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Содержание

ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

Jumabayeva A., Kaibullayeva J., Kaisina A., Nugmanova B., Zhumadilova Z., Botabayeva A., Ualiyeva A., Pashimov M., Kambarova G., Omarova K., Muratbekova A., Balabek A., Yergaliyeva A., Reshidova T., Saktagan A., Kassymova T., Mutaliyeva G., Anuar A., Kudaibergenova Sh.
Midterm results of the observational non-interventional clinical study "Evaluation of the effectiveness of the carnitine orotate and biphenyldimethyldicarboxylate complex in the pathogenetic therapy of metabolic-associated fatty liver disease: a prospective cohort study» 7-16

Nussupova R.R., Pack L.A., Mussazhanova Zh.B., Bolatov A.K., Zhakupov A.K., Muldakhmetov M.S.,
Genetic Analysis of TP53 and CTNNB1 Mutations in Pediatric Medulloblastoma: A Study from Kazakhstan 17-25

Adilgazyuly Sh., Bulegenov T., Mussakhanova A., Altybayeva Zh., Medeulova A., Tokenova Zh., Urazalina N.M.
Assessment of the quality of life of patients with lung cancer in the Abay region 26-31

Тулеуханов С.Т., Зинченко В.П., Қайрат Б.Қ., Тусупбекова Г.А., Малибаева А.Е.
Эпилепсиялық белсенділік кезінде пароксизмальды деполяризациялық ығысу кластерлерінің құрылымына Kv7 тұқымдас калий каналдарының ингибиторлары мен активаторларының әсерін зерттеу 32-39

Petrova Y.V., Ivanova R.L., Goremykina M.V., Serikova T.K., Karakanova A.B., Bakytova A.B., Seitkhan D.S., Nogayeva M.G.
Quality of life and adherence to therapy in patient with rheumatoid arthritis 40-48

Kastey R., Faizullina K., Turganova M., Zhexenova A., Vaičiulis V., Akhtayeva N.
Study of Hospitalized Cases Associated with Acute Cerebrovascular Accidents 49-55

Калимолдина Г.К., Муздубаева Ж.Е., Ботабаева А.С., Оразалина А.С., Каскабаева А.Ш., Жумадилова З.К.
Эндотелиальная дисфункция при неспецифическом язвенном колите и возможности её коррекции при лечении 56-65

Ibekenov O.T., Baymakhanov A.N., Berkinbay A.B., Zheldibaev Ye.M., Duisebekov M.K., Esenbekov N.B., Zhorayev T.S.
Non-varicose bleeding from the upper gastrointestinal tract 66-74

Алимбаева А.Р., Тайоразова Г.Б., Латышев Д.Ю., Лобанов Ю.Ф., Дорохов Н.А., Скударнов Е.В., Болденкова И.Ю., Аильбаева Н.М., Токтамыс Д.Р.
Частота рецидивов гастроэзофагеальной рефлюксной болезни у детей школьного возраста 75-81

Table Of Contents

ORIGINAL ARTICLES

Джумабаева А.Е., Кайбуллаева Д.А., Қайсина Ә.А., Нугманова Б.Т., Жумадилова З.К., Ботабаева А.С., Уалиева А.Е., Пашимов М.О., Камбарова Г.А., Омарова К.С., Муратбекова А.К., Балабек А.Н., Ергалиева А.А., Решидова Т.А., Сақтаған А.Е., Касымова Т.В., Муталиева Г.С., Ануар А.Д., Кудайбергенова Ш.Н.
Промежуточные результаты обсервационного неинтервенционного клинического исследования «Оценка эффективности применения комплекса карнитин оротата и бифенилдиметилдикарбоксилата в патогенетической терапии метаболически-ассоциированной жировой болезни печени: проспективное когортное исследование» 7-16

Нусупова Р.Р., Пак Л.А., Мусажанова Ж.Б., Болатов А.К., Жакупов А.К., Мулдахметов М.С.
Генетический анализ мутаций TP53 и CTNNB1 при медуллобластоме у детей: исследование в Казахстане 17-25

Әділғазыұлы Ш., Булегенов Т., Мусаханова А., Алтыбаева Ж., Медеулова А., Токенова Ж., Уразалина Н.М.
Оценка качества жизни пациентов с раком легкого в Абайском регионе 26-31

Tuleukhanov S.T., Zinchenko V.P., Kairat B.K., Tussupbekova G.A., Malibayeva A.E.
Implications of Kv7 inhibitors and activators of potassium channels on the structure of paroxysismal depolyarisation shift clasters in epileptiform activity 32-39

Петрова Ю.В., Иванова Р.Л., Горемыкина М.В., Серикова Т.К., Караканова А.Б., Бакытова А.Б., Сейтхан Д.С., Ногаева М.Г.
Качество жизни и приверженность терапии пациентов с ревматоидным артритом 40-48

Кастей Р., Файзуллина К., Турганова М., Жексенова А., Вайчюлис В., Ахтаева Н.
Изучение госпитализированных случаев, связанных с острыми нарушениями мозгового кровообращения 49-55

Kalimoldina G.K., Muzdubaeva Zh.E., Botabaeva A.S., Orazalina A.S., Kaskabayeva A.Sh., Zhumadilova Z.K.
Endothelial dysfunction in ulcerative colitis and possibilities for Its correction during treatment 56-65

Ибекенов О.Т., Баймаханов А.Н., Беркинбай А.Б., Желдибаев Е.М., Дуйсебеков М.К., Есенбеков Н.Б., Жораев Т.С.
Неварикозные кровотечения из верхних отделов желудочно-кишечного тракта 66-74

Alimbaeva A.R., Taiorazova G.B., Latyshev D.Yu., Lobanov Yu.F., Dorokhov N.A., Skudarnov E.V., Boldenkova I.Yu., Ailbayeva N.M., Toktamys D.R.
Frequency of relapses of gastroesophageal reflux disease in school-age children 75-81

Баймуханова М.С., Нургалиева Б.К., Ногаева М.Г., Костинов М.П.
Уровень заболеваемости сахарным диабетом 2 типа и хроническим вирусным гепатитом С на 2023 год в городе Алматы
82-88

Maukayeva S.B., Kudaibergenova N.K., Merimgaliyeva A.K., Agybayeva A.M., Abzalkhanova G.T., Orazalina A.S., Yurkovskaya O.A., Goremykina M.V., Zeinolla K.A., Akhmetova A.K.
Analysis of the microflora on dates of the bacteriological laboratory
89-99

Mukasheva G.D., Maukayeva S.B., Kudaibergenova N.K., Shabdarbayeva D.M., Berikuly D., Orazalina A.S., Apbassova S.A., Zhanibekova A., Kalkaman A., Akhmetova A.K.
Analysis of medical students' knowledge about HIV infection
100-106

Sultanbekova B.M., Raushanova A., Akhtayeva N., Alekenova N., Nurbaulina E., Abilov T.
Perceptions of work processes and organizational dynamics in hospital gynecology departments
107-115

Танышева Г.А., Берикханова К.Е., Шегенов Г.А., Нурмагамбетова Д.М., Билялова Г.Т., Советова С.Д., Саркучикова Г.Ж.
Иммунологические изменения при лечении антифосфолипидного синдрома у беременных
116-122

Toleuov E.A., Moldagaliyev T.M., Seksenbayev N.Zh., Akkuzinova K.F., Zhamaliyeva L.M., Bubeliene D., Muzafarov R., Tleubayeva Sh., Malsova B.K.
Suicide across different age groups
123-129

Moldagasimova A.B., Tussupbekova D.M., Sharipova A.T., Rysbekova R.K.
Experience of project work to identify anxiety as a possible factor in teenage suicide and its prevention among schoolchildren in Almaty
130-136

АКТУАЛЬНАЯ ТЕМА - COVID-19

Shakirova A.A., Toktabayeva B.Zh., Orazalina A.S., Abyldazinova A.Zh., Amrenova K.Sh., Abayeva K.D., Zangaliyeva G.M.
The condition of the vascular endothelium in children with COVID-19 and broncho-obstructive syndrome
137-145

Ayazbekov A., Taskynova G., Oshibayeva A., Taubekova M., Tanysheva G.
Long-term consequences of coronavirus infection (SARS-COV-2) in women of childbearing age
146-156

ОБЗОР ЛИТЕРАТУРЫ

Yerketayeva A.Kh., Mussazhanova Zh.B., Kozykenova Zh.Y., Pak L.A., Dushimova Z.D., Toktabayeva B.Zh., Zhazykbayeva L.K., Rakhmankulova A.M.
The Impact of gene mutations in Thyroid Cancer: A review
157-166

Doszhanov I.A., Nurdinov N.S., Abilov T.S., Sadykova K.Zh., Nuskabayeva G.O., Zharkynbekova N.A., Oshibayeva A.E., Aimakhanov M.S.
Exploring the Role of miRNA's in drug-resistant epilepsy: a literature review
167-173

82-88 **Baimukhanova M.S., Nurgalieva B.K., Nogaeva M.G., Kostinov M.P.**
The incidence of type 2 diabetes mellitus and chronic viral hepatitis C in 2023 in Almaty

89-99 **Маукаева С.Б., Кудайбергенова Н.К., Меримгалиева А.К., Агыбаева А.М., Абзалханова Г.Т., Оразалина А.С., Юрковская О.А., Горемыкина М.В., Зейнолла К.А., Ахметова А.К.**
Анализ микрофлоры по данным бактериологической лаборатории

100-106 **Мукашева Г.Д., Маукаева С.Б., Кудайбергенова Н.К., Шабдарбаева Д.М., Берікұлы Д., Оразалина А.С., Апбасова С.А., Жәнібекова А., Қалқаман А., Ахметова А.К.**
Анализ знаний студентов медиков о ВИЧ инфекции

107-115 **Султанбекова Б.М., Раушанова А., Ахтаева Н., Алекенова Н., Нурбаулина Э., Абилов Т.**
Восприятие рабочих процессов и организационной динамики в отделениях гинекологии больниц

116-122 **Tanysheva G.A., Berikkhanova K.E., Shegenov G.A., Nurmagambetova D.M., Bilyalova G.T., Sovetova S.D., Sarkuchikova G.Zh.**
Immunological changes in the treatment of antiphospholipid syndrome in pregnant women

123-129 **Төлеуов Е.Ә., Молдагалиев Т.М., Сексенбаев Н.Ж., Аккузинова К.Ф., Жамалиева Л.М., Бубелиене Д., Музафаров Р.Х., Тлеубаева Ш.М., Мэлсова Б.К.**
Суицид в различных возрастных группах

130-136 **Молдагасимова А.Б., Тусупбекова Д.М., Шарипова А.Т., Рысбекова Р.К.**
Опыт проектной работы по выявлению тревожности, как возможного фактора подросткового суицида и его профилактика среди школьников города Алматы

COVID-19 - TOPICAL SUBJECT

137-145 **Шакирова А.А., Токтабаева Б.Ж., Оразалина А.С., Абылгазинова А.Ж., Амренова К.Ш., Абаева К.Д., Жангалиева Г.М.**
Состояние сосудистого эндотелия у детей с COVID-19 и бронхообструктивным синдромом

146-156 **Аязбеков А., Таскынова Г., Ошибаева А., Таубекова М., Танышева Г.**
Долгосрочные последствия коронавирусной инфекции (SARS-COV-2) у женщин фертильного возраста

REVIEWS

157-166 **Еркетаева А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Пак Л.А., Душимова З.Д., Токтабаева Б.Ж., Жазыкбаева Л.К., Рахманкулова А.М.**
Роль мутации в гене при раке щитовидной железы: Обзор литературы

167-173 **Досжанов И.А., Нурдинов Н.С., Абилов Т.С., Садыкова К.Ж., Нускабаева Г.О., Жаркынбекова Н.А., Ошибаева А.Е., Аймаханов М.С.**
Изучение роли микроРНК в лекарственно-устойчивой эпилепсии. Обзор литературы

Shotpakova A.K., Rakhmanov S.B., Abilov T.S., Zhumabay N.A.
Modern view on the morphofunction of the heart and intracardiac nervous structures
174-184
Almussina A.K., Rakhimzhanova R.I., Dautov T.B., Ganiyeva A.A.
Radiological methods in the diagnosis of atrioventricular septal defect
185-195
Ganiyeva A.A., Rakhimzhanova R.I., Dautov T.B., Abdrakhmanova Zh.S., Almussina A.K., Gani A.B., Duisebayeva N.A., Imangeldina M.S., Bektybayeva N.M.
Modern approaches to the diagnosis, surgical correction, and long-term monitoring of patients with common arterial trunk
196-207
Ерназаров А.А., Ошибаева А.Е., Нускабаева Г.О., Кырыкбаева С.С., Кемельбеков К.С., Аймагамбетова А.О., Дуйсенбаева Б.С.
Анализ факторов риска сердечно-сосудистых заболеваний у молодежи. Обзор литературы
208-218
Маркабаева А.М., Керимкулова А.С., Нурпейсова Р.Г., Зекенова Е.М., Умбетжанова А.Т., Кубекова С.Ж., Алдабекова Г.У.
Программа управления заболеванием при артериальной гипертензии
219-231
Алдабекова Г.У., Мусина А.А., Камалбекова Г.М., Данбаева Ж.С., Хамидуллина З.Г., Оспанова А.Б., Исаева Е.И.
Организационные аспекты управления риск ориентированных технологий в организациях родовспоможения
232-249
Madiyeva M., Kaskabayeva A., Rymbayeva T., Kanapiyanova G., Bersimbekova G., Aubakirov A., Beisenova A.
The Role of Biochemical Markers in Bone Metabolism in Children and Adolescents. Literature review
250-256
Нургалиева Б.К.
Эрадикационная терапия Helicobacter pylori
257-266

КЛИНИЧЕСКИЙ СЛУЧАЙ

Nogayeva M.G., Atasheva A.A., Omargali K.S., Nurgalieva B.K.
Clinical case: poststreptococcal arthritis associated with COVID-19
267-273
Kussainova A.A., Akhmetova A.K., Zhunussova D.K., Yurkovskaya O.A., Dyusseneva D.K., Adilgozhina S.M., Shamshudinov T.M., Bolekbayeva A.Y., Kassym L.T.
Systemic retinoids in the management of moderate-to-severe acne: a clinical case study
274-280
Шалабаев Б.Д., Бейбіт Ә.Б., Нуржанов А.А., Ганиева Е.Д., Сапаев М.Н., Манатова А.М., Куаныш Ж.М., Жарлыганова Д.С.
Вариант хирургического лечения синовиальной саркомы мягких тканей лица
281-287
Кузнецова Т.В., Парфенов А.В., Сурова А.Ж., Бекетова Б.Б., Мадиева М.Р., Раисов Д.Т., Рахимбеков А.В.
Полная транспозиция органов (Situs Viscerum Inversus Totalis) на примере клинического случая
288-295

CLINICAL CASE

Ногаева М.Г., Аташева А.А., Омарғали Қ.С., Нургалиева Б.К.
Клинический случай: постстрептококковый артрит ассоциированный с COVID-19
Кусаинова А.А., Ахметова А.К., Жунусова Д.К., Юрковская О.А., Дюсенева Д.К., Адильгожина С.М., Шамшудинов Т.М., Болекбаева А.Е., Касым Л.Т.
Системные ретиноиды в лечении среднетяжелых и тяжелых форм акне: клинический случай
Shalabaev B.D., Beibit A.B., Nurzhanov A.A., Ganieva E.D., Sapaev M.N., Manatova A.M., Kuanysh Zh.M., Zharlyganova D.S.
Option for surgical treatment of synovial sarcoma of soft tissues of the face
Kuznetsova T.V., Parfenov A.V., Surova A.Zh., Beketova B.B., Madiyeva M.R., Raissov D.T., Rakhimbekov A.V.
Complete Organ Transposition (Situs Viscerum Inversus Totalis): A Clinical Case Study

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MIDTERM RESULTS OF THE OBSERVATIONAL NON-INTERVENTIONAL CLINICAL STUDY "EVALUATION OF THE EFFECTIVENESS OF THE CARNITINE OROTATE AND BIPHENYL DIMETHYL DICARBOXYLATE COMPLEX IN THE PATHOGENETIC THERAPY OF METABOLIC-ASSOCIATED FATTY LIVER DISEASE: A PROSPECTIVE COHORT STUDY»

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Abstract

Introduction. Metabolic dysfunction-associated fatty liver disease (MAFLD) is a widespread pathology requiring effective treatment approaches. One promising direction is the use of a complex of carnitine orotate and biphenyl dimethyl dicarboxylate (COC and BDD), which possess antioxidant and hepatoprotective properties.

Materials and methods. As part of the observational, non-interventional, prospective cohort study KASVM-01 [NCT06078722], the impact of COC and BDD on the progression of MAFLD in patients in the Republic of Kazakhstan was investigated. From February 2023 to July 2024, a total of 121 participants from Almaty and Almaty Region were enrolled in the study and received COC and BDD. The observation period lasted 12 months, with an interim analysis conducted on 78 participants who completed a 24-week treatment course. Anthropometric parameters (BMI, waist circumference), liver steatosis, and fibrosis levels measured via transient elastography (FibroScan) with CAP, ALT, AST, total cholesterol,

triglycerides, and FIB-4 (a non-invasive fibrosis marker) were assessed at baseline and after completing 24 weeks of therapy with COC and BDD.

Results. The interim analysis revealed a statistically significant reduction in ALT levels (from 32.4 to 20.1 U/mL, p<0.001), triglycerides (from 1.4 to 1.3 mmol/L, p=0.007), steatosis grade (from 304 to 283 dB/m, p<0.001), and fibrosis level (from 6.5 to 6.0 kPa, p=0.022). The prevalence of severe steatosis (S3) decreased from 52.7% to 45.7%, whereas mild steatosis (S1, S0) increased to 21.4% and 10%, respectively (p=0.001). The proportion of patients with F3 fibrosis declined from 8.1% to 1.4%, while F2 fibrosis decreased from 27% to 21.4% (p=0.022), indicating an improvement in fibrosis markers. During the observation period, BMI decreased (from 30.4 to 29.8 kg/m²), although the changes were not statistically significant (p=0.214). No significant changes were observed in total cholesterol and FIB-4 levels.

Conclusion. The interim analysis confirmed the effectiveness of COC and BDD in the treatment of MAFLD, demonstrating improvements in biochemical parameters as well as regression of liver steatosis, and fibrosis. Further research and validation of these findings in later stages of observation are necessary to assess the final efficacy and long-term safety of the therapy.

Keywords: *Metabolic dysfunction-associated fatty liver disease, carnitine orotate, biphenyl dimethyl dicarboxylate, liver steatosis, liver fibrosis*

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Резюме

ПРОМЕЖУТОЧНЫЕ РЕЗУЛЬТАТЫ ОБСЕРВАЦИОННОГО НЕИНТЕРВЕНЦИОННОГО КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ «ОЦЕНКА ЭФФЕКТИВНОСТИ ПРИМЕНЕНИЯ КОМПЛЕКСА КАРНИТИН ОРОТАТА И БИФЕНИЛДИМЕТИЛДИКАРБОКСИЛАТА В ПАТОГЕНЕТИЧЕСКОЙ ТЕРАПИИ МЕТАБОЛИЧЕСКИ-АССОЦИИРОВАННОЙ ЖИРОВОЙ БОЛЕЗНИ ПЕЧЕНИ: ПРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ»

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Введение. Метаболически-ассоциированная жировая болезнь печени (МАЖБП) является распространённой патологией, требующей эффективных методов терапии. Одним из перспективных направлений является использование комплекса карнитин-оротата и бифенилдиметилдикарбоксилата (КОК и BDD), обладающего антиоксидантными и гепатопротекторными свойствами.

Материалы и методы. В рамках обсервационного неинтервенционного проспективного когортного исследования KACBM-01 [NCT06078722] изучалось влияние КОК и BDD на течение МАЖБП у пациентов в Республики Казахстан. С февраля 2023 года по июль 2024 года в исследовании в Алматы и Алматинской области приняли участие 121 участник, принимавшие КОК и BDD. Длительность наблюдения составила 12 месяцев, а промежуточный анализ проведён на 78 участниках, завершивших 24-недельный курс лечения. Антропометрические данные (ИМТ, окружность талии), уровни стеатоза и фиброза печени, измеренные с помощью транзиторной эластографии (FibroScan) с CAP, АЛТ, АСТ, общий холестерин, триглицериды и FIB-4 (неинвазивный маркер фиброза), оценивались во время исходного визита и после завершения терапии КОК и BDD на 24-й неделе.

Результаты. По данным промежуточного анализа, отмечено статистически значимое снижение уровня АЛТ (с 32,4 до 20,1 ЕД/мл, p<0,001), триглицеридов (с 1,4 до 1,3 ммоль/л, p=0,007), степени стеатоза (с 304 до 283 дБ/м, p<0,001) и уровня фиброза (с 6,5 до 6,0 кПа, p=0,022). Частота выраженного стеатоза (S3) уменьшилась с 52,7% до 45,7%, тогда как легкие степени стеатоза (S1, S0) возросли до 21,4% и 10% соответственно (p=0,001). Доля пациентов с фиброзом F3 снизилась с 8,1% до 1,4%, а с F2 – с 27% до 21,4% (p=0,022), что свидетельствует об улучшении показателей фиброза. За время наблюдения ИМТ снизился (с 30,4 до 29,8 кг/м²), но статистически значимых различий не выявлено (p=0,214). Существенных изменений общего холестерина и FIB-4 не зафиксировано.

Заключение. Промежуточный анализ подтвердил эффективность применения КОК и BDD в терапии МАЖБП, продемонстрировав улучшение биохимических показателей, а также регрессию стеатоза и фиброза печени. Для окончательной оценки эффективности и долгосрочной безопасности терапии требуется продолжение исследования и подтверждение полученных данных на более поздних этапах наблюдения.

Ключевые слова: *метаболически-ассоциированная жировая болезнь печени, карнитин-оротат, бифенилдиметилдикарбоксилат, стеатоз печени, фиброз печени.*

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Түйіндеме

БАҚЫЛАУЛЫҚ ИНТЕРВЕНЦИЯСЫЗ КЛИНИКАЛЫҚ ЗЕРТТЕУДІҢ АРАЛЫҚ НӘТИЖЕЛЕРІ «КАРНИТИН ОРОТАТЫ МЕН БИФЕНИЛДИМЕТИЛДИКАРБОКСИЛАТ КЕШЕНІН МЕТАБОЛИЗММЕН БАЙЛАНЫСТЫ МАЙЛЫ БАУЫР АУРУЫНЫҢ ПАТОГЕНЕТИКАЛЫҚ ТЕРАПИЯСЫНДА ҚОЛДАНУ ТИІМДІЛІГІН БАҒАЛАУ: ПЕРСПЕКТИВТІ КОГОРТТЫҚ ЗЕРТТЕУ»

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Кіріспе. Метаболизммен байланысты майлы бауыр ауруы (МБМБА) кең таралған патология болып табылады және тиімді емдеу әдістерін қажет етеді. Перспективті бағыттардың бірі – антиоксиданттық және гепатопротекторлық қасиеттері бар карнитин-оротат пен бифенилдиметилдикарбоксилат (КОК және BDD) кешенін қолдану.

Әдістер. KACBM-01 [NCT06078722] обсервациялық, араласпайтын, перспективті когорттық зерттеуі аясында Қазақстан Республикасында КОК және BDD препаратының МБМБА ағымына әсері зерттелді. 2023 жылғы ақпан мен 2024 жылғы шілде аралығында Алматы және Алматы облысында 121 қатысушы осы препараттарды қабылдады. Бақылау ұзақтығы 12 айды құрады, ал аралық талдау 24 апталық емдеу курсын аяқтаған 78 қатысушыда жүргізілді. Антропометриялық көрсеткіштер (ДСИ, бел айналымы), бауыр стеатозы мен фиброз деңгейі (FibroScan CAP көмегімен), АЛТ, АСТ, жалпы холестерин, триглицеридтер және FIB-4 (фиброздың инвазивті емес маркері) бастапқы және 24-апталық терапиядан кейін бағаланды.

Нәтижелер. Аралық талдау бойынша АЛТ деңгейінің (32,4-тен 20,1 ЕД/мл-ге дейін, p<0,001), триглицеридтердің (1,4-тен 1,3 ммоль/л-ге дейін, p=0,007), стеатоз дәрежесінің (304-тен 283 дБ/м-ге дейін, p<0,001) және фиброз деңгейінің (6,5-тен 6,0 кПа-ға дейін, p=0,022) статистикалық тұрғыдан маңызды төмендеуі анықталды. Айқын стеатоздың (S3) жиілігі 52,7%-дан 45,7%-ға дейін төмендеді, ал жеңіл стеатоз деңгейлері (S1, S0) сәйкесінше 21,4% және 10%-ға дейін артты (p=0,001). F3 дәрежесіндегі фиброзы бар науқастар үлесі 8,1%-дан 1,4%-ға дейін, ал F2 деңгейі 27%-дан 21,4%-ға дейін төмендеді (p=0,022), бұл фиброз көрсеткіштерінің жақсарғанын көрсетеді. Бақылау кезеңінде ДСИ 30,4-тен 29,8 кг/м²-ге дейін төмендеді, бірақ статистикалық тұрғыдан маңызды айырмашылықтар анықталған жоқ (p=0,214). Жалпы холестерин мен FIB-4 көрсеткіштерінде айтарлықтай өзгерістер байқалмады.

Қорытынды. Аралық талдау КОК және BDD препараттарын МБМБА емдеуде қолданудың тиімділігін растады, биохимиялық көрсеткіштердің жақсарғанын, сондай-ақ бауыр стеатозы мен фиброзының регрессиясын көрсетті. Терапияның түпкілікті тиімділігі мен ұзақ мерзімді қауіпсіздігін бағалау үшін зерттеуді жалғастыру және алынған мәліметтерді бақылаудың кейінгі кезеңдерінде растау қажет.

Түйінді сөздер: *метаболизммен байланысты майлы бауыр ауруы, карнитин-оротат, бифенилдиметилдикарбоксилат, бауыр стеатозы, бауыр фиброзы.*

Дәйексөз үшін:

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Introduction

The prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) continues to rise rapidly, with some studies indicating a prevalence exceeding 30% [15], highlighting the importance of developing effective pharmacological treatment algorithms to prevent disease progression. The complexity of MAFLD pathophysiology significantly complicates the search for a universal and effective treatment approach.

The fundamental approaches in MAFLD therapy remain lifestyle modifications, including increased physical activity, weight reduction, and smoking cessation. An important addition to these measures is the correction of metabolic factors such as diabetes, obesity, and dyslipidemia [6].

In March 2024, resmetirom was approved for the treatment of MAFLD. The primary mechanisms of this drug include liver fibrosis correction and inflammation reduction. It is essential to understand that the drug was approved, alongside diet and exercise, for adults with MAFLD who have moderate to advanced liver fibrosis (stage F2 or F3) but have not yet developed cirrhosis. Resmetirom remains under clinical investigation, with its efficacy and safety still being studied, and treatment duration has yet to be established. Consequently, the search for optimal MAFLD treatment regimens continues.

One mechanism of MAFLD progression is reduced fatty acid oxidation in hepatocytes, which is closely linked to liver steatosis. It has been proven that mitochondrial dysfunction leads to fat accumulation in the liver, and oxidative stress may explain the mitochondrial dysfunction observed in MAFLD. Carnitine is a well-known modulator of free fatty acid transport and oxidation in mitochondria [16,18], and several studies have demonstrated its antioxidant activity in hepatocytes [5,10,12].

The carnitine orotate complex (Godex®) is a pharmaceutical drug that has demonstrated efficacy in reducing cytolysis in liver diseases [11,20,22]. Recent in vitro and in vivo studies have shown that the carnitine orotate complex can improve metabolic health by influencing glucose and lipid metabolism and significantly reducing liver steatosis [3,8,9,21]. Furthermore, experimental research has identified the molecular mechanism by which the carnitine orotate complex reduces insulin resistance [9].

Given its positive metabolic effects and widespread use, it became relevant to investigate the relationship between carnitine orotate complex use in MAFLD patients in Kazakhstan. A similar study was conducted in 2014 in the country, assessing the efficacy and safety of this complex in a smaller patient cohort with a shorter treatment duration (up to eight weeks) [1].

In November 2022, a Korean study was published examining the long-term use of the carnitine orotate complex (Godex®) (up to 30 days, 30-180 days, and over 180 days) and its impact on mortality. The study found that the most significant reduction in mortality risk was observed in individuals with metabolic risk factors such as obesity, fatty liver disease, dyslipidemia, type 2 diabetes, and metabolic syndrome with prolonged use of the carnitine orotate complex, whereas the effect was weaker in alcohol consumers [19].

Thus, **the aim of this study** was to evaluate the efficacy of carnitine orotate complex and BDD in the pathogenetic therapy of MAFLD in Kazakhstan in routine clinical practice.

Materials and Methods.

An observational, non-interventional, prospective cohort cluster study KASVM-01 [NCT06078722] was conducted to examine the effects of the carnitine orotate complex + biphenyl dimethyl dicarboxylate (COC and BDD) on the progression of MAFLD. The study included adult residents of Kazakhstan. To ensure consistency in enrollment, the recruitment period lasted six months, and the follow-up period was 12 months (*Scheme 1*). As part of routine clinical practice, patients visited their attending physician every six months. According to the study protocol, visits included specific examinations and questionnaires that are part of the standard routine management of MAFLD patients. Only patients with a formally documented and confirmed diagnosis (primary medical documentation) were eligible for inclusion in the study.

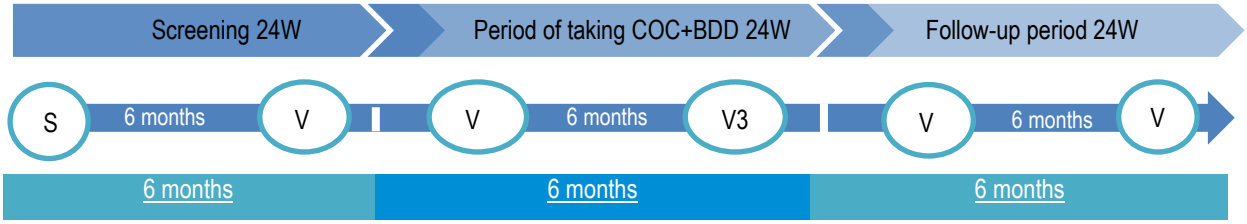
Study cohorts (*Scheme 1*):

• Study cohort: Patients taking COC and BDD, regardless of study participation. Treatment duration: six months, followed by six months of post-treatment observation.

• Control cohort: Patients not taking COC and BDD, regardless of study participation. Observation duration: 12 months.

The study included patients taking or not taking COC and BDD, regardless of sex and age, who were registered as MAFLD patients. Enrollment was conducted by researchers involved in the study across six regions of Kazakhstan: Almaty, Astana, Aktobe, Shymkent, Semey, Turkestan region, and Almaty region.

Inclusion criteria: Patients of both sexes aged 18 to 75 years, who are citizens of the Republic of Kazakhstan; patients with a clinically and laboratory-confirmed diagnosis of MAFLD without severe comorbidities; patients not receiving other adjunctive therapy (metabolic therapy drugs, essential phospholipids, ursodeoxycholic acid, glycyrrhizic acid, ademetionine, and others); patients with a minimum seven-day washout period between discontinuing other adjunctive therapy and starting COC and BDD; patients who voluntarily signed the informed consent form.



Cohort	Observation cohort	Regions
Study cohort	Patients using COC and BDD	Almaty, Almaty region
Control cohort	Patients not using COC and BDD	Astana, Aktobe, Shymkent, Semey, Turkestan region

Scheme 1. Observation period with patient visits depending on COC and BDD intake, cluster distribution of cohorts.

Exclusion criteria: Patients with alcohol abuse according to the AUDIT-C questionnaire; patients taking the carnitine orotate complex for more than four weeks before signing informed consent; patients with contraindications to the carnitine orotate complex; patients diagnosed with diabetes; pregnancy and lactation; concurrent use of levodopa, altretamine, cisplatin, metformin, statins; patients with co-infections (HIV, HBV, HCV); decompensated liver cirrhosis (CTP≥7 points); eGFR ≤15 mL/min/1.73 m²; drug-induced liver injury; use of narcotic and psychotropic substances; malignant liver or other organ tumors (history or present) or clinically significant elevation of alpha-fetoprotein >5 times the normal value; patients with significant biochemical activity (ALT, AST >10 ULN) and total bilirubin >2 ULN; participation in an interventional clinical study.

The enrollment period lasted 18 months with follow-up visits every three months. Based on sample size calculations for parallel groups with binary outcome parameters, the required number of patients in each group was 120. Applying a 10% dropout rate, the final number of study participants in each group was 132, requiring a total of 264 participants.

From February 2023 to July 2024, a total of 121 participants taking COC and BDD were enrolled in the study in Almaty and Almaty region. This interim analysis included 78 participants who completed COC and BDD therapy by September 2024. Anthropometric data (BMI, waist circumference), steatosis and fibrosis levels measured by transient elastography (TE), FibroScan, with CAP, ALT, AST, total cholesterol, triglycerides, and FIB-4 (a non-invasive fibrosis marker) were assessed at the baseline visit and after completing COC and BDD therapy at week 24.

Data presentation and processing methods.

"Waist circumference" and "Total cholesterol" showed normal data distribution, so parametric descriptive methods and tests were applied, while non-parametric methods were used for other parameters. Mean and standard deviation were used to describe "Waist circumference" and "Total cholesterol," while median and interquartile range were used for others. Paired Student's t-test was applied to compare mean values, and the Wilcoxon rank-sum test was used for median values. Frequency analysis was used to describe fibrosis stage, steatosis stage, and interpretation of the FIB-4 test result. To compare frequencies at baseline and week 24, variables were converted into ordinal data and compared using the Wilcoxon rank-sum test. All results were considered statistically significant at $p<0.05$.

Statistical analysis was conducted using Jamovi 2.4.8. The statistical abbreviations and terms used in this article are as follows: Mean - the arithmetic average of the given numbers, SD – standard deviation, Me – median, Min - the smallest value present in the data, Max - the largest value present in the data, Q1 - the lower quartile, the value under which 25% of data points are found when arranged in increasing order, Q3 - the upper quartile, or third quartile, the value under which 75% of data points are found when arranged in increasing order, P-value - defined as the probability, under the assumption of no effect or no difference (null hypothesis), of obtaining a result equal to or more extreme than what was observed.

Results

Over 24 weeks of COC and BDD administration, a statistically significant reduction was observed in ALT levels (U/mL) from 32.4 [19-51.5] to 20.1 [14.9-28.4] ($p<0.001$), triglycerides from 1.4 [1.1-2.2] to 1.3 [1.0-2.0] mmol/L ($p=0.007$), steatosis level based on TE (dB/m) from 304 [268-325] to 283 [246-312] ($p<0.001$), and fibrosis level (kPa) from 6.5 [5.3-8.3] to 6.0 [4.7-7.2] ($p=0.022$).

AST levels showed a slight increase over time: median at the first visit was 23.3 [17.9-38.6], and at week 24, the median was 23.5 [19.1-28.4] mmol/L ($p=0.021$), but at week 24, the variation remained within reference values. The median BMI decreased over 24 weeks from 30.4 to 29.8 kg/m²; however, these differences were not statistically significant ($p=0.214$). Changes in waist circumference over time could not be reliably assessed ($p=0.943$).

The frequency of grade 3 fibrosis based on TE data decreased from 8.1% to 1.4%, and grade F2 fibrosis from 27% to 21.4% ($p=0.022$) over 24 weeks. The frequency of F1 fibrosis increased from 28.4% to 32.9%, and F0 from 35.1% to 42.9%, indicating improvements in fibrosis markers after four weeks of COC and BDD administration.

The frequency of severe steatosis S3 according to TE data decreased from 52.7 to 45.7%, S2 degree also decreased from 29.7 to 22.9%. At the same time, the frequency of a milder degree S1 increased from 17.6 to 21.4% and previously absent cases with S0 – 10% appeared at 24 weeks of treatment with COCs and BDD ($p=0.001$).

When comparing total cholesterol data (Table 1) and interpreting the FIB-4 test results over time, no statistically significant differences were observed (Table 2).

Table 1.

Dynamic changes in indicators of a patient group taking COC and BDD who completed 24-week follow-up.

Indicator	Visit				P value
	Screening		24 weeks		
	Me [Q1-Q3] / Mean±SD	Min-Max	Me [Q1-Q3] / Mean±SD	Min-Max	
BMI, kg/m2	30,4 [28,1-33,1]	22,4-43,1	29,8 [27,3-32,4]	20,7-44,6	0,214
Waist circumference, cm	105±12,5	71-150	105±12,5	73-150	0,943
Fibrosis, kPa	6,5 [5,3-8,3]	3,1-21,1	6 [4,7-7,2]	3-25,8	0,022
Steatosis, dB/m	304 [268-325]	240-400	283 [246-312]	7,1-400	<0,001
AST, U/l	23,3 [17,9-38,6]	1,1-229	23,5 [19,1-28,4]	10-104	0,021
ALT, U/l	32,4 [19-51,5]	8-305	20,1 [14,9-28,4]	8,2-88,7	<0,001
Total cholesterol, mmol/l	5,4±1	3-8,2	5,3±0,9	2,9-8	0,392
Triglycerides, mmol/l	1,4 [1,1-2,2]	0,5-4,2	1,3 [1,0-2,0]	0,5-10,7	0,007
FIB-4 test result	1,1 [0,9-1,3]	0,28-7,5	1,3 [0,9-1,6]	0,21-8,8	0,051

Table 2.

Changes in the dynamics of the FIB-4 test results while taking COC and BDD.

Interpretation of FIB-4 test result	Screening		24 weeks		P
	n	%	n	%	
No significant fibrosis	38	80.9 %	35	63.6 %	0,071
Gray zone	8	17.0 %	18	32.7 %	
Fibrosis stage 4-6 on the Ishak scale	1	2.1 %	2	3.6 %	

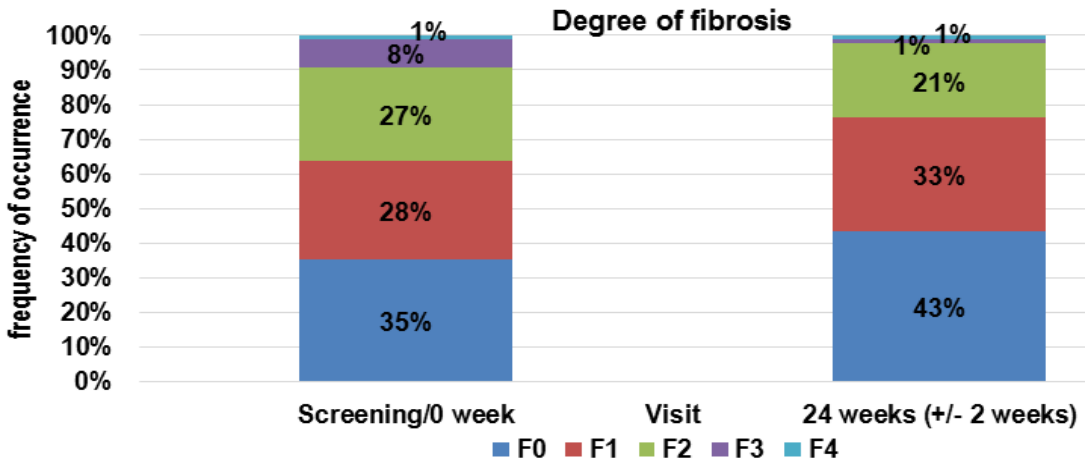


Diagram 1. Frequency of fibrosis according to TE data over time while taking COC and BDD.

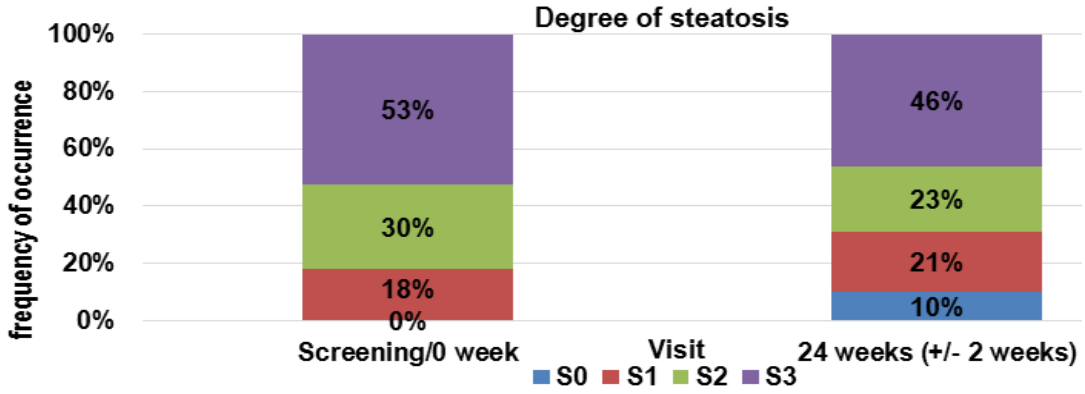


Diagram 2. Frequency of steatosis according to TE data in dynamics against the background of COC and BDD intake.

Discussion

The complex of carnitine orotate and BDD is a pharmaceutical agent used as part of combination therapy for liver diseases. It exhibits detoxifying, antioxidant, and metabolic effects, contributing to the maintenance and restoration of liver function. The drug exerts both functional and histological reparative effects on damaged hepatocytes and acts as a lipotropic factor in hepatic steatosis. It promotes β-oxidation of free fatty acids and their metabolism within hepatocyte mitochondria. The synergistic action of its components enhances glycogen storage, synthetic, and antitoxic functions of the liver. Furthermore, the drug increases hepatic cell sensitivity to insulin, facilitates its secretion, and normalizes ALT levels in the blood, which are elevated due to various liver diseases.

An interim analysis of the observational study KASVM-01 confirmed the potential of COC and BDD in the treatment of MAFLD. The study data demonstrate significant improvements in key biochemical, anthropometric, and instrumental parameters in patients who completed a 24-week therapy course.

A statistically significant reduction in ALT levels was observed over the 24-week treatment period with COC and BDD, indicating a reduction in hepatic inflammation. This effect is further supported by decreased triglyceride levels and hepatic steatosis grade as assessed by transient elastography (TE). These changes are mediated by the positive impact of COC and BDD on β-oxidation of fatty acids in mitochondria, thereby improving lipid metabolism by enhancing fatty acid uptake and consequently reducing lipotoxicity. *Zhang et al.* (2020) [24] and *Li N & Zhao H* (2021) [13] suggest that inhibition of β-oxidation may potentially contribute to reduced mortality in patients with metabolic risk factors upon prolonged administration of COC and BDD [19].

Additionally, the reduction in fibrosis severity, as determined by TE, particularly the decrease in the prevalence of advanced fibrosis (F3) from 8.1% to 1.4%, indicates a favorable long-term prognosis. The increase in mild fibrosis cases (F0 and F1) alongside the decrease in more severe forms supports the potential antifibrotic effect of COC and BDD. This finding aligns with experimental data demonstrating the beneficial role of carnitine in fibrosis regression in the liver [4,14,17,19].

Reducing hepatic fat accumulation in MAFLD is a key aspect of preventing disease progression. Excess lipid accumulation in hepatocytes promotes inflammation, fibrosis, and increases the risk of progression to cirrhosis or hepatocellular carcinoma. Reducing hepatic steatosis not only improves liver function but also decreases cardiometabolic risks, which is particularly important for patients with comorbid obesity and type 2 diabetes. The reduction in severe steatosis cases (S3) and the increase in mild steatosis (S1) or its complete absence (S0) underscore the efficacy of COC and BDD in reducing hepatic fat infiltration. This effect is consistent with the results of the CORONA study conducted by Korean colleagues in patients with type 2 diabetes [3].

Special attention should be given to the impact of COC and BDD on anthropometric parameters. Carnitine plays a crucial role in the transport of fatty acids into mitochondria, where they undergo oxidation with energy release, thereby contributing to lipolysis [23]. Additionally, biphenyldimethyl dicarboxylate activates enzymes involved in lipolysis, collectively leading to a reduction in fat accumulation in the body [7].

A systematic review previously demonstrated that L-carnitine supplementation may contribute to improvements in body weight and body mass index (BMI), particularly in overweight and obese individuals [2].

In the present study, the interim analysis showed a reduction in BMI from 30.4 to 29.8 kg/m². However, this change did not reach statistical significance, which may be due to the limited duration of observation. Nonetheless, the observed trend suggests that these changes may be attributed not only to lifestyle modifications but also to COC and BDD therapy. A longer follow-up and further analysis are required for an objective assessment of this effect.

It should be noted that the presented results are interim and based on data from a cohort of patients receiving COC and BDD in routine clinical practice. The final study analysis will include an evaluation of the efficacy of COC and BDD in managing MAFLD, as well as an inter-cluster comparison to demonstrate the internal validity of the findings and subgroup homogeneity. Despite existing publications supporting the efficacy of COC and BDD in MAFLD therapy [3,8,9,11,20,22], this study is the first to present real-world clinical practice data from the Republic of Kazakhstan.

Thus, the interim findings of the KASVM-01 study demonstrate the promise of COC and BDD in MAFLD treatment, particularly in reducing hepatic inflammation, steatosis, and fibrosis. However, a final assessment of the efficacy of these drugs requires further analysis, including long-term patient follow-up and comparative evaluation with other therapeutic approaches.

Conclusion

The interim analysis results demonstrate that COC and BDD exert a comprehensive positive effect on key parameters in MAFLD patients, including reductions in steatosis and fibrosis. However, for a definitive assessment of treatment efficacy and long-term safety, continued study and confirmation of the obtained data at later observation stages are required. Despite these promising results, additional research is necessary to evaluate the effectiveness of COC and BDD in MAFLD therapy.

The results presented in this publication represent interim data obtained from the cohort receiving COC and BDD for MAFLD as part of routine clinical practice. The final analysis will include an assessment of the effectiveness of COC and BDD in routine MAFLD management between study cohorts, as well as inter-cluster comparisons to demonstrate the internal validity of the results and subgroup homogeneity within clusters. Although the positive experience of using COC and BDD in MAFLD therapy has been extensively covered in prior publications [3, 8,9,17,20,22], this study is the first to present real-world application results of COC and BDD in a patient population receiving treatment as part of routine clinical practice in Kazakhstan.

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GENETIC ANALYSIS OF TP53 AND CTNNB1 MUTATIONS IN PEDIATRIC MEDULLOBLASTOMA: A STUDY FROM KAZAKHSTAN

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Abstract

Background: Medulloblastoma is the most common malignant pediatric brain tumor, exhibiting significant genetic heterogeneity. Mutations in TP53 and CTNNB1 have been implicated in tumorigenesis, prognosis, and treatment response. However, their precise role in medulloblastoma remains incompletely understood. This study aimed to analyze TP53 and CTNNB1 variants in Kazakhstani pediatric medulloblastoma patients and assess their clinical significance.

Methods: A retrospective analysis was conducted on 33 pediatric medulloblastoma cases from 2015 to 2023. Formalin-fixed paraffin-embedded (FFPE) tumor tissues were used for DNA extraction and Sanger sequencing of TP53 (exons 4, 5, 6, 7, 8) and CTNNB1 (exons 3, 4). Genetic variants were classified using ClinVar, ACMG guidelines, and AMP classification. Statistical associations between mutations, clinical features, and outcomes were assessed.

Results: Among 28 successfully sequenced cases, seven TP53 variants were identified: c.214_215delinsTG (p.Pro72Cys), c.215_216delinsGT (p.Pro72Arg), c.300G>A (p.Gln100=), c.356C>G (p.Ala119Gly), c.357C>G (p.Ala119=), c.782+10C>G (splice-region), and c.817C>G (p.Arg273Gly). The p.Pro72Arg variant was significantly associated with metastasis ($p = 0.008$). The c.356C>G (p.Ala119Gly) variant, previously linked to Li-Fraumeni syndrome, was detected in one case. No variants were found in exons 3 and 4 of CTNNB1.

Conclusion: This study highlights the role of TP53 mutations in medulloblastoma progression, particularly their association with metastasis. The absence of CTNNB1 mutations suggests that WNT pathway activation may be rare in this cohort. Further studies with larger sample sizes and functional validation are needed to clarify the prognostic and therapeutic implications of TP53 mutations in pediatric medulloblastoma.

Keywords: *Medulloblastoma, TP53, CTNNB1, pediatric brain tumor, genetic mutations, Sanger sequencing.*

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Резюме

ГЕНЕТИЧЕСКИЙ АНАЛИЗ МУТАЦИЙ TP53 И CTNNB1 ПРИ МЕДУЛЛОБЛАСТОМЕ У ДЕТЕЙ: ИССЛЕДОВАНИЕ В КАЗАХСТАНЕ

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Введение: Медуллобластома — самая распространённая злокачественная опухоль головного мозга у детей, характеризующаяся значительным генетическим разнообразием. Мутации в генах TP53 и CTNNB1 играют роль в опухолеобразовании, прогнозе и ответе на лечение. Однако их точная роль при медуллобластоме до конца не изучена. Целью настоящего исследования явилось изучение вариантов TP53 и CTNNB1 у казахстанских детей с медуллобластомой и оценка их клинического значения.

Методы: Был проведён ретроспективный анализ 33 случаев детской медуллобластомы за период с 2015 по 2023 год. Для экстракции ДНК и последующего секвенирования по Сэнгеру генов TP53 (экзоны 4, 5, 6, 7, 8) и CTNNB1 (экзоны 3, 4) использовались опухолевые ткани, фиксированные в формалине и залитые в парафин (FFPE). Генетические варианты классифицировались согласно базе данных ClinVar, рекомендациям ACMG и классификации AMP. Статистическая связь между мутациями, клиническими характеристиками и исходами была проанализирована.

Результаты: Из 28 успешно секвенированных образцов были выявлены семь вариантов TP53: c.214_215delinsTG (p.Pro72Cys), c.215_216delinsGT (p.Pro72Arg), c.300G>A (p.Gln100=), c.356C>G (p.Ala119Gly), c.357C>G (p.Ala119=), c.782+10C>G (область сплайсинга) и c.817C>G (p.Arg273Gly). Вариант p.Pro72Arg показал значимую ассоциацию с метастазированием (p = 0.008). Вариант c.356C>G (p.Ala119Gly), ранее связанный с синдромом Ли-Фраумени, был выявлен в одном случае. В экзонах 3 и 4 гена CTNNB1 мутаций не обнаружено.

Заключение: Данное исследование подчёркивает роль мутаций TP53 в прогрессировании медуллобластомы, в особенности их связь с метастазированием. Отсутствие мутаций в CTNNB1 указывает на редкость активации WNT-пути в данной когорте. Для более точной оценки прогностического и терапевтического значения мутаций TP53 при детской медуллобластоме необходимы дальнейшие исследования с большим числом пациентов и функциональной валидацией.

Ключевые слова: *медуллобластома, TP53, CTNNB1, опухоль головного мозга у детей, генетические мутации, секвенирование по Сэнгеру.*

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Түйіндеме

TP53 ЖӘНЕ CTNNB1 МУТАЦИЯЛАРЫНЫҢ БАЛАЛАРДАҒЫ МЕДУЛЛОБЛАСТОМАСЫНДА ГЕНЕТИКАЛЫҚ ТАЛДАУЫ: ҚАЗАҚСТАНДА ЗЕРТТЕУ

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Кіріспе: Медуллобластома — балалар арасында ең жиі кездесетін қатерлі ми ісігі болып табылады және генетикалық тұрғыдан алғанда айтарлықтай әртүрлілікпен сипатталады. TP53 және CTNNB1 гендеріндегі мутациялар ісіктің пайда болуына, болжамына және емге жауап беруіне әсер етуі мүмкін. Алайда, бұл мутациялардың медуллобластома кезіндегі нақты рөлі толық анықталмаған. Осы зерттеудің мақсаты — Қазақстандық балалар арасындағы медуллобластома жағдайларында TP53 және CTNNB1 гендерінің варианттарын талдап, олардың клиникалық маңыздылығын бағалау.

Әдістер: 2015 жылдан 2023 жылға дейінгі аралықта балалар арасындағы 33 медуллобластома жағдайына ретроспективті талдау жүргізілді. Формалинмен бекітіліп, парафинге салынған (FFPE) ісік тіндерінен ДНҚ бөліп

алынып, TP53 (4, 5, 6, 7, 8-экзондар) және CTNNB1 (3, 4-экзондар) гендеріне Сэнгер секвенирлеуі жүргізілді. Генетикалық варианттар ClinVar дерекқоры, ACMG нұсқаулығы және AMP классификациясы бойынша сипатталды. Мутациялар мен клиникалық көрсеткіштер арасындағы статистикалық байланыстар талданды.

Нәтижелер: Сәтті секвенирленген 28 жағдайдың ішінде TP53 генінің келесі жеті варианты анықталды: c.214_215delinsTG (p.Pro72Cys), c.215_216delinsGT (p.Pro72Arg), c.300G>A (p.Gln100=), c.356C>G (p.Ala119Gly), c.357C>G (p.Ala119=), c.782+10C>G (сплайсинг аумағы), және c.817C>G (p.Arg273Gly). p.Pro72Arg варианты метастазбен статистикалық түрде сенімді байланыс көрсетті (p = 0.008). Бұған дейін Ли-Фраумени синдромымен байланыстырылған c.356C>G (p.Ala119Gly) варианты бір науқаста анықталды. CTNNB1 генінің 3 және 4-экзондарында ешқандай мутация табылған жоқ.

Қорытынды: Бұл зерттеу TP53 мутацияларының медуллобластоманың өршуіндегі, әсіресе метастазбен байланысындағы рөлін көрсетеді. CTNNB1 мутацияларының болмауы WNT жолының активациясы бұл когортада сирек кездесетінін білдіреді. TP53 мутацияларының болжамдық және терапиялық мәнін нақтылау үшін үлкенірек үлгі көлемімен және функционалдық зерттеулермен қосымша жұмыстар қажет.

Түйінді сөздер: *медуллобластома, TP53, CTNNB1, балалар ми ісігі, генетикалық мутациялар, Сэнгер секвенирлеуі.*

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Introduction

Medulloblastoma, the most common malignant brain tumor in children, represents a significant challenge in pediatric oncology due to its aggressive nature and the complexity of its treatment. Arising from the cerebellum or posterior fossa, this tumor accounts for approximately 20% of all pediatric brain tumors. Its incidence peaks between ages 3 and 8, highlighting a critical period in child development where the impact of both the disease and its treatment can be profound. Despite advancements in multimodal treatment approaches, including surgery, radiation, and chemotherapy, medulloblastoma remains a leading cause of cancer-related morbidity and mortality in children. Recent strides in molecular biology have begun to unravel the genetic and epigenetic underpinnings of this heterogeneous disease, paving the way for more targeted and less toxic therapeutic strategies [12]

However, even in world medicine, the practical use of such approaches is limited. There are currently 4 major genetic types of medulloblastoma with many subtypes, in this connection, some hypotheses have been put forward about the deescalation of therapy [20].

The genetic landscape of pediatric cancers significantly differs from adult cancers, characterized by fewer somatic mutations and a higher frequency of germline alterations in cancer predisposition genes. Pediatric tumors frequently present unique genetic alterations, including gene fusions, enhancer hijacking, and structural variations such as chromothripsis, adding complexity to their genomic profiles. These complexities underscore the need for molecularly targeted diagnostic and treatment strategies [23].

Genetic research plays a pivotal role in advancing the understanding and treatment of medulloblastoma, particularly in pediatric patients. This malignant brain tumor, which primarily affects children, has been linked to several genetic syndromes, including Li-Fraumeni and Gorlin syndromes. However, the specific predisposition genes contributing to medulloblastoma risk remain incompletely defined.

Building on this foundation, recent studies have underscored the importance of germline predisposition in medulloblastoma, revealing that inherited genetic mutations play a more significant role than previously recognized. The largest systematic analysis of genetic susceptibility in medulloblastoma involved screening 110 known cancer predisposition genes in a large patient cohort. They identified six genes, APC, PTCH1, SUFU, TP53, BRCA2, and PALB2, that exhibited significantly higher mutation rates in medulloblastoma patients compared to a control group of 58,000 healthy individuals [23]

Expanding on these findings, ongoing research is now focusing on the molecular properties of medulloblastoma to develop novel therapeutic strategies and refine existing treatment protocols. By further characterizing the genetic landscape of this pediatric brain tumor, scientists aim to uncover additional inherited mutations and epigenetic modifications that may inform both prognosis and treatment approaches. A deeper understanding of the interplay between germline and somatic genetic alterations is crucial for advancing precision medicine in medulloblastoma, with the ultimate goal of improving patient outcomes [25].

Medulloblastoma exemplifies genetic complexity, with four distinct molecular subgroups, WNT, SHH, Group 3, and Group 4, each defined by specific genomic alterations. The genetic mechanisms of Group 3 and Group 4 tumors remain particularly unclear, highlighting the importance of molecular characterization for diagnosis and therapy [19, 26].

Among key genes frequently implicated in pediatric cancers, TP53 and CTNNB1 play critical roles. TP53, a well-known tumor suppressor gene, is frequently mutated in various pediatric tumors, including subsets of medulloblastoma, particularly within the SHH subgroup. Germline TP53 mutations predispose individuals to Li-Fraumeni syndrome, characterized by increased cancer risk, including medulloblastoma. TP53 mutations in medulloblastoma are often linked with chromothripsis events, significantly contributing to tumor pathogenesis and associated with poor clinical outcomes [22, 26].

CTNNB1 encodes β-catenin, a key component of the canonical WNT signaling pathway. Mutations in CTNNB1 are hallmark genetic events in WNT-activated medulloblastomas.

Somatic mutations in exon 3 of CTNNB1 lead to constitutive activation of WNT signaling, promoting uncontrolled cellular proliferation. Notably, the presence of germline APC mutations, responsible for familial adenomatous polyposis, also strongly correlates with the WNT subgroup, although such mutations represent only a small fraction of overall medulloblastoma cases [22, 26].

Considering the pivotal roles of TP53 and CTNNB1 in pediatric tumor biology, targeted sequencing of these genes is crucial for deeper insights into their contributions to tumorigenesis and for improving patient stratification and tailored therapeutic approaches. This study aims to further elucidate the genetic basis and clinical implications of mutations in these critical tumor-associated genes, expanding our understanding of pediatric medulloblastoma genetics [14].

Materials and methods

Sample Collection

We retrospectively randomly selected 33 pediatric cases of medulloblastoma that were surgically removed at the National Scientific Center of Neurosurgery (Astana, Kazakhstan), between 2015 and 2023. These cases were available for analysis. All available specimens consisted of formalin-fixed paraffin-embedded (FFPE) tumor tissues. Histological diagnosis for all cases was reviewed at the Department of Tumor and Diagnostic Pathology, Nagasaki University (Nagasaki, Japan) according to the diagnostic criteria of the WHO classification of tumors of the central nervous system (2021).

Ethical approval for this study was obtained from the Local Ethics Committee of Astana Medical University (№24 of November 11, 2022 of Protocol №2), and written informed consent was obtained from the parents or legal guardians of all patients in accordance with the Declaration of Helsinki.

DNA Extraction

For the analysis of p53 and CTNNB1 mutations, genomic DNA (gDNA) was individually extracted from FFPE tissues by macrodissection. Each 10 μm thick FFPE section was deparaffinized in 80% xylene in a tube. The deparaffinized sample was then washed twice with absolute ethanol and centrifuged at 15,000 g for 15 minutes at 20°C. After drying, the samples were digested with proteinase K overnight at 56°C. DNA extraction was performed using the Maxwell RSC DNA FFPE Kit (Promega, Madison, Wisconsin, USA) and the Maxwell RSC Instrument (Promega) according to the manufacturer's protocol. The concentration of double-stranded DNA was quantitatively determined using the QuantiFluor ONE dsDNA system (Promega).

Sequencing and bioinformatics

For the analysis of gene mutations, MB components were microdissected from each FFPE section and transferred separately into tubes. DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) and checked for genetic alterations. Details of the PCR conditions for detecting genetic alterations are summarized in Table 1.

Table 1.

Details of Genetic Alteration Analyses.

Gene	Exon	Primer sequence	Annealing temperature, *C	Amplication size, bp	# of cycles
p53	Exon 4	5'-TCTGACTGCTCTTTTCACCCA-3'	60	360	35
		5'-TGGAAGCCAGCCCCTCAG-3'			
	Exon 5	5'-ACGCCAACTCTCTCTAGCTC-3'	60	540	35
		5'-AACCAGCCCTGTCGTCTC-3'			
	Exon 6	5'-CTGCTGCTTATTTGACCTCCC-3'	60	190	35
		5'-ATCTCCCAACCTCGTGATCC-3'			
	Exon 7	5'-TTGGGCCTGTGTTATCTCCT-3'	60	300	35
		5'-GGGTCAGAGGCAAGCAGA-3'			
	Exon 8	5'-GGACCTGATTTCCTTACTGCC-3'	60	300	35
		5'-GCTTCTTGTCCTGCTTGCTT-3'			
CTNNB 1	Exon 3	5'-TCTGCTTTTCTTGGCTGTCT-3'	63	480	45
		5'-GTTCTCAAAACTGCATTCTGACT-3'			
	Exon 4	5'-TGCTGAACTGTGGATAGTGAGT-3'	63	480	45
		5'-TCCCCTTGAGCATTTACTTCAA-3'			

Amplicon aliquots were treated with Exo-SAP-IT (USB Corp., Cleveland, OH, USA) and sequenced on an ABI Prism 3130 automated capillary DNA sequencer (Applied Biosystems, Foster City, California, USA) using the BigDye Terminator cycle sequencing ready reaction kit 3.1 (Applied Biosystems).

Statistical analyses. Statistical analyses were performed using Jamovi software (version 2.6.17). Categorical variables were analyzed using or Chi-square tests. The association between genetic variants and clinical characteristics, including tumor stage, metastasis, therapy response, and survival outcomes, was assessed. A p-value <0.05 was considered statistically significant

Results

Total 33 pediatric patients diagnosed with medulloblastoma were included in this study (Table 2). The mean age at diagnosis was 8.64 years (SD = 4.25, range = 1–17 years, median = 8 years). The cohort consisted of 22 males (66.7%) and 11 females (33.3%).

Tumor staging was determined according to the TNM classification. Two patients (6.1%) were classified as T1, 15 patients (45.5%) as T2, three patients (9.1%) as T3A, ten patients (30.3%) as T3B, and three patients (9.1%) as T4. Metastatic disease was observed in nine patients (27.3%), with 24 patients (72.7%) classified as M0, one patient (3.0%) as M1, two patients (6.1%) as M2, and six patients (18.2%) as M3.

Following tumor resection, tumor size classification was recorded. Thirteen patients (39.4%) had S1 tumors, ten patients (30.3%) had S2 tumors, eight patients (24.2%) had S3 tumors, and two patients (6.1%) had S4 tumors. Magnetic resonance imaging (MRI) volumetric assessment showed that 14 patients (42.4%) had no residual tumor (0 cm^3), while eight patients (24.2%) had a residual tumor volume of 1 cm^3, nine patients (27.3%) had 2 cm^3, and two patients (6.1%) had 4 cm^3.

Table 2.

The clinical characteristics of pediatric medulloblastoma patients in Kazakhstan.

Variable		n	%
Gender	Male	22	33.3
	Female	11	66.7
Initial tumor size	T1	2	6.1
	T2	15	45.5
	T3A	3	9.1
	T3B	10	30.3
	T4	3	9.1
Metastasis	M0	24	72.7
	M1	1	3.0
	M2	2	6.1
	M3	6	18.2
Size after surgery	S1	13	39.4
	S2	10	30.3
	S3	8	24.2
	S4	2	6.1
Volume by MRI	0	14	42.4
	1	8	24.2
	2	9	27.3
	4	2	6.1
Histology	Classic	10	30.3
	Nodular	21	63.6
	Extensive nodular	2	6.1
Treatment results	Remission	15	46.9
	Stabilization	13	40.6
	Progression	4	12.5
Outcome	Alive	28	84.8
	Dead	5	15.2

Histopathological analysis revealed that ten patients (30.3%) had the classic medulloblastoma variant, while the majority of patients (63.6%) had the nodular variant. Two patients (6.1%) had the extensive nodular variant.

Patients underwent different treatment regimens, including chemotherapy alone, which was administered to seven patients (21.2%), chemotherapy combined with radiotherapy, which was given to 23 patients (69.7%), and chemotherapy with radiotherapy followed by hematopoietic cell transplantation, which was used in three patients (9.1%). At the time of follow-up, 15 patients (46.9%) had achieved remission, while 13 patients (40.6%) exhibited disease stabilization, and four patients (12.5%) experienced disease progression. Overall, 28 patients (84.8%) were alive, while five patients (15.2%) had succumbed to the disease.

DNA sequencing was successfully performed on 28 patients, as five samples were excluded due to poor DNA quality. Analysis of CTNNB1 revealed no any variants in exons 3 and 4. Among the 28 patients whose DNA sequencing was successfully performed, several variants in the TP53 gene were identified. These variants included missense mutations, synonymous changes, and splice-region alterations, primarily located in exons 4, 7, and 8 (Tables 3 and 4). The most frequently detected variants were c.300G>A (p.Gln100=) and c.215_216delinsGT (p.Pro72Arg) in exon 4, with frequencies of 0.64 and 0.68, respectively. Other detected variants included c.214_215delinsTG (p.Pro72Cys), c.356C>G (p.Ala119Gly), c.357C>G (p.Ala119=), c.782+10C>G (splice-region variant in exon 7), and c.817C>G (p.Arg273Gly) in exon 8.

The classification of TP53 variants based on AMP, ACMG, and ClinVar criteria indicated that c.817C>G (p.Arg273Gly) was pathogenic, while c.356C>G (p.Ala119Gly) was likely pathogenic. Other variants, including c.214_215delinsTG, c.215_216delinsGT, and c.357C>G, were categorized as variants of uncertain significance (VUS). The c.300G>A variant was classified as likely benign, with low oncogenic support.

The analysis of TP53 variants in 28 patients revealed significant differences in the distribution of mutations across clinical and pathological variables (Table 5). Among the four most frequently identified variants, c.214_215delinsTG, c.215_216delinsGT, c.300G>A, and c.357C>G, there were no statistically significant differences in their occurrence between male and female patients. The presence of these variants also did not show a significant correlation with patient age, as the distribution remained relatively uniform across different age groups.

Table 3.

Identified variants in TP53 gene (N=28).

Genetic variant	Protein sequence variant	rs	Variant type	Location	f (study)	f (population)
c.214_215delinsTG	p.Pro72Cys	rs730882014	Missense	Exon 4	0.25	N/A
c.215_216delinsGT	p.Pro72Arg	rs878854066	Missense	Exon 4	0.68	N/A
c.300G>A	p.Gln100=	rs1597373952	Synonymous	Exon 4	0.64	N/A
c.356C>G	p.Ala119Gly	rs2073451331	Missense	Exon 4	0.036	N/A
c.357C>G	p.Ala119=	-	Synonymous	Exon 4	0.18	N/A
c.782+10C>G	-	-	Splice region	Exon 7	0.036	N/A
c.817C>G	p.Arg273Gly	rs121913343	Missense	Exon 8	0.071	N/A

Metastasis status was significantly associated with the presence of TP53 variants. Patients with metastatic disease (M1–M3) had a significantly higher frequency of the c.214_215delinsTG variant (66.7%) compared to non-metastatic patients (M0) (13.6%; $p = 0.008$). Similarly, the c.215_216delinsGT and c.300G>A variants were more frequently observed in patients with metastasis, with statistically significant associations ($p = 0.041$ and $p = 0.006$, respectively). However, no significant correlation was observed between metastasis and the c.357C>G variant ($p = 0.264$).

Table 4.

Classification of identified variants in TP53 gene.

Genetic variant	AMP classification	Oncogenic classification	ACMG classification	ClinVar Clinical Significance
c.214_215delinsTG	Tier 2	Uncertain	VUS	Uncertain
c.215_216delinsGT	Tier 2	Moderate Oncogenic Support	VUS	Likely benign
c.300G>A	Tier 3	Low Oncogenic Support	Likely benign	Likely benign
c.356C>G	Tier 1	Low Oncogenic Support	Likely Pathogenic	Likely Pathogenic-VUS
c.357C>G	Tier 2	Uncertain	VUS	-
c.782+10C>G	Tier 3	Uncertain	VUS	-
c.817C>G	Tier 1	Oncogenic	Pathogenic	Pathogenic

Table 5.

Distribution of TP53 variants across clinical and pathological variables.

Variable	c.214_215delinsTG		c.215_216delinsGT		c.300G>A		c.357C>G	
	n (%)	χ^2, p	n (%)	χ^2, p	n (%)	χ^2, p	n (%)	χ^2, p
Gender		0.207,				0.221,		0.05,
Male (n=18)	5 (27.8%)	p=0.649	12 (66.7%)		11 (61.1%)	p=0.638	3 (16.7%)	p=0.825
Female (n=10)	2 (20.0)		7 (70.0%)		7 (70.0%)		2 (20.0%)	
Age group		-		0.109,		0.233,		1.01,
< 4 years (n=4)	1 (25.0%)		3 (75.0%)	p=0.741	3 (75.0%)	p=0.629	0	p=0.314
4-18 years (n=24)	6 (25.0%)		16 (66.7%)		15 (62.5%)		5 (17.9%)	
Metastasis		7.07,		4.17,		7.54,		1.25,
M0 (n=22)	3 (13.6%)	p=0.008	17 (77.3%)	p=0.041	17 (77.3%)	p=0.006	3 (13.6%)	p=0.264
M1-3 (n=6)	4 (66.7%)		2 (33.3%)		1 (16.7%)		2 (33.3%)	
Histology		3.86,		4.93,		7.71,		0.551,
Classic (n=8)	4 (50.0%)	p=0.145	3 (37.5%)	p=0.085	2 (25.0%)	p=0.021	2 (25.0%)	p=0.759
Nodular (n=19)	3 (15.8%)		15 (78.9%)		15 (78.9%)		3 (15.8%)	
Extensive Nodular (n=1)	0		1 (100%)		1 (100%)		0	
Therapy		0.351,		2..30,		2.21,		0.790,
CTX (n=6)	1 (16.7%)	p=0.839	5 (83.3%)	p=0.316	5 (83.3%)	p=0.331	1 (16.7%)	p=0.674
CTX + RTX (n=19)	5 (26.3%)		13 (68.4%)		12 (63.2%)		4 (21.1%)	
CTX + RTX + HCT (n=3)	1 (33.3%)		1 (33.3%)		1 (33.3%)		-	
Treatment results		1.40,		1.88,		1.99,		1.04,
Remission (n=12)	2 (25.0%)	p=0.497	7 (58.3%)	p=0.392	7 (58.3%)	p=0.371	3 (25.0%)	p=0.594
Stabilization (n=12)	4 (33.3%)		8 (66.7%)		7 (58.3)		2 (16.7%)	
Progression (n=3)	0		3 (100%)		3 (100%)		0	
Outcome		1.56,		2.21,		2.59,		1.01,
Alive (n=24)	7 (29.2%)	p=0.212	15 (62.5%)	p=0.137	14 (58.3%)	p=0.107	5 (20.8%)	p=0.314
Dead (n=4)	0		4 (100%)		4 (100%)		0	

Histological subtype analysis showed that the c.214_215delinsTG variant was more frequently observed in patients with the classic subtype (50.0%) compared to the nodular subtype (15.8%), although this association did not reach statistical significance (p = 0.145). A similar trend was observed for the c.215_216delinsGT and c.300G>A variants, with higher frequencies in the nodular subtype, but only the latter variant showed a statistically significant association (p = 0.021). The c.357C>G variant did not demonstrate a significant association with histological subtypes (p = 0.759).

Evaluation of treatment regimens indicated no statistically significant associations between TP53 variants and the type of therapy received. Patients treated with chemotherapy alone, chemotherapy with radiotherapy, and chemotherapy combined with hematopoietic cell transplantation exhibited similar frequencies of TP53 variants. Similarly, treatment response outcomes, including remission, disease stabilization, and progression, were not significantly associated with the presence of the analyzed TP53 variants.

Survival analysis showed that patients harboring the c.215_216delinsGT and c.300G>A variants had a higher prevalence among those who died compared to survivors. However, the observed differences did not reach statistical significance (p = 0.137 and p = 0.107, respectively). The c.214_215delinsTG and c.357C>G variants were found exclusively in surviving patients, but without statistical significance.

Further individual patient analysis revealed that one patient carrying the c.356C>G variant was a male over four years old with a T2, M0 tumor of the classic histological subtype, who achieved remission following chemotherapy, radiotherapy, and hematopoietic cell transplantation and remained alive at follow-up. Another patient harboring the c.782+10C>G splice-region variant was a male over four years old with a T1, M0 nodular tumor, who also achieved remission following chemotherapy and radiotherapy. Two patients with the c.817C>G variant were female, over four years old, and had T2, M0 tumors with either a classic or

nodular histological subtype, both of whom achieved remission following chemotherapy and radiotherapy

Discussion

Medulloblastoma is the most common malignant pediatric brain tumor, with a highly heterogeneous molecular and clinical profile. In this study, we analyzed 33 pediatric patients with medulloblastoma to assess their clinical characteristics, treatment outcomes, and the presence of TP53 and CTNNB1 gene variants. The median age at diagnosis was 8 years, with a male predominance (66.7%). Tumor classification revealed that the majority of cases were T2 (45.5%) or T3B (30.3%), with metastatic disease present in 27.3% of patients. Treatment regimens varied, with most patients receiving a combination of chemotherapy and radiotherapy (69.7%), while hematopoietic cell transplantation was used in a small subset (9.1%). At the time of follow-up, 46.9% of patients had achieved remission, while 15.2% had succumbed to the disease. Genetic analysis identified several TP53 mutations, including missense and splice-region variants primarily located in exons 4, 7, and 8, with significant associations observed between specific mutations and metastasis. Importantly, no any variants were identified in exons 3 and 4 of CTNNB1, suggesting that mutations in these regions do not play a major role in this cohort. These findings contribute to the growing understanding of the molecular landscape of medulloblastoma and its potential impact on disease progression and patient outcomes.

The Role of TP53 in Medulloblastoma

TP53 is one of the key tumor-suppressor genes encoding the p53 protein, known as the "guardian of the genome." It plays a crucial role in regulating the cell cycle, apoptosis, DNA repair, and other processes that protect cells from carcinogenic mutations. Mutations in TP53 disrupt its function, leading to uncontrolled cell growth [8]

Familial Forms: TP53 mutations can be associated with hereditary syndromes, such as Li-Fraumeni syndrome. Children with this syndrome have an increased risk of developing various types of cancer, including medulloblastoma. This is due to the impaired functionality of p53, making brain cells more susceptible to transformation [11].

Prognosis and Clinical Course: TP53 mutations are linked to a more aggressive course of medulloblastoma. These tumors are often characterized by high levels of aneuploidy (abnormal chromosome numbers), poor prognosis, and a higher recurrence rate. Children with TP53-mutated medulloblastomas may have an increased risk of metastasis and a suboptimal response to standard therapies [24].

Prognostic Markers: In some cases, the presence of TP53 mutations can serve as an indicator of a high risk of tumor recurrence or metastasis, which is crucial for determining the intensity of treatment [10].

The Role of β-Catenin in Medulloblastoma

β-Catenin is a key component of the signaling pathway that regulates cell growth and development through the Wnt/β-catenin pathway. Under normal conditions, β-catenin is stabilized in the cytoplasm and activates the transcription of specific genes involved in cell proliferation and differentiation. However, mutations in the CTNNB1 gene can lead to its accumulation in the cell and the activation of oncogenesis-related genes [16].

Mutations and the WNT Subtype: Mutations in the CTNNB1 gene play a crucial role in one of the molecular subtypes of medulloblastoma—the WNT subtype. This subtype is characterized by Wnt/β-catenin pathway activation, promoting cell proliferation and inhibiting apoptosis. CTNNB1 mutations result in persistent β-catenin activation, which can drive tumor growth [9].

Clinical Significance of the WNT Subtype: Medulloblastomas associated with β-catenin mutations generally have a more favorable prognosis compared to other subtypes. These tumors often exhibit a low rate of metastasis and higher long-term survival rates following treatment. Children with this subtype tend to respond well to standard therapies, including surgery, radiation therapy, and chemotherapy [18].

Risk of Recurrence: Although the WNT subtype has a good prognosis, CTNNB1 mutations may still be associated with recurrence in some cases, particularly when treatment does not include targeted therapy aimed at inhibiting Wnt/β-catenin pathway activity [17].

Many ongoing clinical trials have begun to incorporate insights gained from our deeper understanding of the molecular foundations of medulloblastoma: De-escalation of Treatment for WNT Medulloblastoma, Incorporation of Targeted Therapy for SHH Medulloblastoma, Patient Stratification by Subgroup and Disease Risk [13].

Medulloblastoma is a highly heterogeneous pediatric brain tumor with diverse genetic alterations that influence tumor progression, treatment response, and patient outcomes. In this study, we identified several variants in the TP53 gene, including c.214_215delinsTG (p.Pro72Cys), c.215_216delinsGT (p.Pro72Arg), c.300G>A (p.Gln100=), c.356C>G (p.Ala119Gly), c.357C>G (p.Ala119=), c.782+10C>G (splice-region variant), and c.817C>G (p.Arg273Gly). Our findings align with previous studies emphasizing the role of TP53 mutations in pediatric brain tumors and highlight the clinical and functional variability associated with different TP53 variants.

The Pro72Arg (c.215_216delinsGT) variant has been widely studied in different cancer types. This polymorphism has been reported as one of the most common variants in colorectal cancer among Saudi Arabian patients and has been extensively evaluated in the context of cancer risk [1]. However, previous studies have yielded conflicting results regarding its predictive value. *Asadi et al.* (2017) found no significant association between p.Pro72Arg and colorectal cancer risk in the Iranian Azeri population, whereas *Ounalli et al.* (2023) reported that the Pro72 variant was associated with increased susceptibility to chronic lymphocytic leukemia (CLL) and correlated with adverse prognostic markers such as advanced Binet stage, low hemoglobin levels, and thrombocytopenia [2,21]. Moreover, *Bukovac et al.* (2019) reported high prevalence (44.8%) of Pro72 variants among patients with meningiomas [4]. In Li-Fraumeni syndrome, p.Pro72Arg has been associated with earlier tumor onset, with carriers of the Arg allele developing tumors at a younger age than Pro/Pro patients [3]. Although the precise functional consequences of p.Pro72Arg in medulloblastoma remain unclear, its potential impact on tumor progression warrants further investigation.

The c.356C>G (p.Ala119Gly) variant, classified as likely pathogenic, has been detected in individuals with Li-Fraumeni syndrome [5]. While some studies indicate that p.Ala119Gly disrupts TP53 function, experimental data suggest that it remains proficient in growth suppression [6]. This variant is

located in the DNA-binding domain of TP53, a critical region for tumor suppressor activity, and in silico predictions suggest that it may impact RNA splicing. Given that TP53 is frequently mutated in aggressive cancers, further studies are needed to determine whether p.Ala119Gly contributes to tumorigenesis or affects medulloblastoma progression.

The c.817C>G (p.Arg273Gly) variant, located at a mutation hotspot in TP53, has been implicated in various cancers. Li et al. (2014) [15] demonstrated that different p.R273 mutations exhibit distinct functional consequences, with p.R273H and p.R273C promoting tumor cell proliferation, invasion, and drug resistance, whereas p.R273G appears to be less oncogenic. Molecular dynamics simulations suggest that p.R273G has stronger DNA-binding affinity than the other R273 mutations, which may explain its relatively lower oncogenic potential. However, the clinical significance of p.R273G in medulloblastoma remains unclear and requires further validation.

The c.782+10C>G variant is a splice-region alteration, but computational predictions and clinical evidence suggest that it is likely benign [7]. This variant has not been reported in individuals with Li-Fraumeni syndrome, and functional studies have not demonstrated a significant impact on TP53 function. However, given its proximity to a canonical splice site, further functional analyses are necessary to rule out any potential effects on mRNA splicing.

In our study, the presence of TP53 mutations was significantly associated with metastasis, with certain variants, including p.Pro72Cys, p.Pro72Arg, and p.Gln100=, being more frequently observed in metastatic cases. This finding suggests that specific TP53 variants may contribute to tumor dissemination and could serve as potential biomarkers for disease progression. However, no significant associations were found between TP53 mutations and treatment response, highlighting the complexity of TP53's role in medulloblastoma.

One of the limitations of our study is the small sample size, which may have affected the statistical power of our findings. Additionally, the use of FFPE-derived DNA poses challenges in sequencing accuracy due to potential DNA degradation. Further studies with larger cohorts and functional analyses are needed to confirm the impact of these TP53 variants on medulloblastoma prognosis and treatment response.

Conclusion. Our study identified multiple TP53 variants in pediatric medulloblastoma patients, some of which have been previously implicated in cancer progression. The absence of CTNNB1 mutations in exons 3 and 4 suggests that this gene may not play a major role in medulloblastoma pathogenesis in our cohort. Future research should focus on validating the functional consequences of these TP53 variants and exploring their potential as prognostic markers or therapeutic targets in medulloblastoma

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ASSESSMENT OF THE QUALITY OF LIFE OF PATIENTS WITH LUNG CANCER IN THE ABAY REGION

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Abstract

Background and Objectives. Lung cancer is the leading cause of cancer-related mortality worldwide. Due to late-stage diagnosis, the five-year survival rate remains as low as 15%. Disease progression, symptom severity, and treatment-related adverse effects significantly diminish the quality of life (QoL) in these patients. The objective of this study was to assess the quality of life in patients with lung cancer.

Materials and Methods. This prospective study was conducted from May to October 2024 in the Abay region of the Republic of Kazakhstan and included 123 patients diagnosed with lung cancer. Patient-reported quality of life and symptom burden were evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), with scores ranging from 0 to 100.

Results. Overall quality of life (mean score > 50) and functional scales (mean score > 50) were moderate to good. The highest mean score was observed for social functioning (94±11.3), followed by physical functioning (79.73±13.3), cognitive functioning (76.15±19.5), emotional functioning (74.08±22.6), and role functioning (67±15.4).

Conclusions. This study highlights the necessity of conducting multicenter research to assess quality of life in larger populations of lung cancer patients. It underscores that patient-reported outcomes regarding quality of life should be considered essential in developing new healthcare strategies aimed at improving medical care, including treatment, rehabilitation, and palliative support for oncology patients.

Keywords: *lung cancer, quality of life, public health, medicine*.

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Резюме

ОЦЕНКА КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ С РАКОМ ЛЕГКОГО В АБАЙСКОМ РЕГИОНЕ

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Введение и цель. Рак легких является основной причиной смерти от онкологических заболеваний во всем мире. Из-за поздней диагностики 5-летняя выживаемость составляет всего 15%. Прогрессирование заболевания, тяжесть его симптомов и побочные эффекты значительно снижают качество жизни (КЖ) у этих пациентов. Целью данного исследования была оценка качества у пациентов с раком легких.

Материалы и методы. Проспективное исследование, проводившееся в период с мая по октябрь 2024 года области Абай Республики Казахстан, включало 123 пациента с раком легкого. Качество жизни пациентов и бремя симптомов оценивались с использованием опросника качества жизни Европейской организации по исследованиям и лечению рака (EORTC QLQ C-30) (диапазон значений 0–100).

Результаты. Качество жизни (средний балл> 50) и функциональные измерения (средний балл> 50) были умеренными или хорошими. Самый высокий средний балл был зафиксирован по социальному функционированию 94±11.3 балла, за которым следовали физическое функционирование 79.73±13.3 балла, когнитивное 76.15 ±19.5, эмоциональное 74,08±22.6 и ролевое 67±15.4 функционирование.

Выводы. Исследование подчеркивается необходимость проведения многоцентровых исследований, которые позволят оценить качество жизни в более крупных популяциях пациентов с раком легкого, подчеркивая, что отчеты пациентов о качестве жизни следует считать необходимыми для разработки новых стратегий здравоохранения, которые могли бы повысить уровень предоставляемой медицинской помощи с точки зрения лечения, реабилитации или паллиативной помощи онкологическим больным.

Ключевые слова: *рак легкого, качество жизни, общественное здравоохранение, медицина.*

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Түйіндеме

АБАЙ ӨҢІРІНДЕГІ ӨКПЕ ОБЫРЫ БАР НАУҚАСТАРДЫҢ ӨМІР СҮРУ САПАСЫН БАҒАЛАУ

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Кіріспе және мақсаты. Өкпе обыры бүкіл әлемде онкологиялық аурулардан болатын өлімнің негізгі себебі. Диагноздың кеш қойылуының салдарынан науқастардың өмірінің ұзақттығын 5 жылға арттыру деңгейі тек 15%-ты құрайды. Аурудың асқынуы, оның белгілерінің ауырлығы және емдеуге байланысты теріс жанама әсерлер науқастардың өмір сүру сапасын айтарлықтай төмендетеді. Зерттеудің мақсаты – өкпе обырына душар болған науқастардың өмір сүру сапасын бағалау.

Материалдар мен әдістер. 2024 жылдың мамыр айы мен қазан айы аралығында Қазақстан Республикасы Абай облысында жүргізілген перспективалық зерттеуге өкпе обыры диагнозымен 123 науқас қатысты. Науқастардың өмір сүру сапасы мен симптом ауырлығы Еуропалық онкологиялық зерттеулер және емдеу ұйымының өмір сүру сапасын бағалау сауалнамасы (EORTC QLQ C-30) негізінде бағаланды (бағаның диапазоны 0–100).

Нәтижелер. Өмір сүру сапасы (орташа ұпай > 50) және функциялық көрсеткіштер (орташа ұпай > 50) орташа немесе жақсы деңгейде болған. Ең жоғары орташа ұпай әлеуметтік қызмет бойынша 94 ± 11.3 ұпай, одан кейін физикалық қызмет бойынша – 79.73 ± 13.3, когнитивті қызмет бойынша – 76.15 ± 19.5, эмоционалды – 74.08 ± 22.6 және рөлдік қызмет – 67 ± 15.4 ұпай болды.

Қорытынды. Бұл зерттеу өкпе обыры бар науқастардың ауқымдырақ популяциясындағы өмір сүру сапасын бағалауға мүмкіндік беретін көпорталықты зерттеулер жүргізудің қажеттілігін айқындайды және науқастардың өмір сүру сапасы туралы есептер жаңа денсаулық сақтау стратегияларын әзірлеуде маңызды екенін көрсетеді. Осы стратегиялар онкологиялық аурулары бар науқастарға көрсетілетін медициналық көмектің сапасын емдеу, реабилитация немесе паллиативті көмек салаларында арттыруға бағытталуы тиіс.

Түйінді сөздер: *өкпе обыры, өмір сүру сапасы, қоғамдық денсаулық сақтау, медицина.*

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Introduction

According to the International Agency for Research on Cancer, nearly 20 million new cancer cases and 9.7 million cancer-related deaths were recorded in 2022. Lung cancer was the most commonly diagnosed type, accounting for one in eight cancer cases (12.4%) worldwide. Furthermore, lung cancer remained the leading cause of cancer-related mortality, with an estimated 1.8 million deaths (18.7% of all cases). Among men, lung cancer was the most frequently diagnosed malignancy in 33 countries and the primary cause of cancer-related mortality in 89 countries [1]. Among women, lung cancer was the leading cause of cancer-related death in 23 countries. The one-year survival rate for lung cancer patients, regardless of stage at diagnosis, is approximately 41%, but this rate declines to below 13% over a five-year period [2]. In the Republic of Kazakhstan, breast cancer had the highest incidence in 2022 (13%), followed by lung cancer (10%) and colorectal cancer (9%). However, lung cancer remained the leading cause of cancer-related mortality (16%), followed by gastric cancer (12%), colorectal cancer (11%), and breast cancer (8%) [3].

