm dome at the level of the 3rd rib. (J98.6). Complication: Compression atelectasis (compression) of the left lung: sharply collapsed left lung, filling the pleural cavity by ¼, decreased airiness; foci of acute alveolar emphysema of varying severity and distribution, with thinning and defects

of several interalveolar septa, alternating with areas of collapsed alveoli. Pulmonary artery thromboembolism: the presence of mixed thrombus in the lumen of the pulmonary trunk, both pulmonary arteries, spreading to the branches of smaller caliber in the «tree» type…». Furthermore, toxicological analyses were conducted to rule out any substance abuse or poisoning as contributing factors to the patient's condition. The results were negative for common toxins and drugs, supporting the conclusion that the primary cause of her respiratory failure was related to the diaphragmatic dysfunction rather than external factors.

Discussion

Diaphragmatic relaxation is often overlooked in clinical practice, despite its potential to cause significant respiratory compromise. The pathophysiology often involves an imbalance between the diaphragm's forces and thoracic cavity dynamics, resulting in abnormal positioning [8]. While unilateral and bilateral diaphragmatic dysfunction can lead to respiratory failure, unilateral dysfunction is more common [7,9]. Various etiological factors contribute to diaphragmatic relaxation, including congenital defects and nerve damage; however, many cases remain idiopathic [6]. Research increasingly focuses on perioperative diaphragm protection, as diaphragmatic dysfunction can facilitate atelectasis by negatively affecting lung and chest wall mechanics. For instance, *Hu et al.* (2024) highlight the need to monitor diaphragm function during the perioperative period to mitigate complications associated with mechanical ventilation [4]. Mechanical ventilation, while critical for respiratory support, may lead to «myotrauma» (injury to muscle tissue due to mechanical ventilation) and subsequent diaphragmatic dysfunction (DD). The mechanisms of myotrauma are often linked to inadequate mechanical ventilation support, resulting in patient-ventilator asynchrony (PVA). Understanding these mechanisms is essential for developing myotrauma prevention strategies, focusing on appropriate inspiratory effort levels to avoid over- and under-assistance [3].

Various methods exist for tracking diaphragm activity, though their applicability varies in critically ill patients. While measuring transdiaphragmatic pressure following magnetic stimulation of the phrenic nerves is the gold standard, more practical methods like diaphragmatic ultrasound have proven useful for evaluating diaphragm function, particularly in critically ill patients [5,12]. This non-invasive technique enables clinicians to monitor diaphragm morphology and function effectively, enhancing diagnostic accuracy and expediting treatment decisions [15,17].

The diverse causes of diaphragmatic dysfunction necessitate a comprehensive approach to diagnosis and management. A multidisciplinary approach is crucial in managing patients with diaphragmatic disorders. *Di Buono et al.* (2020) emphasize the importance of early surgical intervention in congenital cases to prevent long-term complications such as pulmonary hypoplasia [2]. Early recognition and referral to surgical specialists can significantly enhance outcomes. Rapid identification of diaphragmatic dysfunction in trauma cases can facilitate timely surgical interventions, potentially reducing morbidity and mortality. Advances in minimally invasive surgical techniques allow for more effective management of diaphragmatic issues, reducing recovery times and associated morbidity. Case studies, such as *Migliore et al.* (2017), illustrate the clinical implications of severe diaphragm dysfunction and highlight the need for targeted interventions [11]. Surgical interventions, such as diaphragmatic plication, have shown promise in restoring normal diaphragm function and alleviating respiratory distress [10,18]. Rehabilitation strategies, including deep diaphragmatic breathing exercises, can improve respiratory function post-injury [3]. *Liu et al.* (2024) emphasize that diaphragmatic breathing not only increases lung capacity but also enhances overall respiratory efficiency [8].

In conclusion, the interplay between clinical practice and forensic analysis is crucial for understanding diaphragmatic dysfunction. Early recognition, effective diagnostic tools, and appropriate management strategies can significantly enhance patient outcomes. Integrating forensic insights into clinical assessments improves our understanding of diaphragmatic dysfunction and contributes to more effective treatment protocols, ultimately leading to better recovery trajectories for affected patients.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

Funding: *This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan: AP19677442 "Modeling of induced pluripotent stem cells (iPSCs) to improve understanding of the mechanisms underlying electrical heart disorders in Kazakhstani patients"; AP23490249 "Functional assessment of novel genetic mutations causing dilated cardiomyopathy using iPSC derived cardiomyocyte modeling in patients of Kazakhstan";*

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Received: 15 May 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.029

UDC 616.13-002.151-053.9-071

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CASE REPORT: HEMORRHAGIC VASCULITIS IN AN ELDERLY PATIENT

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Abstract

Introduction. Hemorrhagic vasculitis (HV), or Schönlein–Henoch purpura, is a systemic vasculitis of small vessels, predominantly mediated by IgA. Although the disease occurs relatively frequently in childhood, its manifestation in elderly patients is much rarer and typically presents with a more severe and torpid course. In older patients, the condition is often accompanied by pronounced visceral complications, including abdominal and renal syndromes, which significantly worsen the prognosis and require special attention in both diagnosis and treatment. This article presents a clinical case of hemorrhagic vasculitis in a geriatric patient. The disease manifested with the classical triad of symptoms: cutaneous purpura, abdominal pain syndrome, and renal involvement.

Objective. To describe a clinical case of hemorrhagic vasculitis in an 86-year-old patient with concomitant cutaneous, abdominal, and renal syndromes on the background of significant comorbidities.

Materials and Methods. This article presents the clinical case of an 86-year-old patient, V., who was admitted to the rheumatology department of the City Rheumatology Center in Almaty with complaints of hemorrhagic rashes on the upper and lower extremities, marked weakness, abdominal pain syndrome, episodes of nausea and vomiting, and oliguria. A comprehensive clinical, laboratory, and instrumental examination was conducted, including complete blood count, biochemical blood tests, urine analysis (including the Nechiporenko test), coagulation profile, immunological studies, abdominal ultrasound, ECG, and echocardiography. The diagnosis was established based on the patient's complaints, clinical presentation, laboratory and instrumental findings, and in accordance with the EULAR (2010) classification criteria for adults.

Results. The patient presented with typical symptoms of cutaneous hemorrhagic syndrome (symmetrical bluish-purple rashes that did not blanch under pressure), abdominal manifestations (nausea, vomiting, pain in the periumbilical area), and signs of renal involvement (episodes of oliguria, leukocyturia, elevated creatinine and urea levels). Under treatment with glucocorticosteroids, immunosuppressive therapy, infusion, and symptomatic therapy, positive dynamics were observed, including a reduction in the severity of skin manifestations, improvement in abdominal and renal symptoms, better laboratory values, and stabilization of the general condition. However, the disease course remained torpid, with prolonged healing of skin lesions, high sensitivity to medication changes, and the need for continuous cardiological and gastroenterological supervision.

Conclusion. Early diagnosis, timely assessment of organ involvement, appropriate use of immunosuppressive and glucocorticosteroid therapy, and careful monitoring of complications are crucial for achieving favorable outcomes.

Key words: *Hemorrhagic Vasculitis, Schönlein–Henoch purpura, Vasculitis, elderly patient, glucocorticosteroid therapy.*

For citation:

Bakytova A.B., Dairabay S.E., Utepova R.B., Nogayeva M.G., Medeulova A.R., Nurgaliyeva B.K. Case report: hemorrhagic vasculitis in an elderly patient // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 243-251. *doi 10.34689/SH.2025.27.4.029*

Резюме

КЛИНИЧЕСКИЙ СЛУЧАЙ: ГЕМОРРАГИЧЕСКОГО ВАСКУЛИТА У ПАЦИЕНТА СТАРЧЕСКОГО ВОЗРАСТА

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Введение. Геморрагический васкулит (ГВ), или пурпура Шёнлейна-Геноха, является системным васкулитом мелких сосудов, преимущественно IgA-опосредованным. Несмотря на относительно частое возникновение заболевания в детском возрасте, его манифестация у пациентов старческого возраста встречается значительно реже и характеризуется более тяжелым, торпидным течением. У пожилых пациентов заболевание часто сопровождается выраженными висцеральными осложнениями, включая абдоминальный и почечный синдромы, что существенно ухудшает прогноз и требует особого внимания в диагностике и лечении. В статье представлен клинический случай геморрагического васкулита у пациента старческого возраста. Заболевание манифестировало классической триадой симптомов: кожным пурпурным, абдоминальным болевым синдромами и поражением почек.

Цель. Описать клинический случай геморрагического васкулита у пациента 86 лет с сочетанным кожным, абдоминальным и почечным синдромами на фоне выраженной коморбидности.

Материалы и методы. В данной статье приведен клинический случай пациента В., 86 лет, поступивший в ревматологическое отделение ГРЦ г. Алматы с жалобами на геморрагические высыпания на коже верхних и нижних конечностей, выраженную слабость, абдоминальный болевой синдромы, эпизоды тошноты, рвоты, также олигурии. Пациенту проведена комплексная клинико-лабораторная и инструментальная диагностика, включающая общий и биохимический анализы крови, анализы мочи (в т.ч. по Нечипоренко), коагулограмму, иммунологические исследования, УЗИ органов брюшной полости, ЭКГ, ЭхоКГ. Диагноз установлен на основании жалоб, клинической картины, лабораторно-инструментальных исследований с учетом классификационных критериев EULAR (2010) для взрослых.

Результаты. Пациент предъявлял типичные жалобы на кожный геморрагический синдромы (симметричные высыпания синюшно-багрового цвета, не исчезающие при надавливании), абдоминальные симптомы (тошнота, рвота, болезненность в околопупочной области) и признаки поражения почек (эпизод олигоурии, лейкоцитурия, повышение уровней креатинина и мочевины). На фоне лечения (глюкокортикостероидная, иммуносупрессивная, инфузионная и симптоматическая терапия) отмечалась положительная динамика в виде уменьшения выраженности кожных проявлений, абдоминальных и почечных синдромов, улучшения лабораторных показателей, стабилизации общего состояния. В то же время течение заболевания оставалось торпидным, с длительным заживлением кожных элементов, высокой чувствительностью к изменению медикаментозной схемы, необходимостью постоянного кардиологического и гастроэнтерологического сопровождения.

Выводы. Ранняя диагностика, оценка органного поражения, назначение иммуносупрессивных и глюкокортикостероидных препаратов и мониторинг осложнений помогает достичь наилучшего результата.