Patients with lung cancer may experience symptoms specific to their disease process, such as cough or dyspnea, as well as more generalized symptoms, including fatigue and loss of appetite [7,14,17,18,11]. However, significant advancements in lung cancer management have occurred over the past decade, including expanded lung cancer screening, improvements in radiotherapy techniques, and therapeutic innovations. These advancements have likely contributed to a documented reduction in lung cancer mortality [8,14,17,18,11,15].

Given the severe course of lung cancer, oncology specialists should focus not only on disease control but also on optimizing patients' quality of life (QoL). Health-related quality of life (HRQoL) is a multidimensional concept that evaluates the functional impact of a patient's health condition and/or treatment. It encompasses physical, role, emotional, social, cognitive, sexual, and spiritual functioning at an individual level [10,11,23,26,28]. HRQoL data serve as a critical parameter for treatment comparisons, support daily clinical decision-making, enhance communication between patients and physicians, and facilitate clinical and economic evaluations to optimize healthcare resource allocation [12].

Patient-reported HRQoL data help clinicians better understand the toxicity and symptoms experienced by patients, as subjective symptoms such as fatigue and pain are often underestimated [3]. Understanding the patient's experience regarding disease-related symptoms and treatment-associated side effects is crucial for improving clinical outcomes [7,24,10,6,13,25,5,16,21].

The objective of this prospective study was to assess the quality of life in patients with lung cancer.

Materials and Methods.

The study sample comprised all lung cancer patients undergoing treatment at the Public Utility Enterprise on the Right of Economic Management «Center for Nuclear Medicine and Oncology» under the Health Department of the Abay Region, Republic of Kazakhstan, between May and October 2024. Inclusion criteria required patients of both sexes, aged 18 years or older, with a confirmed diagnosis of lung cancer, the ability to communicate in Kazakh or Russian, and adequate cognitive function.

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

A total of 123 patients met the inclusion criteria. Demographic characteristics and clinical data related to the disease and treatment were obtained from patients and their medical records.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Semey Medical University (Protocol No. 5, dated December 21, 2023). Written informed consent was obtained from all participants prior to their inclusion in the study.

Quality of Life Assessment

To evaluate quality of life (QoL) and symptom burden, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), version 3.0 [4], was administered after obtaining the necessary authorization. The questionnaire was validated in both Kazakh and Russian languages and was completed by patients. It consists of 30 items and includes functional scales (physical, role, emotional, cognitive, and social functioning), symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/overall quality of life scale. Scores for each scale range from 0 to 100. Higher scores on the functional and global health/QoL scales indicate better functioning and higher quality of life, whereas higher scores on the symptom scales reflect greater symptom burden and distress.

Following a brief explanation of the questionnaire's content and instructions for completion, most patients were able to complete it independently. The average time required to complete the questionnaire was 12 minutes.

Statistical Analysis

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

Results

According to the EORTC QLQ-C30 scale, all functional domain scores exceeded 50 points among lung cancer patients. The highest mean score was recorded for social functioning (94±11.3), followed by physical functioning (79.73±13.3), cognitive functioning (76.15±19.5), emotional functioning (74.08±22.6), and role functioning (67±15.4).

As shown in Table 1, the social functioning score of 94.0 points is a high result, indicating that patients experience minimal limitations in social activities. They can actively participate in social events and maintain relationships with others. The closer the score is to 100, the fewer restrictions in social functioning. The physical functioning score of 79.73 points reflects a good level of physical ability, suggesting that patients retain high functional capacity with minimal limitations in daily activities. A cognitive functioning score of 76.15 points represents a good level of cognitive resilience. Patients do not experience significant difficulties.

Table 1.

Differences in Functional Scale Scores.

Functional Scales Range 0–100	Index (points) Mean (SD)	Total score for the scale	Maximum value	Minimum value
Physical Functioning	79.73	1201	4	1
Role Functioning	67.0	404	4	1
Emotional Functioning	74.08	893	4	1
Cognitive Functioning	76.15	422	4	1
Social Functioning	94.0	849	4	1

with memory or concentration. The emotional functioning score of 74.08 points suggests a relatively high emotional well-being, though some areas for improvement may exist. The role functioning score of 67.0 points indicates moderate limitations in fulfilling usual roles, such as work or daily responsibilities. A score closer to 100 reflects fewer restrictions, whereas a score approaching 0 signifies significant difficulties in performing role-related tasks.

Table 2 presents data on the symptom scale assessment based on the EORTC QLQ-C30 questionnaire.

Table 2.

Symptom Scale Assessment Based on the EORTC QLQ-C30 Questionnaire.

Symptom Scales	Mean, (SD) Range 0–100	Total score for the scale	Minimum value	Maximum value
Fatigue	48.0	900	3	12
Nausea and vomiting	63.0	380	1	4
Pain	100.0	492	1	4
Dyspnea	51.0	311	1	3
Insomnia	39.83	270	1	3
Appetite loss	37.0	260	1	3
Constipation	28.3	227	1	4
Diarrhea	15.7	181	1	3
Financial difficulties	29.0	230	1	3

The Table 2 symptom score of 48 points indicates a moderate level, where symptoms are noticeable but do not reach a critical threshold. Patients may experience episodes of weakness and lack of energy that affect daily activities. Fatigue is not necessarily constant but may worsen at specific times, such as in the evening or after physical exertion. Physicians should carefully assess associated symptoms, including depression, anxiety, sleep quality, and nutritional status. Adjustments to daily routines, sleep improvements, and dietary modifications may help alleviate fatigue.

The nausea and vomiting score of 63 points corresponds to moderately severe symptoms. Patients frequently experience nausea, while vomiting occurs episodically but has a noticeable impact on well-being. These symptoms may lead to reduced appetite, general deterioration of health, and discomfort. It could be a side effect of chemotherapy, radiation therapy, or medication reactions in oncology patients. Pharmacological interventions, such as antiemetic drugs, may be necessary. The pain symptom score of 100 points indicates the maximum level of pain, signifying severe and persistent pain experienced by patients. Pain significantly affects daily activities and necessitates medical treatment. Patients report intense pain that greatly impairs their quality of life, requiring pharmacological management or additional therapeutic interventions. The dyspnea (shortness of breath) score of 51 points suggests a moderate level of breathing difficulty. Although the symptom is present, it does not reach a critical level. Patients experience breathing difficulties during physical exertion (e.g., climbing stairs, brisk walking, or engaging in active movements). Some individuals may report shortness of breath even with minimal activity. While patients do not typically experience significant dyspnea at rest, they may feel breathlessness when speaking or following mild exertion. Episodes of discomfort during deep inhalation, coughing, or a sensation of incomplete inhalation may also occur. Pulmonary function may be partially impaired due to tumor growth, reduced tissue elasticity, pleural effusion, or metastatic involvement. The insomnia symptom score of 39.83 indicates mild to moderate sleep disturbances among patients with lung cancer. Sleep disruption may be attributed to anxiety, treatment-related side effects, pain, or respiratory issues. The loss of appetite symptom score of 37 suggests a moderate level of severity. Patients may occasionally experience appetite reduction, but not to an extent that it becomes a critical concern or a predominant symptom. The constipation symptom score of 28.3 indicates a low severity. Patients may experience constipation occasionally; however, its frequency and intensity are minimal, and the symptom does not significantly impact daily life. The diarrhea symptom score of 15.7 suggests a low degree of severity. While some patients may occasionally experience diarrhea, this symptom does not substantially affect their quality of life. The financial difficulties score of 29 reflects a low level of financial distress. Most patients in the study did not report severe financial burdens related to their illness.

Discussion

According to our study, all functional measurements on the EORTC QLQ-C30 scale exceeded 50 points among patients with lung cancer. The highest mean score was recorded for social functioning (94 points), followed by physical (79.73 points), cognitive (76.15 points), emotional (74.08 points), and role functioning (67 points). These findings are consistent with the study by *Stylianou C. et al.,* where functional measurements also exceeded 50 points, with the highest scores observed for cognitive, emotional, and physical functioning [27]. However, in the study by *Stylianou C. et al.,* social and role functioning had lower scores compared to cognitive, emotional, and physical functioning [27].

The study by *Miller S.V. et al.* demonstrated that, prior to treatment, relatively low general health status and physical functioning scores (79.2 and 87.3 points, respectively) reflected asthenic manifestations [2]. The symptom scale results from our study were as follows: fatigue (48 points), nausea and vomiting (63 points), pain (100 points), dyspnea (51 points), insomnia (39.83 points), loss of appetite (37 points), constipation (28.3 points), diarrhea (15.7 points), and financial difficulties (29 points).

The study by *Stylianou et al.* reported that patients had an average score of <50 on the EORTC QLQ-C30 symptom scales, with the most pronounced symptoms being insomnia, loss of appetite, and fatigue. The lowest scores

were observed for nausea and vomiting, as well as diarrhea. These findings are consistent with our data, where nausea, vomiting, and diarrhea also had relatively low scores; however, pain and dyspnea were rated significantly higher. Similarly, in the study by *Larsson M. et al.,* among 334 patients with lung cancer, the average symptom score was 27.2, with dyspnea, fatigue, and insomnia being the most prevalent symptoms [22]. According to *Lemonnier I. et al.,* among 230 patients with lung cancer, the lowest scores were observed for diarrhea and nausea and vomiting [20].

Numerous studies report that physical symptoms such as dyspnea, fatigue, pain, and insomnia negatively impact the quality of life in patients with lung cancer, whereas social support and resilience are associated with improved quality of life [14,17,18,11,19]. Therefore, oncology specialists should incorporate not only symptom management but also resilience-building and social support into patient treatment plans. Each study has its limitations, including sample size, data collection methods, and population characteristics, which may affect the results and their comparability. Additionally, due to the non-randomized sampling, it is challenging to generalize the findings, as the lack of randomization does not eliminate the possibility that factors other than treatment may influence quality of life and symptom burden.

Conclusions. The findings of our study demonstrated a generally good health status among lung cancer patients. Despite the presence of various disease- and treatment-related symptoms, pain, appetite loss, and fatigue were the most predominant. Our study highlights the necessity of conducting multicenter studies to assess the quality of life in larger populations of lung cancer patients. Moreover, patient-reported outcomes on quality of life should be considered essential for developing new healthcare strategies aimed at improving the standard of care in terms of treatment, rehabilitation, and palliative care for oncology patients.

Study Limitations: *The single-center nature of the study may limit its generalizability, and the absence of long-term follow-up data restricts the assessment of post-discharge outcomes.*

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ЭПИЛЕПСИЯЛЫҚ БЕЛСЕНДІЛІК КЕЗІНДЕ ПАРОКСИЗМАЛЬДЫ ДЕПОЛЯРИЗАЦИЯЛЫҚ ЫҒЫСУ КЛАСТЕРЛЕРІНІҢ ҚҰРЫЛЫМЫНА Kv7 ТҰҚЫМДАС КАЛИЙ КАНАЛДАРЫНЫНЫҢ ИНГИБИТОРЛАРЫ МЕН АКТИВАТОРЛАРЫНЫҢ ӘСЕРІН ЗЕРТТЕУ

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Түйіндеме

Өзектілігі. Эпилепсия ұстамалары гамма-аминомай қышқылы (ГАМҚ) тежегіш жүйесінің әлсіреуінің салдары болып табылады, бұл өз кезегінде нейрондарының өліміне әкелуі мүмкін. Эпилепсияны емдеудің күрделілігі 1000-нан астам геннің экспрессиясымен түсіндіріледі. Эпилептиформды белсенділік негізіндегі клеткалық модельдерді қолдану – эпилепсия табиғатын зерттеу міндетін біршама жеңілдетеді сонымен қатар процестің көптеген қатысушыларының рөлін анықтауға, олардың қатысуымен сигнал беру тізбегін құруға, белсенділігін реттеу механизмдерін анықтауға мүмкіндік береді. Эпилептиформды белсенділікке потенциалға тәуелді кальций каналдары (Kv7) каналдары мен кальций-өткізгіш AMPA рецепторларының әсерінің анықталуы, ғылым саласында үлкен бір қадам бола отырып, гиперқозудың фармакологиялық жолдарын ашады.

Зерттеу мақсаты: Эпилептиформды белсенділіктегі пароксизмальды деполяризациялық ығысу (ПДЫ) кластерлерінің құрылымына Kv7 каналдарының ингибиторы мен активаторларының әсерін анықтау.

Материалдар мен зерттеу әдістері: Тәжірибелерде жаңа туған (1-3 күн) Wistar егеуқұйрықтарының миынан алынған гиппокампалық жасушаларының аралас нейроглиальды культурасы қолданылды. Тәжірибелер гиппокампалық нейрондық культурада өсірудің 12-14 күнінде жүргізілді. Барлық зерттеулер *in vitro* жасушалық деңгейде жүргізілді. Жасушаішілік кальций концентрациясының өзгерісін флуоресценттік микроскопия әдісі арқылы тіркелді. Мембраналық потенциалдың өзгеруі Patch-Clamp әдісі арқылы тіркелді. Алынған нәтижелерді талдау және өңдеу жұмыстары Origin 9.1 және Image J бағдарламалары қолданылды.

Зерттеу нәтижелері: Жүргізілген тәжірибелер кластердің ұзақтығы дискретті (ПДЫ бүтін санына өзгереді) және бақылауда бір кластерге азаятынын көрсетті, бұл стохастикалық процестің кластер индукциясына қатысуын көрсетеді. Kv7 каналдар кластерді қалыптастыруға да, ПДЫ-ның өзіне де қатысады.

Қорытынды: Kv7 тұқымдас калий каналдары ПДЫ кластерінің гиперполяризациядан кейінгі жылдамдығын арттыра отырып, эпилептиформды белсенділіктегі әрекет потенциал жиын ұзақтығын және кальций импульстарының ұзақтығын азайтады. Сондай-ақ, Kv7 каналдарының тікелей активаторлары мен ингибиторлары синхронды жиын белсенділік және Ca^{2+} импульстарының параметрлерін олардың ұзақтығын, амплитудасын өзгертеді, алайда эпилептиформалық белсенділіктегі нейрондардағы деполяризациялық ығысу жиілігі өзгеріссіз қалады.

Түйінді сөздер: *тежегіш нейрондар, әрекет потенциалы, потенциал тәуелді кальций каналдары, спонтанды синхронды активтілік, AMPA рецептор, гиперқозу, эпилепсия, потенциал тәуелді Kv7 калий каналдары.*

Дәйексөз үшін:

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Abstract

IMPLICATIONS OF Kv7 INHIBITORS AND ACTIVATORS OF POTASSIUM CHANNELS ON THE STRUCTURE OF PAROXYSISMAL DEPOLYARISATION SHIFT CLASTERS IN EPILEPTIFORM ACTIVITY

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Relevance: Seizures of epilepsy are a consequence of a weakening of the inhibitory GABAergic system and, due to the presence of positive feedback, can lead to the death of neurons. The complexity of epilepsy treatment is due to the complexity of the process in which the expression of more than 1,000 genes changes. The presence of cellular models of epileptiform activity somewhat simplifies the task of investigating the nature of the phenomenon and allows us to establish the role of many participants in the process, and to build a chain of signal transmission with their participation and to find out the mechanisms of regulation of their activity. The discovery of the involvement of potential-dependent potassium channels (Kv7) and calcium-permeable AMP receptors in epileptiform activity is a definite step in this direction and opens up new ways of pharmacological correction of hyperexcitation.

Aim: To study the effect of Kv7 channel inhibitors and activators on the structure of clusters of paroxysmal depolarization shift (PDS) in epileptiform activity.

Materials and methods: The experiments used a mixed neuroglial culture of hippocampal cells (12-14 DIV) isolated from the brain of newborn (1-3 days old) Wistar rats. All studies were conducted at the cellular level *in vitro*. Changes in intracellular calcium concentration were recorded using fluorescence microscopy. The Patch-Clamp method in the whole-cell configuration was used to register changes in the membrane potential. The analysis and processing of the obtained results was carried out using the Origin 9.1 and Image J programs.

Results and discussion: The experiments show that the cluster duration is discrete (varies by an integer number of PDS) and varies in the control by one PDS, indicating that a stochastic process is involved in cluster induction. Kv7 channels are involved in both cluster formation and the PDSs themselves.

Conclusion: Kv7 family potassium channels decrease the duration of action potential bursts and the duration of calcium pulses during epileptiform activity, increasing the rate of posthyperpolarisation of the PDS cluster. Also direct activators and inhibitors of Kv7 channels change such parameters of synchronous bundle activity and Ca^{2+} impulses as their duration, amplitude, but not the frequency of depolarisation shifts in neurons during epileptiform activity.

Keywords: *inhibitory neurons, action potential, potential-dependent calcium channels, spontaneous synchronous activity, AMPA receptor, hyperexcitation, epilepsy, potential-dependent potassium channels Kv7.*

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Резюме

ИССЛЕДОВАНИЕ ВЛИЯНИЯ ИНГИБИТОРОВ И АКТИВАТОРОВ КАЛИЕВЫХ КАНАЛОВ СЕМЕЙСТВА Kv7 НА СТРУКТУРУ КЛАСТЕРОВ ПАРОКСИЗМАЛЬНОГО ДЕПОЛЯРИЗАЦИОННОГО СДВИГА ПРИ ЭПИЛЕПТИФОРМНОЙ АКТИВНОСТИ

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Актуальность: Приступы эпилепсии являются следствием ослабления тормозной ГАМКергической системы и вследствие наличия положительных обратных связей могут приводить к гибели нейронов. Сложность лечения

эпилепсии обусловлена сложностью процесса, в котором меняются экспрессия более 1000 генов. Наличие клеточных моделей эпилептиформной активности несколько упрощает задачу исследования природы явления и позволяет установить роль многих участников процесса, и выстроить цепочку передачи сигнала с их участием и выяснить механизмы регуляции их активности. Обнаружение участия потенциал-зависимых калиевых каналов (Kv7) и кальций-проницаемых AMPA-рецепторов в эпилептиформной активности является определенным шагом в этом направлении и открывает новые пути фармакологической коррекции гипервозбуждения.

Цель исследования: Изучить влияние ингибиторов и активаторов Kv7-каналов на структуру кластеров пароксизмального деполяризационного сдвига (PDS) при эпилептиформной активности.

Материалы и методы исследования: В экспериментах использовали смешанную нейроглиальную культуру клеток гиппокампа (12-14 DIV), выделенных из головного мозга новорожденных (1–3 дня) крыс линии Wistar. Все исследования проводились на клеточном уровне *in vitro*. Изменения концентрации внутриклеточного кальция регистрировали с помощью метода флуоресцентной микроскопии. Для регистрации изменения мембранного потенциала использовали метод Patch-Clamp в конфигурации whole-cell. Анализ и обработку полученных результатов проводили с помощью программ Origin 9.1 и Image J.

Результаты исследования и обсуждение: Проведенные эксперименты показали, что длительность кластера дискретна (изменяется на целое число PDS) и варьирует в контроле на один кластер, что указывает на участие стохастического процесса в индукции кластера. Каналы Kv7 принимают участие как в формировании кластера, так и самих PDS.

Выводы: Калиевые каналы семейства Kv7 уменьшают длительность пачек потенциалов действия и длительность кальциевых импульсов при эпилептиформной активности, увеличивая скорость постгиперполяризации кластера PDS. А также прямые активаторы и ингибиторы Kv7 каналов меняют такие параметры синхронной пачечной активности ПД и Ca^{2+} импульсов, как их длительность, амплитуду, но не частоту деполяризационных сдвигов в нейронах при эпилептиформной активности.

Ключевые слова: *тормозные нейроны, потенциал действия, потенциал-зависимые кальциевые каналы, спонтанная синхронная активность, AMPA-рецептор, гипервозбуждения, эпилепсия, потенциал-зависимые калиевые каналы Kv7.*

Для цитирования:

Тулеуханов С.Т., Зинченко В.П., Қайрат Б.Қ., Тусупбекова Г.А., Малибаева А.Е. исследование влияния ингибиторов и активаторов калиевых каналов семейства Kv7 на структуру кластеров пароксизмального деполяризационного сдвига при эпилептиформной активности // Наука и Здравоохранение. 2025. Vol.27 (1), С.32-39. *doi 10.34689/SH.2025.27.1.004*

Кіріспе

Эпилепсия мыңдаған ми нейрондарының синхронды қозуының жоғары жиілігімен және әдеттен тыс жоғары деңгейімен бірге жүреді. Эпилепсия - бұл нейрондар тобы гиперқозуының ең жарқын көрінісі (өйткені 1000-нан астам ақуыздың экспрессиясы өзгереді) және мидың әртүрлі аймақтарында пайда болуы мүмкін, сонымен қатар басқа аймақтарды да қамтуы мүмкін [1-3].

Төмен шекті Kv7 типті калий каналдары нейрондардың шамадан тыс қозғыштығын бақылайды, сондықтан бұл каналдардың ингибиторлары эпилепсияға қарсы препараттар, ал активаторлары нейропротекторлар болып табылады. Бұл каналдардың ерекше қабілеттері – қозуды тез уақытта тежелу, төмен шекті деңгейден туындайды (деполяризацияның кішігірім сдысуларында ашылу мүмкіндігі), бұл кішігірім тітіркендіргіштерден қозуды болдырмайды [4, 5].

Қазіргі эпилепсияға қарсы дәрі-дәрмектер жеткіліксіз селективтілікке байланысты күшті жанама әсерлерге ие. Бұл жұмыс белгілі бір нейрондық популяцияларда Kv7 селективті белсендіру жолдарын табуды қамтиды [6-9].

Гиперқозуды тежеуге көптеген әртүрлі калий каналдары қатысады. Әр түрлі калий каналдарының суббірліктерін кодтайтын 90 түрлі ген белгілі. Олардың ішінде біз әдетте G-белоктарымен белсендірілген каналдар тобын (KiR1–6) және потенциал-сезімтал каналдар (Kv1-12) тұқымдасын бөліп аламыз. Барлық каналдардың ішінде Kv7 нейрондық каналдары айтарлықтай ерекшеленеді, оның мутациялары ерте балалық шақта эпилепсияны тудырады. Kv7 эпилепсияны бақылауда жетекші рөл атқарады деп айтуға негіз бар, өйткені Kv7 дигидрохлорид 10,10-бис(4-пиридинилметил)-9 (10H)-антраценон (XE991) каналдарының жоғары селективті антагонисті пейсмейкерлік нейрондарда жоғары жиілікті разрядтарды (~200-300 Гц) мерзімді генерациялау режимін қосады. Бір қызығы, XE991 пресинаптикалық жол қозғалысы ережесі мен постсинаптикалық жауаптың басталуы арасындағы кідірісті арттырады [10-12].

Эпилепсиялық ұстаманың алдындағы нейрондық желідегі "гиперқозу" автоматты тербеліс режимі (interictal spikes in vivo сәйкес келеді) ГАМҚ-тәуелді тежелудің тоқтауы/әлсіреуі немесе ГАМҚергиялық нейрондарының өлімінен туындайды. Ол гиперсинхрондылықпен, төмен жиілікпен, деполяризация импульстарының жоғары амплитудасымен және Ca^{2+} типті base-line импульстарымен сипатталады. Жалпы мидағы эпилептиформды ырғақтар ашылғаннан кейін көп

ұзамай (interictal spikes), бұл тербелістердің/ырғақтың жасушалық корреляциясы бар екендігі дәлелденді, яғни эпилепсия аймағынан алынған ми аймақтарының бөлімдеріндегідей in vitro жасушалық деңгейде байқалады. Бұл режимдегі нейрондар мезгіл-мезгіл (05-0.1 Гц төмен жиілікте) синхронды Ca^{2+} импульстарымен бірге жүретін әрекет потенциал (ӘП) жиілігін (ПДЫ кластерлері) жасайды. ӘП жиілігі екі жоғары жиілікті тербелмелі жүйелерден тұрады, олардың бірі әрекет потенциалы, ал екіншісі баяу пароксизмальды деполяризациялық ығысу (ПДЫ) әрекет потенциал (ӘП) жиілігін басқарады. Әрі қарайғы зерттеулер гиперқозудың бұл түрі ингибиторлық ГАМҚергиялық жүйесінің әлсіреуі нәтижесінде пайда болатынын және эпилепсияда ғана емес, сонымен қатар ишемияда, инсульттерде, Альцгеймер ауруы және Паркинсон ауруында, нейрондық желінің дамуында, мидың травматикалық зақымдануында, нейрондар арасында әртүрлі байланыстар синхронды түрде пайда болған кезде байқалатынын көрсетті. ПДЫ толық жетілген нейрондық желіде даму процестерінің қайталануын бастауға қабілетті деп саналады, мысалы, зақымдану кезінде, мидың шайқалуы кезінде және т.б. Сонымен, инсульттан кейін, бірінші күні үлкен амплитудасы бар синхронды төмен жиілікті импульстар – эпилепсия ұстама алды белгілері болып тіркеледі. Ал эпилепсия ұстамаларының өзі инсульттан кейін бір күннен бір аптаға дейін ғана байқалады.

Осылайша, ПДЫ-дың пайда болу мәселесі және оны басу/реттеу механизмдері гиперқозудың пайда болуын және оның нейрондық өлімдегі рөлін және әртүрлі аурулардағы мидың әртүрлі физиологиялық қозған күйлерінің пайда болуын зерттеуде маңызды болып табылады.

Kv7 типті калий каналдары эпилептиформды белсенділік кезінде гиперполяризацияны бақылауға қатысады деп саналады. Kv7 каналының блокаторы XE991, CP-AMPARs антагонистінің әрекетін ПДЫ кластерлеріне имитациялады. Екі препаратта ПДЫ кластерінің ұзақтығын ұзартады. Өз кезегінде, Kv7 активаторы ретигабин ПДЫ кластерінің ұзақтығын және Ca^{2+} импульсін азайтады. Сонымен қатар, ретигабин ПДЫ кластерінің соңында постгиперполяризацияға әкелді. Осылайша, CP-AMPARs Экспрессиялайтын ГАМҚергиялық нейрондар, басқа ГАМҚергиялық нейрондар постсинаптикалық калий каналдарының белсенділігін модуляциялау арқылы иннервацияланатын глутаматергиялық нейрондардың мембраналық потенциалын реттейді.

Зерттеу материалдары мен әдістері: гиппокамп жасуша культурасы. Тәжірибелерде жаңа туған Sprague– Dawley егеуқұйрықтың миынан (1-3 күн) бөлінген гиппокамп жасушаларының аралас нейроглиальды культурасы қолданылды. Тәжірибе жұмыстары гиппокамп нейрондық культурада өсірудің 12-14 күнінде жүргізілді. Эксперимент алдында жасушалар 30 минут ішінде 28 °C температурада құрамында 156 мМ NaCl, 3 мМ KCl, 2 мМ $MgSO_4$, 1,25 мМ KH_2PO_4, 2 мМ $CaCl_2$, 10 мМ глюкоза HBSS ерітіндісі және 10 мМ HEPES Fura 2 AM (6 мкМ) флуоресцентті зондпен ерітіндісінде жүктелді; pH 7,35. Флуоресценция 0.2 мМ L-аргинин қосылған Хенкс ерітіндісінде тіркелді. Жасуша тығыздығы 15000 кл/$см^2$ болды[13-16].

$[Ca^{2+}]_i$ өлшеу үшін HAMAMATSU C9100 жоғары жылдамдықты монохромды CCD камерасымен жабдықталған Leica DMI6000B инверттелген моторлы микроскопқа негізделген кескінді талдау жүйесі, Leica's ultra-Fast filter Wheels (ауысу уақыты 10-30 мс) қоздырғыш жарық сүзгілерінің жоғары жылдамдықты ауысу жүйесі қолданылды. Leica HC PL apo 20× / 0.7 IMM линзасын қолданды. Флуоресценцияны қоздыру көзі ретінде HBO 103 w/2 жоғары қысымды сынап шамы бар Leica el6000 жарықтандырғышы пайдаланылды. Нейрондардың кальций сигналдары екі толқынды Ca^{2+} сезімтал Fura 2 зондының флуоресценция қарқындылығымен тіркелді. Fura 2 флуоресценциясын қоздыру және тіркеу үшін BP340/30 және BP387/15 қоздыру сүзгілері, FT410 жарық бөлгіші және BP510/84 эмиссиялық сүзгісі бар FU2 (Leica, Германия) жарық сүзгілерінің жинағы пайдаланылды. Екі түрлі каналда алынған уақытша кескіндер сериясы Image J бағдарламасында Time Series Analyzer және RatioPlus бағдарламаларын қолдана отырып өңделді [15-17].

Кескін сериялардың өңдеу кезінде толқын ұзындығы 340 және 380 нм жарықпен қозған кезіндегі Fura 2 флуоресценция сигналдарының қатынасы ретінде көрсетілген жасушаның кальций реакцияларының амплитудасы бағаланды. Графиктер мен статистикалық өңдеу үшін Origin 9.1 бағдарламасы қолданылды. Бір күндік эксперименттер сериясы 5-6 қайталаудан тұрды. Бір тәжірибеде өлшенген жасушалар саны 150-ден 200-ге дейін болды. Жасушалардағы сигналдың бастапқы деңгейі әдетте 0,23 ± 0.07 болды(мұнда және одан әрі орташа ± стандартты ауытқу). Нейрондар астроциттерден синхронды белсенділігі және эксперимент соңында 35 мМ KCl деполяризациясына жылдам Ca^{2+} жауабымен ерекшеленді. Амплитудасы флуоресценция қарқындылығының орташа мәніне сүйене отырып есептелді . Бұл жағдайда орташа өлшеу қателігі 0,04 болды [18-20].

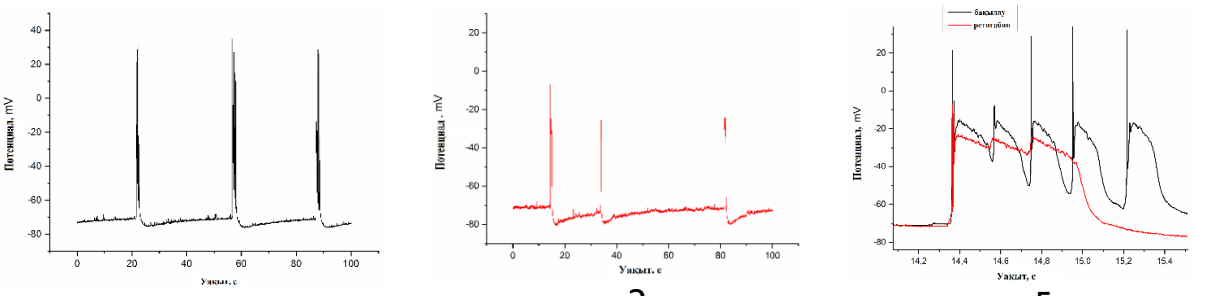
Реагенттерді камерадағы барлық ерітіндіні тез ауыстыруға мүмкіндік беретін арнайы перфузиялық жүйемен қосты, ол камерадағы барлық ерітіндіні толығымен ауыстыруға мүмкіндік береді. Жазу жылдамдығы-секундына 1 кадр. Барлық эксперименттер 28-30 °C температурада орындалады.

Жұмыста: Хенкс ерітінділері, HEPES және бұзау эмбриональды сарысуы (MP Biomedicals, АҚШ); Fura 2/AM, B 27 қоспасы, пропидий йодиді, Hoechst 33342, (Invitrogen, АҚШ); 2-APB, бикукуллин, домой қышқылы, GYKI 52466, UBP302, ATPA, SYM2081, D-AP5, фторвиллардин (FW), гуанфацин (Tocris Bioscience, Ұлыбритания); BCA, PBS, DMEM, форсколин, (Sigma, АҚШ); NH4Cl ("Химмед", Ресей). Рецепторлардың лигандыларын қанықтыру концентрациясында қолданылған.

Статистикалық талдау. Нәтижелер орташа ± стандартты орташа қателік (SEM) немесе жеке жасушалардағы кальций сигналдарының репрезентативті жазбалары ретінде ұсынылған. Суреттерге жазулар: N – белгілі бір экспериментте талданған жасушалар саны, n-тәуелсіз эксперименттер саны. Origin 9.1 бағдарламасы нәтижелерді сызу және статистикалық өңдеу үшін пайдаланылды. Деректер Краскел-Уоллис критерийі арқылы өңделді немесе жұптық салыстырулар (t-тест) қолданылды, айырмашылықтар $P \leq 0.05$ статистикалық мәнімен есептелді.

Зерттеу нәтижелері

Kv7 калий каналдарының ингибиторлары мен активаторларының әсері. Kv7 каналдары ПДЫ реттеуге қатысатынын көрсету мақсатында каналдардың тікелей ингибиторлары мен активаторларын қолданылды.Kv7 ретигабин агонисті қазіргі уақытта антиконвульсант, анальгетик және қабынуға қарсы агент ретінде сынақтан өтуде. 1-суретте бақылауда (эпилептиформды белсенділік жағдайында) және 2,5 мкМ ретигабин қосқаннан кейінгі кластерлер берілген.



А Ә Б

Сурет 1. **Kv7 каналдарының активаторы ретигабиннің ПДЫ кластерінің құрылымына әсері.**
А – Бикукуллин әсер еткен кездегі (эпилептиформды белсенділік) ПДЫ кластерлері;
Ә – Kv7 активаторы ретигабин 2,5 мкМ мөлшерде қосқаннан кейін ПДЫ кластерлері,
Б – ПДЫ кластерлерін салыстыру эпилептиформдық белсенділік жағдайында (қара қисық)
және 2,5 мкМ ретигабин әсерінен кейін (қызыл қисық) /

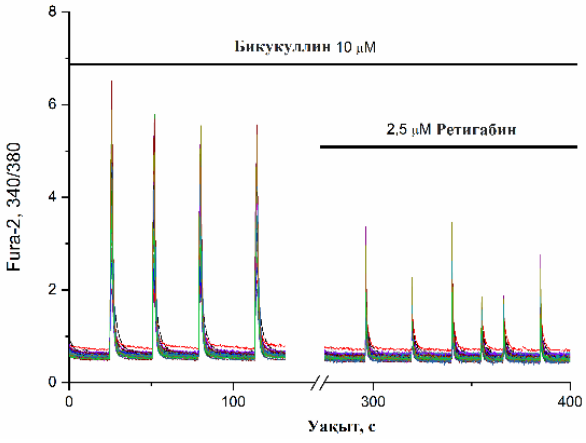
((Figure 1. The effect of the Kv7 channel activator retigabine on the structure of PDS clusters
А – PDS cluster under the influence of bicucullin (epileptiform activity) ; Ә – PDS clusters after addition of the Kv7 activator retigabine 2.5 μm, Б – Comparison of PDS clusters in the case of epileptiform activity (black curve) and after exposure to 2.5 μm retigabine (red curve)).

Бақылауда кластер 5-6 ПДЫ-тен тұрды, активатор қосылғаннан кейін кластердегі ПДЫ саны үшке дейін азайды. Кластердің амплитудасы да біршама азаяды. 2-суретте бақылаудағы Ca^{2+} импульстары (бикукуллин қосылғаннан кейін) және ретигабин қосылғаннан кейін кальций импульстары берілген. Каналдар активаторы Ca^{2+} импульстарының ұзақтығын азайтады және сигнал амплитудасын азайтады. Осылайша, Kv7 кем дегенде кластер және Ca^{2+} сигналдар терминациясына қатысады және олардың ұзақтығын азайтады.

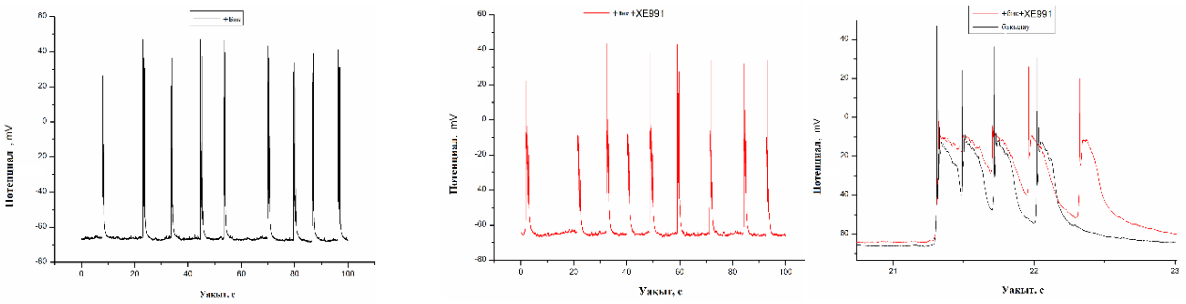
Кластердің ұзақтығы азаяды, кластердегі ПДЫ саны бестен үшке дейін азаяды, кластерден кейінгі гиперполяризация артады. ПДЫ максималды амплитудасы төмендейді.

Ретигабин импульстардың ұзақтығын азайтады және олардың амплитудасын төмендетеді. Ретигабин нейрондардағы калий каналдарының ашылуы арқылы әрекет етеді. Бұл мембрананың тыныштық потенциалын тұрақтандырады және нейрондардың шекті қозғыштығын бақылайды, осылайша потенциалды импульстардың эпилептиформалық әсерінің басталуына жол бермейді.

3-суретте бикукуллин тудырған эпилептиформды белсенділік режимінде нейронның мембраналық потенциалының жазбалары берілген. Бақылаудағы ПДЫ кластерлерінде 3-4 ПДЫ-тен тұрады. Kv7 4-пиридинилметил - 9 (10Н)-антраценон (XE991) блокаторлары гиперполяризация жылдамдығын бәсеңдетеді және қосымша ПДЫ (қызыл қисықтар) пайда болу арқылы ПДЫ кластерінің ұзақтығын арттырады. Ингибитор ПДЫ амплитудасына әсер етпейді, яғни деполяризациялық ығысуға әсер етпейді.



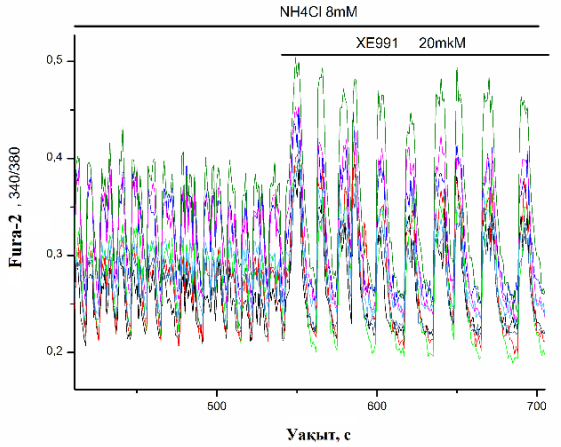
Сурет 2. Эпилептиформды белсенділік кезеңіндегі бақылауда және 2,5 мкМ ретигабина әсерінен кейінгі 37 нейрондағы бикукуллин әсерінен туындаған синхронды Ca^{2+} импульстары /
(Figure 2. Synchronous Ca2 + impulses caused by the action of bicucullin in 37 neurons during the period of epileptiform activity and after exposure to 2.5 μm of retigabine under observation.).



А Ә Б

Сурет 3. Kv7 каналдарының ингибиторы XE991 ПДЫ кластерінің құрылымына әсері.
А - Бикукуллин әсер еткен кездегі (эпилептиформды белсенділік) ПДЫ кластерлері;
Ә – Kv7 блокаторы XE991 10 мкМ мөлшерде қосқаннан кейін ПДЫ кластерлері;
Б – ПДЫ кластерлерін салыстыру эпилептиформдық белсенділік жағдайында (қара қисық) және 10 мкМ XE991 әсерінен кейін (қызыл қисық) /
(Figure 3. The effect of the Kv7 channel inhibitor XE991 on the structure of PDS clusters.
A – PDS clusters during the action of bicuculline (epileptiform activity);
B – PDS clusters after the addition of the Kv7 blocker XE991 at a concentration of 10 μM;
C – Comparison of PDS clusters under epileptiform activity conditions (black curve) and after the effect of 10 μM XE991 (red curve).

Бикукулин хлор және калий каналдарын блоктайтын, ГАМҚ рецепторлардың антагонисты болып табылады. Кластердің ұзақтығы 1 ПДЫ-ке артады. Гиперполяризация жылдамдығы баяулайды. Кластердің гиперполяризациясың фронтары баяуланады.



Сурет 4. 8 мМ NH4Cl қосқанда туындаған эпилептиформды белсенділік кезінде синхронды Ca2+ импульстарына Kv7 каналдарының ингибиторы 20 мкМ XE991 әсері /
(Figure 4. The effect of the Kv7 channel inhibitor XE991 (20 μM) on synchronous Ca^{2+} impulses during epileptiform activity induced by the addition of 8 mM NH_4Cl.).

4-суреттен көріп отырғанымыздай, 8 мМ NH4Cl қосқанда туындаған эпилептиформды белсенділік кезінде синхронды Ca2+ импульстарына Kv7 каналдарының ингибиторы XE991 кальций тербелістері импульстарының ұзақтығын арттырады (шамамен, 6 с-тан 10 с-қа дейін).

Жүргізілген тәжірибелер кластердің ұзақтығы дискретті (ПДЫ бүтін санына өзгереді) және бақылауда бір кластерге азаятынын көрсетті, бұл кластер индукциясындағы стохастикалық процестің қатысуын көрсетеді. Kv7 каналдары кластерді, ПДЫ-ті қалыптастыруда қатысады. ПДЫ кластерінің ұзақтығын Kv7 ингиботоры XE991 көбейтеді, ал Kv7 активаторы ретигабин азайтады. Ингибитор да, активатор да гиперполяризация жүйесіне көбірек әсер етеді және деполяризациялық ығысуға әлсіз әсер етеді. Сонымен қатар, каналдар активаторы ПДЫ кластерінің соңында гиперполяризацияны күшейтеді, бұл инактивацияланған Na+, Ca2+ каналдарын қайта белсендіру үшін қажет.

Талқылау: Kv7 каналдары ПДЫ-ны реттеуге қатысуын көрсету үшін, біз осы каналдардың ингибиторлары мен активаторларын қолдандық. Гиппокамп жасуша культурасында ГАМК(А) - тәуелді тежелуді басуға жауап ретінде нейрондық белсенділіктің синхрондалуы жүреді. Синхрондалу ГАМК секрекциясының импульстарымен және Cl-- каналдарының ашылуымен байланысты қозудың тежелуінің алынып тасталуы есебінен жүреді. Синхронды деполяризация ГАМК(А) рецепторларын бұғаттау арқылы, Ca2+ импульстік амплитудасының жоғарылатады және трансмиттердің бөлінуіне алып келеді. Осылайша, бикукуллин деполяризациялық ығысуды орта есеппен 15 мВ-қа арттырады, бұл тербелістің пайда болуына немесе тербелістерінің синхрондалуына алып келеді. Бұл режимдегі нейронның ӘП өздігінен тоникалық белсенділігі мезгіл-мезгіл ПДЫ кластерлері түріндегі, Ca2+ импульсімен бірге жүретін ӘП-ның спонтанды жиынтық белсенділігімен үзіліп отырады. Кластер екі жоғары жиілікті тербелмелі жүйелерден тұрады, олардың бірі әрекет потенциалы, ал екіншісі, баяу (ПДЫ), ол осы ӘП - ның жиілігін басқарады.

Деполяризациялық сәт деполяризациялық ығысу деп аталады, және ол әдеттен тыс үлкен болғандықтан (≈40 мВ), пароксизмальды деполяризациялық ығысу деп атайды, ал ӘП спонтанды жиынтық белсенділігінін, классикалық тербелістерден ажырату үшін, пароксизмальды деполяризациялық ығысу кластерлері деп атайды. Пароксизмальды деполяризациялық ығысу потенциалының деполяризациялық ыдысуы Na+ каналының қозу потенциалынан төмен аймақта басталып, инактивацияланған Na+ каналдарының реактивация потенциалынан жоғары аймақта аяқталатыны көрсетілген. Сондықтан пароксизмальды

деполяризациялық ығысу көбінесе бір әрекет потенциалына генерацияланады. Мұндай гиперполяризациялық канал ретінде эпилептогенді төмен шекті потенциалды тәуелді Kv7 типті калий каналы болуы мүмкін. Аксонның бастапқы бөлігінде (аксональды төбе аймағында) локализацияланған Kv7 типті калий каналы өзінің қасиеттеріне байланысты тек үлкен деполяризациялық ығысуларды өткізеді және ӘП (кластер) спонтанды белсенділік жиынтығының ұзақтығын анықтайды, өйткені ол осы уақытта инактивацияланған басқа потенциалға тәуелді каналдарға қарағанда ұзағырақ жұмыс істейді. Бұл каналдардың бірегейлігі тек потенциалды ғана емес, сонымен қатар химиялық лигандтарды да, яғни PIP2, G белок және Ca2+- CaM бета-гамма субъбірліктерді басқарудан тұрады. Оның нейрондық қозғыштықты тежеудегі функционалдық маңыздылығы оның KCNQ1, KCNQ4 және KCNQ5 суббірліктеріндегі мутациялар эпилепсияны тудыратындығымен расталады, ал Kv7 каналының агонисті ретигабин ұстаманы басады.

Kv7 активаторы ретигабин қазіргі уақытта ұстамаға қарсы, анальгетикалық және қабынуға қарсы агент ретінде сыналуда. Ретигабин кластердің ұзақтығын қысқартады және пароксизмальды деполяризациялық ығысу кластерінен кейін гиперполяризацияны арттырады. Кластерлердің ұзақтығы ретигабиннің қатысуымен 1,2±0,2 с-тан 0,5±0,2 с-қа дейін азаяды. Пароксизмальды деполяризациялық ығысу құрылымында гиперполяризация фазасы мүлдем жоқ, бұл Kv7 каналдарының кластерлік гиперполяризация және пароксизмальды деполяризациялық ығысу процестеріне қатысуын көрсетеді. Шамасы, пароксизмальды деполяризациялық ығысуды гиперполяризациялайтын каналдарды белсендіру үшін Na+ және K+ каналдарын қайта белсендіруді және ретигабиннің қатысуымен белсенді емес болып қалатын ӘП генерациясын қамтитын оқиғалар тізбегі қажет. Кластердің амплитудасы да біршама төмендейді. Kv7 каналының активаторы Ca2+ импульстарының ұзақтығын және сигнал амплитудасын азайтады. Kv7 каналдары кем дегенде кластерді және Ca2+ сигналын тоқтатуға қатысады және олардың ұзақтығын қысқартады. XE991 кластердің ұзақтығын арттырады және гиперполяризация жылдамдығын төмендетеді. XE991 қатысуымен гиперполяризация жылдамдығы шамамен 3 есе төмендейді. Блокатор пароксизмальды деполяризациялық ығысу амплитудасына әсер етпейді, яғни деполяризациялық ығысуға әсер етпейді. Kv7 канал блокаторы XE991 Ca2+ импульстарының ұзақтығын арттырады. Kv7 каналдары пароксизмальды деполяризациялық ығысу кластерінің қалыптасуына ықпал етеді. Kv7 XE991 блокаторы пароксизмальды деполяризациялық ығысу кластерінің ұзақтығын жоғарлатады, ал Kv7 активаторы ретигабин, керісінше, пароксизмальды деполяризациялық ығысу кластерінің ұзақтығын азайтады. Екі препаратта негізінен гиперполяризацияға әсер етеді ал деполяризациялық ығысуға әсері аз. Сонымен қатар, канал активаторы ПДЫ кластерінің соңындағы гиперполяризацияны күшейтеді. Kv7 каналдарының тікелей блокаторлар мен активаторларының әсері ПДЫ кластерінің ұзақтығын реттейді және посткластерлік реполяризацияға қатысады. Бұл өз кезегінде осы процестерді таңдамалы түрде реттейтін препараттарды іздеудің жаңа жолын ашады (ПДЫ кластерлерінің амплитудасы мен ұзақтығы).

Қорытынды: Осылайша, осы кезеңде біз эпилептиформалық белсенділікті реттеуде Kv7 каналдарының маңызды рөлін көрсеттік. Kv7 тұқымдас калий каналдары ПДЫ кластерінің гиперполяризациядан кейінгі жылдамдығын арттыра отырып, эпилептиформды белсенділікте әрекет потенциалы жиын ұзақтығы және кальций импульстарының ұзақтығын төмендеуі көрсетілген. Kv7 каналдарының тікелей активаторлары мен ингибиторлары синхронды жиын белсенділіктің және Ca2+ импульстарының ұзақтығы, амплитудасы сияқты параметрлерін өзгертеді. Алайда эпилептиформды белсенді нейрондардағы деполяризациялық ығысу жиілігі өзгермейді. Kv7 тұқымдас калий каналдарының постсинапстық калий каналдары, нейрондардың эпилептиформды синхронды белсенділігін реттеуге қатысатыны көрсетілген. Kv7 каналдарының эпилепсияға қарсы әсер ету механизмі ПДЫ кластерінің, ПДЫ гиперполяризациясының, ПДЫ кластерінің (ӘП жиыны) ұзақтығының және Ca2+ сигналының ұзақтығының төмендеуіне байланысты екені көрсетілді.

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QUALITY OF LIFE AND ADHERENCE TO THERAPY IN PATIENT WITH RHEUMATOID ARTHRITIS

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Abstract

Relevance: Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive joint damage and systemic complications. It significantly reduces patients' quality of life (QoL), affecting their physical, psychological, and social well-being. Assessing QoL is a crucial criterion for evaluating treatment effectiveness and requires the use of specialized instruments and questionnaires. This study **aims** to assess changes in QoL and treatment adherence among RA patients over one year of baseline therapy using the SF-36 and HAQ questionnaires.

Materials and Methods: A prospective observational study was conducted on 109 patients with a confirmed RA diagnosis (ACR/EULAR 2010 criteria). Enrollment took place in 2021, with reassessment after 12 months. Clinical parameters (DAS28, VAS), QoL measures (SF-36, HAQ), and treatment adherence (Morisky-Green questionnaire) were evaluated. Data analysis was performed using SPSS 26.0.

Results: The mean age of the patients was 56.3 years, with 77% being women. After one year of therapy, a statistically significant improvement in QoL was observed: the physical component of SF-36 (PCS) increased by 8.3 points, and the psychological component (MCS) increased by 10.6 points ($p < 0.001$). The HAQ index decreased by 0.4 points, indicating improved functional status. However, only 59.6% of patients demonstrated high adherence to treatment, while 40.4% had low adherence, which correlated with poorer QoL scores and higher disease activity.

Conclusions: High treatment adherence positively influences QoL and disease activity in RA patients. Additional strategies, including digital technologies, counseling, and personalized treatment approaches, are necessary to enhance adherence and optimize patient outcomes.

Keywords: *rheumatoid arthritis, quality of life, Health Assessment Questionnaire (HAQ), Medical Outcomes Study 36-Item Short Form (SF-36) adherence to therapy, Morisky-Green questionnaire.*

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Резюме

КАЧЕСТВО ЖИЗНИ И ПРИВЕРЖЕННОСТЬ ТЕРАПИИ ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ

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Актуальность: Ревматоидный артрит (РА) — это хроническое воспалительное заболевание, приводящее к прогрессирующему повреждению суставов и системным осложнениям. Оно значительно снижает качество жизни (КЖ) пациентов, затрагивая их физическое, психологическое и социальное благополучие. Оценка КЖ является важным критерием эффективности терапии и требует использования специализированных инструментов и опросников. **Цель** данного исследования — оценить динамику КЖ и приверженности терапии у пациентов с РА в течение одного года базисного лечения с использованием опросников SF-36 и HAQ.

Материалы и методы: проведено проспективное обсервационное исследование, включающее 109 пациентов с подтвержденным диагнозом РА (критерии ACR/EULAR 2010). Включение в исследование проводилось в 2021 году, повторная оценка осуществлялась через 12 месяцев. Оценивались клинические параметры (DAS28, VAS), показатели КЖ (SF-36, HAQ) и приверженность терапии (опросник Мориски-Грина). Анализ данных выполнялся с использованием программы SPSS 26.0.

Результаты: Средний возраст пациентов составил 56,3 года, 77% участников были женщины. Через год терапии было отмечено статистически значимое улучшение КЖ: физический компонент SF-36 (PCS) увеличился на 8,3 балла, а психологический компонент (MCS) — на 10,6 балла ($p< 0,001$). Индекс HAQ снизился на 0,4 балла, что свидетельствует об улучшении функционального состояния. Однако высокая приверженность терапии наблюдалась только у 59,6% пациентов, тогда как 40,4% имели низкую приверженность, что коррелировало с худшими показателями КЖ и большей активностью заболевания.

Заключение: Высокая приверженность терапии оказывает положительное влияние на КЖ и активность заболевания у пациентов с РА. Для повышения приверженности и оптимизации результатов лечения необходимы дополнительные стратегии, включая цифровые технологии, консультирование и персонализированные подходы к терапии.

Ключевые слова: *ревматоидный артрит, качество жизни, опросник оценки здоровья (HAQ), опросник SF-36, приверженность к терапии, опросник Мориски-Грина.*

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Түйіндеме

РЕВМАТОИДТЫ АРТРИТПЕН АУЫРАТЫН НАУҚАСТАРДЫҢ ӨМІР САПАСЫ ЖӘНЕ ТЕРАПИЯҒА БЕЙІМДІЛІГІ

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Өзектілігі: Ревматоидты артрит (РА) – буындардың прогрессивті зақымдануы мен жүйелі асқынуларға әкелетін созылмалы қабыну ауруы. Ол пациенттердің өмір сүру сапасын (ӨС) айтарлықтай төмендетіп, олардың физикалық, психологиялық және әлеуметтік әл-ауқатына әсер етеді. ӨС бағалау терапияның тиімділігін анықтаудың маңызды критерийі болып табылады және арнайы құралдар мен сауалнамаларды қолдануды талап етеді. Осы **зерттеудің мақсаты** – SF-36 және HAQ сауалнамаларын қолдана отырып, РА-мен ауыратын пациенттердің ӨС динамикасын және терапияға бейімділігін бір жылдық базалық ем аясында бағалау.

Материалдар мен әдістер: ACR/EULAR 2010 критерийлеріне сәйкес РА диагнозы расталған 109 пациентті қамтыған проспективті бақылау зерттеуі жүргізілді. Пациенттер 2021 жылы зерттеуге енгізіліп, 12 айдан кейін қайта бағаланды. Клиникалық параметрлер (DAS28, VAS), ӨС көрсеткіштері (SF-36, HAQ) және терапияға бейімділік (Мориски-Грин сауалнамасы) бағаланды. Деректерді талдау SPSS 26.0 бағдарламасы арқылы жүргізілді.

Нәтижелер: Пациенттердің орташа жасы 56,3 жасты құрады, олардың 77%-ы әйелдер болды. Бір жылдық терапиядан кейін ӨС-тің статистикалық тұрғыдан маңызды жақсаруы байқалды: SF-36 физикалық компоненті (PCS) 8,3 баллға, ал психологиялық компоненті (MCS) 10,6 баллға артты ($p < 0,001$). HAQ индексі 0,4 баллға төмендеп, функционалдық жағдайдың жақсарғанын көрсетті. Алайда, тек 59,6% пациенттер терапияға жоғары

бейімділік танытты, ал 40,4%-ында бейімділік төмен болды, бұл ӨС-тің нашарлауымен және ауру белсенділігінің жоғары болуымен өзара байланыста болды.

Қорытындылар: Терапияға жоғары бейімділік РА-мен ауыратын пациенттердің ӨС мен ауру белсенділігіне оң әсер етеді. Бейімділікті арттыру және емдеу нәтижелерін оңтайландыру үшін цифрлық технологияларды, кеңес беруді және жеке емдеу тәсілдерін қоса алғанда, қосымша стратегиялар қажет.

***Түйінді сөздер**: ревматоидты артрит, өмір сүру сапасы, денсаулықты бағалау сауалнамасы (HAQ), SF-36 сауалнамасы, терапияға бейімділік, Мориски-Грин сауалнамасы.*

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Introduction

Rheumatoid arthritis (RA) is a chronic immunoinflammatory disease characterized by erosive joint damage and systemic involvement of internal organs [4]. Studies have shown that the mortality rate in patients with RA is 54% higher than in the general population, and the risk of cardiovascular complications is doubled [24]. Furthermore, RA has a negative impact on patients' quality of life (QoL), potentially leading to early disability and reduced life expectancy [22, 23].

The QoL of patients with RA is a crucial integrative indicator that reflects not only physical health but also psychological well-being, social activity, and the ability to perform daily tasks [8]. Unlike objective clinical parameters, such as laboratory or instrumental data, QoL is based on patients' subjective perceptions, making it an essential criterion for evaluating treatment effectiveness [8].

Given the multifaceted nature of QoL, its assessment requires the use of validated questionnaires capable of capturing various aspects of patients' lives. In international practice, both disease-specific and generic scales are widely utilized [11, 12, 15].

The Health Assessment Questionnaire (HAQ) was specifically developed for RA patients and is designed to assess functional capacity [1]. It consists of 20 questions grouped into 8 categories, allowing for the calculation of the HAQ index (ranging from 0 to 3.0 points). Scores below 0.5 indicate normal functional ability, whereas an increase in the index reflects greater limitations in activity. A difference of 0.22 points is considered a minimally clinically significant improvement, while a reduction of 0.5 points or more signifies substantial functional enhancement.

Among the general assessment tools, the SF-36 (Medical Outcomes Study 36-Item Short Form) is the most frequently used [6]. The SF-36 questionnaire comprises 36 questions evaluating physical and psychosocial well-being across 8 scales. Two composite scores - the physical component summary (PCS) and the mental component summary (MCS) - enable comparison of a patient's condition with population norms and facilitate monitoring of treatment dynamics.

Recent studies emphasize the importance of regular QoL assessment in RA patients, as it is closely linked to disease activity, treatment efficacy, and prognosis [9, 16]. Lower QoL scores are associated with more severe disease progression, reduced adherence to therapy, and increased healthcare costs. Moreover, a decline in QoL may precede an exacerbation of inflammatory activity, making it a valuable prognostic marker [7].

Thus, the comprehensive assessment of QoL not only provides an objective evaluation of RA patients' health status but also allows for the individualization of therapeutic approaches, thereby enhancing overall treatment effectiveness. Integrating the HAQ and SF-36 questionnaires into clinical practice contributes to a more precise evaluation of patients' conditions and enables timely adjustments to treatment strategies.

Aim: to assess adherence to therapy and quality of life of patients with RA in dynamics (within one year) against the background of active baseline therapy using SF-36 and HAQ questionnaires.

Materials and methods

A prospective observational cross-sectional clinical study was conducted at the Cardio-Rheumatology Department of the University Hospital of NJSC "Semey Medical University" (UH NJSC "SMU") in Semey, Kazakhstan.

The study included 109 patients with a confirmed diagnosis RA in accordance with the 2010 ACR/EULAR classification criteria (American College of Rheumatology/European League Against Rheumatism Rheumatoid Arthritis Classification Criteria). Patients in the observation group were recruited consecutively upon admission between January 1 and December 31, 2021. A repeated assessment of all study parameters was conducted after 12 months. *Inclusion criteria*: verified RA according to the ACR/EULAR 2010 classification criteria and voluntary informed consent. *Exclusion criteria*: pregnancy and lactation, severe and decompensated liver, kidney, cardiovascular diseases, endocrine disorders, other joint diseases, age under 18 years, refusal to participate in the study,

Diagnostic Methods: The diagnosis of RA was established based on all necessary clinical and instrumental examinations following the protocol for the diagnosis and treatment of RA issued by the Ministry of Health of the Republic of Kazakhstan (2016) (M06.0; M05.8) [2]. The radiological stage of RA was determined using the modified Steinbrocker classification. RA activity was assessed using the Disease Activity Score for 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR) at the time of inclusion in the study and again after 12 months.

The DAS 28-ESR includes the counting of painful and swollen joints (out of 28 possible joints), the level of an

inflammatory marker (in this study, ESR) and the patient's subjective assessment of general health by VAS (0-100 mm). The result obtained is a numerical score interpreted as follows: DAS28 > 5.1 indicates high activity, 3.2-5.1 indicates moderate activity, 2.6-3.2 indicates low activity, and <2.6 indicates remission [2].

QoL indicators were assessed using the SF-36 questionnaire HAQ, both at baseline and at the 12-month follow-up visit, conducted by the same physician.

The SF-36 consists of 36 items grouped into eight domains: Physical Functioning (PF), Role Physical (RP) (role limitations due to physical health), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) (role limitations due to emotional health), and Mental Health (MH). The results are presented as two summary scores: the Physical Component Summary (PCS), reflecting physical health, and the Mental Component Summary (MCS), reflecting mental health. Scores range from 0 to 100, with 100 indicating the best possible health status and 0 the worst. An increase of ≥5 points in PCS or MCS was considered an improvement, while an increase of ≥10 points was considered a significant improvement [6,16].

The HAQ measures the degree of disability and difficulty in performing activities of daily living. The questionnaire includes 20 questions in 8 categories: dressing, getting up, eating, walking, hygiene, reaching, grasping and activities of daily living. It is scored on a four-point scale (from 0 - no difficulty to 3 - inability to perform without assistance). A notable improvement was defined as a decrease in HAQ score by ≥0.5 points, while a substantial improvement was defined as a decrease of ≥0.8 points [1,26].

Adherence to treatment was assessed using the Morisky-Green questionnaire, which patients completed during the follow-up visit. This questionnaire comprises four questions designed to identify potential issues with medication adherence:

Do you ever forget to take your medication?

Do you have difficulty remembering to take your medications?

When you feel better, do you sometimes stop taking your medication?

If you feel worse after taking a medication, do you stop taking it?

Responses are scored on a binary scale: "yes" = 0 points, "no" = 1 point. The total score ranges from 0 to 4, with adherence levels classified as follows: 4 points - adherent, 3 points - insufficiently adherent (at risk of becoming nonadherent), and 1-2 points - nonadherent [20].

The efficacy of therapy was evaluated according to the EULAR criteria based on the dynamics of the DAS 28 index and using the ACR 20/ACR 50/ACR 70 response criteria. A decrease in DAS 28 level after 12 months from baseline of >1.2 was considered a "good response", >0.6 and ≤1.2 a "partial response", ≤0.6 from baseline a "poor response" (with moderate activity level) and "no response" with DAS 28 level above 5.1 [10]. According to the ASR criteria, a minimal improvement was considered to be an effect corresponding to a 20% improvement in the following parameters: counting of painful and swollen joints and any 3 of the following 5 parameters: patient's overall assessment of disease activity, physician's overall assessment of disease activity, VAS, HAQ, ESR or CRP, a moderate effect of 50%, and a significant effect of 70% [27].

All patients signed informed voluntary consent for participation in the study, processing, and publication of personal data. The study was approved by the local ethical committee of NJSC "SMU" (protocol No. 2 of 28.10.2020).

Statistical data analysis was performed using SPSS software version 26.0. For descriptive statistics, continuous variables were presented as mean ± standard deviation or median (25th and 75th percentiles), depending on the data distribution. Comparisons of mean values between groups were conducted using Student's t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. To assess changes within groups over time, the paired t-test or Wilcoxon signed-rank test was applied. Effect size (Cohen's d) was calculated as the ratio of the difference in mean values before and after therapy to the standard deviation of the baseline measurement. The interpretation of effect size was as follows: less than 0.2 – no effect, 0.2 to 0.5 – minimal effect, 0.5 to 0.8 – moderate effect, and greater than 0.8 – pronounced effect. Statistical significance was set at $p < 0.05$.

Results

*Demographic and clinical characteristics.*The mean age of the patients was 56.3 ± 12.4 years [min: 24; max: 87]. Among the patients, 77% (n=85) were female and 22% (n=24) were male. The majority of participants 81.7% (n=89) were of Kazakh ethnicity, while 18.3% (n=20) were of Russian ethnicity. The social status distribution was as follows: employed 20.2% (n=22), unemployed 21.1% (n=23), retired 28.4% (n=31). One third of the patients had a disability 30.3% (n=33). Demographic and clinical characteristics of the patients are presented in Table 1.

In the study group, patients with seropositive rheumatoid arthritis predominated, accounting for 68.8% (n=75). The majority of patients were in the advanced (33.9%, n=37) or late (47.7%, n=52) stages of the disease. Radiological stages II and III were the most common, observed in 35.8% (n=39) and 34.9% (n=38) of cases, respectively. Joint function impairment was classified as grade II in 36.7% (n=40) of patients and grade III in 52.3% (n=57). The mean DAS28 was 5.08 ± 1.4 [min: 2.65; max: 8.06]. Anemia was the most frequently diagnosed systemic manifestation, affecting 50.5% (n=55) of patients. RA-related complications were identified in 14.7% (n=16) of cases, with osteoporosis (87.5%, n=14) being the most prevalent. Among comorbidities, arterial hypertension (65.1%, n=71) and gastrointestinal disorders (56.3%, n=40) were the most common.

All patients in the study group (109 patients) were receiving baseline therapy at the time of inclusion in the study. Table 2 presents data on the treatment of patients, including baseline therapy, biologics and glucocorticosteroid use.

Among the baseline drugs, methotrexate (MTX) was used in the majority of cases - 62.4% (n=68) of patients, mostly in parenteral form with a mean dose of 13.6± 2.9 mg [min: 10; max: 20]. Biological therapy was used in 16.5% (n=18) of patients, of which golimumab was received by 13.8% (n=15) and tocilizumab by 2.8% (n=3). Glucocorticosteroids were prescribed in 46.8% (n=51) of cases.

Table 1.

Demographic and clinical characteristics of patients with rheumatoid arthritis.

Demographic characteristics		N	%
Age,years, M ± SD		56.3±12.4 [min: 24; max: 87]	
Gender	Women	85	77
	Men	24	22
Nationality	Kazakh	89	81.7
	Russian	20	18,3
Socialstatus	Employed	22	20,2
	Unemployed	23	21,1
	Pensioners	31	28,4
	Disable	33	30,3
Clinicalcharacteristics	Seropositive	75	68,8
	Seronegative	34	31,2
Duration of disease, years, Me [Q1; Q3]		10 [3; 25]	
Stageofdisease	Veryearly	5	4,6
	Early	15	13,8
	Advanced	37	33,9
	Late	52	47,7
Radiologicalstage	I	13	11,9
	II	39	35,8
	III	38	34,9
	IV	19	17.4
Functionalclass	I	12	11,0
	II	40	36,7
	III	57	52,3
DAS 28, M ± SD		5.08 ± 1.4 [min: 2.65; max: 8.06]	
Of which:	**Systemic manifestations**	55	50,5
	Anaemia	51	92,7
	Rheumatic nodules	4	7.3
	Fever	3	5,5
	Weight loss	3	5,5
	Others	5	9,1
Of which:	**Complications**	16	14,7
	Osteoporosis	14	87,5
	Others	10	62,5
Co-morbidities Of which:	Arterial hypertension	71	65,1
	Coronary artery disease	39	54,9
	Osteoarthritis	13	18,3
	Gastrointestinal pathology	40	56,3
	Others	17	23,9

Table 2.

Characteristics of the therapy administered to patients with rheumatoid arthritis.

Typeoftherapy	N	%
Baseline	109	100
Methotrexate, of which Parenteral (s/c)	68 54	62,4 79,4
Leflunomide	37	33,9
Sulfasalazine	2	2,2
Hydroxychloroquine	2	2,2
Methotrexate + Leflunomide	9	8,4
Biological	18	16,5
Golimumab	15	13,8
Tocilizumab	3	2,8
Glucocorticosteroids	51	46,8

Quality of life assessment. At the time of inclusion in the study, patients with RA demonstrated relatively poor quality of life on most of the SF-36 scales (Table 3). The sum of physical scales was significantly lower than the normative values PCS = 38.0 ± 6.3, with the most pronounced limitations observed for RP = 32.2 ± 11.4 and BP 37.2 ± 13.8. Psycho-emotional state of patients was also moderately reduced, MCS was 57.6 ± 7.7.

After 12 months of follow-up, a significant improvement in functional indices was observed following treatment. PCS - SF-36 increased by 8.3 ± 6.2, d = 1.3 ($p < 0.001$), indicating a clinically meaningful enhancement of physical health and a reduction in pain. MCS - SF-36 also showed a significant increase of 10.6 ± 7.7, d = 1.4 ($p < 0.001$), reflecting a positive impact of therapy on patients' psycho-emotional well-being.

Analysis of individual physical health parameters revealed a statistically significant improvement in physical functioning Δ PF = 10.0 ± 8.2, d = 1.2, ($p < 0.001$) and role-physical functioning Δ RP = 9.6 ± 8.2, d = 1.2, ($p < 0.001$), suggesting an enhanced ability of patients to perform daily physical activities. A statistically significant reduction in bodily pain (BP) by 6.7 ± 8.3 points, d = 0.8 ($p < 0.001$), was also noted, although the effect size was moderate.

Table 3.

Quality of life indicators in patients with rheumatoid arthritis.

Qualityoflifeindicators	At the beginning of treatment		Indynamicsafter 12 months		Differenceaverages(Δ)	Effect size (Cohen's d)(d)
	M ± SD	Range [min; max]	M ± SD	Range [min; max]		
Physicalcomponentsummary	38.0 ± 6.3	-	46.3 ± 8.9	-	+8.3 ± 6.2*	1.3
Physicalfunctioning	40.2 ± 13.8	15; 65	50.2 ± 14,5	20; 80	+10.0± 8.2*	1.2
Rolephysical	32.2 ± 11.4	10; 55	41.8 ± 14.2	20; 75	+ 9.6 ± 8.2*	1.2
Bodilypain	37.2 ± 13.8	15; 60	43,9 ± 15.8	20; 80	+6.7± 8.3*	0.8
Generalhealth	42.3 ± 12.2	20; 65	49.2±13.0	20; 78	+6.9± 9.9*	0.6
Mentalcomponentsummary	57.6 ± 7.7	-	68.3± 7.3	-	+10.6 ± 7.7*	1.4
Vitality	48.8 ± 12.9	25; 75	58,6 ± 15.0	30; 80	+ 9.8 ± 18.7*	0.5
Social	55.4 ± 13..4	30; 80	62,9 ± 12.2	35; 85	+7.5 ± 16.6*	0.5
Roleemotional	60.4 ± 16.3	35; 85	74,0 ± 15,1	35; 90	+13.6± 14.1*	0.9
Mentalhealth	65.9 ± 15.5	35; 90	77,5 ± 14,5	45; 95	+11.7 ±9.7*	1.2
HAQ	2.0 ± 0.6	-	1.5 ± 0.8	-	-0,4 ± 0,4*	0.9
*p< 0.05						

Note: HAQ – Health Assessment Questionnaire.

Notable improvements were also observed in the mental health component: RE increased by 13.6 ± 14.1, d = 0.9, MH improved by 11.7 ± 9.7, d = 1.2 (p < 0.001), indicating reduced emotional distress and overall enhancement of psychological well-being following long-term RA therapy.

Despite the overall positive trend, less pronounced changes were recorded in general health Δ GH = +6.9 ± 9.9, d = 0.6, vitality Δ VT =+9.8 ± 18.7, d = 0.5 and social functioning Δ SF= +7.5 ± 16.6, d = 0.5, which may be attributed to individual differences in patient adaptation and variability in their perception of QoL. Nevertheless, the increase in these scores indicates a positive trajectory (p < 0.001).

Of particular note is the decrease in HAQ score (-0.4 ± 0.4, d = 0.9). Although the reduction in HAQ was statistically significant (p < 0.001), it did not reach the threshold for clinical significance (Δ ≥ 0.5), indicating persistent limitations in daily activities.

*Adherence to treatment.*When adherence was assessed using the Morisky-Green questionnaire, only 59.6% (n=65) of patients demonstrated high adherence to therapy (4 points), while 20.4% (n=22) had low adherence (3 points), and 20.4% (n=22) exhibited insufficient adherence (1–2 points). An analysis of the clinical and laboratory characteristics of patients with different adherence levels (Table 4) revealed that patients with low adherence were significantly older, with a mean age of 57.4 ± 13.0 years compared to 51.9 ± 11.0 years in the high-adherence group (p < 0.001), suggesting that older patients may face greater challenges in maintaining adherence.

Despite a similar disease duration in both groups (p = 0.582), patients with low adherence exhibited significantly higher inflammatory activity, as indicated by elevated DAS28 scores—5.45 [4.9; 6.1] vs. 4.84 [4.1; 5.5] (p = 0.025). Additionally, patients with low adherence reported more severe pain, as reflected in significantly higher VAS scores (p = 0.034), which likely contributed to decreased motivation for regular medication intake.

Functional status, assessed using the HAQ scale, was also significantly worse in the low-adherence group, with scores of 2.0 ± 0.6 vs. 1.5 ± 0.8 in the high-adherence group (p = 0.048), indicating a greater degree of disability among these patients. (Table 4)

Table 4.

Clinical and laboratory characteristics of patients with rheumatoid arthritis depending on overall adherence to therapy.

Indicator	Committed to treatment (n=65)	Not committed to treatment (n=44)	p-value
Age, years	51.9 ± 11.0	57.4 ± 13.0	p < 0,001
Duration of the disease, years	9,8 [4; 22]	11,2 [5; 26]	p = 0,582
ESR, mm/hour	15,4 ± 9,2	20,8 ± 10,5	p = 0,069
CRP	10,1 ± 11,9	12,7 ± 11,5	p = 0,431
DAS28	4,84[4,1; 5,5]	6,45 [5,9; 8,06]	p < 0,001
Number of painful joints	14 [8; 16]	14 [9; 20]	p = 0,202
Number of swollen joints	5 [2; 7]	8 [5; 12]	p = 0,236
VAS, mm	64 [20; 80]	72 [60; 80]	p = 0,034
Morisky-Green scale, scores	3 [2; 4]	2 [1; 3]	p = 0,025
HAQ, scores	1,5 ± 0,8	2,0 ± 0,6	p = 0,048
PCS - SF-36, scores	46.4 ± 8.9	38,0 ± 6	p < 0,001
MCS -SF-36, scores	68,3 ± 7,3	57,6 ± 7,7	p < 0,001

Note: ESR - erythrocyte sedimentation rate, CRP- C- reactive protein, VAS - visual analogue scale, HAQ - health assessment questionnaire, PCS-SF 36 - physical component summary, MCS-SF 36 **-** mental component summary.

Comparison of the total physical and mental components of the SF-36 also showed a statistically significant difference between the high and low adherence groups ($p < 0.001$).

This emphasises not only the importance of adherence to therapy for disease control, but also its impact on patients' general well-being, social engagement and psychological well-being.

Discussion

The present study confirmed that adherence to therapy is a crucial factor in the management of RA, influencing both disease activity and patients' QoL. Patients with high adherence exhibited significantly lower DAS28 scores ($p = 0.025$), better functional status (HAQ, $p = 0.048$), and higher levels of both physical (PCS, $p < 0.001$) and mental (MCS, $p < 0.001$) well-being.

The findings of this study align with previous research. *Gadallah et al.,* 2014 demonstrated that patients with high adherence to methotrexate and biologic therapies were more likely to achieve remission and had superior functional outcomes as assessed by the HAQ and SF-36 scales. [28] Similarly, multiple studies (*Yajima et al.,* 2023; *Jarab et al.,* 2023) have reported that low adherence is associated with higher disease activity and poorer QoL scores [29, 30]. A noteworthy observation was that patients with low adherence were significantly older ($p = 0.002$). This finding is consistent with a study by *Siddique M. et al*., 2024 which indicated that older patients are less likely to adhere to treatment regimens due to factors such as multimorbidity, cognitive impairment, and the complexity of medication management. [5, 7, 30]. These findings highlight the necessity of developing individualized strategies to enhance adherence, particularly in older patients [31].

Despite the important insights gained, this study has certain limitations. Firstly, it was conducted within a single healthcare center, which may restrict the generalizability of the findings to a broader population. Secondly, adherence was assessed using the Morisky-Green questionnaire, a validated but self-reported measure that may introduce information bias. However, the combination of this tool with objective clinical parameters (DAS28, HAQ, SF-36) enhances the reliability of the results.

A key strength of this study is its comprehensive approach, incorporating a simultaneous assessment of adherence, disease activity, and quality of life, thereby providing a more precise understanding of the interconnections between these parameters.

Conclusions

This study highlights the significant impact of adherence to therapy on the QoL and disease activity in patients with RA. Over the course of a year, patients receiving baseline therapy demonstrated notable improvements in both physical and psychological health, as evidenced by increased SF-36 scores and a reduction in HAQ indices. However, adherence to treatment emerged as a critical determinant of therapeutic success—patients with high adherence experienced better disease control, lower DAS28 scores, and superior functional outcomes. Despite these positive trends, nearly 40% of patients exhibited low or insufficient adherence, which correlated with higher disease activity, increased pain perception, and poorer quality of life. This underscores the necessity of targeted interventions to improve adherence, particularly among older patients and those with comorbidities. Strategies such as personalized patient counseling, digital health technologies, and multidisciplinary support should be considered to enhance long-term treatment engagement and optimize outcomes.

Future research should focus on evaluating the effectiveness of adherence-enhancing strategies and their impact on the long-term prognosis of RA patients. Addressing barriers to treatment compliance may ultimately lead to better disease management and improved overall well-being for individuals living with RA.

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STUDY OF HOSPITALIZED CASES ASSOCIATED WITH ACUTE CEREBROVASCULAR ACCIDENTS

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Abstract

Background. Proper organization of the system for providing medical care to patients with cerebral stroke will reduce mortality and reduce the level of disability. All activities are aimed at creating unified principles of diagnostic approaches and management of patients with stroke. A significant role is given to primary prevention by optimizing the system of medical care for stroke patients. Coordinating centers for cerebrovascular pathology and stroke are being created

Aim to analyze cases of hospitalization of patients with acute cerebrovascular accidents from 2012 to 2022 in Almaty city.

Materials and Methods. A retrospective study was conducted. The data analysis period was from 2012 to 2022. The analysis data included the age of the patients, the days spent in bed, the outcome of the disease, and emergency or planned admissions. Data analysis was carried out using the SPSS 13 program.

Results. The age of patients with acute cerebrovascular accidents fluctuated within 10 years in the range of 59.8 as well as bed days was 11.46. The number of emergency hospitalizations was higher in comparison to planned; however, it was positive dynamics in the last five years. In addition, from 2012 the mortality rate decreased, whereas recovery increased, which means there are better results and access to health facilities.

Conclusion. The introduction of stroke programs, as well as improvements in primary health care, has allowed us to improve care for patients. While the prevention and treatment programs still need to be continually improved, considering age, gender, and risk factors and other factors.

Keywords*: acute cerebrovascular accidents, stroke, hospitalization, bed-days; Kazakhstan.*

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Резюме

ИЗУЧЕНИЕ ГОСПИТАЛИЗИРОВАННЫХ СЛУЧАЕВ, СВЯЗАННЫХ С ОСТРЫМИ НАРУШЕНИЯМИ МОЗГОВОГО КРОВООБРАЩЕНИЯ

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Введение. Правильная организация системы оказания медицинской помощи пациентам с церебральным инсультом позволит снизить смертность и снизить уровень инвалидности. Все мероприятия направлены на создание единых принципов диагностических подходов и ведения пациентов с инсультом. Значительная роль отводится первичной профилактике путем оптимизации системы оказания медицинской помощи пациентам, перенесшим инсульт. Создаются координационные центры по цереброваскулярной патологии и инсульту

Цель: анализ случаев госпитализации пациентов с острыми нарушениями мозгового кровообращения в период с 2012 по 2022 год в городе Алматы.

Материалы и методы. Было проведено ретроспективное исследование. Период анализа данных составлял с 2012 по 2022 год. Данные анализа включали возраст пациентов, дни, проведенные в постели, исход заболевания, экстренную или плановую госпитализацию. Анализ данных проводился с помощью программы SPSS 13.

Результаты. Возраст пациентов с острыми нарушениями мозгового кровообращения колебался в течение 10 лет в диапазоне 59,8, а количество койко-дней составило 11,46. Количество экстренных госпитализаций было выше по сравнению с запланированными, однако за последние пять лет это была положительная динамика. Кроме того, с 2012 года уровень смертности снизился, в то время как выздоровление увеличилось, что означает лучшие результаты и прием в медицинские учреждения.

Вывод. Внедрение программ по борьбе с инсультом, а также улучшения в первичной медико-санитарной помощи позволили нам улучшить уход за пациентами. В то время как программы профилактики и лечения по-прежнему нуждаются в постоянном совершенствовании с учетом возраста, пола, факторов риска и других факторов.

Ключевые слова: *острые нарушения мозгового кровообращения, инсульт, госпитализация, койко-дни; Казахстан.*

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Түйіндеме

ЖЕДЕЛ ЦЕРЕБРОВАСКУЛЯРЛЫҚ БҰЗЫЛУЛАРМЕН БАЙЛАНЫСТЫ АУРУХАНАҒА ЖАТҚЫЗЫЛҒАН ЖАҒДАЙЛАРДЫ ЗЕРТТЕУ

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Анықтама. Церебральды инсультпен ауыратын науқастарға медициналық көмек көрсету жүйесін дұрыс ұйымдастыру өлімді азайтуға және мүгедектік деңгейін төмендетуге мүмкіндік береді. Барлық іс-шаралар диагностикалық тәсілдердің бірыңғай қағидаттарын құруға және инсультпен ауыратын науқастарды басқаруға бағытталған. Инсультпен ауыратын науқастарға медициналық көмек көрсету жүйесін оңтайландыру арқылы алғашқы профилактикаға маңызды рөл беріледі. Цереброваскулярлық патология және инсульт бойынша үйлестіру орталықтары құрылуда

Мақсаты 2012-2022 жылдар аралығында Алматы қаласында ми қан айналымы жіті бұзылған пациенттерді емдеуге жатқызу жағдайларын талдау болып табылады.

Материалдар мен Әдістері. Ретроспективті зерттеу жүргізілді. Деректерді талдау кезеңі 2012 жылдан 2022 жылға дейін болды. Талдау деректері пациенттердің жасын, төсекте өткізген күндерін, аурудың нәтижесін, шұғыл немесе жоспарлы ауруханаға жатқызуды қамтыды. Деректерді талдау SPSS 13 бағдарламасы арқылы жүргізілді.

Нәтижелер. Жедел цереброваскулярлық бұзылулары бар науқастардың жасы 10 жыл ішінде 59,8 диапазонында өзгерді, ал төсек күндері 11,46 болды. Шұғыл ауруханаға жатқызу жоспарланғанмен салыстырғанда жоғары болды, бірақ соңғы бес жылда бұл оң динамика болды. Сонымен қатар, 2012 жылдан бастап өлім-жітім деңгейі төмендеді, ал қалпына келтіру өсті, бұл жақсы нәтижелер мен медициналық мекемелерге қабылдауды білдіреді.

Қорытынды. Инсультті емдеу бағдарламаларын енгізу, сондай-ақ алғашқы медициналық-санитарлық көмекті жақсарту пациенттерге күтім көрсетуді жақсартуға мүмкіндік берді. Алдын алу және емдеу бағдарламалары әлі де жасына, жынысына, қауіп факторларына және басқа факторларға байланысты үнемі жетілдіруді қажет етеді.

***Түйін сөздер**: ми қан айналымының жіті бұзылуы, инсульт, ауруханаға жатқызу, төсек-күндер; Қазақстан*

Дәйексөз үшін:

Кастей Р., Файзуллина К., Турганова М., Жексенова А., Вайчюлис В., Ахтаева Н. Жедел цереброваскулярлық бұзылулармен байланысты ауруханаға жатқызылған жағдайларды // Ғылым және Денсаулық сақтау. 2025. Vol.27(1), Б. 49-55. *doi 10.34689/SH.2025.27.1.006*

Introduction

Acute cerebrovascular accident is one of many other pressing problems around the world with depressing rates of morbidity and mortality, as well as disability. Stroke is characterized as a neurological deficit associated with acute focal damage to the central nervous system from a vascular cause [16]. Cerebrovascular disease, which includes ischemic and hemorrhagic stroke, is the third most common cause of death worldwide, with a mortality rate of 86.5 per 100,000 person-years [5]. More than 700 thousand people suffer from stroke each year in the United States, up to 500 thousand people in Canada, up to 1 million people in the European Union, and in the world the number of cases can reach 10 million. The average prevalence of stroke is 200 cases per 100 thousand population annually, although it varies in different regions and depends on race and many other factors [3]. A systematic and meta-analysis found that over the past 40 years, the overall incidence of intracerebral hemorrhage is 29.9 per 100,000 person-years, which has not decreased worldwide, where the incidence in Asian populations is significantly higher than in other continents [20]. Another systematic review found that the cumulative incidence of intracerebral hemorrhage was highest in lower-middle-income countries [7]. Epidural hematomas are present in approximately 2% of patients with traumatic brain injury and account for 5% to 15% of fatal head injuries. The incidence of subdural hematoma is estimated to be between 5% and 25% of patients with major head trauma, while subarachnoid hemorrhage accounts for approximately 5% of all strokes and occurs in approximately 2 to 25 per 100,000 person-years among persons over 35 years of age, and also, intraparenchymal hemorrhages account for 10% to 20% of all strokes [18]. The authors note that globally in 2019, the cost of lost wealth due to stroke was $2059.67 billion, or 1.66% of global GDP; of the subtypes for ischemic stroke was $882.81 billion) for intracerebral hemorrhage was $212.36 billion US dollars, for subarachnoid hemorrhage [4].

In the Republic of Kazakhstan, strokes are in third place in terms of prevalence after diseases of the circulatory system and malignant tumors. According to statistics, in 2015, more than 40 thousand Kazakhstanis suffered a stroke, of which in 24% of cases it was fatal. The incidence in the country ranges from 2.5 to 3.7 cases per 1000 people per year, and the mortality rate ranges from 100 to 180 cases per 100 thousand people, and disability is 104.6 per 100,000 population [1].

Over the past decade, a number of programs and a road map have been introduced to improve the provision of medical care for diseases of the circulatory system, stroke, and injuries in the Republic of Kazakhstan for 2022-2023 [10]. In addition, new treatment methods have been introduced in the regions, as well as high-tech medical services to reduce deaths from heart disease, including stroke and other.

The purpose of our study is to analyze cases of hospitalization of patients with acute cerebrovascular accidents from 2012 to 2022 in Almaty city.

Materials and Methods

This was a retrospective observational study based on data obtained from the National Scientific Center for Health Development in Almaty, Republic of Kazakhstan. The institution's management was informed of the study's progress and raised no objections regarding the publication of the findings in open-access sources. Cases were analyzed according to International Disease Classification Code 10 (ICD-10):

- I 60.0- I 60.9 (Subarachnoid haemorrhage);
- I 61.0-I 61.9 (Intracerebral haemorrhage);
- I 63.0-I 63.9 (Cerebral infarction);
- I69.0 - I69.4 and I69.8 (Sequelae of cerebrovascular disease);
- I70.0- I70.2 and I70.8, I 70.9 (Atherosclerosis);
- I78.0- I78.1 and I78.8 (Diseases of capillaries).

The data analysis period was 10 years, from 2012 to 2022. The analysis data included the age of the patients, the days spent in bed, and the outcome of the disease. The analysis also included data from emergency or planned admissions. Data analysis was carried out using the SPSS 13 program.

The study was approved by local ethics committee of the Kazakh National Medical University (№ 4, 140. 03-05-2023)

Results

Our analysis showed that the age of patients with acute cerebrovascular accidents fluctuated within 10 years in the range of 54.49 years and 61.97 years (table 1). In general, it is worth noting that the number of patients in this nosology group grew from 2012 to 2017 from 63 cases to 269, after which there was a sharp decrease until 2020 (89 patients), and then it increased to 191 cases in 2022. Over the course of ten years, the average bed days of hospitalized cases was 11.46 days.

Cases of emergency hospitalization of patients with this category of nosology are higher than planned ones, which is due to the specifics of the disease. Nevertheless, there is a positive trend in reducing emergency hospitalization cases from 95.2 in 2012 to 53.9 in 2022. The peak increase in cases of urgent hospitalization was 99.4 in 2019 (figure 1). However, the largest number of days is observed in 2014 and 2019 (table 1).

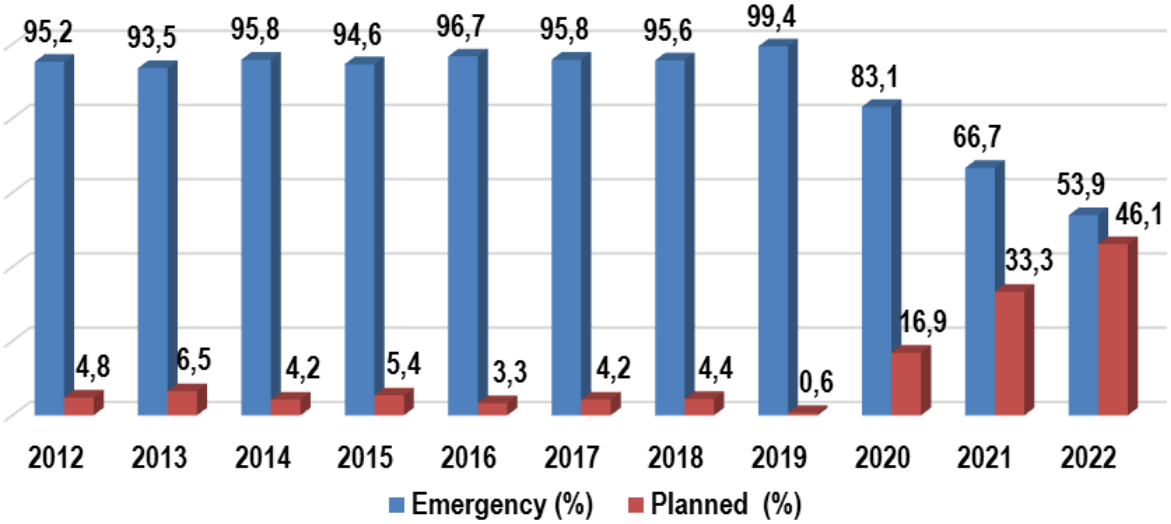

Figure 1. Type of hospitalization from 2012 to 2022.

Table 1.

Characteristics of patients with acute cerebrovascular accidents.

Years	N	Age of patients	Bed days spent
		Mean± Std. Deviation	Mean± Std. Deviation
2012	63	54.49±25.01	10.21±9.76
2013	124	50.24±24.52	10.88±10.26
2014	142	60.20±15.38	14.09±31.66
2015	185	58.79±16.73	12.85±12.64
2016	269	61.07±14.86	11.37±8.93
2017	262	61.40±15.00	10.72±8.39
2018	251	61.49±15.07	11.90±8.30
2019	179	61.97±15.48	12.79±13.1
2020	89	63.34±13.29	8.63±6.95
2021	108	57.67±20.11	10.59±6.87
2022	191	59.73±13.88	10.09±6.47
Total	1863	59.80±16.84	11.46±12.64

Treatment outcome was taken into four categories as death; recovery; no change; and deterioration. The mortality rate was high in 2012 and 2013, but subsequently the dynamics changed to decrease until 2020. The decline was from 50.8% to 15.3% between 2012 and 2017, followed by an increase in 2020 to 27.0%, then a decrease to 14.7% by 2022 (table 2). Regarding recovery cases, the indicator has changed in a positive direction. Patients who were cured in 2012 and 2013 were about 46.0%. However, by 2022 this figure increased to 80.6%. However, there were less downturns between 2019 and 2020 (table 2).

There are cases when the patient's condition remains unchanged. This indicator varied between 3.2% and 6.7%. However, in 2014, 2017, 2019, the rate was above average and amounted to 7.7%, 15.6% and 10.0%, respectively (table 2). Deterioration was identified in few cases in 2013 – 1.6% as well as in 2017 – 0.4%.

Since the city of Almaty is a metropolis where medical organizations of the republican level are located, patients from other cities are accordingly observed. Thus, in dynamics we see that compared to 2012, the number of nonresident patients decreased from 31.4% to 17.5%, where the peak of the decrease was 8.1% in 2015 (figure 2). This decrease is associated with the development of high-tech services and stroke care programs in the country, within the framework of which regional-level hospitals began to introduce the latest treatment methods and technologies.

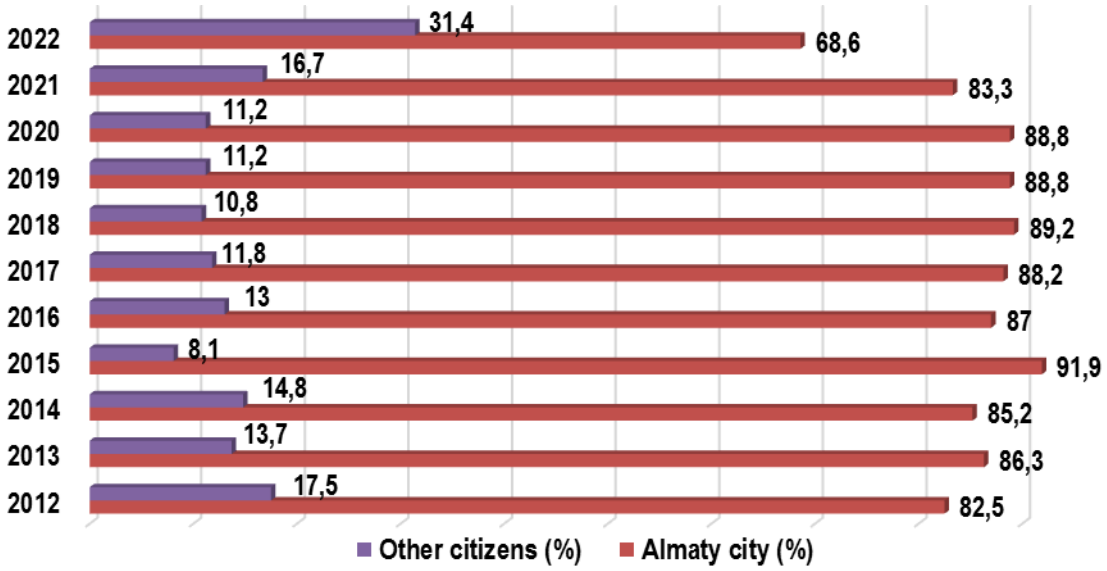

Figure 2. Hospitalization of residents of Almaty and non-residents.

Table 2.

Treatment outcome in four categories during 2012 to 2022.

Years	Death		Recovery		No change		Deterioration	
	N	%	N	%	N	%	N	%
2012	32	**50.8**	29	46.0	2	3.2	0	
2013	63	**50.8**	58	46.8	1	0.8	2	1.6
2014	41	28.9	90	63.4	11	7.7		
2015	50	27.0	129	69.7	6	3.2		
2016	62	23.0	192	71.4	15	5.6		
2017	40	15.3	180	68.7	41	15.6	1	0.4
2018	47	18.7	189	75.3	15	6.0		
2019	38	21.2	123	68.7	18	10.1		
2020	24	27.0	59	66.3	6	6.7		
2021	22	20.4	81	75.0	5	4.6		
2022	28	14.7	154	80.6	9	4.7		

Discussion

Assessing and monitoring the country's socio-demographic indicators is a necessary procedure when planning medical expenses for the quality provision of planned and emergency care for acute cerebrovascular accidents. Overall, the studies show that average hospital stays were about 10 days, which is consistent with our data. It is also noted that women have a lower number of days compared to men [9,21]. Stroke can affect people of any age, although it has traditionally been perceived as a disease of older people, with incidence doubling every ten years after age 55 [15]. In recent years, the average age of stroke patients has been decreasing, and the incidence of strokes and hospitalizations among young people has been increasing worldwide [6,7]. *Octavian Păun co-authors* note that most often stroke occurs in people over 50 years of age. Our study also found that patients were hospitalized at this age [11].

Mortality rates were high in 2020, most likely due to the Covid-19. Research confirms the negative impact of Covid-19 on the condition of patients with stroke and cerebrovascular diseases, which are a risk factor for the deterioration of the health [3,5,19].

The idea of risk factors today is scientifically substantiated and is based on assessing the likelihood of developing acute cerebrovascular accidents depending on clinical, biochemical, and many other characteristics, including the environment. It was found that often the first symptoms of a stroke, headache, are often overlooked, and therefore there is a risk of emergency hospitalization. In our study, the proportion of emergency hospitalization is still higher than planned; accordingly, measures are required to improve the knowledge of medical specialists on the symptoms of this nosology, for timely detection and diagnosis, and therefore the provision of assistance [12]. In a study of two million adults discharged from the emergency department with a primary diagnosis of headache, 0.5% were hospitalized for a major neurological disorder such as cerebral infarction (18%) and transient ischemic attack (12%) [8].

Secondary complications after intracerebral hemorrhage (ICH) can worsen outcome and are associated with early death. Of 10.029 patients with spontaneous intracerebral hemorrhage, the cumulative incidence of secondary complications was 39.9% of which were pneumonia (15.1%), cerebral edema (6.5%), cardiac decompensation (5.9%), urogenital infection (5.5%), hydrocephalus (4.6%), epilepsy (3.4%) and rebleeding (3.4%) [17]. In the future, it is necessary to study the frequency of complications that possibly lead to

deterioration of the condition; in particular, for our study, the years in which the rate of deterioration was the highest would be relevant.

Conclusion

Prevention and treatment still need to be continually improved, taking into account age, gender, and risk factors and other factors. The introduction of stroke programs, as well as improvements in primary health care, has allowed us to improve care for patients with acute cerebrovascular accidents, but targeted strategies must be gradually developed in the future.

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ЭНДОТЕЛИАЛЬНАЯ ДИСФУНКЦИЯ ПРИ НЕСПЕЦИФИЧЕСКОМ ЯЗВЕННОМ КОЛИТЕ И ВОЗМОЖНОСТИ ЕЁ КОРРЕКЦИИ ПРИ ЛЕЧЕНИИ

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Резюме

Введение. Распространённость и тяжесть язвенного колита определяют его актуальность в современном мире. Судя по современным данным, заболевание имеет сложный патогенез, в состав которого входит реакция многих функциональных систем организма. К числу последних может относиться и сосудистый эндотелий, взаимосвязь состояния которого с наличием и течением НЯК, а также роль в процессе лечения малоизучены.

Цель. Определить особенности функции сосудистого эндотелия в соотношении с клиническим течением неспецифического язвенного колита в динамике лечения.

Материалы и методы: Обследованы 68 пациентов с НЯК, распределённые по активности процесса и проводимому лечению, и 80 клинически здоровых лиц контрольной группы. Изучен ряд параметров состояния сосудистого эндотелия: число циркулирующих эндотелиоцитов (ЦЭ), содержание метаболитов NO и эндотелина-1 в крови, степень эндотелий зависимой вазодилятации. Определены частота и сроки развития рецидивов при проспективном наблюдении продолжительностью 1 год.

Результаты. Выявлены значимые различия показателей функции эндотелия между основной и контрольной группами (превышение активности эндотелина-1 на 119,5%; $p<0,01$; содержания ЦЭ – на 88,4%, $p<0,001$). При сравнении между подгруппами больных, выделенными по активности процесса, определены значимые различия между всеми подгруппами по содержанию ЦЭ, но не по остальным параметрам, связанным с эндотелиальной функцией. Однако отмечались особенности в отношении контрольной группы, различий с которой при минимальной степени активности практически не определялось. В процессе лечения также были определены различия между клиническими группами лишь по содержанию ЦЭ – на 18,8% ($p=0,043$). У пациентов с умеренной активностью процесса частота ремиссии была существенно выше при воздействии на эндотелий, а сроки ее развития сокращались. Различия в пользу группы 1 по первому параметру составили 50,8% ($t=0,032$, $p<0,05$), а по второму - 46,3% ($p=0,013$).

Выводы:

1. Течение НЯК сопровождается наличием эндотелиальной дисфункции, определяемого нарушением баланса вазодилятирующих и вазоконстрикторных факторов, снижением вазодилятации, а также повреждением эндотелиального слоя сосудистой стенки.

2. Имеется связь активности процесса и уровня нарушений эндотелиальной функции с увеличением таковых при более высоких степенях активности, что является свидетельством патогенетической роли дисфункции эндотелия при НЯК.

3. Посредством медикаментозного лечения возможно уменьшение степени эндотелиальной дисфункции, сохраняющееся в течение длительного времени.

Ключевые слова: *неспецифический язвенный колит; эндотелиальная дисфункция; вазодилатация; вазоконстрикция.*

Для цитирования:

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Summary

ENDOTHELIAL DYSFUNCTION IN ULCERATIVE COLITIS AND POSSIBILITIES FOR ITS CORRECTION DURING TREATMENT

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Abstract

Introduction. The prevalence and severity of ulcerative colitis (UC) make it a relevant issue in the modern world. According to current data, the disease has a complex pathogenesis involving reactions from various functional systems of the body. One such system is the vascular endothelium, whose condition and relationship with UC progression and treatment outcomes remain poorly studied.

Aim: To determine the characteristics of vascular endothelial function in relation to the clinical course of ulcerative colitis during treatment.

Materials and methods: A total of 68 patients with UC, categorized based on disease activity and treatment regimen, and 80 clinically healthy individuals in the control group were examined. Several endothelial function parameters were analyzed: the number of circulating endothelial cells (CECs), levels of nitric oxide (NO) metabolites and endothelin-1 in the blood, and the degree of endothelium-dependent vasodilation. The frequency and timing of relapses were assessed over a one-year prospective observation period.

Results: Significant differences in endothelial function indicators were observed between the main and control groups (endothelin-1 activity increased by 119.5%, $p<0.01$; CEC levels increased by 88.4%, $p<0.001$). Among subgroups of patients categorized by disease activity, significant differences in CEC levels were identified, but no notable variations in other endothelial function parameters were observed. In comparison with the control group, minimal disease activity did not show significant deviations. During treatment, differences between clinical groups were found only in CEC levels, which decreased by 18.8% ($p=0.043$). In patients with moderate disease activity, remission rates were significantly higher when endothelial function was targeted, and remission was achieved faster. Differences in favor of Group 1 were 50.8% ($t=0.032$, $p<0.05$) for remission rate and 46.3% ($p=0.013$) for remission duration.

Conclusions:

1. The progression of UC is associated with endothelial dysfunction, characterized by an imbalance between vasodilatory and vasoconstrictive factors, reduced vasodilation, and damage to the endothelial layer of the vascular wall.
2. There is a correlation between disease activity and the severity of endothelial dysfunction, with greater dysfunction observed at higher activity levels, suggesting a pathogenic role of endothelial dysfunction in UC.
3. Pharmacological treatment can reduce the degree of endothelial dysfunction, with effects persisting over an extended period.

Keywords: *nonspecific ulcerative colitis; endothelial dysfunction; vasodilation; vasoconstriction.*

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Түйіндеме

БЕЙСПЕЦИФИКАЛЫҚ ОЙЫҚ ЖАРАЛЫ КОЛИТ КЕЗІНДЕГІ ЭНДОТЕЛИЙ ДИСФУНКЦИЯСЫ ЖӘНЕ ОНЫ ЕМДЕУДІҢ ТҮЗЕТУ МҮМКІНДІКТЕРІ

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Кіріспе. Ойық жаралы колиттің таралуы мен ауырлығы оны қазіргі уақыттағы өзекті мәселе болып тұр. Қазіргі мәліметтерге сүйенсек, бұл аурудың патогенезі күрделі, ол ағзаның көптеген функционалдық жүйелерінің реакцияларын қамтиды. Олардың бірі – тамыр эндотелийі, оның жай-күйі мен БЖК (бейспецификалық ойық жаралы колит) ағымы арасындағы байланыс, сондай-ақ емдеу үдерісіндегі рөлі әлі де толық зерттелмеген.

Зерттеудің мақсаты: Бейспецификалық ойық жаралы колиттің клиникалық ағымымен тамыр эндотелийінің қызметінің ерекшеліктерін анықтау.

Материалдар мен әдістер: Бейспецификалық ойық жаралы колитпен ауыратын 68 - пациент зерттелді, олар аурудың белсенділік деңгейі мен қолданылған емдеу әдістеріне қарай топтарға бөлінді. Сондай-ақ, клиникалық тұрғыдан сау 80 - адам бақылау тобына енгізілді. Эндотелий жағдайының бірнеше параметрі зерттелді: қан айналымының құрамындағы эндотелиоциттер (АЭ) саны, азот тотығы (NO) метаболиттері мен эндотелин-1 деңгейі, эндотелийге тәуелді вазодилятация деңгейі. сонымен қатар, 1 жылға созылған проспективті бақылау барысында рецидивтердің жиілігі мен даму мерзімдері анықталды.

Нәтижелер: Негізгі және бақылау топтарындағы эндотелидің қызметінің көрсеткіштері арасында айтарлықтай айырмашылық байқалды (эндотелин-1 белсенділігінің 119,5%-ға артуы, $p<0,01$; айналымдағы эндотелиоциттердің 88,4%-ға көбеюі, $p<0,001$). Ауру белсенділігі бойынша бөлінген науқас топтарының ішінде АЭ деңгейінде елеулі айырмашылықтар анықталды, бірақ эндотелинің қызметіне байланысты басқа параметрлер бойынша айтарлықтай ерекшеліктер байқалмады. Минималды белсенділік деңгейінде бақылау тобымен айырмашылықтар іс жүзінде анықталмады. Емдеу барысында клиникалық топтар арасында тек АЭ деңгейі бойынша айырмашылықтар болды – 18,8%-ға төмендеу ($p=0,043$). Орташа белсенділік деңгейі бар науқастарда эндотелиге әсер ету ремиссия жиілігінің жоғарылауына және оның тезірек дамуына ықпал етті. 1-топтың пайдасына айырмашылықтар ремиссия жиілігі бойынша 50,8% ($t=0,032$, $p<0,05$), ал ремиссия басталу уақыты бойынша 46,3% ($p=0,013$) болды.

Қорытындылар:

1. Бейспецификалық жаралы колит ағымы эндотелидің дисфункциясымен қатар жүреді, бұл вазодилятация мен вазоконстрикция арасындағы теңгерімнің бұзылуы, вазодилятация деңгейінің төмендеуі және қан тамырлары эндотелий қабатының зақымдануымен сипатталады.

2. Ауру белсенділігі мен эндотелидің функциясының бұзылу деңгейі арасында байланыс бар, яғни ауру неғұрлым ауыр болса, эндотелижің дисфункциясы соғұрлым жоғары болады. Бұл эндотелий дисфункциясының бейспецификалық жарыл колиттің патогенезіндегі рөлін көрсетеді.

3. Медикаментозды емдеу эндотелий дисфункциясының деңгейін төмендетуге мүмкіндік береді және оның әсері ұзақ уақыт сақталады.

Түйінді сөздер: *спецификалық емес ойық жаралы колит, эндотелидің дисфункциясы, қан тамырларының кеңеюі, қан тамырларының тарылуы.*

Дәйексөз үшін: *Калимолдина Г.К., Муздубаева Ж.Е., Ботабаева А.С., Оразалина А.С., Каскабаева А.Ш., Жумадилова З.К.* Неспецификалық ойық жаралы колит кезіндегі эндотелий дисфункциясы және оны емдеу кезінде түзету мүмкіндіктері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 56-65. *doi 10.34689/SH.2025.27.1.007*

Актуальность

Неспецифический язвенный колит – тяжёлое хроническое заболевание, имеющее значительную распространённость в мире [11,22]. В различных странах показатель морбидности составляет от 100 до 750 на 100000 населения в развитых и до 1230 на 1000000 населения в развивающихся странах [12,31].

Несмотря на развитие способов лечения, включающих, главным образом, медикаментозную терапию, полное выздоровление при этом заболевании практически недостижимо, а частота и продолжительность ремиссий определяется в первую очередь тяжестью процесса [8,30]. В результате данная патология даёт большое негативное влияние на показатели здоровья населения и наносит существенный экономический ущерб [26].

Основным подходом к лечению при НЯК является патогенетическая терапия, направленная на ограничение общих и местных механизмов воспаления [32]. Одним из возможных направлений при этом оказывается учёт наличия и коррекция эндотелиальной дисфункции [15,28].

Цель исследования: Определить особенности функции сосудистого эндотелия в соотношении с клиническим течением неспецифического язвенного колита в динамике лечения.

Материалы и методы

Проспективное одноцентровое клиническое исследование, проведенное в период с 2021-2024 гг. в Университетском госпитале НАО «Медицинский университет Семей». Тема исследования была одобрена Этической комиссией НАО «Медицинский университет Семей», протокол №7 от 31.03.2022 г.

Число обследованных больных – 68 человек. Контрольную группу здоровых лиц составили – 80 человек.

Первый этап – осуществление комплексного обследования больных с определением эндотелиальной функции после первичного включения в исследование, выявление клинико-лабораторных и клинико-инструментальных ассоциаций.

Второй этап – экспериментальное лечение больных с попыткой воздействия на показатели эндотелиальной функции. Срок проспективного наблюдения – 1 год.

Критерии включения пациентов:

- возраст старше 18 лет и моложе 71 года;
- верифицированный диагноз язвенного колита;
- наличие информированного согласия пациента на участие в исследовании, проведение дополнительных методов лечения и использование данных в научной работе.

Критерии исключения:

- молниеносная форма течения колита;
- наличие сопутствующей тяжелой соматической, онкологической, инфекционной патологии, не позволяющей провести обследование в полном объеме или модифицирующей исследуемые патогенетические механизмы;
- беременность и ранний послеродовый период;
- отказ от участия в исследовании на любом этапе до окончания анализа материалов.

Общая и клиническая характеристика больных (таблица 1).

Таблица 1.

Характеристика обследованных больных НЯК и распределение их по группам в отношении проводимого лечения / *(Table 1. Characteristics of the studied patients with Ulcerative Colitis and their distribution by group in relation to the treatment administered)*

Показатель		Группа 1, n=35		Группа 2, n=33	
		число обследованных	%	число обследованных	%
1		2	3	4	5
Средний возраст, лет		46,5±5,3		47,1±5,0	
Пол:	Мужской	16	45,7	16	48,5
	Женский	19	54,3	17	51,5
Распределение по локализации процесса	Дистальный колит	15	42,9	12	36,4
	Левосторонний колит	16	45,7	15	45,5
	Тотальный колит	4	11,4	6	18,2
Распределение в зависимости от степени активности НЯК	Минимальная (1 ст.)	3	8,6	2	6,1
	Умеренная (2 ст.)	23	65,7	22	66,7
	Резко выраженная (3 ст.)	9	25,7	9	27,3
Распределение в зависимости от течения НЯК	Острое	4	11,4	6	18,2
	Хроническое непрерывное	20	57,1	17	51,5
	Хроническое рецидивирующее	11	31,4	10	30,3
Распределение в зависимости от степени тяжести НЯК	1 ст.	7	20,0	6	18,2
	2 ст.	21	60,0	20	60,6
	3 ст.	7	20,0	7	21,2

Среди обследованных пациентов было практически равное число мужчин и женщин. Отмечалось умеренное преобладание дистальной локализации колита и относительная редкость тотального колита. В 2/3 случаев была определена умеренная степень активности колита и только у 5 пациентов – минимальная. По течению заболевания преобладали хроническое непрерывное и хроническое рецидивирующее. В 60% случаев была определена 2 степень тяжести заболевания, по 20% первая и третья степени.

Общая характеристика контрольной группы.

В качестве контрольной группы обследованы 80 человек в возрасте от 20 до 70 лет, средний возраст – 45,8±5,7 года, 40 мужчин и 40 женщин, клинически здоровых, т.е., не имеющих на момент обследования хронических заболеваний в стадии суб- и декомпенсации, острых заболеваний, которым никогда в жизни не устанавливался диагноз язвенного колита и других хронических заболеваний толстой кишки вне зависимости от стадии.

Первичное обследование пациентов осуществлялось при включении их в исследование, в условиях стационара (1-2 сутки пребывания), повторное – через 1 месяц после первичного. Срок проспективного наблюдения за клиническим течением заболевания составил 1 год.

Методы исследования: Общеклинические, лабораторные, инструментальные.

В работе использованы данные полного клинико-лабораторного и инструментального обследования пациентов в соответствии с Протоколом диагностики и лечения.

Методы исследования состояния эндотелия.

Содержание эндотелина-1 определяли методом иммуноферментного анализа с использованием диагностикума Human EDN1 ELISA Kit, Fine Biotex, EH0648.

Метаболиты NO в крови определяли по методике Карпюк В.Б. и соавт. [2]

Выявление изменения поперечного размера просвета a.brachialis при использовании пробы с реактивной гиперемией (эндотелийзависимая реакция) производилось линейным способом, предложенным D. Celermajer и соавт. в модификации Затейщикова Д.А. [1].

Для количественного обнаружения находящихся в крови циркулирующих (слущенных) эндотелиальных клеток (ЦЭ) использована методика, основанная на подсчёте эндотелиальных клеток вместе с красными кровяными пластинками с последующей АДФ-зависимой агрегацией тромбоцитов и выделением пула ЦЭ [18].

Статистические методы.

При анализе использованы параметрические и непараметрические методы. Сравнение количественных признаков проводилось с помощью критерия Стьюдента, для непрерывных переменных – парного критерия Стьюдента, при несовпадении с условиями применимости – по критерию Манна-Уитни и в динамике – по критерию Вилкоксона. Сравнение относительных значений проводилось с использованием критерия χ^2 Пирсона. Граничным уровнем для опровержения нулевой гипотезы принимали $p<0,05$ [17].

Результаты исследования

1 этап.

Данные о состоянии исследованных показателей функции сосудистого эндотелия при сравнении основной и контрольной группы представлены в таблице 2.

Таблица 2.

Сравнительная характеристика показателей сосудистого эндотелия у пациентов общей группы и клинически здоровых лиц / *(Table 2. Comparative characteristics of vascular endothelial parameters in patients of the overall group and clinically healthy individuals).*

Показатель	Контроль, n=80	Больные НЯК, n=68	P
Мет.NO, %	76,2±4,7	103,9±7,7	0,019
Эндотелин-1, нг/мл	0,78±0,09	1,71±0,13	0,004
ЭЗВД, %	18,9±1,1	14,0±1,2	0,022
ЦЭ на 1000 тр.	1,7±0,1	3,2±0,3	0,001

Реакция со стороны сосудистого эндотелия на патологический процесс при НЯК была выраженной. Все исследованные показатели имели значимые различия с контролем. Содержание метаболитов NO у пациентов превышало контрольное на 36,4% ($p<0,05$), а активность эндотелина -1 – на 119,5% ($p<0,01$).

Средний показатель ЭЗВД был ниже у пациентов на 25,9% ($p<0,05$). Напротив, содержание циркулирующих эндотелиоцитов было резко превышено (на 88,4%, $p<0,001$).

Далее было проведено распределение полученных результатов в зависимости от степени активности НЯК (таблица 3).

Таблица 3.

Показатели эндотелиальной функции у пациентов с различной степенью активности НЯК /
(Table 3. Endothelial function parameters in patients with varying degrees of ulcerative colitis activity).

Показатель	Группа обследованных			
	Контроль, n=80	НЯК 1 ст. активности, n=36	НЯК 2 ст. активности, n=21	НЯК 3 ст. активности, n=11
Мет.NO, %	76,2±4,7	93,5±6,9	104,7±8,5	131,8±12,7*
Эндотелин-1, нг/мл	0,78±0,09	1,33±0,12	1,69±0,15*	2,13±0,25*
ЭЗВД, %	18,9±1,1	15,5±1,1	14,3±1,2	9,1±1,0*#
ЦЭ на 1000 тр.	1,7±0,1	2,8±0,2*	3,1±0,2*	5,0±0,4*#
Примечание: * - различия с показателем контрольной группы имеют значимость, $p<0,05$ # - различия с показателем группы НЯК 1 ст. активности имеют значимость, $p<0,05$				

По ряду исследованных параметров имелась существенная зависимость состояния эндотелиальной функции от степени активности НЯК. Сравнение осуществлялось как с контролем, так и между подгруппами пациентов, выделенными по данному признаку.

Значимое превышение содержания метаболитов NO в крови над контрольной группой было определено только при 3 ст. активности НЯК. Различия составили RR=1,73, p=0,043. В то же время между подгруппами пациентов с разной степенью активности процесса не было значимых различий.

По активности эндотелина-1 значимое превышение над контрольной группой было определено в подгруппах пациентов со 2 ст. активности (RR=2,17, p=0,025) и с 3 ст. активности (RR=2,73, p=0,011), но не при 1 ст. активности. Также не было значимых различий между подгруппами.

Анализ различий по показателю ЭЗВД определил наличие значимых различий в двух случаях – между пациентами с 3 ст. активности НЯК и контрольной группой (RR=2,07, p=0,028) и 1 и 3 ст. активности (RR=1,70, p=0,044).

Содержание циркулирующих эндотелиоцитов в крови значимо превосходило контрольный показатель во всех подгруппах обследованных. При 1 ст. активности различия были наименьшими (RR=1,65, p=0,047); при 2 ст. активности – более выраженными (RR=1,82, p=0,033) и при 3 ст. активности – максимальными (RR=2,95, p=0,009). Также было определено превышение показателя при 3 ст. активности над 1 ст. активности (RR=1,79, p=0,040) и над 2 ст. активности (RR=1,62, p=0,048).

Таким образом, по всем исследованным параметрам значимые различия с контролем удалось установить только в подгруппе с 3 ст. активности НЯК, при этом показатели ЭЗВД и содержания в крови ЦЭ имели также превышение в этой подгруппе над лицами с меньшей степенью активности процесса.

2 этап.

На втором этапе было осуществлено сравнение результатов воздействия стандартного лечения (группа 1) и разработанного подхода с дополнительной коррекцией функции сосудистого эндотелия (группа 2) на показатели эндотелиальной функции

При анализе показателей состояния сосудистого эндотелия значимыми показателями были приняты содержание метаболитов монооксида азота в крови, активность эндотелина-1, эндотелий-зависимая вазодилятация и число циркулирующих эндотелиоцитов в крови.

Следует отметить, что первый из представленных параметров можно связать не только с функцией эндотелия, но и кишечного эпителия, который при НЯК заведомо имеет нарушения функции. Однако, в соответствии с исследованиями [3], наиболее мощным источником NO в ЖКТ является тонкая кишка. Продукция NO эпителием толстой кишки никак не может быть сравнима с эндотелиальной [5].

При анализе полученных данных было выявлено, что содержание метаболитов NO в крови у пациентов обеих групп было значимо повышено (на 34,5% в группе 1 и на 36,2% - в группе 2). При этом достигнутое снижение в группе 1 не дало нормализации показателя (превышение на 30,6%, p=0,043), а в группе 2 – обеспечило таковую. Различия с группой 1 при этом не были значимыми.

Содержание эндотелина-1 повышается при многих патологических состояниях (воспалительные заболевания, онкологическая патология, сердечно-сосудистые заболевания, патогенез которых связан с атеросклерозом сосудов). В нашей работе мы определили наличие значимого повышения данного показателя при первичном обследовании пациентов (на 98,7% в группе 1 и на 103,8% - в группе 2, p=0,018 и p=0,014 соответственно). При контрольном обследовании через 1 мес. различия с контролем для группы 1 составили 75,6% (p=0,037) и для группы 2 – 16,7% (p>0,05). Между группами различия в этот срок были значимыми (33,6%, p=0,040).

Показатель эндотелийзависимой вазодилятации является одним из ключевых в отношении комплексной характеристики функционального состояния эндотелия. Несмотря на сомнения некоторых исследователей в его точности и воспроизводимости [6], современное оборудование для ультразвуковой диагностики позволяет получить адекватные данные, могущие являться основной для доказательных исследований [4].

Таблица 4.

Показатели сосудистого эндотелия у больных НЯК в начале и динамике лечения / *(Table 4. Vascular endothelial parameters in patients with ulcerative colitis at baseline and during treatment).*

Показатель	Контрольная группа, n=80	Группа 1, n=35	Группа 2, n=33	Группа 1	Группа 2
Мет.NO, %	76,2±4,7	102,5±7,3*	103,8±7,5*	99,5±7,7*	85,1±6,5
Эндотелин-1, нг/мл	0,78±0,09	1,55±0,11*	1,59±0,12*	1,37±0,10*	0,91± 0,10@#
ЭЗВД, %	18,9±1,1	14,2±0,9*	14,0±0,8*	13,5±0,9*	15,9±1,1
ЦЭ на 1000 тр.	1,7±0,1	3,3±0,2**	3,2±0,2**	3,2±0,2**	2,6±0,1*@#
Примечания: * - различия с контрольной группой статистически значимы, p<0,05, ** - p<0,01; @ - различия между показателями до и после лечения значимы, p<0,05; # - различия между показателями в группах после лечения значимы, p<0,05					

В нашей работе было определено снижение показателя, значимое в группах 1 и 2 до лечения и в группе 1 – при повторном обследовании, соответствующие различия с контролем составили 24,9% (p=0,027), 25,8% (p=0,021) и 28,6% (p=0,019). В группе 2 было определено повышение показателя, не имеющее статистической значимости ни в отношении контрольной группы, ни группы 1.

Признаком повреждения сосудистого эндотелия служит повышение содержания в крови циркулирующих эндотелиоцитов. Нами были выявлены значимые различия с контрольной группой в обеих группах исследования в оба срока наблюдения. При исходном обследовании степень превышения достигала 94,1% и 88,2% (p=0,008, p=0,009). Через 1 мес. соответствующие различия составили 88,1% (p=0,008) и 52,9% (p=0,016), а между группами – 18,8% (p=0,043).

Таким образом, анализ показателей состояния сосудистого эндотелия во всех случаях продемонстрировал наличие значимых отклонений от контроля в стороны снижения вазодилятирующей и повышения вазоконстрикторной функции, что характерно для многих форм патологии [29]. При применении разработанного подхода к лечению наблюдалось снижение степени нарушений, не доходящее до полной нормализации, но по части показателей достигающее степени значимости в отношении группы 1.

Кроме того, была проанализирована частота и сроки наступления клинической ремиссии при аналогичном распределении обследованных (рисунки 1 и 2).

У пациентов с 1 ст. активности полная ремиссия была достигнута на 1-2 неделях лечения, главным образом, в условиях стационара. Поэтому графического отображения полученных данных мы не приводим.

У пациентов со 2 ст. активности заболевания частота ремиссии была существенно выше в основной группе, а сроки ее развития сокращались.

По первому из указанных параметров различия в пользу группы 1 составили 50,8% (t=0,032, p<0,05). По второму параметру различия составили 46,3% (p=0,013).

Таким образом, применение разработанного способа у пациентов данной категории способствует повышению частоты клинической ремиссии на 1/3 и сокращение сроков её достижения наполовину.

Число пациентов с 3 ст. активности в подгруппах было небольшим (n=7). Соответственно, даже при наличии различий последние не имели статистической значимости. Превышение частоты достижения ремиссии в пределах срока наблюдения в группе 1 составило 66,7% (t=0,347, p>0,05). Срок наступления ремиссии в группе 1 также был меньшим, различия составили 27,3% (p=0,104).

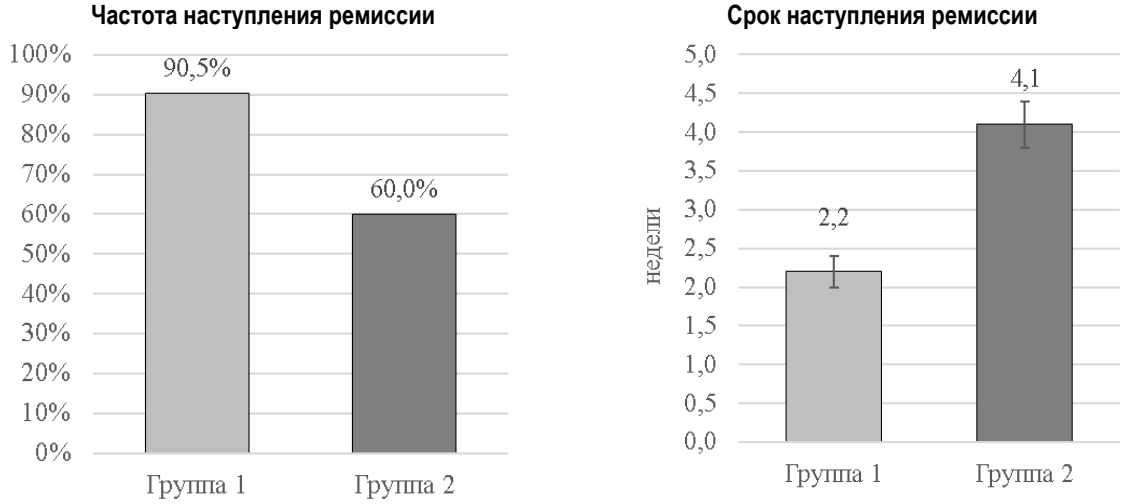

Рисунок 1. Частота (в срок до 3 мес.) и время наступления клинической ремиссии у больных НЯК 2 степени активности.

(Figure 1. Frequency (within 3 months) and time to clinical remission in patients with ulcerative colitis of activity grade 2).

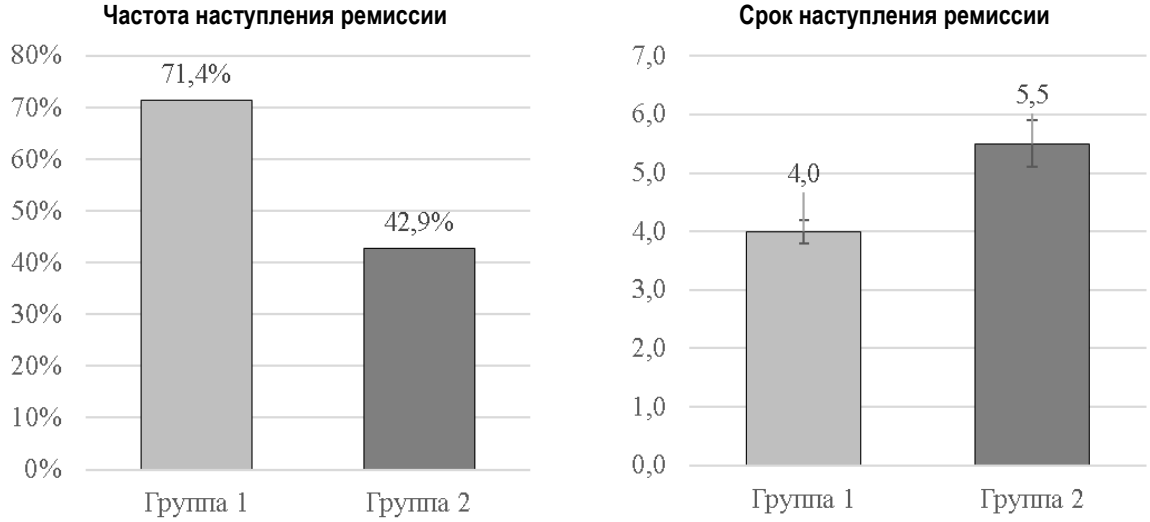

Рисунок 2. Частота (в срок до 3 мес.) и время наступления клинической ремиссии у больных НЯК 3 степени тяжести.

(Figure 2. Frequency (within 3 months) and time to clinical remission in patients with severe ulcerative colitis.)

Учитывая относительно небольшое число обследованных, достигших клинической ремиссии, во всех подгруппах, для анализа её продолжительности мы не распределяли данные в зависимости от степени активности процесса. Полученные результаты анализа представлены на рисунке 3.

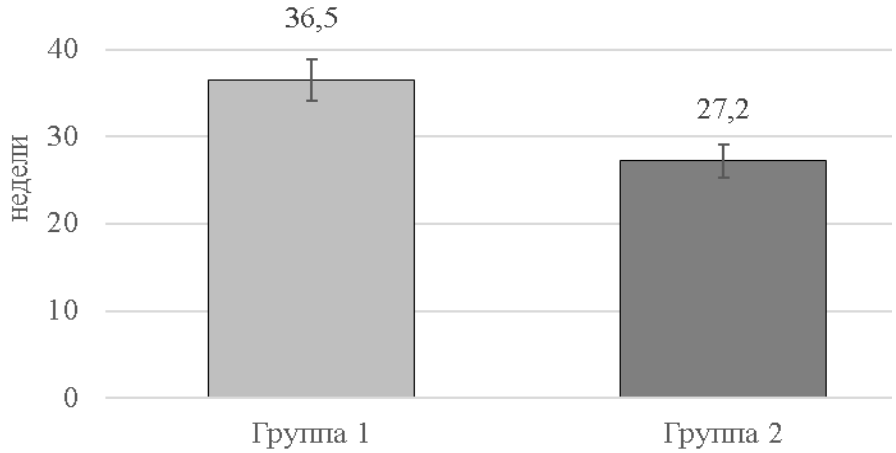

Рисунок 3. Средняя продолжительность клинической ремиссии у больных НЯК в зависимости от лечения.

(Figure 3. Average duration of clinical remission in patients with UC depending on treatment).

Обсуждение результатов

Эндотелиальная дисфункция при воспалительных заболеваниях является одним из типических процессов и тесно связана с другими патогенетическими механизмами [10]. Так, прослежено взаимное влияние нарушений эндотелиальной функции и состояния иммунной системы на уровне регуляторных [25] и клеточных эффекторных факторов [16]. Еще более известны ассоциации эндотелиальной дисфункции с активацией сосудисто-тромбоцитарного звена системы гемостаза и повышением риска активации коагуляционного каскада [21,27,33], что определяет снижение микроциркуляции в зоне воспаления и вероятность макроциркуляторных нарушений [9].

В нашем исследовании было определено в первую очередь – наличие эндотелиальной дисфункции как в целом по группе обследованных пациентов с неспецифическим язвенным колитом, так и у подавляющего большинства таковых. При этом все определяемые факторы (повреждение эндотелия, гиперактивация проагрегантных свойств, нарушение регуляции тонуса сосудов) оказались выявлены. Во-вторых, было доказано наличие достоверной взаимосвязи степени нарушений со стороны эндотелия и активности НЯК. Данный аспект косвенно подтверждает роль эндотелиальной дисфункции в патогенезе заболевания, на что также имеются указания в зарубежных исследованиях последних лет. В-третьих, определены возможности медикаментозной коррекции дисфункции эндотелия, влияние использованного способа на исследованные показатели эндотелиальной функции и течение НЯК.

При сравнительном анализе с исследованиями, выполненными в аналогичном направлении, следует отметить сходство результатов по направленности и уровню нарушений эндотелия в отношении его повреждения, определяемого по содержанию в крови десквамированных клеток [19,20], а также наличие в литературе различных данных в отношении баланса вазоконстрикторных и вазодилятирующих факторов [14,23]. Сложные связи продукции монооксида азота как сосудистым эндотелием, так и эпителием кишечника, не позволяют однозначно оценить роль содержания метаболитов оксида азота в крови как маркёра конкретного патогенетического механизма, если это не синдром ишемии-реперфузии [24]. Тем не менее, выявленные в нашем исследовании показатели вполне укладываются в гипотезу о превышении проагрегантного и прокоагулянтного потенциала эндотелия при НЯК [7,13].

Недостатком исследования, как мы полагаем, является отсутствие экспериментального (на животных) подтверждения сформулированной гипотезы. Также, по необходимости, мы обследовали ограниченный контингент пациентов, который был распределён, вдобавок, на дополнительные подгруппы для оценки взаимосвязей. Положительным моментом мы считаем проведение лечения и оценку результатов в сравнении с исходными показателями и контролем в течение достаточно продолжительного периода времени.

Заключение.

1. Течение НЯК сопровождается наличием эндотелиальной дисфункции, определяемой нарушением баланса вазодилятирующих и вазоконстрикторных факторов, снижением вазодилятации, а также повреждением эндотелиального слоя сосудистой стенки.

2. Имеется связь активности процесса и уровня нарушений эндотелиальной функции с увеличением таковых при более высоких степенях активности, что является свидетельством патогенетической роли дисфункции эндотелия при НЯК.

3. Посредством медикаментозного лечения возможно уменьшение степени эндотелиальной дисфункции, сохраняющееся в течение длительного времени.

Вклад авторов - *все авторы одинаково относятся к поиску литературы и написанию этой статьи.*

Разногласия-*авторы утверждают, что разногласий нет.*

Финансирование - *не проводилось.*

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NON-VARICOSE BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT

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Abstract

Introduction. Non-variceal upper gastrointestinal bleeding (NVUGIB) is one of the most critical issues in emergency surgery. This pathology is characterized by a high prevalence and significant mortality rates, especially among elderly patients and individuals with comorbid conditions.

Aim. To study the treatment outcomes of patients with non-variceal upper gastrointestinal bleeding.

Materials and methods. A retrospective study was conducted among n = 667 patients who received inpatient treatment at the surgical department of the City Emergency Hospital in Almaty from January 1, 2019, to December 31, 2023. Mean values (M ± m) and differences between arithmetic means were assessed using Student's *t*-test. The relationship between clinical parameters and outcomes was evaluated using the chi-square (χ^2) test. Risk factors for adverse outcomes (mortality, rebleeding, need for surgical treatment) were analyzed using logistic regression. The impact of factors was assessed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI). A *p*-value < 0.05 was considered statistically significant.

Results. The primary causes of bleeding were acute ulcers (60.4%), Mallory-Weiss syndrome (20.4%), chronic ulcers (13.2%), and bleeding of unknown etiology (6.0%). According to the Forrest classification, the most common form was IIB (54.5%). The overall rebleeding rate was 6.9%, while the total mortality rate was 3.6%. Mortality rates by etiology were as follows: acute ulcers – 2.7%, chronic ulcers – 5.6%, Mallory-Weiss syndrome – 0.7%, and bleeding of unknown etiology – 17.5%. The average surgical intervention rate during the study period was 2.8%.

Conclusions. Thus, non-variceal upper gastrointestinal bleeding remains a pressing issue in gastroenterology and surgery, requiring a comprehensive approach to diagnosis and treatment. The study confirmed the high prevalence of peptic ulcer disease, Mallory-Weiss syndrome, and erosive lesions as leading causes of bleeding. The main risk factors for NVUGIB include the use of anticoagulants, nonsteroidal anti-inflammatory drugs, and cardiovascular diseases, highlighting the necessity of careful medication management in patients at high risk of bleeding.

Keywords: *peptic ulcer disease, gastrointestinal bleeding, endoscopic hemostasis, acute ulcers, non-variceal bleeding.*

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Резюме

НЕВАРИКОЗНЫЕ КРОВОТЕЧЕНИЯ ИЗ ВЕРХНИХ ОТДЕЛОВ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Введение. Неварикозные кровотечения из верхних отделов желудочно-кишечного тракта (НВК ВОЖКТ) — одна из важнейших проблем в экстренной хирургии. Данная патология характеризуется высокой распространённостью и значительными показателями летальности, особенно среди пациентов старших возрастных групп и лиц с сопутствующими патологиями.

Цель. Изучение результатов лечения пациентов с неварикозными кровотечениями из верхних отделов желудочно-кишечного тракта.

Материалы и методы. Ретроспективное исследование проведено среди n=667 пациентов, получивших стационарное лечение в хирургическом отделении Городской больницы скорой неотложной помощи г. Алматы в период с 1 января 2019 года по 31 декабря 2023 года. Средние значения (M±m) и различия между средними арифметическими величинами оценивались с использованием критерия Стьюдента (t). Для оценки связи между клиническими параметрами и результатами использовался критерий χ^2 (хи-квадрат). Оценка факторов риска развития неблагоприятных исходов (летальности, рецидива кровотечения, потребности в хирургическом лечении) проводилась с использованием логистической регрессии. Влияние факторов оценивалось путем расчета отношения шансов (OR) с 95% доверительным интервалом (95% ДИ). Значение $p<0,05$ считалось статистически значимым.

Результаты. Основными причинами кровотечений были острые язвы (60,4%), синдром Мэллори-Вейса (20,4%), хронические язвы (13,2%) и кровотечения неизвестной этиологии (6,0%). По классификации Forrest наиболее часто встречалась форма IIB (54,5%). Общий уровень рецидив кровотечений составил 6,9%, а общая летальность — 3,6%. Всего летальность составила 3,6%. Из них при острых язвах — 2,7%, хронических язвах — 5,6%, синдроме Мэллори-Вейса — 0,7%, кровотечениях неясной этиологии — 17,5%. Хирургическая активность в исследуемый период составила в среднем 2,8%.

Выводы. Таким образом, неварикозное кровотечение из верхних отделов желудочно-кишечного тракта остается актуальной проблемой гастроэнтерологии и хирургии, требующей комплексного подхода к диагностике и лечению. Проведенное исследование подтвердило высокую распространенность язвенной болезни, синдрома Мэллори-Вейса и эрозивных поражений как ведущих причин кровотечений. Основными факторами риска развития НВК ВОЖКТ остаются прием антикоагулянтов, нестероидных противовоспалительных препаратов, сердечно-сосудистые заболевания, что требует тщательной коррекции медикаментозной терапии у пациентов с высокой предрасположенностью к кровотечениям.

Ключевые слова: *язвенная болезнь, желудочно-кишечное кровотечение, эндоскопический гемостаз, острые язвы, неварикозные кровотечения.*

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Түйіндеме

ЖОҒАРҒЫ АСҚАЗАН-ІШЕК ЖОЛДАРЫНАН ВАРИКОЗДЫ ЕМЕС ҚАН КЕТУ

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Кіріспе. Жоғары асқазан-ішек жолдарынан варикозды емес қан кетулер (ЖАІЖ ВЕҚ) жедел хирургиядағы ең маңызды мәселелердің бірі. Бұл патология егде жастағы науқастар мен қосалқы аурулары бар адамдар арасында жоғары таралуымен және өлім-жітім көрсеткіштерінің айтарлықтай деңгейімен сипатталады.

Мақсаты. Жоғарғы асқазан-ішек жолдарының варикозды емес қан кетулері бар науқастардың емдеу нәтижелерін зерттеу.

Материалдар мен тәсілдер. Ретроспективті зерттеу Алматы қаласындағы Жедел жәрдем қалалық ауруханасының хирургия бөлімшесінде 2019 жылғы 1 қаңтар мен 2023 жылғы 31 желтоқсан аралығында стационарлық ем қабылдаған n=667 науқас арасында жүргізілді. Орташа мәндер (M±m) мен орташа

арифметикалық шамалар арасындағы айырмашылықтар Стьюдент критерийі (t) көмегімен бағаланды. Клиникалық параметрлер мен нәтижелер арасындағы байланысты бағалау үшін χ^2 (хи-квадрат) критерийі қолданылды. Қолайсыз нәтижелердің (өлім-жітім, қан кетудің қайталануы, хирургиялық емдеуге қажеттілік) даму қаупі факторларын бағалау логистикалық регрессия әдісі арқылы жүргізілді. Факторлардың әсері шанс қатынасы (OR) және 95% сенімділік интервалын (95% CI) есептеу арқылы бағаланды. $p<0,05$ мәні статистикалық тұрғыдан маңызды деп қабылданды.

Нәтижелер. Қан кетудің негізгі себептері жедел ойық жаралар (60,4%), Мэллори-Вейсс синдромы (20,4%), созылмалы ойық жаралар (13,2%) және этиологиясы белгісіз қан кетулер (6,0%) болды. Forrest жіктемесі бойынша жиі кездесетін түр IIB (54,5%) анықталды. Жалпы қан кетудің қайталану деңгейі 6,9%, ал жалпы өлім-жітім 3,6% құрады. Өлім-жітім көрсеткіші жедел ойық жаралар кезінде — 2,7%, созылмалы ойық жараларда — 5,6%, Мэллори-Вейсс синдромында — 0,7%, этиологиясы белгісіз қан кетулерде — 17,5% деңгейінде тіркелді. Зерттелген кезеңде хирургиялық белсенділік орташа 2,8% жетті.

Қорытындылар. Осылайша, жоғарғы асқазан-ішек жолдарының варикозды емес қан кетулері гастроэнтерология мен хирургиядағы өзекті мәселе болып қала беруде, оның диагностикасы мен емдеуіне кешенді тәсіл қажет. Зерттеу нәтижелері ойық жара ауруының, Мэллори-Вейсс синдромының және эрозиялық зақымданулардың қан кетудің негізгі себептері екенін растады. ЖАІЖ ВЕК дамуының негізгі қауіп факторлары антикоагулянттар мен стероидты емес қабынуға қарсы препараттарды қабылдау, жүрек-қан тамырлары аурулары, бұл қан кетуге жоғары бейімділігі бар науқастарда дәрілік терапияны мұқият түзетуді талап етеді.

Түйінді сөздер: *асқазан мен он екі елі ішектің ойық жарасы, асқазан-ішек қан кетулері, эндоскопиялық гемостаз, жедел ойық жаралар, варикоздық емес қан кетулер.*

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Introduction

Non-Variceal Upper Gastrointestinal Bleeding (NVUGIB) is one of the most severe and life-threatening conditions encountered in surgical practice. According to global statistics, the incidence of NVUGIB ranges from 84 to 160 cases per 100,000 population annually. Mortality among patients with this pathology varies between 5% and 21% [4, 9].

Epidemiological studies indicate that men are significantly more affected by NVUGIB than women, with a male-to-female ratio ranging from 2:1 to 3:1. The highest incidence is observed in individuals aged 40 to 70 years. Mortality associated with NVUGIB remains substantial, reaching 3% to 8%, particularly among elderly patients and those with severe comorbidities. However, over the past 10–15 years, mortality rates have declined due to the widespread adoption of endoscopic hemostasis and advancements in intensive care [10].

A retrospective study encompassing data from 101,703 patients across 254 medical institutions in Kazakhstan between 2014 and 2023 revealed a 24.5% increase in NVUGIB cases, rising from 7,497 to 9,331. Over this period, men accounted for 69.3% of cases, while women represented 30.7%. The mortality rate for NVUGIB decreased from 5.9% to 3.0% [6].

The outcomes of NVUGIB treatment are influenced by multiple factors, including patient age, comorbidities, the source of bleeding, the volume of blood loss, the implementation of endoscopic hemostasis, recurrence of bleeding, and other clinical variables [8].

Over the past decade, mortality rates from upper gastrointestinal bleeding (UGIB) have significantly declined due to advancements in pharmacotherapy, intraluminal endoscopy, widespread use of endoscopic hemostasis, and improvements in intensive care [4, 6, 11]. Current meta-analyses demonstrate that the efficacy of combined endoscopic hemostatic techniques ranges from 54% to 98% [4, 12].

Despite these advancements, the recurrence rate of bleeding following endoscopic hemostasis for peptic ulcer bleeding remains as high as 18%, with mortality exceeding 7%–9%. Moreover, patients with refractory or recurrent bleeding often require complex surgical interventions [5, 8].

Aim: To evaluate the treatment outcomes of patients with non-variceal upper gastrointestinal bleeding (NVUGIB).

Materials and methods. A retrospective study was conducted among n=667 patients who received inpatient treatment at the Surgical Department of the City Emergency Hospital in Almaty between January 1, 2019, and December 31, 2023, for non-variceal upper gastrointestinal bleeding.

Inclusion criteria:

- Patients aged 18 years and older who were urgently hospitalized due to non-variceal bleeding from the esophagus, stomach, or duodenum.

Exclusion criteria:

- Bleeding from esophageal and gastric varices.
- Bleeding from the lower gastrointestinal tract or pulmonary sources.
- Bleeding from malignant tumors of the upper gastrointestinal tract.

The study analyzed medical records of patients diagnosed with non-variceal UGIB, classified according to the ICD-10 system:

- K25.0 – Acute gastric ulcer with bleeding
- K26.0 – Acute duodenal ulcer with bleeding
- K27.0 – Peptic ulcer of unspecified location, acute with bleeding
- K28.0 – Acute gastrojejunal ulcer with bleeding
- K25.4 – Chronic or unspecified gastric ulcer with bleeding

- K26.4 – Chronic or unspecified duodenal ulcer with bleeding
- K22.6 – Gastroesophageal laceration-hemorrhagic syndrome
- K92.2 – Unspecified gastrointestinal hemorrhage

The study examined bleeding frequency concerning age and sex, length of hospital stay, surgical intervention rates, in-hospital and postoperative mortality, effectiveness of endoscopic hemostasis, and other clinical parameters.

All patients underwent a comprehensive analysis of clinical data, including laboratory and instrumental diagnostic findings. The endoscopic appearance of bleeding was assessed using the Forrest classification, endorsed by the European Society of Gastrointestinal Endoscopy (ESGE).

Statistical methods were employed for data processing. Mean values (M±m) and differences between arithmetic means were evaluated using Student's t-test (t-test). The association between clinical parameters and outcomes was assessed using the chi-square test (χ^2). Differences were considered statistically significant at $p<0.05$.

Data analysis was conducted using SPSS Statistics and Microsoft Office Excel. The normality of variable distribution was verified using the Shapiro–Wilk test. Normally distributed data were presented as means and standard deviations (M±m), and group comparisons were performed using Student's t-test.

For assessing associations between clinical parameters and outcomes, the chi-square test (χ^2) was used. Categorical variables were presented as frequencies (n) and percentages (%).

Risk factors for adverse outcomes (mortality, bleeding recurrence, and the need for surgical intervention) were evaluated using logistic regression. The impact of factors was assessed by calculating the odds ratio (OR) with a 95% confidence interval (95% CI). A p-value <0.05 was considered statistically significant.

Study Results.

Among the total cohort of 667 patients, 153 (22.9%) were hospitalized in 2019, 101 (15.1%) in 2020, 115 (17.2%) in 2021, 154 (23.1%) in 2022, and 144 (21.6%) in 2023 with signs of upper gastrointestinal bleeding. The decrease in the number of treated patients in 2020–2021 was due to the City Emergency Hospital functioning as a COVID-19 facility during the pandemic.

Patients were classified according to the World Health Organization (WHO) age classification. Males accounted for 445 (66.7%) of cases, while females represented 222 (33.3%). The mean patient age was 58.40±14.50 years, with an average of 58.00±14.30 years for men and 59.10±14.70 years for women, showing a statistically significant difference of 1.0±0.4 years ($p<0.01$). The highest incidence of NVUGIB was observed in the 60–74 age group (n=218, 32.7%), followed by the 45–59 age group (n=181, 27.1%) and the 18–44 age group (n=174, 26.1%).

Table 1.

Distribution of patients by gender and age.

Age Group (WHO Classification)		Total (n)	%	Male		Female	
				Total (n)	%	Total (n)	%
18–44 years	young age	174	26,1%	127	19%	47	7,1%
45–59 years	middle age	181	27,1%	123	18,4%	58	8,7%
60–74 years	elderly age	218	32,7%	138	20,7%	80	12%
75–90 years	senile age	89	13,3%	56	8,4%	33	4,9%
90+ years	longevity	5	0,8%	1	0,1%	4	0,7%
Total		667	100%	445	66,7%	222	33,3%

Between 2019 and 2023, an analysis of the etiology of non-variceal upper gastrointestinal bleeding (NVUGIB) among 667 patients revealed that acute ulcers accounted for 60.4% (n=403) of all cases. Chronic ulcers were notably less common, comprising 13,2% (n=88). A striking observation was the increasing prevalence of Mallory-Weiss syndrome, which rose to 20.4% (n=136) of all NVUGIB cases. Meanwhile, bleeding of unknown etiology remained relatively stable at 6.0% (n=40) (Figure 1).

Statistical analysis demonstrated that the proportion of acute ulcers was significantly higher than that of chronic ulcers ($\chi^2=9.45$, $p=0.002$). Moreover, there was a statistically significant upward trend in the incidence of Mallory-Weiss syndrome in recent years ($\chi^2=4.89$, $p=0.027$).

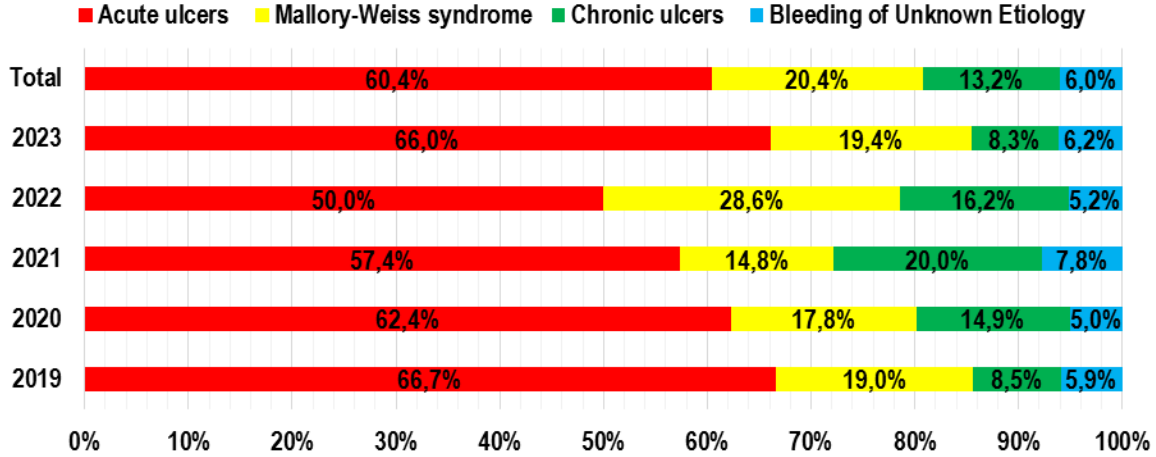

Figure 1. Distribution of patients by etiology of bleeding.

The primary risk factors for gastrointestinal bleeding included frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, and antiplatelet agents. Among the 667 patients, 463 had comorbid conditions: 35 (7.5%) had more than five diseases, 52 (11.2%) had five, 81 (17.5%) had four, 129 (27.9%) had three, 108 (23.3%) had two, and 58 (12.5%) had one comorbidity.

Cardiovascular diseases (21.7%) and respiratory conditions, including COVID-19 (13.2%), were the most prevalent comorbidities. Over the five-year study period, the proportion of patients with comorbidities fluctuated between 59% and 88% (Table 2). These findings underscore the impact of multimorbidity on the risk of gastrointestinal bleeding and highlight the necessity of a personalized treatment approach.

Statistical analysis confirmed that the presence of three or more comorbidities significantly increased the risk of gastrointestinal bleeding (χ^2=12.31, p<0.001). Cardiovascular diseases (21.7%) and respiratory disorders, including COVID-19 (13.2%), were the most influential factors. The use of anticoagulants and antiplatelet agents was associated with an elevated risk of gastrointestinal bleeding (OR=2.47, 95% CI: 1.58–3.85, p<0.001), whereas NSAID use increased the likelihood of bleeding by 1.8 times (OR=1.79, 95% CI: 1.02–3.15, p=0.042).

Table 2.

Distribution of Comorbidities in Patients with Non-Variceal Upper Gastrointestinal Bleeding (2019–2023).

№	Comorbidities	Total (n=463)	2019 (n=153)	2020 (n=101)	2021 (n=115)	2022 (n=154)	2023 (n=144)
1	Cardiovascular diseases	145 (21.7%)	28 (18.3%)	22 (21.8%)	25 (21.7%)	40 (26.0%)	30 (20.8%)
2	Respiratory diseases, including COVID-19	88 (13.2%)	32 (20.9%)	33 (32.6%)	6 (5.2%)	10 (6.5%)	7 (4.9%)
3	Renal diseases	80 (12.0%)	14 (9.2%)	12 (11.9%)	15 (13.0%)	22 (14.3%)	17 (11.8%)
4	Diabetes mellitus	70 (10.5%)	12 (7.8%)	11 (10.9%)	14 (12.2%)	18 (11.7%)	15 (10.4%)
5	Liver diseases	72 (10.79%)	20 (13.1%)	9 (8.9%)	12 (10.4%)	18 (11.7%)	13 (9.0%)
6	Musculoskeletal diseases	8 (1.2%)	1 (0.7%)	2 (2.0%)	0 (0.0%)	2 (1.3%)	3 (2.1%)
	Total	463 (69.4%)	107 (69.9%)	89 (88%)	72 (62.6%)	110 (71.4%)	85 (59%)

Drug-induced gastrointestinal (GI) tract lesions, particularly those associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants, and antiplatelet agents, represent a significant concern in clinical practice. Despite their proven efficacy, these medications have a broad range of adverse effects, including the development of peptic ulcers, gastritis, and GI bleeding, making their use potentially hazardous, especially in long-term therapy or in patients with comorbid conditions.

Among the study population, 25.2% of patients (168 cases) developed GI bleeding due to medication use, leading to drug-induced ulcers. The administration of anticoagulants and antiplatelet agents was associated with a significantly higher risk of GI bleeding compared to NSAID use (χ^2=6.85, p=0.008), emphasizing their role as major risk factors. NSAIDs were used by 55 patients (8.2%), while anticoagulants and antiplatelets were taken by 113 patients (16.9%). The latter group exhibited an increased risk of GI bleeding due to impaired coagulation and a higher probability of hemorrhagic complications (Table 3).

Upon admission, esophagogastroduodenoscopy (EGD) was performed in 95.9% of patients (640 out of 667). In 15 cases, EGD had been conducted at another hospital, while 7 patients were referred after undergoing endoscopic examination at an outpatient clinic. In 5 cases (0.7%), EGD was not performed due to the patients' critical condition.

Table 3.

Frequency of Drug-Induced Gastrointestinal Lesions.

№	Type of Medication	Total (n=667)	2019 (n=153)	2020 (n=101)	2021 (n=115)	2022 (n=154)	2023 (n=144)
1	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	55 (8.2%)	5 (0.7%)	12 (1.8%)	10 (1.5%)	15 (2.2%)	13 (1.9%)
2	Anticoagulants, Antiplatelet Agents	113 (16.9%)	19 (2.8%)	18 (2.7%)	22 (3.3%)	30 (4.5%)	24 (3.6%)
	Total	168 (25.2%)	24 (3.6%)	30 (4.5%)	32 (4.8%)	45 (6.7%)	37 (5.5%)

The Forrest classification of gastrointestinal bleeding is instrumental in determining the degree of hemorrhagic activity and guiding further treatment strategies [3, 12]. The majority of patients with hemorrhages fell into the IIB category—364 cases (58.6%). This type remained consistently prevalent across all study years, peaking in 2021 with 76 cases (66.1%). Category IIA accounted for 83 cases (12.4%), most frequently recorded in 2019 (30 cases, 19.6%). Types IA and IB had comparable incidence rates, with 65 (9.7%) and 64 (9.6%) cases, respectively. Type III hemorrhages were diagnosed infrequently, occurring in only 12 cases (1.8%). The highest number of severe hemorrhages (IA and IB) was recorded in 2023, potentially due to an increase in patients with complicated ulcers (Table 4).

Statistical analysis of the distribution of hemorrhage types according to the Forrest classification revealed significant differences in the prevalence of IIA and IIB types (χ^2=10.21, p=0.001). Additionally, in 2023, the proportion of severe hemorrhages (IA and IB) was significantly higher compared to previous years (χ^2=5.78, p=0.016).

According to the Gorbashko classification (1982), patients with mild bleeding accounted for 31.8%, while those with moderate bleeding constituted 55.2%, representing the highest proportion among all groups. Severe bleeding was observed in 13.0% of cases (Table 5).

Table 4.

Distribution of Patients by Forrest Classification.

Forrest Classification	Total	2019 (n=153)	2020 (n=101)	2021 (n=115)	2022 (n=154)	2023 (n=144)
Ia	65 (9.7%)	9 (5.9%)	12 (11.9%)	8 (7.0%)	14 (9.1%)	22 (15.3%)
Ib	64 (9.6%)	13 (8.5%)	9 (8.9%)	6 (5.2%)	17 (11.0%)	19 (13.2%)
IIa	83 (12.4%)	30 (19.6%)	14 (13.9%)	7 (6.1%)	16 (10.4%)	16 (11.1%)
IIb	364 (54.5%)	88 (57.5%)	38 (37.6%)	76 (66.1%)	86 (55.8%)	76 (52.8%)
IIc	52 (7.9%)	5 (3.3%)	17 (16.8%)	11 (9.6%)	13 (8.4%)	6 (4.2%)
III	12 (1.8%)	4 (2.6%)	2 (2.0%)	5 (4.3%)	0 (0.0%)	1 (0.7%)
Total	640 (95.9%)	149 (22.3%)	92 (13.8%)	113 (16.9%)	146 (21.9%)	140 (21%)

Table 5.

Distribution of patients by severity of blood loss according to the Gorbashko classification.

№	Year	Total Number	Severity of Hemorrhage		
			Mild	Moderate	Severe
1	2019	153	37 (24.2%)	96 (62.7%)	20 (13.1%)
2	2020	101	40 (39.6%)	52 (51.5%)	9 (8.9%)
3	2021	115	36 (31.3%)	65 (56.5%)	14 (12.2%)
4	2022	154	52 (33.8%)	79 (51.3%)	23 (14.9%)
5	2023	144	47 (32.6%)	76 (52.8%)	21 (14.6%)
Total		667 (100%)	212 (31.8%)	368 (55.2%)	87 (13.0%)

An analysis of mortality among patients with gastrointestinal bleeding over the period from 2019 to 2023 has revealed the following trends: the overall mortality rate was 3.6% (24 cases out of 667). The highest mortality rate was recorded in 2021 at 7.83% (9 cases out of 115), which was associated with the concentration of COVID-19 pneumonia cases complicated by gastrointestinal bleeding in the surgical department. In 2022, the mortality rate declined to 4.55% (7 cases out of 154). In contrast, the mortality rates in 2019 and 2020 remained relatively low—1.31% and 2.0%, respectively. In 2023, four deaths were recorded (2.8%), indicating a trend toward stabilization compared to the peak observed in 2021 (Figure 2).

A year-by-year mortality analysis identified statistically significant differences, with the highest rate occurring in 2021 (χ^2 = 12.34, p = 0.002). In subsequent years, a declining trend in mortality was noted, potentially attributable to improvements in treatment strategies and a reduction in the impact of COVID-19.

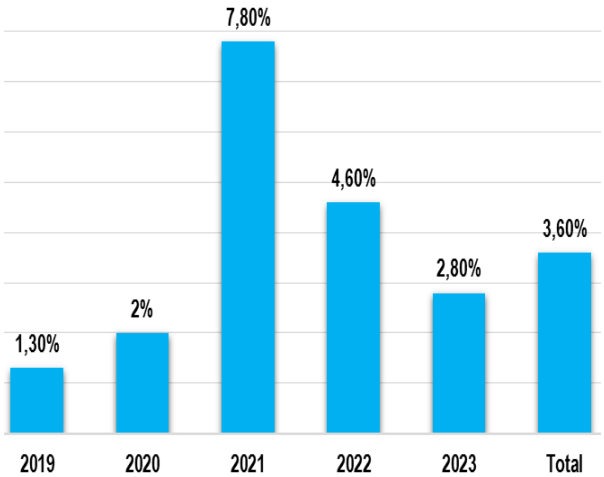

Figure 2. Mortality Rates by Year.

The standard conservative treatment was administered to 374 patients (56.1%). The primary hemostatic and wound-healing agents prescribed included proton pump inhibitors (570 patients, 85.5%), hemostatic agents (635 patients, 95.2%), and antiulcer medications (639 patients, 95.8%).

Endoscopic hemostasis was performed in 274 patients (42.8%). Injection hemostasis was used in 80.2% of cases (n=220), as injection methods are considered the safest and most effective. Hemostatic clipping was performed in 17 patients (6.2%), argon plasma coagulation in 12 patients (4.4%), and combined hemostasis in 25 patients (9.1%), reflecting the complexity of these procedures and potential complications.

Surgical intervention was less frequently required, performed in only 19 patients (2.8%). The most common procedure was gastrotomy with ulcer suturing (17 cases, 89.5%). Gastric resection was necessary in only two patients (10.5%). The low frequency of surgical interventions can be attributed to the effectiveness of conservative and endoscopic treatment methods (Figure 3).

The overall rebleeding rate was 33 patients (12.04%). Emergency procedures in this group included successful repeat endoscopic hemostasis in 28 patients (84.8%) and open surgery in 5 patients (15.2%).

Among 65 patients classified as Forrest Ia, endoscopic hemostasis was performed, but 9 patients (3.3%) required open surgery due to ongoing bleeding. Similarly, 62 patients with Forrest Ib received endoscopic hemostasis, with 7 cases (2.6%) necessitating surgical intervention. Among 76 patients with Forrest IIa, only 3 (1.1%) required surgery. In contrast, none of the 71 patients with Forrest IIb experienced rebleeding (0%).

The overall mortality rate was 3.6%. Among patients with acute ulcers, mortality was 2.7% (11 of 403 cases), while patients with chronic ulcers had a higher mortality rate of 5.6% (5 of 88 cases). Patients with Mallory-Weiss syndrome had a mortality rate of 0.7% (1 of 136), whereas those with gastrointestinal bleeding of unknown etiology had the highest mortality rate of 17.5% (7 of 40). The elevated mortality in this group was associated with severe

initial conditions and significant comorbidities, including decompensated cardiovascular, respiratory, and gastrointestinal diseases, as well as severe hepatic and renal pathology.

In five cases (0.7%), esophagogastroduodenoscopy (EGD) was not performed due to the patient's critical condition, and in two cases (0.3%), the bleeding source remained unidentified.

Patients with bleeding of unknown etiology had the highest risk of mortality (OR=6.89, 95% CI: 2.35–20.20, p<0.001) compared to those with peptic ulcer disease. Additionally, mortality among patients with chronic ulcers was significantly higher than in those with acute ulcers (OR=2.13, 95% CI: 1.01–4.51, p=0.048).

Analysis of treatment efficacy demonstrated that the frequency of surgical interventions was significantly lower than that of endoscopic and conservative treatments (χ^2=18.21, p<0.001). Among patients who underwent endoscopic hemostasis, the highest efficacy was observed in the Forrest IIb group, where no cases of recurrent bleeding were recorded (χ^2=7.89, p=0.019). Conversely, patients classified as Forrest Ia and Ib exhibited a significantly higher risk of requiring surgical intervention compared to Forrest IIa (OR=3.24, 95% CI: 1.41–7.43, p=0.005).

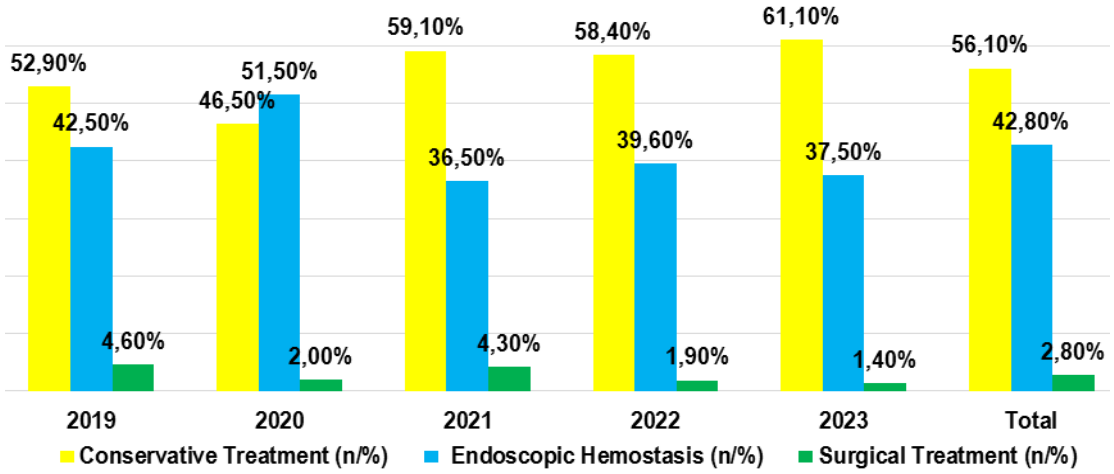

Figure 3. Treatment Outcome Indicators.

Despite significant advancements in medical technologies and improvements in treatment methods, the overall surgical activity during the study period averaged 2.8%. Notably, postoperative mortality was absent in 2019, 2020, and 2023, highlighting the high level of safety associated with the performed procedures. However, in 2021, the postoperative mortality rate reached 40.0% (2 out of 5 patients), while in 2022, it was 33.3% (1 out of 3 patients). Analysis of postoperative mortality rates revealed statistically significant differences between the years (χ^2=8.94, p=0.011) (Figure 4).

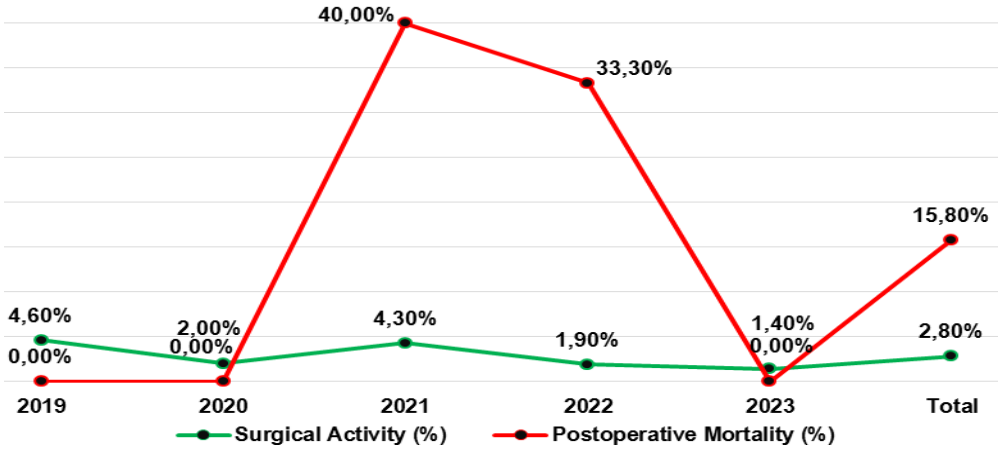

Figure 4. Surgical Activity Indicators.

Discussion

Non-variceal upper gastrointestinal bleeding (NVUGIB) remains a serious medical challenge requiring a comprehensive approach to diagnosis and treatment. As demonstrated in our study, the primary causes of NVUGIB include peptic ulcer disease and Mallory-Weiss syndrome, which align with findings from other studies, such as the research by *Joon S.K. et al.* (2020), confirming the high prevalence of these conditions among NVUGIB patients [9]. Upper gastrointestinal tract diseases are characterized not only by their high incidence but also by a significant risk of severe complications, including massive hemorrhage and mortality, particularly in elderly patients and those with comorbidities [4].

Our results, based on 667 patients, confirmed that endoscopy remains the principal method for both diagnosing and treating NVUGIB. This is consistent with the recommendations of the European Society of Gastrointestinal Endoscopy (ESGE), which asserts that endoscopic hemostasis is the cornerstone of NVUGIB

management [3]. Specifically, injection therapy and argon plasma coagulation have been identified as highly effective techniques for bleeding control. These findings are further supported by *Iulia R. et al.* (2022), who emphasized the importance of employing various endoscopic methods to achieve hemostasis in NVUGIB cases [8].

At the same time, surgical interventions, such as gastrotomy or subtotal gastrectomy, remain relevant in cases where conservative or endoscopic treatments prove ineffective. This necessity is corroborated by the study of *Blatchford O. et al.* (2000) [3].

The Forrest classification, utilized in our study, demonstrated high accuracy in assessing the severity of bleeding and selecting the optimal treatment strategy. According to *Joseph J.S. et al.* (2018), this scale effectively stratifies patients and guides therapeutic decisions [10]. Additionally, key risk factors such as ischemic heart disease, anticoagulant therapy, and nonsteroidal anti-inflammatory drug (NSAID) use significantly increase the likelihood of recurrent bleeding episodes, as highlighted in the study by Sun G.L. (2022) [13].

In our study, the overall mortality rate among NVUGIB patients was 3.6%, which falls within the range reported by Carolina P. et al. (2020), where NVUGIB-related mortality was associated with patient age, comorbid conditions, and bleeding severity [4]. These findings underscore the critical importance of early diagnosis and timely intervention to mitigate mortality risks.

Additionally, our findings were compared with Russian studies. *Tarasov E.E. et al.* (2019) reported an NVUGIB mortality rate of 9.9%, identifying key risk factors such as severe blood loss, high Charlson comorbidity index, and the necessity for open surgery [2]. Notably, recurrent bleeding significantly increased the risk of unfavorable outcomes (51.6% among deceased patients vs. 8.2% among survivors, $p<0.001$), emphasizing the need for close monitoring and timely intervention.

Furthermore, the study by *Khitaryan A.G. et al.* (2020) revealed that NVUGIB-related mortality ranges from 5.0% to 19.0%, reaching 40.0% in patients with severe recurrent hemorrhage. Key predictors of recurrent bleeding included severe Forrest Ia hemorrhage, high comorbidity index, Rockall score ≥8, systolic blood pressure ≤100 mmHg, heart rate ≥100 bpm, low total protein levels, and anemia (Hb ≤100 g/L) [12]. Our study corroborates the significance of these factors, particularly in patients with recurrent bleeding, highlighting the necessity for thorough preoperative assessment and timely surgical decision-making [2].

Despite significant advancements in diagnostic and therapeutic methods, mortality and recurrence rates remain high, emphasizing the need for further research and refinement of NVUGIB management strategies. The study results reinforce the importance of an integrated approach encompassing pharmacotherapy, endoscopic interventions, and, when necessary, surgical treatment. Future developments may require the enhancement of existing risk prediction models to improve prognostication and optimize treatment strategies [3, 6].

Our study possesses several key features, including a lower mortality rate (3.6%) compared to Russian studies, high efficacy of endoscopic hemostasis—particularly argon plasma coagulation, and a detailed analysis of risk factors such as anticoagulant use and comorbid conditions. Additionally, the use of the Forrest classification ensured precise treatment stratification, while a comprehensive approach integrating pharmacotherapy, endoscopy, and surgical intervention when necessary further optimized patient outcomes. These findings underscore the ongoing need for multidisciplinary management and continuous advancements in NVUGIB treatment protocols.

Thus, non-variceal upper gastrointestinal bleeding (NVUGIB) remains a pressing issue in gastroenterology and surgery, necessitating a comprehensive approach to diagnosis and treatment. The present study confirmed the high prevalence of peptic ulcer disease, Mallory-Weiss syndrome, and erosive lesions as the leading causes of hemorrhage. The primary risk factors for NVUGIB include the use of anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and cardiovascular and pulmonary comorbidities, underscoring the need for meticulous adjustment of pharmacotherapy in patients with a high predisposition to bleeding.

The application of endoscopic hemostasis, particularly argon plasma coagulation, demonstrated high efficacy in controlling hemorrhage and reducing the need for surgical intervention. The use of the Forrest classification facilitated timely risk stratification and the selection of optimal treatment strategies. Despite significant advancements, the recurrence of bleeding remains a major concern, highlighting the need for further investigation into risk factors and the refinement of therapeutic approaches.

Conclusions:

1. The proportion of patients of working age (18–60 years) was 53.2%, with the most frequently affected age group being 60–74 years (32.7%).

2. Males accounted for 66.7% and females for 33.3%. The mean patient age was 58.40±14.50 years, with a gender-based age difference of 1.0±0.4 years.

3. The leading causes of hemorrhage were acute ulcers (60.4%), Mallory-Weiss syndrome (20.4%), chronic ulcers (13.2%), and bleeding of unknown etiology (6.0%).

4. According to the Forrest classification, type IIB lesions were the most common (54.5%).

5. The predominant comorbid conditions included cardiovascular diseases (21.7%) and respiratory disorders, including COVID-19 (14.7%). The primary cause of drug-induced ulcers was NSAID use (8.2%), followed by anticoagulant and antiplatelet therapy (16.9%).

6. The overall rebleeding rate was 6.9%, while the total mortality rate reached 3.6%. Specifically, mortality was 2.7% in acute ulcers, 5.6% in chronic ulcers, 0.7% in Mallory-Weiss syndrome, and 17.5% in cases of bleeding of unknown etiology. The average surgical intervention rate during the study period was 2.8%.

7. Endoscopic hemostasis was performed in 274 patients (42.8%) and proved highly effective, significantly reducing the need for surgical procedures and lowering the risk of complications. Repeat endoscopic hemostasis was successfully performed in 84.8% of cases.

Study Limitations: *The single-center nature of the study may limit its generalizability, and the absence of long-term follow-up data restricts the assessment of post-discharge outcomes.*

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ЧАСТОТА РЕЦИДИВОВ ГАСТРОЭЗОФАГЕАЛЬНОЙ РЕФЛЮКСНОЙ БОЛЕЗНИ У ДЕТЕЙ ШКОЛЬНОГО ВОЗРАСТА

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Резюме

Введение. Гастроэзофагеальная рефлюксная болезнь (ГЭРБ) — одно из наиболее распространенных заболеваний верхних отделов желудочно-кишечного тракта. Распространенность заболевания варьируется и, в зависимости от региона мира, а у детей и подростков может составлять от 11,6% до 32,9%. На сегодня, данных о частоте и характере рецидивов у детей школьного возраста с эндоскопической позитивной формой ГЭРБ недостаточно.

Цель. Определить частоту и характер рецидивов эндоскопически позитивной формой гастроэзофагеальной рефлюксной болезни у детей школьного возраста.

Материалы и методы. В исследование включено 52 детей школьного возраста, средний возраст – 11,7±2,3, из них мальчиков- 45, девочек.- 7, всем пациентам на начальном этапе установлен диагноз эндоскопически позитивной гастроэзофагеальной рефлюксной болезни и проведен курс терапии ингибиторами протонной помпы в дозе 1 мг/кг массы продолжительностью от 4 до 8 недель. У всех пациентов на момент завершения терапии отмечалось купирование клинических симптомов заболевания. Контрольное обследование проводилось при возникновении клинических признаков обострения. Оценивалась динамика клинический симптомов и состояние пищевода по данным эндоскопического исследования. Анализ значимости различий качественных признаков проведён с помощью критерия χ^2. Различия при $p < 0,05$ расценивали как значимые.

Результаты. Эндоскопически позитивная (эрозивная) форма гастроэзофагеальной рефлюксной болезни у детей школьного возраста имеет хроническое рецидивирующее течение. Ежегодно, клинические признаки обострения возникают примерно у половины детей (от 44,2% до 59,6%). Основными клиническими симптомами обострения являются изжога и абдоминальная боль.

Выводы: Эндоскопические признаки обострения эрозивного эзофагита у пациентов с клиническими симптомами обострения через 6 -12 месяцев выявляются в 35,4% случаев, через 12-24 месяца в 36,0% случаев и при наблюдение более 24 месяцев в 52, 1% случаев. Значимой динамики степени эрозивных изменений при оценке по Лос-Анджелесской классификации за период наблюдения не выявлено.