Ключевые слова: *геморрагический васкулит, Шенлейн-Генох, пурпура, васкулит, глюкокортикостероидная терапия.*

Для цитирования:

Бакытова А.Б., Дайрабай С.Е., Утепова Р.Б., Ногаева М.Г., Медеулова А.Р., Нургалиева Б.К. Клинический случай: геморрагического васкулита у пациента старческого возраста // Наука и Здравоохранение. 2025. Vol.27 (4), С. 243-251. *doi 10.34689/SH.2025.27.4.029*

Түйіндеме

КЛИНИКАЛЫҚ ЖАҒДАЙ: ЕГДЕ ЖАСТАҒЫ НАУҚАСТАҒЫ ГЕМОРРАГИЯЛЫҚ ВАСКУЛИТ

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Кіріспе. Геморрагиялық васкулит (ГВ), немесе Шенлейн-Генох пурпурасы - ұсақ қантамырлардың, көбінесе IgA-мен байланысты жүйелі васкулиті болып табылады. Бұл ауру балаларда жиі кездескенімен, егде жастағы адамдарда сирек дамиды және әдетте ауыр, баяу (торпидті) ағыммен сипатталады. Қарт науқастарда аурудың ағымы жиі висцералды асқынулармен, атап айтқанда абдоминалдық және бүйректік синдромдармен қатар жүреді, бұл аурудың ағымын едәуір нашарлатып, диагностикалық және терапиялық тәсілдерге ерекше назар аударуды

талап етеді. Бұл мақалада егде жастағы науқаста дамыған геморрагиялық васкулиттің клиникалық жағдайы сипатталады. Аурудың манифестациясы классикалық үштік симптомдармен байқалды: терідегі пурпура, абдоминалдық ауырсыну және бүйрек зақымдануы.

Мақсаты. 86 жастағы, айқын коморбидтілікті иеленген науқастағы терілік, абдоминалдық және бүйректік синдромдарының үйлесуімен жүретін геморрагиялық васкулиттің клиникалық жағдайын сипаттау.

Материалдар мен әдістер. Мақалада Алматы қаласындағы «Қалалық ревматология орталығының» ревматология бөлімшесіне түскен В. есімді, 86 жастағы науқастың клиникалық жағдайы ұсынылады. Науқас аяқ-қолдарындағы геморрагиялық бөртпелерге, айқын әлсіздікке, абдоминалдық ауырсынуға, жүрек айнуы мен құсуға, сондай-ақ олигурияға шағымданған. Диагностика шеңберінде жалпы және биохимиялық қан талдаулары, зәр талдаулары (оның ішінде Нечипоренко әдісімен), коагулограмма, иммунологиялық зерттеулер, құрсақ қуысы ағзаларының ультрадыбыстық зерттеуі, ЭКГ және ЭхоКГ жүргізілді. Диагноз науқастың шағымдары, клиникалық белгілері мен зертханалық-аспаптық зерттеу нәтижелері негізінде, ересектерге арналған EULAR (2010) классификациялық критерийлеріне сүйене отырып қойылды.

Нәтижелер. Науқас геморрагиялық терілік синдромға (басқанда жоғалмайтын, симметриялы, көгілдір-қызғылт түсті бөртпелер), абдоминалдық симптомдарға (жүрек айну, құсу, кіндік маңындағы ауырсыну), сондай-ақ бүйрек қызметінің бұзылу белгілеріне (олигоурия эпизоды, лейкоцитурия, креатинин мен мочевинаның жоғары деңгейі) тән шағымдармен түсті. Глюкокортикостероидтық, иммуносупрессивті, инфузиялық және симптоматикалық терапия аясында тері көріністері мен абдоминалдық және бүйрек синдромдарының азаюы, зертханалық көрсеткіштердің жақсаруы және жалпы жағдайдың тұрақтануы байқалды. Алайда аурудың ағымы баяу (торпидті) сипатта болып, тері элементтерінің ұзақ жазылуы, дәрілік емдеу режиміне жоғары сезімталдық, тұрақты кардиологиялық және гастроэнтерологиялық бақылауды қажет етті.

Қорытынды. Геморрагиялық васкулиттің ерте диагностикасы, ағзалық зақымдану деңгейін уақтылы бағалау, глюкокортикостероидтық және иммуносупрессивті емді дұрыс тағайындау мен асқынуларды жүйелі бақылау оң нәтижелерге қол жеткізуге мүмкіндік береді.

Түйінді сөздер: *геморрагиялық васкулит, Шенлейн–Генох пурпурасы, васкулит, егде жастағы науқас, глюкокортикостероидтық терапия.*

Дәйексөз үшін:

Бакытова А.Б., Дайрабай С.Е., Утепова Р.Б., Ногаева М.Г., Медеулова А.Р., Нургалиева Б.К. Клиникалық жағдай: егде жастағы науқастағы геморрагиялық васкулит // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 243-251. *doi 10.34689/SH.2025.27.4.029*

Introduction

The clinical association of purpura, arthralgia, and arthritis was first described in 1837 by the German physician Johann Lukas Schönlein. Schönlein–Henoch purpura, or Henoch–Schönlein purpura (HSP), also known as hemorrhagic vasculitis (HV), is a systemic hypersensitivity vasculitis caused by the deposition of immune complexes in small blood vessels, including the renal glomeruli and mesangium [8]. On the skin, it manifests as non-thrombocytopenic purpura or urticaria. Worldwide, IgA nephropathy is the most common cause of primary glomerulonephritis. The detection of IgA deposits in small blood vessels and renal glomeruli is diagnostic in the majority of cases [8]. HV (IgA vasculitis) in elderly patients is significantly less common than in children and young adults, but it has a more severe and indolent course. In patients aged over 65 years, the disease is often accompanied by marked renal dysfunction and systemic complications. A higher mortality is also observed, especially in cases of late diagnosis [8].

Studies by American researchers emphasize that skin manifestations may be less typical (sometimes without distinct purpura), which complicates early disease detection [6]. Moreover, elderly patients more often present with comorbidities that mask or intensify the clinical picture of IgA vasculitis.

Table 1 presents descriptions of clinical cases reported by foreign authors (with references and author names) [14, 11, 5, 10, 15, 13, 7, 9].

However, in some cases, as our practice has shown, the cutaneous form of hemorrhagic vasculitis (HV) in elderly patients can have a severe course and prolonged healing, even with an adequate choice of therapy. The severity of the disease is determined by systemic manifestations, particularly gastrointestinal involvement, leading to hepatitis, pancreatitis, and lesions of the intestines and kidneys. The pathogenesis of HV is currently poorly understood. In about 40% of children and adults, the disease is triggered by various risk factors or triggers. In children, these include viral and bacterial infections (Streptococcus sp., Salmonella sp., Shigella sp., Campylobacter sp., Yersinia enterocolitica, Helicobacter pylori, Mycoplasma pneumoniae, Legionella sp., Staphylococcus aureus, Mycobacteria tuberculosis, parvovirus B19, hepatitis B and C viruses, HIV, parasitic infections: Toxocara canis, amebiasis). In adults and elderly patients, in addition to infections, the disease is often triggered by medications and toxins (antibiotics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, cinchona alkaloids, vitamin A, streptokinase, nonsteroidal anti-inflammatory drugs, chlorpromazine, cocaine).

Less common triggers in elderly and senile patients include comorbid conditions and the following states: paraneoplastic syndrome, lymphoma, liver diseases, diabetes mellitus, intestinal diseases, and joint disorders.

Table 1.

Descriptions of clinical cases of IgA vasculitis.

№	Description of clinical case	Clinical features	Reference
1	Multi-organ involvement in a 72-year-old woman	Intestinal intussusception, renal failure, cardiac complications. Treatment: steroids, hemofiltration	https://pubmed.ncbi.nlm.nih.gov/40184107/
2	Refractory IgA vasculitis in a 90-year-old patient	Purpura, anorexia, steroid resistance. Azathioprine added to treatment	https://pubmed.ncbi.nlm.nih.gov/36249629/
3	IgA vasculitis with severe complications in a 65-year-old man	GI bleeding, cutaneous vasculitis, neurological symptoms, renal involvement. Therapy: pulse steroids, cyclophosphamide	https://pubmed.ncbi.nlm.nih.gov/35637989/
4	IgA vasculitis without purpura in a 76-year-old woman	Diarrhea, pain, no skin rash; IgA deposits on biopsy. Treated with factor XIII concentrate	https://pubmed.ncbi.nlm.nih.gov/33950360/
5	IgA vasculitis with leg edema in a 74-year-old man	Edema, ankle pain, vasculitic rash	https://pubmed.ncbi.nlm.nih.gov/37529819/
6	IgA vasculitis with GI symptoms in a 78-year-old man	Bloody diarrhea, mesenteric edema, renal failure	https://pubmed.ncbi.nlm.nih.gov/39034162/
7	IgA vasculitis following rotavirus infection in an elderly patient	Small bowel inflammation, vasculitis, proteinuria; positive response to steroids	https://pubmed.ncbi.nlm.nih.gov/28174414/
8	IgA vasculitis with nephropathy in a 61-year-old man	Purpura, pain, intestinal wall thickening, ascites, IgA deposits. Improvement with steroids	https://pubmed.ncbi.nlm.nih.gov/31280225/

Triggers may also include diseases and conditions accompanied by structural abnormalities of immunoglobulin A (IgA), its subclasses, and the complement system [3]. The most typical morphological sign of renal involvement in HV is the presence of IgA deposits in the endothelium of capillaries and in the glomerular mesangium, thickening of the capillary loops, endothelial proliferation, fibrinoid swelling of the vessel walls, lymphohistiocytic infiltration of capillaries, perivascular inflammation of renal arterioles, glomeruli, tubules, and renal stroma [2].

The diagnosis of HV is based on the presence of classification criteria in patients. For adults, the criteria were developed by the American College of Rheumatology (ACR) in 1990. In children, the “gold standard” for diagnosis is the EULAR/PRINTO/PRES criteria, developed jointly by the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trials Organization (PRINTO), and the Paediatric Rheumatology European Society (PRES) [12]. The ACR (1990) criteria and the revised 2010 EULAR/PRINTO/PRES criteria are presented in Table 2.

Table 2.

Diagnostic criteria for Henoch-Schonlein purpura.

ACR Criteria* (1990)	EULAR/PRINTO/PRES Criteria** (2010)
• Age ≤20 years	• Purpura or petechiae
• Palpable purpura	+
• Acute abdominal pain	**+** at least one of the following: - Abdominal pain - Joint inflammation or pain - Renal involvement -Leukocytoclastic vasculitis with preceding IgA deposition or proliferative glomerulonephritis
• Granulocytes in the walls of small arterioles or venules	

Note: *At least two criteria are required to establish the diagnosis. The presence of purpura or petechiae is mandatory, and at least one additional criterion is required to confirm the diagnosis.*

The same classification criteria (EULAR/PRINTO/PRES, 2010) apply to elderly patients. These include purpura or petechiae along with at least one of the following additional criteria: (1) abdominal pain; (2) joint inflammation or pain; (3) renal involvement; (4) leukocytoclastic vasculitis with prior IgA deposition or proliferative glomerulonephritis with prior IgA deposition. At least two criteria are required to establish the diagnosis: the presence of purpura or petechiae is mandatory, plus at least one additional criterion. An important addition is the assessment of target organ function, particularly renal function. The EULAR (2023) guidelines emphasize the need to screen for nephropathy and hematuria at the first suspicion of vasculitis in elderly patients.