Ключевые слова. *гастроэзофагеальная рефлюксная болезнь, дети.*

Для цитирования:

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Abstract

FREQUENCY OF RELAPSES OF GASTROESOPHAGEAL REFLUX DISEASE IN SCHOOL-AGE CHILDREN

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Introduction Gastroesophageal reflux disease (GERD) is one of the most common diseases of the upper gastrointestinal tract. The prevalence of the disease varies and, depending on the region of the world, and in children and adolescents can be from 11.6% to 32.9%. Currently, there is insufficient data on the frequency and nature of relapses in school-age children with endoscopically positive GERD.

Aim. To determine the frequency and nature of relapses of endoscopically positive gastroesophageal reflux disease in school-age children.

Materials and methods. The study included 52 school-age children, average age - 11.7±2.3, including 45 boys, 7 girls, all patients were initially diagnosed with endoscopically positive gastroesophageal reflux disease and received a course of therapy with proton pump inhibitors at a dose of 1 mg / kg of weight for a duration of 4 to 8 weeks. All patients had relief of clinical symptoms of the disease at the end of therapy. A follow-up examination was carried out when clinical signs of exacerbation occurred. The dynamics of clinical symptoms and the state of the esophagus were assessed according to endoscopic examination data. The analysis of the significance of differences in qualitative features was carried out using the χ^2 criterion. Differences at $p < 0.05$ were considered significant.

Results. Endoscopically positive (erosive) form of gastroesophageal reflux disease in school-age children has a chronic relapsing course. Annually, clinical signs of exacerbation occur in about half of the children (from 44.2% to 59.6%). The main clinical symptoms of exacerbation are abdominal pain and heartburn.

Conclusion. Endoscopic signs of exacerbation of erosive esophagitis in patients with clinical signs of exacerbation are detected after 6-12 months in 35.4% of cases, after 12-24 months in 36.0% of cases and with observation for more than 24 months in 52.1% of cases. No significant dynamics of the degree of erosive changes when assessed according to the Los-Angeles classification were revealed during the observation period.

Keywords: *erosive esophagitis, children.*

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Түйіндеме

МЕКТЕП ЖАСЫНДАҒЫ БАЛАЛАРДА ГАСТРОЭЗОФАГЕАЛЬДІ РЕФЛЮКС АУРУЫНЫҢ ҚАЙТАЛАНУ ЖИІЛІГІ

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Кіріспе. Гастроэзофагеальды рефлюкс ауруы (Gerd) - жоғарғы асқазан-ішек жолдарының ең көп таралған ауруларының бірі. Аурудың таралуы әлемнің әр аймағына байланысты өзгереді, ал балалар мен жасөспірімдерде 11,6% - дан 32,9% - ға дейін болуы мүмкін . Бүгінгі таңда эндоскопиялық оң Gerd формасы бар мектеп жасындағы балаларда қайталану жиілігі мен сипаты туралы мәліметтер жеткіліксіз.

Мақсат. Мектеп жасындағы балалардағы гастроэзофагеальді рефлюкс ауруының эндоскопиялық оң түрімен қайталану жиілігі мен сипатын анықтаңыз.

Материалдар мен әдістер. Зерттеуге мектеп жасындағы 52 бала, орташа жасы - 11,7±2,3, оның ішінде ұлдар - 45, қыздар.- 7. барлық пациенттерге бастапқы кезеңде эндоскопиялық оң гастроэзофагеальді рефлюкс ауруы диагнозы қойылды және ұзақтығы 4-тен 8 аптаға дейінгі массасы 1 мг/кг дозада Протонды сорғы ингибиторларымен терапия курсы жүргізілді. Барлық пациенттерде терапия аяқталған кезде аурудың клиникалық белгілері тоқтатылды. Бақылау тексерісі өршудің клиникалық белгілері пайда болған кезде жүргізілді. Эндоскопиялық зерттеуге сәйкес клиникалық симптомдардың динамикасы және өңештің жағдайы бағаланды. Сапалық белгілердің айырмашылықтарының маңыздылығын талдау σ2 критерийі арқылы жүзеге асырылады. P<0,05-тегі айырмашылықтар маңызды деп саналды.

Нәтижелер. Мектеп жасындағы балалардағы гастроэзофагеальді рефлюкс ауруының эндоскопиялық оң (эрозиялық) түрі созылмалы қайталанатын курсқа ие. Жыл сайын алаудың клиникалық белгілері балалардың жартысына жуығында пайда болады (44,2% - дан 59, 6% - ға дейін). Өрттің негізгі клиникалық белгілері-күйдіргі және іштің ауыруы.

Қорытынды: 6-12 айдан кейін өршудің клиникалық белгілері бар пациенттерде эрозиялық эзофагиттің өршуінің эндоскопиялық белгілері 35,4% жағдайда, 12-24 айдан кейін 36,0% жағдайда және 24 айдан астам бақылау кезінде 52, 1% жағдайда анықталады. Бақылау кезеңінде Лос-Анджелес классификациясы бойынша бағалау кезінде эрозиялық өзгерістер дәрежесінің маңызды динамикасы анықталған жоқ.

Түйінді сөздер: *гастроэзофагельді рефлюкс ауруы, балалар.*

Дәйексөз үшін:

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Введение

Гастроэзофагеальная рефлюксная болезнь (ГЭРБ) - одно из наиболее распространенных заболеваний верхних отделов желудочно-кишечного тракта [4,1,9] Распространенность заболевания варьируется и, в зависимости от региона мира, а у детей и подростков может составлять от 11,6% до 32,9% [8,3,2]. Частота обострений и факторы риска рецидивирующего течения гастроэзоофагеальной рефлюксной болезни до конца не изучены. На сегодня больше известны факторы развития, чем рецидива ГЭРБ [7]. Во взрослой популяции к факторам риска развития ГЭРБ относят возраст, пол, ожирения, генетические факторы, образ жизни, особенности диеты, употребление алкоголя, курение [11,13,10]. Что касается педиатрической популяции риск развития ГЭРБ выше у пациентов с врожденными аномалиями пищевода, неврологическими заболеваниям (ДЦП и др.), хроническими обструктивными заболевания верхних дыхательных путей. Другие факторы менее изучены. Частота рецидивов и причины рецидивирующего течения ГЭРБ до настоящего времени изучены недостаточно. По данным *Wei-Yi Lei* в течение первого года наблюдения рецидив наблюдается у 30,4% взрослых пациентов с ГЭРБ. В этом исследовании многофакторный анализ показал, что более высокий показатель по шкале GERDQ был единственным независимым фактором риска рецидива ГЭРБ [6]. Одно из исследований показало, что взрослые пациенты с ГЭРБ с более коротким интервалом между ужином и сном (поздний ужин) имели более высокую частоту рецидивов симптомов [12]. Еще одно исследование показало, что наличие регургитации является независимым прогностическим фактором рецидива [7]. Одно из немногих исследование, проведенных на педиатрическом контингенте больных показало, что у детей с излеченным эрозивным эзофагитом в 83% случаев наблюдаются клинические рецидивы, а из 83%

у 45% наблюдаются эндоскопические рецидивы. Корреляция эндоскопического рецидива с клиническими симптомами низкая. В этом исследовании более высокие степени эзофагита и более высокий ИМТ явились факторами риска эндоскопического рецидива [5]. Таким образом, изучение частоты и факторов риска рецидивов эрозивного эзофагита у детей является актуальной задачей.

Цель исследования. Определить частоту и характер рецидивов эндоскопически позитивной формы гастроэзофагеальной рефлюксной болезни у детей школьного возраста

Материалы и методы.

Дизайн исследования: проспективное когортное исследование. Работа выполнена в соответствии с нормативными актами этического комитета ФГБОУ ВО «Алтайский государственный медицинский университет» Министерства здравоохранения Российской Федерации, разработанными согласно с Хельсинской декларацией Всемирной ассоциации «Этические принципы проведения научных медицинских исследований с участием человека» (2000г.) и «Правилами клинической практики в РФ» (Приказ Минздрава РФ №266 от 19.06.2003г.).

Проект научной работы рассмотрен и одобрен на заседании комитета по этике 28.06.2023 г. (протокол №6 ПК) «Течение и исходы ГЭРБ у детей школьного возраста».

В исследование включено 52 детей школьного возраста, средний возраст – 11,7±2,3, из них мальчиков - 45, девочек - 7.

Основные критерии включения:

1 Наличие эрозивных изменений в пищеводе по данным эндоскопии на момент включения в исследование;

2. Отсутствие факторов и заболеваний, потенциально влияющих на течение ГЭРБ (заболевания нервной системы, склеродермия, оперативные вмешательства на пищеводе, муковисцидоз и заболевания с хроническим кашлем и др.)

3. Наличие клинических признаков обострения на момент контрольного обследования.

4. Добровольное согласие.

На момент включения в исследование, после проведенного комплексного исследования, всем пациентам был выставлен диагноз эндоскопически позитивной гастроэзофагеальной рефлюксной болезни и проведен курс терапии ингибиторами протонной помпы в дозе 1 мг/кг веса продолжительностью от 4 до 8 недель. У всех пациентов на момент завершения терапии отмечалось купирование клинических симптомов заболевания.

Контрольное обследование проводилось при наличии клинических признаков обострения. В интервале от 6 до12 месяцев контроль произведен у 31 пациента. В интервале от 12 до 24 обследовано 25 детей, и в срок более чем через 24 месяца контроль произведен у 23 пациентов.

Оценивалась динамика клинических симптомов и состояние пищевода по данным эндоскопического исследования.

Статистический анализ. Анализ значимости различий качественных признаков проведён с помощью критерия χ^2. Различия при $p < 0,05$ расценивали как значимые.

Результаты

В интервале 6-12 месяцев клинические признаки обострения заболевания выявлены у 31(59, 6%) ребенка. Они заключались в возобновлении абдоминальных болей у 29/31 (93,5%) детей, изжога возобновилась/впервые возникла у 8/31 (25,8%), 8/31 (25,8 %) детей предъявляли жалобы на отрыжку и 10/31 (32,3%) детей на тошноту. Данные о соотношении симптомов вначале заболевания и на момент обострения представлены в таблице 1.

Таблица 1.

Клинические симптомы обострения ГЭРБ через 6-12 месяцев наблюдения / *Table 1. Clinical symptoms of GERD exacerbation after 6-12 months of follow-up*

Симптом	Изжога	Боли в животе	Отрыжка	Рвота	Халитоз	Тошнота
Первичное обследование (n=31)	12 (38,7%)	29 (93,5%)	13 (41,9%)	2 (6,5%)	1 (3,2%)	10 (32,3%)
Через 6-12 месяцев (n=31)	8 (25,8%)	26 (83,4%)	8 (25,8%)	0 (0,0%)	1 (3,2%)	5 (16,1%)
p	0,278	0,229	0,180	0,151	1,000	0,139

При проведении фиброгастродуоденоскопии, эндоскопическое обострение эрозивного эзофагит на момент контроля выявлено у 11/31 (35,4%) детей (Рис.1).

Динамика выраженности эрозивных изменений оценена у 8 из 11 пациентов с признаками эндоскопического обострения. У всех 8 детей стадия эндоскопических изменений соответствовала стадии установленной в начале наблюдения. Так, у трех пациентов в начале наблюдения и на момент контрольного обследования выявлен эзофагит стадии А, у одного пациента стадии С и у четырех - стадии В по Лос-Анджелесской классификации.

В интервале от 12 до 24 месяцев повторному обследованию подверглись 25 (48, 1%) детей с клиническими признаками обострения. Наиболее частыми признаками обострения также были абдоминальные боли, отмеченные у 24/25 (96,0%) детей, изжога у 9/25 (36,0%), тошнота у 7/25 (28,0%) и отрыжка у 6/25 (24,0%) от числа обследованных. Данные о соотношении симптомов вначале и на момент обострения заболевания представлены в таблице 2.

Эндоскопические признаки обострения эрозивного эзофагита на данном этапе выявлены у 9/25 (36,0%) от числа обследованных (Рис.1).

Таблица 2.

Клинические симптомы обострения ГЭРБ через 12-24 месяцев наблюдения / *Table 2. Clinical symptoms of GERD exacerbation after 12-24 months of follow-up*

Симптом	Изжога	Боли в животе	Отрыжка	Рвота	Халитоз	Тошнота
Первичное обследование (n=25)	8/25 (32, 0%)	23/25 (92, 0%)	7/25 (28,0%)	2/25 (8,0%)	2/25 (8,0%)	9/25 (36,0%)
Через 12 -24 месяцев (n=25)	9/25 (36,0%)	24/25 (96, 0%)	6/25 (24,0%)	0/25 (0,0%)	2/25 (8,0%)	7/25 (28,0%)
p	0.766	0.552	0.748	0.149	1.000	0.545

Динамика эрозивных изменений оценена у пяти из девяти пациентов. В четырех случаях на момент начала наблюдения и контроля сохранялась стадия В и в одном случае произошла трансформация стадии А в стадию В по Лос-Анджелесской классификации.

При наблюдении более 24 месяцев признаки обострения заболевания отмечены у 23(44, 2%) детей. Ведущим признаком обострения были также абдоминальные боли, отмеченные у 20/23 (86,9%), изжога у 47,8% (доля больных с изжогой выросла по сравнению с началом наблюдения), тошнота у 6/23 (26,0%), отрыжка у 8/23 (15,1%) от числа обследованных. Данных о соотношении симптомов в начале наблюдения и на момент обострения заболевания представлены в таблице 3.

Эндоскопические признаки обострения эрозивного эзофагита выявлены у 12/23 (52,1%) пациентов, таким, образом, доля больных с эндоскопическими признаками рецидива возрастает по мере увеличение длительности течения заболевания (Рис. 1).

Таблица 3.

Клинические симптомы обострения ГЭРБ через 24 и более месяцев наблюдения / *Table 3. Clinical symptoms of GERD exacerbation after 24 months or more of follow-up.*

Симптом	Изжога	Боли в животе	Отрыжка	Рвота	Халитоз	Тошнота
Первичное Обследование (n=23)	7/23 (30,4%)	20/23 (86,9%)	8/23 (15,1%)	2/23 (8,7%)	1/23 (4,3%)	6/23 (26,0%)
Через 24 и более месяцев (n=23)	11/23 (47,8%)	20/23 (86,9%)	5/23 (21,7%)	0/23 (0,0%)	2/23 8,7%)	6/23 (26,0%)
p	0.227	1, 000	0.326	0.312	0.551	1, 000

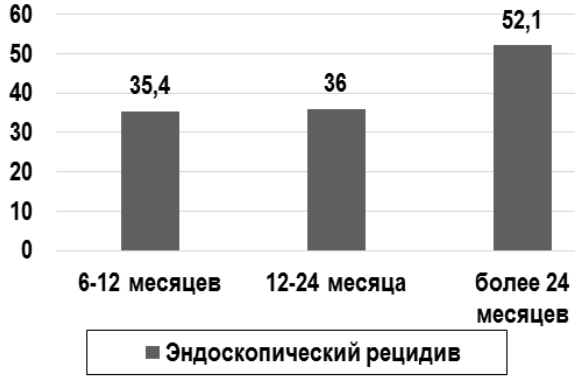

Рисунок 1. Доля больных (%) с эндоскопическими признаками обострения за период наблюдения.
(Figure 1. Proportion of patients (%) with endoscopic signs of exacerbation during the follow-up period).

Оценка динамики выраженности эндоскопических признаков эзофагита проведена у пяти из двенадцати детей, в трех случаях отмечается трансформация эзофагита стадии В в стадию А, в одном случае из стадии А в стадию В, и в одном случает сохраняется стадия В по Лос-Анджелесской классификации. Таким образом, в большинстве наблюдений прогрессирования выраженности эрозивных изменений в пищеводе за период наблюдения не произошло.

Обсуждение результатов

Большинство авторов считают, что гастроэзофагеальная рефлюксная болезнь (ГЭРБ), включая её эрозивную форму, у детей, как и у взрослых, характеризуется хроническим, рецидивирующим течением. Несмотря на это, объем систематических исследований, посвящённых частоте, особенностям клинических и эндоскопических рецидивов у детей, остается ограниченным. Такая ситуация обуславливает актуальность дальнейшего изучения данного вопроса, особенно с учётом увеличения заболеваемости ГЭРБ в детском возрасте.

По результатам нашего исследования, клинические признаки обострения заболевания через 6–12 месяцев наблюдения были зарегистрированы у 59,6% детей. В период от 12 до 24 месяцев рецидивы наблюдались у 48,1% пациентов, а при длительности наблюдения свыше 24 месяцев – у 44,2%. Эти данные свидетельствуют о снижении частоты рецидивов с течением времени, однако остаются высокими даже при длительном мониторинге. Аналогичные результаты приводятся в других исследованиях, например, согласно данным, представленным в работе [5], у 83,3% пациентов (20 из 24) рецидив наступил в среднем через 14,6 месяцев, при этом 95% доверительный интервал составил от 6,7 до 25,7 месяцев. Таким образом, можно сделать вывод, что большинство детей с ГЭРБ подвержены повторным эпизодам обострений, требующим внимания и коррекции терапии.

Клиническими проявлениями рецидива в нашем исследовании наиболее часто выступали абдоминальная боль и изжога. Интересно отметить, что с увеличением длительности наблюдения удельный вес пациентов, жалующихся на изжогу, возрастал. Это может быть связано как с прогрессированием заболевания, так и с возрастными изменениями восприятия и описания симптомов детьми. Помимо изжоги, некоторые пациенты сообщали о срыгиваниях,

нарушении аппетита, раздражительности, что также может служить косвенными признаками рецидива.

Что касается эндоскопических признаков рецидива, они были зафиксированы у 35,4% детей в течение первых 6–12 месяцев наблюдения, у 36,0% – в течение 12–24 месяцев, и у 52,1% – при длительности наблюдения более 24 месяцев. Полученные данные свидетельствуют о том, что несмотря на возможное клиническое улучшение, морфологические признаки воспаления пищевода могут сохраняться или рецидивировать, особенно при длительном течении заболевания. Это подчеркивает необходимость регулярного эндоскопического контроля у детей с выраженной клинической симптоматикой.

Таким образом, можно заключить, что при наличии клинических симптомов обострения у детей с ГЭРБ, в значительном числе случаев (от одной трети до половины) имеются также и эндоскопические признаки рецидива. Кроме того, с увеличением длительности наблюдения, вероятность выявления морфологических изменений возрастает. Это указывает на необходимость длительного динамического наблюдения и комплексного подхода к ведению пациентов с данной патологией, включая не только симптоматическое лечение, но и мероприятия, направленные на профилактику обострений и поддержание ремиссии. Также представляется целесообразным более широкое внедрение персонализированных схем терапии и стратификации пациентов по риску рецидива, что позволит повысить эффективность лечения и улучшить качество жизни больных.

Заключение

Эндоскопически позитивная (эрозивная) форма гастроэзофагеальной рефлюксной болезни у детей школьного возраста имеет хроническое рецидивирующее течение. Ежегодно клинические признаки обострения возникают примерно у половины детей (от 44,2% до 59,6%). Основными клиническими симптомами обострения являются абдоминальная боль и изжога. Эндоскопические признаки обострения эрозивного эзофагита у пациентов с клиническими признаками обострения через 6 -12 месяцев выявляются в 35,4% случаев, через 12-24 месяца в 36,0% случаев и при наблюдение более 24 месяцев в 52,1% случаев. Значимой динамики степени эрозивных изменений при оценке по Лос-Анджелесской классификации за период наблюдения не выявлено.

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УРОВЕНЬ ЗАБОЛЕВАЕМОСТИ САХАРНЫМ ДИАБЕТОМ 2 ТИПА И ХРОНИЧЕСКИМ ВИРУСНЫМ ГЕПАТИТОМ С НА 2023 ГОД В ГОРОДЕ АЛМАТЫ

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Резюме

Актуальность. Гепатит С и сахарный диабет 2 типа представляют собой значительные проблемы для здравоохранения во всем мире, и их совместное течение усиливает нагрузку на систему здравоохранения. В последние годы наблюдается рост заболеваемости как гепатитом С, так и диабетом 2 типа, особенно в урбанизированных регионах, таких как Алматы [2,10]. Согласно данным, собранным из государственной информационной системы «Электронный регистр диспансерных больных», в Алматы наблюдается значительный рост случаев гепатита С и диабета 2 типа за период с 2018 по 2023 год [8]. В частности, в исследованиях показано, что количество пациентов с диабетом 2 типа увеличилось, что частично связано с повышенной инсулинорезистентностью у пациентов с гепатитом С. Влияние этих заболеваний на общественное здоровье и экономические расходы требует повышенного внимания и разработки целевых стратегий вмешательства [12,13,15].

Цель: оценить распространенность коморбидности СД2 и ВГС среди жителей города Алматы в 2023 году.

Материалы и методы: Использованы данные государственной информационной системы «Электронный регистр диспансерных больных», основанной на МКБ-10, для анализа случаев СД2 и ВГС. Применен описательный кросс-секционный дизайн и логистическая регрессия для оценки взаимосвязей между заболеваниями.

Результаты: в 2023 году в Алматы было зарегистрировано 475 случаев коморбидности СД2 и ВГС. Распространенность ВГС среди пациентов с СД2 составила - 0,85%, а заболеваемость СД2 среди пациентов с ВГС - 9,03%.

Выводы: Результаты показали, что коморбидность СД2 и ВГС остается значимой проблемой общественного здравоохранения в Алматы. Необходимо усилить профилактические меры и улучшить программы скрининга, особенно среди групп высокого риска, для снижения распространенности этих заболеваний.

Ключевые слова: *сахарный диабет, гепатит С, фиброз, гепатогенный диабет.*

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Abstract

THE INCIDENCE OF TYPE 2 DIABETES MELLITUS AND CHRONIC VIRAL HEPATITIS C IN 2023 IN ALMATY

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Introduction: Hepatitis C and type 2 diabetes mellitus are significant public health problems worldwide, and their co-occurrence increases the burden on the healthcare system. In recent years, there has been an increase in the incidence of

both hepatitis C and type 2 diabetes, especially in urbanized regions such as Almaty [2,10]. According to data collected from the state information system “Electronic Register of Dispensary Patients”, there has been a significant increase in hepatitis C and type 2 diabetes cases in Almaty from 2018 to 2023 [8]. In particular, studies have shown that the number of patients with type 2 diabetes has increased, which is partly due to increased insulin resistance in patients with hepatitis C. The impact of these diseases on public health and economic costs requires increased attention and the development of targeted intervention strategies [12,13,15].

Aim.: to estimate the prevalence of comorbidity of T2DM and HCV among residents of Almaty in 2023.

Materials and methods: Data from the state information system "Electronic Register of Dispensary Patients" based on ICD-10 were used to analyze cases of T2DM and HCV. A descriptive cross-sectional design and logistic regression were used to assess the relationships between the diseases.

Results: In 2023, 475 cases of comorbidity of T2DM and HCV were registered in Almaty. The prevalence of HCV among patients with T2DM was 0.85%, and the incidence of T2DM among patients with HCV was 9.03%.

Conclusions: The results showed that the comorbidity of T2DM and HCV remains a significant public health problem in Almaty. It is necessary to strengthen preventive measures and improve screening programs, especially among high-risk groups, to reduce the prevalence of these diseases.

Keywords: *diabetes mellitus, hepatitis C, fibrosis, hepatogenic diabetes.*

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Түйіндеме

АЛМАТЫ ҚАЛАСЫНДА 2023 ЖЫЛҒА 2 ТИПТІ ҚАНТ ДИАБЕТІ ЖӘНЕ СОЗЫЛМАЛЫ ВИРУСТЫ С ГЕПАТИТІ АУРУЫНЫҢ ДЕҢГЕЙІ

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Кіріспе: С гепатиті және 2 типті қант диабеті бүкіл әлемде денсаулық сақтаудың маңызды мәселелерін білдіреді және олардың бірге болуы денсаулық сақтау жүйесіне жүктемені арттырады. Соңғы жылдары, әсіресе, Алматы сияқты урбанизацияланған аймақтарда С гепатитімен де, 2 типті қант диабетімен де сырқаттанушылықтың өсуі байқалады [2,10]. «Диспансерлік науқастардың электрондық тізілімі» мемлекеттік ақпараттық жүйесінен жиналған мәліметтерге сәйкес, Алматыда 2018 жылдан 2023 жылға дейін С гепатиті және 2 типті қант диабеті жағдайларының айтарлықтай өскені байқалады [8]. Атап айтқанда, зерттеулер көрсеткендей, 2 типті қант диабетімен ауыратын науқастардың саны өсті, бұл ішінара С гепатиті бар науқастарда инсулинге төзімділіктің артуына байланысты. Бұл аурулардың қоғамдық денсаулыққа және экономикалық шығындарға әсері назар аударуды және дамытуды талап етеді. мақсатты араласу стратегиялары [12,13, 15].

Мақсаты: 2023 жылы Алматы қаласының тұрғындары арасында T2DM және HCV ілеспелі аурулардың таралуын бағалау болды.

Материалдар мен әдістер: T2DM және HCV жағдайларын талдау үшін ICD-10 негізіндегі «Диспансерлік науқастардың электрондық тізілімі» мемлекеттік ақпараттық жүйесінің деректері пайдаланылды. Аурулардың байланысын бағалау үшін сипаттамалық қима дизайн және логистикалық регрессия қолданылды.

Нәтижелер: 2023 жылы Алматы қаласында 475 Т2ДМ және ВСВ ілеспелі ауру жағдайы тіркелді. T2DM бар науқастар арасында HCV таралуы 0,85%, ал HCV бар науқастар арасында T2DM жиілігі 9,03% құрады.

Тұжырымдар: Нәтижелер T2DM және HCV ілеспелі аурулары Алматыда қоғамдық денсаулық сақтаудың маңызды проблемасы болып қала беретінін көрсетті. Алдын алу шаралары мен скринингтік бағдарламаларды, әсіресе қауіпті топтар арасында, осы аурулардың таралуын азайту үшін күшейту қажет.

Негізгі сөздер*: қант диабеті, С гепатиті, фиброз, гепатогенді қант диабеті.*

Дәйексөз үшін:

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Введение

Согласно данным Всемирной организации здравоохранения, в 2014 году заболеваемость сахарным диабетом среди взрослого населения (старше 18 лет) составила 8,5%. К 2019 году диабет стал прямой причиной 1,5 миллиона смертей, при этом 48% летальных исходов, связанных с диабетом, произошли у лиц моложе 70 лет. Диабет также ассоциировался с 460 000 смертей, вызванных почечной патологией, связанной с этим заболеванием, а повышенный уровень глюкозы в крови был причиной около 20% летальных исходов от сердечно-сосудистых заболеваний [9,18].

Между 2000 и 2019 годами стандартизированный по возрасту показатель смертности от диабета увеличился на 3%. В странах с уровнем дохода ниже среднего смертность от диабета выросла на 13% [8]. По состоянию на 2021 год, около 58 миллионов человек в мире живут с хронической инфекцией вируса гепатита С (ХВГС) [12]. Основной репликацией ВГС являются гепатоциты печени, но репликация была также выявлена в других органах, включая островковые клетки поджелудочной железы [13,4].

По данным Национального регистра сахарного диабета Республики Казахстан (2021 г.), в Казахстане зарегистрировано 23 233 пациента с хроническим гепатитом С и 382 000 пациентов с сахарным диабетом, из которых 352 000 страдают сахарным диабетом 2 типа [4]. Эти данные указывают на недостаточную диагностику инфекции HCV-инфекции и позднее выявление сахарного диабета 2 типа.

В ходе анализа влияния эрадикации HCV-инфекции на гликемический контроль отмечено значительное улучшение у пациентов с циррозом, генотипом ВГС 3 и/или в возрасте до 60 лет. Более выраженное снижение уровня глюкозы в крови после устойчивого вирусологического ответа (УВО) наблюдалось у пациентов с циррозом, вероятно, вследствие высокой продолжительности инсулинорезистентности. Таким образом, эрадикация HCV-инфекции может оказывать более выраженное влияние на гликемический контроль у пациентов с продвинутым заболеванием.

Многие исследования [1,8,19] показали, что пациенты с хроническим гепатитом достигли стойкого улучшения контроля гликемии, при этом у четырех пациентов появилась возможность отказаться от противодиабетической терапии. В противоположность этому, у пациентов с компенсированным циррозом отмечалось лишь временное улучшение, и через год после лечения показатели HbA1c возвращались к исходным значениям. Эти результаты демонстрируют, что устранение вируса оказывает не только положительное влияние на состояние печени, но и долгосрочное благоприятное воздействие на течение сахарного диабета.

Цель: целью нашего эпидемиологического исследования было изучение распространения коморбидности сахарного диабета 2 типа и вирусного гепатита С в городе Алматы за 2023 год.

Материалы и методы

Данные для исследования были предоставлены Республиканским центром электронного здравоохранения (РЦЭЗ), полученные через портал «Электронный регистр диспансерных больных» (РДБ)», в которой регистрируются пациенты с хроническими заболеваниями на основе Международной классификации болезней 10-го пересмотра (МКБ-10).Данные включали первичный учет заболеваемости сахарным диабетом 2 типа (СД2) и вирусным гепатитом С (ВГС) среди пациентов в Алматы за 2023 год. Это позволило собрать информацию о пациентах, зарегистрированных в системе за 2023 год, и провести оценку распространенности и коморбидности этих заболеваний. Вся использованная информация была обезличенной, что исключает возможность идентификации пациентов. В соответствии с национальным законодательством и этическими нормами, получение информированного согласия от пациентов в данном случае не требовалось.

Критерии включения и исключения: включались пациенты старше 18 лет, имеющие диагнозы СД2 и ХВГС (дополнительные критерии не применялись, чтобы избежать избыточного ограничения выборки). Исключались пациенты с острыми формами заболеваний и те, у кого была недостаточна информация для точной классификации заболеваний по МКБ-10.

Дизайн исследования: Исследование проводилось с использованием описательного кросс-секционного дизайна, что позволило оценить распространенность заболеваний в конкретный период времени (2023 год). Для обработки данных использовался метод частотного анализа для оценки распространенности СД2 среди пациентов с ВГС и наоборот. Для определения значимости различий и оценок ассоциаций применялись методы логистической регрессии. Это позволило выявить ключевые факторы, влияющие на вероятность наличия коморбидности у пациентов с гепатитом С. Результаты исследования были представлены с использованием графиков и таблиц, что упростило интерпретацию и понимание данных. Визуализация включала распределение по возрасту, полу и временные тренды регистрации пациентов.

Результаты

В 2023 году в Алматы было зарегистрировано 475 случаев коморбидности сахарного диабета 2 типа и вирусного гепатита С.

Из общего числа пациентов с диагнозом СД2 (n=56027) у 0,85% (n=476) был зарегистрирован ВГС. В то же время из 5263 пациентов с диагнозом ВГС у 9,03% (n=475) был выявлен СД2. Эти данные указывают на перекрывающиеся группы пациентов, где значительная доля больных имеет оба заболевания, что подтверждает необходимость усиления программ скрининга (Диаграмма 1).

Диаграмма 2 показывает половое распределение пациентов с диагнозами сахарный диабет и хронический вирусный гепатит С в городе Алматы за 2023 год. График показывает значительное преобладание женщин среди пациентов по сравнению с мужчинами. Число женщин составляет - 244, тогда как количество мужчин — 231. Это может указывать на более высокую распространенность данных заболеваний среди женского населения или

на большую обращаемость женщин за медицинской помощью. Статистические различия между полами могут быть связаны как с биологическими факторами, так и с различиями в поведении, связанном с охраной здоровья. Данные подчеркивают необходимость учета гендерных аспектов при разработке профилактических и лечебных программ для этих заболеваний в регионе.

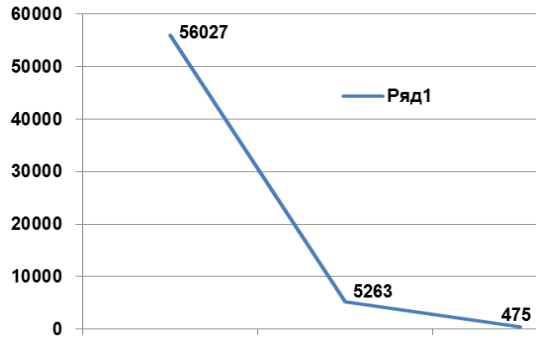

Диаграмма 1. Распространенность хронического гепатита С и сахарного диабета 2 типа в городе Алматы на 2023 г.

/ Diagram 1. Prevalence of chronic hepatitis C and type 2 diabetes mellitus in Almaty for 2023 /.

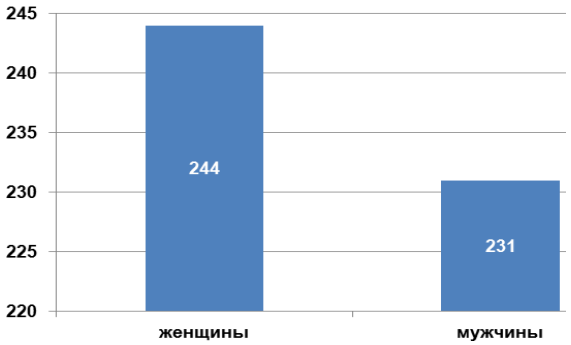

Диаграмма 2. Половое распределение пациентов с диагнозами сахарный диабет и хронический вирусный гепатит С в городе Алматы за 2023 год

/ Gender distribution of patients diagnosed with diabetes mellitus and chronic viral hepatitis C in Almaty in 2023 /

Распределение пациентов, состоящих на диспансерном учете в связи с вирусным гепатитом С (ВГС) и сахарным диабетом 2 типа (СД 2 типа) в городе Алматы показано на рисунке (Диаграмма 3). График включает три категории пациентов: тех, кто изначально был поставлен на учет по ВГС (n-149), тех, кто встал на учет сначала по СД 2 типа (n-315), и пациентов, которые одновременно были зарегистрированы с обоими диагнозами (n-11).

Преобладание числа пациентов, поставленных на учет сначала по СД 2 типа (n-315), по сравнению с пациентами, учтенными первично по ВГС (n-149), может свидетельствовать о приоритете учета диабета над гепатитом. Это, возможно, связано с более частым выявлением СД 2 типа на ранних стадиях или с высокой обращаемостью пациентов с данным диагнозом.

Небольшое количество пациентов (n-11), зарегистрированных одновременно с обоими диагнозами, может указывать на ограниченные возможности для своевременного выявления и диагностики сопутствующих заболеваний, либо на позднее выявление одного из заболеваний у пациентов с уже существующим диагнозом. Необходима усиленная диагностика на наличие ВГС у пациентов с диагнозом СД 2 типа и наоборот. Это особенно важно в силу известной ассоциации между этими двумя состояниями, где одно заболевание может увеличивать риск развития другого

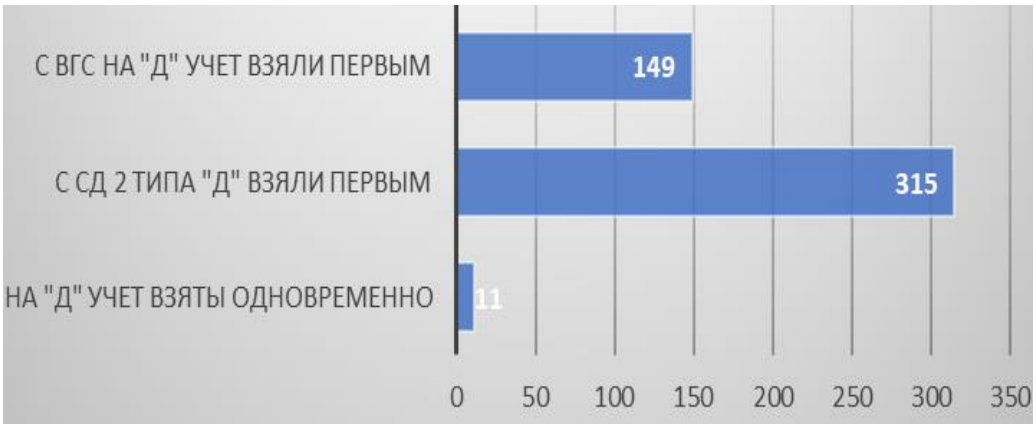

Диаграмма 3. Взятие на «Диспансерный учет» с учетом сроков постановки диагнозов

/ Diagram 3. Registration at the «Dispensary register» /.

На основе полученных данных был составлен график, отражающий возрастное распределение пациентов с коморбидностью хронического вирусного гепатита С и сахарного диабета 2 типа в Алматы за 2023 г. (Диаграмма 4). Из данных видно, что наибольшее количество пациентов с коморбидностью хронического гепатита С и сахарного диабета 2 типа приходится на возрастную группу 60-69 лет (n-191), что может указывать на повышенную уязвимость к данным заболеваниям в этом возрасте. Наименьшее количество пациентов отмечается в группе 18-29 лет (n-1), что, вероятно, связано с меньшей длительностью влияния факторов риска и меньшей накопленной хронической патологией у молодых людей. Наблюдаемые возрастные различия могут быть связаны с несколькими факторами: возрастные изменения иммунной системы и увеличение воспалительного фона, что может способствовать развитию обеих

патологий, снижение чувствительности к инсулину и метаболические нарушения, которые могут развиваться с возрастом и усиливаться при наличии гепатита С, кумулятивное воздействие факторов риска, таких как курение, употребление алкоголя, ожирение и хронический стресс, которые могут негативно влиять на организм и способствовать прогрессированию обеих болезней.

На представленном графике проанализированы временные интервалы между регистрацией сахарного диабета 2 типа (СД2) и хронического вирусного гепатита С (ВГС), что позволяет оценить динамику выявления коморбидности в зависимости от длительности наблюдения (Диаграмма 5).

Наибольшая частота выявления второго диагноза наблюдается в первый год после постановки первичного диагноза. В течение первого года зарегистрировано 237 случаев, что составляет абсолютный максимум на всем временном интервале. Данный факт может свидетельствовать о более активном клиническом мониторинге и диагностическом поиске у пациентов сразу после выявления одного из заболеваний, что способствует раннему обнаружению коморбидности. Существенное снижение выявляемости во второй и третий годы. На второй год зарегистрировано 57 случаев, на третий — 54 случая, что указывает на резкое уменьшение диагностической активности или на снижение вероятности выявления коморбидности по мере увеличения временного интервала. Стабилизация показателей в последующие годы. В период с четвёртого по десятый год количество случаев выявления второго диагноза значительно снижается и варьирует от 27 до 1 случая в год. Это может отражать недостаточную интенсивность наблюдения за пациентами в долгосрочной перспективе, а также ограниченную диагностическую активность при длительно текущих заболеваниях. Позднее выявление коморбидности спустя более 10 лет. В группе пациентов с интервалом выявления более 10 лет зарегистрировано 20 случаев. Данный показатель указывает на возможное позднее обнаружение коморбидности у пациентов, длительно состоящих на диспансерном учете с одним из диагнозов.

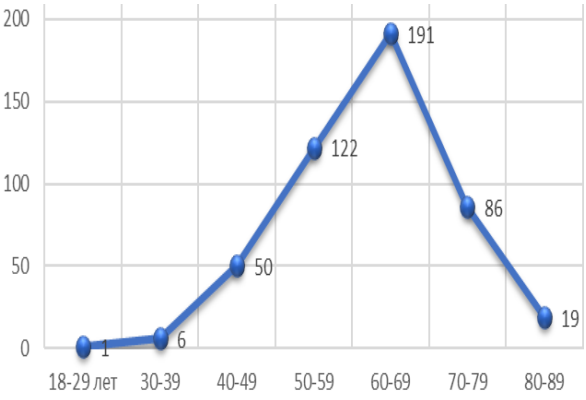

Диаграмма 4. Возрастное распределение пациентов с коморбидностью хронического вирусного гепатита С и сахарного диабета 2 типа в Алматы за 2023 г.

/ Diagram 4. Age distribution of patients with comorbidity of chronic viral hepatitis C and type 2 diabetes mellitus in Almaty in 2023 /.

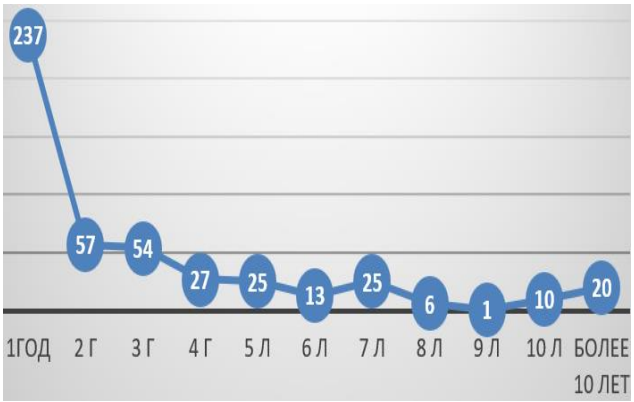

Диаграмма 5. Сроки учета коморбидности СД2 и ВГС: анализ временных интервалов между регистрацией заболеваний.

/ Diagram 5. Timing for recording the comorbidity of T2DM and HCV: analysis of time intervals between registration of diseases /.

Обсуждение результатов:

На основании проведённого исследования были достигнуты цели, направленные на изучение распространённости и эпидемиологических особенностей коморбидности сахарного диабета 2 типа (СД2) и хронического вирусного гепатита С (ВГС) среди населения города Алматы за 2023 год. Результаты анализа демонстрируют, что наибольшая вероятность выявления второго диагноза (СД2 или ВГС) приходится на первый год после регистрации одного из заболеваний. Резкое снижение частоты выявления коморбидности в последующие годы свидетельствует о необходимости оптимизации мониторинга и диагностического поиска в долгосрочной перспективе. Особое внимание должно быть уделено пациентам с длительно текущими заболеваниями для своевременного выявления и коррекции коморбидных состояний, что позволит улучшить прогноз и качество их жизни.

Впервые изучена распространённость сахарного диабета 2 типа (СД2) и хронического вирусного гепатита С (ВГС) в Алматы. Наибольшее число коморбидных случаев зарегистрировано в возрастной группе 60–69 лет, что подчёркивает необходимость целенаправленных профилактических и лечебных мероприятий среди пожилых пациентов. Меньше всего сочетание вирусного гепатита С и сахарного диабета выявлено у пациентов младше 30 лет, что свидетельствует о меньшей кумулятивной нагрузке факторов риска в данной группе. Анализ также выявил большее количество случаев коморбидности среди женщин, что требует анализа причин гендерных различий — как биологических, так и социально-поведенческих [2,4,6].Преобладание сахарного диабета 2 типа увеличивается среди мужчин и женщин, но у мужчин сахарный диабет диагностируется у более молодых и с более низким ИМТ, чем у женщин. В мире на 17.7 миллионов мужчин больше с сахарным

диабетом 2 типа, чем женщин. У женщин чаще встречается ожирение, высока роль стресса, изменение гормонального фона. Во время беременности может развиться гестационный диабет, что является фактором риска диабета 2 типа. После менопаузы у женщин увеличивается ИМТ, появляется избыточный вес, что увеличивает риск развития у женщин сахарного диабета 2 типа [1]. Некоторые исследования подтвердили, что гепатит С увеличивает риск сахарного диабета 2 типа. Donna L White с соавторами в 2008 выявили в ретроспективных и проспективных исследованиях выявили высокий риск диабета 2 типа с вирусным гепатитом С в сравнении с группой, не инфицированной гепатитом С [3,5,7,17]. Молекулярные механизмы позволяют объяснить, почему HCV-инфекция может увеличить риск развития СД2 или ухудшить гликемический контроль у пациентов с установленным СД2. ВГС приводит к усилению регуляции воспалительных цитокинов, таких как TNF-α, что приводит к фосфорилированию серина IRS и маркирует белок для деградации. Основной белок вируса гепатита С также стимулирует передачу сигнала цитокином 3 (SOCS3), вызывая IRS деградацию. Эти механизмы предотвращают последующие эффекты активации AKT, что приводит к резистентности к инсулину [11].

Преобладание пациентов, изначально поставленных на учет по СД 2, над пациентами с первичным учётом по ВГС указывает на приоритетность диагностики диабета. Это также может свидетельствовать о необходимости повышения внимания к скринингу ВГС у пациентов с СД2 и наоборот. Лечение пациентов с коморбидностью требует взаимодействия инфекционистов, эндокринологов и других специалистов для комплексного подхода к терапии и профилактике осложнений. В связи с полученными нами результатами, необходимо усиление профилактических программ для лиц старше 60 лет, включая регулярный скрининг на СД2 и ВГС, пересмотр протоколов диспансерного учета для улучшения диагностики сопутствующих заболеваний, повышение осведомленности среди пациентов о рисках коморбидности через образовательные программы, особенно для пожилых групп населения.

Заключение

Таким образом, в нашем исследовании, результаты не только достигли поставленной цели, но и выявили ключевые направления для совершенствования профилактических, диагностических и лечебных подходов. Выявленная высокая распространенность коморбидности ВГС и СД 2 типа среди старшей возрастной группы и гендерные различия подчеркивают необходимость дальнейшего изучения и разработки целенаправленных программ для раннего выявления и эффективного лечения данных заболеваний. Внедрение предложенных мер позволит снизить распространённость коморбидных состояний, уменьшить бремя заболеваний на систему здравоохранения и улучшить качество жизни пациентов с СД2 и ВГС в Казахстане.

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Данный материал не был опубликован в других изданиях и не находится на рассмотрении в других издательствах.

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ANALYSIS OF THE MICROFLORA ON DATES OF THE BACTERIOLOGICAL LABORATORY

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Abstract

Introduction. Bacteriological laboratories play a key role in the diagnosis of infectious diseases, the study of pathogenic microorganisms, and the development of prevention methods. Close collaboration between clinical microbiologists and attending physicians is necessary to optimize microbiological research. This article discusses the main areas of work of the bacteriological laboratory, diagnostic methods, and the role of laboratories in the fight against infectious diseases.

The purpose of the study. To analyze the structure and properties of pathogens isolated from the patients' material and the choice of drugs for initial empirical antimicrobial therapy.

Research materials and methods. A retrospective continuous copying of research results from the journals of the bacteriological laboratory of the Center for Phthisiopulmonology and Infectious Diseases in Semey for 2024. Identification of pathogens obtained from various patient materials was carried out in accordance with the regulatory documents governing the work of bacteriological laboratories. Sensitivity to antimicrobial drugs was determined by the disco diffusion method. Statistical processing was carried out in the Excel program.

The results of the study. In total, 37790 analyzes from 31689 individuals were performed in the bacteriological laboratory of Semey in 2024. The main areas of the laboratory's work were the isolation of salmonella, shigella, opportunistic pathogenic flora, pathogenic staphylococcus, feces for dysbiosis, pathogens of droplet infections (meningococcal infection, diphtheria, pertussis), blood tests, biomaterial studies for pathogenic flora, serological studies. In intestinal infections, pathogenic flora, conditionally pathogenic flora, pathogenic staphylococcus, and stool examination for dysbiosis were determined. Of airborne infections, studies were conducted on meningococcal infection, whooping cough and diphtheria. Blood tests for hemoculture and striality were carried out in the laboratory. The laboratory also conducted studies of various biomaterials for pathogenic flora: eyes, ENT organs, wounds, breast milk, genitals, urine, sputum, cadaverous material. The analysis of the microbial landscape revealed that bacteria from the genera of Streptococcus, Staphylococcus, Candida, Escherichia coli, etc. were most often isolated. The bacteriological laboratory performs serological studies.

Conclusions. The work of specialists in microbiological laboratories plays a crucial role in the effective prevention and control of infections, since the identification of the pathogen allows doctors to prescribe treatment in a timely and effective manner and thereby prevent the spread of infections.

Keywords: *bacteriological laboratory, pathogens, infectious diseases.*

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Резюме

АНАЛИЗ МИКРОФЛОРЫ ПО ДАННЫМ БАКТЕРИОЛОГИЧЕСКОЙ ЛАБОРАТОРИИ

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Введение. Бактериологические лаборатории играют ключевую роль в диагностике инфекционных заболеваний, исследовании патогенных микроорганизмов и разработке методов профилактики. Для оптимизации микробиологических исследований необходимо тесное взаимодействие между клиническими микробиологами и лечащими врачами. В этой статье рассматриваются основные направления работы бактериологической лаборатории, методы диагностики и роль лабораторий в борьбе с инфекционными болезнями.

Цель исследования. Провести анализ структуры и свойств возбудителей, выделяемых из материала больных и выбор препаратов для стартовой эмпирической антимикробной терапии.

Материал и методы исследования. Проведена ретроспективная сплошная выкопировка результатов исследований из журналов бактериологической лаборатории Центра фтизиопульмонологии и инфекционных болезней г. Семей за 2024 год. Идентификацию возбудителей, полученных из различного материала больных, проводили согласно нормативным документам, регламентирующим работу бактериологических лабораторий. Определение чувствительности к антимикробным препаратам осуществлялось диско-диффузионным методом. Статистическая обработка проводилась в программе Excel.

Результаты исследования. Всего за 2024 год по бактериологической лаборатории г. Семей было выполнено 37790 анализов от 31689 лиц. Основными направлениями работы лаборатории были выделение сальмонеллы, шигеллы, условно-патогенной флоры, патогенного стафилококка, кал на дисбактериоз, возбудителей капельных инфекций (менингококковая инфекция, дифтерия, коклюш), исследования крови, исследования биоматериала на патогенную флору, серологические исследования. При кишечных инфекциях определяли патогенную флору, условно патогенную флору, патогенный стафилококк и исследование кала на дисбактериоз. Из воздушно-капельных инфекций исследования проводили на менингококковую инфекцию, коклюш и дифтерию. В лаборатории были проведены исследования крови на гемокультуру и стерильность. Также в лаборатории провели исследования различного биоматериала на патогенную флору: глаза, ЛОР органы, раны, грудное молоко, половые органы, моча, мокрота, трупный материал. При анализе микробного пейзажа выявлено, что чаще всего выделяли бактерии из семейства Streptococcus, Staphylococcus, Candida, Escherichia coli и др. Бактериологическая лаборатория также выполняет серологические исследования.

Выводы. Работа специалистов в микробиологических лабораториях играет решающую роль в эффективной профилактике инфекций и борьбе с ними, так как определение возбудителя позволяет врачам своевременно и эффективно назначить лечение и тем самым предовратить распространение инфекций.

Ключевые слова: *бактериологическая лаборатория, возбудители, инфекционные болезни.*

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Түйіндеме

БАКТЕРИОЛОГИЯЛЫҚ ЗЕРТХАНАНЫҢ МӘЛІМЕТТЕРІ БОЙЫНША МИКРОФЛОРАНЫ ТАЛДАУ

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Кіріспе. Бактериологиялық зертханалар жұқпалы ауруларды диагностикалауда, патогендік микроорганизмдерды зерттеуде және алдын алу әдістерін әзірлеуде шешуші рөл атқарады. Микробиологиялық зерттеулерді оңтайландыру үшін клиникалық микробиологтар мен емдеуші дәрігерлер арасында тығыз өзара әрекеттесу қажет. Бұл мақалада бактериологиялық зертхана жұмысының негізгі бағыттары, диагностика әдістері және жұқпалы аурулармен күресудегі зертханалардың рөлі қарастырылады.

Зерттеудің мақсаты. Науқастардың материалынан бөлінетін қоздырғыштардың құрылымы мен қасиеттеріне талдау жүргізу және таңдау бастапқы эмпирикалық микробқа қарсы терапияға арналған препараттар.

Зерттеу материалы мен әдістері. 2024 жылы Семей қ. фтизиопульмонология және жұқпалы аурулар Орталығының бактериологиялық зертханасының журналдарынан зерттеу нәтижелерін ретроспективті үздіксіз көшірме жасалды. Науқастарының әртүрлі материалдарынан алынған қоздырғыштарды сәйкестендіру бактериологиялық зертханалардың жұмысын реттейтін нормативтік құжаттарға сәйкес жүргізілді. Микробқа қарсы препараттарға сезімталдықты анықтау диско-диффузия әдісімен жүзеге асырылды. Статистикалық өңдеу Excel бағдарламасында жүргізілді**.**

Зерттеу нәтижелері. 2024 жылы Семей қаласының бактериологиялық зертханасында 31689 адамнан 37790 талдау жасалды. Зертхана жұмысының негізгі бағыттары – сальмонелла, шигелла, шартты-патогенді флора, патогенді стафилококк бөлінуі, дисбактериозға нәжіс, тамшы инфекцияларының қоздырғыштары (менингококк инфекциясы, дифтерия, көкжөтел), қан анализі, патогендік флораға биоматериалды зерттеу, серологиялық зерттеу. Ішек инфекцияларында патогендік флора, шартты патогендік флора, патогендік стафилококк және дисбактериозға нәжісті зерттеу анықталды. Ауа-тамшы инфекцияларына зерттеулер менингококк инфекциясына, көкжөтелге және дифтерияға жүргізілді. Зертханада гемокультура мен стерильділікке қан анализі жүргізілді. Сондай-ақ, зертханада патогендік флораға арналған әртүрлі биоматериалдарға зерттеулер жүргізілді: көз, ЛОР мүшелері, жаралар, емшек сүті, жыныс мүшелері, зәр, қақырық, мәйіт материалы. Микробтық пейзажды талдау кезінде Streptococcus, Staphylococcus, Candida, Escherichia coli және т.б. тұқымдасынан бактериялар жиі бөлінді. Бактериологиялық зертханада сонымен қатар серологиялық зерттеулер жүргізеді.

Қорытындылар. Микробиологиялық зертханалардағы мамандардың жұмысы инфекциялардың тиімді алдын алуда және олармен күресуде шешуші рөл атқарады, өйткені қоздырғышты анықтау дәрігерлерге емдеуді уақтылы және тиімді тағайындауға және осылайша инфекциялардың таралуын болдырмауға мүмкіндік береді.

Түйінді сөздер: *бактериологиялық зертхана, қоздырғыштар, жұқпалы аурулар.*

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Introduction

Bacteriological laboratories are an integral part of the healthcare system and scientific research. They play a key role in the diagnosis of infectious diseases, the study of pathogenic microorganisms, and the development of prevention methods [1,3,4,6,14].

A bacteriological laboratory is a type of microbiological laboratory in which bacteriological research is carried out. Bacteriological laboratories can be scientific, industrial, medical, veterinary, etc. Medical bacteriological laboratories as independent structural units are organized at sanitary and epidemiological stations (SES) (sanitary and bacteriological laboratories), in infectious diseases hospitals, general type hospitals, some specialized hospitals (for example, in tuberculosis, rheumatology, skin and venereology) and in polyclinics (clinical bacteriological laboratories). Bacteriological laboratories at the SES examine environmental objects for general bacterial contamination, as well as infection with conditionally pathogenic and pathogenic microflora: air, water, soil, food; they examine organized groups and individuals for carriers of pathogenic bacteria of the intestinal group, corynebacteria diphtheria, whooping cough, paracoccus, meningococcus.

The work of the microbiological laboratory in conjunction with other departments of the SES has a specific task - improving the environment and reducing the incidence of diseases in the population. Bacteriological laboratories at medical and preventive institutions perform the tests necessary to establish and clarify the diagnosis of an infectious disease, contributing to the correct choice of specific treatment and determining the time of discharge of the patient from the infectious diseases hospital. The subject of research in bacteriological laboratories are: secretions from the human body: urine, feces, sputum, pus, as well as blood, cerebrospinal fluid and cadaveric material; environmental objects: water, air, soil, food, flushing from inventory items, hands, etc. [2,13,16].

The bacteriological laboratory conducts research on isolation, identification, and determination of antibiotic sensitivity of pathogenic and conditionally pathogenic microorganisms isolated from various biomaterials. The most common resistant bacteria are Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Streptococcus pneumoniae, followed by Salmonella spp. The only way out today is the rational use of antibiotics already available in our arsenal, which will not only keep the growth of resistance of microorganisms to them, but also increase the effectiveness of the treatment of infectious diseases [8,18].

To optimize microbiological research, it is necessary close interaction between clinical microbiologists and attending physicians

This article discusses the main areas of work of the bacteriological laboratory, diagnostic methods, and the role of laboratories in the fight against infectious diseases.

Aim. To analyze the structure and properties of pathogens isolated from the patients' material and the choice of drugs for initial empirical antimicrobial therapy.

Research materials and methods. A retrospective continuous copying of research results from the journals of the bacteriological laboratory of the Center for Phthisiopulmonology and Infectious Diseases in Semey for 2024 was carried out to identify pathogens obtained from various patient materials (feces, wound discharge, pharynx and nose, sputum, urine, vagina, etc.) in Semey. The study used an AutoMic-i600 microbiological analyzer.The management of this clinic is familiar with the progress of the research. There are no objections to the further publication of the research results in the open press. The identification of bacteria was carried out in accordance with the regulatory documents governing the work of bacteriological laboratories. Sensitivity to antimicrobial drugs was determined by the disco diffusion method. Descriptive statistics were used for the analysis in this article. Statistical processing was carried out in the Excel program.

The research topic was approved at the meeting of the Ethics Committee of the NCJSC «Semey Medical University» (Protocol No. 3 dated 02/25/2024).

Informed consent of patients to participate in the study is not required, since data obtained as part of regular laboratory diagnostics were used.

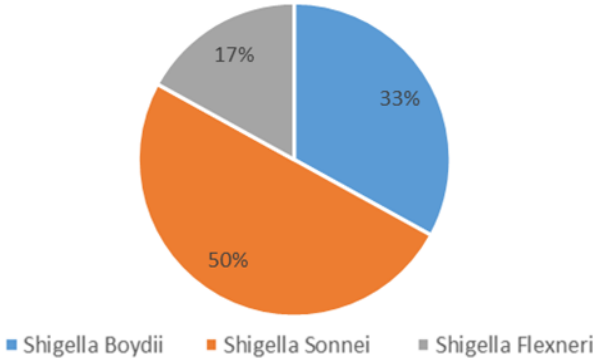
Research results

In total, 37790 analyzes from 31689 individuals were performed in the bacteriological laboratory of Semey in 2024. The main areas of the laboratory's work were the isolation of salmonella, shigella, opportunistic pathogenic flora, pathogenic staphylococcus, feces for dysbiosis, pathogens of droplet infections (meningococcal infection, diphtheria, pertussis), blood tests, biomaterial studies for pathogenic flora, serological studies. The sensitivity of microbes to antibiotics is also being determined in the laboratory.

In intestinal infections, pathogenic flora, conditionally pathogenic flora, pathogenic staphylococcus, and stool examination for dysbiosis were determined. 18,012 analyses (48%) on pathogenic flora were performed.

4,310 (11%) Salmonella tests were performed on These dates 3,937 individuals, of which 70 (1.6%) from 47 patients were positive. Salmonella enteritidis was detected in all patients from the landscape of isolated cultures. This culture is usually detected in feces [11,17].

13,702 (36%) analyses from 12,976 individuals were conducted for Shigella, of which 12 (0.09%) from 10 patients were positive. In the landscape of the isolated cultures, Shigella Boydii was isolated – 4 (33%) from 3 individuals, Shigella Sonnei - 6 analyzes (50%) from 5 individuals, Shigella Flexneri 2A – 2 analyzes (17%) from two individuals (Figure 1).



As can be seen from Figure 1, Shigella Sonnei prevails, followed by Shigella Boydii and Shigella Flexneri 2A closes. This distribution is usually seen in patients with dysentery [5].

2,148 (6%) tests were performed on conditionally pathogenic microflora (CPF) from 296 individuals, of which pathogens were isolated from feces in 1,691 (79%) analyses from 193 individuals, and 457 (21%) from 103 patients from gastric lavage. 140 analyses were confirmed, of which Proteus Vulgaris – 5 (4%), Proteus Mirabilis – 5 (4%), Enterobakter – 9 (6%), Citrobakter – 10 (7%), Staphylococcus Aureus – 33 (24%), Klebsiella – 76 (54%), Pseudomonas Aerugynosae – 2 (1%) (Figure 2).

As can be seen from Figure 2, more than half were Klebsiella, one third were Staphylococcus Aureus, and to a lesser extent the remaining pathogens. The same picture is observed in other study [12].

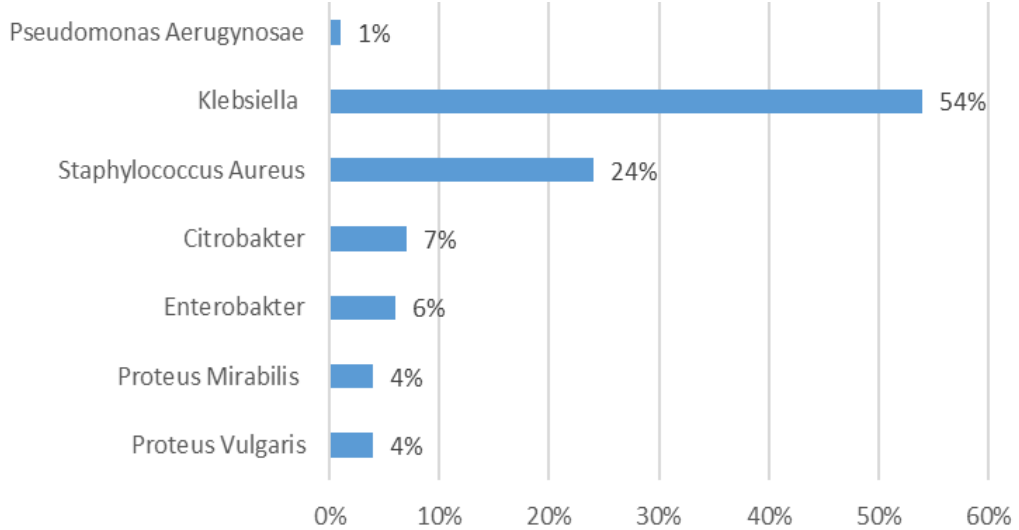


Figure 2. Microbial landscape of CPF.

3 stool tests from 2 individuals for pathogenic staphylococcus were performed, of which 2 tests from 2 individuals came out positive.

244 tests were performed on dysbiosis from 243 individuals, dysbiosis was detected in 208 cases from 203 individuals [2].

Of airborne infections, studies were conducted on meningococcal infection, whooping cough and diphtheria. A total of 5,309 (14%) were conducted analyses from 2,769 individuals. 513 (10%) tests from 391 people were conducted for meningococcal infection, 428 (8%) tests from 194 people for whooping cough, and 4,368 (82%) tests from 2,184 people for diphtheria. All the tests were negative.

The laboratory conducted 443 (1%) blood tests from 443 people, including 141 blood culture tests and 303 sterility tests [7]. 4 sterility tests were positive: Stapyilococcus epidermidis, Klebsiella pneumonia, Stapyilococcus hominis, Abiotrophia defective.

The laboratory also conducted studies of various biomaterials for pathogenic flora: eyes, ENT organs, wounds, breast milk, genitals, urine, sputum, cadaveric material (Table 1).

Table 1. **Landscape of isolated cultures from biomaterial.**

	Eyes	ENT	Wounds	Breast milk	Genitals	Urine	Sputum	Cadaveric material	Total
1	2	3	4	5	6	7	8	9	10
Number of tests	585/295	2024/1946	165/156	11/6	587/587	1596/1596	6277/6277	162/30	11407/10893
Number of positive tests	153/91	1358/1233	54/50	3/2	281/261	375/374	5307/4592	105/17	7647/6629
Staphylococcus aureus	37/22	322/296	6/3	3/2	15/15	4/4	346/247	13/1	476/591
Staphylococcus epidermidis	90/51	4/4	3/3		23/23				120/81
Staphylococcus gallinarum							1/1		1/1
Staphylococcus haemolyticus	4/2				2/2	1/1			7/5
Staphylococcus lugdunensis	2/1								2/1
Staphylococcus hominis	2/1								2/1
Staphylococcus sciuri					1/1				1/1
Staphylococcus lentus		2/2							2/2
Staphylococcus simulans							2/2		2/2
Streptococcus pneumoniae		37/37					1293/1286		1330/1323
Staphylococcus haemolyticus		119/118	2/2		6/6	3/3	847/845	2/2	973/975
Streptococcus pyogenes	4/2	297/291	4/4		14/14	1/1	909/907	8/2	1237/1221
Streptococcus sanguinis		68/67	1/1		1/1		241/236		311/305
Streptococcus suis		4/4			1/1		14/14		19/19
Streptococcus mitis		7/7	1/0				65/65		73/72
Streptococcus uberis	1/1	107/107	1/1		8/8	3/3	347/344		467/467
Streptococcus mutans		15/14					29/27		44/41
Streptococcus thoraltentis		8/8					14/14		22/22
Streptococcus anginosus						1/1	3/3		4/4
Streptococcus gordonii							2/2		2/2
Streptococcus hyantestinalis		14/13					41/38		55/51

Continuation of the Table 1

1	2	3	4	5	6	7	8	9	10
Streptococcus salivarus		1/1					16/16		17/17
Streptococcus ovalis		1/1					16/16		17/17
Streptococcus parasanguines							1/1		1/1
Streptococcus hominis	3/2								3/2
Streptococcus caprae	1/1				1/1				2/2
Streptococcus pluranimalibm						1/1			1/1
Streptococcus disgalactia							1/1		1/1
Streptococcus vestibularis							1/1		1/1
Streptococcus perosus							1/1		1/1
Streptococcus galatyticus							1/1		1/1
Streptococcus intermedius		1/1							1/1
Enterococcus faecalis	4/4		2/2		29/28	11/11			46/45
Enterococcus faecium			2/1		2/2	6/6			10/9
Enterococcus cassielilarum					1/1				1/1
Enterococcus galinarum	2/1								2/1
Escherichia coli	2/2		22/22		84/84	198/198		9/1	315/307
Escherichia hermannii			2/2		2/2	8/2			12/12
Enterobakter					2/2	4/4			6/6
Enterobacter cloacae			2/2		5/5	7/7	1/1		15/15
Enterobakter aminigensis		1/1				2/2			3/3
Enterobakter Brevis						1/1			1/1
Citrobakter						1/1			1/1
Citrobacter broakii			1/1			2/2			3/3
Citrobakter freuindii					1/1				1/1
Citrobakter malonaticus						1/1			1/1
Klebsiella		1/1				1/1			2/2
Klebsiella pneumoniae		45/43	5/5		9/9	45/44	65/56	37/8	206/165
Klebsiella oxitocae		1/1					1/1		2/2
Klebsiella aerogenes		6/6	1/1		5/5	3/3	4/2	4/1	23/18
Pseudomonas aeruginosa		5/5	3/3		1/1	17/17	54/47	1/0	81/73

Continuation of the Table 1

1	2	3	4	5	6	7	8	9	10
Pseudomonas luteola							1/1		1/1
Pseudomonas putida						1/1			1/1
Pseudomonas mendocina							1/1		1/1
Proteus vulgaris						7/7		5/1	12/8
Proteus mirabilis	1/1		1/1		4/4	17/17	2/2		25/25
Proteus penneri						1/1			1/1
Proteus morganii						1/1			1/1
Salmonella enteritidis			1/1						1/1
Shigella Sonnei						1/1			1/1
Prevotella intermedia		1/1	1/1		1/1	2/2			5/5
Candida		117/79			25/17		390/133	4/0	536/229
Candida albicans		99/66	1/0		14/9		313/115	7/0	434/190
Candida lusitaniae		4/3					10/2		14/5
Candida krusei		17/13			8/2		68/30		93/45
Candida thopicalis		3/3					13/4		16/7
Candida dublinensis		25/18					47/11	7/1	79/30
Candida guilermondii		1/1					6/2		7/3
Candida parapsilosus		5/4					11/8		16/12
Candida glabrata		2/2			3/3		14/8		19/13
Candida kefur		3/0					4/1		7/1
Candida auris		3/3					12/6		15/9
Candida pseudothopicalis							4/3		4/3
Candida norvegensis							1/0		1/0
Candida pelliculosa							1/0		1/0
Плесень							2/0	4/0	6/0
Abiothofiae detectiva		10/10					74/74		84/84
Actinomycis naeslundii		2/2					5/5		7/7
Actinomycis lucrii							2/2		2/2
Acinetobacter colcaoceticus			1/1		9/9	10/10	1/0	4/1	25/21
Acinetobacter Baumanii			1/1		1/1	6/6	2/2		10/10
Burkholderia ceracia					2/2	3/3	1/1		6/6
Hellicoccus kunsii							3/3		3/3
Lecteria adecurbroxylata						1/1	1/1		2/2

Continuation of the Table 1

Cronobacter malonaticus					1/1	1/1			2/2
Stenotrophomonas maltophini						2/2			2/2
Serratia plymutica							1/1		1/1
Gemella sanguinis							1/1		1/1
Providencia rettgerii						1/1			1/1

As can be seen from Table 1, a total of 11,407 (30%) of 10,893 individuals were executed. 7,647 (67%) tests from 6,629 individuals turned out to be positive. The analysis of microflora, depending on the material, showed the following picture. The number of eye tests was 585, positive – 153 (26%), the flora was mainly represented by Staphylococcus epidermidis and Staphylococcus aureus. The number of tests with ENT organs was 2,024, positive – 1,358 (67%). The most common were Staphylococcus aureus, Streptococcus pyogenes, Staphylococcus haemolyticus, Streptococcus uberis, and Candida. These dates are confirmed by study of other authors [15]. There were 165 tests from wound, 54 of them were positive (33%). Escherichia coli appeared among the pathogens [9,10]. Breast milk was studied from 11 people, positive 3 (27%) assays (Staphylococcus aureus). Genital seeding was 587 people, which is 281 (48%) - a positive result. The microbes Candida and Escherichia coli evolved. The urine of 1,596 individuals was studied, with 375 (23%) positive tests. Escherichia coli dominated the analyses. Sputum culture was performed by 6,277 people, and a positive result was obtained in 5,307 (85%) cases. Among the microbes were Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus haemolyticus, Streptococcus uberis and Staphylococcus aureus. 162 tests of sheets of cadaveric material were studied, and positive result was in 105 (65%). Klebsiella pneumoniae prevailed.

The analysis of the microbial landscape revealed Streptococcus pneumoniae (1330), Streptococcus pyogenes (1237), Staphylococcus haemolyticus (973), Candida (536), Staphylococcus aureus (476), Streptococcus uberis (467), Candida albicans (434), Escherichia coli (315) and others.

The bacteriological laboratory performs serological studies (passive hemagglutination reaction (PHAR), agglutination reaction (AR)). A total of 205 (0.5%) tests were conducted from 129 individuals, including PHAR with Salmonella diagnosticum (101), PHAR with Vi antigen (2), PHAR with Shigella diagnosticum (52), PHAR with Tularemia antigen (2), AR with pertussis/paracoccussis (48) antigen from 24 individuals. No positive titers were found.

The sensitivity of various pathogens to antibiotics was determined in the laboratory. The sensitivity of Streptococcus pneumoniae to antibiotics Gentamycin, Vancomycin, Linezolid, Penicillin, Moxifloxacin, Ceftoroline, Erythromycin, Clindamycin, Daptomycin was determined. Resistance of the pathogen was observed to Ampicillin, Tetracycline, Ciprofloxacin, Trimethoprim, Rifampin. Sensitivity and resistance to antibiotics were determined in Staphylococcus aureus. The pathogen was sensitive to the following antibiotics: Gentamycin, Ciprofloxacin, Nitrofurantoin, Teicoplanin, Vancomycin. Resistance to the microbe was revealed to Ampicillin, Penicillin, Oxacillin. Klebsiella pneumoniae was sensitive to Imipenem, Minocyline, Amikacin, Pipercallin and resistant to Nitrofurantoin, Trimethoprim, Cefazolin, Tobramycin.

Discussion

Data about the structure of the microflora are varied in different hospitals. In dynamic in Saratov multidisciplinary hospital structure of pathogens may change, but some microorganisms remain dominant. These include Staphylococcus aureus in the nose and pharynx, Escherichia coli and Staphylococcus aureus in the wound materials, Streptococcus pneumoniae and Candida in the sputum, Escherichia coli in the cervical canal.

Analyze of the resistance of Staphylococcus aureus to antibacterial drugs (ABD) revealed the increase in resistance to Ceftriaxone, Oxacillin. Regarding resistance of Proteus has increased to Ampicillin. At the same time, the resistance of Staphylococcus haemolyticus to macrolides and aminoglycazides decreased. The isolated Enterobacter strains proved to be resistant to Ampicillin (and Amoxicillin/clavulanate, respectively) in 100% of cases. No Vancomycin-resistant strains have been identified. Regarding Staphylococcus epidermidis resistance to antibacterial drugs has significantly decreased. Analyze of the resistance of Escherichia coli to antibacterial drugs detected that 100% of the strains are not sensitive to unprotected Aminopenicillins (due to the production of b-lactamases). The resistance of Escherichia coli to Cephalosporins has increased, which causes the ineffectiveness of therapy. The isolated strains of Pseudomonas aeruginosa are resistant to anti-pseudomonas preparations (Ciprofloxacin, Ceftazidime). The resistance of enterococci to antimicrobial drugs is growing. Regarding the resistance of fungi of the genus Candida to Nystatin revealed [19].

The structure of the microflora isolated from biomaterial of patients in different departments of Hanoi National Hospital of pediatrics revealed the following data. A total of 140 biomaterials from 74 patients hospitalized in the anesthesiology and intensive care unit, infectious diseases department, and gastroenterology department were tested. In biomaterial of patients treated in anesthesiology and intensive care unit Enterobacteriaceae (38,5%) prevailed, in infectious hospital Gram-negative non-fermenting bacteria (46,5%) presented, in gastroenterology department Gram-positive microbes (39,3%) presented.

The structure of the microflora of the hospital, according to the selected hospital environment, gram-positive flora prevailed (60.2% in anesthesiology and intensive care unit

and 50,7% - in infectious diseases department). A wide range of Enterobacteriaceae and Gram-negative non-fermenting microbes with wide spectrum of resistance were found in National Hospital of pediatrics [20].

Bacteriological laboratory of the Center for Phthisiopulmonology and Infectious Diseases in Semey revealed a predominance of Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus haemolyticus, Candida, Staphylococcus aureus, Streptococcus uberis, Candida albicans, Escherichia coli.

The sensitivity of Streptococcus pneumoniae to antibiotics Gentamycin, Vancomycin, Linezolid, Penicillin, Moxifloxacin, Ceftoroline, Erythromycin, Clindamycin, Daptomycin was determined. Resistance of the pathogen was observed to Ampicillin, Tetracycline, Ciprofloxacin, Trimethoprim, Rifampin. Staphylococcus aureus was sensitive to Gentamycin, Ciprofloxacin, resistant to Ampicillin, Penicillin. Klebsiella pneumoniae was susceptible to Imipinem, Minocyline and resistant to Nitrofurantoin, Trimethoprim. The sensitivity of Candida to Fluconazole, Micafungin and resistance to Voriconazole was determined.

The dates of bacteriological laboratory of the Center for Phthisiopulmonology and Infectious Diseases in Semey reflect the general situation with microflora and resistance to antibacterial drugs in the world. The Atomic-i600 microbiological analyzer allows accurate and fast testing of various biological samples, which significantly increases the reliability and speed of obtaining results.

Conclusions

Thus, the work of specialists in microbiological laboratories plays a crucial role in the effective prevention and control of infections, since the identification of the pathogen allows doctors to prescribe treatment in a timely and effective manner and thereby prevent the spread of infections.

Despite the successes, bacteriological laboratories face a number of challenges. One of the main ones is the growth of antibiotic-resistant strains. This is due to the frequent and improper use of antibiotics, as well as the lack of awareness among patients about the importance of following doctors' prescriptions. Another important problem is the shortage of qualified personnel in the laboratories. In this regard, it is necessary to raise the level of training of specialists, introduce new educational programs, and provide laboratories with modern equipment. In our study, AutoMic-i600 was used to analyze microbial strains, which ensured high data accuracy and increased the efficiency of sample processing.

The work of a bacteriological laboratory is a complex, multifaceted process that includes diagnosis, monitoring, scientific research and prevention of infectious diseases. With the development of new technologies and diagnostic methods, the role of the bacteriological laboratory in healthcare continues to grow. It is important to continue investing in the education of specialists and the development of laboratory facilities in order to improve the quality of diagnosis and treatment of infectious diseases.

The systematic introduction of new technologies and research methods into the work of bacteriological laboratories contributes to improving infection control and improving public health.

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Contribution of authors. *All authors were equally involved in the writing of this article.*

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ANALYSIS OF MEDICAL STUDENTS' KNOWLEDGE ABOUT HIV INFECTION

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Abstract

Introduction: HIV infection continues to be a significant public health issue globally, particularly among vulnerable populations such as young people, including medical students. As future healthcare providers, the level of knowledge among medical students regarding HIV transmission, prevention, and management is crucial not only for their own health but also for controlling the spread of the infection within the broader community. Furthermore, their understanding influences attitudes toward people living with HIV, fostering a more non-discriminatory, supportive healthcare environment.

Objective: To assess the level of HIV knowledge among medical students and identify factors influencing their awareness.

Materials and Methods: A cross-sectional study was conducted using an anonymous online survey administered to 152 medical students. The survey assessed various aspects of HIV knowledge, including transmission routes, prevention methods, target cells of the virus, and its effects on the immune system. Statistical analysis was performed using Fisher's exact test, and $p < 0.05$ was considered statistically significant.

Results: The overall level of HIV knowledge among students was moderate. Age and field of study significantly influenced awareness levels ($p < 0.05$), with senior-year students and those studying General Medicine demonstrating better knowledge. Significant differences were found regarding HIV transmission routes ($p = 0.022$), target cells ($p = 0.001$), and the virus's impact on the immune system ($p = 0.046$). Senior students and those specializing in general medicine demonstrated better knowledge (43.3% correct answers), while college students had the lowest results (19.4%).

Conclusion: The findings underscore the necessity for enhancing HIV education within medical curricula. It is particularly important to focus on comprehensive education regarding the mechanisms of virus transmission, its pathophysiological impact on the immune system, and evidence-based prevention strategies. Targeted educational interventions should be implemented, particularly for junior students and those outside of General Medicine, to ensure a well-rounded understanding across all medical disciplines.

Keywords: *HIV, students, medical education, prevention, awareness.*

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Резюме

АНАЛИЗ ЗНАНИЙ СТУДЕНТОВ МЕДИКОВ О ВИЧ ИНФЕКЦИИ

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Введение: Инфекция ВИЧ продолжает оставаться важной проблемой общественного здравоохранения по всему миру, особенно среди уязвимых групп, таких как молодежь, включая медицинских студентов. Уровень знаний медицинских студентов о передаче, профилактике и лечении ВИЧ критически важен не только для их собственного здоровья, но и для контроля за распространением инфекции в обществе. Кроме того, их понимание влияет на отношение к людям, живущим с ВИЧ, способствуя созданию более неконфликтной и поддерживающей медицинской среды.

Цель: Оценить уровень знаний о ВИЧ среди медицинских студентов и выявить факторы, влияющие на их осведомлённость.

Материалы и методы: Проведено поперечное исследование с использованием анонимного онлайн-опроса, в котором участвовали 152 студента. Опрос оценивал различные аспекты знаний о ВИЧ, включая пути передачи, методы профилактики, целевые клетки вируса и его влияние на иммунную систему. Статистический анализ был выполнен с использованием точного теста Фишера, где $p < 0,05$ считалось статистически значимым.

Результаты: Общий уровень знаний о ВИЧ среди студентов был умеренным. Возраст и специальность значительно влияли на уровень осведомленности ($p < 0,05$), студенты старших курсов и изучающие общую медицину продемонстрировали лучшие результаты. Были выявлены значительные различия по вопросам путей передачи ВИЧ ($p = 0,022$), целевых клеток ($p = 0,001$) и влияния вируса на иммунную систему ($p = 0,046$). Старшие студенты и те, кто учится на общей медицине, показали лучшие результаты (43,3% правильных ответов), в то время как студенты младших курсов имели самые низкие результаты (19,4%).

Заключение: Результаты подчеркивают необходимость улучшения образовательных программ по ВИЧ в медицинских вузах. Особое внимание следует уделить обучению механизмам передачи вируса, его патофизиологическому воздействию на иммунную систему и профилактическим стратегиям, основанным на доказательствах. Необходимы целевые образовательные вмешательства, особенно для студентов младших курсов и тех, кто учится не на общей медицине, чтобы обеспечить всестороннее понимание в различных медицинских дисциплинах.

Ключевые слова: *ВИЧ, студенты, медицинское образование, профилактика, осведомленность.*

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Түйіндеме

МЕДИЦИНАЛЫҚ СТУДЕНТТЕРДІҢ ВИЧ ИНФЕКЦИЯСЫ ТУРАЛЫ БІЛІМІН ТАЛДАУ

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Кіріспе: ЖИТС инфекциясы бүкіл әлем бойынша маңызды қоғамдық денсаулық мәселесі болып қала береді, әсіресе осал топтар арасында, мысалы, жас адамдар мен медициналық студенттер. Медициналық студенттердің ЖИТС-тің берілуі, алдын алу және басқару туралы білім деңгейі тек олардың өз денсаулығы үшін ғана емес, инфекцияның таралуын бақылау үшін де өте маңызды. Сонымен қатар, олардың түсінігі ЖИТС-пен өмір сүретін адамдарға деген қарым-қатынасты қалыптастыруға, кемсітушілікке жол бермейтін және қолдаушы медициналық орта құруға ықпал етеді.

Мақсаты: Медицина студенттерінің АИТВ туралы білім деңгейін бағалап, оған әсер ететін факторларды анықтау.

Материалдар мен әдістер: 152 медициналық студентке анонимді онлайн сауалнама жүргізілген көлденең зерттеу жүргізілді. Сауалнамада ЖИТС туралы білімнің түрлі аспектілері, оның ішінде берілу жолдары, алдын алу

әдістері, вирустың мақсатты жасушалары және иммундық жүйеге әсері бағаланды. Статистикалық талдау Фишердің дәлдік тесті арқылы жүргізілді, $p < 0.05$ мәні статистикалық маңыздылық деп саналды.

Нәтижелер:Медициналық студенттер арасында ЖИТС туралы білім деңгейі орташа болды. Жас пен оқу бағыты ақпараттық деңгейге елеулі әсер етті ($p < 0.05$), жоғары курс студенттері мен жалпы медицина саласында оқитындар жақсырақ білім көрсетті. ЖИТС-тің берілу жолдары ($p = 0.022$), мақсатты жасушалар ($p = 0.001$) және вирустың иммундық жүйеге әсері ($p = 0.046$) туралы айтарлықтай айырмашылықтар анықталды. Жоғары курс студенттері мен жалпы медицина саласында оқитындар білімдерін жақсы көрсетті (43.3% дұрыс жауап), ал колледж студенттерінің нәтижелері ең төмен болды (19.4%).

Қорытынды: Зерттеу нәтижелері медициналық білім бағдарламаларында ЖИТС бойынша білімді арттыру қажеттілігін көрсетеді. Вирус таралу механизмдерін, оның иммундық жүйеге патофизиологиялық әсерін және дәлелдерге негізделген алдын алу стратегияларын жан-жақты оқытуға ерекше назар аудару өте маңызды. Студенттерге, әсіресе төменгі курс студенттеріне және жалпы медицина саласынан тыс оқитындарға арналған мақсатты білім беру шаралары енгізілуі тиіс.

Түйінді сөздер: *ЖИТС, студенттер, медициналық білім, алдын алу, ақпараттылық.*

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Introduction

HIV infection remains one of the most significant public health issues worldwide. According to the World Health Organization (WHO), in 2023, there were approximately 39 million people living with HIV globally, a significant proportion of whom are young people, including medical students [21]. In this context, the level of awareness among medical students about HIV is of particular importance, as they are the future professionals responsible for diagnosing, treating, and preventing the infection.

Future medical professionals play a key role in the fight against the spread of HIV and in providing care to patients. However, numerous studies highlight gaps in their knowledge about the virus, its modes of transmission, and prevention methods [15].

Research shows that the level of awareness among students about HIV varies depending on the country, curriculum, and the age of the respondents. For example, a study among students in Cameroon found that only 55% of senior students had sufficient knowledge about HIV transmission mechanisms [16].

Medical students are the future doctors and healthcare workers who will play a crucial role in the fight against HIV. Their level of knowledge and professional training directly impacts the quality of diagnosis, treatment, and patient counseling. Various studies point to existing gaps in medical students' knowledge about HIV [14].

A study conducted in India showed that even among senior students, less than 50% correctly identify the primary modes of HIV transmission [4]. In another study conducted in the United States, it was found that medical students are less likely to recommend pre-exposure prophylaxis (PrEP) for high-risk HIV patients, indicating insufficient training in this area [7].

Particular concern is raised by the persistent stigma surrounding HIV patients among future healthcare professionals. A study conducted in Jordan revealed that a high level of negative attitudes toward people living with HIV is directly linked to low levels of student knowledge [6]. Similar results were obtained in Saudi Arabia, where students with a higher level of awareness exhibited more tolerant attitudes toward HIV patients [4].

One of the factors influencing students' knowledge of HIV is the curriculum. Some studies emphasize the need for more comprehensive HIV/AIDS courses in medical schools [19].

Given the increasing number of HIV cases among young people, particularly in developing countries, it is crucial to regularly assess the level of knowledge among medical students. This would allow for the adaptation of educational programs and the enhancement of future specialists' training in infectious diseases [12].

Thus, **the aim of this study** is to analyze the level of knowledge of medical students about HIV, identify the primary gaps in awareness, and assess the impact of age and specialty on the degree of awareness.

Materials and methods of research

The study design is a cross-sectional study.

Data were collected using a questionnaire created through the Google Forms online service, ensuring convenience for participants and anonymity. Participation in the survey was voluntary, with participants being informed in advance about the study's objectives and assured that their responses would remain anonymous.

Sample

A total of 152 respondents participated in the study, of which 65.1% were women and 34.9% were men. The age distribution of the participants was as follows: 17-19 years - 68 participants (44.7%), 20-22 years - 62 participants (40.8%), and 23 years and older - 22 participants (14.5%). The respondents were enrolled in different fields of study: General Medicine - 53 participants (34.9%), College - 49 participants (32.2%), Dentistry - 36 participants (23.7%), and Pediatrics - 14 participants (9.2%).

Data Collection Method

The questionnaire, which included a variety of questions on the topic of HIV, was designed to assess students' knowledge in various aspects of the disease. Survey participants were asked to select the most appropriate answers from the provided options.

Data Analysis Methods

Statistical methods implemented in the SPSS software (Statistical Package for the Social Sciences) were used for data analysis. Fisher's exact test was used to check the

statistical significance of differences between groups. This allowed for the evaluation of whether significant differences existed between various subgroups of respondents in terms of key parameters (e.g., knowledge level by age or specialization). A p-value of < 0.05 was considered statistically significant, enabling conclusions about the relevance of the identified differences.

Research results

Table 1 presents the results of respondents' awareness of HIV transmission routes. The overall level of knowledge was moderate. In the age group of 17-19 years, 25.4% of participants correctly identified transmission routes such as the use of shared needles when using drugs, mother-to-child transmission during pregnancy or childbirth, blood transfusion, and unprotected sexual contact. In the 20-22 age group, 55.2% provided correct answers, while among respondents over 23 years old, the figure was 19.4% (p = 0.001 General medicine students demonstrated the highest results, with 43.3% correct answers, while college students showed the lowest level of awareness at 19.4%. Statistically significant differences between the age groups were confirmed (p = 0.022).

Table 1.

Awareness of HIV transmission routes.