The manifestations of HV in elderly patients are characterized by an atypical course and a high risk of complications, which require special attention in clinical practice [13]. It is important to note that elderly patients often have comorbidities and age-related features, which require an individualized approach that takes into account drug interactions, careful monitoring, and dose adjustments of selected medications. In our clinical case, the patient had several comorbid conditions, which required special attention in the treatment of HV.

Regarding geographic features of organ involvement in HV: analysis of 42 studies covering 4,064 adult patients with IgA vasculitis revealed the following regional differences ([Worldwide Distribution and Extracutaneous Manifestations of Henoch-Schönlein Purpura in Adults: Narrative Review - PMC], Table 3).

Table 3.

Diagnostic criteria for Henoch-Schonlein purpura.

Region	Mean age (years)	Men (%)	Gastrointestinal involvement (%)	Musculoskeletal symptoms (%)	Genitourinary involvement (%)
Europe	49.3	62.2	58.2	57.9	67.2
America	48.6	47.7	31.4	47.7	47.0
Asia	29.8	51.4	44.7	47.4	72.3

According to Table 3, gastrointestinal (GI) and musculoskeletal involvement are more frequently observed in Europe (58.2% and 57.9%, respectively), whereas in Asia genitourinary involvement is more common (72.3%). Regarding prevalence and incidence in children:

USA: 6.1–20.4 cases per 100,000 children per year;

UK and France: 20–70 cases per 100,000 children per year;

Asia: up to 56 cases per 100,000 children per year.

In adults globally: 1.4–5.1 cases per 100,000 adults per year. The peak incidence in adults occurs between 50 and 60 years of age [6].

Objective: To present a clinical case description of hemorrhagic vasculitis in an 86-year-old patient with combined cutaneous, abdominal, and renal syndromes on the background of pronounced comorbidity.

Clinical case

Patient V., 86 years old, presented to the City Rheumatology Center (CRC) of Almaty with complaints of a hemorrhagic rash on the upper and lower limbs, heaviness in the lower limbs, nausea, vomiting, diarrhea up to 3 times per day, cramping pain in the periumbilical area, loss of appetite, fever up to 38°C, and marked general weakness.

The patient provided informed consent to participate in the study and did not object to the publication of the treatment results with personal data anonymized.

From the patient's history:

According to the patient, two weeks before the onset of the disease he had an acute respiratory viral infection (ARVI). In early September 2024, a rash appeared on the upper limbs and in the umbilical area. He consulted his district general practitioner accompanied by his son and was referred to an allergist and dermatologist. On 12.09.2024, the allergist suggested the diagnosis "dermatitis?", and the dermatologist's conclusion was "hemorrhagic vasculitis?"

On 13.10.2024, symptoms of nausea, vomiting, episodes of oliguria, fever up to 38°C, and general weakness appeared, and he was examined by a rheumatologist at the City Rheumatology Center (CRC) of Almaty. Laboratory tests: Complete blood count (CBC) on 11.09.2024: ESR – 28 mm/h, hemoglobin – 133 g/L, leukocytes – 10.1×10^3/μL, platelets – 424×10^3/μL, eosinophils – 0.06×10^3/μL, lymphocytes – 3.1×10^3/μL. Biochemical blood test: urea – 13.9 mmol/L, creatinine – 194 μmol/L, CRP – 27 mg/L. Urinalysis on 13.09.2024: protein negative, leukocyturia. Based on complaints and clinical-laboratory data, the patient was hospitalized at the CRC of Almaty with the diagnosis: Hemorrhagic vasculitis.

Medical history:

The patient denies viral hepatitis, tuberculosis, and sexually transmitted diseases. Family history is unremarkable. Bad habits: denies smoking, does not consume alcohol. No history of allergies. The patient is followed up by a cardiologist with the diagnosis: ischemic heart disease (IHD), unstable angina IIIB according to Braunwald. Myocardial revascularization with stenting of the right coronary artery (RCA) and posterolateral branch (PLB) on 25.07.2024. Status post coronary artery bypass grafting (CABG) of the left anterior descending artery (LAD), posterior interventricular artery (PDA), and diagonal branch (DB) (October 2019, 3 grafts). Status post pacemaker (PM) implantation due to sick sinus syndrome (SSS) (December 2022). Persistent atrial flutter. CHA2DS2-VASc score 5. HAS-BLED score 2. EHRA class IIb. Acute heart failure, type 1. Grade III arterial hypertension, very high cardiovascular risk. Cerebrovascular disease (CVD). Atherosclerosis. Stenotic lesions of the carotid arteries. On 02.08.2024, the patient was urgently hospitalized at the City Cardiology Center (CCC) of Almaty with the diagnosis: acute coronary syndrome (ACS) without ST-segment elevation. Emergency coronary angiography with stenting of the RCA and its posterolateral branch (PLB-RCA) was performed. The patient is on standard IHD therapy. Surgeries: CABG in October 2019. Pacemaker implantation for SSS in December 2022. Coronary angiography with stenting of RCA and PLB-RCA in August 2024. The patient is also followed up by a gastroenterologist with the diagnosis: chronic gastroduodenitis (currently in remission). Cystectomy in 1999. Epidemiological history: no contact with infectious patients.

Objective findings at the time of examination:

General condition: moderate severity due to cutaneous, abdominal, and renal syndromes. Consciousness: clear. Body type: normosthenic. Skin: widespread, symmetrical hemorrhagic rash on the skin of the upper and lower limbs, acute inflammatory in nature, bluish-purple color, confluent, does not blanch on pressure, with telangiectasias (Figure 1).

Peripheral lymph nodes are not palpable. Peripheral edema is moderate in the legs. Respiratory system: the



Picture 1. Hemorrhagic rash on the legs.

chest is of normal shape, participates symmetrically in the act of breathing. Percussion: clear lung sounds over all fields. Auscultation: vesicular breathing, no wheezing. Respiratory rate: 16 per minute.

Cardiovascular system: no visible abnormalities in the heart area. The borders of relative cardiac dullness are normal. Auscultation: irregular rhythm (atrial flutter). Heart rate: 76–135 bpm. Pulse rate: 76-135 bpm. Blood pressure: 110/70 mmHg. Heart sounds are muffled. No pathological murmurs. Digestive system: the tongue is dry, coated with a white film. The abdomen is soft, moderately tender. The liver is at the costal margin. The spleen is not palpable. Tendency to constipation noted. Musculoskeletal system: the joints show no significant visible deformities or exudative changes. Urinary system: negative costovertebral angle tenderness on both sides. Urination is painless, the patient notes decreased urine output.

Laboratory tests:

Name	Indicators
CBC from 13.09.2024	Hemoglobin – 125 g/L, erythrocytes – 4.0×10^{12}/L, color index – 0.93, platelets – 327×10^{9}/L, leukocytes – 9.5×10^{9}/L; segmented neutrophils – 81%, monocytes – 2%, lymphocytes-17%, ESR-28 mm/h. **Note**: slight leukocytosis, elevated ESR.
CBC from 18.09.2024	Hemoglobin – 137 g/L, erythrocytes – 4.4×10^{12}/L, color index – 0.93, platelets – 344×10^{9}/L, leukocytes – 14.9×10^{9}/L, segmented neutrophils – 71%, monocytes – 7%, lymphocytes-22%, ESR – 6 mm/h. **Note**: leukocytosis.
Urinalysis from 13.09.2024	Volume: 60.0 mL, color – straw yellow, clarity – clear, specific gravity – 1015 g/L, reaction – acidic, protein – absent, squamous epithelium – 3-4 units, leukocytes – 6-7 per field of view. **Note**: leukocyturia.
Nechiporenko urine test from 13.09.2024	Leukocytes – large number; erythrocytes: 1000.
Biochemical blood test from 13.09.2024	Glucose – 9.1 mmol/L, cholesterol – 3.3 mmol/L, total protein – 68 g/L, CRP – 27 mg/L, urea – 13.9 mmol/L, creatinine – 194 μmol/L, potassium – 4.0, sodium – 140, ALT – 15.3 U/L, AST – 14.8 U/L, total bilirubin – 9.1 μmol/L, amylase – 28.3 U/L. **Note**: elevated glucose, urea, creatinine, and CRP levels.
Biochemical blood test from 18.09.2024	C-reactive protein – 2.7 mg/L.
Coagulogram from 13.09.2024	APTT – 29 sec, prothrombin index – 126%, fibrinogen A – 2.88 g/L, thrombin time – 26 sec, INR – 1.08, prothrombin time – 12.7 sec, D-dimer – 1.65, INR – 1.05, fibrinogen – 3.5 g/L.
Immunological tests from 13.09.2024	ANCA-screen – 0.4, antibodies to mitochondria AMA-M2 – 1.2 IU/mL.
CBC from 18.10.2024	Hemoglobin – 152 g/L, erythrocytes – 4.93×10^{12}/L, color index – 0.92, platelets – 329×10^{9}/L, leukocytes – 8.9×10^{9}/L, ESR - 2mm/h. **Note**: within normal limits.
Biochemical blood test from 18.10.2024	Glucose – 5.64 mmol/L, cholesterol – 4.16 mmol/L, ALT – 25 U/L, AST – 20 U/L, creatinine – 117 μmol/L, urea – 8.60 mmol/L, CRP – 2.7 mg/L. **Note**: decreasing levels of creatinine and urea in dynamics.
Urinalysis from 18.10.2024	Volume: 60.0 mL, color – straw yellow, clarity – clear, specific gravity – 1024 g/L, reaction – acidic, protein – absent. **Note**: within normal limits.
From 15.09.2024: microreaction, ELISA for hepatitis B and C viruses, Wright-Hedelson reaction, HIV – negative results.	

Instrumental studies:

Name	Indicators
Chest X-ray in 2 projections	Conclusion: no pulmonary pathology detected.
ECG:	Atrial fibrillation with an average ventricular rate of 83 bpm, normosystole, fine-wave form. Rightward deviation of the electrical axis. Decreased metabolism in the lower-lateral region of the VS.
Echocardiography:	CABG. Right heart pacemaker. Aortic root is not dilated, wall thickened. Heart chambers are not dilated. Valves are thickened. Left ventricular contractility is reduced. Left ventricular wall hypertrophy. Type 1 diastolic dysfunction of the left ventricle. Mitral valve regurgitation grade 1, aortic valve regurgitation grade 1. Tachycardia. Hypokinesia zone in the LV walls.
Abdominal and kidney ultrasound	Diffuse changes in liver parenchyma. Signs of portal hypertension. Reactive pancreatitis. Thickened renal pelvis walls bilaterally.
Doppler ultrasound of veins and arteries of lower limbs	Conclusion: atherosclerosis of the arteries of the lower limbs. Altered blood flow in the right posterior tibial artery. No evidence of venous or arterial thrombosis of the lower limbs. Edema of soft tissues of both lower limbs.
EGD	Conclusion: erosions of the duodenal bulb. Mixed gastritis, cardia insufficiency.

In the inpatient setting, the diagnosis was established: hemorrhagic vasculitis, activity grade II, mixed form (cutaneous-abdominal, renal), acute course. Recommended: anti-inflammatory immunosuppressive therapy with methylprednisolone 8 mg/day, followed by dose reduction by ¼ tablet every 7 days under control of blood sugar and blood pressure. Basic anti-inflammatory therapy (BAIT): sulfasalazine: 1st week – 500 mg, 1 tablet once a day after meals for 7 days. 2nd week – 500 mg, 1 tablet twice a day (morning and evening) after meals for 7 days. 3rd week – 500 mg, 1 tablet three times a day after meals, long-term, under rheumatologist supervision. Gastroprotective therapy: rabeprazole (Rabemac) 20 mg, 1 tablet once a day 30 minutes before meals during the period of steroid intake. If epigastric pain intensifies, use of antacid therapy was recommended.



Picture 2. Hemorrhagic rash on the legs during treatment.

Discussion

At present, there are no specific diagnostic serological laboratory tests or biomarkers for IgA vasculitis. However, serum IgA levels are elevated in 50–70% of patients with IgA vasculitis [10]. In this clinical case, the patient exhibited a rapidly progressive form of the disease, accompanied by hemorrhagic rashes on the upper and lower limbs, heaviness in the legs, nausea, vomiting, diarrhea up to 3 times a day lasting 4 days, transient cramping pain in the periumbilical region, and episodes of oliguria. Following anti-inflammatory and immunosuppressive therapy, a marked reduction was observed in cutaneous, abdominal, renal, intoxication, and asthenic syndromes. Considering the history of transient pain in the umbilical area, nausea, vomiting, diarrhea, and the primary cardiovascular disease, basic anti-inflammatory therapy included sulfasalazine 1,500 mg and methylprednisolone 8 mg in combination with antiplatelet, angioprotective therapy and antacid medications. In dynamics, normalization of ESR to 2 mm/h, leukocyte levels to 8.9/L, CRP to 2.7 mg/L was noted, and leukocyturia disappeared in urinalysis. Early corticosteroid therapy is an important aspect of treatment aimed at reducing inflammation and preventing complications. However, it is important to consider age-related features and complications of steroid therapy, especially in elderly patients, such as increased susceptibility to infections and femoral neck fractures [1].

Methylprednisolone was prescribed in the initial phase of the disease to control symptoms and reduce the activity of the inflammatory process, to achieve rapid regression of skin lesions, strictly under the supervision of a rheumatologist, with monitoring of blood pressure, heart rate, and clinical-laboratory parameters. The steroid therapy was short-term and at the lowest effective dose to reduce the likelihood of side effects. Sulfasalazine, a folic acid antagonist, acts by blocking endothelin receptors (ET-A and ET-B) on the smooth muscle lining of blood vessels. This action reduces vasoconstriction, improves oxygen delivery to tissues, and alleviates symptoms such as shortness of breath and fatigue. The drug demonstrates a rapid onset of therapeutic effect, is effective in patients regardless of age or disease duration and seroreactivity, does not interact with other medications, and can be used in combination with other antirheumatic drugs [4].

The clinical features of this case include male sex, age 86 years, cutaneous-abdominal and renal syndromes, and comorbid conditions in the medical history. The use of sulfasalazine, which is not part of the standard treatment regimen for Henoch-Schönlein purpura, made it possible to achieve a reduction in skin lesions and abdominal syndrome in a short time. According to our observations, sulfasalazine is a relatively safe and effective antirheumatic drug and may serve as an alternative therapeutic option for the treatment of IgA vasculitis.

Conclusion

IgA vasculitis (Henoch-Schönlein purpura) is traditionally considered a childhood disease; however, its manifestation in old age represents a clinically significant phenomenon with a number of features. In elderly patients, the course of the disease is often severe, with more pronounced visceral involvement and a higher risk of complications. Unlike children, in elderly individuals hemorrhagic vasculitis is less often accompanied by the typical triad of symptoms (purpura, arthralgia, abdominal syndrome) and often presents predominantly as nephropathy [5]. Moreover, advanced age is associated with a weakened immune response, multiple comorbidities, and polypharmacy, which can mask the clinical picture and influence therapeutic strategy. Immunosuppressive therapy (glucocorticosteroids and cytostatics), which is standard for severe IgA vasculitis, requires caution in elderly and senile patients due to the increased risk of infections, osteoporosis, hyperglycemia, and other side effects [14].

It should also be noted that in the elderly and senile population, IgA vasculitis may have a paraneoplastic nature associated with oncological diseases, especially in cases of late onset and refractory course. Therefore, in the diagnosis of IgA vasculitis in elderly patients, oncological vigilance and comprehensive evaluation are essential.

Thus, the presence of comorbidities, the high risk of drug interactions, and the increased mortality in cases of late diagnosis emphasize the clinical significance of timely recognition of IgA vasculitis in geriatric practice, requiring an interdisciplinary approach. Early diagnosis, assessment of organ involvement, individualized treatment selection, and monitoring of complications help achieve the best outcomes in the management of this category of patients.

Conflict of interest: *The authors declare that there is no conflict of interest and that no part of this article has been published in the public domain or is under consideration by other publishers.*

Contribution of the authors: *Conceptualization – Nogayeva Maral, methodology – Bakytova Aidana, Utepova Roza, Dayrabai Symbat, validation of results – Medeulova Aigul, Nurgaliyeva Bayan.*

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Funding*: The authors declare no funding. This is a voluntary work.*

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Received: 19 May 2025 / Accepted: 07 August 2025 / Published online: 28 August 2025

DOI 10.34689/SH.2025.27.4.030

UDC 616.52-002-053.2

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CASE REPORT: PAPULAR ACRODERMATOSIS OF CHILD, OR GIANOTTI-CROSTI SYNDROME

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Abstract

Gianotti-Crosti syndrome is a benign skin disorder, predominantly occurring in children, characterized by a symmetrical papular or papulovesicular rash localized on the face, extremities, and buttocks caused by a viral infection or hypersensitivity. We report a case of 18-month-old male child presenting with GCS with typical manifestations of this syndrome. The report offers a detailed chronology of the disease course, including the onset, evolution, and resolution of symptoms. We describe in detail the course of the disease, diagnostic signs and approach to patient management, emphasizing the importance of differential diagnosis in pediatric practice and highlighting the self-limiting nature of the syndrome.

Keywords: *Gianotti-Crosti syndrome, papular acrodermatitis, childhood exanthems, viral skin eruptions, Epstein-Barr virus.*

For citation: Messova A.M., Tuleubaeva A.A., Abdrakhmanova S.T., Altybayeva S.M., Kadirova A.K., Perfilyeva O.O., Ashirov B.A. Case report: Papular acrodermatosis of child, or Gianotti-Crosti syndrome // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 252-256. *doi 10.34689/SH.2025.27.4.030*

Резюме

КЛИНИЧЕСКИЙ СЛУЧАЙ: ПАПУЛЕЗНЫЙ АКРОДЕРМАТИТ ДЕТЕЙ, ИЛИ СИНДРОМ ДЖАНОТТИ-КРОСТИ

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Синдром Джанотти-Крости — доброкачественное заболевание кожи, встречающееся преимущественно у детей, характеризующееся симметричной папулезной или папуловезикулярной сыпью, локализующейся на лице, конечностях и ягодицах, вызванной вирусной инфекцией или гиперчувствительностью. В статье описан случай 18-месячного мальчика с Синдромом Джанотти – Крости и типичными проявлениями этого синдрома. В работе представлена подробная хронология течения заболевания, включая начало, развитие и разрешение симптомов. Мы подробно описываем течение заболевания, диагностические признаки и подход к ведению пациента, подчеркивая важность дифференциальной диагностики в педиатрической практике и подчеркивая самоограничивающийся характер синдрома

Ключевые слова: *Синдром Джанотти-Крости, папулёзный акродерматит, экзантема у детей, вирусные кожные высыпания, вирус Эпштейна-Барр.*

Для цитирования: *Месова А.М., Тулеубаева А.А., Абдрахманова С.Т., Алтыбаева С.М., Кадирова А.К., Перфильева О.О., Аширов Б.А.* Клинический случай: папулезный акродерматит детей, или синдром Джанотти-Крости // Наука и Здравоохранение. 2025. Vol.27 (4), С. 252-256. *doi 10.34689/SH.2025.27.4.030*

Түйіндеме

КЛИНИКАЛЫҚ ЖАҒДАЙ: БАЛАЛАРДЫҢ ПАПУЛЯРЛЫ АКРОДЕРМАТИТІ НЕМЕСЕ ДЖАНОТТИ-КРОСТИ СИНДРОМЫ

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Джанотти–Крости синдромы - негізінен балаларда кездесетін, симметриялы папулалық немесе папуловезикулярлы бөртпелермен сипатталатын терінің қатерсіз зақымдануы. Бөртпелер әдетте аяқ-қолдарда, бетте және жамбас аймағында орналасады. Синдромның дамуында вирустық инфекциялар немесе жоғары сезімталдық реакциялары басты этиологиялық факторлар ретінде қарастырылады. Мақалада Джанотти-Крости синдромы бар 18 айлық баланың жағдайы және осы синдромның типтік көріністері сипатталған. Жұмыста аурудың басталуын, дамуын және симптомдардың шешілуін қоса алғанда, аурудың ағымының егжей-тегжейлі хронологиясы берілген. Аурудың клиникалық ағымы, диагностикалық ерекшеліктері және емдеу мен бақылау тәсілдері егжей-тегжейлі баяндалып, педиатриялық тәжірибеде дифференциалды диагностиканың маңыздылығы мен синдромның өздігінен шектелетін табиғаты атап өтіледі.

Түйін сөздер: *Джанотти-Крости синдромы, папулалық акродерматит, балалардағы бөртпелер, вирустық тері бөртпелері, Эпштейн-Барр вирусы.*

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Introduction

Gianotti-Crosti Syndrome (GCS), also known as infantile papular acrodermatitis, is a rare self-resolving exanthem. The peak incidence occurs in children between one to six years and the frequency of the disease is not related to the sex of the child. The main clinical manifestation is a symmetrical monomorphic rash affecting mainly the extremities, it rarely spreads to the face and torso. The appearance of other symptoms is individual and in some cases this syndrome may be accompanied by diarrhea, fever, hepatomegaly and generalized lymphadenopathy. A characteristic peculiarity is a sudden monochrome and monomorphic rash, represented by pink, pale red, less often flesh-colored or purple papules. Itching is quite common. On average, GCS passes on its own within 2-8 weeks. But sometimes there were cases when the rash lasted from 5 days to 12 months. The rash disappears without a trace, without scarring, leaving behind pigmentation, which disappears quite quickly. [1, 2, 3]

The etiology of this syndrome is not fully understood, but it is often associated with Epstein-Barr virus, hepatitis B, cytomegalovirus and enterovirus infections. Sometimes GCS manifests itself as a post-vaccination phenomenon. In addition, there are no statistics on GCS, as it is often not diagnosed or misdiagnosed. [1, 2, 3, 4]

Clinical case

An 18-month-old male child was admitted to the emergency department with a complaints of fever, skin lesions and tonic convulsions. The rush was symmetrical, well-demarcated and localized on the upper and lower extremities.