Variables		How is HIV transmitted?				p- value
		Correct answers		Incorrect answers		
		n	%	n	%	
Age group	17-19	17	25.4%	51	60.0%	0.001*
	20-22	37	55.2%	25	29.4%	
	23 and more	13	19.4%	9	10.6%	
Speciality	College	13	19.4%	36	42.4%	0.022*
	General medicine	29	43.3%	24	28.2%	
	Pediatrics	8	11.9%	6	7.1%	
	Dentistry	17	25.4%	19	22.4%	

Table 2 shows the data on respondents' awareness of HIV target cells. In the 17-19 age group, 41.7% of respondents correctly answered the question about T-lymphocytes CD4+ being the primary target for HIV. In the 20-22 age group, 42.6% provided correct answers, while among participants older than 23, the figure was 15.7%. However, statistically significant differences between age groups were not found (p = 0.410). General medicine students showed the highest level of awareness (41.7%), while college students - the lowest (27.0%). Statistically significant differences between specialties were confirmed (p = 0.001).

Table 2.

Awareness of HIV target cells.

Variables		What type of cell is the main target of HIV in the body?				p- value
		Correct answers		Incorrect answers		
		n	%	n	%	
Age group	17-19	48	41.7%	20	54.1%	0.410
	20-22	49	42.6%	13	35.1%	
	23 and more	18	15.7%	4	10.8%	
Speciality	College	31	27.0%	18	48.6%	0.001*
	General medicine	48	41.7%	5	13.5%	
	Pediatrics	13	11.3%	1	2.7%	
	Dentistry	23	20.0%	13	35.1%	

The results of awareness regarding the consequences of HIV infection for the immune system are presented in Table 3. In the 17-19 age group, 42.9% of respondents correctly indicated that HIV causes a decrease in the number of CD4+ T-lymphocytes. In the 20-22 age group, 42.0% provided correct answers, while among respondents older than 23, the figure was 15.2%. However, no statistically significant differences were found between the age groups (p = 0.731) General medicine students demonstrated the best results (41.1%), and pediatrics students - the lowest. Statistically significant differences were confirmed (p = 0.046).

Table 3.

Concepts of the immune system in HIV.

Variables		What happens to the immune system as a result of HIV infection?				p- value
		Correct answers		Incorrect answers		
		n	%	n	%	
Age group	17-19	48	42.9%	20	50.0%	0.731
	20-22	47	42.0%	15	37.5%	
	23 and more	17	15.2%	5	12.5%	
Speciality	College	33	29.5%	16	40.0%	0.046*
	General medicine	46	41.1%	7	17.5%	
	Pediatrics	8	7.1%	6	15.0%	
	Dentistry	25	22.3%	11	27.5%	

Table 4 shows the results of awareness regarding viral load in HIV. In the 17-19 age group, 46.4% of respondents correctly answered the question about viral load as the amount of virus in the blood. In the 20-22 age group, 38.1% provided correct answers, while among participants older than 23, the figure was 15.5%. But statistically significant differences were not observed (p = 0.747). General medicine students demonstrated a better level of knowledge (showing 42.9% correct answers) than students of other specialties, and statistically significant differences were found with p = 0.004.

Table 4.

Knowledge of viral load in HIV.

Variables		What is viral load in the context of HIV?				p- value
		Correct answers		Incorrect answers		
		n	%	n	%	
Age group	17-19	39	46.4%	29	42.6%	0.747
	20-22	32	38.1%	30	44.1%	
	23 and more	13	15.5%	9	13.2%	
Speciality	College	30	35.7%	19	27.9%	0.004*
	General medicine	36	42.9%	17	25.0%	
	Pediatrics	7	8.3%	7	10.3%	
	Dentistry	11	13.1%	25	36.8%	

Table 5 presents data on knowledge of HIV treatment methods. In the 17-19 age group, 49.1% of respondents were aware of existing treatment methods, such as antiretroviral therapy (ART). In the 20-22 age group, 34.9% provided correct answers, while among participants older than 23, the figure was 16.0%. Statistically significant differences between age groups were not found (p = 0.081). General medicine students demonstrated the highest level of knowledge (40.6%) while dentistry students showed the lowest level of awareness (15.1%). Statistically significant differences were found with p=0.002.

Table 5.

HIV Treatment Awareness.

Variables		What is the most effective treatment for HIV?				p- value
		Correct answers		Incorrect answers		
		n	%	n	%	
Age group	17-19	52	49.1%	16	34.8%	0.081
	20-22	37	34.9%	25	54.3%	
	23 and more	17	16.0%	5	10.9%	
Speciality	College	36	34.0%	13	28.3%	0.002*
	General medicine	43	40.6%	10	21.7%	
	Pediatrics	11	10.4%	3	6.5%	
	Dentistry	16	15.1%	20	43.5%	

Discussion

The results of this study confirm the findings of previous research, indicating a moderate level of awareness of about HIV among medical students and significant differences in knowledge depending on age and specialization of study. Based on the results obtained, it is evident that there are significant gaps in the awareness of HIV transmission, consequences, and treatment among medical students. While certain groups, such as general medicine students, demonstrated a relatively higher level of knowledge compared to students from other specialties, significant discrepancies were observed across different age groups and fields of study. The data also highlight a concerning lack of awareness regarding key aspects of HIV, such as viral load and the immune system's response to the infection.

The analysis of the obtained data shows that senior students and those studying general medicine demonstrated a higher level of knowledge about key aspects of HIV infection compared to junior students and college students. These results are consistent with the study by *Haroun D. et al.* (2016), which found a higher level of knowledge among senior students in the UAE [10].

According to the study by *Zhang L. et al.* (2022), it was found in China that senior students were significantly more informed about HIV transmission mechanisms and treatment methods than first-year students [22].

In another study conducted in Jordan, it was found that even among senior students, there were gaps in understanding HIV transmission mechanisms and the principles of antiretroviral therapy (*Sallam M. et al.,* 2022) [18]. These data highlight the need for continued HIV education programs not only within the basic infectious disease course but also throughout the entire period of medical education.

However, despite the positive trend in knowledge as education levels increase, certain gaps remain even among senior students. *Tatsilong H.O. et al.* (2016) found that over 40% of senior students in Cameroon still could not accurately identify HIV transmission routes [20], which correlates with our results.

The lowest levels of knowledge were observed in questions related to HIV target cells, associated infections, and viral load. Similar conclusions were made in studies by *Li G. et al.* (2019) [13] and *Obeagu E.L. et al.* (2023) [16], where it was noted that understanding the biological mechanisms of the infection remains weak even among medical students.

Furthermore, in the study by *Alawad M. et al*. (2019), conducted in Saudi Arabia, it was noted that medical students who had completed specialized courses in infectious diseases demonstrated a higher level of knowledge compared to those who had not taken such courses [1]. This highlights the need to improve educational programs.

The study by *Alhasawi A.M. et al.* (2019), conducted in Kuwait, showed that a significant number of students had incorrect perceptions about HIV transmission methods. For example, approximately 30% of respondents mistakenly believed that HIV could be transmitted through kissing or insect bites [2]. This underscores the necessity of focusing on evidence-based data in educational programs.

Moreover, some participants demonstrated misconceptions about the impact of HIV on the immune system, emphasizing the need for a more in-depth exploration of this issue in educational programs [19]. These results confirm the necessity of revising curricula and enhancing attention to HIV-related education for students. The study by *Khasawneh et al.* (2020) demonstrated that incorporating interactive and clinical teaching methods significantly improves students' knowledge about HIV [11].

An important aspect is also the increase in awareness about HIV prevention, including post-exposure prophylaxis and the principles of antiretroviral therapy. The study by *Parameshwaran V. et al.* (2017) showed that students who underwent specialized courses in infectious diseases demonstrated better knowledge and a more positive attitude toward patients with HIV [17].

One of the most problematic topics identified during the analysis remains viral load and the significance of antiretroviral therapy. The study by *Alizadeh Otaghvar H. et al.* (2023) notes that less than 50% of students are aware that adequate therapy reduces the risk of HIV transmission to minimal levels [3].

Another important aspect identified during the study is the link between students' knowledge levels and their attitudes toward people living with HIV. According to the study by Arthur S. et al. (2021), students with low levels of knowledge about HIV are more likely to display stigmatizing attitudes toward patients [5]. *Zhang L. et al.* (2022) also noted that in countries with insufficient HIV awareness among medical students, there are more biased opinions about people with HIV, which negatively affects future doctors' willingness to provide medical care to such patients [21].

To improve students' knowledge and combat stigmatization, the implementation of new teaching methods is necessary. The study by *Arthur S. et al.* (2021) confirms that the use of interactive methods, such as clinical case simulations and role-playing, significantly increases students' awareness [5].

Obeagu E.L. et al. (2023) also recommend incorporating specialized HIV modules into mandatory medical school programs, which will help address gaps in knowledge about viral load, antiretroviral therapy, and prevention of transmission [16].

Based on the obtained data, it can be concluded that enhancing students' knowledge about HIV is possible through the modernization of educational programs. Specifically, the studies by *Fisher C.B. et al.* (2020) and de *Vries E. et al.* (2020) recommend the introduction of courses using role-playing, simulated patients, and clinical cases for better understanding of HIV infection aspects [9,8].

Conclusions

Age and specialty play a significant role in the level of knowledge students have about HIV. Young people aged 17-19 have a lower level of awareness compared to older students (20-22 years old). Students studying general medicine also demonstrate a better understanding of HIV compared to those from other medical fields, such as pediatrics and dentistry, as well as college students. Among the most problematic topics for respondents are HIV transmission routes ($p = 0.022$), HIV target cells ($p = 0.001$), and the impact of HIV on the immune system ($p = 0.046$).

In this regard, it is necessary to strengthen educational programs for junior students and those studying non-medical specialties. It is particularly important to focus on HIV transmission routes, its impact on the immune system, and key associated infections. Specialized lectures and courses for students in pediatrics, dentistry, and colleges are also recommended to enhance their awareness.

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PERCEPTIONS OF WORK PROCESSES AND ORGANIZATIONAL DYNAMICS IN HOSPITAL GYNECOLOGY DEPARTMENTS

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Abstract

Introduction. Providing quality care is a priority of the healthcare system. One of the key attributes of quality care is effective teamwork within hospital departments and communication between medical specialists and patients.

Aim: to study the current practice and perceptions of work processes and organizational dynamics in hospital gynecology departments in Almaty city.

Materials and methods. The cross-sectional study was conducted in the first half of 2024. We developed a survey for hospital gynecologists, which was conducted with the support of the Almaty city health department and the heads of medical organizations. Participation in the survey was voluntary and anonymous, and respondents could complete it at any time convenient for them.

Results. The survey showed that the majority of respondents, both doctors and nurses had more than 11 years' of work experience, and most reported job satisfaction. A large portion of respondents, especially nurses (75.6%), believed that medical errors resulted in reprimands, while 46.3% agreed that the administration regularly reviews processes to improve patient safety. Additionally, 47.2% felt that incident reporting often focused on the person rather than the issue, with 42.2% of nurses disagreeing compared to 31.7% of doctors. While 50.8% of doctors and 51.1% of nurses agreed that the department promotes learning from mistakes, 24.4% of nurses were uncertain, and 20.4% expressed fear when raising concerns, with nurses experiencing more fear ($p < 0.001$). Furthermore, 34.3% of respondents, particularly doctors (46%), believed the manager expects faster work under pressure, while 48.9% of nurses were unsure.

Conclusion. Both groups reported high professional experience and job satisfaction, but nurses expressed more uncertainty, particularly regarding error management and communication. The findings highlight the need for better communication, increased support for nurses, and a stronger safety culture that encourages staff to voice concerns without fear.

***Keywords**: gynecology, women's health, medical care, hospital.*

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Резюме

ВОСПРИЯТИЕ РАБОЧИХ ПРОЦЕССОВ И ОРГАНИЗАЦИОННОЙ ДИНАМИКИ В ОТДЕЛЕНИЯХ ГИНЕКОЛОГИИ БОЛЬНИЦ

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Актуальность. Предоставление качественной помощи является приоритетом системы здравоохранения. Одним из ключевых атрибутов качественной помощи является эффективная командная работа в отделениях больницы и коммуникация между врачами-специалистами и пациентами.

Цель: изучить текущую практику и восприятие рабочих процессов и организационной динамики в отделениях гинекологии больницы города Алматы.

Материалы и методы. Поперечное исследование проводилось в первой половине 2024 года. Мы разработали опрос для врачей-гинекологов больницы, который проводился при поддержке Управления здравоохранения города Алматы и руководителей медицинских организаций. Участие в опросе было добровольным и анонимным, и респонденты могли заполнить опросник в любое удобное для них время.

Результаты. Опрос показал, что большинство респондентов, как врачей, так и медсестер, имели стаж работы более 11 лет, и большинство из них сообщили об удовлетворенности работой. Большая часть респондентов, особенно медсестер (75,6%), считали, что врачебные ошибки приводят к выговорам, в то время как 46,3% согласились с тем, что администрация регулярно пересматривает процессы для повышения безопасности пациентов. Кроме того, 47,2% считают, что сообщения об инцидентах часто фокусируются на человеке, а не на проблеме, при этом 42,2% медсестер не согласны с этим по сравнению с 31,7% врачей. В то время как 50,8% врачей и 51,1% медсестер согласились с тем, что отделение поощряет обучение на ошибках, 24,4% медсестер не уверены, а 20,4% выражают страх при выражении опасений, причем медсестры испытывают больший страх ($p < 0,001$). Кроме того, 34,3% респондентов, особенно врачи (46%), считают, что руководитель ожидает более быстрой работы в условиях давления, в то время как 48,9% медсестер не уверены.

Выводы. Обе группы сообщили о высоком профессиональном опыте и удовлетворенности работой, но медсестры выразили большую неуверенность, особенно в отношении управления ошибками и коммуникации. Результаты подчеркивают необходимость лучшей коммуникации, усиления поддержки медсестер и более сильной культуры безопасности, которая побуждает персонал высказывать опасения без страха.

Ключевые слова: *гинекология, женское здоровье, медицинская помощь, больница.*

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Түйіндеме

ГИНЕКОЛОГИЯЛЫҚ БӨЛІМШЕЛЕРДЕ ЖҰМЫС ҮДЕРІСТЕРІ МЕН ҰЙЫМДЫҚ ДИНАМИКАНЫ ҚАБЫЛДАУ

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Кіріспе. Сапалы көмек көрсету денсаулық сақтау жүйесінің басымдықтарының бірі болып табылады. Сапалы көмектің негізгі атрибуттарының бірі-аурухана бөлімшелеріндегі тиімді топтық жұмыс пен дәрігер-мамандар мен науқастар арасындағы байланыс.

Зерттеудің мақсаты: Алматы қаласы ауруханасының гинекология бөлімшелеріндегі жұмыс үрдістері мен ұйымдастыру динамикасын қабылдау және ағымдағы тәжірибені зерделеу.

Материалдар мен әдістері. Көлденең зерттеу 2024 жылдың бірінші жартысында жүргізілді. Біз Алматы қаласы Денсаулық сақтау басқармасының және медициналық ұйымдардың басшыларының қолдауымен жүргізілген ауруханаңың гинеколог-дәрігерлеріне сауалнама әзірледік. Сауалнамаға қатысу ерікті және анонимді болды, ал респонденттер сауалнаманы өздеріне ыңғайлы кез келген уақытта толтыра алды.

Нәтижесі. Сауалнама нәтижелері көрсеткендей, респонденттердің көпшілігі, соның ішінде дәрігерлер мен медбикелер, 11 жылдан астам еңбек өтілі бар екенін және өз жұмысынан қанағаттанатынын білдірді. Респонденттердің басым бөлігі, әсіресе медбикелер (75,6%), дәрігерлік қателіктер сөгіс алуға әкеледі деп санайды, ал 46,3%-ы әкімшілік науқастардың қауіпсіздігін арттыру үшін процестерді жүйелі түрде қайта қарайды деген пікірге келісті. Сонымен қатар, 47,2% инциденттер туралы есептер мәселенің өзіне емес, жеке адамға бағытталған деп

санайды, бірақ бұл пікірмен медбикелердің 42,2%-ы келіспейді, ал дәрігерлердің арасында бұл көрсеткіш 31,7%-ды құрайды. Дәрігерлердің 50,8%-ы және медбикелердің 51,1%-ы бөлімшенің қателіктерден сабақ алуды ынталандыратынын қолдады, бірақ медбикелердің 24,4%-ы сенімсіз, ал 20,4%-ы алаңдаушылықтарын білдіруден қорқады, бұл қорқыныш әсіресе медбикелер арасында көбірек байқалды (p < 0,001). Сонымен қатар, респонденттердің 34,3%-ы, әсіресе дәрігерлер (46%), басшылық қысым жағдайында жұмысты тезірек орындауды талап етеді деп санайды, ал медбикелердің 48,9%-ы бұл пікірге сенімсіз.

Қорытынды. Екі топ та өздерінің кәсіби тәжірибелерінің жоғары екенін және жұмыстарына қанағаттанатынын айтты, бірақ медбикелер, әсіресе қателіктерді басқару мен коммуникацияға қатысты, үлкен сенімсіздік білдірді. Нәтижелер медбикелерге қолдауды күшейтуді, жақсырақ коммуникацияны және қызметкерлерге алаңдаушылықтарын қорықпай айтуға мүмкіндік беретін қауіпсіздік мәдениетін нығайтудың қажеттілігін атап көрсетеді.

Түйінді сөздер: *гинекология, әйелдер денсаулығы, медициналық көмек, аурухана.*

Дәйексөз үшін: *Султанбекова Б.М., Раушанова А., Ахтаева Н., Алекенова Н., Нурбаулина Э., Абилов Т.* Гинекологиялық бөлімшелерде жұмыс үдерістері мен ұйымдық динамиканы қабылдау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 107-115. *doi 10.34689/SH.2024.27.1.013*

Introduction

The problem of preserving and strengthening women's health is the most pressing today, due to the increase in gynecological disease in world. The greatest burden of gynecological pathology in terms of morbidity and mortality is borne by women in middle- and low-income countries, where among women of reproductive age, rates of loss of productive life due to gynecological diseases are higher than for other important global health priorities, such as maternal health, tuberculosis, malaria and cardiovascular diseases [23].

The gynecologic care delivery model revealed age-related differences in women's use of gynecologic care across different care settings [4]. Every organization, regardless of its size, activity, or specificity, at one time or other faces obstacles that can only be overcome by transforming its structures, processes, and resources. The definition of management as a process of readapting an organization to changing internal and external operating conditions by initiating processes of continuous quality improvement seems to be most relevant when taking into account the specifics of a hospital's activities in a dynamic business environment. Hospital-based obstetrics and gynecology medical practices engage in clinical care, teaching, research, or leadership in the field of obstetrics and gynecology. A special role is given to ensuring multidisciplinary teamwork [5], which can be organized in multidisciplinary hospitals with an established process of structural units. In addition, proper leadership and teamwork can improve the team environment and ensure patient safety, which is one of the important aspects in the healthcare system [10,17,20]. Patient safety is also affected by the communication skills of medical staff, in particular the frequent use of medical terms makes it difficult for patients to understand, which can lead to a decrease in patient safety. Also, errors can occur in communications between medical staff when someone misunderstands what is required from another person [12]. Because of this, when studying the activities of a structural unit of a medical organization, it is important to analyze the relationship of the unit manager with other employees, how teamwork is carried out and other aspects.

Recently, providing quality medical care has become an important factor. One of the attributes of quality care is ensuring proper management in a medical organization, where doctors can work in more comfortable conditions. To do this, it is important to collect feedback, provide processes for receiving complaints and suggestions from employees of the organization, and other activities. Training employees of a medical organization can help overcome any difficulties in providing high-quality and safe care to patients, including in gynecological departments [22]. In the Republic of Kazakhstan, institutional development of quality and accreditation of medical organizations began at the end of 2010. Since then, numerous training events have been held. However, there are very few studies on the organization of gynecological care in hospitals in large cities.

Therefore, the **aim** of our research is to study the current practices and perceptions of work processes and organizational dynamics in hospital gynecology departments in Almaty city.

Materials and methods

The cross-sectional study was conducted in the first half of 2024. We developed a survey for gynecologists working in multidisciplinary hospitals in Almaty. The questionnaire consisted of three sections: the work of the unit, the branch manager's role, and communication. The questionnaire was pre-tested with the participation of 10 doctors, and after making minor adjustments, it was distributed to gynecologists in Almaty's multidisciplinary hospitals. The survey was conducted with the support of the Health Department and the heads of medical organizations. It was administered online via Google Forms, and participation was voluntary and anonymous. Respondents could complete the survey at their convenience.

In 2024, in hospital gynecology departments in Almaty city registered 67 gynecologists, 53 nurses. To identify the sample size, we based on the cross-sectional study design formula, hence the sample size calculation formula is:

$$\boldsymbol{n = deff \times \frac{N \cdot \hat{p}(1-\hat{p})}{(N-1)\frac{d^2}{z_{\alpha}^2} + \hat{p}(1-\hat{p})}}$$

According to a 95% confidence level and a 5% margin of error, the minimum sample size required was 57 for gynecologists and 47 for nurses. However, we aimed to

include a larger number of respondents to account for incomplete responses. As a result, the analysis included completed questionnaires from 63 gynecologists and 45 nurses. To compare the two groups (gynecologists and nurses), we used the chi-square (χ^2) test to analyze the relationships between categorical variables. The χ^2 statistic is compared with the critical value to determine the statistical significance of differences between the groups. If χ^2 is greater than the critical value, the null hypothesis is rejected and a conclusion is made about the presence of differences between the groups. All statistical analyses were performed using the MS Excel and SPSS13.

The study design was approved by the Local Committee on Bioethics, Kazakhstan (IRB-A832, 21 May 2024).

Results

The average age of the doctors who took part in the survey was 41.63 years, whereas nurses was 43.18 years. More than half of the respondents in both groups have over 11 years of work experience, which indicates a high level of professional experience of the study participants. About half of the respondents have been working in this organization for more than five years. The largest number of respondents in both groups expressed satisfaction with their work. The answer to the question of whether the hospital administration regularly reviews work processes in the department to identify the need for changes to improve patient safety is statistically significant. 46.3% of respondents agreed with this statement, and the indicator was more pronounced among nurses. At the same time, 17.6% of survey participants noted uncertainty on this issue ($p<0,001$). The largest number of respondents in both groups (57.1% of doctors and 75.6% of nurses) noted that in this department, employees feel that medical errors will result in reprimands or other measures ($p<0,001$). 47.2% of respondents agreed with the statement that in hospital gynecology departments, when reporting an event, it seems that it is not the essence of the problem that is being discussed, but the person who caused the error or incident. About 16.7% of participants noted uncertainty on this issue. The largest number of nurses (42.2%) disagreed with this statement, while among doctors this figure was (31.7%), $p=0.045$. 50.8% of physicians and 51.1% of nurses agreed with the statement that when employees make mistakes, the unit focuses on learning rather than blaming individuals. However, twice as many nurses (24.4%) were undecided. 38.1% of physicians disagreed with this statement ($p<0.001$). In both groups, more than half of respondents disagreed with the statement that the pace of work in this department is so fast that it negatively impacts patient safety ($p = 0.02$). Also, 50.0% of survey participants disagreed with the statement that this department lacks support for staff involved in patient safety errors, while 18.5% of respondents expressed uncertainty on this issue ($p = 0.02$), table 1.

Table 1.

Organization of work in the workplace.

Questions		Gynecologists N (%)	Nurse N (%)	Total N (%)	P value
1		2	3	4	5
Work experience	Less than 1 year	2 (3.2%)	3 (6.7%)	5 (4.6%)	0.807
	1 to 5 years	8 (12.7%)	7 (15.6%)	15 (13.9%)	
	6 to 10 years	12 (19.0%)	8 (17.8%)	20 (18.5%)	
	11 or more years	41 (65.1%)	27 (60.0%)	68 (63.0%)	
	Total	63 (100.0%)	45 (100.0%)	108 (100.0%)	
How many years have you been working in this organization?	Less than 1 year	9 (14.3%)	10 (22.2%)	19 (17.6%)	0.432
	1 to 5 years	21 (33.3%)	11 (24.4%)	32 (29,6%)	
	6 to 10 years	17 (27.0%)	9 (20.0%)	26 (24.1%)	
	11 or more years	16 (25.4%)	15 (33.3%)	31 (28.7%)	
Are you satisfied with the hospital's operating hours?	Yes	57 (90.5%)	40 (88.9%)	97 (89.8%)	0.788
	No	6 (9.5%)	5 (11.1%)	11 (10.2%)	
In this unit, we work together as an effective team	Strongly Disagree	4 (6.3%)	3 (6.7%)	7 (6.5%)	0.770
	Disagree	8 (12.7%)	3 (6.7%)	11 (10.2%)	
	Neither Agree nor Disagree	3 (4.8%)	4 (8.9%)	7 (6.5%)	
	Agree	41 (65.1%)	31 (68.9%)	72 (66.7%)	
	Strongly Agree	7 (11.1%)	4 (8.9%)	11 (10.2%)	
We have enough staff in this unit to handle the workload	Strongly Disagree	4 (6.3%)	7 (15.6%)	11 (10.2%)	0.393
	Disagree	8 (12.7%)	4 (8.9%)	12 (11.1%)	
	Neither Agree nor Disagree	3 (4.8%)	3 (6.7%)	6 (5.6%)	
	Agree	37 (58,7%)	27 (60.0%)	64 (59.3%)	
	Strongly Agree	11 (17,5%)	4 (8.9%)	15 (13.9%)	
The staff in this unit work longer hours than necessary to care for patients	Strongly Disagree	12 (19.0%)	3 (6.7%)	15 (13.9%)	0.056
	Disagree	9 (14.3%)	6 (13.3%)	15 (13.9%)	
	Neither Agree nor Disagree	14 (22.2%)	8 (17.8%)	22 (20.4%)	
	Agree	24 (38.1%)	28 (62.2%)	52 (48.1%)	
	Strongly Agree	4 (6.3%)	0 (0.0%)	4 (3.7%)	

Continuation of the Table 1.

Questions		Gynecologists N (%)	Nurse N (%)	Total N (%)	P value
1		2	3	4	5
Hospital administration regularly reviews the work processes in the unit to determine if changes are needed to improve patient safety	Strongly Disagree	9 (14.3%)	11 (24.4%)	20 (18.5%)	0.001*
	Disagree	16 (25.4%)	3 (6.7%)	19 (17.6%)	
	Neither Agree nor Disagree	11 (17.5%)	8 (17.8%)	19 (17.6%)	
	Agree	16 (25.4%)	23 (51.1%)	39 (36.1%)	
	Strongly Agree	11(17.5%)	0 (0.0%)	11 (10.2%)	
In this unit, staff feel that medical errors will be dealt with in the form of reprimands or other actions	Strongly Disagree	0 (0.0%)	7 (15.6%)	7 (6.5%)	<0.001
	Disagree	21 (33.3%)	4 (8.9%)	25 (23.1%)	
	Neither Agree nor Disagree	6 (9.5%)	0 (0.0%)	6 (5.6%)	
	Agree	28 (44.4%)	27 (60.0%)	55 (50.9%)	
	Strongly Agree	8 (12.7%)	7 (15.6%)	15 (13.9%)	
In this unit, when an event is reported, it seems to be describing the person (discussing the person who caused the error or event) rather than the issue itself	Strongly Disagree	4 (6.3%)	11 (24.4%)	15 (13.9%)	0.045
	Disagree	16 (25.4%)	8 (17.8%)	24 (22.2%)	
	Neither Agree nor Disagree	14 (22.2%)	4 (8.9%)	18 (16.7%)	
	Agree	25 (39.7%)	19 (42.2%)	44 (40.7%)	
	Strongly Agree	4 (6.3%)	3 (6.7%)	7 (6.5%)	
In stressful times, the staff in this unit help each other	Strongly Disagree	8 (12.7%)	7 (15.6%)	15 (13.9%)	0.052
	Disagree	4 (6.3%)	7 (15.6%)	11 (10.2%)	
	Neither Agree nor Disagree	7 (11.1%)	0 (0.0%)	7 (6.5%)	
	Agree	21 (33.3%)	20 (44.4%)	41 (38.0%)	
	Strongly Agree	23 (36.5%)	11 (24.4%)	34 (31.5%)	
There is a problem with disrespectful behavior from staff in this unit	Strongly Disagree	16 (25.4%)	7 (15.6%)	23 (21.3%)	0.218
	Disagree	28 (44.4%)	26 (57.8%)	54 (50.0%)	
	Neither Agree nor Disagree	6 (9.5%)	3 (6.7%)	9 (8.3%)	
	Agree	9 (14.3%)	9 (20.0%)	18 (16.7%)	
	Strongly Agree	4 (6.3%)	0 (0.0%)	4 (3.7%)	
When staff make mistakes, this unit focuses on learning rather than blaming individuals	Strongly Disagree	8 (12.7%)	11 (24.4%)	19 (17.6%)	<0.001
	Disagree	16 (25.4%)	0 (0.0%)	16 (14.8%)	
	Neither Agree nor Disagree	7 (11.1%)	11 (24.4%)	18 (16.7%)	
	Agree	13 (20.6%)	23 (51.1%)	36 (33.3%)	
	Strongly Agree	19 (30.2%)	0 (0.0%)	19 (17.6%)	
The pace of work in this unit is so fast that it negatively impacts patient safety.	Strongly Disagree	12 (19.0%)	7 (15.6%)	19 (17.6%)	0.027
	Disagree	24 (38.1%)	14 (31.1%)	38 (35.2%)	
	Neither Agree nor Disagree	10 (15.9%)	8 (17.8%)	18 (16.7%)	
	Agree	17 (27.0%)	9 (20.0%)	26 (24.1%)	
	Strongly Agree	0 (0.0%)	7 (15.6%)	7 (6.5%)	
This unit is evaluating changes to improve patient safety to see how well they have worked	Strongly Disagree	13 (20.6%)	7 (15.6%)	20 (18.5%)	0.943
	Disagree	4 (6.3%)	4 (8.9%)	8 (7.4%)	
	Neither Agree nor Disagree	11 (17.5%)	8 (17.8%)	19 (17.6%)	
	Agree	24 (38.1%)	19 (42.2%)	43 (39.8%)	
	Strongly Agree	11 (17.5%)	7 (15.6%)	18 (16.7%)	
This unit lacks support for staff involved in patient safety errors.	Strongly Disagree	20 (31.7%)	7 (15.6%)	27 (25.0%)	0.023
	Disagree	16 (25.4%)	11 (24.4%)	27 (25.0%)	
	Neither Agree nor Disagree	6 (9.5%)	14 (31.1%)	20 (18.5%)	
	Agree	21 (33.3%)	13 (28.9%)	34 (31.5%)	
This unit continues to experience the same patient safety issues	Strongly Disagree	20 (31.7%)	11 (24.4%)	31 (28.7%)	0.779
	Disagree	20 (31.7%)	14 (31.1%)	34 (31.5%)	
	Neither Agree nor Disagree	10 (15.9%)	10 (22.2%)	20 (18.5%)	
	Agree	13 (20.6%)	10 (22.2%)	23 (21.3%)	

The largest number of respondents, especially nurses, noted that the department manager takes staff suggestions for improving patient safety seriously (p = 0.004). However, only a third of respondents agreed that the department manager expects them to work faster under pressure, even if this means reducing the time to complete tasks. This figure was 34.3%, while among doctors it reached 46%, which is twice as high as among nurses 17,8%. In addition, the largest number of nurses 48,9% expressed uncertainty in their answers to this question (p<0,001). In our unit, information about changes based on event reports reaches employees as follows: 39.8% say they are always informed, 18.5% say they are informed most of the time, while 25.0% say they are rarely informed (p = 0.030). As for employee

statements, 37.0% of respondents said they always speak up if they notice something that could negatively impact patient care. However, this figure is higher among physicians at 42.9%, while among nurses it is only 28.9% (p = 0.01). In addition, 42.9% of physicians and 28.9% of nurses always speak up if they see someone with authority doing something unsafe for patients (p = 0.01). When department staff speak up, those with more authority are the ones who mostly express concerns about patient safety, with the figure for doctors being 42.9%, while it is significantly lower among nurses at only 13.3% (p<0,001). As for whether staff are afraid to ask questions when something seems wrong, 20.4% of respondents said this happens most of the time, while 9.3% said it happens sometimes. The feeling of fear is more pronounced among nurses than among other staff (p<0,001), table 2.

Table 2.

Communication in the workplace.

Questions		Gynecologists N (%)	Nurse N (%)	Total N (%)	P value
1		2	3	4	5
The department manager takes seriously staff suggestions for improving patient safety	Strongly Disagree	7(11.1%)	9(20.0%)	16(14.8%)	0.004
	Disagree	12(19.0%)	3(6.7%)	15(13.9%)	
	Neither Agree nor Disagree	8(12.7%)	0 (0.0%)	8(7.4%)	
	Agree	24(38.1%)	29(64.4%)	53(49.1%)	
	Strongly Agree	12(19.0%)	4(8.9%)	16(14.8%)	
The department manager wants us to work faster during busy times. even if that means cutting back on time	Strongly Disagree	11(17.5%)	3(6.7%)	14(13.0%)	<0.001
	Disagree	15(23.8%)	12(26.7%)	27(25.0%)	
	Neither Agree nor Disagree	8(12.7%)	22(48.9%)	30(27.8%)	
	Agree	29(46.0%)	8(17.8%)	37(34.3%)	
The department manager takes action to address patient safety issues that are brought to their attention	Strongly disagree	7(11.1%)	6(13.3%)	13(12.0%)	0.787
	Disagree	4(6.3%)	3(6.7%)	7(6.5%)	
	Neither agree nor disagree	4(6.3%)	4(8.9%)	8(7.4%)	
	Agree	32(50.8%)	24(53.3%)	56(51.9%)	
	Strongly agree	12(19.0%)	4(8.9%)	16(14.8%)	
	Does not apply or don't know	4(6.3%)	4(8.9%)	8(7.4%)	
We are informed of errors that occur in our department	Never	3(4.8%)	7(15.6%)	10(9.3%)	0.134
	Rarely	16(25.4%)	10(22.2%)	26(24.1%)	
	Sometimes	13(20.6%)	12(26.7%)	25(23.1%)	
	Most of the time	4(6.3%)	0 (0.0%)	4(3.7%)	
	Always	27(42.9%)	16(35.6%)	43(39.8%)	
When errors occur in our department. we discuss ways to prevent them from happening again	Never	3(4.8%)	3(6.7%)	6(5.6%)	0.794
	Rarely	17(27.0%)	10(22.2%)	27(25.0%)	
	Sometimes	8(12.7%)	8(17.8%)	16(14.8%)	
	Most of the time	12(19.0%)	11(24.4%)	23(21.3%)	
	Always	23(36.5%)	13(28.9%)	36(33.3%)	
In our department. we are informed of changes that are made based on event reports	Never	7(11.1%)	3(6.7%)	10(9.3%)	0.030
	Rarely	17(27.0%)	10(22.2%)	27(25.0%)	
	Sometimes	4(6.3%)	0 (0.0%)	4(3.7%)	
	Most of the time	8(12.7%)	12(26.7%)	20(18.5%)	
	Always	27(42.9%)	16(35.6%)	43(39.8%)	
	Does not apply or don't know	0 (0.0%)	4(8.9%)	4(3.7%)	
In our department. staff speak up when they see something that could negatively impact patient care	Never	3(4.8%)	3(6.7%)	6(5.6%)	0.012
	Rarely	17(27.0%)	7(15.6%)	24(22.2%)	
	Sometimes	4(6.3%)	3(6.7%)	7(6.5%)	
	Most of the time	12(19.0%)	11(24.4%)	23(21.3%)	
	Always	27(42.9%)	13(28.9%)	40(37.0%)	
	Does not apply or don't know	0 (0.0%)	8(17.8%)	8(7.4%)	
When staff in our department see someone with a lot of authority doing something that is unsafe for patients. they speak up	Never	11(17.5%)	7(15.6%)	18(16.7%)	0.019
	Rarely	9(14.3%)	3(6.7%)	12(11.1%)	
	Sometimes	4(6.3%)	10(22.2%)	14(13.0%)	
	Most of the time	12(19.0%)	8(17.8%)	20(18.5%)	
	Always	27(42.9%)	13(28.9%)	40(37.0%)	
	Does not apply or don't know	0 (0.0%)	4(8.9%)	4(3.7%)	

Continuation of the Table 2.

Questions		Gynecologists N (%)	Nurse N (%)	Total N (%)	P value
1		2	3	4	5
When department staff speak up. those with more authority openly voice concerns about the safety of their patients.	Never	7(11.1%)	3(6.7%)	10(9.3%)	<0.001
	Rarely	13(20.6%)	7(15.6%)	20(18.5%)	
	Sometimes	12(19.0%)	9(20.0%)	21(19.4%)	
	Most of the time	4(6.3%)	12(26.7%)	16(14.8%)	
	Always	27(42.9%)	6(13.3%)	33(30.6%)	
	Does not apply or don't know	0 (0.0%)	8(17.8%)	8(7.4%)	
In our department. staff are afraid to ask questions when something doesn't seem right	Never	26(41.3%)	7(15.6%)	33(30.6%)	0.001
	Rarely	13(20.6%)	18(40.0%)	31(28.7%)	
	Sometimes	4(6.3%)	6(13.3%)	10(9.3%)	
	Most of the time	12(19.0%)	10(22.2%)	22(20.4%)	
	Always	8(12.7%)	0 (0.0%)	8(7.4%)	
	Does not apply or don't know	0 (0.0%)	4(8.9%)	4(3.7%)	

Discussion

In our analysis, respondents indicated that hospital management regularly reviews work processes, a finding that aligns with the study by *Deepak Bhati et al.,* which highlighted the crucial role of data-driven measurement, analysis, and benchmarking in evaluating hospital performance [2].

We found that more than half of the respondents, particularly nurses, believe that medical errors will lead to reprimands or other consequences. Similarly, other research has identified negative perceptions of medication errors among Jordanian nurses or in Uganda it was found that the most medical staff believed that the law does not protect the reporting of medical errors [3,14]. However, in Iranian study highlighted four key barriers to error reporting among nurses [16]. These barriers include concerns about maintaining professional reputation and avoiding stigma, fear of repercussions such as legal issues and organizational challenges, feelings of insecurity due to being blamed, and a lack of administrative support and failure to investigate the root causes of errors. *Désirée Klemann and co-authors* identified several risk factors for medical errors in gynecology departments, including delays in care, poor coordination and management of care, and shortages of supplies, staff, and knowledge [11]. These factors were observed both at the individual healthcare worker level (e.g., non-compliance with protocols, delays in decision-making) and at the system level (e.g., lack of protocols, insufficient staff and equipment). To prevent such errors in the future, healthcare managers must conduct a more thorough examination of these issues. Medical errors are a significant public health issue, with varying estimates of incidence and cost, ranging from 200,000 to 400,000 preventable harms annually in the U.S. While the definition of medical errors varies, they are associated with high morbidity, mortality, and economic burden, impacting patients, healthcare workers, and facilities. Efforts to improve patient safety include identifying error types, promoting error reporting, and creating a culture of safety, where corrective measures and prevention strategies can be implemented across healthcare settings [18]. A positive trend is that more than half of respondents noted the availability of training and management support, especially when medical errors occur. This may be due to the introduction of an accreditation system, which includes aspects of ongoing employee training and strengthening of work on patient safety issues [1,3,15]. *Thomas E. MacGillivray* highlighted that the U.S. healthcare system is transitioning from a fee-for-service model to value-based care to enhance quality and reduce costs. While transparency can promote quality improvement, it may also lead to unintended consequences, such as risk aversion, which could negatively impact individual patient care and overall population health outcomes [13]. Daily practice shows that the department manager expects them to work faster under pressure, even if this means reducing the time it takes to complete tasks, which can also affect the quality of work and lead to errors. *Berihun Alemayehu Addis and co-authors* found that the prevalence of time management practices among healthcare professionals was 66.1%. A qualitative study revealed that factors such as increased age, satisfaction with compensation and benefits, adequate staffing levels, task planning, being efficient with time, and a high level of work responsibility were significant contributors to effective time management practices [3]. Another study also highlighted that one of the primary stressors experienced by nurses is the perception of time constraints. Given the potential adverse effects of perceived time pressure on nurses, it seems reasonable that nurse managers' ability to guide nurses in reducing this pressure, thereby facilitating more informed decisions, could enhance nurses' well-being and performance. Similar research in nursing suggests that, to improve patients' perceptions of the care they receive, nurse managers should implement strategies to alleviate nurses' perceived time pressure [6,7,19]. Healthcare organizations could enhance time management by offering training on planning, providing orientation for newly hired staff, promoting efficiency, encouraging responsibility at work, and designing attractive compensation and benefits packages [3]. *Also Marja Silén-Lipponen et al. [*21] identified that factors such as fear of errors, team turnover, and emotional strain contribute to mistakes, while familiarity, safety controls, and error documentation help prevent medical errors and fear of the medical specialist. At the organizational level, error prevention requires proper scheduling, management, competency, and a conducive environment.

Limitations of this study include limited sample size and geographic scope, as it was conducted in a specific region and within a select group of hospitals in Almaty, which may impact the generalizability of the findings to other regions or health systems. Additionally, the use of a self-administered online questionnaire may introduce response biases such as social desirability bias or under-reporting of negative perceptions, particularly regarding sensitive topics such as errors and reprimands. The cross-sectional study design provides only a snapshot of the data at one point in time, limiting the ability to establish causal relationships between management practices, error reporting, and patient safety outcomes. Additionally, reliance on self-reported perceptions by healthcare workers may not accurately reflect actual practice or documented errors, and the inclusion of objective data such as incident reports, performance reviews, or patient outcomes would have strengthened the findings.

Future research should focus on longitudinal studies to examine how changes in organizational practices, error reporting, and safety culture impact patient outcomes and health care worker well-being over time. To increase the generalizability of findings, studies could be expanded to include a larger, more diverse sample that includes hospitals from different regions, countries, and health care settings. Additionally, future research should examine how institutional policies, such as accreditation systems and safety protocols, impact health care worker behavior, error reporting, and overall safety culture in health care settings.

Conclusion

Both groups reported high levels of professional experience and expressed general satisfaction with their work, though nurses exhibited more uncertainty in some areas. A significant number of respondents, particularly nurses, feel that medical errors result in reprimands, indicating a potential issue with the department's approach to error management. While many agreed that the focus should be on learning from mistakes, nurses were more likely to remain undecided on this matter. There were notable gaps in communication, with many staff reporting being infrequently informed about changes based on event reports. Overall, the findings suggest a need for improved communication, support for nurses, and a stronger culture of safety that encourages staff to speak up without fear.

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ИММУНОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ ПРИ ЛЕЧЕНИИ АНТИФОСФОЛИПИДНОГО СИНДРОМА У БЕРЕМЕННЫХ

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Резюме

Актуальность: Одним из ведущих факторов, снижающих уровень репродуктивного здоровья, является антифосфолипидный синдром.

Цель: Определение иммунологических изменений при лечении АФС у беременных.

Материалы и методы: Исследование проводилось среди беременных с АФС, которые подразделены на 2 группы. Группы были репрезентативны по возрасту, паритету, акушерской и соматической патологии, но отличались по методам лечения. В I группу сравнения (традиционного ведения) вошли 28 беременных с АФС. В данной группе все беременные получали традиционную терапию АФС, включающую антикоагулянты, антиагреганты, глюкокортикоиды. Во II - основную группу вошли 48 беременных с АФС. В данной группе всем беременным на фоне традиционной терапии дополнительно в комплексе применялись системная энзимотерапия и плазмоферез.

Результаты: Достоверные различия также были зафиксированы между контрольной и основной группой по уровню циркулирующих иммунных комплексов через 10 и 30 дней после начала лечения, которые составили 23,6% и 29,7% соответственно ($p<0,05$; $p<0,01$). В основной группе уже через 10 суток была отмечена положительная динамика, уменьшение абсолютного и относительного числа беременных с диагностическим титром обоих маркеров ВА и аКЛ (на 41,7%). Относительные показатели выявления диагностического титра ВА и аКЛ через 30 суток имели тенденцию к уменьшению по сравнению с контролем, различия с группой традиционного ведения оставались достоверными ($p<0,05$). По результатам исследования содержание иммуноглобулинов у беременных контрольной группы и основной группы не имело достоверных различий.

Заключение: Таким образом, комплексная терапия антифосфолипидного синдрома достоверно эффективна, быстрее приводит к нормализации показателей иммунной системы у беременных с АФС.

Ключевые слова: *антифосфолипидный синдром, беременность, системная энзимотерапия, плазмоферез.*

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Abstract

IMMUNOLOGICAL CHANGES IN THE TREATMENT OF ANTIPHOSPHOLIPID SYNDROME IN PREGNANT WOMEN

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Relevance: One of the leading factors that reduce the level of reproductive health is antiphospholipid syndrome.

Aim: Determination of immunological changes during the treatment of APS in pregnant women.

Materials and methods: The study was conducted among pregnant women with APS, which were divided into 2 groups. The groups were representative in terms of age, parity, obstetric and somatic pathology, but differed in treatment methods. The first comparison group (traditional management) included 28 pregnant women with APS. In this group, all pregnant women received traditional therapy for APS, including anticoagulants, antiplatelet agents, and glucocorticoids. The second - main group included 48 pregnant women with APS. In this group, all pregnant women, along with traditional therapy, additionally received systemic enzyme therapy and plasmapheresis.

Results: Significant differences were also recorded between the control and main groups in the level of circulating immune complexes 10 and 30 days after the start of treatment, which amounted to 23.6% and 29.7%, respectively ($p<0.05$; $p<0.01$). In the main group, positive dynamics were noted after 10 days, a decrease in the absolute and relative number of pregnant women with a diagnostic titer of both markers of VA and aCL (by 41.7%). Relative indicators of detection of the diagnostic titer of VA and aCL after 30 days tended to decrease compared to the control, the differences with the traditional management group remained reliable ($p<0.05$). According to the results of the study, the content of immunoglobulins in pregnant women in the control group and the main group did not have significant differences.

Conclusion: Thus, complex therapy of antiphospholipid syndrome is reliably effective and leads to faster normalization of immune system parameters in pregnant women with APS.

Keywords: *antiphospholipid syndrome, pregnancy, systemic enzyme therapy, plasmapheresis.*

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Түйіндеме

ЖҮКТІ ӘЙЕЛДЕРДЕГІ АНТИФОСФОЛИПИДТІ СИНДРОМДЫ ЕМДЕУДЕГІ ИММУНОЛОГИЯЛЫҚ ӨЗГЕРІСТЕР

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Өзектілігі: Репродуктивті денсаулық деңгейін төмендететін жетекші факторлардың бірі - антифосфолипидті синдром.

Зерттеудің мақсаты: Жүкті әйелдерде АФС емдеу кезіндегі иммунологиялық өзгерістерді анықтау.

Материалдар мен әдістері: Зерттеу АФС бар жүкті әйелдер арасында жүргізілді, олар 2 топқа бөлінді. Топтар жас, паритет, акушерлік және соматикалық патология бойынша репрезентативті болды, бірақ емдеу әдістері бойынша ерекшеленді. І салыстырмалы тобына (дәстүрлі емдеу) АФС бар 28 жүкті әйел кірді. Бұл топта барлық жүкті әйелдер дәстүрлі емдеу: антикоагулянттар, антиагрегантттар және глюкокортикоидтарды қоса кабылдады, Екінші негізгі топқа АФС бар 48 жүкті әйел кірді. Бұл топтағы барлық жүкті әйелдер дәстүрлі терапия фонында жүйелі ферменттік терапия және плазмаферезбен қосымша емделді.

Нәтижелері: Айналымдағы иммундық кешендердің деңгейлері бойынша емдеу басталғаннан кейін 10 және 30 күннен кейін салыстыру тобы мен негізгі топ арасында да айтарлықтай айырмашылықтар тіркелді, олар сәйкесінше 23,6% және 29,7% құрады ($p<0,05$; $p<0,01$). Кешенді емдеудің негізгі тобында 10 күннен кейін екі маркердің диагностикалық титрі бар жүкті әйелдердің абсолютті және салыстырмалы санының айтарлықтай төмендеуінен тұратын оң динамика анықталды (екі жағдайда да 41,7%). Негізгі топ және дәстүрлі емдеу тобынан айырмашылығы байқалды, 30 күннен кейін ҚЖА және аКЛ диагностикалық титрінің анықтау көрсеткіштері негізгі топта төмендеді, айырмашылықтар дәлелді ($p<0,05$). Зерттеу нәтижелері бойынша бақылау тобындағы және негізгі топтағы жүкті әйелдерде иммуноглобулиндердің құрамында айтарлықтай айырмашылықтар болған жоқ.

Қорытынды: Осылайша, антифосфолипидті синдромға арналған кешенді терапия сенімді түрде тиімді және АФС бар жүкті әйелдерде иммундық жүйенің параметрлерін тез қалыпқа келтіреді.

Түйінді сөздер: *антифосфолипидті синдром, жүктілік, жүйелі ферменттік терапия, плазмаферез.*

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Введение

Антифосфолипидный синдром (АФС) при беременности является очень сложной и актуальной проблемой. Характерные для синдрома венозные и артериальные тромбозы, обусловленные циркуляцией антифосфолипидных антител в крови, приводят к различным осложнениям и негативным последствиям беременности, которые требуют улучшения терапии[3]. Репродуктивное здоровье является результатом множества различных аспектов, характеризующих состояние женского организма в связи с беременностью и родами. При этом принципиальную роль играет отсутствие у женщины системных и других хронических заболеваний и патологических состояний[2-4]. К сожалению, у женщин репродуктивного возраста нередко возникают состояния, снижающие репродуктивное здоровье, ухудшающие течение беременности, условия и исходы родов. Результаты ряда исследований показывают, что антифосфолипидный синдром является одним из ведущих факторов снижения уровня репродуктивного здоровья[5-8].

Патогенетические механизмы, связанные с антифосфолипидным синдромом, различны, они осуществляются путем нарушения маточно-плацентарного кровообращения у плода и нарушения системного кровообращения у матери [1,9-11].

Цель исследования: Определение динамики иммунологических изменений при лечении антифосфолипидного синдрома у беременных.

Материалы и методы:

Данное клиническое исследование является наблюдательным, некомбинированным. Тип исследования – когортное, проспективное. Данное исследование проводилось в периоде 2021-2023г.г., в г.Семей. Всего участвовали -76 человек с АФС и 30 человек контрольной группы. Всех женщин с АФС разделили на 2 группы: группа сравнения и основная группа. Для обследования брали анализы крови до начала лечения, через 10 и 30 суток от начала лечения. Лабораторные исследования проводились на базе Перинатального центра г.Семей, лаборатории Олимп.

При проведении лечения у беременных с АФС проводились иммунологические исследования с целью определения воздействия применяемого нами способа лечения на параметры иммунной системы[4,12-15].

Критерии включения: беременные с одноплодной беременностью и наличие антифосфолипидного синдрома.

Критерии исключения: беременные с многоплодной беременностью, без наличия антифосфолипидного синдрома.

Для достижения цели исследования беременные с АФС подразделены на 2 группы. Группы были репрезентативны по возрасту, паритету, акушерской и соматической патологии, но различались по методам лечения.

В I группу сравнения (группа традиционного лечения) вошли 28 беременных с АФС. В этой группе все беременные получали традиционную терапию, включающую антикоагулянты, антиагреганты и глюкокортикоиды [16-21].

Во II - основную группу включены 48 беременных с антифосфолипидным синдромом, которым проводилось комплексное лечение (системная энзимотерапия и плазмаферез на фоне традиционной терапии).

Контрольная группа, n=30, куда вошли беременные без осложнений и АФС.

Исследованы циркулирующие иммунные комплексы у беременных.

На участие в исследовании у всех пациенток имелось информированное согласие. Руководство учреждения, где проводилось исследование, было ознакомлено с ходом проведения исследования. Публикация результатов исследования в открытой печати согласована с руководством учреждения, возражений нет.

При проведении статистического анализа данных, представленных в работе, полученные результаты исследования вносились в базы данных, подготовленные в программе Microsoft Excel XP. Система обработки данных включала автоматизированную проверку качества подготовки информации, обработку результатов данных по задаваемым критериям.

При анализе использованы параметрические и непараметрические методы. Непрерывные величины представлены в виде средних арифметических значений и ошибки среднего (M±m). Сравнение количественных признаков проводилось с помощью критерия Стьюдента, для непрерывных переменных – парного критерия Стьюдента.

При наличии частотных таблиц определялись относительные величины частоты наблюдений исследуемого признака и оценка их точности и надежности. Проверка гипотез о значимости относительных частот в нескольких независимых выборках (группах) с использованием непараметрического критерия Пирсона χ^2 (хи-квадрат).

$$\chi^2 = \sum(n_{1i} - n_{2i})^2/n_{2i}$$

где n_{1i}- наблюдаемое число случаев признака в i-ячейке частотной таблицы.

n_{2i}– теоретическое (рассчитанное как среднеожидаемое) число случаев признака в i - ячейке частотной таблицы.

Оценка связи качественных признаков по величине инерции и оценка значимости этой связи по критерию χ^2. Качество решения оценивалось по специфическим критериям.

В качестве достоверной разницы статистической значимости принимали $p<0,05$.

Результаты исследования:

В обеих клинических группах женщин с АФС уровень циркулирующих иммунных комплексов был достоверно выше, чем в контрольной группе во все сроки обследования. При этом, в группе традиционной терапии наблюдалась тенденция к увеличению среднего значения этого показателя (от превышения 68,4% до начала лечения, до 83,6% через 10 дней и до 87,3% через 30 дней, $p<0,01$ во все указанные периоды). В ходе комплексного лечения в основной группе наблюдалось снижение уровня циркулирующих иммунных комплексов (с 74,5% до 40,3% - через 10

суток, p<0,01 и 31,7% - через 30 суток p<0,05). Между 1-й и 2-й группами в последние два периода также зафиксированы достоверные различия, которые составили 23,6% и 29,7% соответственно (p<0,05; p<0,01).

Достоверные различия между исследуемыми группами женщин зафиксированы также по уровню некоторых интерлейкинов.

При анализе содержания в крови ФНОα выявлено очень резкое превышение данного показателя над уровнем контрольной группы в начале исследования, оно было 4-кратным в обеих подгруппах. В группе сравнения было зарегистрировано только умеренное и недостоверное снижение данного показателя через 10 суток и тенденция к росту – через 30 суток. В основной группе степень превышения к 30 суткам была уменьшена до 2-кратного, различия как с исходным уровнем содержания интерлейкина, так и с группой сравнения были достоверными (на 49,6% и 46,5% соответственно, p<0,05 в обоих случаях).

По IL-2 в группе традиционной терапии отмечалось достоверное превышение показателя во все сроки обследования, причем до начала лечения различия между средними значениями равнялись 40,1% (p<0,05), через 10 суток – 52,1% (p<0,05), а дальнейшее нарастание показателя дало через 30 суток различия, достигающие 94,2% (p<0,01). Во 2-й группе, наоборот, при использовании комплексной терапии наблюдалась тенденция к снижению этого показателя, если достоверные различия с контрольной группой наблюдались в первые два периода обследования (39,5% и 37,5% соответственно), то в третьем периоде выявлены только различия с группой традиционной терапии (39,0%, p<0,05).

Средний уровень IL-4 был неоправданно высоким в первый и второй периоды исследования. В группе традиционной терапии достоверное увеличение наблюдалось через 30 дней после первичного обследования (на 21,4%, p<0,05). В основной группе, напротив, достоверные различия с контрольной группой выявлены только в начальном периоде (25,0%, p<0,05), в последующем наблюдалось снижение содержания данного цитокина, в результате которого оно при втором и третьем обследовании не имело достоверных различий с контролем.

По показателю в крови IL-6 не выявлено достоверных различий с контрольной группой во всех трех обследованиях.

По уровню IL-10 у беременных с АФС наблюдались тенденции к снижению, причем в группе традиционной терапии она достигала степени достоверности через 30 суток после исходного исследования (на 14,9%, p<0,05), а в основной группе – имела достоверные различия в исходном периоде (на 20,0%, p<0,05), которые впоследствии нивелировались.

Полученные данные представлены в таблице 1.Заметно, что содержание иммуноглобулинов исследованных классов у беременных контрольной группы и основной группы не имело достоверных различий.

Кроме этого осуществлен анализ влияния проведенной терапии на содержание в крови маркеров АФС - волчаночного антикоагулянта и аКЛ. Полученные данные представлены в таблице 2.

Таблица 1

Динамика иммунологических изменений при лечении антифосфолипидного синдрома у беременных.

Показатели	Контрольная группа, n=30	Группа сравнения (традиционной терапии), n=28			Основная группа (применения препарата СЭТ и ПА в комплексе с традиционной терапией), n=48		
		До начала лечения	10 суток	30 суток	До начала лечения	10 суток	30 суток
IgG, г/л	11,83±0,45	10,61±0,70	10,93±0,66	11,06±0,70	10,12±0,83	11,25±0,88	11,40±0,65
IgM, г/л	1,30±0,10	1,27±0,09	1,31±0,10	1,44±0,09	1,25±0,08	1,32±0,07	1,35±0,07
ЦИК, ЕОП	7,50±0,39	12,63±0,82**	13,77±0,55**	14,05±0,71**	13,09±0,59**	10,52±0,60*#	9,88±0,46*##
ФНОα, пг/мл	6,75±0,45	28,13±2,60**	24,07±2,51**	25,40±2,66**	26,94±2,43**	18,16±2,03**	13,52±1,67*#
IL-2, пг/мл	8,15±0,59	11,42±0,73*	12,40±0,81*	15,83±0,77**	11,37±0,64*	11,21±0,67*	9,65±0,53##
IL-4, пг/мл	6,40±0,40	7,59±0,61	7,45±0,54	7,77±0,48*	8,00±0,35*	7,31±0,40	7,02±0,29
IL-6, пг/мл	5,73±0,39	5,90±0,42	6,12±0,39	6,04±0,29	6,12±0,31	5,84±0,35	6,10±0,25
IL-10, пг/мл	9,44±0,57	8,11±0,49	8,52±0,36	8,03±0,40*	7,55±0,37*	8,42±0,51	8,93±0,42

Примечание: * - различия с исходным показателем достоверны, p<0,05, ** - p<0,01
- различия с группой традиционной терапии достоверны, p<0,05, ## - p<0,01

Таблица 2.

Изменения содержания в крови маркеров ВА и аКЛпри лечении АФС.

Показатели	Группа сравнения (традиционной терапии), n=28						Основная группа (применения препарата СЭТ и ПА в комплексе с традиционной терапией), n=48					
	До начала лечения		10 суток		30 суток		До начала лечения		10 суток		30 суток	
	абс.	%	абс.	%	абс.	%	абс.	%	абс.	%	абс.	%
ВА	26	92,9 ±4,9	21	75,0 ±8,2	24	85,7 ±6,6	45	93,8 ±3,5	25	52,1 ±7,2*	24	50,0 ±7,2*
аКЛ	25	89,3 ±5,8	25	89,3 ±5,8	26	92,9 ±4,9	47	97,9 ±2,1	27	56,3 ±7,2*	25	52,1 ±7,2*

*Примечание:** - различия между группами достоверны, p<0,05

В группе традиционного ведения после 10 суток лечения наблюдалось снижение числа случаев выявления диагностического титра ВА на 17,9% (p>0,05), частота выявления аКЛ не изменилась. Через 30 суток отмечалась тенденция к повышению частоты выявления ВА и аКЛ по отношению к показателям через 10 суток.

Напротив, в группе применения комплексной терапии уже через 10 суток была определена положительная динамика, заключающаяся в достоверном уменьшении абсолютного и относительного числа беременных с диагностическим титром обоих маркеров (на 41,7% в обоих случаях). Относительные показатели выявления диагностического титра ВА и аКЛ через 30 суток имели тенденцию к уменьшению, различия с группой традиционного ведения оставались достоверными (p<0,05).

Обсуждение результатов:

После анализа результатов, полученных при исследовании IgG, IgM, установлено, что достоверных различий в уровнях иммуноглобулинов изучаемых классов у беременных контрольной группы и основной группы не выявлено.

Достоверные различия также были зафиксированы между контрольной и основной группой по уровню циркулирующих иммунных комплексов через 10 и 30 дней после начала лечения, которые составили 23,6% и 29,7% соответственно (p<0,05; p<0,01).

В начале исследования TNFα в крови показал очень резкое увеличение этого показателя от уровня контрольной группы. В группе сравнения зафиксировано лишь умеренное и недоказанное снижение этого показателя через 10 суток и незначительное увеличение через 30 дней. Напротив, в основной группе степень превышения к 30-му дню снизилась в 2 раза, причем различия как с контрольной группой, так и с группой сравнения были очевидными (49,6% и 46,5% соответственно, p<0,05 в обоих случаях).

По ИЛ-2 в основной группе зарегистрирована тенденция к снижению данного показателя, причем при наличии достоверных различий с контрольной группой в первые два периода исследования (39,5% и 37,5% соответственно), а в третьем периоде различия выявлены только с группой сравнения (39,0%, p<0,05).

По показателю ИЛ-4 достоверные различия в основной группе с контрольной выявлены только в начальный период (25,0%, p<0,05), затем наблюдалось снижение, достоверных различий с контрольной группой не было во время второго и третьего периодах обследования, так и группой сравнения..

Уровни IL-6 в сыворотке существенно не отличались от контрольной группы и группы сравнения во всех трех периодах исследованиях, в начале, через 10 и через 30 суток лечения.

У беременных с АФС уровень IL-10 имел тенденцию к снижению, а в группе традиционной терапии он достиг значимости через 30 дней после первоначального исследования. Между группами сравнения и основной группой статистически значимых различий не выявлено по данному параметру.

Кроме того, согласно табл. 1, зафиксированы достоверные различия между группой традиционного лечения и основной группой по параметрам ВА и АКЛ. По наличию диагностического титра ВА и аКЛ через 30 суток имелись тенденции к уменьшению относительно группы сравнения, различия оставались статистически значимыми (p<0,05).

Имеются данные, что в группе пациенток, получавших комплексную терапию в виде профилактических доз НМГ, низких доз ацетилсалициловой кислоты и курсов в/в иммуноглобулина, риски развития плацента-ассоциированных осложнений и железодефицитных состояний оказались ниже относительно других групп, что свидетельствует о более высокой эффективности этой схемы терапии [1]. Однако развитие внутрипеченочного холестаза при беременности реже встречалось в группе пациенток, получавших курсы мембранного ПФ, в отличие от применения курсов ВВИГ, что может быть объяснено дополнительным эффектом эфферентных методов терапии и может быть учтено при дифференцированном подходе к ведению пациенток с наличием патологии печени и желчного пузыря [1]

В нашем исследовании были использованы методы лечения СЭТ и плазмаферез на фоне применения НМГ, результаты иммунологических показателей таких, Как ЦИК, TNFα, ИЛ-2 показали статистически значимые различия с группой сравнения. А также по маркерам АФС имеется статистически значимые различия с группой сравнения, следовательно данная комплексная терапия (СЭТ, ПА, НМГ) является эффективной.

Заключение

Предполагая потенцирование эффектов системной энзимотерапии (СЭТ), плазмафереза (ПА) и низкомолекулярных гепаринов (НМГ) разработана комплексная терапия АФС с одновременным в комплексе применением вышеназванных методов лечения[2,3,4,5].Таким образом, комплексная терапия антифосфолипидного синдрома, включающая применение СЭТ и плазмафереза на фоне традиционного лечения достоверно эффективна, быстрее приводит к нормализации показатели иммунной системы у беременных с АФС.

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SUICIDE ACROSS DIFFERENT AGE GROUPS

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Abstract

Introduction: Suicide remains one of the leading causes of death worldwide and has a significant impact on public health. In Kazakhstan, as in other countries, suicide rates vary depending on age group, gender, and socio-economic factors. The analysis of data on mortality from self-harm in the age groups 15-19, 20-24, 25-29, 30-34, 35-39 years and 40 years and older reveals the main trends and risk factors.

Aim: To analyze suicide mortality in Kazakhstan in various age groups, to identify gender differences and time trends.

Materials and methods: The study uses data from the Global Burden of Disease, GBD 2021, provided by the Institute for Health Indicators and Assessment (IHME). The data covers the period 2017-2021 and includes information on mortality by age group and gender. The analysis was carried out using a comparative statistical method, including an assessment of absolute mortality rates, the percentage of mortality and the dynamics of changes over the years.

Results: The analysis showed that the highest mortality rate from suicide is observed in the age groups of 25-29 and 30-34 years, while in younger and older age categories the indicators are lower. Men show significantly higher mortality rates than women, which is consistent with global data. Time trends show fluctuations in mortality associated with socio-economic changes and crises.

Conclusions: The highest suicide mortality rate was recorded among the age groups of 25-29 and 30-34 years. Men in Kazakhstan are significantly more likely to commit suicide than women. Time trends show fluctuations in the death rate, which requires further monitoring. Comprehensive measures are needed to reduce suicide rates, including the availability of psychological care and early intervention programs. The continuation of the study is necessary to analyze trends for 2022-2024.

Keywords: *suicide, mortality, Kazakhstan, age groups, mental health.*

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Резюме

СУИЦИД В РАЗЛИЧНЫХ ВОЗРАСТНЫХ ГРУППАХ

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Введение: Суицид остается одной из ведущих причин смертности во всем мире и оказывает значительное влияние на общественное здоровье. В Казахстане, как и в других странах, уровень самоубийств варьируется в зависимости от возрастной группы, пола и социально-экономических факторов. Анализ данных о смертности от

суицидов в возрастных группах 15–19, 20–24, 25–29, 30–34, 35–39 лет и 40 лет и старше позволяет выявить основные тенденции и факторы риска.

Цель: Анализ смертности от суицидов в Казахстане в различных возрастных группах, определение половых различий и временных тенденций.

Материалы и методы: В исследовании использованы данные Global Burden of Disease, GBD 2021, предоставленные Institute for Health Indicators and Assessment (IHME). Данные охватывают период 2017–2021 годов и включают информацию о смертности по возрастным группам и полу. Анализ проводился с использованием сравнительного статистического метода, включающего оценку абсолютных показателей смертности, процентного уровня летальности и динамики изменений по годам.

Результаты: Анализ показал, что наибольший уровень смертности от суицидов наблюдается в возрастных группах 25–29 и 30–34 года, тогда как в более молодых и старших возрастных категориях показатели ниже. Мужчины демонстрируют значительно более высокие уровни смертности по сравнению с женщинами, что согласуется с мировыми данными. Временные тренды показывают колебания смертности, связанные с социально-экономическими изменениями и кризисами.

Выводы: самый высокий уровень смертности от суицидов зафиксирован среди возрастных групп 25–29 и 30–34 года. Мужчины в Казахстане значительно чаще совершают суицид, чем женщины. Временные тренды показывают колебания уровня смертности, что требует дальнейшего мониторинга. Для снижения уровня суицидов необходимы комплексные меры, включая доступность психологической помощи и программы раннего вмешательства. Необходимо продолжение исследования для анализа тенденций за 2022–2024 годы.

Ключевые слова: *суицид, смертность, Казахстан, возрастные группы, психическое здоровье.*

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Түйіндеме

ӘРТҮРЛІ ЖАС ТОПТАРЫНДАҒЫ СУИЦИД

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Кіріспе: Суицид – бүкіл әлемде өлімнің жетекші себептерінің бірі болып қала береді және қоғамдық денсаулыққа айтарлықтай әсерін тигізеді. Қазақстанда, басқа елдердегі сияқты, суицид деңгейі жас топтарына, жынысына және әлеуметтік-экономикалық факторларға байланысты өзгеріп отырады. 15–19, 20–24, 25–29, 30–34, 35–39 жас және 40 жастан асқан жас топтарындағы суицид көрсеткіштерін талдау арқылы негізгі үрдістер мен қауіп факторларын анықтауға мүмкіндік ашылады.

Мақсаты: Қазақстандағы әртүрлі жас топтарында суицидтен болған өлімді талдау, жыныстық айырмашылықтар мен уақыттық тенденцияларды анықтау.

Материалдар мен әдістер: Зерттеуде Global Burden of Disease, GBD 2021 деректері қолданылды, оларды Institute for Health Indicators and Assessment (IHME) ұсынған. Деректер 2017–2021 жылдар аралығын қамтиды және өлім көрсеткіштері жас топтары мен жынысы бойынша бөлінген. Талдау салыстырмалы статистикалық әдістерді қолдану арқылы жүргізілді, оған өлімнің абсолюттік көрсеткіштерін бағалау, өлім деңгейінің пайыздық мөлшерін анықтау және жылдар бойынша динамикалық өзгерістерді талдау кірді.

Нәтижелер: Талдау нәтижелері көрсеткендей, ең жоғары суицид деңгейі 25–29 жас және 30–34 жас аралығындағы топтарда байқалады, ал жасөспірімдер мен егде жастағы топтарда көрсеткіштер төмен. Ер адамдар әйелдерге қарағанда айтарлықтай жоғары суицид деңгейін көрсетеді, бұл жаһандық деректермен сәйкес келеді. Уақыттық трендтер әлеуметтік-экономикалық өзгерістер мен дағдарыстарға байланысты өлімнің ауытқуын көрсетеді.

Қорытындылар: Суицидтен болған ең жоғары өлім 25–29 және 30–34 жас топтарында тіркелді. Қазақстанда ер адамдардың суицид деңгейі әйелдерге қарағанда айтарлықтай жоғары. Уақыттық трендтер өлім деңгейінің

ауытқуын көрсетеді, бұл тұрақты мониторингті қажет етеді. Суицид деңгейін төмендету үшін кешенді шаралар, соның ішінде психологиялық көмекке қолжетімділікті арттыру және ерте араласу бағдарламалары қажет. 2022–2024 жылдардағы тенденцияларды талдау үшін зерттеуді жалғастыру қажет.

Түйінді сөздер: *суицид, өлім, Қазақстан, жас топтары, психикалық денсаулық.*

Дәйексөз үшін:

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Introduction

Suicide remains one of the leading causes of mortality worldwide, exerting a significant impact on public health. According to the World Health Organization (WHO), more than 700,000 people die by suicide annually, surpassing the number of deaths caused by wars and violence [7]. In recent decades, attention to this issue has increased, as suicide rates remain consistently high in many countries despite preventive measures and mental health support programs [8]. Age groups demonstrate considerable variability in suicide mortality rates. According to WHO research, the most vulnerable age categories include young people aged 15–19, 20–24, 25–29, 30–34, 35–39, and 40 years and older [7]. Each of these groups is affected by specific risk factors influencing suicide mortality [5, 1]. Among those aged 15–19, the primary causes of suicidal behavior include mental disorders, peer pressure, cyberbullying, and family conflicts [7, 20]. Young adults aged 20–24 face challenges related to job searching, unstable relationships, and the transition to independent living [9, 14]. In the 25–29 age group, economic factors, debt obligations, and workplace-related issues become more prominent [10, 22]. For individuals aged 30–34, suicide rates remain high due to a combination of professional burdens, family responsibilities, and chronic stressors [11, 24]. Those in the 35–39 age group experience additional challenges such as health issues, emotional burnout, and career dissatisfaction [12, 16]. Individuals aged 40 and older often encounter midlife crises, depression, family problems, and a perceived loss of life prospects [19, 25]. Suicide rates among the elderly also remain high, particularly among men over 70 years old [18, 21]. Research indicates that elderly individuals who are single, suffer from physical illnesses, chronic pain, social isolation, and the loss of loved ones are at a significantly higher risk of suicide [18, 26]. Limited access to medical and psychological care, as well as the stigma surrounding mental illness, also play a crucial role. Differences in suicide rates are influenced by a complex interplay of factors, including socioeconomic conditions, mental health status, healthcare accessibility, and cultural characteristics [3, 27]. In high-income countries, suicide mortality rates tend to be higher among men, whereas in low- and middle-income countries, women are at greater risk of attempting suicide [7, 28]. Gender differences in suicidal behavior can also be attributed to the methods used in suicide attempts and societal expectations imposed on men and women across different cultures [2, 6].

In European countries, suicide mortality among adolescents aged 15–19 varies but remains a significant concern. For example, in Lithuania, Hungary, and Russia, suicide rates among young people exceed the regional average [28]. The primary contributing factors include mental health disorders, family conflicts, and peer pressure. Young adults aged 20–24 are also at high risk. In Eastern European countries such as Poland and the Czech Republic, suicide rates in this age group are higher than in Western Europe [30]. The most significant risk factors include unemployment, social adaptation difficulties, and depression. The 25–29 age group faces additional challenges such as economic instability, labor market fluctuations, and family responsibilities. In countries such as Finland and Sweden, suicide rates in this age group remain relatively high [29]. Individuals aged 30–34 in European countries, particularly those with high-income levels, experience pressures associated with career advancement, mortgage obligations, and family commitments. In the Baltic States (Latvia, Lithuania, Estonia), mortality rates in this age group are notably high [28]. For those aged 35–39, suicide rates are particularly high in Eastern European countries, where social and economic factors such as unemployment and high alcohol consumption play a significant role. Finally, individuals aged 40 and older remain at risk. In Germany, France, and the United Kingdom, suicide rates in this age group have remained consistently high, particularly among men. Risk factors include midlife crises, depression, and chronic illnesses [28, 30].

East Asia, including countries such as China, Japan, South Korea, North Korea, Mongolia, and Taiwan, exhibits diverse trends in suicide mortality. According to WHO data from 2019, the suicide rate in the Southeast Asia region was 10.2 per 100,000 people, exceeding the global average of 9.0 per 100,000 [31]. The age structure of suicides in these countries varies, but certain age groups show increased vulnerability. In particular, adolescents and young adults (15–29 years old) are at significant risk. Contributing factors include academic pressure, unemployment, social isolation, and mental disorders [32]. For example, South Korea has a high youth suicide rate, often linked to intense educational stress and a highly competitive environment [33]. Among those aged 30–39, suicide rates remain high, particularly among men. Causes may include workplace stress, family obligations, and economic difficulties [34]. In Japan, middle-aged men frequently experience workplace pressures and societal expectations, which can lead to suicidal ideation and actions [35]. After the age of 40, suicide trends vary. Some countries observe a decline in suicide rates, whereas others, particularly among the elderly, report stable or increasing suicide mortality. In South Korea, for instance, older individuals frequently face poverty and

social isolation, contributing to high suicide rates in this demographic [36]. Gender differences also play a crucial role. In many countries, men die by suicide more often than women. However, in China, past statistics showed similar suicide rates among men and women, particularly in rural areas. In recent years, the gender gap has widened, with an increase in male suicides in urban areas [36]. Risk factors for suicidal behavior in the region vary and include mental disorders such as depression and anxiety, socioeconomic difficulties, cultural expectations, and the stigma surrounding mental illness. For example, in Japan and South Korea, strong societal pressure to conform to social norms can discourage individuals from seeking help for mental health issues [33]. Suicide prevention requires a comprehensive approach that considers the cultural, social, and economic characteristics of each country. Improving access to mental health services, educational programs to raise awareness of mental disorders, social support for vulnerable groups, and economic assistance can all contribute to reducing suicide rates [32]. The present study aims to analyze suicide mortality rates across different age groups in Kazakhstan, identifying key trends. The research utilizes data from international organizations, scientific studies, and national reports, providing an objective and comprehensive perspective on the issue.

Materials and methods

Data Sources and Study Scope

The analysis of suicide mortality prevalence is based on data from the Global Burden of Disease (GBD) 2021 study, provided by the Institute for Health Metrics and Evaluation (IHME) [4, 7]. The dataset includes suicide mortality indicators in Kazakhstan, disaggregated by age groups, gender, and observation years from 2017 to 2021 [6, 11].

Age Groups and Study Population

The study encompasses the following age categories: 15–19 years; 20–24 years; 25–29 years; 30–34 years; 35–39 years; 40 years and older [7, 9]. Data are presented separately for both genders (male and female), as well as in an aggregated format (combined for both sexes) [6, 13].

Methodology of Analysis

The analysis includes the following key components: assessment of absolute mortality counts, expressed in numerical values [4, 10]; determination of percentage mortality rates for each age group [5, 15]; calculation of confidence intervals to provide more precise estimations of data variability [12, 19]; trend analysis across years, based on available time series data [13, 23].

Statistical Analysis

To evaluate the dynamics of suicide mortality across various age groups, a comparative analysis was conducted, including: comparison of mortality rates among different age groups [14, 22]; identification of gender-specific predisposition to suicide [15, 17]; detection of temporal trends (increase or decrease in suicide mortality over the study period) [16, 18].

Results

Comparison of Suicide Mortality Across Age Groups

The analysis of suicide mortality in Kazakhstan revealed significant variations among different age groups. The highest mortality rates were recorded in the 25–29 and 30–34 age groups, whereas younger age categories (15–19 years) exhibited relatively lower suicide mortality levels. As age progresses, mortality rates decline again after 40 years. These disparities may be attributed to social, economic, and psychological factors affecting stress levels and access to support systems at different life stages (Figure 1).

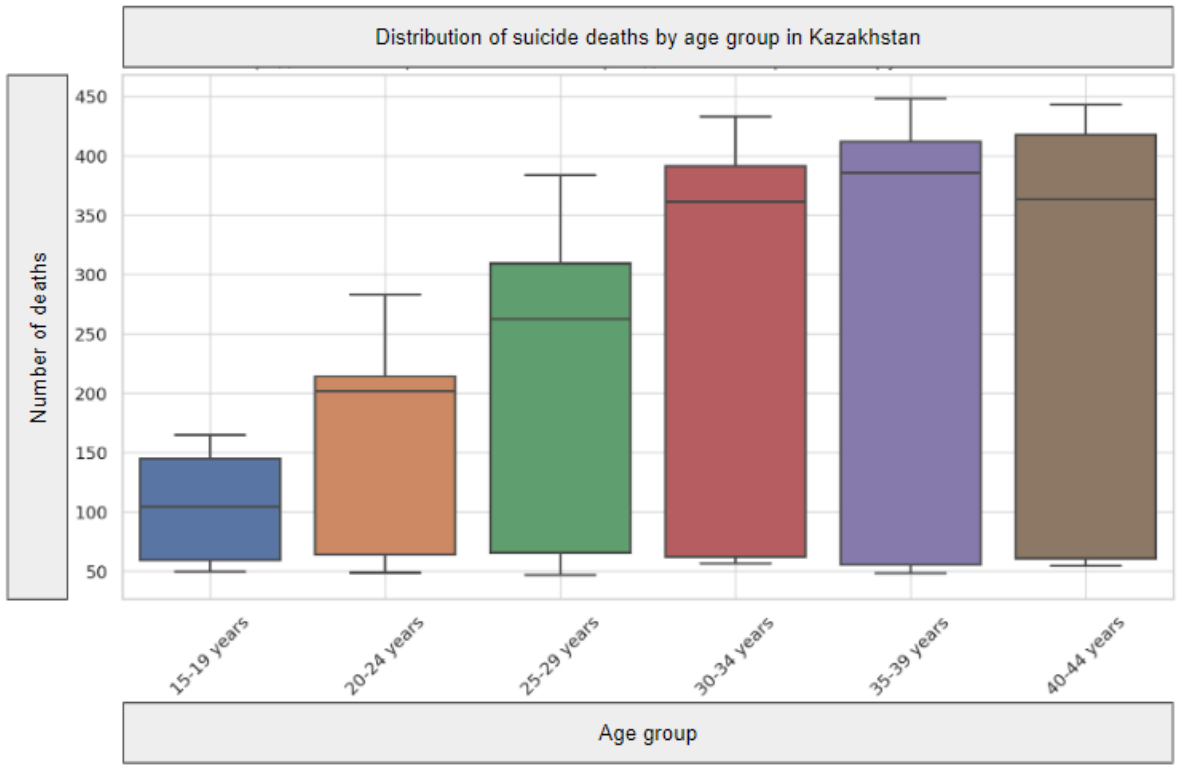

Figure 1. Comparison of mortality rates between age groups.

Gender Differences in Suicide Mortality

A comparative gender analysis indicated that men exhibit significantly higher suicide mortality rates than women. This trend aligns with global data, which suggest that men are more likely to die by suicide due to various factors, including social expectations, access to lethal means, and a lower propensity to seek psychological assistance (Figure 2).

Figure 2. Determining the gender with the highest predisposition to suicide.

Temporal Trends in Suicide Mortality

An analysis of multi-year data revealed fluctuations in suicide mortality rates over time. Certain age groups experienced increases in suicide mortality during specific periods, potentially linked to economic crises, changes in social policies, or other external influences. The most stable mortality trends were observed among individuals aged 15–19 years and 40 years and older, whereas age groups between 25 and 34 years exhibited more pronounced fluctuations (Figure 3).

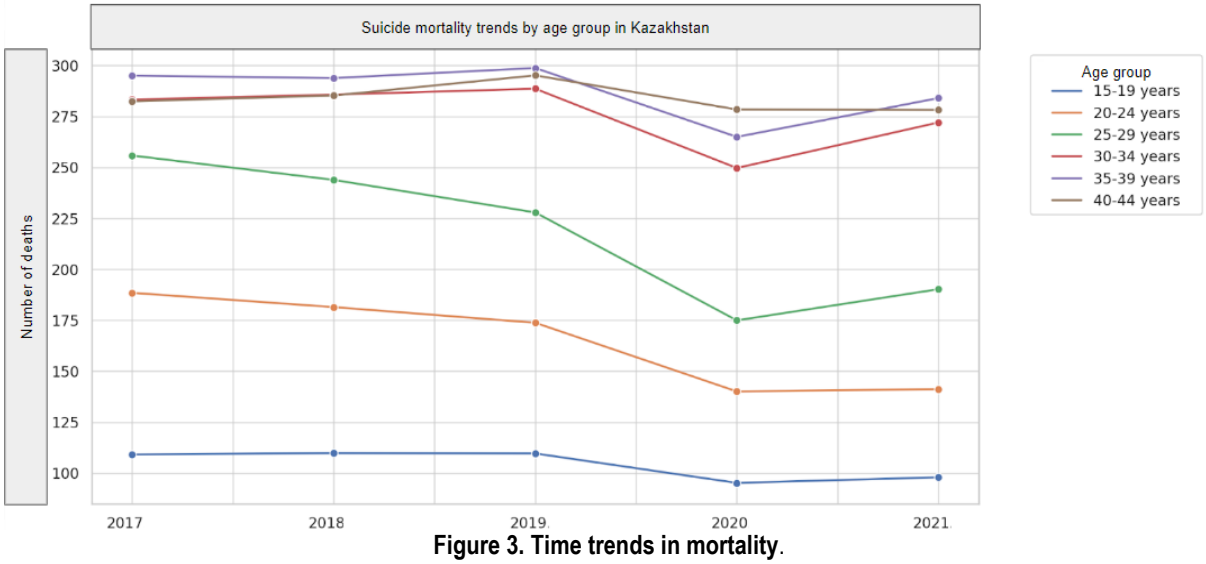

Figure 3. Time trends in mortality.

Discussion

The study results confirm significant variations in suicide mortality rates depending on age, gender, and temporal trends [2, 10]. High suicide mortality among young and middle-aged men necessitates a more detailed examination of risk factors, including unemployment rates, access to psychiatric care, alcohol consumption levels, and cultural attitudes toward mental health issues [5, 12]. A key aspect of this research is the comparative analysis with other countries in the region [3, 14]. For instance, Kazakhstan exhibits trends similar to some Central Asian countries, yet differs from East Asia, where female suicide mortality rates tend to be higher than in Kazakhstan [7, 20]. This discrepancy may reflect differences in social support

systems and cultural norms [9, 26]. The analysis of temporal trends highlights fluctuations in suicide mortality across various age groups, emphasizing the need for continuous monitoring of socioeconomic factors and the development of effective prevention strategies [8, 21]. Mental health policies should prioritize early identification of high-risk groups and improving access to specialized mental health services [6, 28].

Limitations of the study

This study is based on data from 2017 to 2021, as detailed age-group-specific data for 2022, 2023, and 2024 were not yet available [7, 11]. This limitation restricts the ability to analyze the most recent suicide mortality trends, highlighting the need for further research as new data become available [12, 27].

Conclusions

1. The highest suicide mortality rates are observed in the 25–29 and 30–34 age groups, highlighting the need for targeted support measures for this population.
2. Men are significantly more likely to die by suicide than women, aligning with global trends.
3. The analysis of temporal trends revealed fluctuations in suicide mortality, emphasizing the necessity for regular monitoring and adaptive prevention strategies.
4. Comprehensive mental health interventions are required, including early intervention programs, improved access to psychological support, and efforts to address social and economic risk factors.
5. Further research is needed to achieve a more precise understanding of the socioeconomic factors influencing suicide rates, as well as comparative studies with other countries.

Authors' Contribution

All authors contributed equally to the writing of this article.

Conflict of Interest

The authors declare no conflicts of interest.

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EXPERIENCE OF PROJECT WORK TO IDENTIFY ANXIETY AS A POSSIBLE FACTOR IN TEENAGE SUICIDE AND ITS PREVENTION AMONG SCHOOLCHILDREN IN ALMATY

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Abstract

Introduction: In Kazakhstan, teenage suicide is the second leading cause of death among adolescents aged 15-19, second only to road accidents. According to UNESCO, more than 300 cases of suicide among adolescents are recorded in the country every year, and this figure continues to grow. Most often, adolescent suicides are committed due to high anxiety, depression, stressful situations at school, social problems and peer pressure. In 2023, 204 cases of completed suicide were recorded among children aged 11 to 17.

Aim. To highlight the experience of project work on identifying anxiety as a possible factor in teenage suicide and its prevention among schoolchildren in the city of Almaty.

Materials and methods: A prospective cohort study involving 7862 students in grades 5-11 of schools in the Almaly and Bostandyk districts of Almaty was conducted from October 7, 2024, to December 31, 2024. The participants in the study were tested and interviewed in order to identify children with anxiety. Testing of students in grades 5-8 was carried out using the School Anxiety Questionnaire (Phillips B.N. [5]). Testing of students in grades 9-11 was carried out using the Anxiety Level Diagnostics Method (Beck A. [2]).

Results: Signs of high anxiety were identified in 327 (4.2%) children who received individual work from the center's psychologists and school specialists.

Conclusions: High anxiety is already recorded among students in grades 5-11. The main factors of high anxiety are: social (bullying, loneliness, problems in the family, peer pressure), economic (poverty, unemployment of parents, financial instability in the family) and psychological (depression, anxiety, low self-esteem, lack of support, mental disorders. There is insufficient access to psychological help and prevention of anxiety as a factor in teenage suicide. It is important to develop support in families, schools and workplaces of parents or guardians.

Keywords: teenage suicide, risk factors, prevention.

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Резюме

ОПЫТ ПРОЕКТНОЙ РАБОТЫ ПО ВЫЯВЛЕНИЮ ТРЕВОЖНОСТИ, КАК ВОЗМОЖНОГО ФАКТОРА ПОДРОСТКОВОГО СУИЦИДА И ЕГО ПРОФИЛАКТИКА СРЕДИ ШКОЛЬНИКОВ ГОРОДА АЛМАТЫ

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Введение: В Казахстане подростковый суицид занимает второе место среди причин смерти среди подростков в возрасте 15-19 лет, уступая только дорожно-транспортным происшествиям. По данным ЮНЕСКО, каждый год в стране фиксируется более 300 случаев суицидов среди подростков, и этот показатель продолжает расти. Чаще

всего суициды среди подростков совершаются по причине высокой тревожности, депрессии, стрессовых ситуаций в школе, социальных проблем и давления со стороны сверстников. За 2023 год было зафиксировано 204 случая завершенного суицида среди детей в возрасте с 11 до 17 лет.

Цель. Осветить опыт проектной работы по выявлению тревожности, как возможного фактора подросткового суицида и его профилактика среди школьников города Алматы.