On clinical examination, the rash consisted of pink, edematous, hemispherical papules 1–3 mm in diameter. The lesions were symmetrical with distinct edges, bluish discoloration and purulent content on an erythematous background. Scaling was noticed on the surface of the rash and post-inflammatory pigmentation on the face (Figure 1-6).

The patient's general condition was severe due to symptoms of intoxication, oropharyngeal inflammation, widespread rash and hyperthermia. Submandibular lymphadenopathy was present with tender notes on palpation. Examination of the oropharynx detected diffuse erythema (“red throat”), tonsillar hypertrophy and purulent exudate that removable with a spatula without bleeding.

Laboratory tests of the blood panel revealed leukocytosis (19.02 × 10^9/L), thrombocytosis (354.0 × 10^9/L), hypercreatinemia (18.0 mmol/L) and increased C-reactive protein (21 g/L). Urinalysis showed ketonuria. Coagulation testing showed prolonged thrombin time (16.9 sec) and an increased INR of 1.3. CLIA showed a procalcitonin level of 0.270 ng/ml. Bacteriological cultures from the pharynx and wound secretions grew Streptococcus pyogenes, group A. Following a dermatovenerology consultation a clinical diagnosis of Gianotti-Crosti syndrome was established.

Discussion

GCS is considered to be a result of delayed-type hypersensitivity (type IV) mediated by T lymphocytes. After

primary infection, hematogenous dissemination of the virus occurs, followed by deposition of antigens in the skin. This leads to activation of T-cells and the development of an inflammatory reaction in the epidermis and dermis. [2]

The child's skin manifestations were typical of Gianotti-Crosti syndrome, but were characterized by some morphological variability depending on the anatomical localization. The rashes were represented mainly by symmetrical erythematous papules localized on the face, buttocks, and extensor surfaces of the extremities. The rash predominantly consisted of dense, flat or slightly raised papules measuring 1–3 mm in diameter, pinkish, with well-defined borders and a smooth surface on the face and upper extremities. Individual papulovesicular elements with serous contents were detected on the lower extremities and buttock. The skin background between the rashes was intact. Itching and burning were absent. [2, 3]

Infectious mononucleosis, atopic dermatitis, papular urticaria, chickenpox, Kawasaki syndrome, and vasculitis were included in the differential diagnosis. However, the pattern of the rash, clinical, and laboratory data excluded these conditions [2,3]. Multiple viral infections have been linked to the occurrence of Gianotti-Crosti Syndrome in reported cases [4-13].



Fig.1. Gianotti-Crosti Syndrome



Fig.2. Gianotti-Crosti Syndrome



Fig.3. Gianotti-Crosti Syndrome



Fig.4. Gianotti-Crosti Syndrome



Fig.5. Gianotti-Crosti Syndrome

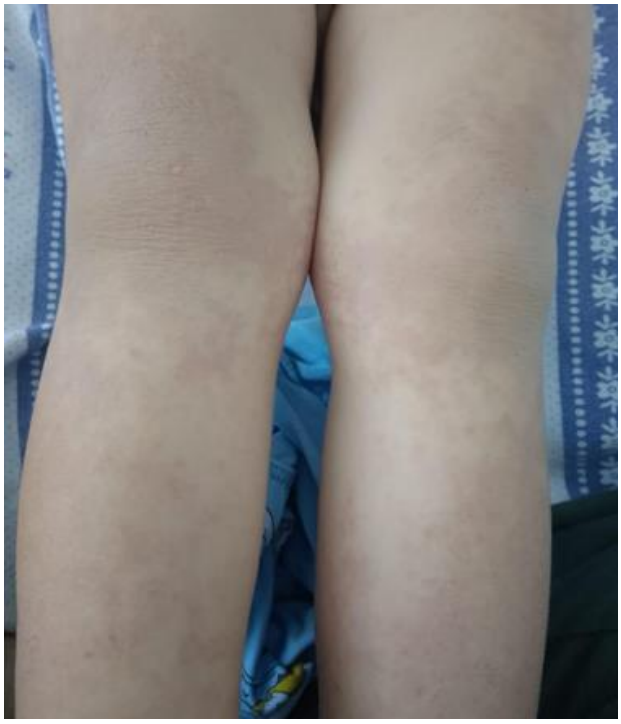


Fig.6. Gianotti-Crosti Syndrome

Table 1.

Characteristic of GCS cases reported in literature.

	Authors	Age	Country	Year	Virus associated
1	Lin et al.	2 years	Taiwan	2015	HBV
2	Leung et al.	18 months	USA	2004	EBV
3	Caputo et al.	3 years	Italy	2007	CMV
4	Oranje et al.	4 years	Netherlands	2010	Coxsackie B
5	Neri et al.	6 years	Italy	2016	HHV-6
6	Watanabe et al.	1 year	Japan	2002	Parvovirus B19
7	Wu et al.	2.5 years	China	2018	EBV
8	Chen et al.	3 years	Taiwan	2020	Hepatitis A
9	Yoshikawa et al.	5 years	Japan	2013	HHV-7
10	Ghosh et al.	2 years	India	2021	COVID-19

The diagnosis of GCS is clinical and does not require biopsy or specific treatment. However, our patient had a bacterial oropharyngeal infection with group A streptococcus (GAS), which was detected by throat swab culture. Antibiotic therapy, NSAIDs for temperature control, antihistamines, and tissue regeneration ointment were prescribed and the condition resolved without complications. Although GCS is a benign, self-limited disease, it is important to recognize it to avoid unnecessary diagnostic and therapeutic interventions.

Conclusion

We reported a clinical case of GCS in an 18-month-old child. Healthcare providers should recognize this uncommon, transient skin condition linked to viral pathogens.

Conflict of Interest. *The authors declare that they have no conflict of interest.*

Contribution of authors. *All authors were equally involved in the writing of this article.*

Funding: *No funding was provided.*

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Received: 03 July 2025 / Accepted: 02 August 2025 / Published online: 28 August 2025
DOI 10.34689/SH.2025.27.4.031
UDC 535.23:613.648

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TOTAL MORTALITY DYNAMICS OF THE POPULATION OF THE ABAY AND BESKARAGAI DISTRICTS EXPOSED TO RADIATION AS A RESULT OF NUCLEAR WEAPONS TESTS (1949-1975)

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Abstract

Introduction. Mortality rates are an indicator of population health in various countries worldwide. They are influenced by sociodemographic factors, the state of the healthcare system, and environmental factors, including exposure to ionizing radiation.

The aim of our study is to analyze mortality rates in the Abay and Beskaragay districts of the Abay region exposed to radiation as a result of nuclear weapons testing from 1949 to 1975.

Materials and Methods. The study data consisted of cause-of-mortality certificates for the population of three districts in the region from 1949 to 1975. The population of two districts (Abay and Beskaragay) was exposed to effective equivalent doses of 625 to 870 mSv. The comparison group consisted of residents of the Kokpekty district. A total of 16,348 cause-of-mortality certificates were copied and analyzed. Effective equivalent doses of radiation exposure for the population of the study areas were obtained from the State Scientific Automated Medical Registry database.

Results. A significant increase in overall mortality rates for the population of all age groups in the Beskaragay district of the Abay region was found 4-21 years after the onset of irradiation compared to the rates in the control Kokpekty district. No significant differences were found in overall mortality rates in the Abay district compared to the control group. A modifying effect of age on overall mortality rates was established for the population of the exposed groups. In subsequent years (26-49 years after the onset of irradiation), 6 to 8 peaks of significantly higher overall mortality rates were recorded among men and women in the Beskaragay district compared to the control group. Among men and women in the Abay district, the overall mortality rate did not differ significantly from the control group.

Conclusion. The overall mortality curve was remittent, with significant peaks alternating with plateaus in some years. No dose-response relationship was found for overall mortality rates in the study areas.

Key words: *total mortality, radiation exposure, effective equivalent doses of radiation, population.*

For citation:

Kissina R.M., Smailova Zh.K., Pivina L.M., Chaizhunussova N.Zh., Orekhov A.Yu., Lipikhina A.V., Massabayeva M.R., Baibussinova A.Zh., Ygiyeva D.G., Batenova G.B., Sabitova V.R., Kozhanova S.K., Mukanova D.A., Abenova M.B., Lepesbayev M.N., Akhmadiyeva T.A., Orazalina A.S., Apbassova S.A., Shabdarbayeva D.M., Dyussupov A.A. Total Mortality dynamics of the population of the Abay and Beskaragai districts exposed to radiation as a result of nuclear weapons tests (1949-1975) // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (4), pp. 257-265. *doi 10.34689/SH.2025.27.4.031*

Резюме

ДИНАМИКА ОБЩЕЙ СМЕРТНОСТИ НАСЕЛЕНИЯ РАЙОНОВ АБАЙ И БЕСКАРАГАЙ, ПОДВЕРГШЕГОСЯ ОБЛУЧЕНИЮ В РЕЗУЛЬТАТЕ ИСПЫТАНИЙ ЯДЕРНОГО ОРУЖИЯ (1949-1975 ГГ.)

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Введение. Показатели смертности являются индикатором состояния здоровья населения различных стран мира. На них оказывают влияние социально-демографические факторы, состояние системы здравоохранения страны проживания, а также экологические факторы, к которым относится воздействие ионизирующей радиации.

Целью нашего исследования является анализ показателей смертности населения Абайского и Бескарагайского районов области Абай, подвергшихся радиационному воздействию вследствие испытаний ядерного оружия, за период с 1949 по 1975 гг.

Материалы и методы. Материалами исследования послужили акты-сертификаты причин смертности населения трех районов области за период с 1949 по 1975 гг. Население двух районов (Абайского и Бескарагайского,) подвергалось облучению в диапазоне эффективных эквивалентных доз 625 - 870 мЗв. Группа сравнения была представлена населением Кокпектинского района. Выкопировано и проанализировано 16 348 актов- сертификатов причин смертности. Эффективные эквивалентные дозы облучения населения исследуемых районов были взяты из базы данных Государственного научного автоматизированного медицинского регистра.

Результаты. Установлено достоверное увеличение коэффициентов общей смертности населения всех возрастных групп Бескарагайского района области Абай через 4-21 год от начала облучения по сравнению с показателями контрольного Кокпектинского района. Не обнаружено существенных различий в уровнях общей смертности населения Абайского района по сравнению с контрольной группой. Установлено модифицирующее влияние на показатели общей смертности возраста населения экспонированных групп. В последующие годы (26-49 лет от начала облучения) среди мужчин и женщин Бескарагайского района зарегистрировано от 6 до 8 пиков существенного превышения уровня общей смертности по сравнению с показателями контроля. Среди мужчин и женщин Абайского района уровень общей смертности среди мужчин и женщин существенно не отличался от показателей контроля.

Заключение. Кривая уровня общей смертности носила ремитирующий характер с чередованием существенных подъемов с последующей нивелировкой в отдельные годы. Не установлено закономерностей «доза-эффект» для показателей общей смертности населения изучаемых районов.

Ключевые слова: общая смертность, радиационное воздействие, эффективные эквивалентные дозы облучения, население.

Для цитирования:

Кисина Р.М., Смаилова Ж.К., Пивина Л.М., Чайжунусова Н.Ж., Орехов А.Ю., Липихина А.В., Масабаева М.Р., Байбусинова А.Ж., Ыгиева Д.Г., Батенова Г.Б., Сабитова В.Р., Кожанова С.К., Муканова Д.А., Абенова М.Б., Лепесбаев М.Н., Ахмадиева Т.А., Оразалина А.С., Апбасова С.А., Шабдарбаева Д.М., Дюсупов А.А. Динамика общей смертности населения районов Абай и Бескарагай, подвергшегося облучению в результате испытаний ядерного оружия (1949-1975 гг.) // Наука и Здравоохранение. 2025. Vol.27 (4), С.257-265. *doi 10.34689/SH.2025.27.4.031*

Түйіндеме

ЯДРОЛЫҚ ҚАРУДЫ СЫНАУ НӘТИЖЕСІНДЕ СӘУЛЕЛЕНУГЕ ҰШЫРАҒАН АБАЙ ЖӘНЕ БЕСҚАРАҒАЙ АУДАНДАРЫ ХАЛҚЫНЫҢ ЖАЛПЫ ӨЛІМ-ЖІТІМІНІҢ ДИНАМИКАСЫ (1949-1975 ЖЖ.)

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[2] Абай облысы бойынша сот-медициналық сараптама орталығы, Семей қ., Қазақстан Республикасы;

Кіріспе. Өлім-жітім көрсеткіштері әлемнің әртүрлі елдеріндегі халық денсаулығының жай-күйін сипаттайтын маңызды индикатор болып табылады. Өлім-жітім деңгейіне әлеуметтік-демографиялық факторлар, тұрғылықты елдің денсаулық сақтау жүйесінің жағдайы, сондай-ақ экологиялық факторлар, соның ішінде иондаушы сәулеленудің әсері ықпал етеді.

Зерттеудің мақсаты — ядролық қаруды сынау нәтижесінде радиациялық әсерге ұшыраған Абай облысының Абай және Бесқарағай аудандары халқының 1949–1975 жылдар аралығындағы өлім-жітім көрсеткіштерін талдау.

Материалдар мен әдістер. Зерттеу материалдары ретінде 1949–1975 жылдар аралығындағы облыстың үш ауданы халқының өлім себептері жөніндегі акт-сертификаттар пайдаланылды. Абай және Бесқарағай аудандарының халқы тиімді эквиваленттік сәулелену дозаларының 625–870 мЗв диапазонында сәулеленуге

ұшыраған. Салыстыру тобы ретінде Көкпекті ауданының халқы алынды. Барлығы 16 348 өлім себептері жөніндегі акт-сертификат көшіріліп, талданды. Зерттелген аудандар халқының тиімді эквиваленттік сәулелену дозалары туралы мәліметтер мемлекеттік ғылыми автоматтандырылған медициналық регистрдің деректер базасынан алынды.

Нәтижелер. Сәулелену басталғаннан кейін 4–21 жыл аралығында Абай облысының Бесқарағай ауданында барлық жас топтарындағы халықтың жалпы өлім-жітім коэффициенттерінің бақылау тобы болып табылатын Көкпекті ауданының көрсеткіштерімен салыстырғанда сенімді түрде жоғарылағаны анықталды. Абай ауданы халқының жалпы өлім-жітім деңгейі бақылау тобымен салыстырғанда елеулі айырмашылықтар көрсетпеді. Экспонирленген топтарда жас ерекшелігінің жалпы өлім-жітім көрсеткіштеріне модификациялаушы әсері анықталды. Кейінгі жылдары (сәулелену басталғаннан кейін 26–49 жыл) Бесқарағай ауданында ерлер мен әйелдер арасында жалпы өлім-жітім деңгейінің бақылау көрсеткіштерінен 6–8 рет айқын арту шектері тіркелді. Абай ауданында ерлер мен әйелдердің жалпы өлім-жітім деңгейі бақылау тобынан елеулі түрде ерекшеленбеді.

Қорытынды. Жалпы өлім-жітім деңгейінің динамикасы толқын тәрізді сипатта болып, айқын жоғарылаулар мен кейінгі жылдардағы көрсеткіштердің тегістелуі кезектесіп отырды. Зерттелген аудандар халқының жалпы өлім-жітім көрсеткіштері үшін «доза–әсер» типіндегі айқын заңдылықтар анықталған жоқ.

***Түйінді сөздер**: жалпы өлім-жітім, радиациялық әсер, тиімді эквиваленттік сәулелену дозалары, халық.*

Дәйексөз үшін:

Кисина Р.М., Смаилова Ж.К., Пивина Л.М., Чайжунусова Н.Ж., Орехов А.Ю., Липихина А.В., Масабаева М.Р., Байбусинова А.Ж., Ыгиева Д.Г., Батенова Г.Б., Сабитова В.Р., Кожанова С.К., Муканова Д.А., Абенова М.Б., Лепесбаев М.Н., Ахмадиева Т.А., Оразалина А.С., Апбасова С.А., Шабдарбаева Д.М., Дюсупов А.А. Ядролық қаруды сынау нәтижесінде сәулеленуге ұшыраған Абай және Бесқарағай аудандары халқының жалпы өлім-жітімінің динамикасы (1949-1975 жж.) // Ғылым және Денсаулық сақтау. 2025. Vol.27 (4), Б. 257-265. *doi 10.34689/SH.2025.27.4.031*

Introduction

Mortality rates from various causes, primarily from oncological diseases and diseases of the circulatory system, as well as overall mortality, are indicators of the health status of the population in various countries around the world. These indicators are influenced by socio-demographic factors, such as the level of national income, the state of the healthcare system in the country of residence, the age structure of the population, the level of education of the population, nutrition, as well as environmental factors. One of such environmental risk factors for residents of some areas of the Abay region (former Semipalatinsk region) over a long period of time, starting in 1949, is exposure to ionizing radiation in the range of medium and low doses. During the testing period at the Semipalatinsk nuclear test site from 1949 to 1989, 468 nuclear charges were detonated, including 117 ground and air explosions. As a result of the tests, hundreds of thousands of residents of the territories adjacent to the test site, including several generations, were exposed to repeated external and internal irradiation [8, 14]. Undoubtedly, exposure to ionizing radiation had a negative impact on the health of the exposed population.

The aim of our study is to analyze mortality rates of the population of the Abay and Beskaragay districts of the Abay region, exposed to radiation as a result of nuclear weapons testing, for the period from 1949 to 1975.

Materials and Methods

Characteristics of the Study Population

The study was conducted using death certificates for the causes of death in three districts of the Abay region from 1949 to 1975. The population of two districts (Abay and Beskaragay) was exposed to effective equivalent doses of 625 to 870 mSv. The comparison group consisted of the population of the Kokpekty district and was adequate in terms of size, age, and sex composition; residents of this district were virtually not exposed to radiation (effective equivalent doses ranged from 50 to 70 mSv).

Data from cause-of-mortality reports were entered into the State Scientific Automated Medical Registry (SSAMR) database, which contains information on individuals directly exposed to ionizing radiation as a result of nuclear weapons testing at the Semipalatinsk nuclear test site, as well as their subsequent generations. In addition, for each registry member, information is available on the calculated individual equivalent dose of radiation, health status, the presence of chronic diseases, causes of death, and the presence of radiation and non-radiation health risk factors. This information is necessary for the development of strategies aimed at preserving and improving the health of residents affected by the test site's activities. The registry was created in 2002 in collaboration with Japanese colleagues from the Radiation Effect Research Foundation and with the support of the Ministry of Health of the Republic of Kazakhstan [1,6].

Over the entire study period, male represented an average of 46.9% of the population in the districts studied, while female accounted for 53.1%. The population of the Abay district varied from 12,000 to 18,000 people, while the Abay and Kokpekty districts had a population of 24,000 to 32,000 people. Kazakhs predominated in the Abay and Kokpekty districts, while Caucasians (Russians and Ukrainians) predominated in the Beskaragay district. The age groups from 0 to 19 years constituted an average of 46%. From 1949 to 1975, 16,348 death certificates were copied and analyzed (Table 1). Causes of death were coded according to the Statistical Classification of Diseases, Injuries, and Causes of Death, 10th Revision (ICD-10), indicating the underlying disease that led to death.

Table 1.

Number of acts of causes of death in the studied areas (1949-1975, absolute numbers).

District	Male	Female	Total
Abay	1 825	1 560	3 386
Beskaragaysky	3 690	3 099	6 789
Kokpekty	3 280	2 893	6 173

Effective equivalent doses to the population of the study areas were selected from the State Scientific Automated Medical Registry database. The dose calculations are based on a joint US-Russian dose reconstruction methodology developed based on the combined experience of experts from various countries [4, 5, 12, 15]. The characteristics of the effective equivalent doses to the population of the study areas are presented in Table 2.

Table 2.

Characteristics of average effective equivalent doses of radiation to the population of the studied areas.

District	External irradiation dose, mGy	Internal radiation dose, mSv	Effective equivalent dose, mSv
Abay	355,0	270,0	624,0
Beskaragaysky	670,0	200,0	870,0
Kokpekty			50,0-70,0*

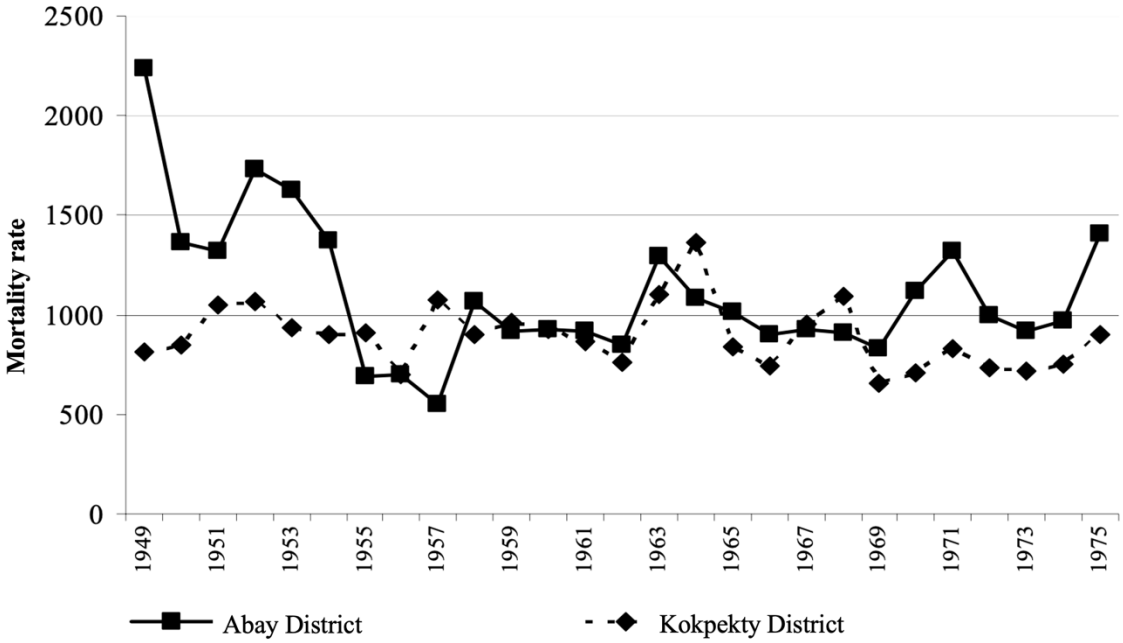
Statistical Analysis

Statistical data processing was performed using SPSS (v.20) and Jamovi (v.2.5). Mortality rates per 100,000 population were calculated and subsequently standardized (ASR). Standardized mortality ratios (SMRs) were calculated. It was taken into account that the comparison group (residents of the Kokpekty district) corresponded in age structure to the entire population of men and women exposed to radiation. Mortality analysis was conducted by time period (1949–1975, 1975–1997). The level of statistical significance was set at $p < 0.05$.