Материалы и методы. Проспективное когортное исследование с участием 7862 учащихся 5-11 классов школ Алмалинского и Бостандыкского районов города Алматы проведено с 7 октября 2024 года по 31 декабря 2024 года. С участвующими в исследовании проводились тестирование и устный опрос с целью выявления детей с тревожностью. Тестирование учащихся 5–8 классов было осуществлено посредством методики «Опросник школьной тревожности» (Филлипс Б.Н. [5]). Тестирование учащихся 9–11 классов было осуществлено посредством методики «Методика диагностики уровня тревоги» (Бек А. [2]).

Результаты: Признаки высокой тревожности были выявлены у 327 (4,2%) детей, которым проводилась индивидуальная работа психологами центра и школьными специалистами.

Выводы: Высокая тревожность уже фиксируется среди учащихся 5-11 классов. Основными факторами высокой тревожности являются: социальные (буллинг, одиночество, проблемы в семье, давление со стороны сверстников), экономические (бедность, безработица родителей, финансовая нестабильность в семье) и психологические (депрессия, тревожность, низкая самооценка, отсутствие поддержки, психические расстройства

Недостаточна доступная психологическая помощь и профилактика тревожности, как фактора подросткового суицида. Важно развивать поддержку в семьях, школах и на рабочих местах родителей или опекунов.

Ключевые слова: *подростковый суицид, факторы риска, профилактика.*

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Түйіндеме

АЛМАТЫ ҚАЛАСЫНЫҢ ОҚУШЫЛАРЫ АРАСЫНДА ЖАСӨСПІРІМДЕР СУИЦИДІНІҢ ЫҚТИМАЛ ФАКТОРЫ РЕТІНДЕ МАЗАСЫЗДЫҚТЫ АНЫҚТАУ ЖӘНЕ ОНЫҢ АЛДЫН АЛУ БОЙЫНША ЖОБАЛЫҚ ЖҰМЫС ТӘЖІРИБЕСІ

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Кіріспе: Қазақстанда жасөспірімдер суициді 15-19 жас аралығындағы жасөспірімдер арасындағы өлім себептері арасында жол-көлік оқиғаларынан кейін екінші орында тұр. ЮНЕСКО мәліметтері бойынша, елде жыл сайын жасөспірімдер арасында 300-ден астам суицид оқиғасы тіркеледі және бұл көрсеткіш өсуде. Көбінесе жасөспірімдер арасындағы суицид жоғары мазасыздық, депрессия, мектептегі стресстік жағдайлар, әлеуметтік мәселелер және құрдастарының қысымы салдарынан болады. 2023 жылы 11 мен 17 жас аралығындағы балалар арасында аяқталған суицидтің 204 жағдайы тіркелді.

Мақсаты: Алматы қаласының оқушылары арасында жасөспірімдер суицидінің ықтимал факторы ретінде мазасыздықты анықтау және оның алдын алу бойынша жұмыс тәжірибесін жариялау.

Материалдар мен әдістер. Алматы қаласы Алмалы және Бостандық аудандары мектептерінің 5-11 сыныптарының 7862 оқушысының қатысуымен 2024 жылғы 7 қазаннан 2024 жылғы 31 желтоқсанға дейін перспективалық когорттық зерттеу жүргізілді. Зерттеуге қатысушылармен мазасызданған балаларды анықтау мақсатында тестілеу және ауызша сауалнама жүргізілді. 5-8 сынып оқушыларын тестілеу "Мектептегі мазасыздық сауалнамасы" әдісі арқылы жүзеге асырылды (Филлипс Б.Н. [5]). 9-11 сынып оқушыларын тестілеу "Дабыл деңгейін диагностикалау әдістемесі" (Бек А. [2]) әдістемесі арқылы жүзеге асырылды.

Нәтижелер: Орталықтың психологтары мен мектеп мамандары жеке жұмыс жасаған 327 (4,2%) балада жоғары мазасыздық белгілері анықталды.

Қорытынды: 5-11 сынып оқушылары арасында жоғары мазасыздық қазірдің өзінде тіркелуде. Жоғары мазасыздықтың негізгі факторлары: әлеуметтік (қорқыту, жалғыздық, отбасындағы проблемалар, құрдастарының қысымы), экономикалық (кедейлік, ата-аналардың жұмыссыздығы, отбасындағы қаржылық тұрақсыздық) және психологиялық (депрессия, мазасыздық, өзін-өзі бағалаудың төмендігі, қолдаудың болмауы, психикалық бұзылулар) болып бөлінеді. Жасөспірімдердің суицид факторы ретінде қол жетімді психологиялық көмек пен

мазасыздықтың алдын алу жеткіліксіз. Ата-аналардың немесе қамқоршылардың отбасыларында, мектептерінде және жұмыс орындарында қолдауды дамыту маңызды.

Түйінді сөздер: *жасөспірімдердің суициді, қауіп факторлары, алдын алу.*

Дәйексөз үшін: *Молдагасимова А.Б., Тусупбекова Д.М., Шарипова А. Т., Рысбекова Р.К.* Алматы қаласының оқушылары арасында жасөспірімдер суицидінің ықтимал факторы ретінде мазасыздықты анықтау және оның алдын алу бойынша жобалық жұмыс тәжірибесі // Ғылым және денсаулық сақтау. 2025. Vol.27 (1), 130-136 ББ. doi 10.34689/SH.2025.27.1.016

Introduction

According to the World Health Organization (WHO), Kazakhstan is among the countries with a high suicide rate. According to the Statistics Committee of the Republic of Kazakhstan, the suicide rate among men is significantly higher than among women. The most vulnerable group are young people aged 15 to 29. Statistics show that in rural areas the suicide rate is higher than in cities, which may be due to the low availability of medical and psychological care. In recent years, there has also been an increase in the number of suicides among children and adolescents, which requires special attention from society and the state [10].

In Almaty, there is an alarming trend of increasing suicides among adolescents, which makes the problem one of the key ones in the field of public health [11].

The main factors aggravating the situation are:

- lack of qualified specialists,
- low awareness of teachers about the signs of suicidal behavior,
- insufficient parental involvement,
- stigmatization of seeking psychological help.

In 2024, the city experienced several tragic incidents, including suicides of 12-year-old girls, highlighting the need for urgent measures to prevent suicidal behavior among young people.

To address this issue, Kazakhstan approved a Comprehensive Plan to Protect Children from Violence, Prevent Suicide, and Ensure Their Rights and Well-Being for 2023–2025. This plan aims to improve the mental health of adolescents, develop prevention programs, and raise public awareness of the importance of mental well-being among young people.

Adolescents facing crisis situations often do not know where to turn. Existing hotlines are not well-known, which reduces their effectiveness.

On July 26, 2023, at a meeting of the Academic Council (Protocol No. 6), a scientific and technical project was considered on the topic: "Center for psychological support of minors with suicidal tendencies" (hereinafter referred to as the Center) on the basis of the State Enterprise on the Right of Economic Management "City Polyclinic No. 3" of the Health Department of Almaty. The members of the Council recognized the problem as relevant and approved the proposed project.

This Center pursues the goal of a comprehensive study of the problem of suicide among children, identifying its main risk factors, as well as analyzing existing preventive measures in the school environment, which corresponds to the points of the Comprehensive Plan for 2023-2025.

At the preparatory stage, the scientific and methodological basis for conducting the experimental study was determined, methodological recommendations “Psychological support for minors with suicidal tendencies” were prepared, an analysis of scientific literature on the possibilities of diagnosing anxiety in students of comprehensive schools was made, and testing procedures were selected aimed at identifying signs of anxiety in students of comprehensive schools using digital and cloud technologies.

Throughout its activities, the Center has been actively cooperating with the Organizational and Analytical Center for Suicides at the Almaty Mental Health Center (MHC). The management of the MHC is familiar with the progress of the research, facilitates part of the work and does not object to further coverage of the research results in the open press. Within the framework of this project, the management of the MHC allocated a suicidologist, together with whom an individual treatment, health improvement and psychological rehabilitation plan was developed within the framework of clinical diagnostic and treatment protocols approved by the Ministry of Health of the Republic of Kazakhstan. An individual plan was drawn up for each parent and child separately, which are adjusted during the course of treatment by a suicidologist, psychologist and the deputy director for medical work of CP No. 3.

In 2024, the Center continued its work to identify children and adolescents with suicidal tendencies. Since 21.02.2024, the Center's work has been expanded to the district level. Joint events were held with district educational organizations to identify mental disorders and deviations in the school contingent.

On April 10, 2024, a tripartite memorandum was signed between the Center, the heads of the education departments of the Almaly and Bostandyk districts and the heads of educational schools, with the aim of interconnected work between teachers, school psychologists and psychologists of the Center on the interaction of government agencies to prevent suicides among students.

Aim: to highlight the experience of project work on identifying anxiety as a possible factor in teenage suicide and its prevention among schoolchildren in the city of Almaty.

Materials and methods.

A prospective cohort study involving 7862 students in grades 5-11 of schools in the Almaly and Bostandyk districts of Almaty was conducted from October 7, 2024 to December 31, 2024. Inclusion criteria: students in grades 5-11 of schools in the Almaly and Bostandyk districts. Exclusion criteria: students in elementary grades, as well as other schools and those who refused to undergo testing or an oral survey. Testing and an oral survey were conducted by psychologists of the center in order to identify children

with anxiety. All participants have informed voluntary consent to participate in the study, provided by their parents (legal representatives). Testing of students in grades 5-8 was carried out using the School Anxiety Questionnaire (Phillips B.N. [5]) method. to study the level and nature of anxiety associated with school learning. The test consists of 58 questions. The answers were supposed to be closed, either "Yes" or "No". This test provided information on the general level of school anxiety, which was structured according to the degree of expression in various aspects of learning: social stress, educational needs, self-expression, knowledge testing, failure to meet the expectations of others, low resistance to stress, relationships with teachers.

Testing of students in grades 9–11 was carried out using the method “Method of diagnostics of anxiety level” (Beck A. [2]), on the subject of anxiety and assessment of the degree of its severity. The questionnaire consists of 21 items. Each item includes one of the typical symptoms of anxiety, physical or psychological. Each item was assessed by the respondent from 0 (the symptom did not bother) to 3 (the symptom bothered very much). Filling out the scale took no more than 10 minutes, independently. Persons who received high scores on the scale should be referred for consultation to a specialist.

Children with identified high anxiety were administered individual questionnaires that took into account the specifics of a certain age group. These methods allowed us to obtain information about the child's mental state. Specialized tests were also used for middle and adolescent age: Eysenck Personality Questionnaire (Eysenck G., Eysenck S) [1]), Cattell Personality Questionnaire R.: adolescent modification [6]. The questionnaire is designed to identify the personality traits of adolescents and high school students aged 12 to 16-18 years, their mental status. The adolescent 14-factor technique contains 142 questions with three answer options for choosing the most appropriate one. The average time to complete Cattell R.'s questionnaire for adolescents was 30-40 minutes. Suicidal Risk Questionnaire (Razuvaeva T.N. [8]) for assessing the degree of risk of developing suicidal behavior. Serves as an express test. It evaluates the socio-cultural risks of suicidal behavior and obtains generalized information about the mental state of the individual.

For senior school-age participants, the method of diagnosing interpersonal relationships (T. Leary [7]) was used, designed to study the subject's ideas about himself and the ideal "I", as well as to study relationships in small groups. With the help of this method, the predominant type of relationship to people in self-assessment and mutual assessment is revealed.

Personality questionnaire Mini-Mult (Berezina F., Miroshnikov M. [3]). The questionnaire is clinical and is aimed at diagnosing pathological personality traits. It is important to note that it only indicates their severity, but not the presence of the disease. The questionnaire allows you to assess the communicative, behavioral side of the personality of adolescents.

Results:

In 2023, a trial testing stage was launched among children of educational schools (hereinafter referred to as ES) attached to GP No. 3 to identify anxiety. The total number of participants covered by the study was 1,295, of which 810 were students in grades 5–8 and 485 were students in grades 9–11.

Among students in grades 5–8, 62 (7.7%) were identified who needed a psychologist's consultation to clarify their current mental state.

Among students in grades 9–11, 55 (11.3%) were identified who were experiencing moderate anxiety. Of the 55, 47 also needed a psychologist's consultation.

Thus, the total number of students with anxiety symptoms according to the testing results was 117 students (9%) in grades 5–8 and 9–11. Of these, 2 students (1.7%) were referred to the CPC to work with a psychotherapist.

In 2024, psychodiagnostic testing was conducted in 17 schools in the Almaly and Bostandyk districts among 7,862 students, of which 4,914 were students in grades 5-8 and 2,948 were students in grades 9-11.

Among students in grades 5-8, 172 students (3.5%) were identified with moderate anxiety, of which 11 (6.3%) needed to consult a psychologist to clarify their current mental state.

Among students in grades 9-11, 155 (5.2%) were identified as experiencing moderate anxiety. Of which 10 (6.4%) also needed to consult a psychologist.

Thus, the total number of students with anxiety symptoms according to the testing results was 327 students (4.1%) in grades 5-8 and grades 9-11.

Medical psychologists work with 21 students, of which 10 children (47.6%) undergo psycho-correctional work, for the remaining 11 (52.4%) children a schedule of personal meetings with the Center's psychologist for further psycho-correctional work has been drawn up. 9 children were referred to the Center for Mental Health, of which 5 students contacted the Center for Mental Health, 4 students contacted private psychotherapists, the remaining 297 students were referred to school psychologists for consultation.

Corrective work was carried out with the identified children and consultations for parents. 235 parents (72%) covered by the information activities of the Center agreed to participate in psychological support, which increases the level of awareness of the risks of anxiety and self-destruction of children.

Consulting and work with 327 children with anxiety and their parents demonstrate a significant contribution to improving the psychological stability of families.

The behavior of adolescents with anxiety has various causes, which can be divided into psychological, social, biological and informational violence. In the process of interviewing and testing, the main causes of anxiety in children of the specified groups were identified (Table 1).

Psychologists of the center in the process of preventive measures for the identified category of children with anxiety and their teachers for the prevention of child suicide carried out the following measures:

- Psychological training for students on the topic "You can't do this to me!" with the aim of providing an opportunity to "think" about various forms of violence and develop rules for responsible and safe behavior. Participants discussed how to recognize manifestations of violence in their own behavior and the behavior of others, learned how to develop their own potential, as well as effective ways to resist violence.

- Training on the topic: "Mobbing, bullying, khayzing - how are they dangerous for schoolchildren?" to create a safe psychological space for children in an educational organization and to form a stable friendly attitude in the school community. As a result of the training, children acquired the skill of constructive response in conflict, reducing aggression and self-image.
- Training for school teachers on the topic "Suicide. Understanding and prevention at school". The purpose of the training is improving the professional competencies of class teachers and school teachers in matters of preventing suicidal behavior of students and preventing child neglect and juvenile delinquency.

Table 1.

Causes of anxiety in adolescents in grades 5-8 and 9-11.

Category of factors	Specific factors
Psychological	— Depression, anxiety disorders; — Emotional instability; — Low self-esteem; — Feelings of loneliness, helplessness; — Autoaggression, tendency to self-punishment.
Social	— Family conflicts (divorce, violence, neglect); — Bullying (bullying at school, online); — Lack of support from peers and adults; — Social isolation; — Pressure from the environment.
Biological	- Hereditary predisposition (family history of mental disorders or suicide); - Neurotransmitter dysfunction; - Pubertal hormonal changes.
Information violence	— Exposure to destructive content on social networks; — Participation in suicidal online groups; — Romanticization and propaganda of suicide in the media.

In the course of the work of the Center, aimed at preventing suicidal behavior among schoolchildren, the following **difficulties** arose:

- **Low level of perception and acceptance of the initiative** – at the initial stage of the project implementation, there was insufficient understanding of the importance of the services provided and the effectiveness of the proposed work methods on the part of the administration of educational institutions, school psychologists and the students themselves.
- **Lack of clear delineation of functional responsibilities** – at present, there is no clear boundary between the areas of responsibility of school psychologists and medical specialists, which leads to duplication of functions, inconsistency of actions and a decrease in the overall effectiveness of providing psychological assistance.
- **The competitive factor** – there are elements of competition between the various specialists and institutions involved in the work to prevent suicidal behavior, which can hinder constructive interaction and coordination of efforts within the framework of a unified approach to solving the problem.

Medical effectiveness:

1. Provision of specialized assistance. The center provides psychological support to children, including work with suicidal tendencies in children, which reduces the likelihood of repeated suicide attempts. Individual treatment and rehabilitation plans have been developed for children with identified psychoemotional problems.
2. Development of technologies and availability of assistance. The introduction of a chat bot and a hotline simplifies access to psychologists, ensuring anonymity and involvement of children and parents.
3. The use of tests (school anxiety, Beck test [2], etc.) allows us to systematize the work and quickly identify those in need of help.

Discussion of results

Childhood anxiety is a common mental disorder. It is estimated that more than 7% of adolescents aged 13 to 17 years have been diagnosed with anxiety, and more than 36% of children with behavioral problems have been diagnosed with anxiety disorders [1].

A systematic review of studies conducted in 27 countries estimated that the global prevalence of anxiety disorders in children is 6.5%. [2] In the United States, nearly 1 in 12 children aged 3 to 17 years have anxiety. [12] The National Institute of Mental Health estimates that the prevalence of anxiety disorders in adolescents aged 13 to 18 years is 1 in 4, and the prevalence of severe anxiety is about 1 in 17. [3] Prevalence rates are approximately 20% for specific phobias, 9% for social anxiety disorder, 8% for separation anxiety disorder, and 2% each for agoraphobia, panic disorder, and generalized anxiety disorder [3].

The relevance of the problem is confirmed by international studies. According to the UNICEF report [10] “Child Suicide in Kazakhstan” (R. Haarr, 2012), the level of teenage suicides in the country remains one of the highest. However, due to cultural taboos and social pressure, official statistics may be understated, since many cases are recorded as accidents.

A study conducted in 2015–2019 in Ust-Kamenogorsk and Semey revealed an alarming link between Internet addiction and suicide attempts. Of the 477 cases studied, 321 were boys, 156 were girls, the average age was 16.3±1.1 years. It was found that teenagers addicted to the Internet are 74.2% more likely to attempt suicide. This is especially evident in the 16–18 age group. Our study also found a link between internet addiction and suicide attempts. [13]

With the increasing digitalization of society, it is important to:

- control the online environment,
- increase the digital literacy of teenagers,
- develop psychological support programs on the Internet.
- Strengths of the study:
- for the first time, a comprehensive methodology has been developed,
- use of several types of questionnaires,
- availability of a Telegram bot for anonymous communication with children and parents,

• development of a website for registration and analysis of all cases.

The study examines all factors that influence suicidal behavior in adolescents: psychological, familial, social, biological, and the impact of cyberbullying.

Risk factors for anxiety disorders in children and adolescents include low socioeconomic status, exposure to violence, trauma, and biological factors such as heredity and temperament. Parental anxiety predisposes children to a higher risk of functional impairment and anxiety disorders [4].

Over the past decade, concern has grown about the impact of social media use and interaction with online content on anxiety symptoms and the development of anxiety disorders in children and adolescents. The impact can have positive and negative associations and vary by gender, age, social media platform, and time spent using. Fear of missing out and confirmation seeking drive interactions and time spent on social media and can lead to increases in general anxiety symptoms (more common in boys) and body image anxiety (more common in girls) [5]. Cyberbullying can lead to increased anxiety and risk of anxiety disorders, particularly in marginalized young people, although positive effects of increased connections to online communities have been noted [5]. The impact of the COVID-19 pandemic on the mental health of children and adolescents has become a growing concern.

A 2021 meta-analysis of over 80,000 young people in 29 studies found a pooled prevalence of clinically elevated anxiety symptoms of 21%, with higher prevalence rates found in data collected later in the pandemic and among girls [6].

The U.S.A. Preventive Services Task Force recommends screening for anxiety disorders in children and adolescents aged eight to 18 years (grade B recommendation). There is insufficient evidence to support screening in children under eight years of age. [7]

There is sufficient empirical evidence to show significant improvement in childhood anxiety disorders with psychotherapy or pharmacotherapy, with a combination of treatments. In this regard, and given the age-related perception and interpretation of questionnaire questions, the study did not include primary school-aged children, since the reliability of self-assessment data in this group is limited.

Only joint efforts by society will help change the situation and reduce the number of tragedies. To do this, it is necessary:

• popularize psychological assistance among teenagers and their parents,

• implement preventive programs in schools,

• improve the qualifications of teachers and doctors,

• create accessible and convenient support services in the digital space.

Conclusions

The social effectiveness of the Center's activities is manifested in improving the psychological climate among children and adolescents, reducing suicide cases, raising awareness among parents and teachers, and creating a safer school and family space. The Center solves significant social problems and contributes to strengthening the well-being of society, but expanding its scope requires active work with schools that have failed, attracting funding, and deepening interaction with government agencies.

The Center is a link between the school and the clinic (diagnosing self-destructive behavior is a complex task for both psychologists, teachers, and other school specialists, as well as for the medical staff of the clinic, but at the moment there is no strong relationship between the specialists of the clinic and the school).

Reducing anxiety in adolescents is one of the key points in reducing suicides among young people. This problem remains serious for the city of Almaty and requires joint efforts of the state, society, healthcare, and education. Implementing effective prevention programs, ensuring access to psychological assistance and improving socio-economic conditions will help reduce the suicide rate among teenagers.

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THE CONDITION OF THE VASCULAR ENDOTHELIUM IN CHILDREN WITH COVID-19 AND BRONCHO-OBSTRUCTIVE SYNDROME

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Abstract

Introduction: The impact of SARS-CoV-2 infection on the human organism has proven to be more diverse than that of previously known viral infections. However, the full spectrum of the long-term consequences of the disease, especially in children, has not been thoroughly studied. One key area of concern is the development of broncho-obstructive syndrome (BOS) as a post-COVID-19 complication, which involves airway inflammation and hyperreactivity. This study investigates the relationship between endothelial dysfunction and BOS in pediatric patients following SARS-CoV-2 infection.

Objective: To explore the endothelial status in children with SARS-CoV-2 infection and its association with the development of BOS, and to assess the role of endothelial dysfunction markers—circulating endothelial cells (CECs), endothelin-1, and nitric oxide metabolites—in this context.

Methods: A retrospective study was conducted between 2020 and 2022, involving 486 children. The study included two primary groups: (1) Control: Healthy children with no history of SARS-CoV-2 infection or BOS; children with SARS-CoV-2 infection but no BOS, and (2) Main: Children with BOS but no SARS-CoV-2 infection; children with SARS-CoV-2 infection followed by the development of BOS. Endothelial function was assessed by measuring levels of CECs, endothelin-1, and nitric oxide metabolites.

Results: The study found significantly elevated CECs and endothelin-1 levels, along with decreased nitric oxide metabolites, in children who developed BOS following SARS-CoV-2 infection. The highest levels of endothelial dysfunction markers were observed in this group, suggesting a synergistic effect of SARS-CoV-2 infection and BOS on endothelial damage. Notably, 64.3% of children in this group exhibited elevated CEC levels, reflecting severe endothelial dysfunction. Endothelin-1 levels were also significantly higher in children with BOS after SARS-CoV-2 infection (0.46 ± 0.02 fmol/mL) compared to healthy controls and children with BOS without a history of SARS-CoV-2 infection. These findings highlight the critical role of endothelial dysfunction in the pathogenesis of post-COVID-19 respiratory complications.

Conclusion: SARS-CoV-2 infection contributes to significant endothelial dysfunction in children, particularly in those who develop BOS. The combination of SARS-CoV-2 infection and BOS exacerbates endothelial damage, which likely plays a critical role in the pathogenesis of post-COVID-19 respiratory complications. These findings suggest the need for further research into therapeutic strategies aimed at correcting endothelial dysfunction, potentially improving outcomes for pediatric patients suffering from long-term respiratory sequelae following COVID-19.

Keywords: *SARS-CoV-2, Endothelial Dysfunction, Circulating Endothelial Cells (CECs), Broncho-Obstructive Syndrome (BOS), Pediatric COVID-19, Endothelin-1, Nitric Oxide Metabolites, Post-COVID-19 Complications, Vascular Endothelium, Respiratory Complications.*

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Резюме

СОСТОЯНИЕ СОСУДИСТОГО ЭНДОТЕЛИЯ У ДЕТЕЙ С COVID-19 И БРОНХООБСТРУКТИВНЫМ СИНДРОМОМ

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Введение: Воздействие инфекции SARS-CoV-2 на человеческий организм оказалось более разнообразным, чем у ранее известных вирусных инфекций. Однако полный спектр долгосрочных последствий заболевания, особенно у детей, еще не был тщательно изучен. Одной из ключевых проблем является развитие бронхообструктивного синдрома (БОС) как постковидного осложнения, которое включает воспаление дыхательных путей и гиперреактивность. Это исследование направлено на изучение связи между эндотелиальной дисфункцией и БОС у детей после инфекции SARS-CoV-2, и на определение роли маркеров эндотелиальной дисфункции - циркулирующих эндотелиальных клеток (ЦЭК), эндотелина-1 и метаболитов оксида азота - в этом контексте.

Методы: Ретроспективное исследование было проведено в период с 2020 по 2022 год и охватило 486 детей. Исследование включало две основные группы: (1) Контрольная группа: здоровые дети, не имеющие истории инфекции SARS-CoV-2 или БОС; дети с инфекцией SARS-CoV-2, но без БОС, и (2) Основная группа: дети с БОС, но без инфекции SARS-CoV-2; дети с инфекцией SARS-CoV-2, за которой последовало развитие БОС. Функция эндотелия оценивалась путем измерения уровней ЦЭК, эндотелина-1 и метаболитов оксида азота.

Результаты: Исследование показало значительное повышение уровней ЦЭК и эндотелина-1, а также снижение метаболитов оксида азота у детей, развивших БОС после инфекции SARS-CoV-2. Наибольшие уровни маркеров эндотелиальной дисфункции были обнаружены в этой группе, что свидетельствует о синергетическом эффекте инфекции SARS-CoV-2 и БОС на повреждение эндотелия. Особенно важно, что 64,3% детей в этой группе продемонстрировали повышенные уровни ЦЭК, что отражает тяжелую эндотелиальную дисфункцию. Уровни эндотелина-1 также были значительно выше у детей с БОС после инфекции SARS-CoV-2 (0,46 ± 0,02 фмоль/мл) по сравнению с здоровыми детьми и детьми с БОС без истории инфекции SARS-CoV-2. Эти результаты подчеркивают важнейшую роль эндотелиальной дисфункции в патогенезе респираторных осложнений после COVID-19.

Выводы: Инфекция SARS-CoV-2 способствует значительной эндотелиальной дисфункции у детей, особенно у тех, кто развивает БОС. Сочетание инфекции SARS-CoV-2 и БОС усугубляет повреждение эндотелия, что, вероятно, играет ключевую роль в патогенезе респираторных осложнений после COVID-19. Эти данные подчеркивают необходимость дальнейших исследований терапевтических стратегий, направленных на коррекцию эндотелиальной дисфункции, что может улучшить исходы лечения педиатрических пациентов, страдающих от долгосрочных респираторных последствий после COVID-19.

Ключевые слова: *SARS-CoV-2, эндотелиальная дисфункция, циркулирующие эндотелиальные клетки (ЦЭК), бронхообструктивный синдром (БОС), детский COVID-19, эндотелин-1, метаболиты оксида азота, постковидные осложнения, сосудистый эндотелий, респираторные осложнения.*

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Түйіндеме

COVID-19 ЖӘНЕ БРОНХООБСТРУКТИВТІ СИНДРОМЫ БАР БАЛАЛАРДА ТАМЫР ЭНДОТЕЛИІНІҢ ЖАҒДАЙЫ

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Кіріспе: SARS-CoV-2 инфекциясының адам организміне әсері бұрын белгілі вирустық инфекцияларға қарағанда әртүрлірек болып шықты. Дегенмен, аурудың ұзақ мерзімді салдары, әсіресе балаларда, толық зерттелген жоқ. Негізгі мәселелердің бірі – бронхообструктивті синдромның (БОС) постковидтік асқыну ретінде дамуы, оған тыныс жолдарының қабынуы және гиперреактивтілік кіреді. Бұл зерттеу SARS-CoV-2 инфекциясынан кейінгі балаларда эндотелиалды дисфункция мен БОС арасындағы байланысты, сонымен қатар эндотелиалды дисфункция маркерлерінің – айналымдағы эндотелиалды клеткалар (АЭК), эндотелин-1 және азот оксидінің метаболиттерінің рөлін анықтауға бағытталған.

Әдістері: 2020-2022 жылдар аралығында ретроспективті зерттеу жүргізіліп, 486 бала қамтылды. Зерттеу екі негізгі топты қамтыды: (1) Бақылау тобы: SARS-CoV-2 инфекциясы немесе БОС анамнезі жоқ дені сау балалар; SARS-CoV-2 инфекциясы бар, бірақ БОС-ы жоқ балалар, және (2) Негізгі топ: SARS-CoV-2 инфекциясы жоқ, бірақ БОС-ы бар балалар; SARS-CoV-2 инфекциясынан кейін БОС дамыған балалар. Эндотелий функциясы АЭК, эндотелин-1 және азот оксидінің метаболиттері деңгейін анықтау арқылы бағаланды.

Нәтижелер: Зерттеу SARS-CoV-2 инфекциясынан кейін БОС дамыған балаларда ЦЭК және эндотелин-1 деңгейінің айтарлықтай жоғарылағанын, ал азот оксидінің метаболиттерінің төмендегенін көрсетті. Эндотелиалды дисфункция маркерлерінің ең жоғары деңгейі осы топта байқалды, бұл SARS-CoV-2 инфекциясы мен БОС-тың эндотелийге зақым келтірудегі синергетикалық әсерін көрсетеді. Ерекше маңыздысы, осы топтағы балалардың 64,3%-ында АЭК деңгейінің жоғарылауы байқалды, бұл эндотелиалды дисфункцияның ауыр түрін көрсетеді. SARS-CoV-2 инфекциясынан кейін БОС дамыған балаларда эндотелин-1 деңгейі де дені сау балаларға және SARS-CoV-2 инфекциясы анамнезі жоқ БОС-ы бар балаларға қарағанда айтарлықтай жоғары болды (0,46 ± 0,02 фмоль/мл). Бұл нәтижелер COVID-19-дан кейінгі респираторлық асқынулар патогенезінде эндотелиалды дисфункцияның маңызды рөлін атап өтеді.

Қорытынды: SARS-CoV-2 инфекциясы балаларда, әсіресе БОС дамығандарда, эндотелиалды дисфункцияның айтарлықтай дамуына ықпал етеді. SARS-CoV-2 инфекциясы мен БОС-тың бірігуі эндотелий зақымдануын шиеленістіреді, бұл COVID-19-дан кейінгі респираторлық асқынулар патогенезінде маңызды рөл атқарады. Бұл деректер эндотелиалды дисфункцияны түзетуге бағытталған терапиялық стратегияларды одан әрі зерттеу қажеттілігін көрсетеді, бұл COVID-19-дан кейінгі ұзақ мерзімді респираторлық салдарларға шалдыққан балалардың емдеу нәтижелерін жақсартуы мүмкін.

Түйін сөздер: *SARS-CoV-2, эндотелиалды дисфункция, айналымдағы эндотелиалды клеткалар (АЭК), бронхообструктивті синдром (БОС), балалардағы COVID-19, эндотелин-1, азот оксидінің метаболиттері, постковидтік асқынулар, қан тамырлары эндотелийі, респираторлық асқынулар.*

Дәйексөз үшін: *Шакирова А.А., Токтабаева Б.Ж., Оразалина А.С., Абылгазинова А.Ж., Амренова К.Ш., Абаева К.Д., Жангалиева Г.М.* COVID-19 және бронхообструктивті синдромы бар балаларда тамыр эндотелиінің жағдайы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 137-145. *doi 10.34689/SH.2025.27.1.017*

Introduction

The impact of SARS-CoV-2 infection on the human organism has proven to be more diverse than that of previously known viral infections [1-3]. However, the full spectrum of the long-term consequences of the disease, especially in children, has not been thoroughly studied. The delayed development (or detection) of widespread morbidity has resulted in a shorter observation period, a limited number of patients, and a restricted range of clinical examinations [4]. Although the study of COVID-19 incidence in children and its consequences began in mid-2020, many aspects remain unexplored.

One of the key areas in studying the pathophysiology of COVID-19 is the identification of its impact on the vascular endothelium [5]. The endothelium, which is widely distributed throughout the body and performs a variety of functions, has been shown to be significantly affected by SARS-CoV-2. Endothelial dysfunction has been implicated in the outcomes of various diseases, leading some authors to conclude that COVID-19 often manifests due to severe endothelial dysfunction [6]. Specifically, endothelial dysfunction is thought to play a crucial role in post-viral complications such as broncho-obstructive syndrome, a condition involving airway inflammation and hyperreactivity that can result from viral infections.

However, the specific effects of endothelial dysfunction on the development of organ pathology in children, particularly those unrelated to the cardiovascular system, remain poorly understood. Additionally, there is a lack of information regarding the role of endothelial dysfunction in the development of BOS in children who have recovered from COVID-19.

The aim of this study is to determine the characteristics of vascular endothelial conditions in children with SARS-CoV-2 infection, particularly focusing on the relationship between SARS-CoV-2 infection and the development of broncho-obstructive syndrome. By assessing key markers of endothelial dysfunction—circulating endothelial cells, endothelin-1, and nitric oxide metabolites—the study seeks to identify how endothelial injury contributes to the pathogenesis of broncho-obstructive syndrome in children post-SARS-CoV-2 infection.

Materials and Methods

Study Design

This retrospective study was conducted at the Private Multidisciplinary Clinic Institution "Venera" in Semey, Republic of Kazakhstan, from 2020 to 2022. The study was approved by the local ethics committee on October 22, 2022 (Protocol No. 1).

Inclusion Criteria

Children aged 2–18 years were eligible for inclusion if they had a history of recurrent broncho-obstructive syndrome (BOS) or if BOS was identified during the study. The study population included children with a history of SARS-CoV-2 infection or asymptomatic SARS-CoV-2 infection, confirmed by either a positive PCR test or the detection of diagnostic IgG antibodies to SARS-CoV-2. Written informed consent from parents or legal guardians was obtained for participation and the anonymous use of study data.

Exclusion Criteria

Children were excluded if they were younger than 2 years or older than 18 years, had severe congenital bronchopulmonary or cardiovascular diseases, or had immunodeficiencies. Additionally, children under 5 years with clinically verified bronchial asthma were excluded from the study. Children whose legal guardians did not provide written consent or who withdrew consent at any stage of the study were also excluded.

Study Population

A total of 486 children were enrolled in the study and categorized into a main group (259 children) and control group (227 children), based on the presence of bronchial obstruction syndrome (BOS) and the history of SARS-CoV-2 infection:

- **Main Groups:**
  - BOS without SARS-CoV-2 infection: 198 children diagnosed with BOS but with no history of SARS-CoV-2 infection.
  - BOS after SARS-CoV-2 infection: 61 children who developed BOS following SARS-CoV-2 infection.
- **Control Groups:**
  - Healthy Control: 120 children without BOS and without a history of SARS-CoV-2 infection, confirmed by detailed anamnesis and repeated analysis for the presence of antibodies.
  - SARS-CoV-2 Control: 107 children who had SARS-CoV-2 infection but did not develop BOS. This group included children who had clinically symptomatic COVID-19 (confirmed by PCR or clinical symptoms) as well as those who tested positive for SARS-CoV-2 antibodies (diagnostic IgG titers) without exhibiting clinical symptoms.

Methods for Studying Vascular Endothelial State

Vascular endothelial function was assessed using blood test results, which included the following parameters: Circulating Endothelial Cells, Endothelin-1, Nitric Oxide Metabolites.

Statistical Analysis

Data were analyzed using nonparametric tests due to the nature of the distributions. Comparisons between independent groups were performed using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

The analysis of vascular endothelial markers revealed significant differences in endothelial dysfunction across the study groups, with particular emphasis on circulating endothelial cells (CECs), endothelin-1, and nitric oxide (NO) metabolites.

Circulating Endothelial Cells (CECs)

The levels of CECs varied significantly across the study groups (Figure 1). In the healthy control group, the average CECs count was 1.2 ± 0.1 per 10^3 platelets. In children with a history of SARS-CoV-2 infection but no BOS, the CECs count increased to 1.8 ± 0.1 per 10^3 platelets. The main group with persistent BOS without prior SARS-CoV-2 infection had a lower CECs level of 1.4 ± 0.1 per 10^3 platelets. The highest CECs level was observed in children who developed BOS following SARS-CoV-2 infection (3.3 ± 0.2 per 10^3 platelets).

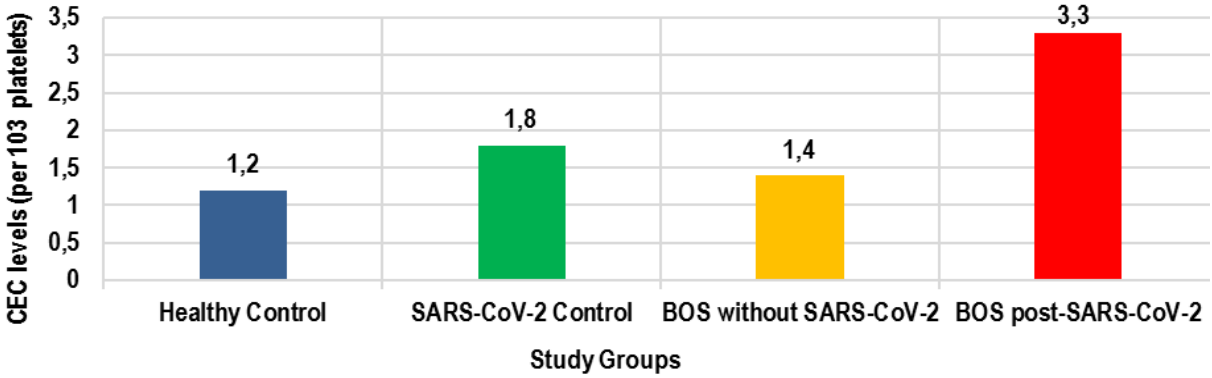

Figure 1. Levels of Circulating Endothelial Cells in Children Across Study Groups.

The graph shows the mean CECs levels (per 10^3 platelets) across two study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2).

Figure 2 presents the distribution of CECs levels across the study groups. The proportion of children with higher CECs levels increased in groups with a history of SARS-CoV-2 infection and BOS development. In the healthy control group, most children had CEC levels below 1.5 per 10^3 platelets, with only a small fraction exceeding this threshold. In contrast, BOS post-SARS-CoV-2 group had the highest percentage of children with CECs levels exceeding 2.5 per 10^3 platelets, indicating significant endothelial dysfunction.

Endothelin-1 Levels

Endothelin-1 concentrations were assessed across both control and main study groups (Figure 3). The healthy control group had an average endothelin-1 level of 0.32 ± 0.02 fmol/mL. In the SARS-CoV-2 control group, the endothelin-1 level was slightly higher at 0.35 fmol/mL. In the main groups, children with BOS without a history of SARS-CoV-2 infection had endothelin-1 levels of 0.39 ± 0.01 fmol/mL, while the highest levels were observed in the group of children who developed BOS following SARS-CoV-2 infection, with an average of 0.46 ± 0.02 fmol/mL.

Figure 4 illustrates the gradation of endothelin-1 concentrations among the groups. The distribution of endothelin-1 levels shifted towards higher values in children with BOS, particularly in those with a prior SARS-CoV-2 infection. The healthy control group primarily had endothelin-1 concentrations below 0.40 fmol/mL, whereas in the BOS post-SARS-CoV-2 group, more than half of the children had endothelin-1 levels exceeding 0.50 fmol/mL. This trend highlights the potential role of endothelial dysfunction in the pathogenesis of BOS following SARS-CoV-2 infection.

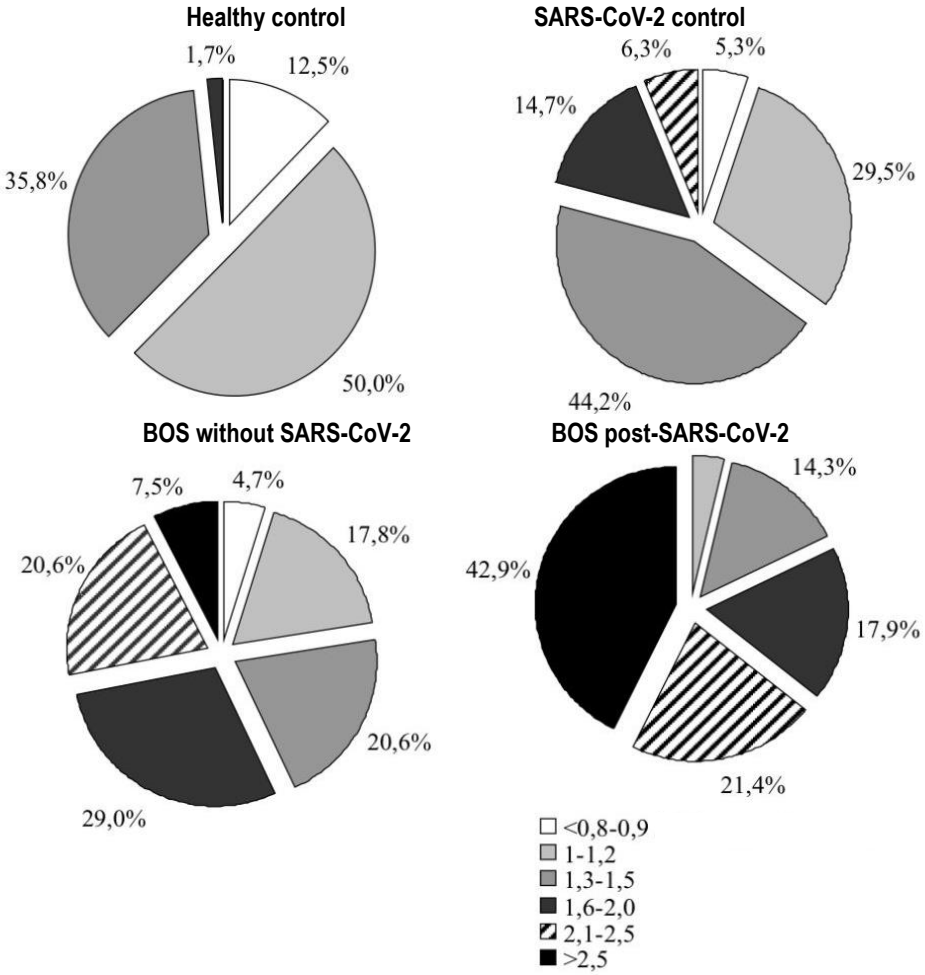

Figure 2. Distribution of Circulating Endothelial Cell Levels Across Study Groups.

Figure illustrates the distribution of CECs levels among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradients correspond to specific concentration ranges: <0,8-0,9 per10^9 platelets,1-1,2 per10^3 platelets, 1,3-1,5 per10^3 platelets, 1,6-2,0 per10^3 platelets, 2,1-2,5 per10^3 platelets, >2,5 per10^3 platelets.

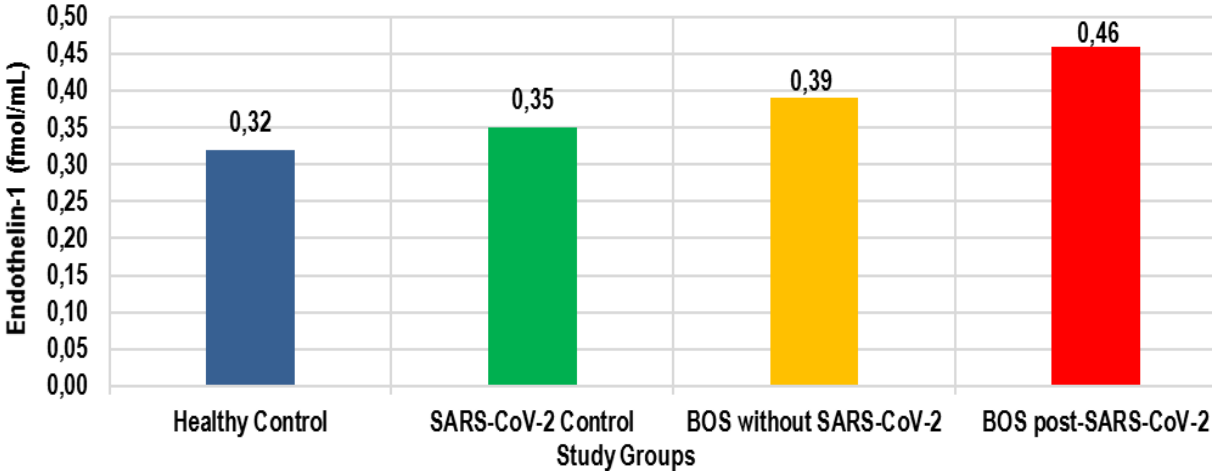

Figure 3. Levels of Endothelin-1 in Children Across Study Groups.

The graph illustrates the mean endothelin-1 concentrations (fmol/mL) in children from the study groups: Control (healthy control and SARS-CoV-2 control), BOS without SARS-CoV-2 infection, and BOS post-SARS-CoV-2 infection.

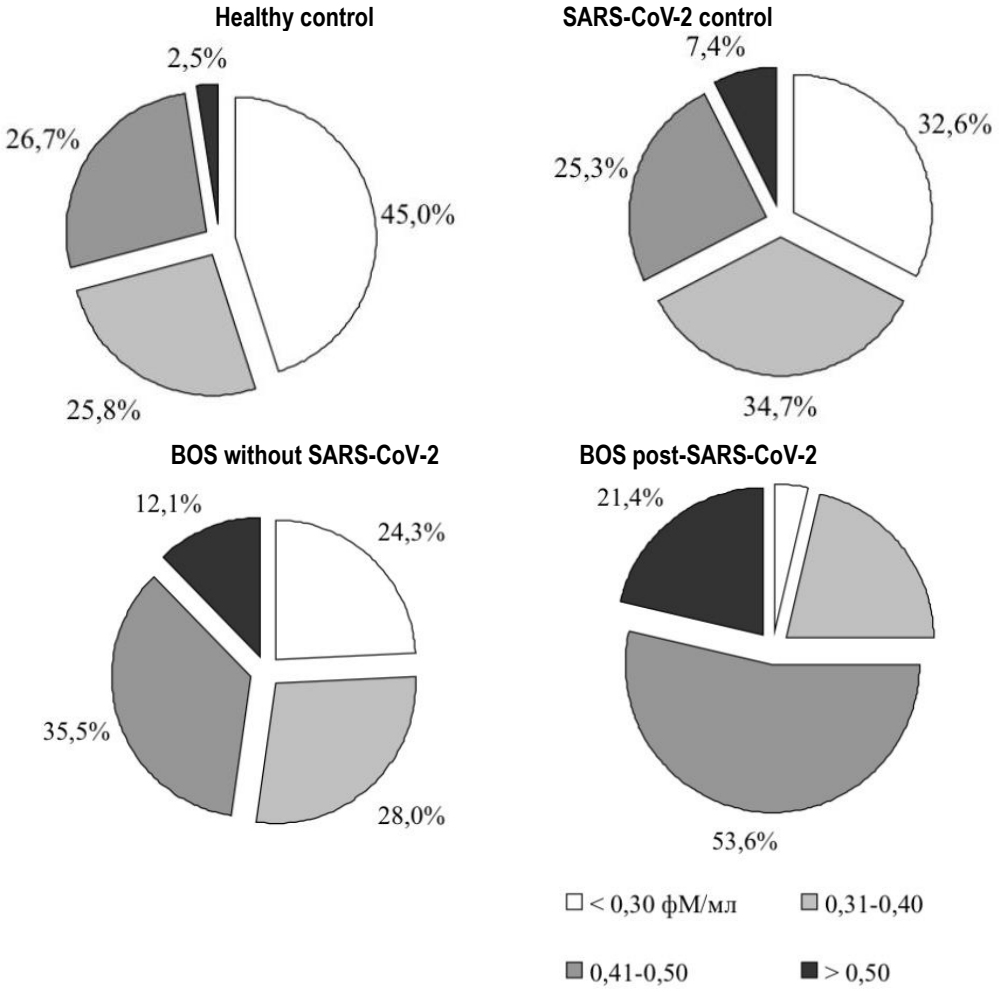

Figure 4. Distribution of Endothelin-1 Concentrations Across Study Groups.

Figure shows the gradation of endothelin-1 concentrations among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradient corresponds to specific concentration ranges: < 0.30 fmol/mL, 0.31–0.40 fmol/mL, 0.41–0.50 fmol/mL, > 0.50 fmol/mL.

Nitric Oxide (NO) Metabolites

The levels of NO metabolites varied across the different study groups (Figure 5). The healthy control group had an average NO metabolite level of 3.3 ± 0.2 µM/L. The SARS-CoV-2 control group, which included children with a history of SARS-CoV-2 infection but no BOS, showed a slightly lower average of 3.2 ± 0.2 µM/L.

In the main groups, the children with BOS but no history of SARS-CoV-2 infection had a NO metabolite level of 3.1 ± 0.3 µM/L, while the lowest level was observed in the group with BOS post-SARS-CoV-2 infection, which had an average of 2.2 ± 0.1 µM/L.

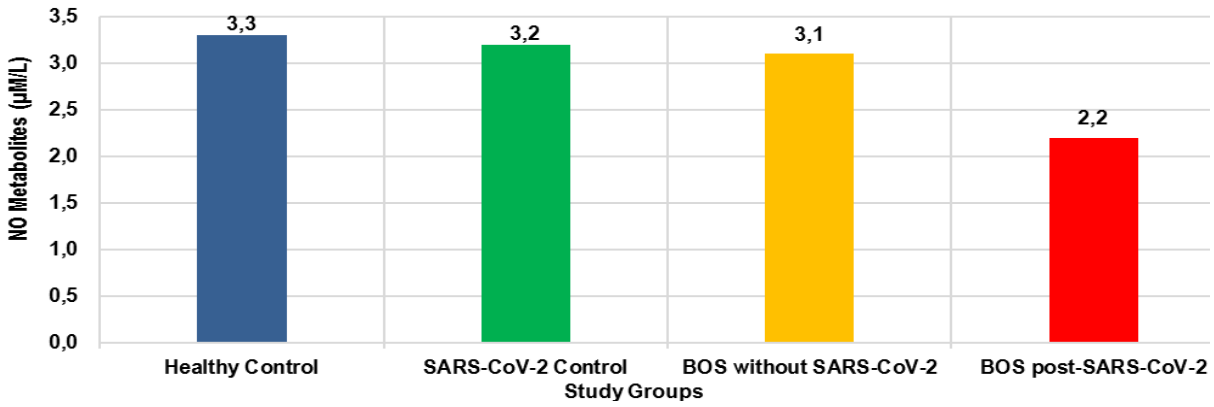

Figure 5. Levels of Nitric Oxide Metabolites in Children Across Study Groups.

The graph illustrates the mean NO metabolite levels (µM/L) in children from the control (healthy control and SARS-CoV-2 control) and main groups (BOS without SARS-CoV-2 and BOS after SARS-CoV-2).

Figure 6 shows the distribution of NO metabolite levels among the study groups. The majority of children in the healthy control and SARS-CoV-2 control groups had NO metabolite levels between 3.0–3.5 μM/L. However, in children with BOS, particularly those with a history of SARS-CoV-2 infection, NO levels shifted downward, with a higher proportion of individuals having concentrations below 2.5 μM/L. This reduction suggests impaired endothelial function and nitric oxide bioavailability in these patients.

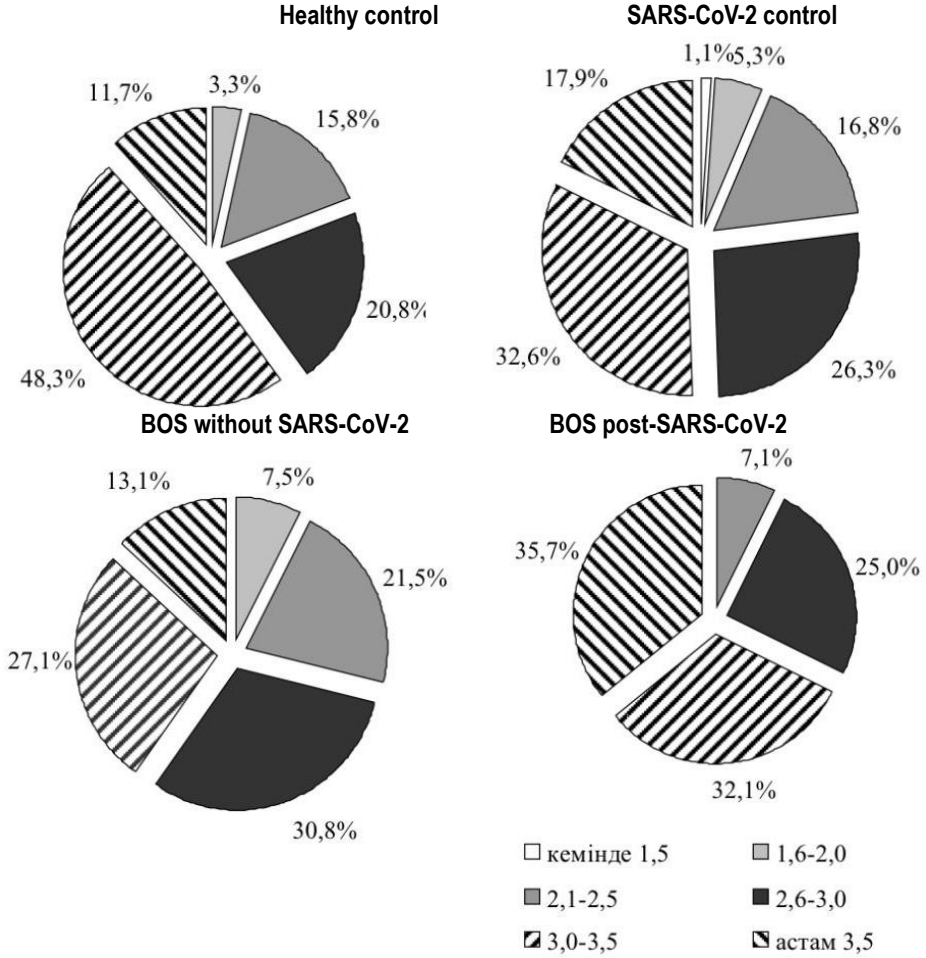

Figure 6. **Distribution of Nitric Oxide Metabolite Levels Across Study Groups.**

Figure illustrates the distribution of NO metabolite levels among the study groups: Control (healthy control and SARS-CoV-2 control) and Main Group (BOS without SARS-CoV-2 and BOS after SARS-CoV-2). The color gradient corresponds to specific concentration ranges: < 1,5 μM/L, 1,6-2,0 μM/L, 2,1-2,5 μM/L, 2,6-3,0 μM/L, 3,0-3,5 μM/L, > 3,5 μM/L.

Thus, the data demonstrate that SARS-CoV-2 infection (especially when followed by the development of BOS) leads to significant endothelial dysfunction, as reflected by increased levels of CECs and endothelin-1, alongside decreased levels of NO metabolites. These changes are most pronounced in children who developed BOS post-SARS-CoV-2 infection, suggesting a synergistic effect of the infection and the development of BOS on endothelial damage.

Discussion. The SARS-CoV-2 pandemic has been associated with a variety of negative health outcomes, some of which persist long after recovery. One of the most significant findings in adults is the development of endothelial dysfunction, which plays a central role in the pathogenesis of cardiovascular and systemic complications [8-11]. The endothelium is particularly vulnerable to SARS-CoV-2 due to the virus's binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is widely expressed on endothelial cells [12]. However, much less is known about the impact of COVID-19 on endothelial function in children, particularly with respect to post-infection syndromes like broncho-obstructive syndrome (BOS).

Endothelial dysfunction is recognized for its involvement in regulating vascular tone, hemostasis, and the repair of damaged blood vessels, all of which are crucial for maintaining cardiovascular health [13,14]. This dysfunction, when it occurs, disrupts normal vascular homeostasis, potentially leading to a cascade of pathophysiological consequences. In adults, endothelial dysfunction has been implicated in various organ systems, including the kidneys, lungs, and gastrointestinal tract [16-20]. However, research on how endothelial dysfunction affects children after SARS-CoV-2 infection, especially in the context of BOS, remains limited.

Our study highlights the significant role that endothelial dysfunction plays in pediatric patients post-COVID-19, particularly in those who develop BOS. The findings show that children with COVID-19 who subsequently developed BOS had markedly higher levels of circulating endothelial cells (CECs) and endothelin-1, alongside reduced nitric oxide (NO) metabolites. Specifically, CECs were elevated to

3.3 ± 0.2 per 10^3 platelets, endothelin-1 levels were increased to 0.46 ± 0.02 fmol/mL, and NO metabolites were reduced to 2.2 ± 0.1 μM/L. These changes in endothelial markers point to a disruption in endothelial function, which may contribute to the development of post-COVID-19 complications, including BOS.

Interestingly, children who had SARS-CoV-2 infection but did not develop BOS exhibited moderate endothelial dysfunction, with elevated CECs (1.8 ± 0.1 per 10^3 platelets). However, the combination of SARS-CoV-2 infection and BOS led to a much more pronounced effect on endothelial health. This group showed the highest levels of CECs and endothelin-1, paired with the lowest levels of NO metabolites. This finding suggests that SARS-CoV-2 infection and BOS may act synergistically, amplifying endothelial damage and worsening post-viral complications. This aligns with previous findings in adults, where endothelial dysfunction has been linked to the severity of COVID-19 outcomes [8-11]. Notably, this study is one of the first to demonstrate these effects in children, specifically in relation to BOS.

The elevated CEC levels observed in children with BOS post-SARS-CoV-2 infection (64.3% prevalence) further support the notion of significant endothelial dysfunction in this group. These findings are consistent with the endothelial damage observed in adults with COVID-19, reinforcing the idea that endothelial injury is central to the clinical severity of post-viral complications. Additionally, the reduction in NO metabolites in children with BOS suggests that impaired nitric oxide production is contributing to vasoconstriction, inflammation, and thrombosis. This could help explain the increased risk of severe respiratory complications in these children, as impaired NO synthesis compromises vascular tone and immune function.

Moreover, the elevated endothelin-1 levels in children with BOS post-SARS-CoV-2 infection suggest a link between endothelial dysfunction and bronchial hyperreactivity and airway obstruction. Endothelin-1 is a potent vasoconstrictor and is known to play a role in airway remodeling and inflammation. Our data support the hypothesis that endothelial dysfunction exacerbates these processes, contributing to the development and worsening of BOS.

These findings underscore the potential for targeting endothelial dysfunction as a therapeutic strategy in children who develop BOS following SARS-CoV-2 infection. Future research should focus on exploring interventions aimed at restoring endothelial function to mitigate long-term health consequences and improve clinical outcomes in this vulnerable population.

Limitations of the study.

This study has several limitations that should be considered when interpreting the findings.

One notable limitation is the absence of longitudinal follow-up data. Without tracking the children over an extended period, it is challenging to assess the long-term effects of endothelial dysfunction. It remains uncertain whether the observed endothelial changes persist or resolve with time.

Additionally, while the study carefully categorized participants based on SARS-CoV-2 infection status and the presence of BOS, there may be unmeasured confounding factors that could influence the results. Factors such as pre-existing respiratory conditions, genetic predispositions, or environmental exposures could contribute to endothelial dysfunction and the development of BOS.

Conclusion.

SARS-CoV-2 infection results in significant endothelial dysfunction in children, particularly in those who develop BOS. The presence of BOS post-SARS-CoV-2 infection leads to exacerbated endothelial damage, as evidenced by elevated levels of circulating endothelial cells and endothelin-1, alongside reduced nitric oxide metabolites. These alterations in endothelial function suggest that the combination of BOS and SARS-CoV-2 infection may synergistically worsen endothelial injury.

The observed endothelial dysfunction is likely to contribute to bronchial hyperreactivity, inflammation, and airway obstruction, emphasizing its role in the pathophysiology of BOS. This dysfunction could be an important factor in the long-term respiratory complications experienced by children who have had COVID-19.

Given these findings, further studies are needed to explore the underlying mechanisms of endothelial dysfunction in pediatric COVID-19 and develop potential therapeutic strategies to mitigate the long-term effects of endothelial injury and improve clinical outcomes for affected children.

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LONG-TERM CONSEQUENCES OF CORONAVIRUS INFECTION (SARS-COV-2) IN WOMEN OF CHILDBEARING AGE

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Abstract

Introduction: The long-term effects of COVID-19 on women's general and reproductive health remain insufficiently studied.

Aim: To evaluate the overall and reproductive health status of women after COVID-19, as well as the prevalence and nature of long-lasting post-COVID symptoms.

Methods: A descriptive study was conducted using a questionnaire collecting data on age, height, health status before and after COVID-19, pregnancy and delivery outcomes, frequency of medical consultations, and duration and nature of post-COVID symptoms. Data analysis was performed with IBM SPSS Statistics 19.

Results: Approximately 80% (n≈239) of women aged 21–35 rated their pre-COVID health as good or better; after infection, the proportion of "very good" ratings decreased to 3.7%. Preterm births and miscarriages accounted for 32%. Post-COVID symptoms (fatigue, musculoskeletal pain, sleep disturbances, hair loss, reduced skin elasticity) persisted for more than 3 months in most respondents.

Conclusions: COVID-19 exerts a prolonged negative impact on the general and reproductive health of women of reproductive age. These findings emphasize the need for comprehensive evaluation and rehabilitation strategies post-infection.

Keywords: *COVID-19, women's health, reproductive health, post-COVID syndrome, long-term symptoms*

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Резюме

ДОЛГОСРОЧНЫЕ ПОСЛЕДСТВИЯ КОРОНАВИРУСНОЙ ИНФЕКЦИИ (SARS-COV-2) У ЖЕНЩИН ФЕРТИЛЬНОГО ВОЗРАСТА

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Введение: Долгосрочное влияние перенесенной коронавирусной инфекции (COVID-19) на общее и репродуктивное здоровье женщин остается недостаточно изученным.

Цель: Оценить общее и репродуктивное здоровье женщин после COVID-19, а также распространенность и характер постковидных симптомов.

Методы: Проведено описательное исследование с использованием анкетирования. Сбор данных включал возраст, рост, состояние здоровья до и после COVID-19, исходы беременности и родов, частоту обращений к врачам, длительность и характер постковидных симптомов. Анализ выполнен с помощью IBM SPSS Statistics 19.

Результаты: Около 80% (n≈239) женщин 21–35 лет оценивали здоровье до COVID-19 как хорошее или лучше; после инфекции доля «очень хороших» оценок снизилась до 3,7%. Преждевременные роды и выкидыши составили 32%. Постковидные симптомы (усталость, боли в мышцах и суставах, нарушения сна, выпадение волос, снижение упругости кожи) сохранялись более 3 месяцев у большинства респонденток.

Выводы: COVID-19 оказывает негативное длительное влияние на общее и репродуктивное здоровье женщин репродуктивного возраста. Полученные данные подчеркивают необходимость комплексной оценки и реабилитации после перенесенной инфекции.

Ключевые слова: *COVID-19, женское здоровье, репродуктивное здоровье, постковидный синдром, длительные симптомы*

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Түйіндеме

ФЕРТИЛЬДІ ЖАСТАҒЫ ӘЙЕЛДЕРДЕГІ КОРОНАВИРУСТЫҚ ИНФЕКЦИЯНЫҢ (SARS-COV-2) ҰЗАҚ МЕРЗІМДІ САЛДАРЫ

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Кіріспе: COVID-19 індетін бастан өткерген әйелдердің жалпы денсаулық жағдайы мен репродуктивтік функциясына әсері толық анықталмаған.

Мақсаты: COVID-19 індетін өткерген әйелдердің жалпы және репродуктивтік денсаулық жағдайын, ұзақ мерзімді постковидтік белгілердің таралуын бағалау.

Әдістер: Зерттеу сипаттамалық кескінді зерттеу үлгісінде жүргізілді. Респонденттерге жас, бой, COVID-19-ға дейінгі және кейінгі денсаулық жағдайы, жүктілік және босану нәтижелері, медициналық көмекке жүгіну жиілігі, постковидтік белгілердің ұзақтығы мен сипаты туралы сауалнама жүргізілді. Нәтижелер IBM SPSS Statistics 19 бағдарламасымен талданды.

Нәтижелер: 21–35 жас аралығындағы әйелдердің 80%-да (n≈239) жалпы денсаулық жағдайы COVID-19-ға дейін жақсы деп бағаланды (шамамен 80%), алайда аурудан кейін «өте жақсы» бағасы 3,7%-ға, «жақсы» 44,3%-ға дейін төмендеді. Мерзімінен бұрын босану және түсік жағдайлары 32%-ды құрады. Постковидтік белгілердің қатарында қатты шаршау, бұлшықет-буын аурулары, ұйқының бұзылуы, шаштың түсуі, тері серпімділігінің төмендеуі жиі байқалды. Көпшілігінде (шамамен 60%-дан астам) белгілер 3 айдан аса уақытқа созылды.

Қорытынды: COVID-19 әйелдердің жалпы және репродуктивтік денсаулығына ұзақ мерзімді теріс әсерін тигізеді. Алынған мәліметтер репродуктивтік жастағы әйелдерде постковидтік синдромның кешенді бағасы мен оңалту шараларының маңыздылығын көрсетеді.

Түйінді сөздер*: COVID-19, әйелдер денсаулығы, репродуктивтік денсаулық, постковидтік синдром, ұзақ мерзімді белгілер.*

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Introduction

The coronavirus infection caused by the SARS-CoV-2 virus presents a significant challenge to contemporary medicine and public health. Since 2020, the pandemic has assumed a global scale, profoundly altering the lives of millions. In addition to the conventional respiratory symptoms (dry cough, shortness of breath, fever), recent investigations have concentrated on the long-term repercussions of the COVID-19 epidemic, elucidating its effects on various bodily systems, including the reproductive system of women of childbearing age [1], [2].

The potential influence of SARS-CoV-2 on female reproductive health is posited to stem from the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors in reproductive tissues, such as the ovary and endometrium. These receptors are integral to viral entry into cells and the regulation of physiological processes pertinent to fertility [3], [4]. The pronounced expression of ACE2 in the endometrium, coupled with its age-dependent characteristics, suggests an age-specific vulnerability to tissue infection, necessitating further inquiry [5], [6]. However, conflicting evidence regarding the absence of viral detection in vaginal and cervical tissues [7], [8] underscores the necessity of clarifying the mechanisms by which the virus impacts the reproductive system.

The ramifications of the COVID-19 pandemic on the hormonal system and menstrual cycle are currently subjects of active discourse within the scientific literature. The significance of investigating the long-term consequences of the COVID-19 pandemic on women of childbearing age is underscored by observed alterations in the menstrual cycle, diminished ovarian reserve in women over 35 years of age, and severe forms of the disease, as well as potential risks associated with the endometrium [9], [10]. Conversely, other studies indicate that hormonal profiles and ovarian reserve do not exhibit average changes in women experiencing mild disease manifestations [11], [12].

Infection has been demonstrated to influence the frequency, nature, and duration of menstrual cycles. Symptoms associated with post-COVID syndrome, including chronic fatigue and joint and muscle pain, have garnered widespread attention within the scientific community [13]. Women may exhibit heightened susceptibility to substantial changes in overall health relative to men. Moreover, COVID-19 may induce alterations in body mass, skin condition, hair loss, and other physical manifestations. The utilization of contraceptive methods and pregnancy planning assumes particular importance among women affected by COVID-19, as post-COVID complications may hinder safe conception and childbirth [14].

The COVID-19 pandemic has transformed the way patients seek medical care. Among women, there has been an increase in visits to healthcare professionals for preventive check-ups related to reproductive health, alongside a deterioration in overall health status. However, concerns persist regarding the availability and quality of medical care provided [15].

Additionally, the pandemic has profoundly affected psycho-emotional well-being. Women have reported elevated levels of anxiety, depression, and sleep disturbances, attributed not solely to the infection but also to stress arising from socio-economic fluctuations [16].

Although numerous international studies have examined the impact of COVID-19 on women's health, there exists a paucity of data reflecting the regional specificities of Kazakhstan [17]. This study aims to address this gap and formulate recommendations for enhancing the organization of gynecological care during the pandemic and post-pandemic periods. Consequently, this research will elucidate key aspects of the COVID-19 epidemic's impact on women's reproductive health, overall health, psycho-emotional state, and contraceptive use, while assessing the frequency of medical care-seeking behavior.

The primary objective of this study is to evaluate the long-term consequences of coronavirus infection (SARS-CoV-2) in women of childbearing age, with a particular emphasis on alterations in the menstrual cycle, ovarian reserve, and endometrium.

Objectives of the Study:

1. To ascertain the incidence of premature birth, miscarriage, and variability in menstrual cycle frequency among women affected by COVID-19.

2. To compare self-assessed general health status prior to and subsequent to COVID-19, and determine the prevalence of chronic fatigue, joint and muscle pain, and other symptoms associated with post-COVID syndrome.

3. To investigate the frequency and rationale behind women's visits to medical institutions, including gynecological assessments, following COVID-19.

4. To evaluate the influence of COVID-19 on psycho-emotional health (anxiety, sleep disturbances), physical changes (body weight, skin condition, hair loss), and challenges concerning contraceptive use and pregnancy planning.

The findings of this study will provide a foundation for addressing existing gaps in the understanding of the impact of COVID-19 on women's reproductive health and for the development of effective preventive and therapeutic measures.

Methodology

Type of Study

This study is a cross-sectional observational quantitative research aimed at examining the impact of COVID-19 on women's reproductive health in Kazakhstan. The collected data allowed for consideration of seasonal variations in respiratory diseases.

Participant Selection Method

Women who had previously contracted COVID-19 were selected from the initial population using a simple random sampling method. Participation in the study was voluntary.

Inclusion Criteria:

– Women aged 18–50 years;

– A confirmed COVID-19 diagnosis based on medical records;

– Provision of written informed consent [18].

Exclusion Criteria:

– Presence of severe chronic diseases that could influence the results (e.g., oncological diseases, hematologic disorders, uncontrolled diabetes);

– Pregnancy at the time of completing the questionnaire.

The initial calculations were based on the minimum sample size required for testing statistical hypotheses (significance level $\alpha=0.05$; statistical power $\beta=0.80$). A total of 607 participants were selected for the study, ensuring sufficient statistical power for the analysis.

Measurement Methodology

Data were collected using a questionnaire consisting of 30 questions, categorized as follows:

– Socio-demographic data (age, height, etc.);

– Subjective assessment of overall health status before and after COVID-19;

– Symptoms associated with post-COVID syndrome;

– Reproductive health and contraception usage.

All data were gathered in a standardized format through either personal interviews or online surveys.

Data Processing and Analysis Methods

Data were processed using IBM SPSS Statistics 19 software. The processing stages included: verifying data completeness and accuracy, calculating frequencies, means (M), standard deviations (SD), and medians (Me); hypothesis testing using parametric and non-parametric methods (Student's t-test for independent samples, chi-square test for categorical data analysis, correlation analysis using Pearson's coefficient for normal distribution and Spearman's coefficient for non-normal distribution).

The normality of distribution was assessed using the Shapiro-Wilk test. A significance level of $p<0.05$ was

considered statistically significant. Confidence intervals were also calculated for key parameters. When necessary, multivariate analysis methods were employed to interpret interrelationships.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision) and was approved by the relevant medical institution's ethics committee [19]. Participants provided written informed consent for participation and data processing. Personal information was anonymized and used solely for research purposes. All described methods were developed and applied in strict adherence to the study protocol, ensuring the possibility of replicating the study under similar conditions.

Results

The following data present the demographic analysis of the sample. The study group primarily consisted of women of active reproductive age (21–35 years) and of average height (mostly between 161–170 cm). Thus, the sample was relatively homogeneous in terms of age and anthropometric characteristics.

Analyzing age distribution, the majority of participants were aged between 21 and 35 years (approximately 80%). Women under 20 and over 40 were represented in minimal proportions, indicating that the sample was concentrated within the reproductive age range (Table 1).

Table 1

Age Structure Results.

Age	Number of Participants (N)	Percentage (%)
Under 20	1	0.3%
21–30	130	43.3%
31–35	109	36.3%
36–40	52	17.3%
Over 40	8	2.7%

The majority of respondents were between 161–170 cm in height (approximately 42%), while those ranging from 151–180 cm accounted for nearly 90% of the sample. No participants were shorter than 150 cm, while only 10% exceeded 180 cm in height.

Table 2

Distribution and Normality Test Results.

Variable	Mean (M)	Standard Deviation (SD)	Median (Me)	Shapiro-Wilk (p-value)	Normality (Yes/No)
Age	31.2	6.7	30	0.045	No
Height	165.3	5.8	165	0.134	Yes
General health before COVID-19	4.2	0.8	4	0.032	No
General health after COVID-19	3.7	0.9	3.5	0.021	No

The table above presents the distribution and normality of key quantitative variables. According to the Shapiro-Wilk test, the variables "age," "general health before COVID-19," and "general health after COVID-19" did not meet normality assumptions ($p < 0.05$). However, the "height" variable followed a normal distribution ($p = 0.134$). These findings indicate the need for non-parametric statistical methods.

Table 3

Correlation Analysis

Variables	Pearson (r)	Spearman (ρ)	p-value
Age ↔ General health before COVID-19	-0.35	-0.32	<0.001
Age ↔ General health after COVID-19	-0.42	-0.39	<0.001
Height ↔ General health after COVID-19	0.12	0.15	0.032

This table presents the correlation between key variables. A negative correlation was observed between age and general health before COVID-19 (Pearson's $r = -0.35$, Spearman's $\rho = -0.32$, $p < 0.001$), indicating that older women rated their health lower. Similarly, a negative correlation was found between age and general health after COVID-19 ($r = -0.42$, $\rho = -0.39$, $p < 0.001$). Additionally, a weak positive correlation was observed between height and general health after COVID-19 ($r = 0.12$, $\rho = 0.15$, $p = 0.032$), suggesting that taller women rated their health slightly better.

Table 4

Group Comparisons for Key Indicators

Variable	Group 1 (M ± SD)	Group 2 (M ± SD)	p-value (t-test)	p-value (Mann-Whitney)
General health before COVID-19	4.3 ± 0.7	3.9 ± 0.9	0.012	0.018
General health after COVID-19	3.8 ± 0.9	3.4 ± 1.1	0.045	0.054

The table presents the comparison results between groups. A significant difference was found in general health before COVID-19 between Group 1 (mean = 4.3 ± 0.7) and Group 2 (mean = 3.9 ± 0.9) ($p = 0.012$). A statistically significant difference was also observed in general health after COVID-19 ($p = 0.045$), indicating variations in post-COVID health conditions among different groups.

Table 5

Regression Analysis Results

Variable	Coefficient (B)	Standard Error (SE)	p-value	95% CI (Lower–Upper)
Age	-0.15	0.05	<0.001	-0.25 – -0.05
Post-COVID fatigue	-0.20	0.08	0.032	-0.36 – -0.04
General health before COVID-19	0.30	0.10	0.002	0.10 – 0.50

The results of the regression analysis show that older women had lower overall health levels (coefficient B = -0.15, p < 0.001), and those experiencing post-COVID fatigue also exhibited a decline in health (B = -0.20, p = 0.032). In contrast, better general health before COVID-19 had a positive effect on post-COVID health outcomes (B = 0.30, p = 0.002). The 95% confidence intervals confirm the statistical significance of these variables.

Table 6

Univariate Analysis.

Question No.	Category (Frequency >5%)	n	(%)
1	2	3	4
1. Your Age	21–30 years	130	43.3%
	31–35 years	109	36.3%
	36–40 years	52	17.3%
2. Your Height	151–160 cm	68	22.7%
	161–170 cm	127	42.3%
	171–180 cm	75	25.0%
	Above 180 cm	30	10.0%
3. Health Status Before Experiencing COVID-19	Very good	38	12.7%
	Good	202	67.3%
	Satisfactory	59	19.7%
4. Health Status After Experiencing COVID-19	Very good	11	3,7%
	Good	133	44.3%
	Satisfactory	152	50.7%
5. Pregnancy Outcome During COVID-19	Full-term birth (≥37 weeks)	204	68.0%
	Preterm birth (22–36.6 weeks)	91	30.3%
6. Number of Births During COVID-19	First	45	15.0%
	Second	58	19.3%
	Third or more	197	65.7%
7. Doctor Visits in the Last Year (After COVID-19)	No	172	57.3%
	Yes, once	119	39.7%
8. Reason for Doctor Visit	Acute illness	18	6.0%
	Feeling unwell	94	31.3%
	Preventive check-up	180	60.0%
9. Acute Respiratory Illness in the Last Year (Flu, etc.)	No	108	36.0%
	Yes, once	84	28.0%
	Yes, twice or more	108	36.0%
10. Presence of Chronic Diseases (Hypertension, Diabetes, etc.)	No	300	100%
11. Severe Fatigue, Weakness, Decreased Work Capacity	No	114	38.0%
	Yes, first 3 months	90	30.0%
	Yes, first 6 months	46	15.3%
	Yes, more than 6 months	50	16.7%
12. Muscle, Bone, and Joint Pain	No	116	38.7%
	Yes, first 3 months	91	30.3%
	Yes, first 6 months	46	15.3%
	Yes, more than 6 months	47	15.7%
13. Unusual Headaches	No	128	42.7%
	Yes, first 3 months	86	28.7%
	Yes, first 6 months	41	13.7%
	Yes, more than 6 months	45	15.0%
14. Visual Floaters, Dizziness, Tinnitus	No	131	43.7%
	Yes, first 3 months	95	31.7%
	Yes, first 6 months	36	12.0%
	Yes, more than 6 months	38	12.7%
15. Chest Pain, Palpitations, Blood Pressure Fluctuations	No	143	47.7%
	Yes, first 3 months	82	27.3%
	Yes, first 6 months	36	12.0%
	Yes, more than 6 months	39	13.0%
16. Excessive Sweating, Hot Flashes	No	132	44.0%
	Yes, first 3 months	92	30.7%
	Yes, first 6 months	37	12.3%
	Yes, more than 6 months	39	13.0%

Continuation of the table 1.

1	2	3	4
17. Chest Tightness, Breathing Difficulties	No	130	43.3%
	Yes, first 3 months	94	31.3%
	Yes, first 6 months	40	13.3%
	Yes, more than 6 months	36	12.0%
18. Unexplained Fear, Anxiety, Suicidal Thoughts	No	291	97.0%
19. Sleeping Difficulties (Insomnia at Night, Drowsiness During the Day)	No	122	40.7%
	Yes, first 3 months	95	31.7%
	Yes, first 6 months	42	14.0%
	Yes, more than 6 months	41	13.7%
20. Skin Rashes	No	292	97.3%
21. Hair Loss	No	112	37.3%
	Yes, first 3 months	90	30.0%
	Yes, first 6 months	47	15.7%
	Yes, more than 6 months	51	17.0%
22. Body Weight Changes (Weight Loss/Gain)	No	276	92.0%
	Yes, first 3 months	22	7.3%
23. Skin Dryness and Decreased Elasticity	No	133	44.3%
	Yes	167	55.7%
24. Libido Disorders	No	194	64.7%
	Yes, first 3 months	78	26.0%
	Yes, first 6 months	23	7.7%
25. Changes in Menstrual Regularity and Characteristics	No	239	79.7%
	Yes	61	20.3%
26. Difficulties in Planning the Next Pregnancy	No	232	77.3%
	Yes	68	22.7%
27. Postpartum Scheduled Gynecological Examination	No	236	78.7%
	Yes	64	21.3%
28. Abnormalities Detected During Routine Check-up	No	212	70.7%
	Yes	88	29.3%
29. Consideration of Pregnancy Planning Information	No	188	62.7%
	Yes	37	12.3%
	I don't know about such information	75	25.0%
30. Contraception if Not Planning the Next Pregnancy	No protection (nothing used)	190	63.3%
	Protection used (all methods combined)	110	36.7%
	Intrauterine device	97	32.3%

An analysis of respondents' overall health status before contracting COVID-19 revealed that approximately 80% rated their health as "good" or better. Specifically, 67.3% assessed their health as "good," 12.7% as "very good," and 0.3% as "excellent." Notably, no respondents rated their health as "poor" before the infection. However, after experiencing COVID-19, these ratings changed: the proportion of respondents rating their health as "very good" dropped to 3.7%, while those considering it "good" decreased to 44.3%. The "excellent" category disappeared entirely, and the "satisfactory" category increased to 50.7%, with 1.3% rating their health as "poor." This indicates a general deterioration in health following COVID-19.

Among women who were pregnant during the pandemic, 68% had full-term deliveries (≥37 weeks), while 30.3% experienced preterm births (22–36.6 weeks), and 1.7% had miscarriages after 12 weeks. These findings suggest that COVID-19 may have influenced pregnancy outcomes, increasing the risk of complications. Additionally, among women who gave birth during the pandemic, only 15% were first-time mothers, while 19.3% were experiencing their second childbirth, and 65.7% had their third or more childbirths, indicating a relatively experienced group of respondents.

The frequency of medical visits post-COVID-19 revealed that 57.3% of respondents did not consult a doctor in the past year, while 39.7% had one visit, and 3% sought medical attention twice or more. The reasons for seeking medical care were as follows: 60% underwent routine check-ups, 31.3% reported nonspecific discomfort, 6% sought care due to acute illness, and 2.7% required medical attention due to chronic disease exacerbation. Notably, none of the respondents had pre-diagnosed chronic diseases before the pandemic, which may require further investigation.

The incidence of acute respiratory infections in the year following COVID-19 varied: 36% did not experience any respiratory illnesses, 28% reported being sick once, and 36% suffered from respiratory infections twice or more. This suggests variable immune responses, where some individuals may have developed increased resistance to

respiratory pathogens, while others exhibited increased susceptibility.

A univariate analysis identified the widespread persistence of post-COVID symptoms over time. Overall, 62% of respondents reported experiencing severe fatigue, weakness, and reduced work capacity (30% within the first three months, 15.3% up to six months, and 16.7% beyond six months). Similar trends were observed for musculoskeletal pain (61.3%), headaches (approximately 57%), vision and hearing disturbances (56.3%), cardiac discomfort (52.3%), excessive sweating (56%), and respiratory difficulties (56.7%). Psycho-emotional disturbances were relatively rare (3%) but not entirely absent. Sleep disturbances were reported by 59.3% of respondents. Dermatological changes were infrequent (2.7%), but skin dryness and decreased elasticity were noted in 55.7% of cases. Hair loss was observed in 62.7% of respondents (30% within the first three months, 15.7% up to six months, and 17% beyond six months).

Reproductive health was also affected, with 20.3% reporting menstrual cycle irregularities and 22.7% experiencing difficulties in planning their next pregnancy. Libido disorders were reported by 35.3% (26% within the first three months, 7.7% up to six months, and 1.7% beyond six months). After childbirth during the pandemic, 78.7% of respondents did not undergo a scheduled gynecological examination, while 21.3% did, among whom 29.3% were diagnosed with abnormalities. Only 12.3% of respondents actively sought information about pregnancy planning, whereas 62.7% showed no interest, and 25% were unaware of such information. A significant proportion (63.3%) did not use any contraception, increasing the risk of unplanned pregnancies. Among those using contraception, 32.3% opted for intrauterine devices, 4.3% used hormonal methods, and no respondents reported using barrier methods.

For a more in-depth understanding, a multifactorial analysis (Appendix A) was conducted. This approach required grouping certain categories. For instance, while the univariate analysis categorized symptom duration into three periods (up to 3 months, up to 6 months, and beyond 6 months), the multifactorial analysis simplified this into two categories: "up to 3 months" and "more than 3 months." This helped streamline statistical modeling and better capture the long-term impact of symptoms. Similarly, preterm births and miscarriages were combined into a single 32% category, facilitating a more comprehensive evaluation of pregnancy complications.

Appendices 1.

Multifactorial Analysis Results.

Indicators		Group		p	CI [95% CI]
		Positive result	Negative result		
1. Your age:	Under 30 years old	131 (43,7%)	154 (51%)		-
	31-35 years old	109 (36,3%)	51 (16,9%)	0,059	0,23 [0,48-1,03]
	36-40 years old	52 (17,3%)	56 (18,5%)	0,666	0,52 [1,2-2,75]
	Above 40 years old	**8 (2,7%)**	**41 (13,6%)**	**<0,001**	**3,31 [14,73-65,58]**
2. Your height:	Up to 160 cm	68 (22,7%)	87 (28,8%)		-
	161-170 cm	127 (42,3%)	155 (51,3%)	0,476	0,4 [0,78-1,54]
	Above 171 cm	105 (35%)	60 (19,9%)	0,172	0,28 [0,59-1,26]
3. How would you rate your overall health before experiencing COVID-19?	Good	202 (67,3%)	228 (75,5%)		-
	Very good/excellent	39 (13%)	38 (12,6%)	0,510	0,25 [0,7-2]
	Satisfactory/poor	59 (19,7%)	36 (11,9%)	0,225	0,67 [1,93-5,59]
4. How would you rate your overall health after experiencing COVID-19?	Good	133 (44,3%)	202 (66,9%)		-
	Very good	11 (3,7%)	27 (8,9%)	0,724	0,33 [1,27-4,88]
	Satisfactory	156 (52%)	73 (24,2%)	0,233	0,21 [0,56-1,45]
5. If you were pregnant during the COVID-19 pandemic, how did your pregnancy end?	Full-term birth (≥37.0 weeks of pregnancy)	204 (68%)	285 (94,4%)		-
	Preterm birth (22.0-36.6 weeks of pregnancy), miscarriage	96 (32%)	17 (5,6%)	0,163	0,12 [0,42-1,42]
6. If you gave birth during the COVID-19 pandemic, which birth was it for you?	First	45 (15%)	66 (21,9%)		-
	Second	**58 (19,3%)**	**34 (11,3%)**	**0,016**	**0,12 [0,31-0,8]**
	Third or more	197 (65,7%)	202 (66,9%)	0,054	0,18 [0,42-1,02]
7. In the last year after having COVID-19, have you visited a doctor regarding your health?	No	172 (57,3%)	227 (75,2%)		-
	Yes, once	119 (39,7%)	54 (17,9%)	0,167	0,75 [1,97-5,14]
	Yes, two or more times	**9 (3%)**	**21 (7%)**	**<0,001**	**9,11 [93,57-961,18]**
9. In the last year after having COVID-19, have you experienced an acute respiratory illness (flu, parainfluenza, acute respiratory infections, acute respiratory viral infections)?	No	108 (36%)	232 (76,8%)		-
	Yes, once	**84 (28%)**	**32 (10,6%)**	**<0,001**	**0,04 [0,12-0,32]**
	Yes, two or more times	108 (36%)	38 (12,6%)	0,646	0,2 [0,73-2,75]
11. After having COVID-19, did you experience severe fatigue, general weakness, or reduced work capacity?	No	114 (38%)	261 (86,4%)		-
	Yes, in the first 3 months	90 (30%)	29 (9,6%)	0,073	0 [0,07-1,29]
	Yes, for more than 3 months	**96 (32%)**	**12 (4%)**	**<0,001**	**0 [0-0,07]**

Continuation ot he appendices 1.