Results

An analysis of the obtained study results showed that overall and oncological mortality rates for male and female of different age groups in some cases had significant differences in dynamics between the exposed and control groups. Therefore, the analysis of mortality rates was conducted separately for men and women and for different age and sex groups. Among both male and female, the age-standardized overall mortality rates (ASR) for the population of the Abay district did not differ significantly from the control rates over the entire study period. The mortality rate fluctuated within a small range, averaging 580.2–1250.3 per 100,000 population (Figure 1). It should be noted that in the baseline period (1949–1952), due to high infant and child mortality, as well as tuberculosis mortality among the adult population, overall mortality rates in the Abay district were quite high and averaged 1100–2400 per 100,000 population.

A) Male, 1949-1975



B) Female, 1949-1975.

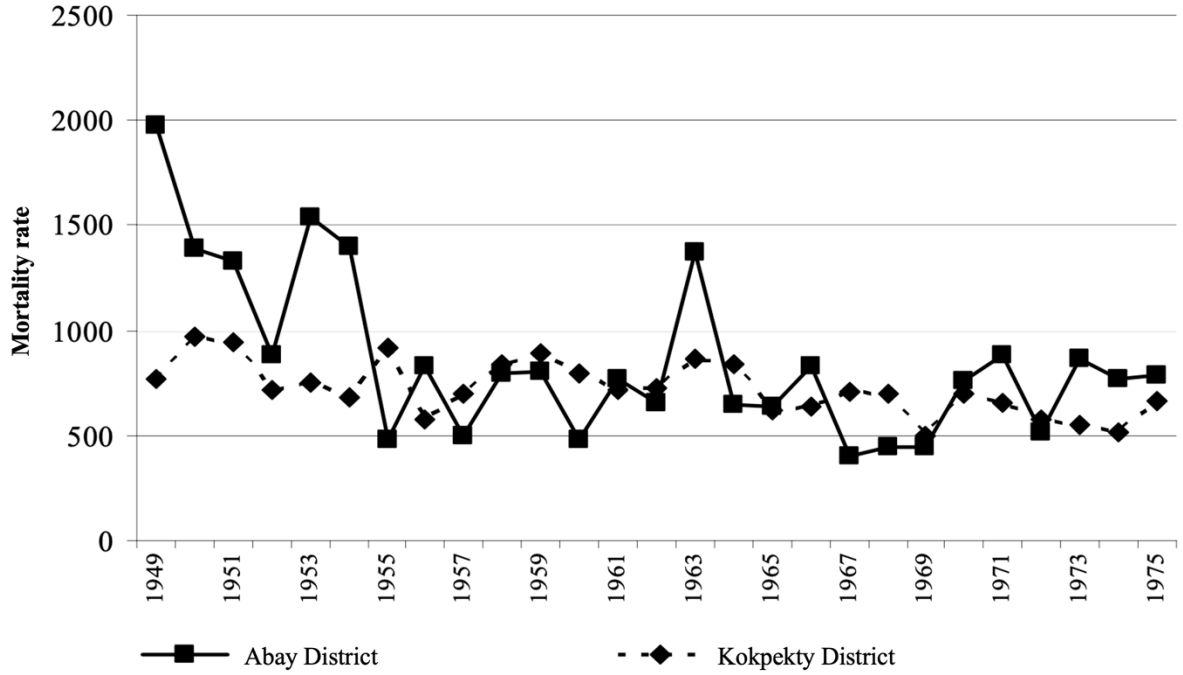
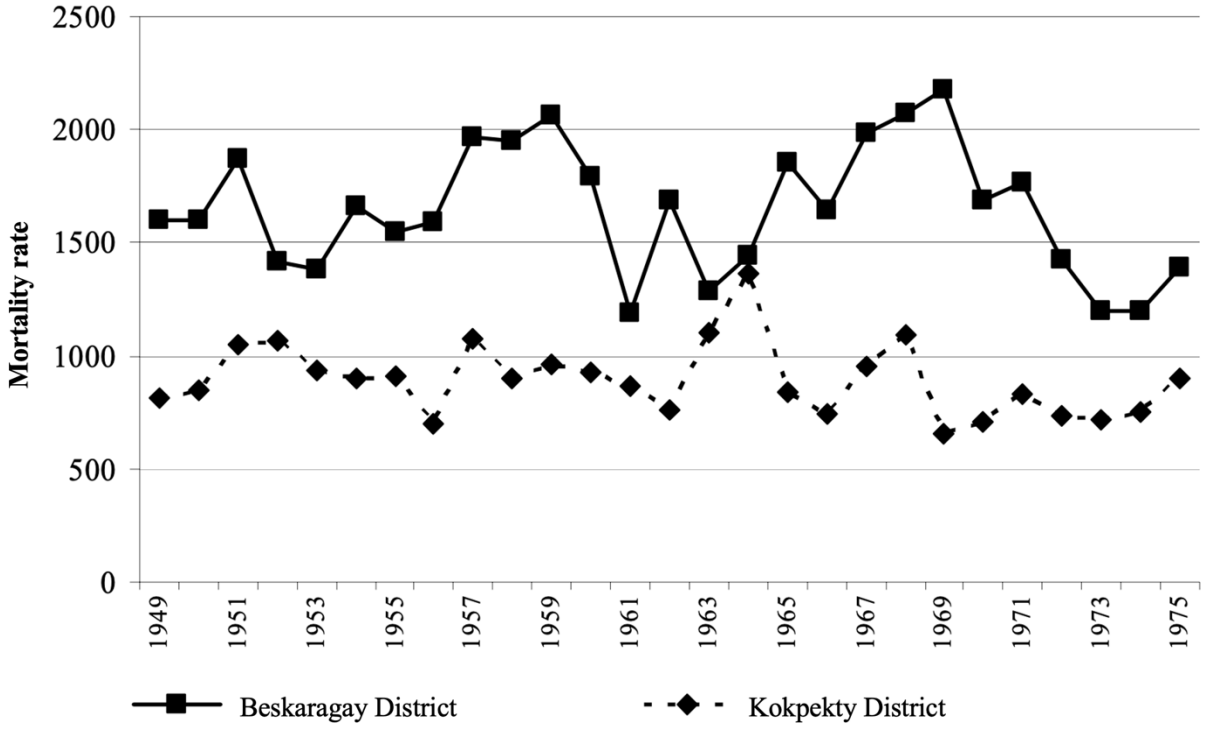


Figure 1. Mortality rates (ASR) in the residents of the Abay and Kokpekty districts.

Positive dynamics of standardized overall mortality rates among male and female was established among residents of the Beskaragay district in certain time intervals. Thus, among women of the Beskaragay district, due to increased infant and child mortality in the initial period, the overall mortality rate was significantly higher than in the control district. Beginning in 1955 (5 years after irradiation), the standardized overall mortality rate among female of the Beskaragay district increased significantly. Thus, in 1957 it was 1306.9 (1096.7-1557.5) per 100,000 population, in the control district – 697.0 (570.5-851.6) per 100,000 population (P<0.05; SMR=187%). By 1963-1964, the ASR in the exposed district leveled out with the control rate. Since 1965, another significant increase in ASR was recorded in the Beskaragay district - 1285.7 (1087.1-1520.5) per 100,000 population, in the control district - 621.7 (509.3-758.7) per 100,000 population (SMR = 207%). In 1971, the ASR of the exposed group was 1655.6 (1430.0-1916.8) per 100,000 population, in the control district - 547.7 (447.5-670.9) per 100,000 population (P < 0.01; SMR = 180%) (Figure 2).

A) Male, 1949-1975.



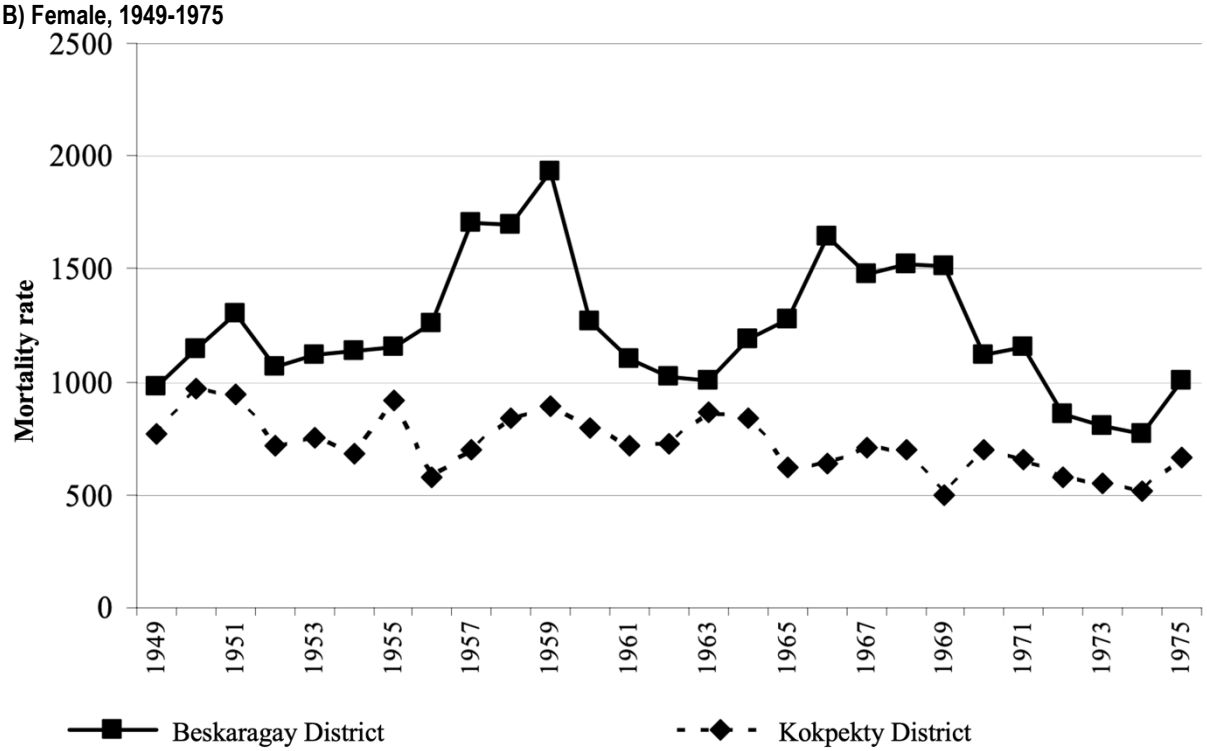


Figure 2. Mortality rates (ASR) in the residents of the Beskaragay and Kokpekty districts