1	2	3	4	5	6
12. After having COVID-19, did you notice the onset of muscle, bone, or joint pain?	No	116 (38,7%)	260 (86,1%)		-
	Yes, in the first 3 months	91 (30,3%)	29 (9,6%)	0,350	0,2 [4,29-91,36]
	Yes, for more than 3 months	93 (31%)	13 (4,3%)	0,221	0,27 [9,03-306,51]
13. After having COVID-19, did you experience non-specific headaches?	No	128 (42,7%)	259 (85,8%)		-
	Yes, in the first 3 months	86 (28,7%)	33 (10,9%)	0,971	0,08 [0,96-10,82]
	Yes, for more than 3 months	86 (28,7%)	10 (3,3%)	0,056	0 [0,05-1,08]
14. After having COVID-19, did you notice "floaters" in your vision, dizziness, tinnitus, or hearing loss?	No	131 (43,7%)	259 (85,8%)		-
	Yes, in the first 3 months	**95 (31,7%)**	**33 (10,9%)**	**0,013**	**2,49 [70,48-1997,32]**
	Yes, for more than 3 months	**74 (24,7%)**	**10 (3,3%)**	**0,024**	**1,77 [72,14-2945,56]**
15. After having COVID-19, did you experience chest pain, frequent heart palpitations, or changes in your usual blood pressure levels (either high or low)?	No	143 (47,7%)	262 (86,8%)		-
	Yes, in the first 3 months	82 (27,3%)	30 (9,9%)	0,113	0,58 [9,75-162,76]
	Yes, for more than 3 months	75 (25%)	10 (3,3%)	0,844	0,04 [1,45-59,97]
16. After having COVID-19, did you notice excessive sweating at night or during the day, or sudden hot flashes?	No	132 (44%)	264 (87,4%)		-
	Yes, in the first 3 months	92 (30,7%)	27 (8,9%)	0,645	0,14 [1,83-23,96]
	Yes, for more than 3 months	76 (25,3%)	11 (3,6%)	0,654	0,04 [0,54-8,04]
17. After having COVID-19, did you notice a feeling of chest tightness or breathing difficulties?	No	130 (43,3%)	263 (87,1%)		-
	Yes, in the first 3 months	**94 (31,3%)**	**29 (9,6%)**	**0,048**	**0 [0,05-0,98]**
	Yes, for more than 3 months	76 (25,3%)	10 (3,3%)	0,582	0,01 [0,36-13,78]
19. Since having COVID-19, have you had trouble sleeping (insomnia at night, drowsiness during the day)?	No	122 (40,7%)	259 (85,8%)		-
	Yes, in the first 3 months	95 (31,7%)	29 (9,6%)	0,951	0,05 [0,91-16,82]
	Yes, for more than 3 months	83 (27,7%)	14 (4,6%)	0,083	0,63 [32,66-1691,51]
21. After having COVID-19, did you notice hair loss?	No	112 (37,3%)	261 (86,4%)		-
	Yes, in the first 3 months	**90 (30%)**	**26 (8,6%)**	**0,002**	**0 [0,01-0,17]**
	Yes, for more than 3 months	**98 (32,7%)**	**15 (5%)**	**0,005**	**0 [0,01-0,21]**
23. Since having COVID-19, has your skin become dry and less elastic?	Yes	167 (55,7%)	35 (11,6%)		-
	No	133 (44,3%)	267 (88,4%)	0,079	0,81 [6,48-52,06]
24. After having COVID-19, did you experience libido disorders?	No	194 (64,7%)	266 (88,1%)		-
	Yes, in the first 3 months	78 (26%)	25 (8,3%)	0,306	0,4 [2,75-19,16]
	Yes, for more than 3 months	28 (9,3%)	11 (3,6%)	0,031	1,25 [11,39-103,98]
25. After having COVID-19, has the regularity and nature of your menstruation changed?	Yes	61 (20,3%)	5 (1,7%)		-
	No	239 (79,7%)	297 (98,3%)	0,203	0,46 [4,19-37,98]
26. After having a pregnancy/ delivery affected by COVID-19, did you experience difficulties in planning your next pregnancy?	Yes	68 (22,7%)	8 (2,6%)		-
	No	232 (77,3%)	294 (97,4%)	0,688	0,19 [1,53-12,12]
27. After pregnancy, did you undergo a routine gynecological examination ("screening"): gynecological consultation, ultrasound of pelvic organs, oncocytology, etc.?	Yes	64 (21,3%)	38 (12,6%)		-
	No	236 (78,7%)	264 (87,4%)	0,271	0,08 [0,41-2]
28. If you underwent a routine gynecological examination after pregnancy during the COVID-19 pandemic, were any abnormalities detected?	Yes	88 (29,3%)	13 (4,3%)		-
	No	212 (70,7%)	289 (95,7%)	0,063	0,91 [5,28-30,45]
29. Do you seek information on family planning?	Yes	37 (12,3%)	55 (18,2%)		-
	No	**188 (62,7%)**	**242 (80,1%)**	**0,032**	**0,09 [0,28-0,9]**
	I am not aware of such information	**75 (25%)**	**5 (1,7%)**	**<0,001**	**0 [0,01-0,12]**
30. If you are not planning your next pregnancy at this time, what contraception method do you use?	No contraception	190 (63,3%)	118 (39,1%)		-
	I use an intrauterine device	**97 (32,3%)**	**158 (52,3%)**	**<0,001**	**7,19 [15,15-31,9]**
	Other	**13 (4,3%)**	**26 (8,6%)**	**<0,001**	**4,07 [20,83-106,64]**

Categories that increase the chances of a positive outcome are marked in pink, while those that decrease the chances are marked in green.

For example, in the univariate analysis, prolonged fatigue was divided into 15.3% (up to 6 months) and 16.7% (beyond 6 months), whereas in the multifactorial analysis, these groups were merged into a single 32% category representing symptoms lasting more than three months. A similar pattern was observed for hair loss: the 15.7% (up to 6 months) and 17% (beyond 6 months) groups were combined into 32.7%. Sleep disturbances lasting beyond three months were recorded at 27.7%. This consolidation provided a clearer picture of long-term symptom persistence, aiding statistical analysis.

The multifactorial analysis (Appendix A) confirmed that many post-COVID symptoms persisted for more than three months, highlighting the long-term impact of COVID-19 on quality of life. Symptoms such as fatigue, hair loss, sleep disturbances, and respiratory difficulties were persistent among a significant proportion of respondents. Similarly, aggregating adverse pregnancy outcomes into a single category provided a clearer understanding of the pandemic's negative reproductive health effects.

Age was identified as a significant factor in health outcomes. Women over 40 years old had a significantly higher likelihood of negative outcomes, with 13.6% of this group experiencing complications compared to 51% among women under 30 years old ($p < 0.001$; OR = 3.31, 95% CI [14.73–65.58]). A statistically significant difference was also observed in the 31–35 age group, where the probability of a positive outcome was lower ($p = 0.059$; OR = 0.23, 95% CI [0.48–1.03]).

Height parameters were also analyzed, but no significant differences were found between groups. For example, the proportion of negative outcomes was 28.8% among women shorter than 160 cm, 51.3% among those 161–170 cm ($p = 0.476$), and 19.9% among women taller than 171 cm ($p = 0.172$).

Pre- and post-COVID health assessments significantly influenced outcomes. Among women who rated their pre-COVID health as "good," 75.5% experienced negative outcomes, compared to only 11.9% among those who rated their health as "satisfactory" or "poor" ($p = 0.225$; OR = 0.67, 95% CI [1.93–5.59]). Among women whose health worsened after COVID-19, the incidence of negative outcomes was 24.2% ($p = 0.233$; OR = 0.21, 95% CI [0.56–1.45]).

The data suggest a decline in quality of life following COVID-19, emphasizing the need for further research considering multifactorial models. As demonstrated in Appendix A, category consolidation facilitated the identification of stable and significant trends. The findings underscore the importance of rehabilitation, preventive measures, and informational campaigns for women affected by COVID-19.

Discussion. This study has demonstrated that women who have experienced COVID-19 exhibit a decline in overall health, along with the emergence or exacerbation of post-COVID symptoms, including psycho-emotional disorders, reproductive system changes, and specific patterns in seeking medical care. Furthermore, a significant proportion of respondents reported symptoms persisting for more than three months, indicating the presence of a prolonged post-COVID syndrome.

One of the novel and significant aspects of this research is the comprehensive nature of the observed changes, which encompass multiple dimensions, ranging from general well-being to reproductive health, sexual function, and dermatological aspects, including skin and hair conditions. Our findings align with certain international studies, confirming that post-COVID symptoms can persist over an extended period in individuals across various age groups, even in the absence of chronic diseases [4], [5], [14], [20]. However, previous studies have largely examined reproductive consequences in a fragmented manner, making direct comparisons challenging. The differences between our findings and some prior studies may be attributed to the nature of our sample, which primarily included women of reproductive age without officially registered chronic illnesses. This factor could influence susceptibility to post-COVID complications and the characteristics of reported symptoms. When comparing findings across studies, it is essential to consider inclusion criteria, socio-demographic background, and access to medical care.

A notable strength of this study lies in the detailed analysis of symptom dynamics post-infection, employing a multifactorial approach to integrate data and identify overarching trends. This methodology allowed for the monitoring of various health aspects—ranging from general well-being to reproductive changes—over an extended period, revealing the persistence or transformation of symptoms. Additionally, the inclusion of a population without evident chronic diseases helped minimize the confounding influence of comorbidities on the results.

Nevertheless, the study has several limitations. First, the reliance on survey-based data collection and the absence of objective clinical measurements complicate the validation of causal relationships between COVID-19 and the observed changes. Second, the sample predominantly comprised women of reproductive age, which restricts the generalizability of the findings to other age groups. Third, the lack of long-term follow-up data on the same respondents, as well as the absence of objective health assessments (such as laboratory or instrumental diagnostics), may limit the reliability of certain conclusions. Another drawback is the absence of a control group, which prevents a precise evaluation of the distinct characteristics of post-COVID symptoms. While these limitations should be taken into account when interpreting the results, they do not invalidate the study's key findings.

The findings underscore the necessity of close monitoring of women following COVID-19, particularly concerning reproductive health and long-term post-COVID manifestations. From a practical perspective, these results can facilitate the early detection and management of post-COVID disorders related to reproduction, sleep, and psycho-emotional well-being. However, the application of these findings in clinical practice requires an individualized approach, further confirmatory studies, and potential integration into future clinical guidelines.

Future research should expand the demographic scope, incorporating women of various ages and differing baseline health conditions. A promising direction involves a long-term, dynamic cohort study complemented by clinical and laboratory assessments. This approach would enable the identification of more precise predictors of prolonged post-COVID symptoms and their impact on reproductive

function. Additionally, new hypotheses may emerge regarding the underlying mechanisms of the observed changes, including potential immuno-hormonal alterations and their role in post-COVID syndrome development. However, such hypotheses remain preliminary and require further substantiation.

The interpretation of these findings should consider the primary aim of this study—to evaluate the impact of COVID-19 on women's general and reproductive health. While the data indicate the persistence of post-COVID changes, they do not provide sufficient evidence to draw conclusions about the long-term economic or social effectiveness of specific interventions. Nonetheless, the results emphasize the importance of a comprehensive rehabilitation approach for women recovering from COVID-19 and outline directions for further in-depth investigations.

Recommendations for Pregnancy Planning

Based on the study findings, recommendations for pregnancy planning post-COVID-19 have been developed. Women should undergo a thorough assessment of their general health status following COVID-19. This evaluation should include blood tests, hormonal assessments, and examinations of the cardiovascular and respiratory systems. The study indicates that a higher baseline level of preconception health increases the likelihood of favorable pregnancy outcomes.

Women should undergo routine gynecological examinations, including ultrasound assessments, oncocytology, and hormonal balance evaluations, as key steps in pregnancy preparation. According to the study data, women who did not undergo scheduled gynecological check-ups after COVID-19 were more likely to experience reproductive abnormalities ($p = 0.08$; OR = 0.41–2). Given COVID-19's substantial impact on the immune system, women are advised to maintain a diet rich in vitamins and minerals. Strengthening immunity through the intake of micronutrients such as vitamins D and C, iron, and zinc is particularly important.

The study findings also suggest that post-COVID psycho-emotional disturbances (e.g., insomnia, fatigue) may contribute to adverse health outcomes. Therefore, psychological support and, if necessary, professional counseling are recommended for affected women. Light physical activities, such as yoga or swimming, can enhance overall health and improve the body's readiness for pregnancy. This is particularly relevant for women experiencing post-COVID fatigue or weakness ($p < 0.001$; OR = 0.07, 95% CI [0–0.07]).

For women who do not plan to conceive following COVID-19 recovery, selecting appropriate contraceptive methods is crucial. According to the study results, women using intrauterine devices were more likely to experience favorable outcomes ($p < 0.001$; OR = 7.19, 95% CI [15.15–31.9]). Furthermore, comprehensive education on pregnancy planning is essential. The study found that women lacking adequate information had a higher likelihood of negative outcomes ($p < 0.001$; OR = 0.01, 95% CI [0.01–0.12]). Healthcare institutions should develop specialized programs to provide women with information on pregnancy planning and the potential long-term effects of COVID-19.

Conclusion. This study has demonstrated that COVID-19 infection in women of reproductive age is associated with a deterioration in overall health, along with the development of various post-COVID symptoms affecting reproductive function, psycho-emotional stability, and somatic and dermatological parameters. Some symptoms persisted for more than three months, contributing to the formation of a prolonged post-COVID syndrome. The findings highlight the importance of comprehensive medical surveillance, preventive strategies, and rehabilitation measures aimed at the timely identification and management of post-COVID disorders.

To gain a deeper understanding of COVID-19's long-term consequences and identify risk factors more precisely, further research is required. This should include long-term dynamic monitoring, objective clinical and laboratory assessments, and comparative analyses with control groups. Such studies will facilitate the development of effective medical strategies tailored to women recovering from COVID-19.

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THE IMPACT OF GENE MUTATIONS IN THYROID CANCER: A REVIEW

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Abstract

Introduction: Thyroid cancer is a common endocrine malignancy, with DICER1 mutations emerging as significant contributors to its development and progression. The identification of these mutations through molecular genetic analysis, particularly in poorly differentiated thyroid carcinomas and pediatric follicular thyroid carcinomas, has provided valuable insights into the pathophysiological mechanisms underlying the disease. Studies by Volante et al. and Lee et al. have highlighted the importance of genetic testing for DICER1 mutations in guiding clinical management, enabling more precise risk stratification, and tailoring patient-specific therapeutic approaches. Despite these advances, critical gaps remain in our understanding of the full spectrum of DICER1-associated phenotypes and the molecular mechanisms involved. Future research is needed to elucidate the biological pathways influenced by DICER1 mutations and to explore the potential for targeted therapies. Additionally, developing strategies for early detection and personalized treatment plans based on genetic profiles could significantly improve patient outcomes.

This review **aims** to analyze publications devoted to the significant role of DICER1 mutations in thyroid cancer.

Search strategy: The literature search was performed in the electronic databases PubMed, WoS, Scopus, Google Scholar over the past 10 years: from 2014 to 2024, but information about topic (the Impact of DICER1 Mutations on Thyroid Cancer) was not full. Most of the valuable information related to the problem, found in the databases, was from 2005–2007, 2009, and 2011–2013, and was included in the review. These sources do not fall into the specified depth, but were accepted for analysis because they contain conceptual information. Criteria for inclusion of publications in the review: publications in full text access in Russian and English, bearing statistically confirmed conclusions. Exclusion criteria: abstracts of reports, newspaper publications, paid access articles, personal communications.

Results: This review synthesizes current insights into the mechanisms of formation of the DICER1 gene mutation. Despite these advances, there is no complete spectrum of DICER1-related phenotypes and molecular mechanisms involved in this process. Further research is needed to clarify the biological pathways affected by DICER1 mutations and explore the potential of targeted therapies. In addition, the development of early detection strategies and personalized treatment plans based on genetic profiles can significantly improve patient outcomes. This review highlights the need for continued research on DICER1 gene mutations to fully exploit their potential in improving the diagnosis, management, and treatment of thyroid cancer.

Conclusions: The presented data allow us to formulate a clinical and pathophysiological approach to the clinic and treatment of thyroid cancer. Conducting genetic analysis for DICER1 gene mutations can lead to the development of personalized and effective treatment plans. The study of DICER1 mutations will improve patient outcomes by improving the approach to the diagnosis and treatment of thyroid cancer. Thus, the detection of the presence of a DICER1 gene mutation in thyroid cancer is an important part in the management of patients with thyroid cancer, which will also improve the outcome of the disease.

Keywords*: papillary thyroid carcinoma, well-differentiated thyroid cancer, DICER1 mutation, DICER1 in thyroid tumor, DICER1 in endocrine pathology*.

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Резюме

РОЛЬ МУТАЦИИ В ГЕНЕ ПРИ РАКЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ.

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Введение: Рак щитовидной железы - распространенное эндокринное злокачественное новообразование, в развитии и прогрессировании которого значительную роль играет мутация гена DICER1. Выявление этих мутаций с помощью молекулярно-генетического анализа, особенно в низко дифференцированных карциномах щитовидной железы и детских фолликулярных карциномах щитовидной железы, позволило получить ценные сведения о патофизиологических механизмах, лежащих в основе этого заболевания. Исследования Volante et al. и Lee et al. подчеркнули важность генетического тестирования на мутации DICER1 для руководства клиническим лечением, более точной стратификации риска и подбора терапевтических подходов с учетом индивидуальных особенностей пациента.

Целью данного обзора являлась систематизация данных о роли мутаций DICER1 при раке щитовидной железы.

Стратегия поиска: Поиск литературы проводился в электронных базах данных PubMed, WoS, Scopus, Google Scholar за последние 10 лет: с 2014 по 2024 год, но информация по теме (влияние мутаций DICER1 на рак щитовидной железы) была неполной. Большая часть ценной информации, описывающей проблему, найденную в базах данных за 2005–2007, 2009, 2011–2013 годы, была включена ввиду отражения основной проблемы темы. Критерии включения публикаций в обзор: публикации в полнотекстовом доступе на русском и английском языках, содержащие статистически подтвержденные выводы. Критерии исключения: тезисы докладов, газетные публикации, статьи в платном доступе, личные сообщения.

Результаты: В представленном обзоре систематизированы современные взгляды на механизмы формирования мутации гена DICER1. Несмотря на эти достижения, нет полного спектра фенотипов, связанных с DICER1, и молекулярных механизмов, вовлеченных в этот процесс. Разработка стратегий раннего выявления и персонализированных планов лечения на основе генетических профилей может значительно улучшить результаты лечения пациентов. Данный обзор подчеркивает необходимость продолжения исследований мутаций гена DICER1 для полного использования их потенциала в улучшении диагностики, ведения и лечения рака щитовидной железы.

Выводы: Представленные данные позволяют сформулировать клинико-патофизиологический подход к клинике и лечению рака щитовидной железы. Проведение генетического анализа на мутации гена DICER1 может привести к разработке персонализированных и эффективных планов лечения. Исследование мутаций DICER1 улучшат результаты лечения пациентов за счет совершенствования подхода к диагностике и лечению рака щитовидной железы. Таким образом, выявление наличия мутации гена DICER1 при раке щитовидной железы является важной частью при ведении пациентов с раком щитовидной железы, которая улучшит так же исход течения заболевания.
***Ключевые слова**: папиллярная карцинома щитовидной железы, высокодифференцированный рак щитовидной железы, мутация DICER1, DICER1 при опухоли щитовидной железы, DICER1 при эндокринной патологии.*

Для цитирования:

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Түйіндеме

ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІНДЕГІ ГЕНІНІҢ МУТАЦИЯСЫНЫҢ РӨЛІ: ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе; Қалқанша безінің обыры кең таралған эндокриндік қатерлі ісік болып табылады, бұл ретте DICER1 мутациялар оның дамуы мен ілгерілеуінің елеулі фактор атқарады. Бұл мутацияларды молекулалық-генетикалық талдаудың көмегімен, әсіресе қалқанша безінің нашар сараланған карциномаларында және қалқанша безінің педиатриялық фолликулярлық карциномаларында сәйкестендіру аурудың негізінде жатқан патофизиологиялық тетіктер туралы құнды ақпарат берді. Volante et al. Ли және басқалар клиникалық жүргізу, қауіптерді неғұрлым дәл стратификациялауды қамтамасыз ету және емделушіге тән терапевтік тәсілдерді бейімдеу бойынша DICER1 мутацияларына генетикалық тестілеудің маңыздылығын атап өтті. Осы жетістіктерге қарамастан, DICER1-associated фенотиптері мен тартылған молекулалық механизмдердің толық спектрін түсінуде сыни олқылықтар бар. Болашақ зерттеулер DICER1 мутациялар әсер ететін биологиялық жолдарды анықтау үшін және мақсатты бағытталған терапияның әлеуетін зерттеу үшін қажет. Бұдан басқа, генетикалық бейіндер негізінде ерте анықтау стратегиялары мен дербестендірілген емдеу жоспарларын әзірлеу пациенттерді емдеу нәтижелерін айтарлықтай жақсартуы мүмкін. Бұл шолуда қалқанша безі обырын диагностикалауды, емдеуді және емдеуді жақсарту үшін олардың әлеуетін толық пайдалану үшін DICER1 мутацияларын зерттеуді жалғастыру қажеттігі атап өтіледі.

Бұл шолудың мақсаты: қалқанша безінің қатерлі ісігіндегі DICER1 мутацияларының рөлі туралы деректерді жүйелеу.

Іздеу стратегиясы: маңызды әдебиеттерді ізденіс PubMed, Web of Science дерекқорларынан және электронды дерекқорларында жүргізілді: 2014 жылдан 2024 жылға дейін, бірақ тақырып бойынша ақпарат (DICER1 мутациясының қалқанша безінің қатерлі ісігіне әсері) толық болмады. 2005-2007, 2009, 2011-2013 жылдардағы мәліметтер базасында табылған мәселені сипаттайтын құнды ақпараттың көп бөлігі танысу үшін енгізілген. Бұл көздер көрсетілген тереңдікке сәйкес келмейді, бірақ талдау үшін қабылданды, өйткені олар тұжырымдамалық ақпаратты қамтиды. Басылымдарды шолуға қосу критерийлері: статистикалық расталған қорытындыларды қамтитын орыс және ағылшын тілдеріндегі толық мәтінді қол жетімділіктегі басылымдар. Ерекшелік критерийлері: баяндамалар тезистері, газет басылымдары, ақылы мақалалар, жеке хабарламалар.

Нәтижесі: Ұсынылған шолуда DICER1 генінің мутациясын қалыптастыру механизмдері туралы заманауи көзқарастар жүйеленген. Осы жетістіктерге қарамастан, DICER1-мен байланысты фенотиптердің толық спектрі және процеске қатысатын молекулалық механизмдер жоқ. DICER1 мутациялары әсер ететін биологиялық жолдарды анықтау және мақсатты терапияның әлеуетін зерттеу үшін қосымша зерттеулер қажет. Сонымен қатар, ерте анықтау стратегияларын және генетикалық профильдерге негізделген жекелендірілген емдеу жоспарларын әзірлеу пациенттердің нәтижелерін айтарлықтай жақсарта алады. Бұл шолу қалқанша безінің қатерлі ісігін диагностикалауды, басқаруды және емдеуді жақсартуда олардың әлеуетін толық пайдалану үшін DICER1 генінің мутацияларын зерттеуді жалғастыру қажеттілігін көрсетеді.

Қорытынды: Ұсынылған деректер клиникаға және қалқанша безінің қатерлі ісігін емдеуге клиникалық-патофизиологиялық тәсілді тұжырымдауға мүмкіндік береді. DICER1 генінің мутациясына генетикалық талдау жүргізу жекелендірілген және тиімді емдеу жоспарларын жасауға әкелуі мүмкін. DICER1 мутациясын зерттеу қалқанша безінің қатерлі ісігін диагностикалау және емдеу тәсілін жақсарту арқылы пациенттердің нәтижелерін жақсартады. Осылайша, қалқанша безінің қатерлі ісігінде DICER1 генінің мутациясының болуын анықтау қалқанша безінің қатерлі ісігі бар науқастарды басқарудың маңызды бөлігі болып табылады, бұл аурудың ағымының нәтижесін жақсартады.

Түйінді сөздер: *қалқанша безінің папиллярлы карциномасы, қалқанша безінің жоғары сараланған қатерлі ісігі, DICER1 мутациясы, қалқанша безінің ісігіндегі DICER1, эндокриндік патологиядағы DICER1.*

Дәйексөз үшін: Еркетаева *А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Пак Л.А., Душимова З.Д., Токтабаева Б.Ж., Жазыкбаева Л.К., Рахманкулова А.М.* Қалқанша безінің қатерлі ісігіндегі генінің мутациясының рөлі. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 157-166. *doi 10.34689/SH.2025.27.1.019*

Introduction

Thyroid carcinoma one of the most prevalent malignancy among adolescent and young adult females, with its incidence steadily rising across all age demographics, as evidenced in various epidemiological studies [37, 47]. Concurrently, nodular thyroid disease is notably prevalent within the adolescent population, with the widespread adoption of cervical ultrasonography revealing an increasing number of previously subclinical thyroid nodules.

The presentation of thyroid carcinoma in pediatric and adolescent cohorts exhibits several distinctive clinical characteristics when contrasted with the adult population.

Notably, these younger patients demonstrate a significantly higher propensity for both regional and distant metastasis at the time of diagnosis. Moreover, recurrence rates are disproportionately elevated in this demographic compared to their adult counterparts 72]. Intriguingly, despite the more substantial initial disease burden, prognostic outcomes for children and adolescents with thyroid carcinoma remain exceptionally favorable [60]. Furthermore, certain histopathological subtypes of papillary thyroid carcinoma (PTC), such as the diffuse sclerosing and solid variants, are more frequently encountered in pediatric and adolescent patients than in adults [32, 38]. However, the underlying biological and molecular mechanisms that contribute to the divergent clinical behavior of pediatric versus adult PTC remain poorly understood and have yet to be elucidated in the current scientific literature.

According to the literature, the probability of recurrence of thyroid cancer in children after primary surgical treatment depends on the morphological structure of the tumor and ranges from 7 to 47%. The study of the molecular mechanisms of these tumors is becoming extremely relevant, providing the opportunity to improve diagnosis, prognosis, and the future development of new targeted chemotherapeutic agents.

Thyroid cancer arise from the follicular epithelial cells or parafollicular C cells. The most common neoplasms arising from follicular cells with 4 histological types are papillary thyroid carcinomas (PTC; 80-85%), follicular thyroid cancers (FTC; 10-15%), poorly differentiated thyroid cancer (PDTC; less than 2%), and anaplastic thyroid cancer (ATC; less than 2%). PTC and FTC are termed well-differentiated thyroid cancer (WDTC), the commonest in thyroid tumor cases. The genetic landscape of differentiated thyroid cancer comprises alterations, such as BRAF and RAS mutations, and RET/PTC rearrangements, which in turn converge to activate the MAPK oncogenic pathway [72, 60]. The notion that advanced tumors dedifferentiate from WDTC towards PDTC or ATC, as is suggested by the existence of both differentiated and anaplastic foci within undifferentiated tumors, is experienced. Of particular importance is the presence of the BRAFV600E mutation or RAS mutation in about 23% and 20% of the cases of ATC, respectively. However, other mutations, such as TP53 and TERT promoter ones, along with these earlier mentioned driver mutations, are more often found in ATC [32, 42]. It is thus postulated that this accumulation of additional pathogenic alterations within oncogenes and tumor suppressor genes is a key driver of the advancement from WDTC towards PDTC and ATC.

In addition to these well-characterized mutations, emerging evidence highlights the role of DICER1 mutations in thyroid carcinogenesis. DICER1, an essential enzyme in microRNA (miRNA) processing, plays a critical role in gene regulation [2]. Mutations in DICER1 have been identified in various types of thyroid cancer, particularly in FTC and PDTC, where they contribute to the dysregulation of miRNA processing and subsequent aberrant gene expression [21, 49]. Patients harboring DICER1 mutations often present with more aggressive disease phenotypes and poorer clinical outcomes, and these mutations have been associated with familial thyroid cancer syndromes [28, 56]. Ongoing research continues to explore the interaction of DICER1 mutations with other genetic alterations, such as BRAF and RAS mutations, further elucidating their role in thyroid cancer progression [41, 51].

PTC, the most prevalent form of thyroid cancer, constitutes over 80% of all thyroid malignancies [9]. The rising incidence of thyroid cancer is largely attributed to increased diagnoses of small PTCs, which, although generally indolent and highly curable, exhibit a significant recurrence rate—about 20% at 10 years and 30% at 30 years post-treatment [43, 62]. This recurrence can have profound psychosocial and economic impacts, diminishing the quality of life for patients.

Despite the overall low mortality associated with thyroid cancer, standard treatments—such as surgical resection combined with radioiodine ablation therapy—are highly effective for most patients [8]. However, an increased risk of mortality exists when the cancer becomes surgically inoperable or loses its ability to take up radioiodine [66]. Currently, the mortality rate for thyroid cancer in the United States stands at approximately 1,530 cases per year [59]. Consequently, accurate risk stratification and prognostic evaluation are critical in managing patients and reducing both recurrence and mortality rates associated with thyroid cancer [48].

Search strategy. The literature search was performed in the electronic databases PubMed, WoS, Scopus, Google Scholar over the past 10 years: from 2014 to 2024, but information about the topic (the Impact of DICER1 Mutations on Thyroid Cancer) was not full. Most of valuable information which is described the problem founded in databases were from 2005-2007, 2009, 2011-2013, they were included to review. These sources do not fall into the specified depth, but were accepted for analysis because they contain conceptual information. *Criteria for inclusion* of publications in the review: publications in full text access in Russian and English, bearing statistically confirmed conclusions. *Exclusion criteria*: abstracts of reports, newspaper publications, paid access articles, personal communications. From the remaining articles, a plan was formed to write a literature review according to the following sequence: «DICER 1 gene mutations», «DICER1 mutations on thyroid cancer», «Molecular genetic alterations in thyroid cancer». The search was performed by keywords like "well differentiated thyroid cancer," "DICER1 endocrine pathology". According to the topic, depth of research, and keywords, 94 articles were found, of which 73 were selected for review. The source selection algorithm is presented in Figure 1.

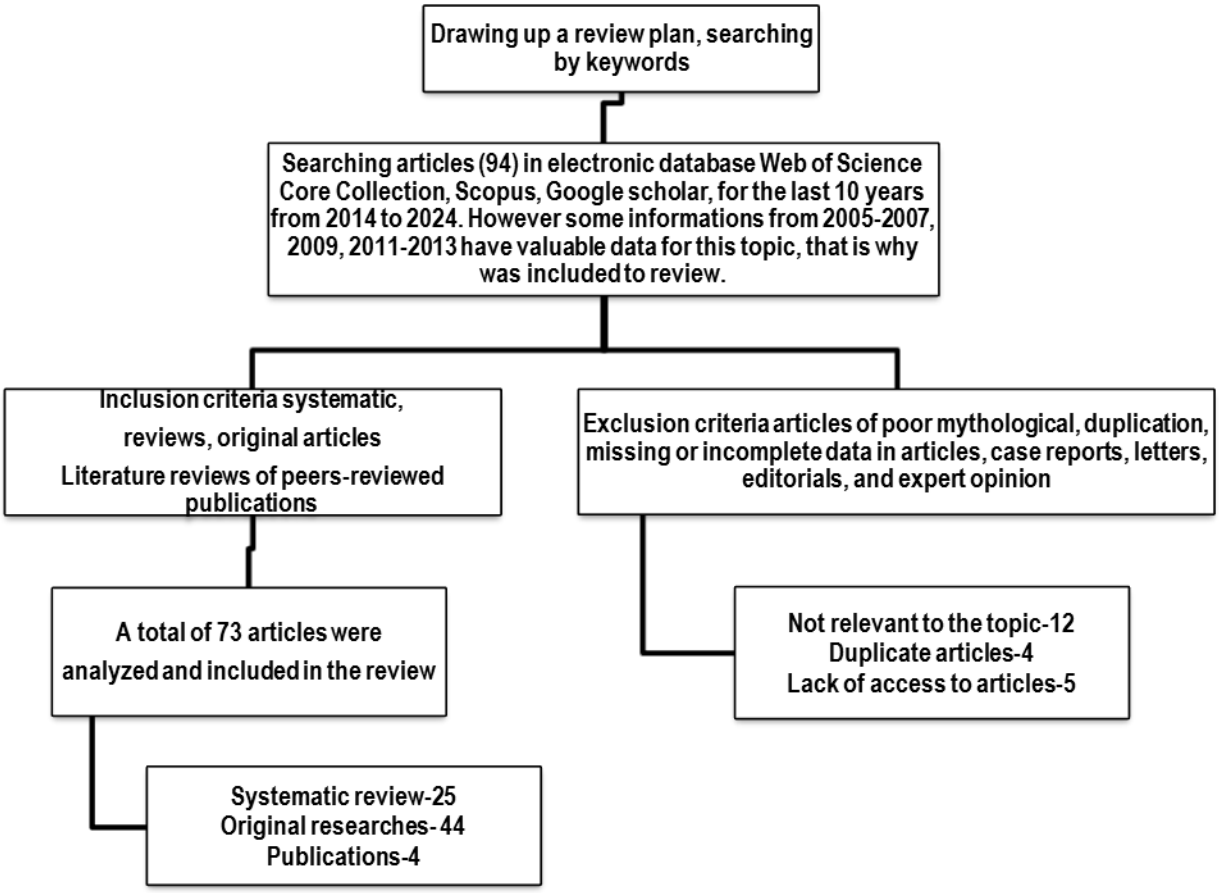

Figure 1. Article selection algorithm.

DICER1 Mutation and Its Role in Endocrine Tumors

The thyroid gland is the least studied of tumors with respect to mutations in DICER1 because, although tumors of the thyroid are the most common among the endocrine glands. The DICER1 gene, which is important for the maturation of microRNAs (miRNAs) has undergone serious work on endocrine tumors such as thyroid neoplasia. DICER1 is localized on the long arm of chromosome 14(14q32.13) and has 36 exons. Interest in DICER and its encoding protein has steadily increased in light of miRNA research, a class of short non-coding RNA molecules of roughly 22 nucleotides in length originally discovered by Ambros V. in 1993. MicroRNAs inhibit gene expression negatively at the post-transcriptional level and are involved in various biological processes such as cell proliferation and apoptosis [42].

At present, in the world literature, there is no reliable data on the impact of inactivating mutations of the DICER1 gene on the development of malignant tumors of the thyroid. Some authors have proposed that exposure to previous chemotherapy may be one of the possible factors that contribute to differentiated thyroid cancer development in such patients [2]. Other researchers suggested that DICER1 promotes thyrocyte proliferation. DICER1 mutations can actually correlate with well-differentiated thyroid carcinoma. Moreover, DICER1 protein is downregulated in papillary thyroid carcinomas, and basal expression of DICER1 is crucial for thyroid differentiation. Currently, at least two heterozygous germ-line mutations mapping to exons 8 or 25 of the DICER1 gene have been reported in patients with PTC. PTC was described in a family with papillary thyroid cancer: in a mother and her two daughters aged 12 and 14 years [4-7, 11, 21]. Michael Solarski presents an overview illustrating how mutations in DICER1 impair normal miRNA biogenesis, thereby significantly modifying gene expression. These disturbances have considerable influences on cell proliferation and differentiation, which constitute critical processes in the determination of the inception and progression of thyroid tumors. In fact, the consequence of DICER1 mutations on thyroid cancer appears particularly significant within the full spectrum of tumors, prominently FTC and PDTC, whereby aberrations in miRNA processing may promote tumor aggressiveness. In this malignancy, by modulating the aggressiveness of the tumors, DICER1 mutations could lead to the occurrence of more aggressive phenotypes, generally with poor clinical outcomes. Furthermore, mutations could also influence a tumor's response to the therapy, providing crucial opportunities for targeted treatment. For example, the extent to which normal miRNA processing is restored could render DICER1 mutant forms of thyroid cancers less aggressive. It may also open up options for targeted treatments.

Furthermore, Michael Solarski emphasizes the importance of DICER1 in the broader context of endocrine tumors, noting that the gene’s role extends beyond thyroid cancer to include other endocrine-related malignancies. The review also discusses how DICER1 mutations, when present alongside other genetic alterations such as BRAF or RAS mutations, may exacerbate tumorigenesis and

contribute to resistance to conventional therapies. This interaction highlights the complexity of genetic and epigenetic factors in thyroid cancer progression. Given these findings, DICER1 mutations could serve as both a prognostic marker and a potential therapeutic target in thyroid cancer. Understanding the specific mechanisms by which DICER1 mutations drive thyroid cancer progression remains a critical area of ongoing research. The insights from Michael Solarski underscore the need for further studies to explore how restoring miRNA processing in DICER1-mutant tumors could lead to improved treatment outcomes. Additionally, the potential for personalized treatment strategies that specifically target the molecular consequences of DICER1 mutations is an exciting area of therapeutic development. This review aims to analyze publications devoted to the significant role of DICER1 mutations in thyroid cancer, further elucidating their implications for recurrence, diagnosis, and personalized treatment strategies. [46]

DICER1 Syndrome and Thyroid Cancer

DICER1 syndrome is a hereditary condition characterized by a predisposition to various neoplasms, including thyroid cancer. De Kock L. emphasizes that pathogenic variants of DICER1 are linked to a broad spectrum of tumors, with significant implications for the thyroid gland. The study by De Kock L. provides valuable insights into how these genetic mutations contribute to thyroid cancer development, particularly in individuals with a familial history of the disease. DICER1 syndrome offers a unique framework for understanding the inherited patterns of thyroid cancer, which can differ significantly from sporadic cases.

One of the key findings in De Kock L. is the importance of early genetic testing for individuals with a family history of DICER1-related tumors. Identifying these pathogenic variants early on can lead to more effective monitoring and management strategies, potentially reducing the risk of aggressive thyroid cancer. The study also highlights how DICER1 mutations may affect the therapeutic responses in thyroid cancer patients, particularly those with hereditary cancer syndromes. Understanding these variations is crucial for developing personalized treatment plans that account for the genetic background of the patient.

De Kock L. also discusses the broader implications of DICER1 mutations beyond thyroid cancer, noting that these mutations are linked to a variety of endocrine and non-endocrine tumors. This broad spectrum of associated neoplasms underscores the complexity of DICER1 syndrome and the need for a multidisciplinary approach to patient care. The research points to the potential benefits of integrating genetic counseling into routine clinical practice for patients at risk of DICER1-related cancers. Moreover, Kock et al. suggest that further studies are needed to explore the long-term outcomes of individuals with DICER1 mutations, particularly regarding their risk for developing multiple types of cancer over their lifetime.

The findings of De Kock L. underscor the critical role of DICER1 in both the development and progression of thyroid cancer. This study contributes to the growing body of evidence that highlights the importance of genetic factors in cancer biology. As such, the insights from this research may lead to improved screening protocols and more targeted therapeutic interventions for patients with DICER1 syndrome. This review aims to analyze publications focused on the significant role of DICER1 mutations in thyroid cancer, further elucidating their implications for recurrence, diagnosis, and personalized treatment strategies. [10, 12-15] DICER1 is now accepted as a driver of pediatric thyroid nodules. Research has demonstrated an association between DICER1 somatic or germline mutations and pediatric follicular thyroid carcinoma. Can be low-risk malignancies in papillary thyroid carcinoma associate with DICER1-mutation. Some researchers approved that poorly differentiated thyroid carcinomas (PDTC) in pediatric patients are associated with DICER1 mutations, and some may be part of a DICER1 tumor syndrome. PDTC of childhood and adolescence is very rare and information is limited. Findings of some authors indicate that pediatric DICER1 mutation genetically different from adult PDTC that is strongly associated with DICER1 mutations. [12] Medullary thyroid cancer (MTC) in children poses the necessity to rule out multiple endocrine neoplasia syndrome (MEN type 2). It's noteworthy that familial cases of follicular cell-derived tumors, aside from MTC, are uncommon. Exploring the role of microRNAs as potential biomarkers in pediatric thyroid carcinomas is an emerging area of research, and expanding our understanding in this realm could pave the way for more nuanced diagnostic approaches and tailored treatments in pediatric thyroid cancer DICER 1 gene expression associated with aggressive features in patients with PTC, while with DICER1 syndrome associated DTC, which is mostly define in patients young age, and form low risk group with low probability for metastasis. [1-7, 11, 51].

Prevalence and Diagnosis of Implications for Clinical Practice

The identification of DICER1 mutations provided by molecular genetic analysis, such as next-generation sequencing, which is plays a crucial role in the clinical management of thyroid cancer, particularly in cases with poorly differentiated features. Volante et al. conducted a clinicopathologic study of 183 patients with poorly differentiated thyroid carcinomas characterized by trabecular, insular, and solid patterns, highlighting the aggressive nature of these tumors. The study underscored the importance of accurate histopathologic assessment in conjunction with genetic testing to better understand the prognosis and potential for recurrence in thyroid cancer patients.[68, 18-19]

Lee et al. further emphasized the significance of DICER1 mutations, particularly in pediatric follicular thyroid carcinomas, where these mutations are predominant. The identification of these pathogenic variants is paramount for assessing the risk of differentiated thyroid cancer recurrence, particularly in younger patients. The genetic insights provided by these studies are crucial for tailoring patient-specific therapeutic approaches, which can significantly improve clinical outcomes.[20-24]

In clinical practice, integrating genetic testing for DICER1 mutations into the diagnostic and treatment planning process allows for more precise risk stratification. For instance, patients with DICER1 mutations may require more intensive monitoring and potentially more aggressive treatment to mitigate the higher risk of recurrence and progression. Volante et al.

highlighted the need for early and accurate identification of poorly differentiated thyroid carcinomas, which can inform the choice of therapeutic strategies and improve survival rates. [25-27, 30, 31, 39, 68]

Molecular genetic analysis with next generation sequencing (NGS) narrowed down (for the particular family) the association of PTC with germline DICER1 mutations in the family under consideration. An experiment with a knock-in mice model validated these studies and clearly demonstrated that the thyroid condition occurred mainly through the knockout of Dicer1 in thyroid cells. According to new studies, some cell types have been shown to carry low levels of DICER1 and high levels of the associated proteins suggested to play a role in the development of thyroid cancer. Nevertheless, as indicated by one study, such cells when combined with environmental agents got transformed into a disorganized state that is typical of cancer tissue, before manifesting the pure cancer phenotype. Likewise, actually the role of DICER1 in cancer is dual: the mutation either enhances the protein or reduces its phosphopeptides. This occurs through the VAV1 kinase regulated DICER1 as it phosphorylates at a tyrosine residue to form a phosphopeptide that reduces the cis-modifications. NGS-based cancer gene panels can be included in childhood patients with different genetic syndromes to accurately detect the patient's disease and also to prevent cancer diseases from developing. The clinical management that includes a genetic cancer test remains the perfect course of action to take as among other things, the patient receives a clear prognosis and also, the risk predispositions are additionally understood. Children who undergo genetic tests and periodic tests might have a higher chance of resolving DNA issues and thus they will show a reduced amount of cancer diseases and more of those cases that appear will have a clear predisposing genetic factor [31,33-36, 40]

The next generation sequencing and other advanced molecular procedures in the clinical setting leads to diagnosing DICER1 mutations at early stages which is especially the case for pediatric patients. On this note. as per observations of Lee et al., they have suggested that short inhibitory RNA molecules can be designed specifically for the targets as they have a particular inferable transcript complex with the RNA molecule. Also, the RNAi technology when used in therapy cells is better than in the usual cells; RNAi technology is being developed for gene silencing as a radiation-free treatment technology. [63-67] Besides, the things that have to be kept in mind are: the regular patient monitoring of those with DICER1 mutations and the prompt detection of the recurrence or the progression of the disease through active intervention.

The clinical studies of Volante et al., for example and Lee et al. As also noted by Lee et al., Volante et al., the management of thyroid cancer is a multidisciplinary challenge that should consider both histopathologic and genetic data to aid treatment decisions. Clinical implications are considerable as they allow for tailored, patient-centered care in patients with thyroid cancer. This strategy elevates the odds of getting the best, and highest quality care while at the same time minimizing overtreatment in patients with very low-risk profiles. [53-58, 61] Second, genetic testing as part of a clinical trial offers patients with an increased risk to thyroid cancer (DICER1 mutation) the best possibility in counseling and the management of their mutation carrier status. Exploiting genetic findings to individualize therapy is an important advance in oncology that facilitates target-based, yet minimally invasive strategies for chemotherapy. Conclusion: Molecular genetic analysis is essential to improve thyroid cancer diagnosis and therapy, and DICER1 mutations should be assessed [39,68,69,71]

Conclusion

The literature on DICER1 mutations underscores their significant impact on the development and progression of thyroid cancer. Basic- molecular alterations provide clues to pathophysiologic basis providing new distinguishing points of prospective clinical management as well as therapeutics. Nevertheless, despite the advances made, substantial ignorance of DICER1-associated phenotypes and molecular mechanisms still exists. In-depth exploration of the role of DICER1 in thyroid cancer will still demand rigorous and targeted research. Here is the suggested functional link of mutation gene DICER 1 active state of cancer approved with this review. Molecular genetic studies with NGS will allow one to deduce an unequivocal link between PTC and a DICER1 defect, by which can be defined both risk of malignant activation, type-of Mutations and recurrents, available; of treating disease in patient based on which treatment. Future work should focus on distinguishing affected biological pathways due to DICER1 mutations and defining a window to develop targeted therapies. Furthermore, the development of candidate molecular tests for identifying patient sub-populations in which genetic profiles could be useful may facilitate more personalized and effective treatment regimes. Also, these data suggest a primary driver of oncogenic activation for the DICER1 in pediatric low-risk PTCs pushed the molecular pathogenesis of PTCs. Future studies of DICER1 mutations are likely to lead to improved management practices for thyroid cancer diagnosis and treatment in patients. To sum up: DICER1 in thyroid cancer is an urgent field to address studies that can have a substantial impact on patient outcome.

Conflict of Interest

The authors declare no conflicts of interest. Additionally, no part of this article has been previously published or is under consideration by other publishers.

Author Contributions

As this is a review article, all authors contributed to the literature search using separate methodologies, and the decision to exclude certain materials was made collectively.

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EXPLORING THE ROLE OF miRNA's IN DRUG-RESISTANT EPILEPSY. A LITERATURE REVIEW

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Abstract

Background: Drug-resistant epilepsy is a complex clinical problem with a multifactorial basis, including both environmental and genetic factors, affecting one in three patients. Understanding the genetic factors underlying this resistance may improve prognosis and support the development of new targeted therapies. This systematic review examines the potential of microRNA (miRNA)-based therapies in overcoming pharmacoresistance, exploring their role in modulating epileptogenic processes and serving as biomarkers for personalized treatment.

Aim: The aim of this study is to explore the important role of miRNA expression in the development of drug-resistant epilepsy by conducting a systematic review using databases such as Scopus, PubMed, Google Scholar, Lilacs, and Cuiden.

Search strategy: A systematic review of the literature was conducted using the Scopus, PubMed, Google Scholar, and SciVerse databases. Data from news articles, press releases, or websites were excluded. The search covered the last 5 years (2019–2024) and was performed in PubMed, Scopus, and Web of Science databases. Relevant articles were cited, focusing on topics closely related to the subject of this study. The literature review specifically investigated the role of miRNA in drug-resistant epilepsy and included open-access review articles in the field of epilepsy. The article was prepared as part of a study funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP23489425).

Results: During the open-access literature search, 112 articles in English were identified. Duplicate publications, animal studies, and publications in languages other than English were excluded from the evaluation. After careful review, 32 articles were selected for full analysis.

Conclusion: Expanding research on the heritability of drug-resistant epilepsy through miRNA studies, particularly in Kazakhstan, will facilitate early diagnosis, improve treatment approaches, and ultimately enhance patient quality of life.

Keywords: *Drug-resistant epilepsy; microRNA; seizure; epileptogenesis; antiepileptic drugs.*

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Резюме

ИЗУЧЕНИЕ РОЛИ МИКРОРНК В ЛЕКАРСТВЕННО-УСТОЙЧИВОЙ ЭПИЛЕПСИИ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Лекарственно-устойчивая эпилепсия представляет собой сложную клиническую проблему многофакторного характера, включающего как влияние окружающей среды, так и генетические факторы, затрагивающую одного из трёх пациентов. Понимание генетических механизмов, лежащих в основе этой устойчивости, может улучшить прогноз заболевания и способствовать разработке новых таргетных терапевтических подходов. В данном систематическом обзоре рассматриваются перспективы применения терапий на основе микроРНК (miRNA) для преодоления фармакорезистентности, их роль в модуляции эпилептогенеза, а также потенциал в качестве биомаркеров для персонализированного лечения.

Цель: Целью данного исследования является изучение значимой роли экспрессии микроРНК в развитии лекарственно-устойчивой эпилепсии посредством проведения систематического обзора с использованием баз данных Scopus, PubMed, Google Scholar, Lilacs и Cuiden.

Стратегия поиска: Был проведен систематический обзор литературы с использованием баз данных Scopus, PubMed, Google Scholar и SciVerse. Источники, такие как новостные статьи, пресс-релизы и материалы с сайтов, были исключены из рассмотрения. Поиск охватывал публикации за последние 5 лет (2019–2024 годы) в базах данных PubMed, Scopus и Web of Science. Были проанализированы релевантные статьи, непосредственно связанные с тематикой исследования. В обзор включались в основном статьи открытого доступа, посвящённые роли микро РНК в лекарственно-устойчивой эпилепсии. Статья подготовлена в рамках исследования, финансируемого Комитетом науки Министерства науки и высшего образования Республики Казахстан (грант № AP23489425).

Результаты: В результате поиска литературы открытого доступа было выявлено 112 статей на английском языке. Из рассмотрения были исключены дублирующиеся публикации, исследования на животных и публикации на других языках. После тщательного отбора для полного анализа были выбраны 32 статьи.

Заключение: Расширение исследований наследственных факторов лекарственно-устойчивой эпилепсии с использованием анализа микроРНК, особенно в Казахстане, будет способствовать ранней диагностике, совершенствованию методов лечения и, в конечном итоге, улучшению качества жизни пациентов.

Ключевые слова: *лекарственно-устойчивая эпилепсия; микроРНК; приступ; эпилептогенез; противоэпилептические препараты.*

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Түйіндеме

ДӘРІГЕ ТӨЗІМДІ ЭПИЛЕПСИЯДА МИКРОРНҚ-ЛАРДЫҢ РӨЛІН ЗЕРТТЕУ. ӘДЕБИЕТТІК ШОЛУ

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Кіріспе: Дәріге төзімді эпилепсия – қоршаған орта және генетикалық факторларды қамтитын көпфакторлы күрделі клиникалық мәселе болып табылады және әрбір үшінші науқаста кездеседі. Бұл төзімділіктің генетикалық негіздерін түсіну аурудың болжамын жақсартып, жаңа мақсатты терапиялық тәсілдерді дамытуға мүмкіндік береді. Осы жүйелі шолуда фармакорезистенттілікті еңсеруде микроРНҚ (miRNA) негізіндегі терапиялардың әлеуеті, олардың эпилептогенез үдерістерін модуляциялаудағы рөлі және дербестендірілген ем үшін биомаркерлер ретінде қолданылу мүмкіндіктері қарастырылады.

Мақсаты: Осы зерттеудің мақсаты - Scopus, PubMed, Google Scholar, Lilacs және Cuiden дерекқорларын пайдалана отырып жүйелі шолу жүргізу арқылы дәріге төзімді эпилепсияның дамуына микроРНҚ экспрессиясының маңызды рөлін зерттеу.

Іздеу стратегиясы: Scopus, PubMed, Google Scholar және SciVerse дерекқорларында әдебиеттерге жүйелі шолу жүргізілді. Жаңалықтар мақалалары, баспасөз хабарламалары және веб-сайт материалдары шолудан шығарылды. Іздеу соңғы 5 жылды (2019–2024) қамтыды және PubMed, Scopus және Web of Science базаларында жүргізілді. Зерттеу тақырыбына тікелей қатысты мақалалар таңдалып алынды. Шолу негізінен эпилепсия саласындағы микроРНҚ рөліне арналған ашық қолжетімді мақалаларды қамтыды. Бұл мақала Қазақстан Республикасы Ғылым және жоғары білім министрлігінің Ғылым комитеті қаржыландыратын зерттеу жобасы аясында дайындалды (Грант № AP23489425).

Нәтижелер: Ашық қолжетімді әдебиеттерді іздеу нәтижесінде ағылшын тіліндегі 112 мақала анықталды. Қайталанатын жарияланымдар, жануарларға жүргізілген зерттеулер және ағылшын тілінен басқа тілдердегі мақалалар бағалауға енгізілмеді. Мұқият іріктеуден кейін толық талдау үшін 32 мақала таңдап алынды.

Қорытынды: Қазақстанда микроРНҚ зерттеулері арқылы дәріге төзімді эпилепсияның тұқым қуалаушылығын зерттеуді кеңейту ерте диагностиканы жеңілдетеді, емдеу тәсілдерін жақсартады және нәтижесінде пациенттердің өмір сүру сапасын арттырады.

Түйінді сөздер: *дәріге төзімді эпилепсия; микроРНҚ; ұстама; эпилептогенез; эпилепсияға қарсы препараттар.*

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Introduction

Epilepsy is a common and severe neurological disorder characterized by recurrent seizures, affecting 0.5% to 1% of the population in developed countries and even more in developing regions [1], [2]. According to the latest International League Against Epilepsy (ILAE) classification, seizures are categorized as focal, generalized, or of unknown onset. Types of epilepsy include generalized, focal, and a newly combined category, which helps in selecting appropriate antiepileptic drugs (AEDs) [4]. Regardless of the cause, recurrent seizures lead to various physical, psychological, and social challenges, which can largely be mitigated through effective seizure control.

The primary goal of antiepileptic treatment is to achieve seizure freedom. While many patients gain good control with AED therapy, approximately one-third experience seizures resistant to these treatments, a condition known as drug-resistant epilepsy (DRE). DRE is associated with increased morbidity and mortality, along with psychosocial and cognitive difficulties, ultimately reducing quality of life [5]. The factors contributing to drug resistance are complex, involving a combination of environmental, genetic, disease-related, and drug-related influences. Research suggests that microRNAs (miRNAs) play a crucial role in drug resistance mechanisms by modulating gene expression and influencing neuronal pathways [6], [7], [8].

The definition of drug resistance has evolved over time, typically focusing on the number of treatment failures, the endpoint (e.g., seizure freedom), and the time required to achieve this endpoint. According to statistics, approximately 7% to 20% of children and 30% to 40% of adults exhibit resistance to pharmacological intervention.

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small, non-coding RNA molecules, typically 21–25 nucleotides in length, that play a key role in regulating gene expression [9]. They exert their effects by binding to complementary sequences in target messenger RNAs (mRNAs), leading to either mRNA degradation or inhibition of its translation. This post-transcriptional regulation allows miRNAs to finely tune gene expression across a wide range of biological processes.

The biogenesis of miRNAs is a multistep process that includes transcription, processing, export, maturation, and functional regulation. Initially, miRNAs are transcribed from DNA by RNA polymerase II or III, forming primary miRNA (pri-miRNA) transcripts. Pri-miRNA is then processed in the nucleus by the Drosha enzyme within a microprocessor complex to form precursor miRNA (pre-miRNA). This short, hairpin-like precursor is exported to the cytoplasm via Exportin-5, where it undergoes further processing by the Dicer enzyme, generating a double-stranded RNA molecule. One strand of this duplex is incorporated into the RNA-induced silencing complex (RISC), while the other strand is typically degraded (Figure 1) [10].

The miRNA within the RISC complex then targets mRNAs, leading to their degradation or translational repression, ultimately regulating gene expression. This finely tuned process allows miRNAs to play pivotal roles in various biological functions and cellular processes [10].

The Role of MicroRNAs in Epileptogenesis

Epileptogenesis, the process by which epilepsy develops following an initial insult such as a stroke or traumatic brain injury, occurs in three distinct phases: acute, latent, and chronic. The latent phase is characterized by molecular and structural changes in the brain, including neuronal loss, inflammation, and synaptic reorganization, which eventually lead to recurrent spontaneous seizures. However, the precise mechanisms underlying these processes remain unclear. As epilepsy progresses into the chronic phase, the condition worsens over time, highlighting the urgent need for novel treatment strategies [11].

Recent studies have underscored the pivotal role of microRNAs (miRNAs) in the regulation of epileptogenesis, offering promising therapeutic avenues, particularly in drug-resistant epilepsy (DRE). miRNAs are crucial in neuronal

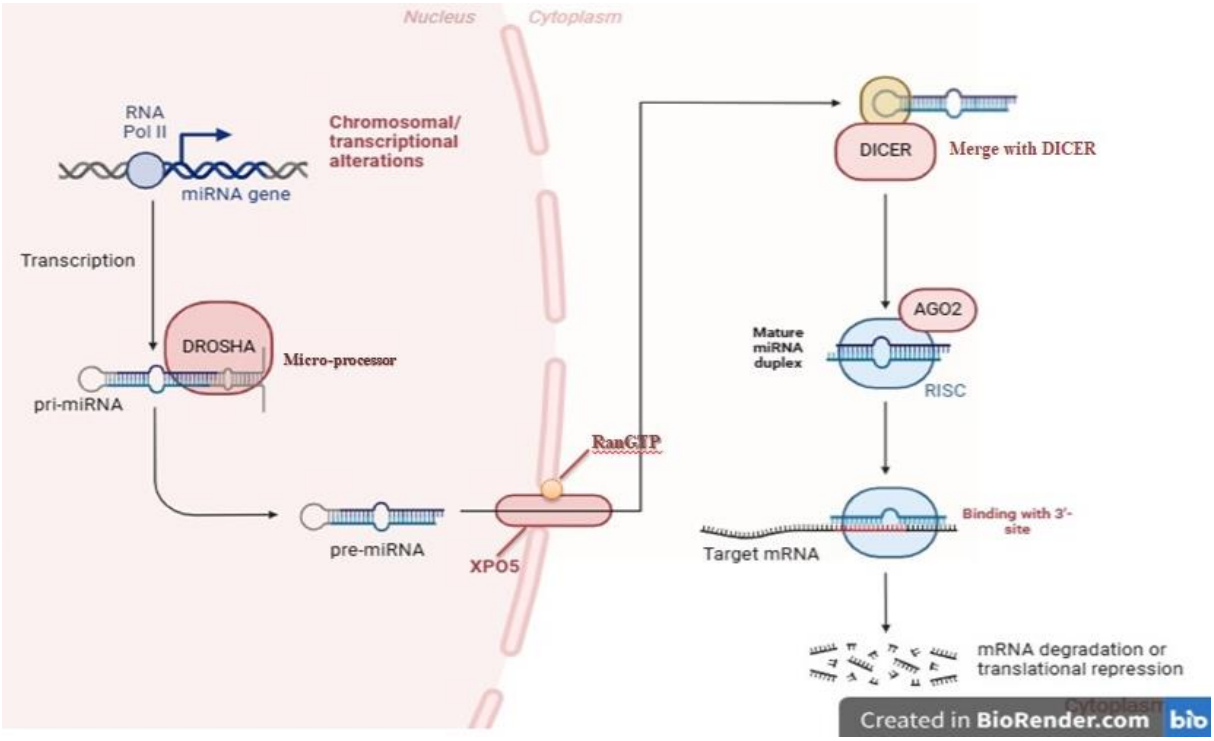

Figure 1. Biogenesis of miRNAs (created by the author using BioRender.com).

development, synaptic plasticity, and neuroprotection, influencing differentiation, learning processes, and responses to injury. They also play a key role in modulating inflammation, neuronal excitability, and synaptic transmission, making their dysregulation a potential contributor to epilepsy pathophysiology [12].

Among the identified miRNAs, miR-324-5p has been recognized as a key regulator of neuronal excitability. Experimental models have demonstrated that altering its expression can significantly influence seizure susceptibility, suggesting its potential as a therapeutic target for seizure control in DRE. Similarly, miR-335-5p has been shown to regulate voltage-gated sodium channel (VGSC) expression, with its increased levels reducing seizure severity and improving survival rates, whereas its inhibition enhances susceptibility to seizures [13].

Moreover, integrative network analyses of miRNA and mRNA expression profiles during epileptogenesis have provided deeper insights into the dynamic regulatory mechanisms involved. These studies have identified differentially expressed miRNAs throughout epilepsy progression, further reinforcing their potential as biomarkers and therapeutic targets. The evaluation of circulating miRNAs as preclinical biomarkers has also shown promise in predicting the risk of epileptogenesis. Their minimally invasive nature offers an opportunity for early diagnosis and intervention, potentially improving clinical outcomes for individuals at risk of developing epilepsy.

Furthermore, therapeutic strategies aimed at modulating miRNA expression are actively being investigated to combat DRE. Approaches such as miRNA mimics and inhibitors are being explored to restore the balance of dysregulated miRNAs, potentially enhancing the efficacy of existing antiepileptic drugs (AEDs) [12]. These innovative strategies not only hold the potential to improve patient outcomes but also pave the way for personalized treatment regimens based on an individual's unique miRNA profile.

Collectively, these findings emphasize the critical involvement of miRNAs in epileptogenesis and drug resistance, highlighting their potential role in the development of novel therapeutic strategies and diagnostic tools. Further research into miRNA-based interventions may provide a significant breakthrough in epilepsy management, particularly for patients with drug-resistant forms of the disorder.

Additionally, miRNAs serve as powerful modulators of post-transcriptional gene expression and are significantly dysregulated throughout epileptogenesis (Figure 1). Their dynamic expression patterns make them valuable molecular biomarkers for diagnosing epilepsy, assessing the risk of its development, and monitoring treatment response. As ongoing research continues to identify and validate key miRNAs involved in epilepsy pathophysiology, their clinical application as diagnostic and prognostic tools is becoming increasingly feasible (Table 1).

The first study on miRNAs in human epilepsy, published in 2010, identified increased hippocampal levels of miR-146a, which is associated with the regulation of inflammatory responses [14]. Subsequent research focused on five specific miRNAs: miR-132, miR-34a, miR-134, miR-184, and miR-128, each demonstrating potential importance in different physiological and pathological contexts [14], [15], [16], [17]. Notably, in mouse models, inhibition of miR-134 after status epilepticus significantly reduced the onset of spontaneous seizures [18], while reduced expression of miR-128 led to increased motor activity and fatal epilepsy [17].

Recent targeted and genome-wide miRNA profiling studies have identified more than 100 miRNA alterations in epilepsy patients and animal models, suggesting that epilepsy is associated with widespread changes in miRNA expression [19].

Table 1.

Key miRNA biomarkers in the diagnosis, prediction, and management of epileptogenesis.

№	MicroRNAs	Disease	Function	References
1	miR-146a	Epilepsy as a neurodegenerative disease	Control of apoptosis	Srinivasan et al., 2013
2	miR-211-5p	Epilepsy, ferroptosis	Regulates neuronal ferroptosis and oxidative stress associated with epilepsy.	X. Li et al., 2024
3	miR-335-5p	Epilepsy, adeno-associated virus	Suppresses the expression of voltage-gated sodium channels and may be a target for seizure control.	Heiland et al., 2023
4	mirR-34c-5p	Epilepsy, hippocampal neuron damage	In drug-resistant epilepsy, miR-34c-5p downregulation enhances neuroinflammation, exacerbating hippocampal neuronal loss.	Fu et al., 2020
5	miR-485	Hippocampal epilepsy	Overexpression significantly reduces seizure frequency and epileptiform firing of hippocampal DG neurons.	K. Wang et al., 2021
6	miR-146a, miR-134	Epilepsy	Improve blood flow in patients with drug-resistant seizures.	Leontariti et al., 2020, Organista-Juárez et al., 2019
7	miR-146a, miR-155, miR-134, miR-21, miR-22	Drug-resistant epilepsy	Predicted any reductions in seizures with the modified Atkins diet in adult patients with DRE after three months	Samões et al., 2024
8	miR-146a	Drug-resistant epilepsy	Reduced expression is associated with predisposition to drug-resistant epilepsy.	Boschiero et al., 2020
9	miR-146a	Drug-resistant epilepsy	Functional polymorphism of the miR-146a gene is associated with drug-resistant epilepsy and seizure frequency.	Cui et al., 2015
10	miR-139-5p	Epilepsy	Confers antiepileptic drug sensitivity in refractory epilepsy via inhibition of MRP1.	L. Wang et al., 2020
11	miR-212-3p and miR-132-3p	Mesial temporal lobe epilepsy (MTLE)	Both miRNAs work synergistically to control Sox11 expression	Haenisch et al., 2015

miRNA Profile in Brain Tissues of Patients with Drug-Resistant Epilepsy

In recent decades, with the development of next-generation sequencing (NGS), biomarker studies aimed at identifying diagnostic and prognostic miRNAs have become more widespread. The gold standard research design for these studies includes a discovery phase and validation phases, during which candidate biomarkers are selected from large sets of molecules. In the discovery phase, high-throughput technologies such as microarrays and RNA sequencing are used for sample profiling. Due to their high costs, both arrays and RNA sequencing allow for the identification of hundreds of compounds, though often in limited patient populations. This can lead to small sample sizes and higher rates of false positives and negatives, requiring additional testing. During the validation phase, quantitative PCR (qPCR) remains the gold standard for sensitivity and reliability, although it is also costly [20].

Traditional miRNA profiling studies in pharmacoresistant epilepsy are limited because tissue biopsies can only be obtained from patients undergoing brain surgery after the failure of other therapies. The lack of comparison with non-seizure, drug-sensitive patients and the limited number of samples hinder the understanding of large-scale miRNA dysregulation and the creation of independent discovery and validation cohorts. Additionally, samples are typically collected after therapeutic failure, making it difficult to assess the effect of an antiepileptic drug (AED) on miRNA levels [21], [22], [23].

This field still requires significant high-throughput profiling using NGS to identify miRNAs specific to drug-resistant epilepsy (DRE) patients. *Zucchini et al.* (2014) conducted the first rare tissue miRNA profiling study on 14 paraffin-embedded hippocampal or temporal lobe samples from DRE patients with hippocampal sclerosis. Although the study primarily focused on granule cell pathology (GCP), it also investigated the role of miRNAs in pharmacoresistance. The researchers identified miR-487a as the most significantly dysregulated miRNA in DRE patients [24].

De Matteis et al. found that miR-301a-3p was significantly overexpressed in a patient with drug-resistant mesial temporal lobe epilepsy (mTLE) who died of sudden unexpected death in epilepsy. Among the miRNAs studied miR-301a-3p, miR-194-5p, miR-30b-5p, miR-342-5p, and miR-4446-3p only miR-301a-3p showed significant dysregulation in both the tissue and plasma of patients with epilepsy compared to a non-epileptic control group [25].

Bencurova et al. also detected miR-301a-3p using NGS but did not observe a similar pattern in a larger qPCR cohort. They examined post-mortem changes and found a decrease in miRNA levels after 32 hours, suggesting strong stability. Their study, the first to use high-throughput NGS in DRE tissue, identified novel differentially expressed miRNAs (miR-1260a, miR-1260b, and miR-4443) associated with disorders other than epilepsy [26].

In contrast, well-studied miRNAs such as miR-146a, miR-132-3p, miR-132-5p, and miR-134-5p did not show changes in expression due to the unique profile of the hippocampus. *Organista-Juarez et al.* found a positive correlation between miR-146a levels, the number of AEDs used, and seizure frequency, suggesting a compensatory function in neuroinflammation [2].

Che et al. conducted an exploratory biomarker study in DRE patients with localized cortical dysplasia and found strong validity for miR-323a-5p [27]. Similarly, *Sun et al.* (2016) observed an increase in miR-129-2-3p in the same cohort. Another study found that miR-4521 was differentially regulated. These studies included various approaches, such as ROC analysis, AUC values, and confidence intervals, though sensitivity or specificity data were not published [28], [29].

Lee et al. [30] and *Gong et al.* [31] found that miR-153 plays a role in refractory epilepsy by affecting the HIF-1α pathway. In the discovery phase, Lee et al. found that miR-153 expression was downregulated in DRE patients, while HIF-1α expression was upregulated in non-epileptic controls. Both studies indicated that miR-153 targets the 3' UTR region of HIF-1α. Overexpression of miR-153 inhibits HIF-1α, while inhibition of miR-153 increases HIF-1α levels, suggesting a regulatory function of miR-153 in pharmacoresistance [30], [31].

Zorin et al. (2018) mentioned that different physiological parameters should be used to predict the course of epilepsy. Using cluster analysis and logistic regression, the research team identified patterns that could help predict drug resistance. These methods can also be applied to study genetic markers, providing new insights into the mechanisms of drug resistance [32].

Conclusion. Based on the analysis of the scientific literature, it is evident that expanding research on the heritability of drug-resistant epilepsy through miRNA studies is crucial, particularly in relation to risk factors prevalent in the region of Kazakhstan. The presented information enhances applied knowledge for primary care physicians and hospitals, contributing to improved early diagnosis and prevention of epileptic disorders in the future.

Integrating genetic and physiological data can significantly enhance the prediction of drug-resistant epilepsy. A review of the literature on the role of miRNA in drug-resistant epilepsy underscores the need for further research in this area. Such studies have the potential to facilitate the development of new antiepileptic drugs, improve the accuracy of timely diagnosis, refine treatment strategies, and support socio-psychological interventions. These advancements will positively influence the prescription of appropriate medications, the optimization of drug dosages, and, ultimately, the social functioning and quality of life for patients with epilepsy.

Conflict of interest. *The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.*

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All authors read and approved the final version of the paper.

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MODERN VIEW ON THE MORPHOFUNCTION OF THE HEART AND INTRACARDIAC NERVOUS STRUCTURES

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Abstract

Introduction. Over the past 10 years, there has been a high mortality rate from cardiovascular system pathologies associated with the autonomic nervous system. Mortality from heart pathology and its complications is mainly observed among the working-age population. At the same time, the relationship between the cardiac conduction system and the autonomic nervous system, as well as their role in regulating the stable functioning of the heart, occupy a significant place in modern scientific hypotheses proposed by a number of researchers. In this regard, research in this area remains highly relevant.

Aim: To analyze the scientific literature on the morphofunctional basis of the regulation of cardiac activity and intracardiac nervous structures.

Search Strategy: The search for articles was conducted using the databases of PubMed, Google Scholar, Embase, and the Cochrane Library, as well as data from domestic scientific publications. The search covered a 10-year period (2014–2024). A total of 71 scientific publications were analyzed.

Results. As a result of the study, explanations are provided regarding the relevance of morphological research on the cardiovascular system, along with modern scientific conclusions on the morphological function of the heart's nervous structures.

Conclusion. The significance of morphological structures, including intracardiac nerve plexuses, nodes, and fibers, which play a crucial role in the stable functioning of the heart, has been established.

Keywords: *cardiovascular system, structure of the heart, nervous structures of the heart, autonomous regulation, heart failure.*

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Резюме

СОВРЕМЕННЫЙ ВЗГЛЯД НА МОРФОФУНКЦИЮ СЕРДЦА И ВНУТРИСЕРДЕЧНЫХ НЕРВНЫХ СТРУКТУР

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Введение. За последние 10 лет регистрируется высокая смертность от патологий сердечно-сосудистой системы, связанных с вегетативной нервной системой. Смертность от патологии сердца и ее осложнений в основном отмечается среди лиц трудоспособного возраста. При этом взаимосвязь между проводящей системой сердца и

автономной нервной системой и их роль в регулировании устойчивой деятельности сердца занимают большое место в современных научных гипотезах целого ряда ученых. В этой связи актуальны исследования в этом направлении.

Цель исследования. Анализ научной литературы по вопросу морфофункционального обоснования регуляции сердечной деятельности и внутрисердечных нервных структур.

Стратегия поиска. Поиск статей проведен с использованием баз данных поисковых систем PubMed, Google Scholar, Embase, Cochrane Library, а также данных отечественных научных изданий. Глубина поиска 10 лет (2014 - 2024 гг.). Всего было проанализировано 71 научных публикаций.

Результаты. В результате анализа литературы обобщены данные об актуальности морфологического исследования сердечно-сосудистой системы, современных научных выводов по морфо-функции нервных структур сердца.

Заключение. Определено значение морфологических структур и внутрисердечных нервных сплетений, узлов и волокон, занимающих важное место в стабильном функционировании сердца.

Ключевые слова: сердечно-сосудистая система, строение сердца, нервные структуры сердца, автономная регуляция, сердечная недостаточность.

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Түйіндеме

ЖҮРЕК ЖӘНЕ ЖҮРЕКІШІЛІК ЖҮЙКЕ ҚҰРЫЛЫМДАРЫНЫҢ МОРФОФУНКЦИЯСЫ ТУРАЛЫ ЗАМАНАУИ КӨЗҚАРАС

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Кіріспе. Соңғы 10 жылда вегетативті жүйке жүйесімен байланысты жүрек – тамырлар жүйесінің патологияларынан болатын өлім-жітімнің жоғары деңгейі тіркелуде. Жүрек патологияларынан және оның асқынуларынан болатын өлім-жітім негізінен еңбекке қабілетті жастағы тұлғалардың арасында байқалады. Бұл ретте, жүректің өткізгіш жүйесі мен автономды жүйке жүйесі арасындағы өзара қатынас және жүректің тұрақты қызметінің реттелуіндегі рөлі бірқатар ғалымдардың заманауи ғылыми гипотезаларында үлкен орын алады. Осыған байланысты осы бағыттағы зерттеулер өзекті.

Зерттеу мақсаты. Жүрек қызметін реттеу және жүрек ішілік жүйке құрылымдарының морфофункционалдық негізделуі сұрақтары бойынша ғылыми әдебиеттерді талдау.

Іздеу стратегиясы. Мақалаларды іздеу PubMed, Google Scholar, Embase, Cochrane Library мәліметтер қоры бойынша, сонымен қатар отандық ғылыми басылымдар мәліметтерін қолдана отырып жүргізілді. Іздеу жылдықты соңғы 10 жыл (2014 – 2024 жж.). Барлығы 71 ғылыми жарияланымдарға талдау жасалды.

Нәтижелер. Зерттеу нәтижесінде жүрек – тамырлар жүйесін морфологиялық тұрғыдан зерттеудің өзектілігі, жүректің жүйке құрылымдарының морфо-функциясы бойынша заманауи ғылыми тұжырымдар туралы түсініктер берілді.

Қорытынды. Жүректің тұрақты қызмет атқаруында маңызды орын алатын морфологиялық құрылымдар және жүрек ішілік жүйке өрімдері, түйіндері мен талшықтардың маңызы анықталды.

Түйінді сөздер: жүрек – тамырлар жүйесі, жүрек құрылысы, жүректің жүйке құрылымдары, автономды реттелу, жүрек жетіспеушілігі.

Дәйексөз үшін:

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Introduction

The regulation of the cardiovascular system, particularly the functioning of the heart as the central organ of the vascular system, its conduction system development, and characteristics, remains a critical area of research in modern morphology. While there is ample literature on the structural features of the heart wall, angiogenesis, and vascular-related changes, these topics continue to occupy a leading position in contemporary research.

In this regard, the interaction between the heart's conduction system and the autonomic nervous system, as well as their role in regulating the heart's steady functioning, is emphasized in numerous modern scientific hypotheses. Despite centuries of studying the anatomical features of the autonomic nervous system, the autonomic nature of the enteral division (related to the digestive system), distinct from its two main divisions, is often overlooked. Similarly, within the heart, alongside extrinsic neural structures, the morphological diversity of intrinsic neural structures, which perform autonomous functions akin to the enteral division, has been highlighted.

Advances in neuroanatomical, neurohistological, and immunohistochemical research methodologies have accelerated investigations into the heart's neural structures. Current studies increasingly focus on the morphology of extracardiac nerve plexuses and fibers in comparison to intramural neural structures, yielding valuable insights into the functional regulation of the heart and its unique features.

Thus, understanding the morphofunctional characteristics and variability of the heart's autonomous (intracardiac neural structures) nervous structures is essential for comprehending cardiac function and associated disorders [4, 6, 11, 13, 15, 17, 28].

Among cardiac pathologies associated with neural structures, sudden cardiac death (SCD) remains a significant concern due to its high incidence rate. This condition poses a severe and unpredictable challenge in the field of general medicine, as it often occurs in individuals with no prior history of cardiac disease or detectable pathology. The absence of any warning signs or preceding symptoms complicates its prediction and prevention. According to several researchers, sudden cardiac death is closely linked to the neural structures of the heart.

However, studies by *Dainius H. Pauza and Dmitrij Kvitko* suggest that the coordinating neural structures within the heart, though substantial, do not constitute a fully autonomous system akin to the enteral division. Instead, these structures are part of the conduction system, which is widely recognized for regulating the heart's rhythmic activity. Despite this knowledge, the detailed morphology of the tens of thousands of intrinsic neurons within the heart and their specific characteristics remains under-researched. This gap in understanding makes it challenging to provide comprehensive information about the heart's neural structures and their functional features. Moreover, changes in intracardiac neural structures are believed to underlie various cardiac arrhythmias, leading to dilated cardiomyopathy and heart failure. These findings underscore the importance of further research into the role of neural structures in cardiac pathophysiology [25, 29, 38, 41, 44, 67].

Thus, scientific studies aimed at investigating the features of cardiac neural structures remain highly relevant today. According to data from the World Health Organization and scientific literature, cardiovascular diseases have the highest mortality rate globally. Among these, pathologies associated with disruptions in the heart's neural structures are particularly challenging to diagnose and are significant contributors to sudden cardiac death. Consequently, studying the morphology of neural structures, particularly intracardiac neural networks, has become one of the priority areas in contemporary research.

Aim: To analyze the scientific literature on the morphofunctional basis of the regulation of cardiac activity and intracardiac nervous structures.

Search Strategy

The literature review for this article was conducted using databases such as PubMed, Google Scholar, Embase, and Cochrane Library, along with references from domestic scientific publications. The review focused on scientific articles published over the past decade (2014–2024). It also included randomized studies, systematic reviews, and meta-analyses related to the topic.

To comprehensively explore the relevance of the topic, a range of keywords and terms were used: cardiac function regulation, myocardial cellular composition, cardiomyocyte types, extracardiac neural structures, intracardiac neural structures, autonomic regulation, cardiac ganglia, cardiac nerve plexuses, adrenergic and cholinergic ganglia, and immunohistochemical studies of neural structures. In total, 71 scientific publications were analyzed during the literature review, providing a detailed characterization of the topic's relevance.

Results and Discussion

A Modern Perspective on the Morphology of Intracardiac Neural Structures

Research on the neural regulation of cardiac function ranks among the most pressing issues in contemporary morphophysiology and practical cardiology. Given the heart's primary role as a pump, its consistent operation ensures stable and efficient hemodynamics. In this context, the maintenance of steady cardiac activity is largely influenced by extracardiac neural regulation, which includes the sympathetic and parasympathetic nervous systems. These systems function as a unified neuroendocrine network, providing stimulatory and inhibitory control mechanisms. However, in addition to external neural structures, the role of intracardiac neural structures is particularly significant in maintaining consistent heart function. These structures are increasingly being recognized as a distinct system. The morphology of intracardiac neural structures and their distribution underscore their unique role in cardiac regulation [39, 60, 68].

Further exploration into the intricate organization and functionality of intracardiac neural elements highlights their importance in both physiological and pathological states of the heart. Understanding their interaction with extracardiac systems is crucial for advancing cardiac research and developing targeted interventions for various cardiac disorders.

Morphological and Functional Features of Intracardiac Neural Structures

Literature data and several research studies have confirmed that sympathetic fibers within the myocardium are located along the coronary arteries. Additionally, afferent and efferent sympathetic fibers are positioned within the superficial layer of the epicardium, extending deeply to reach the endocardium. In contrast, the parasympathetic fibers, particularly those associated with the vagus nerve, are primarily intramural or sub-endocardial and ascend to the sub-epicardial region near the atrioventricular groove.

The parasympathetic division plays a significant role in regulating cardiac function by modulating norepinephrine levels. This regulation occurs through the suppression of cAMP-mediated phosphorylation of cardiac proteins such as phospholamban, thereby altering sympathetic activity. Research also reveals that neuropeptides released from sympathetic nerve endings can suppress the effects of the vagus nerve on the heart. However, it is incorrect to state that the heart and its vascular functions are entirely dependent on the ganglionic (autonomic) nervous system, as the cardiovascular system possesses its intrinsic regulatory mechanisms.

From a morphological perspective, the peripheral autonomic innervation of the heart is highly complex and distinctive. The heart, like other somatic organs, is equipped with segmental–peripheral and cranial-level interactions through the peripheral sympathetic and parasympathetic divisions. These interactions facilitate ganglionic innervation, enabling organs to respond rapidly to changes in the body's vital activities. This system also supports the autonomous regulation of individual organs through specific morphological structures, influencing inter-organ autonomic interactions.

This morphofunctional interdependence highlights the complexity of cardiac regulation and its intricate relationship with other organs. The vegetative provision of the heart's contractile function is closely tied to the peripheral autonomous regulation of pacemaker activity within the sinoatrial node, supported by intracardiac neural structures (ICNS). Despite its integration with the heart's overall physiological role, the sinoatrial node remains the primary pacemaker under both normal and pathological conditions.

To fulfill this role, the sinoatrial node is capable of receiving efferent information at both intra- and extracardiac levels. Hemodynamic participation in the body's adaptive processes to environmental changes is achieved through a complex regulatory system that governs cardiac activity. This regulation occurs not only at the extracardiac level but also through the intrinsic regulatory complex located within the heart's morphologically unique and architecturally complex structures [20, 37, 59, 69].

The self-regulation of cardiac function involves a morphologically complex system facilitated by several structures. According to the scientific literature, these structures include intracellular and intercellular processes, with the most critical being the intracardiac neural structures (ICNS). Some researchers refer to the ICNS as the metasympathetic division in their studies.

The complexity of cardiac function is directly related to the morpho-functional properties of the myocardium. The myocardium's primary mass comprises working cardiomyocytes (contractile), followed by sinoatrial (pacemaker), transitional, conductive, and secretory cardiomyocytes. The self-regulation of cardiac activity is significantly influenced by metabolic processes within these cardiomyocytes and the transfer of excitation between cells through transitional intercellular processes. This interaction ensures the myocardium's complex and uninterrupted contractions [33, 35, 43].

Among the key contributors to cardiac self-regulation are the intramural neural formations located within the heart's layers (ICNS). These structures include autonomic neurons, preganglionic, and postganglionic fibers found within the neural ganglia of the heart. While these structures are part of the peripheral division of the autonomic nervous system and function as autonomous structural-functional components within the heart, their precise roles remain a subject for further research.

The lack of consensus regarding the morphofunctional characteristics of these structures complicates understanding the development and function of the cardiac neural network, ganglionic apparatus, and neuromuscular connections. These characteristics also depend on the unique features of each organism. Morphologically, the ICNS begins with sensory receptor structures located in the heart tissue and its segments. These receptors are diverse and situated intramurally, receiving signals about the heart's condition and activity, converting them, and transmitting them via afferent pathways.

Research into purinergic regulation during early postnatal ontogenesis reveals that P2X receptor subtypes located within the heart have heterochronic effects on cardiac contractile and chronotropic functions, varying across different heart regions. Intramural neurons are interconnected through synapses and interact via associative fibers, enabling effector responses through axon reflex mechanisms.

The ICNS possesses an extensive mediator system that influences impulse transmission and modulation, affecting conduction speed and response variability. Studies show that the number of these neurons varies among mammals. For instance, in humans (including children), approximately 94,000 neurons are found in epicardial plexuses, with additional neurons grouped or isolated. Subepicardial ganglia can number up to 1,500. This extensive neural network supports viewing the ICNS as an independent system.

Neurons within the ICNS are categorized as motor adrenergic, motor cholinergic, sensory, and interneurons. Adrenergic and cholinergic neurons, in particular, respond to various stimuli differently. Mechanoreceptors influence this response; for example, reduced blood pressure in the left ventricle triggers enhanced myocardial contraction through adrenergic ICNS neurons. Conversely, cholinergic neurons exhibit lower excitability and require stronger stimuli to activate, which in turn suppress adrenergic neuron activity [18, 40, 47, 48, 70].

The ICNS serves as a delicate integrative mechanism that not only evaluates blood circulation within the heart chambers but also monitors changes in the overall arterial and venous systems. In response to these changes, the ICNS ensures adaptive adjustments in cardiac function through autoregulatory mechanisms.

This integrative role highlights the ICNS's essential contribution to maintaining hemodynamic stability by dynamically responding to physiological and pathological changes within the cardiovascular system.

Aspects of Research Focused on Heart Pathologies

When analyzing the genesis and consequences of cardiovascular system pathologies, it has become evident that diseases with a neurogenic origin are a current and relevant issue, requiring an expansion of research. Scientific studies focused on the features of heart nerve structures in various pathologies have resulted in differing opinions among scientists, providing insight into the complex morphofunctional relationship between the heart's conduction system and the ganglionic nervous system, and shedding light on their variability.

Disruption of heart rhythm can occur when the autonomic nervous system fails to fully or partially ensure the functional conduction system. In such cases, functional disorders occur within the nerve cells, fibers, and the networks of ganglia, including the sinoatrial and atrioventricular nodes.

According to the research of Fedulova M.V., Pigolkin Y.I., and Toklu H.Z., the mechanism of arrhythmia is very complex, with multiple causes. On one hand, it is based on centers located in the brain, specifically in the nuclei of the medulla oblongata. On the other hand, it is based on the damage to the autonomic nerve ganglia and their peripheral parts, as well as the associated morphological structures. Therefore, it is well known that changes in the heart's nervous structures can lead to sudden death. For infants under one year of age, forensic examinations have revealed that in over 92% of cases, morphological changes are observed in the nerve ganglia, alongside changes in the layers of the heart wall. These changes are associated with hypertrophy of cardiomyocytes, which, in turn, are predicted to lead to disruptions in the heart's contraction function. This hypothesis is supported by morphological criteria such as changes in the heart's conduction system, apoptosis in neurons, fragmentation of nerve fibers, and axonal degeneration. Furthermore, the primary mechanism behind arrhythmia is the death of atypical cardiomyocytes. These conclusions were drawn from complex studies that identified these morphological changes through scientific research. [19, 26, 27, 52, 64].

Scientific conclusions regarding the role of ganglionic regulation in the genesis of heart arrhythmias have led to the formation of two opposing views. In particular, during ischemic heart disease, increased sympathetic activity is known to contribute to the development of arrhythmias, while activation of the parasympathetic component has the opposite, protective effect. However, in cases of sudden death with autonomic dysfunction, morphological studies of the myocardium reveal a sharp decrease in catecholamines in adrenergic fibers and changes in the vegetative nerve ganglia. Furthermore, ischemia of the ventricular walls leads to activation of the parasympathetic component in some areas, while ischemia in other areas increases the tone of sympathetic afferent nerves. This suggests that during heart pathologies, the intramural neural structures and autonomic nervous system exert various effects, and also that changes in myocardial contraction due to remodeling during ischemic heart disease lead to structural alterations in the neural components. These morphological alterations cause electrical instability, which can result in fatal arrhythmias.