Among male in the Beskaragay district, standardized overall mortality rates significantly exceeded those in the control district throughout almost the entire study period. Three time periods with significant increases in ASR rates were recorded: from 1952 (2 years after the start of exposure) to 1962 (12 years after the start of exposure); from 1965 (15 years after the start of exposure) to 1968 (18 years after exposure); from 1969 (19 years after exposure) to 1975 (25 years after the start of exposure). In 1957, the ASR in the exposed area was 1677.6 (1411.2-1985.7) per 100,000 population, in the control district- 910.8 (758.6-1093.0) per 100,000 population ($P < 0.05$; SMR = 210%); in 1960 - 2068.5 (1810.7-2363.1) per 100,000 population, in the control district- 718.5 (597.8- 863.5) per 100,000 population ($P < 0.01$; SMR = 290%) (Figure 2).

Thus, analysis of standardized overall mortality rates among the populations of the exposed and control areas revealed significant fluctuations depending on the temporal distribution and gender of individuals in the study groups. No modifying effect of radiation dose on changes in ASR rates was detected. For example, among the population exposed to an average dose of 625 mSv (Abay district), no significant differences in ASR were found compared to the control group. In another case, with exposure to an average dose of 870 mSv (Beskaragay district), significant excesses in standardized overall mortality rates were found at various time intervals after exposure compared to control rates.

Discussion

A retrospective assessment (1949-1998) of the overall mortality rate of the population of the Abay and Beskaragay districts of the Semipalatinsk region exposed to radiation allowed us to identify the characteristics and patterns of influence of the main modifying factors (dose magnitude and type of exposure, gender, age, time at risk) on significant changes in mortality levels and structure. Preliminary processing of the study results revealed the lowest overall mortality rate among the population of the control Kokpekty district throughout the entire period compared to those in other districts.

Among the exposed districts, the lowest overall mortality rates, not significantly different from the control rates, were recorded among the population of the Abay district (weighted average cumulative effective equivalent dose of radiation to the population of 624.0 mSv).

An analysis of standardized overall mortality rates for the populations of exposed and control areas revealed significant fluctuations depending on the temporal distribution and gender of individuals in the study groups. No modifying effect of radiation dose on changes in ASR rates was detected. We believe that most of our calculations for reconstructing effective equivalent radiation doses are rather arbitrary and subject to a certain degree of error. The dose range established for the population of specific areas can be classified as low and medium radiation doses. Its variations within a range of up to 870 mSv significantly reduce the ability to determine sensitivity thresholds for certain excess somatic and oncological diseases that cause death. The insignificant variation in minimum and maximum radiation doses in specific areas complicates the identification of dose-response relationships for the dynamics of excess somatic diseases, taking into account their temporal distribution.

In our radiation-epidemiological analysis of the study results, we assumed that there can be no single cause for the increase or decrease in overall mortality rates, even with such a significant excess as ionizing radiation. The polymorphism of causes of overall mortality in population groups of any size and ethnic composition determines its level at any time, and is

dependent on modifying factors such as gender, age, and a combination of endogenous and exogenous factors.

At present, despite a significant number of publications, the somatic effects of exposure to ionizing radiation on the human body remain the least studied [3]. Early reports on the life expectancy of bombing survivors noted the absence of increased mortality from diseases not caused by neoplasms; they even revealed a lower level compared to the control cohort [13]. The situation changed with the accumulation of data on the Life Span Study cohort [16]. For 1958-1990, the relative risk (RR) of myocardial infarction for both sexes at a radiation dose of 1 Gy compared to the control cohort was 1.17. The highest risk was characteristic of individuals irradiated before the age of 40 years. Moreover, no dependence on gender or time elapsed since the bombing was found [11]. There is an association with radiation exposure of such manifestations of atherosclerosis as stroke and isolated systolic hypertension [7]. However, in terms of significance as a risk factor, radiation is inferior to such well-known factors as lifestyle and hypertension.

A study of mortality among atomic bomb survivors revealed a statistically significant increase in non-oncologic mortality rates depending on the radiation dose. Data were summarized for 86,572 atomic bomb survivors [13]. Of these, 27,000 non-oncologic mortality cases were registered, which occurred in the cohort from October 1, 1950, to December 31, 1990 [10]. A clear dose-response relationship was found in the excess of diseases such as cardiovascular, respiratory, and gastrointestinal tract diseases. The incidence of the above-mentioned diseases increased with increasing dose. An assessment of radiation-related non-oncologic mortality in the cohort showed that these diseases account for 50-100% of the number of solid cancers. However, these data did not explain the dose-response relationship [2]. No evidence was obtained against a linear relationship, but statistically consistent indicators with curvilinear dose-response functions demonstrate zero risk for doses below 0.5 Sv. The authors believe that the obtained data on reliable changes in the excess relative risk depending on age and exposure allow us to consider the dependence on these factors statistically insignificant. At the same time, a significant dependence on the dose level on the mortality rate from blood diseases with an excess relative risk several times greater than that for solid cancers was established [2].

Somewhat different results were obtained in a radiation-epidemiological analysis of non-oncologic morbidity among Chernobyl accident liquidators [9, 10]. The data were obtained from a cohort of 68,309 liquidators with verified medical data. It was established that, of all classes of non-oncologic diseases, statistically significant radiation risks were recorded in the first 3 years only for cerebrovascular diseases (ERR Gy(-1)=1.17 at a 95% confidence interval of (0.45; 1.88).

Conclusion

A significant increase in overall mortality rates was observed in all age groups of the Beskaragay district of the Abay region 4-21 years after the onset of irradiation compared to the control Kokpekty district. No significant differences were found in overall mortality rates in the exposed Abay district compared to the control district. A modifying effect of age on overall mortality rates was established for the population of the exposed districts.

In subsequent years (26-49 years after the onset of irradiation), six to eight peaks of significantly higher overall mortality rates were recorded among men and women in the Beskaragay district compared to control rates. Among men and women in the Abay district, the overall mortality rate did not differ significantly from the control rates. The overall mortality curve was remitting, with alternating significant increases followed by a plateau in some years.

No dose-response relationships were found for overall mortality rates in the studied districts.

***Informed consent statement**. Not applicable.*

***Funding.** This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan BR28512329: "Integral assessment of the effect of ionizing radiation on the health of descendants of people exposed to radiation".*

***Declaration of competing interest**. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

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ERRATUM 1

In the article **«PREVALENCE OF NODULAR THYROID DISORDERS IN THE SEMEY REGION»** by E**spenbetova M.Zh., Bidakhmetova A.M., Baimukhanova A.A., Krykpayeva A.S., Uasheva L.B.** (Science & Healthcare, 2024, Vol. 26 (5), pp. 41–46, *DOI 10.34689/SH.2024.26.5.005*, a typographical error was made in the section "Funding."

It should read as follows:

Funding. The work was carried out within the framework of the project *IRN AP 19680072 "The role of molecular diagnostics in thyroid neoplasms,"* financed by the Ministry of Education and Science of the Republic of Kazakhstan, instead of the previously published "IRN AP 19860072."

The authors apologize for this inaccuracy.

ИСПРАВЛЕНИЕ 1

В статье **«ЧАСТОТА ВСТРЕЧАЕМОСТИ УЗЛОВЫХ ФОРМ ЩИТОВИДНОЙ ЖЕЛЕЗЫ ПО СЕМЕЙСКОМУ РЕГИОНУ», авторов Еспенбетова М.Ж, Бидахметова А.М., Баймуханова А.А., Крыкпаева А.С., Уашева Л.Б.** (Наука и здравоохранение, 2024. Vol.26 (5), С. 41-46. *DOI 10.34689/SH.2024.26.5.005*, в разделе «Финансирование» допущена опечатка.

Следует читать:

Финансирование. Работа выполнена в рамках проекта: *ИРН AP 19680072 «Роль молекулярной диагностики при новообразованиях щитовидной железы»*, за счет финансирования МОН РК. вместо ранее опубликованного: «ИРН AP 19860072».

Авторы приносят извинения за допущенную неточность.

ERRATUM 2

In the article **«PROGNOSTIC SIGNIFICANCE OF GENETIC TUMOR MARKERS IN THYROID NEOPLASMS: LITERATURE REVIEW» by Espenbetova M.Zh., Bidakhmetova A.M., Krykpayeva A.S., Uasheva L.B., Syzdykbayev M.K., Baimukhanova A.A., Baurzhan A.B.** (Science & Healthcare, 2024, Vol. 26 (5), pp. 204–212, doi 10.34689/SH.2024.26.5.024), a typographical error was made in the section **"Funding."**

It should read as follows:

Funding. The work was carried out within the framework of the project *IRN AP 19680072 "The role of molecular diagnostics in thyroid neoplasms,"* financed by the Ministry of Education and Science of the Republic of Kazakhstan.

The authors apologize for this inaccuracy

ИСПРАВЛЕНИЕ 2

В статье **«PROGNOSTIC SIGNIFICANCE OF GENETIC TUMOR MARKERS IN THYROID NEOPLASMS: Literature Review», авторов Еспенбетова М.Ж., Бидахметова А.М., Крыкпаева А.С., Уашева Л.Б., Сыздыкбаев М.К., Баймуханова А.А., Бауржан А.Б.** (Наука и здравоохранение, 2024. Т.26 (5). С. 204-212. doi 10.34689/SH.2024.26.5.024), в разделе **«Финансирование»** допущена опечатка.

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Funding. The work was carried out within the framework of the project: *IRN AP 19680072 "The role of molecular diagnostics in thyroid neoplasms",* financed by the Ministry of Education and Science of the Republic of Kazakhstan.

Авторы приносят извинения за допущенную неточность.

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ERRATUM 266-266 ***ТҮЗЕТУ***

НАО «Медицинский университет Семей»

Министерство здравоохранения Республики Казахстан

Редакционно-издательский отдел.

071400, г. Семей, ул. Абая Кунанбаева, 103.

Подписано в печать 28.08.2025 г.

Формат 60х90/8. Печать цифровая.

Усл. п. л. 33,8. Заказ 189.

Тираж 500 экз.