The mechanism of neurovascular changes associated with heart pathologies cannot be considered in isolation. Depending on the stages of ontogenesis, including age-related changes, these alterations may appear as a manifestation on their own or may be exhibited simultaneously with other pathologies, potentially supporting one another. Scientific studies have shown that early involution of the sympathetic component appears around the age of 35-40. Forensic examinations in cases of death unrelated to heart disease show that structural changes in vascular and vegetative nerve fibers are indicative of disruptions in nerve trophism. With aging, involutive changes in sympathetic innervation increase, and reactive changes in adrenergic neurons can lead to further destructive changes. Additionally, powerful stimuli like myocardial stretch receptors and the stimulation of cholinergic neurons with low excitability in vagus nerve fibers result in heart rate slowing, which in turn inhibits adrenergic neurons. These phenomena are further exacerbated by the presence of atherosclerotic changes, leading to the development of additional pathologies [1, 5, 8, 10, 21].

According to the studies by Pooja Bhadoria and R. Ambiga, today, left ventricular hypertrophy (myocardium) is considered one of the manifestations of heart remodeling caused by arterial hypertension. Changes in the left ventricular myocardium are multifactorial and often occur in stages. Therefore, even mild left ventricular hypertrophy is a significant factor contributing to the onset of cardiovascular diseases, lowering the prognosis of patients with arterial hypertension, increasing the risk of myocardial infarction and sudden cardiac death, and leading to arrhythmias and heart failure. Cardiovascular diseases are the leading cause of death in many developed countries, accounting for 40% of all deaths. In this context, left ventricular myocardial hypertrophy is frequently observed in many such diseases.

During the development of cardiovascular disease, the dysfunction of the left ventricle, manifesting as a decrease in systolic (contractile) and/or diastolic (active relaxation) function, is common. This dysfunction is associated with an increase in the heart's pumping function and minute volume through compensatory mechanisms. Among these mechanisms, the primary role is played by the hypertrophy of the left ventricle with an increase in muscle mass [32, 57, 63].

The remodeling of heart structures, influenced by external environmental factors and age-related changes, involves a process of adaptation. Additionally, changes in the endothelial cells of blood vessels and subsequent structural remodeling are well documented. Research in this area has focused on the connection between left ventricular myocardial hypertrophy and the heart's neural structures, leading to investigations of gene polymorphism. These studies show that complex morphological changes in the sympathetic-adrenal system occur, indicating that the sympathetic system's effect on adrenergic receptors influences cardiac neural structures through the presynaptic inhibition of norepinephrine release, thus affecting autonomic regulation.

Similar changes in the heart's neural structures have been identified under physical stress. Morphologically, these include changes in nerve cells of the nodal apparatus, functional load in conductive cardiomyocytes, hypertrophy, and acute swelling, while limiting physical load is associated with reparative changes. In comparative studies of alcoholic cardiomyopathy and ischemic heart diseases, changes in vascular and cellular membrane permeability have been shown to disrupt electrical impulse conduction and generation, leading to ventricular fibrillation.

These changes represent the remodeling of the conduction system of cardiomyocytes and the heart's neural structures (GITQ). Hypertrophic cardiomyopathy, typically seen in secondary (arterial hypertension) hypertrophy, often presents as asymmetric concentric hypertrophy of the left ventricle, despite the variety of myocardial remodeling patterns. Modern perspectives on hypertrophic cardiomyopathy suggest that without a clear assessment of remodeling, numerous variations in the structural changes of the left ventricle exist depending on the exact location of hypertrophy. In contemporary cardiovascular research, the concept of "remodeling" is not universally defined. Remodeling refers to a complex process of structural and functional disruption of the heart, resulting from excessive load or loss of part of the viable myocardium. It is crucial to understand the evolutionary responses that allow damaged tissue to quickly adapt to new conditions in response to pathological agents affecting the heart [9, 30, 34, 46, 53, 55, 58].

Thus, the study of the characteristics of intracardiac neural structures in various cardiovascular pathologies shows that these structures are characterized by a range of features, from simple morphological changes to alterations at the cellular level. Age-related changes in the intracardiac neural structures, along with general hemodynamic patterns, are capable of receiving information from the heart wall and intracardiac morphofunctional indicators, which, through integration with the extrinsic nervous system, can alter the heart's contractile activity. It can be predicted that the autonomous system of the intracardiac neural structures plays a key role in maintaining the heart's stable rhythm and that these structures undergo changes in the form of remodeling during pathological conditions.

Conclusion

Recent scientific research over the past decade has established a link between the autonomic nervous system and cardiovascular system pathologies in relation to mortality. This highlights the significant relevance of contemporary scientific studies focusing on cardiovascular issues. A key feature of these studies is the high mortality rate from heart-related complications, particularly among individuals of working age. As outlined in the literature, sudden cardiac death and secondary manifestations of certain changes lead to disruptions in the heart's contractile function, primarily due to alterations in the heart's neural structures.

Given that coronary circulation is primarily regulated by the autonomic nervous system, autonomic-reflex changes, such as hemodynamic, metabolic, and energy disturbances, are considered prognostic indicators of functional changes. Heart rhythm, as an indicator of these changes, is influenced by the dynamic interactions of the morphological divisions of the ganglionic nervous system, affecting the heart's conductive system and intracardiac neural structures. In maintaining heart function, the role of the extrinsic neural structures (the peripheral part of the autonomic nervous system), along with the cellular elements (neurons, contractile cardiomyocytes), and particularly intracardiac neural structures (intracardiac nervous system and heart's autonomic nervous system), is pivotal [2, 14, 22, 23, 31, 36, 42, 51, 54, 65].

Efferent neurons within the intracardiac neural structures not only serve as a means of transmitting impulses from preganglionic fibers to postganglionic fibers but also play a critical role in regulating other vital heart functions. The most important factor influencing the heart's rhythmic contraction and its changes is the interaction between impulses from preganglionic fibers and those participating in the autonomous regulation process. As a result, the heart's regular and rhythmic contraction is controlled through the complex mechanisms of intense impulse transmission. Thus, studying the architecture of intracardiac neural structures, their morphological components, and changes in the context of cardiovascular pathologies remains a crucial area of scientific research [3, 12, 16, 24, 45, 49, 50, 56, 61, 62, 66].

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RADIOLOGICAL METHODS IN THE DIAGNOSIS OF ATRIOVENTRICULAR SEPTAL DEFECT

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Abstract

The article is devoted to the optimization of radiation research methods in the diagnosis and evaluation of the effectiveness of surgical correction of atrioventricular septal defect. Congenital heart defects are among the most common cardiovascular abnormalities and represent a leading cause of death in infants during the first year of life. The article emphasizes the need for special attention to children with congenital heart disease, as well as adult patients with residual disorders such as pulmonary hypertension, atrioventricular valve insufficiency, arrhythmias, and others. Recommendations for organizing medical care for adults with congenital heart disease include coordinating the activities of regional centers, educational programs for patients and their families, as well as training cardiologists. The article highlights the importance of interaction between different levels of health systems to ensure effective treatment and follow-up of patients with congenital heart disease.

Keywords*: heart disease, congenital heart defects, heart valve disease, heart failure.*

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Резюме

ЛУЧЕВЫЕ МЕТОДЫ ИССЛЕДОВАНИЯ В ДИАГНОСТИКЕ АТРИОВЕНТРИКУЛЯРНОГО СЕПТАЛЬНОГО ДЕФЕКТА

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Статья посвящена оптимизации лучевых методов исследования в диагностике и оценке эффективности хирургической коррекции атриовентрикулярного септального дефекта. Врожденные пороки сердца представляют собой распространенную патологию сердечно-сосудистой системы, являющуюся одной из основных причин смерти детей первого года жизни. Статья подчеркивает необходимость особого внимания к детям с врожденным пороком сердца, а также взрослым пациентам с резидуальными расстройствами, такими как легочная гипертензия, недостаточность атриовентрикулярных-клапанов, аритмии и другие. Рекомендации по организации медицинской помощи взрослым с врожденным пороком сердца включают координацию деятельности региональных центров, образовательные программы для пациентов и их семей, а также подготовку кардиологов. Статья подчеркивает важность взаимодействия различных уровней систем здравоохранения для обеспечения эффективного лечения и наблюдения за пациентами с врожденным пороком сердца.

Ключевые слова: *болезни сердца, врожденные сердечные дефекты, заболевания сердечных клапанов, сердечная недостаточность.*

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Түйіндеме

АТРИОВЕНТРИКУЛЯРЛЫҚ СЕПТАЛЬДЫ АҚАУДЫ БАҒАЛАУДА СӘУЛЕЛІК ДИАГНОСТИКА ӘДІСТЕРІ

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Мақала атриовентрикулярлық септальды ақауды хирургиялық түзетудің тиімділігін диагностикалау мен бағалаудағы сәулелік зерттеу әдістерін оңтайландыруға арналған. Туа біткен жүрек ақаулары-өмірдің бірінші жылындағы балалардың өлімінің негізгі себептерінің бірі болып табылатын жүрек-қантамыр жүйесінің кең таралған патологиясы. Мақалада туа біткен жүрек ақауы бар балаларға, сондай-ақ өкпе гипертензиясы, атриовентрикулярлық клапанының жеткіліксіздігі, аритмия және т.б. сияқты қалқанша безінің бұзылуы бар ересек пациенттерге ерекше назар аудару қажеттілігі көрсетілген. Туа біткен жүрек ақауы бар ересектерге медициналық көмекті ұйымдастыру бойынша ұсыныстарға аймақтық орталықтардың қызметін үйлестіру, пациенттер мен олардың отбасыларына арналған білім беру бағдарламалары және кардиологтарды даярлау кіреді. Мақалада туа біткен жүрек ақауы бар науқастарды тиімді емдеу мен бақылауды қамтамасыз ету үшін денсаулық сақтау жүйесінің әртүрлі деңгейлерінің өзара әрекеттесуінің маңыздылығы көрсетілген.

***Түйін сөздер**: жүрек аурулары, туа біткен жүрек ақаулары, жүрек клапандарының аурулары, жүрек жеткіліксіздігі.*

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Introduction

Congenital heart defects (CHD) present a considerable challenge in the field of pediatric cardiology, impacting the health and survival rates of children in profound ways. Atrioventricular septal defect (AVSD) is a notable type of congenital heart disease (CHD) characterized by its complexity, which necessitates a thorough approach to diagnosis, management, and ongoing patient care. The optimization of radiological diagnostic techniques is critical in determining the efficacy of surgical AVSD repair and enhancing treatment results.

The purpose of this article is to evaluate contemporary techniques for the diagnosis and treatment of CHD, as well as the approaches to monitoring children and adult patients with residual issues following surgery. Recommendations for arranging medical treatment for individuals with CHD are reviewed, including not only clinical but also social and psychological elements of care for this patient population. The need of coordinating efforts at all levels of health care to guarantee appropriate treatment and monitoring of patients with CHD is stressed as a critical component of enhancing therapeutic results and quality of life in this group.

The review's objectives are to investigate the capabilities of radiation research methodologies in the diagnosis and assessment of the success of surgical repair of an atrioventricular septal defect utilizing echocardiography and CT angiocardiography.

Search Strategy: A literature review on the subject "Radiation research methods in the diagnosis of atrioventricular septal defect" was conducted using the Medline and PubMed databases. The search period was ten years (2013-2023), however, materials from 1989, 1996, and 2005 were also utilized since they contained conceptual information.

Inclusion criteria: Studies on the diagnosis and treatment of AVSD using radiological methods in both children and adults were included. Publications from 2013 to 2023 and earlier works with conceptual significance were considered.

Exclusion criteria: Studies without reference to AVSD or without imaging methods were excluded. Non-peer-reviewed sources and articles in languages inaccessible for analysis were not considered.

Keywords: heart disease, congenital heart defects, heart valve disease, heart failure.

Background

Congenital heart disease (CHD) is a prevalent pathology in cardiovascular illnesses and one of the leading causes of mortality in infants in their first year of life. The term "congenital" refers to a condition that exists at birth. The phrases "congenital heart defect" and "congenital heart anomaly" are often used interchangeably, although "defect" provides a more accurate description [12, 18, 27].

Congenital heart disease refers to a structural abnormality of the heart and major arteries that develops

during the embryonic stage, leading to various hemodynamic challenges. Consequently, these abnormalities may lead to heart failure and progressive changes in the body's tissues.

The clinical manifestations of congenital heart disease vary depending on the specific type of abnormality present.

Symptoms may be nonexistent or threatening. When symptoms appear, they are diverse and include fast breathing, cyanosis (blue skin), poor weight growth, and weariness. It is vital to remember that CHD is not accompanied by chest discomfort. CHD accounts for 40% of all congenital defects, which includes intrauterine fetal mortality and early miscarriages. The frequency of cardiac lesions in live-born neonates ranges from 8 to 14 occurrences per 1000 live births. CHD is responsible for at least 11% of newborn mortality and around 50% of all fatalities related to abnormalities. [12, 18]. In today's society, the number of adult patients with congenital heart abnormalities has increased significantly. Over the previous several decades, the proportion of persons identified with congenital heart disease has steadily increased in rich countries. In 1940, only 30% of individuals with coronary heart disease reached adulthood; now, that figure has risen to 85%. The number of adult patients living with coronary heart disease is expected to rise further as a consequence of advances in pediatric cardiology and medical therapy.

The atrioventricular septum is composed of two main components: atrial and ventricular. The atrial section, also known as the atrial segment of the atrioventricular canal, is located between the anterior and inferior margins of the fossa ovalis and the common atrioventricular canal. The endocardial cushion extends to the posterior wall of the common atrium, where it presents itself.

The ventricular section, also known as the entry segment of the ventricular septum, is made up of muscular tissue that lies underneath the tricuspid valve and continues forward toward the membranous septum. This structure develops as endocardial cushion tissue proliferates toward the heart's apex. When this component is lacking or underdeveloped, the ventricular septum seems to be projecting, resulting in an atrioventricular canal-type ventricular septal defect (VSD), also known as an inlet or posterior VSD. The degree of development of the intake septum varies, with some examples showing as a tiny and restrictive defect, while others are big and non-restrictive [12].

Atrioventricular septal defects

The following terms pertain to CHD: common atrioventricular canal, atrioventricular septal defects, atrioventricular defects, patent common atrioventricular canal, and endocardial cushion defect.

Atrioventricular canal (AVC) is a congenital heart defect characterized by a common atrioventricular (AV) valve ring, varying degrees of insufficiency in the mitral and tricuspid components, and the presence of a primary atrial septal defect (ASD) and an inflow ventricular septal defect (VSD) in complete AVC cases. Atrioventricular canals account for 2-6% of all congenital heart abnormalities (CHD). AVC comes in three forms: full, intermediate, and incomplete. Atrioventricular septal defect (ASD) affects more than 75% of people with Down syndrome [15,51,71].

Atrial septal defect (ASD) is one of the most common congenital heart abnormalities seen in adults. It occurs when the right and left atria do not close properly. Most ASDs are diagnosed and addressed in childhood. Individuals with atrial septal defects rarely exhibit symptoms during early childhood. On the other hand, babies have been seen to have episodes of congestive heart failure (CHF) and recurring pneumonia. Notable features include a unique right ventricular impulse and detectable pulsing of the pulmonary artery. The initial heart sound may be normal or divided, indicating that the tricuspid valve has closed [68]. Defects in both the atrial and ventricular septa describe AVSD, a congenital heart abnormality also known as a shared or partly separated atrioventricular connection. The conditions defining AVSD in its partial form include an atrial septal defect, many atrioventricular valves, an entrance ventricular septal defect, and a cleft in the mitral valve. Different forms of atrial septal defects are distinguished by a single common atrioventricular valve, an atrial septal defect, and a nonrestrictive inflow ventricular septal defect [2,5,23].

Morphological features of the defect. General morphological characteristics of all AVD forms:

1. Inadequate inflow segment of the interventricular septum (IVS) combined with the absence of a membranous septum, giving the IVS its unique "scoop-shaped" appearance.

2. The presence of a single atrioventricular valve, usually with five cusps.

3. The atrioventricular valve leaflets adhere abnormally to the interventricular septum edge.

4. A tricuspid shape of the left (mitral) portion of a single atrioventricular valve caused by a crack in the anterior mitral valve cusp.

5. The left (mitral) component of the common atrioventricular valve is displaced towards the left ventricular outflow tract (LVOT). 6. The inflow tract contracts, the LVOT elongates and becomes constricted, and the aortic root moves anteriorly and to the right.

7. A primary atrial septal defect (ASD) is present in the inferior portion of the interatrial septum, directly superior to the single atrioventricular valve. The cusps of the single atrioventricular valve form the inferior limit of the atrial septal defect (ASD) [16,48].

An atrioventricular defect (AVD) is a congenital cardiac condition marked by the complete or partial absence of the septal barrier between the atria and ventricles. A complete atrioventricular septal defect appears as a single, centrally located lesion in the heart septum. This congenital abnormality causes a significant blood shunt from the left to the right at both the atrial and ventricular levels of the heart.

Epidemiology and causes

AVSD has an estimated prevalence of 0.24 to 0.31 per 1,000 live births, with no significant gender differences [1,75]. This congenital heart abnormality is strongly associated to Down syndrome. Concurrent defects, such as ventricular hypoplasia and inherited disorders like Down syndrome, impair the long-term prognosis after AVSD repair; nonetheless, considerable advances in surgical treatments in recent decades have dramatically improved survival rates. The purpose of this research is to investigate the etiology, epidemiology, and pathophysiology of AVSD, as well as current treatment techniques, potential implications, and clinical significance [38, 39].

Throughout fetal development, the interatrial and interventricular septa progressively arise, allowing for the anatomical segmentation of the heart. Endocardial ridges form at the atrioventricular junction and extend perpendicularly to the septal structure inside the heart. These ridges are essential for accurately dividing the right and left heart chambers and developing two distinct atrioventricular valves: the tricuspid valve on the right and the mitral valve on the left. These valves allow for unidirectional blood flow from the atria to the ventricles. Impairments in endocardial ridge formation may induce irregularities in chamber division and valve development, resulting in atrioventricular septal defects. The size of the primary atrial septal defect (ASD) and the inlet ventricular septal defect (VSD) determines the severity of the defect [65].

Genetic mutations are the primary cause of AVSD, with the majority of cases connected with syndromic illnesses. An atrioventricular septal defect affects about one out of every six people with Down syndrome. Atrioventricular septal defects and other congenital cardiac abnormalities in this patient group have been linked mostly to the Down Syndrome Cell Adhesion Molecule (DSCAM) gene. Apart from syndromic linkages, autosomal dominant inheritance patterns have been noted in gene modifications linked to AVSD. Moreover, non-syndromic AVSD [43] has been associated to maternal diseases including obesity and prenatal hyperglycemia.

Pathophysiology

Early development of the atrioventricular septum and valves is mostly dependent on the bilateral mesenchymal structures known as endocardial cushions inside the common atrioventricular canal. At the end of the fourth week of pregnancy, the endocardial cushions begin to fuse together, forming a wall between the atrium and ventricle. When the fusion process is not completed correctly, AVSD may emerge to varying degrees. The atrioventricular valve's anatomy may produce both complete and partial atrioventricular systolic dysfunction. A complete atrioventricular septal defect is identified by three characteristics: the presence of a single common atrioventricular valve, an ostium primum atrial septal defect, and an inlet ventricular septal defect. A failed endocardial cushion fusion results in the absence of the atrioventricular septum [21].

A condition known as partial AVSD has an ostium primum atrial septal defect, an inlet ventricular septal defect, and a gap in the mitral valve. The atrioventricular valves remain distinct, which distinguishes this condition. This insufficiency occurs when the endocardial cushions do not fully blend together [26, 44].

Classification

Atrioventricular septal defects are a diverse set of congenital heart defects that differ in their anatomical arrangement, the presence and severity of septal and valvular abnormalities. Based on anatomical features, these can be classified as whole, partial, or intermediate types.

Rastelli's categorization is based on the attachment of the superior bridging leaflet to the interventricular septum and identifies three forms of AVSD [27,28,33].

● Type A: The bridging leaflet connects to the crest of the interventricular septum, resulting in a minor deficit.

● Type B leaflets adhere to an aberrant papillary muscle formation in the right ventricle, extending over the interventricular septum.

● Type C: The leaflet stays loose and does not connect to the septum, resulting in a significant deficiency.

Clinical presentation

The clinical expression of the AVSD is determined by the defect type, the level of blood shunting; valve functioning, and the presence of other abnormalities. Significant left-to-right shunting and pulmonary volume overload usually cause AVSD in infants and young children to manifest as signs of heart failure. According to Rigby (2021), these symptoms include tachypnea, insufficient weight gain, feeding difficulties, and substantial fatigue with modest activity.

Patients with a complete atrioventricular septal defect have more severe symptoms due to considerable volume overflow and early development of pulmonary hypertension. Cardiomegaly is often detected by clinicians during physical exams, which is supported by chest radiography data, according to *Boutayeb A. et al*. Auscultation may also reveal a systolic murmur caused by regurgitation via the common atrioventricular valve [9].

Partial AVSD, on the other hand, may be asymptomatic during infancy and remain undiagnosed until later in life, particularly when pulmonary hypertension or progressive valve dysfunction develops. According to *Van der Linde D. et al. (*2011), these patients may have little symptoms in the early stages but later develop exertional dyspnea, arrhythmias, and signs of right ventricular failure. [66]

The clinical course of AVSD is inextricably linked to the presence of concurrent illnesses. Atrioventricular septal defect (AVSD) is seen in 40-50% of Down syndrome cases, and it is often associated with other cardiac and extracardiac anomalies. According to *Craig B. et al*. (2006), these patients have an increased risk of developing pulmonary hypertension due to abnormal pulmonary vascular development [16].

Surgical treatment

Surgical repair of an atrioventricular septal defect (AVSD) is the conventional therapy for removing anatomical flaws, restoring normal hemodynamics, and limiting the development of pulmonary hypertension. The kind of AVSD, the patient's age, the extent of the defect, and any concomitant diseases all influence the surgical procedure used. The major method is biventricular repair, which entails closing both atrial and ventricular septal defects and reconstructing the atrioventricular valve [24]. According to *Atik E. et al.*, the two most widely employed procedures are double patch repair (Double Patch) and modified single patch repair [6, 46].

The double patch method uses two independent patches to repair the atrial and ventricular septal defects, resulting in exact anatomical restoration of the septa and valves. This method is recommended for individuals with significant abnormalities and complicated valve architecture. *Wang G. et al.* (2020) found that double patch repair promotes long-term structural stability while reducing the probability of residual defects [37,72].

In contrast, the modified single patch approach uses a single patch to correct both atrial and ventricular septal defects. This approach is less intrusive and requires less

cardiopulmonary bypass time, making it ideal for newborns and high-risk surgery patients. However, as *Husain A. et al* (2021) point out, the single patch approach may be less successful in situations of big defects or considerable valvular insufficiency [37].

Palliative surgical methods are used for individuals who have a functioning single ventricle and cannot be repaired completely. These instances need a tiered strategy that includes shunt treatments (e.g., the Blalock-Taussig shunt) to increase pulmonary blood flow and the Fontan surgery, which directs venous blood flow to the pulmonary arteries while bypassing the right heart. *Goo H.W. et al.* (2018) found that graded palliative operations are still a feasible choice for individuals with significant morphological defects that limit biventricular restoration. [30].

Postoperative follow-up is essential for determining the efficacy of surgical repair and identifying problems. The most frequent surgical complications are residual septal abnormalities, atrioventricular valve regurgitation, and arrhythmias. These problems often need extra surgical or medicinal interventions. According to *Song L.* et al. (2019), contemporary imaging methods like 3D echocardiography and CT provide early diagnosis and intervention in postoperative problems. [58].

Surgical therapy for AVSD has considerably decreased mortality and improved patients' quality of life. However, long-term results are determined by the accuracy of preoperative diagnoses, surgical method selection, and postoperative monitoring efficacy [12,50,35,36,70].

Suggestions for monitoring after surgery: During the first month following hospital release, a pediatric cardiologist should do weekly and, if required, more frequent evaluations using echocardiography and electrocardiography.

Depending on the severity of residual problems, a pediatric cardiologist may often recommend further monitoring with echocardiography and electrocardiography 1-2 times per year.

Children with residual problems (pulmonary hypertension, atrioventricular valve insufficiency, arrhythmia, etc.) need more regular monitoring [53,58,59].

Prognosis

An untreated atrioventricular septal defect (AVSD) has a bad outlook. Surgical intervention significantly enhances long-term survival rates, with more than 90% of patients surviving for up to 15 years post-treatment. Approximately 50% of affected neonates encounter complications such as pulmonary infections or cardiac failure, leading to mortality within the first year of life [30]. Survivors of infancy frequently develop permanent pulmonary vascular disease, potentially leading to shunt reversal. However, 9% to 10% of these patients need reoperation within the same time range owing to persistent or increasing abnormalities [17,29,58].

The defects are associated with each other. Although ventricular septal defect (VSD) is often seen as a single congenital aberration, it may also coexist with other structural heart problems. VSD is often a component of complicated congenital diseases like tetralogy of Fallot and transposition of the major arteries. It may also be associated with anomalies such as subaortic stenosis and aortic coarctation. In the presence of a subarterial VSD, increasing prolapse of the aortic valve leaflets—most typically affecting the right coronary cusp — can lead to deteriorating aortic valve insufficiency over time [45,65].

Diagnosis of atrioventricular septal defect. Based on heart failure symptoms and clinical examination findings, a cardiologist — a specialist in congenital heart defects — makes the diagnosis. Moreover, instrumental studies are necessary to support the diagnosis and consist in:

- Chest X-ray: An X-ray examination of the heart, blood vessels, lungs, and surrounding tissues.

- An electrocardiogram (ECG) identifies the cause of the rhythm as well as any abnormalities in the heart's electrical activity.

- echocardiography: in real time, using sound waves, a picture of the internal architecture of the heart is formed, and the speed, blood flow, and pressure in the heart chambers are measured.

- Cardiac catheterization assesses heart function, valve condition, pressure, oxygen content, and detects intracardiac shunting.

- angiocardiography is an invasive radiation diagnostic technology that involves infusing a radiopaque substance into the bloodstream to visually reveal the cavities of the heart and blood arteries.

There are additional non-ionizing radiation investigations, such as MRI and ultrasound, that may be used to diagnose and guide therapy. Ultrasound examination (ultrasound) is a commonly used form of instrumental diagnostics for numerous organs and tissues in the human body. This technology relies on ultrasonic waves' capacity to enter live tissue, with the speed of wave passage varying depending on the kind of tissue. A unique sensor in the ultrasound machine captures the reflected ultrasound and, using the data, creates a picture of the item under examination. Ultrasound offers several advantages over other diagnostic methods, including the ability to obtain information about organ size, shape, and morphology, minimal patient preparation, absolute safety for human health, and real-time research.

Medical imaging tools in clinical settings play an important role in determining a patient's overall diagnosis and treatment strategy. The usage of different imaging modalities in medical radiation is growing as technology progresses in the medical sciences. Medical imaging methods use a multidisciplinary approach to determine the correct diagnosis for a given patient in order to create a tailored treatment plan. These imaging methods may be used non-invasively to observe a person's interior organs without requiring surgery. They may be used to diagnose and treat a variety of conditions. Medical imaging approaches rely on radiation from the electromagnetic spectrum [41, 42, 52]. Ultrasound is one of many medical imaging procedures, including MRI, radiography, CT, and angiograms.

The approaches discussed above are highly beneficial for monitoring the patient's illness development after it has already been identified and/or is getting treatment. The great majority of imaging procedures rely on the use of X-rays and ultrasonography. These medical imaging techniques are employed at all levels of care. Furthermore, they play a vital role in public health and preventive medicine, as well as curative and, subsequently, palliative

care. The primary objective is to determine the proper diagnosis [5, 7, 10, 16, 31, 60]. Advantages and dangers of medical imaging using radiation:

Benefits

• Enables medical professionals to conduct thorough examinations of internal organs, circulatory system, tissues, and skeletal structures.

• Provides valuable data for determining surgical intervention needs.

• Uses fluoroscopic imaging to perform minimally invasive operations such as catheter insertion and stent implantation.

Hazards

• Surgery raises the risk of developing cancer in the long run.

• Contrast chemicals used in certain imaging modalities may cause allergic reactions in some individuals.

Fluoroscopy, utilized for surgical operations, might cause temporary skin irritation or hair loss due to higher radiation exposure compared to traditional imaging modalities.

Nuclear medicine and angiographic imaging can be classified into several types of biological process imaging. Radiopharmaceuticals are typically modest quantities of radioactive tracers that are utilized in molecular imaging. Magnetic resonance imaging (MRI) and ultrasound are two more non-radioactive imaging techniques. MRI employs powerful magnetic fields, which have no known long-term health consequences in humans. Diagnostic ultrasound (DUS) devices employ high-frequency sound waves to generate pictures of interior organs and soft tissues. Some medical imaging procedures employ radiation, such as X-rays, which are beamed onto the human body. As X-rays flow through the body, some are absorbed, and the resultant picture is detected on the other side [7,60,69].

Echocardiographic examination

Echocardiography is a form of ultrasonography that examines structural and functional changes in the heart and its valves. This approach offers information on the location, size, number of faults, the degree of volume overflow in the left ventricle, the severity of pulmonary hypertension, and other parameters. In cases of ventricular septal defect (VSD), echocardiography detects intermittent echo signals in the septal region, which indicate blood shunting and are visualized using color and continuous Doppler mapping modes.

As with any complete echocardiographic examination for congenital heart defects (atrioventricular septal defect), a step-by-step segmental analysis should be performed [4,47,54,57,62]. The most significant preoperative information for cardiac surgeons with such a diagnosis includes changes shown in Table 1.

Transesophageal echocardiography in patients with partial or unrepaired atrial septal defects (ASD) provides detailed visualization of defect boundaries, identifies the presence of ventricular septal defects (VSD), and assesses heart valve morphology and function, ventricular size, degree of subaortic stenosis (if present), pulmonary artery pressure, tricuspid regurgitation, and simultaneous measurement of systemic and pulmonary pressures [19,24,62].

If subaortic stenosis is diagnosed, Doppler echocardiography is performed. Echocardiography is useful for evaluating mitral valve function, detecting subaortic stenosis, identifying ventricular septal defects (VSD), and assessing arterial hypertension in patients who have recently had surgery [3, 4, 8, 60].

Table 1.

Echocardiographic Parameters for AVSD Assessment.

Category	Parameter
Atria	• Size of the atrias • Position of the interatrial • Size of the AVSD • Direction of the shunt
AVC anatomy	• Atrioventricular openings • Cusps • Superior communicating leaflet • Left mural leaflet • Chordae • Type • Left papillary muscles
AVC function	• Atrioventricular canal regurgitation • Localization and mechanism of regurgitation • Presence of the stenosis
Ventricles	• Right and left ventricles • Ventricular imbalance • Direction of the shunt • Gradient • Assessment of right ventricular pressure • Additional ventricular septal defects • Ventricular outflow tract obstruction • Severity and mechanism of obstruction
Subpulmonary infundibulum	• Right ventricular outflow tract obstruction
Aorta	• Presence of coarctation of the aorta

In addition, it is a crucial diagnostic and monitoring approach for atrial septal defect (ASD), allowing for timely intervention and therapy. [55,60,61]. Transthoracic echocardiography is the principal diagnostic tool for children, adolescents, and the majority of adults with good acoustic windows. The research needs the collection of the following data.

• Quantity and location of defects;

• Measurements of heart chamber dimensions;

• Evaluation of ventricular function;

• Determination of aortic valve insufficiency and/or tricuspid regurgitation;

• Identification of pulmonary artery stenosis;

• Systolic pressure measurement in the right ventricle.

Adults with an inadequate acoustic window may need transesophageal echocardiography.

Doppler echocardiography in surgical patients should concentrate on the following goals.

• detecting the existence, absence, and location of residual defects;

• measuring pulmonary artery pressure using the velocity of tricuspid or pulmonary regurgitation jets;

• diagnosing aortic insufficiency and pulmonary trunk stenosis;

• assessing ventricular function. [18,34,40,60].

Intraoperative echocardiography assessment. The objectives of the pre-bypass echocardiographic

examination. Preoperative information should be obtained largely by transthoracic echocardiography, with additional imaging as clinically indicated. As a result, the pre-bypass transesophageal echocardiography examination should concentrate on these specific aspects: The diagnosis, anatomy of the atrioventricular valve, and pathogenesis of atrioventricular valve regurgitation were all verified [20,22].

Transesophageal echocardiography is performed prior to bypass surgery. While transesophageal echocardiography is most often used for intraoperative evaluations, epicardial echocardiography is recommended when transthoracic echocardiography is not possible [49].

The primary positions in transesophageal echocardiography are:

1. Four-chamber view. This is one of the most essential methods of transesophageal echocardiographic examination for analyzing the common atrioventricular canal since it allows for the assessment of practically all components. This posture corresponds to the apical four-chamber view in transthoracic examination. Due to heart dilatation, particularly in the right ventricle, the multiplanar array may need to be rotated by 20-40° to acquire the most correct picture to increase the right ventricular chambers and the true 4-chamber section [14].

2. Five chamber view. The left ventricular outflow pathway is evaluated utilizing two-dimensional imaging and color Doppler mapping.

3. Long axis. Similar to the five-chamber picture.

4. Short-axis plane. An image of the aortic valve, as well as the right ventricular afferent and efferent tracts. When evaluating residual regurgitation and new stenosis of the right half of the common atrioventricular canal, the four-chamber view is enhanced [32,56,63].

2.2 Cardiac Computed Tomography: Diagnostic Challenges and Error

Computed tomography (CT) is a non-invasive imaging method that uses X-ray attenuation variations to generate high-resolution, submillimeter axial pictures of anatomical structures at various tissue densities. Iodine-based contrast agents are often used to improve organ contrast and distinguish between normal and diseased tissues. CT angiography is used to evaluate cardiovascular architecture by administering a contrast agent intravenously using a controlled injection method. This approach uses extensive post-processing and 3D reconstruction to create a three-dimensional (3D) depiction of the heart and main blood arteries [25,73]. ECG-gated imaging methods have advanced cardiac CT, allowing for more accurate evaluation of both structural and functional elements of the heart. With the increasing use of cardiac CT in coronary artery examination, radiologists regularly come across incidental discoveries of non-coronary congenital cardiac abnormalities that may have gone unnoticed [13,66,67]. According to estimates, around 3,000 adults per million people suffer from congenital heart disease (CHD) [52,74]. VSDs and ASDs account for roughly half of all congenital abnormalities in CHD patients [64]. While minor flaws may stay asymptomatic throughout life, major flaws may demand prompt medical attention.

Diagnosing Ventricular Septal Defects in Adults:

• Small VSDs, especially those with progressive aortic valve prolapse, can worsen aortic insufficiency over time.

• Undiagnosed pulmonary valve stenosis (RVS) in conjunction with VSD can lead to high flow velocities and tricuspid regurgitation, potentially resulting in a misdiagnosis of pulmonary hypertension.

• Subtricuspid VSD may cause incorrect left-to-right shunting.

Recommendations to Improve Continuity of Care and Medical Support for Adults with CHD:

I. Ensure Comprehensive and Accessible Medical Care:

1. Creating a healthcare system that ensures access to specialist CHD treatment while also meeting the medical, psychological, and social requirements of adult patients.

2. Creating and executing educational programs for CHD patients, families, and healthcare providers to provide a smooth transition from childhood to adult cardiac treatment.

3. Improving cardiology training programs (for both pediatric and adult cardiologists) to better grasp the specific etiology and treatment of CHD in adults.

4. Improving teamwork at all levels of the healthcare system (local, regional, and national) to meet the demands of the rising CHD population.

II. Organizational Framework for Adult CHD Care.

Coordination and Integration of Services:

1. Regional centers with specialized resources should manage CHD care for adults, ensuring continuity of care and ongoing patient monitoring.

2. Referral pathways to leading national cardiac surgery and cardiology institutions should be established for advanced treatment.

3. Pediatricians and pediatric cardiologists should ensure a structured transition of medical records to regional centers when patients transition to adult care.

4. Emergency medical teams should work with regional centers to ensure that adult CHD patients are effectively managed.

III. Medical Documentation and Access to Information: Adult CHD patients should get personalized "medical passports" with detailed medical information, emergency contacts, and care plans connected to regional CHD centers.

IV. Support for Patients with Additional Needs: Patients with CHD who have cognitive impairments or psychosocial issues should not have difficulty getting treatment. Caregivers must advocate for their patients' medical needs.

V. Outpatient Follow-Up and Medical Accessibility: Each CHD patient should be fully registered with a primary care physician. This guarantees that medical data are easily accessible and that local cardiologists and regional CHD centers may work together more effectively.

VI. Primary care doctors who care for adult CHD patients should have direct access to referral networks and inpatient services at specialist CHD facilities as needed [56].

Conclusions:

1. Optimization of radiological examination techniques: The use of modern radiological modalities such as radiography, CT angiography, and MRI is critical for diagnosing and assessing the effectiveness of surgical surgery for atrioventricular septal defect.

2. The importance of medical imaging: Techniques such as ultrasonography are critical for obtaining information

about the structure and function of the heart in individuals with congenital cardiac abnormalities.

3. A personalized therapy strategy necessitates the cooperation of several experts and healthcare levels to address the clinical, social, and psychological aspects of CHD patients.

4. Follow-up and monitoring: Medical imaging techniques are essential for post-surgical evaluations in patients with congenital heart disease (CHD), facilitating the assessment of disease progression and the effectiveness of treatments.

5. The necessity for additional research: Further research into optimizing radiological assessment procedures for congenital heart disease could enhance diagnosis, treatment, and prognosis, thereby improving the quality of life for affected individuals.

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MODERN APPROACHES TO THE DIAGNOSIS, SURGICAL CORRECTION, AND LONG-TERM MONITORING OF PATIENTS WITH COMMON ARTERIAL TRUNK

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Abstract

Introduction. Common truncus arteriosus (CTA) is a rare and severe congenital heart defect characterized by a single common vessel supplying both systemic and pulmonary circulations, leading to serious hemodynamic abnormalities. Without timely diagnosis and surgical intervention, approximately 80% of patients die within the first year of life. Modern imaging methods, such as echocardiography, CT, and MRI, allow for more precise identification of anatomical features, improving prognosis and treatment options. Advances in cardiac surgery have enabled early complete correction, though patients still require long-term monitoring due to the risk of complications. Research into modern approaches for the diagnosis and treatment of CTA is essential to improving the quality of life and survival rates for patients with this condition.

Aim: To investigate modern diagnostic methods and surgical correction techniques for common truncus arteriosus, assessing their effectiveness and impact on long-term treatment outcomes for patients with this rare congenital heart defect.

Search strategy: Key terms used to increase search accuracy included "common arterial trunk," "truncus arteriosus," "diagnostic methods", "echocardiography", "computed tomography", "cardiac catheterization", "magnetic resonance imaging", "surgical treatment", "long-term outcomes", "congenital heart defects." *Inclusion Criteria:* Publications with full-text articles available through open access or subscription resources; studies describing modern diagnostic methods (echocardiography, CT, MRI, cardiac catheterization) and surgical treatment of CTA; articles focused on the outcomes of surgical interventions and long-term results for patients with this defect. Publications in English and Russian from the last 20 years. Review articles, meta-analyses, and clinical studies with clear conclusions and results were prioritized. *Exclusion Criteria:* Duplicated publications, repeated articles, and resources with paid access if full texts could not be obtained; conference abstracts, promotional articles, short reviews, or materials without clear scientific conclusions; studies not directly related to the diagnosis and treatment of CTA, such as epidemiology or genetic research without a focus on clinical treatment methods. The search was not limited to specific time frames, as both recent studies and foundational works, such as the *Collett and Edwards* classification of 1949, were included to cover the evolution of CTA understanding from early anatomical descriptions to modern diagnostic and therapeutic methods. A total of 74 articles meeting the inclusion criteria were selected and analyzed.

Results and conclusions: Study results indicate that modern imaging methods, such as echocardiography, CT, and MRI, play a crucial role in the accurate diagnosis and treatment planning for common truncus arteriosus. These methods allow the identification of anatomical features, complications, and associated anomalies, which are critical for successful surgical correction. Early complete correction in the neonatal period significantly reduces the risk of complications, such as pulmonary hypertension and valve dysfunction. The use of biocompatible conduits and prosthetics also improves treatment outcomes, although regular monitoring is required. Long-term follow-up using high-precision imaging techniques helps to detect and correct late complications promptly, enhancing quality of life and increasing survival rates for patients with CTA.

Keywords: *common truncus arteriosus, diagnosis, early neonatal correction, long-term surgical outcomes.*

Резюме

СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ, ХИРУРГИЧЕСКОЙ КОРРЕКЦИИ И ДОЛГОСРОЧНОМУ НАБЛЮДЕНИЮ ПАЦИЕНТОВ С ОБЩИМ АРТЕРИАЛЬНЫМ СТВОЛОМ

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Актуальность. Общий артериальный ствол — редкий и тяжёлый врожденный порок сердца, при котором один общий сосуд снабжает как системное, так и легочное кровообращение, что приводит к серьёзным гемодинамическим нарушениям. Без своевременной диагностики и хирургического лечения около 80% пациентов умирают в течение первого года жизни. Современные методы визуализации, такие как эхокардиография, КТ и МРТ, позволяют более точно выявлять анатомические особенности порока, что улучшает прогноз и выбор лечения. Прогресс в кардиохирургии открыл возможности для ранней полной коррекции, однако пациенты всё ещё нуждаются в долгосрочном наблюдении из-за риска осложнений. Исследование современных подходов к диагностике и лечению ОАС имеет большое значение для улучшения качества жизни и выживаемости пациентов с данным пороком.

Цель. Изучить современные методы диагностики и хирургической коррекции общего артериального ствола, оценить их эффективность и влияние на долгосрочные результаты лечения пациентов с этим редким врожденным пороком сердца.

Стратегия поиска. Использовались такие ключевые слова: "common arterial trunk", "truncus arteriosus", "diagnostic methods", "echocardiography", "computed tomography", "cardiac catheterization", "magnetic resonance imaging", "surgical treatment", "long-term outcomes", "congenital heart defects". *Критерии включения:* Публикации, содержащие полные тексты статей, доступные в открытом доступе или через подписные ресурсы. Исследования, описывающие современные методы диагностики (эхокардиография, КТ, МРТ, катетеризация сердца) и хирургического лечения общего артериального ствола. Статьи, посвященные результатам хирургических вмешательств и долгосрочным исходам у пациентов с данным пороком. Публикации на английском и русском языках, опубликованные за последние 20 лет. Обзорные статьи, мета-анализы и клинические исследования с чёткими выводами и результатами. *Критерии исключения:* Дубликаты публикаций, повторяющиеся статьи и материалы с платным доступом, если полные тексты не могли быть получены. Тезисы конференций, рекламные статьи, краткие обзоры или материалы без чётких научных выводов. Статьи, не имеющие прямого отношения к диагностике и лечению общего артериального ствола, такие как исследования по эпидемиологии или генетическим аспектам без фокуса на клинические методы лечения. Поиск не ограничивался конкретными временными рамками, поскольку были включены как современные исследования, так и классические фундаментальные работы, такие как исследование *Collett u Edwards* (1949), которое заложило основы классификации общего артериального ствола. Это позволило охватить все этапы эволюции понимания данного порока сердца, от ранних анатомических описаний до современных методов диагностики и лечения. Было отобрано и проанализировано 74 статьи, соответствующие критериям включения.

Результаты и выводы. Результаты исследования показывают, что современные методы визуализации, такие как эхокардиография, КТ и МРТ, играют ключевую роль в точной диагностике и планировании лечения общего артериального ствола. Эти методы позволяют выявлять анатомические особенности порока, его осложнения и сопутствующие аномалии, что критически важно для успешной хирургической коррекции. Ранняя полная коррекция,

выполненная в неонатальном периоде, значительно снижает риск осложнений, таких как легочная гипертензия и дисфункция клапанов. Использование биосовместимых кондуитов и протезов также улучшает результаты лечения, хотя требует регулярного мониторинга. Долгосрочное наблюдение с применением высокоточных методов визуализации помогает своевременно выявлять и корректировать поздние осложнения, улучшая качество жизни и увеличивая выживаемость пациентов с данным пороком.

Ключевые слова: *общий артериальный ствол, диагностика, ранняя неонатальная коррекция долгосрочные результаты хирургического лечения.*

Түйіндеме

ТУА БІТКЕН ЖАЛПЫ ТРУНКУС АРТЕРИОЗЫ БАР НАУҚАСТАРДЫҢ ДИАГНОСТИКАСЫНЫҢ, ХИРУРГИЯЛЫҚ ТҮЗЕУІНІҢ ЖӘНЕ ҰЗАҚ МЕРЗІМДІ БАҚЫЛАУЫНЫҢ ЗАМАНАУИ ТӘСІЛДЕРІ

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Өзектілігі: туа біткен жалпы трункус артериозы — сирек және ауыр туа біткен жүрек ақауы, мұнда бір ортақ артерия жүйелік және өкпелік қан айналымын қамтамасыз етеді, бұл ауыр гемодинамикалық бұзылыстарға алып келеді. Уақытында диагностика мен хирургиялық емдеу жүргізілмесе, науқастардың шамамен 80%-ы өмірінің бірінші жылында қайтыс болады. Қазіргі заманғы визуализация әдістері, мысалы, эхокардиография, КТ және МРТ, ақаудың анатомиялық ерекшеліктерін дәл анықтауға мүмкіндік береді, бұл болжам мен емдеу таңдауын жақсартады. Кардиохирургиядағы прогресс ерте толық түзетуді жүзеге асыруға мүмкіндік берді, бірақ науқастар әлі де асқынулардың қаупіне байланысты ұзақ мерзімді бақылауды қажет етеді. Туа біткен жалпы трункус артериозының диагностикасы мен емдеудегі қазіргі тәсілдерді зерттеу осы ақауы бар науқастардың өмір сүру сапасы мен тіршілігін жақсарту үшін маңызды..

Мақсаты: туа біткен жалпы трункус артериозын диагностикалаудың және хирургиялық түзетудің қазіргі әдістерін зерттеу, олардың тиімділігін және осы сирек туа біткен жүрек ақауымен науқастарды ұзақ мерзімді емдеу нәтижелеріне әсерін бағалау.

Іздеу стратегиясы: Іздеудің дәлдігін арттыру үшін "common arterial trunk", "truncus arteriosus", "diagnostic methods", "echocardiography", "computed tomography", "cardiac catheterization", "magnetic resonance imaging", "surgical treatment", "long-term outcomes", "congenital heart defects" сияқты негізгі сөздер пайдаланылды. *Қосу критерийлері:* Толық мәтінді мақалаларға қолжетімділігі бар немесе жазылу негізінде қолжетімді басылымдар. Жалпы артериялық діңгекті заманауи диагностикалау әдістерін (эхокардиография, КТ, МРТ, жүрек катетеризациясы) және хирургиялық емдеуді сипаттайтын зерттеулер. Аталған ақауы бар пациенттердегі хирургиялық ем мен ұзақ мерзімді нәтижелерге арналған мақалалар. Соңғы 20 жыл ішінде ағылшын және орыс тілдерінде жарияланған өзекті деректерді қамту үшін басылымдар. Нақты қорытындылар мен нәтижелері бар шолу мақалалары, мета-анализдер және клиникалық зерттеулер. *Шығару критерийлері:* Қайталанатын басылымдар, толық мәтіндерге қол жеткізу мүмкін болмаған жағдайда ақылы қолжетімділікке ие мақалалар. Конференция тезистері, жарнамалық мақалалар, қысқа шолулар немесе ғылыми дәлелдемелері жоқ материалдар. туа біткен жалпы трункус артериозын диагностикалау және емдеуге тікелей қатысы жоқ мақалалар. *Іздеу тереңдігі:* Іздеу нақты уақыт шеңберімен шектелмеген, себебі қазіргі зерттеулер мен *Collett және Edwards* (1949) зерттеуі сияқты негізгі классикалық жұмыстар қамтылды. Бұл туа біткен жалпы трункус артериозы ақауын түсінудегі барлық даму кезеңдерін, ерте анатомиялық сипаттамалардан бастап

заманауи диагностикалық және емдеу әдістеріне дейін қамтуға мүмкіндік берді. Іздеу нәтижесінде қосу критерийлеріне сәйкес келетін 74 мақала талданды.

Нәтижелер және қорытындылар: Зерттеу нәтижелері көрсеткендей, эхокардиография, КТ және МРТ сияқты заманауи визуализация әдістері туа біткен жалпы трункус артериозын толық диагностикалау мен емдеуді жоспарлауда маңызды рөл атқарады. Бұл әдістер ақаудың анатомиялық ерекшеліктерін, асқынуларын және қатар жүретін аномалияларды анықтауға мүмкіндік береді, бұл хирургиялық түзетудің сәтті өтуіне өте маңызды. Неонаталдық кезеңде жасалған ерте толық ем өкпе гипертензиясы мен клапандардың дисфункциясы сияқты асқыну қаупін айтарлықтай төмендетеді. Биологиялық үйлесімді кондуиттер мен протездерді қолдану емдеу нәтижелерін жақсартады, дегенмен тұрақты мониторинг қажет. Жоғары сапалы визуализация әдістерін қолдана отырып, ұзақ мерзімді бақылау кеш асқынуларды уақытылы анықтап, түзетуге көмектеседі, пациенттердің өмір сүру сапасын жақсартады және өмір сүру деңгейін арттырады.

Түйінді сөздер: *туа біткен жалпы трункус артериозы, диагностика, ерте неонаталдық түзету, хирургиялық емдеудің ұзақ мерзімді нәтижелері.*

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Introduction

The common arterial trunk (CAT) is a rare but extremely serious congenital heart defect characterized by a single common vessel that supplies systemic, pulmonary, and coronary blood flow. The incidence of this defect among congenital heart anomalies is less than 3%, making it a subject of significant attention in cardiology and cardiac surgery. This defect is usually associated with a ventricular septal defect (VSD), which further complicates the clinical picture and therapeutic approach [4, 11]. Without timely surgical intervention, 80% of patients die within the first year of life, emphasizing the need for early diagnosis and effective surgical correction [12, 23, 25].

Recent advances in diagnostics and surgery have significantly improved patient outcomes, yet challenges related to diagnosis and long-term prognosis remain relevant. In recent decades, there has been a significant improvement in imaging methods, including echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI), enabling more accurate identification of anatomical features and associated anomalies of the defect. These methods play a key role in planning surgical interventions and determining the optimal timing for surgeries.

Prenatal diagnosis of CAT remains challenging despite advancements in fetal echocardiography. The difficulty in accurately identifying the anomaly in utero is due to the diverse morphological manifestations of the defect, the presence of associated malformations, and limitations in visualization techniques during intrauterine development. On the other hand, successful prenatal diagnosis allows for better planning of perinatal management and early surgery, reducing the risk of complications associated with late diagnosis [12, 13, 15, 24].

The surgical treatment of CAT has undergone significant changes in recent decades. Previously used methods, such as delayed correction with palliative pulmonary artery banding, have proven ineffective and show high complication rates. The modern approach involves early complete correction of the defect, preferably in the neonatal period, which is associated with better outcomes and lower risks of developing pulmonary hypertension and other complications. However, early surgical intervention is accompanied by several technical challenges due to the small size of the newborn's heart and vessels, as well as the need for prostheses and conduits to restore blood flow. These materials have a limited lifespan, necessitating repeat surgeries as the child grows, which is a significant risk factor in the long-term perspective [4, 11, 19, 31, 34].

One of the key issues in surgical treatment is the condition of the common trunk valve, which can range from mild to severe insufficiency or stenosis. The valve's condition greatly affects outcomes both during surgical correction and in the postoperative period. Severe regurgitation or stenosis requires additional intervention to correct valve dysfunction, which can significantly complicate the surgery and worsen the prognosis. Technically complex surgeries involving valve reconstruction are associated with a high risk of complications and often require repeat surgical interventions in the future.

Long-term treatment outcomes for patients with CAT depend not only on the success of the primary surgery but also on appropriate monitoring and management of emerging complications. The most common complications after surgical correction include pulmonary artery stenosis,

dysfunction of prosthetic conduits and valves, and the development of pulmonary hypertension. These issues require dynamic observation, visualization methods for assessing blood flow, and timely re-correction. According to the literature, patients who have undergone CAT correction require lifelong monitoring, as emerging issues such as implant wear and progression of pulmonary hypertension may need to be addressed over time.

Modern diagnostic methods play a key role in managing patients with CAT. Echocardiography remains the primary method for both prenatal and postnatal periods, facilitating initial diagnosis and assessment of heart condition. However, in complex cases, particularly with associated anomalies such as interrupted aortic arch or coronary artery defects, more precise methods like CT and MRI are required. These methods allow for the visualization of complex anatomical features and aid in planning surgical intervention, especially in cases where precise determination of blood flow sources and valve condition is needed. Additionally, the use of modern technologies such as 3D modeling helps surgeons better prepare for operations, which improves treatment outcomes [28, 42, 70].

Thus, the relevance of studying CAT is driven by the need to improve diagnostic methods, enhance surgical treatment outcomes, and develop effective strategies for the long-term monitoring of patients. Given the rarity of this defect and high mortality among untreated patients, further advancement in both diagnostic and therapeutic approaches is required to improve the prognosis and quality of life for patients with this severe congenital pathology [20, 29, 31].

Aim: To study modern diagnostic and surgical correction methods for the common arterial trunk, evaluating their effectiveness and impact on long-term outcomes for patients with this rare congenital heart defect.

Search Strategy: Leading international databases of scientific publications, including PubMed, Scopus, and Google Scholar, were used for the review. The selection of these resources was based on their authority and access to up-to-date scientific information, allowing for a comprehensive analysis of modern diagnostic and treatment methods for CAT. Search Terms:To enhance search accuracy, key terms such as “common arterial trunk,” “truncus arteriosus,” “diagnostic methods,” “echocardiography,” “computed tomography,” “cardiac catheterization,” “magnetic resonance imaging,” “surgical treatment,” “long-term outcomes,” and “congenital heart defects” were used. These terms were chosen based on the study’s objectives to cover all aspects of diagnosis, surgical treatment, and long-term patient monitoring with CAT. *Inclusion Criteria:* Publications with full-text articles available in open-access or subscription-based resources; studies describing modern diagnostic methods (echocardiography, CT, MRI, cardiac catheterization) and surgical treatment of CAT; articles focused on surgical outcomes and long-term results in patients with this defect. Publications in English and Russian from the last 20 years were included to encompass current data. Review articles, meta-analyses, and clinical studies with clear conclusions and results were included. *Exclusion Criteria:* Duplicate publications, repeated articles, and paid-access materials if full texts could not be obtained; conference abstracts, promotional articles, short reviews, or materials without clear scientific conclusions; studies not directly related to CAT diagnosis and treatment, such as epidemiological or genetic studies without a clinical focus. *Search Depth:* The search was not limited to specific timeframes, as both modern studies and classic foundational works, such as the *Collett and Edwards* classification (1949), were included to cover all stages of understanding the defect, from early anatomical descriptions to modern diagnostic and treatment approaches. Analysis and Systematization: A thorough study and analysis of selected publications were conducted. Particular attention was paid to articles describing comparative studies of diagnostic methods (echocardiography, CT, MRI) and surgical intervention outcomes. Conclusions were systematized for further use in the study. Eighty articles meeting the inclusion criteria were selected and analyzed.

Discussion

Etiology and Pathogenesis

The etiology and pathogenesis of CAT are not fully understood; however, it is known that this defect forms in the early stages of embryonic development during cardiovascular system formation. CAT arises from disruptions in the septation of the common arterial trunk into the aorta and pulmonary artery, related to insufficient development of the aortopulmonary septal complex, leading to a single vessel exiting the heart and supplying both systemic and pulmonary circulation.

Several risk factors are associated with CAT development, one of the most significant being genetic predisposition. Studies show that this defect may be associated with chromosomal abnormalities, such as a deletion on chromosome 22q11.2, also known as DiGeorge syndrome. This syndrome includes multiple congenital anomalies, including various heart defects, and in 20-30% of cases, CAT is associated with this chromosomal pathology. Genetic predisposition necessitates screening in patients with a family history of congenital heart defects or syndromic conditions.

Embryology and External Factors

Embryologically, the common arterial trunk develops during weeks 4–8 of gestation, when the arterial trunk separates, forming distinct pathways for systemic and pulmonary circulation. Disruption in this process can be triggered by external teratogenic factors, such as maternal infections (notably rubella and cytomegalovirus), alcohol or drug use, or certain medications taken during the first trimester of pregnancy. These factors can impact the normal development of the fetal cardiovascular system, contributing to the formation of the defect [4, 11, 70].

Pathogenesis

The pathophysiology of CAT is linked to significant hemodynamic disturbances, as arterial and venous blood mix within the heart and exit through a single vessel. This results in considerable blood flow imbalances between the pulmonary and systemic circulations, causing pulmonary circulation overload and increasing the risk of pulmonary hypertension. The lack of oxygen in systemic circulation leads to chronic hypoxia of organs and tissues, potentially delaying development in newborns and infants.

Additionally, the pathogenesis of CAT is complicated by the underdevelopment of the common trunk valve, often leading to substantial regurgitation that further disrupts

hemodynamics. Combined with a ventricular septal defect, this creates a condition where mixed blood is directed both to the lungs and systemic circulation, resulting in systemic oxygen deficiency and increased cardiovascular strain [12, 19].

Thus, the etiology and pathogenesis of CAT involve genetic, embryological, and environmental factors that disrupt the normal development of the aortopulmonary septum and the formation of the fetal circulatory system.

Classification of the Common Arterial Trunk

The common arterial trunk (truncus arteriosus communis) is a complex congenital heart defect, wherein a single vessel exits the heart, supplying both systemic and pulmonary circulations. The classification of this defect is based on anatomical features, such as the origin of the pulmonary arteries from the common trunk and the structure of its valve. Major classification systems developed by Collett and Edwards and by Van Praagh help describe anatomical variations of the defect and determine the most appropriate surgical approach.

Collett and Edwards Classification

In 1949, Collett and Edwards proposed one of the first classification systems for the common arterial trunk, which remains relevant today [23, 24, 28]. This classification divides CAT into four types based on how the pulmonary arteries originate from the common trunk:

1. **Type I (Common trunk with a single pulmonary orifice)**: In this type, the pulmonary arteries originate from the common trunk as a single vessel, which then divides into the right and left pulmonary arteries. This type is the most common, occurring in about 60% of CAT cases, and allows for simpler corrective procedures since the pulmonary arteries already have a common origin, facilitating surgical reconstruction.
2. **Type II (Pulmonary arteries arise separately from the posterior surface of the common trunk)**: In this type, each pulmonary artery (right and left) has a separate origin from the posterior surface of the common trunk. This type is less common, and its anatomical characteristics can create challenges in surgery, as each artery opening requires individual reconstruction for adequate pulmonary blood flow.
3. **Type III (Pulmonary arteries arise separately from the lateral surfaces of the common trunk)**: Each pulmonary artery also has a separate origin but from the lateral walls of the common trunk, making them more distant from each other. As with Type II, the complexity of surgical correction increases, as each pulmonary vessel requires separate reconstruction.
4. **Type IV (Pulmonary blood supply through collateral vessels without major pulmonary arteries)**: In this type, major pulmonary arteries are absent, and pulmonary blood flow is supplied by collateral vessels branching from the aorta or other vascular structures. This type has been excluded from the common arterial trunk classification in modern contexts, as it aligns more with the diagnosis of pulmonary atresia with collateral vessels. However, it is still occasionally referenced in clinical practice as a rare variant of CAT.

Van Praagh Classification

Van Praagh developed a classification system for the common arterial trunk in 1965, emphasizing differences in the aortopulmonary septum and valve morphology [28, 30, 42]. The Van Praagh classification divides the defect into two main categories—A and B—based on the presence or absence of the aortopulmonary septal complex:

1. **Type A (With an aortopulmonary septal complex)**: This type includes partial septation of the common trunk into pulmonary and aortic components. The pulmonary arteries may originate from the aortopulmonary septum or other parts of the common trunk. Subtypes of Type A depend on the pulmonary artery separation method and include:
   - **A1**: The pulmonary arteries arise from the common trunk as a single vessel that then divides into right and left branches.
   - **A2**: The pulmonary arteries arise separately from the common trunk, with individual openings.
   - **A3**: Absence of pulmonary arteries, with pulmonary blood supply occurring through collateral vessels (similar to Type IV in the Collett and Edwards classification).
2. **Type B (Without an aortopulmonary septal complex)**: In this type, the aortopulmonary septum is completely absent, and pulmonary blood flow is supplied by collateral vessels. Type B commonly includes severe valve regurgitation, complicating surgery, and worsening prognosis.

Additional Classification Considerations

Both the Collett and Edwards and Van Praagh classification systems are foundational; however, further morphological characteristics may be considered for a more precise patient assessment and surgical strategy selection:

- **Common Trunk Valve**: The valve may have two to five leaflets, with three-leaflet valves being the most common. Abnormalities, such as bicuspid or quadricuspid valves, can lead to regurgitation, necessitating additional corrective measures during surgery.
- **Coronary Artery Condition**: Coronary arteries may arise from different locations with various deviations from normal structure. Some anatomical variations, such as anomalous origins, increase the risk of myocardial ischemia and require a specialized approach in surgical correction.
- **Associated Cardiac Anomalies**: Patients with CAT often present with other congenital heart defects, such as ventricular septal defects (VSD), interrupted aortic arches, or other vascular anomalies. These associated defects also influence surgical strategy and affect treatment outcomes.

Clinical Significance of Classification

Classifying the common arterial trunk is essential for selecting the optimal surgical approach. Types of defects in which pulmonary arteries have a single origin or proximity are considered technically simpler for surgical intervention. Conversely, types with separate pulmonary artery origins or without major pulmonary arteries require complex reconstructive procedures, increasing the risk of postoperative complications and the need for repeat surgeries [14, 19, 37, 43, 62].

Using a classification system enables surgeons to better plan operations and assess the risk of potential complications. For example, types of CAT with pronounced valve regurgitation and coronary artery anomalies necessitate a specialized approach to blood flow restoration and are often associated with extended postoperative recovery.

Thus, the Collett and Edwards and Van Praagh classification systems provide a detailed description of the morphological features of CAT, essential for adequate surgical planning and long-term monitoring.

Diagnosis of Common Arterial Trunk

Diagnosing CAT, a rare and serious congenital heart defect, requires a comprehensive approach and the use of various imaging techniques to assess the defect's anatomical features, and the degree of functional impairment, and to select the optimal treatment strategy. Several diagnostic methods are involved, each providing key data and contributing to a complete patient assessment.

Chest Radiography

Chest radiography is a basic and often initial imaging method that can indicate the presence of cardiopulmonary abnormalities characteristic of the common arterial trunk. The radiograph may reveal cardiomegaly, an enlargement of the heart caused by abnormal blood flow combined with cardiac overload. Signs of pulmonary hypertension are also often detected due to increased blood flow to the lungs from inadequate separation of circulations. Pulmonary vessels appear enlarged and are easily distinguishable on the radiograph. While chest radiography does not provide precise visualization of the heart and vessels, it remains valuable for an initial patient assessment and for identifying additional pathologies, such as pulmonary hypertension or congestion in the lungs. This method is also used for dynamic monitoring during the postoperative period [26, 27].

Echocardiography

Echocardiography, or ultrasound of the heart, is the primary diagnostic method for the common arterial trunk, both in the prenatal and postnatal periods. This non-invasive method does not involve ionizing radiation and provides real-time imaging of the heart and major vessels. In the prenatal period, echocardiography can detect the defect as early as the 18th–24th weeks of pregnancy, allowing early planning for delivery and subsequent treatment of the newborn [28, 30]. Postnatal echocardiography accurately determines the anatomical features of the heart, including:

- **Common Arterial Trunk**: Echocardiography allows visualization of a single vessel exiting the heart and assessment of the trunk's valve structure, which may have two, three, or four leaflets.
- **Valve Regurgitation**: Using Doppler imaging, an integral part of echocardiography, it is possible to assess backflow through the common trunk valve and measure the degree of insufficiency.
- **Pulmonary Arteries**: Echocardiography helps determine the origin of the pulmonary arteries from the common trunk, which is crucial for preoperative planning.
- **Ventricular Septal Defect (VSD)**: Nearly all CAT patients have a VSD, which can be visualized with echocardiography and measured to assess the need for intervention.

Echocardiography is widely used both for diagnosis and for evaluating heart conditions before and after surgery. Depending on the complexity of the defect and associated anomalies, additional echocardiographic studies may be conducted using various modes to gain a comprehensive view of the cardiovascular system.

Computed Tomography (CT)

Contrast-enhanced CT provides detailed three-dimensional images of the heart and vessels, making it a vital part of preoperative assessment, particularly in complex cases. CT allows for clear visualization of CAT anatomy, including the origin and location of the pulmonary arteries, which is especially important for surgical planning [30, 38]. CT also enables the following:

- **Assessment of Pulmonary Artery Stenosis**: Identifying and measuring stenosis in the pulmonary arteries if present.
- **Detection of Abnormal Collateral Vessels**: Revealing compensatory collateral vessels that may develop to offset impaired blood flow.
- **Evaluation of Coronary Artery Anomalies**: Determining the origin of the coronary arteries, which is crucial to avoid ischemic complications post-surgery.

The three-dimensional images obtained via CT give surgeons precise data on the structure of the heart and vessels, allowing for low-risk surgical planning. CT is also beneficial postoperatively for evaluating the condition of implanted conduits and identifying possible complications, such as stenosis or thrombosis [54, 66, 74].

Magnetic Resonance Imaging (MRI)

MRI is preferred for long-term monitoring of heart and vessel conditions post-surgery. Unlike CT, MRI does not involve ionizing radiation, making it safer for patients who require frequent imaging, especially children [38, 40, 54]. MRI provides detailed heart and vessel images and allows for the assessment of functional blood flow parameters:

- **Blood Flow and Valve Functionality**: MRI precisely measures blood volumes passing through vessels and valves, and reveals regurgitation in cases of valve insufficiency.
- **Assessment of Pulmonary Hypertension**: MRI evaluates pulmonary blood flow and assesses pulmonary hypertension risk, particularly important for CAT patients.
- **Monitoring Conduits and Prostheses**: MRI is useful postoperatively to detect potential complications, such as conduit stenosis or prosthetic wear, allowing for timely intervention.

The main limitation of MRI is the requirement for patient immobility during scanning, which may necessitate sedation for children. Additionally, the presence of metal implants can complicate MRI imaging, requiring alternative imaging methods in such cases.

Heart Catheterization and Angiography

Heart catheterization is performed less frequently but remains an important method for assessing hemodynamic parameters, particularly in patients suspected of having pulmonary hypertension. Catheterization allows measurements of pressures in various heart chambers and vessels and helps determine resistance in pulmonary vessels. This method provides the following information:

- **Pulmonary Artery Pressure Assessment**: Elevated pressure may indicate pulmonary hypertension, influencing the choice of surgical treatment.
- **Anatomical Angiography**: During catheterization, angiography with contrast dye visualizes the coronary arteries, pulmonary vessels, and aorta, helping to detect

vessel anomalies and plan interventions, such as stent placement in cases of stenosis.

- **Interventional Procedures**: Catheterization can also be used to expand narrowed vessels or place stents if blood flow is obstructed.

Although invasive, catheterization is often essential for precise preoperative planning and vessel condition assessment when other methods fail to provide sufficient information.

Genetic Testing and Additional Studies

Since CAT may be associated with genetic anomalies, such as a 22q11.2 deletion (DiGeorge syndrome), genetic testing is often recommended for patients. This testing evaluates inheritance risks and identifies accompanying genetic factors that could affect prognosis and treatment strategies. Additional laboratory studies may also be conducted to assess the condition of other organs and systems before surgery.

Diagnosing CAT requires the use of multiple imaging methods to obtain a complete picture of the heart and vessel condition. Echocardiography is the primary method for initial diagnosis and postoperative monitoring. CT and MRI offer detailed data on anatomical and functional blood flow parameters, especially useful for preoperative planning. Heart catheterization, although used less often, is essential for pressure assessment and interventional procedures when necessary. This comprehensive approach minimizes risks and enhances surgical outcomes [31, 55, 59].

Surgical Treatment

The surgical treatment of common arterial trunk is aimed at addressing hemodynamic abnormalities, separating systemic and pulmonary blood flow, and restoring the normal structure of the heart and major vessels. Early complete surgical correction in neonatal or infancy stages is considered the "gold standard" for treating this defect. This intervention reduces the risk of severe pulmonary hypertension and other complications that are inevitable with conservative management [1, 3, 5, 9, 49, 50, 55, 59]. The main goal of surgery is to create two separate pathways for blood circulation and eliminate the interventricular septal defect, significantly improving the patient's quality of life and reducing the risk of complications in the future [59, 61, 62, 63, 64].

Historical Overview of Treatment Methods

Before the introduction of complete correction methods for CAT, palliative surgery was the primary treatment method. This approach included banding the pulmonary arteries to reduce pulmonary blood flow, temporarily alleviating the patient's condition but not providing long-term improvement. Palliative operations were performed in cases where the patient's condition did not allow for complete intervention, or where the complete intervention was technically challenging [7, 8, 9, 19, 21, 22, 23]. However, high risks of complications and limited long-term outcomes made palliative surgeries undesirable, and they are now used only in rare cases when radical correction is not feasible.

In the mid-1980s, advancements in cardiac surgery enabled the first successful complete correction of CAT in newborns, marking a turning point in the treatment of this defect. Since then, the methodology and techniques of the operation have undergone significant changes to increase intervention success and minimize postoperative complications [10, 12, 28, 29, 68, 69].

Modern Surgical Methods

Modern approaches to the surgical correction of CAT involve early intervention, typically performed within a few weeks or months of life. The surgery aims to fully separate pulmonary and systemic blood flows and correct all anatomical defects associated with the defect [13, 15, 16, 24, 32, 71].

Main Stages of Surgical Correction

1.**Closure of the Ventricular Septal Defect (VSD):** A key step of the operation is the closure of the VSD, which is present in nearly all patients with CAT. This defect is usually closed using a patch made from the patient's pericardium or synthetic material. Closing the VSD prevents blood mixing between the left and right ventricles, necessary for restoring normal blood flow and preventing hypoxia of organs and tissues [16, 18, 34, 35].

2.**Reconstruction of the Right Ventricular Outflow Tract (RVOT):** After closing the VSD, the surgeon reconstructs the RVOT, creating a separate path for pulmonary blood flow. A conduit connecting the right ventricle to the pulmonary arteries is used for this purpose, which can be made from various materials, including biological or synthetic prostheses. Biological conduits (e.g., from human or animal tissue) have high biocompatibility, but their lifespan is limited, especially in children, requiring replacement as the patient grows [14, 15, 68, 70, 73].

3.**Reconstruction of the Common Arterial Trunk:** After creating the pulmonary pathway, the surgeon proceeds to reconstruct the common arterial trunk to ensure normal systemic blood flow. This involves removing the pulmonary arteries' orifice from the common trunk and creating a direct pathway for aortic blood flow. The common trunk's vessel wall usually requires reinforcement with patches to ensure normal aortic functionality and prevent the development of stenosis and other complications [42, 44, 71, 72].

4.**Valve Repair or Replacement:** The common trunk valve is often underdeveloped or has significant regurgitation, necessitating further correction. Minor defects may allow for valve repair to improve its function. In more severe cases, when the valve is fully dysfunctional, it is replaced with a prosthesis, which may be biological or mechanical, depending on the patient's age, degree of damage, and material availability [32, 35, 36, 37, 43].

Choice of Materials for Conduits and Valves

One important aspect of surgical correction of CAT is the choice of suitable materials for conduits and valves. Biological materials, such as homograft's (donor tissues) and xenografts (animal tissues), have good biocompatibility and can reduce the risk of thrombosis [43, 49, 50]. However, their lifespan is limited, especially in children, and they are prone to calcification and wear. Synthetic materials, such as polytetrafluoroethylene (PTFE), are less prone to calcification and have a longer service life but require anticoagulants to prevent thrombosis. The use of bioresorbable materials that adapt to a child's growth is a promising area of development, although these technologies are still in the early stages [37, 44, 48, 73].

Risks and Complications

The surgical treatment of CAT carries a range of risks and complications, depending on the technical aspects of the operation and the patient's overall condition [2, 6, 23]. The most common complications include:

- **Thrombosis and Thromboembolism:** Conduits and prostheses are at risk of thrombus formation, especially when synthetic materials are used. Patients are often prescribed anticoagulants to prevent thrombosis, although their use may be limited due to bleeding risk, particularly in children.
- **Infectious Complications:** Infection of surgical wounds or prostheses is a serious complication that can lead to sepsis and requires long-term antibacterial therapy. Antibiotics and strict control of sterility help reduce the risk of infection.
- **Pulmonary Hypertension:** Patients with CAT may develop pulmonary hypertension due to pulmonary blood flow overload, complicating the postoperative period and requiring vasodilators and other medications to stabilize the condition.
- **Valve and Conduit Dysfunction:** As conduits and prosthetic valves are subject to wear and calcification, dysfunction may arise over time, necessitating regular monitoring and replacement as needed. The rate of reoperations remains high for CAT patients, especially among children who grow quickly and need larger prostheses and conduits as they age.

Early Neonatal Correction

Early complete defect correction is preferable, as it prevents irreversible changes in pulmonary vessels and other organs. In the neonatal period, surgery can be technically challenging due to the small size of the heart and vessels but provides the best long-term results. Early correction also minimizes the risk of severe pulmonary hypertension and related complications [41, 50, 64, 67].

Postoperative Monitoring and Support

After surgery, patients require intensive monitoring and specialized care, especially in the first weeks following the intervention. Intensive care methods, such as nitric oxide inhalation and extracorporeal membrane oxygenation (ECMO) in cases of respiratory or heart failure, are used. Postoperative medication often includes heart and lung function support, blood pressure control, and thrombosis prevention [7, 11, 12, 14, 15, 22, 23, 31, 39, 52, 58].

In addition, regular imaging methods such as echocardiography, CT, and MRI are used to assess the condition of prostheses, conduits, and valves, as well as to detect possible complications at early stages [18, 19, 20, 21, 24, 25, 28]. Many CAT patients require reoperations during their lifetime, making postoperative monitoring a crucial component of successful treatment [60, 64, 65, 67].

Prospects for Improving Surgical Treatment

With technological advancements, new methods and materials are emerging that could significantly improve CAT surgical outcomes. One promising area is using 3D printing to model complex cases and create individualized conduits and prostheses. These technologies help surgeons better prepare for surgery and minimize complications. Another promising area is the development of biocompatible and growing conduits that can adapt to the child's growth, reducing the need for reoperations [11, 18, 41, 60, 64]. Research is also underway in gene and cell therapy to improve tissue regeneration and adaptation processes, which could significantly increase implant longevity and improve patient outcomes.

Thus, surgical treatment of common arterial trunk is a complex process that requires highly qualified specialists, modern materials, and constant monitoring. Modern methods significantly improve patient prognosis for this defect, but risks and complications require attention [2, 6, 45, 46, 57, 58, 67]. As technology develops and new methods emerge, CAT patients will have more opportunities for a full life with minimal post-treatment consequences.

Long-Term Outcomes and Patient Follow-Up

Long-term follow-up for CAT patients is an integral part of treatment. After the primary surgery, various complications may arise, such as prosthetic valve dysfunction, pulmonary artery stenosis, and the development of pulmonary hypertension. The most common complications include valve insufficiency progression and conduit dysfunction, requiring periodic updates.

Regular imaging studies, such as echocardiography, MRI, and CT, allow for assessing heart and vessel conditions, detecting early-stage complications, and preventing their further development. In some cases, catheterization may be needed for interventional procedures such as stent placement or stenosed vessel dilation [19, 21, 32, 48, 50, 53, 56, 58, 65]. CAT patients should also be monitored by a cardiologist throughout their life, as there is a risk of late complications, including pulmonary hypertension and prosthesis wear.

In recent years, the use of 3D technologies, such as 3D printing, has been actively developing to model complex cases and prepare for operations. These technologies help surgeons better plan interventions and assess heart anatomy, increasing accuracy and reducing complication risk [30, 33, 36, 39, 41, 56]. In addition, new interventional cardiology methods and improved materials for prostheses and conduits also contribute to better long-term outcomes.

Conclusion

The common arterial trunk is a rare and complex congenital heart defect that requires early diagnosis and a specialized treatment approach. The prognosis for patients with this defect is significantly improved by modern diagnostic methods and surgical treatment. Despite advancements in cardiac surgery and diagnostics, the common arterial trunk remains a challenging medical issue due to its anatomical variability, the need for lifelong monitoring, and potential complications that may necessitate repeat interventions.

The defect classification systems proposed by Collett and Edwards, as well as Van Praagh, allow cardiac surgeons to better plan treatment by taking into account the location of the pulmonary arteries and the anatomical features of the common arterial trunk. Each classification emphasizes different aspects of the defect's morphology, supporting an individualized approach to treatment and enhancing the success rate of surgical interventions.

Diagnostic methods such as echocardiography, computed tomography, magnetic resonance imaging, and catheterization play a crucial role in accurate visualization of the heart and major vessels. Echocardiography remains the primary method for both diagnosis and monitoring, enabling detection of structural abnormalities and assessment of the

heart's condition postoperatively. Computed tomography and magnetic resonance imaging provide high-quality imaging, especially valuable in complex cases and for long-term follow-up. Catheterization helps evaluate the functional status of the heart and blood vessels, particularly when hemodynamic parameters and pulmonary pressure information are required.

Surgical treatment of the common arterial trunk aims to separate pulmonary and systemic blood flow and to correct anatomical defects. The main steps of surgery include closing the ventricular septal defect, reconstructing the right ventricular outflow tract, and restoring aortic blood flow. The use of conduits and prostheses facilitates the establishment of a functionally complete circulation; however, it requires regular follow-up due to possible material wear and the need for replacements as the patient grows.

Long-term follow-up for patients with a common arterial trunk is essential due to their susceptibility to complications such as pulmonary artery stenosis, prosthetic valve dysfunction, and pulmonary hypertension. Modern imaging methods, including magnetic resonance imaging and echocardiography, allow for timely detection and correction of emerging issues, thereby enhancing the quality of life and survival rates for these patients.

In conclusion, managing patients with a common arterial trunk requires a comprehensive and individualized approach, starting with early diagnosis, the application of high-precision imaging techniques, and continuing with long-term postoperative follow-up. With further advancements in technology, such as 3D printing, improved prosthetic materials, and expanded genetic diagnostic capabilities, there is potential to improve the prognosis and quality of life for patients with this complex congenital defect.

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АНАЛИЗ ФАКТОРОВ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ У МОЛОДЕЖИ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Сердечно-сосудистые заболевания (ССЗ) часто считаются недугами, присущими пожилым людям, однако тревожный рост их распространенности среди молодого населения подчеркивает необходимость более глубокого понимания факторов риска и профилактических мер.

Цель: анализ факторов риска сердечно-сосудистых заболеваний у молодого населения от 18 до 45 лет.

Стратегия поиска. Обзор литературы. Глубина исследования составила 7 лет с 2017 по 2024 годы в следующих базах данных: Pubmed, Google Scholar, Web of Science Core Collection. Критерии включения: анализ описательных, аналитических, клинических исследований и систематических обзоров, на английском языке не зависимости от страны и национальности. Критерии исключения: дети, подростки и лица старше 45 лет.

Результаты и выводы: Анализ литературы выявил основные факторы риска ССЗ среди молодого населения, такие как гиподинамия, несбалансированное питание, курение, стресс и употребление наркотических веществ, независимо от половой пренадлежности, страны и национальности.

Ключевые слова: *сердечно-сосудистые заболевания, молодежь, факторы риска.*

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Abstract

STUDY OF CARDIOVASCULAR DISEASE RISK FACTORS IN YOUNG PEOPLE. LITERATURE REVIEW

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Introduction. Cardiovascular diseases (CVD) are often considered diseases inherent in the elderly, but the alarming increase in their prevalence among young people underscores the need for a deeper understanding of risk factors and preventive measures.

Aim: to analyze risk factors for cardiovascular diseases in the young population based on scientific literature.

Search strategy. Literature review. The study depth was 7 years from 2017 to 2024 in the following databases: Pubmed, Google Scholar, Web of Science Core Collection. Inclusion criteria included a review and analysis of descriptive, analytical, clinical studies and systematic reviews published in the last 7 years in English.

Results and conclusions: The analysis of the literature revealed the main risk factors for CVD among the young population, such as physical inactivity, unbalanced diet, smoking, stress and drug use, which require further study.

Keywords: *cardiovascular diseases, youth, risk factors.*

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Түйіндеме

ЖАСТАРДАҒЫ ЖҮРЕК-ҚАН ТАМЫРЛАРЫ АУРУЛАРЫНЫҢ ҚАУІП ФАКТОРЛАРЫН ЗЕРТТЕУ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Жүрек-қан тамырлары аурулары (ЖҚА) көбінесе егде жастағы адамдарға тән аурулар болып саналады, бірақ олардың жастар арасында таралуының алаңдатарлық өсуі қауіп факторлары мен алдын алу шараларын тереңірек түсіну қажеттілігін көрсетеді.

Мақсаты: ғылыми әдебиеттер деректері негізінде жас популяциядағы жүрек-қан тамырлары ауруларының қауіп факторларын талдау.

Іздеу стратегиясы. Әдебиетке шолу. Зерттеудің тереңдігі 7 жылды құрады , 2017 жылдан 2024 жылдар аралығында келесі дерекқорларда жүргізілді: Pubmed, Google Scholar, Web of Science Core Collection. Қосылу критерийлері соңғы 7 жылда ағылшын тілінде жарияланған сипаттамалық, аналитикалық, клиникалық зерттеулер мен жүйелі шолуларды шолу мен талдауды қамтиды.

Нәтижелер мен қорытындылар: Әдебиеттерді талдау арқылы жас популяцияда жүрек-қан тамырлары ауруларының негізгі қауіп факторлары анықталды, олар физикалық белсенділік, теңгерімсіз тамақтану, темекі шегу, стресс және есірткіні қолдану болып табылады, олар қосымша зерттеуді қажет етеді.

Түйінді сөздер: *жүрек-қан тамырлары аурулары, жастар, қауіп факторлары.*

Дәйексөз үшін: *Ерназаров А.А., Ошибаева А.Е., Нускабаева Г.О., Кырыкбаева С.С., Кемельбеков К.С., Аймагамбетова А.О., Дуйсенбаева Б.С.* Жастардағы жүрек-қан тамырлары ауруларының қауіп факторларын зерттеу. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 208-218. *doi 10.34689/SH.2025.27.1.024*

Введение

Сердечно-сосудистые заболевания (ССЗ) продолжают оставаться одной из ведущих причин смертности и инвалидности во всем мире, причем их факторы риска формируются уже в детском и подростковом возрасте [51,77]. Многие иследователи выделяют среди ключевых факторов риска артериальную гипертензию, ожирение, дислипидемию, низкую физическую активность, а также психосоциальные аспекты, такие как тревожные расстройства и депрессия [4,5,6,7,8,16].

Эпидемиологические данные свидетельствуют, что распространенность и заболеваемость ССЗ среди молодежи наиболее высоки в странах с низким уровнем дохода (Южный Судан, Бенин, Буркина-Фасо, Гамбия, Конго, Никарагуа, Афганистан), однако в странах с высоким уровнем дохода (Чили, Гайана) это бремя также возрастает [51,52,65,76].

Гендерные различия в эпидемиологии ССЗ выражаются в том, что у мужчин чаще регистрируются одни типы заболеваний,такие как ишемическая болезнь сердца, тромбозы, кардиомиопатии и миокардиты, тогда как у женщин часто встречаются артериальная гипертония, митральный пролапс, аритмии, спонтанный разрыв коронарной артерии и.т.д. [51,52,65].

Ранняя диагностика и устранение факторов риска у детей и подростков имеют решающее значение для предотвращения распространения сердечно-сосудистых заболеваний во взрослом возрасте [77].

Также следует отметить, что остается актуальным двунаправленная связь между тревожными и депрессивными состояниями и ССЗ у подростков,

которая способствует как развитию, так и ухудшению прогноза заболеваний. Это особенно актуально для молодого населения, сталкивающихся с такими стрессовыми ситуациями, как обучение в университете или адаптация к рынку труда [4,16].

Несмотря на снижение частоты острого коронарного синдрома среди пожилых, у молодежи (особенно у мужчин) подобного снижения не отмечается [76]. В исследованиях *Rodgers J.L. et al. u Shi H. et al.* возраст от 18 до 44 лет принят в качестве критерия молодости согасно класификации ВОЗ и обусловлено уникальностью факторов риска в этой возрастной группе. Традиционные механизмы развития атеросклероза реже встречаются у молодых людей, где ишемическая болезнь сердца у пациентов до 44 года составляет лишь 3% от всех случаев ИБС. Тем не менее, сердечно-сосудистые заболевания продолжают быть ведущей основанием заболеваемости и летальности среди молодых людей [64,70].

Цель: анализ факторов риска сердечно-сосудистых заболеваний у молодого населения от 18 до 45 лет.

Стратегия поиска

В рамках данного исследования был проведен углубленный поиск релевантных исследований на английском языке в электронных базах данных: PubMed, Google Scholar и Web of Science Core Collection, за период с 2017 по 2024 год. Публикации содержали результаты исследовании, сосредоточенные на факторе риска ССЗ, эпидемиологические исследования, опубликованные рецензируемые работы, а также многоцентровые исследования. *Критерии включения:* анализ описательных, аналитических, клинических исследований и систематических обзоров, на английском языке не зависемости от страны и национальности (от 18 до 45 лет). *Критерии исключения:* дети, подростки и лица старше 45 лет. Ключевые запросы проводились по следующим словам: сердечно-сосудистые заболевания, молодежь и факторы риска. В результате данного поиска было выявлено 80 релевантных статей. Алгоритм отбора источников представлен на рис 1.

Рисунок 1. Схема отбора статей.

Результаты

За последние годы наблюдается существенный рост заболеваемости и распространенности ССЗ среди молодого населения в возрастной группе от 18 до 44 лет. Исследование *Roth G.A. et al.* показывает, что глобальная распространенность ССЗ увеличилась на 93 %, а смертность от них выросла примерно на 54 %, что составляет треть всех ежегодных случаев смерти в мире [65]. Кроме того, в период с 1999 по 2019 годы наблюдался значительный рост как заболеваемости, так и стандартизированных по возрасту показателей распространенности таких заболеваний, как ревматическая болезнь сердца, инсульт, ишемическая болезнь сердца (ИБС) и эндокардит [33,40]. По данным *Li Y. et al., Masaebi F. et al. u Mikkilä V. et al.,* несмотря на значительный прогресс в профилактике, ранней диагностике и лечении, ССЗ продолжают оказывать существенное социально-экономическую наргузку на систему здравоохранение [38,40,46].

Неинфекционные заболевания

Среди молодого населения отмечается значительное увеличение распространенности ряда сердечно-сосудистых заболеваний (ССЗ), таких как ревматическая болезнь сердца, инсульт и ишемическая болезнь сердца (ИБС) [65].

По результатам исследования *Roth GA et al.* среди молодого населения отмечается значительное увеличение распространенности ряда сердечно-сосудистых заболеваний (ССЗ), таких как ревматическая болезнь сердца, инсульт и ишемическая болезнь сердца (ИБС) [65]. Согласно результатам исследования *Armocida B et al.,* неинфекционные заболевания (НИЗ) у лиц молодого возраста несмотря на большинтсво иследовании остаются недостаточно изученными [7].

Среди молодых женщин в возрасте 30–39 лет наблюдается повышенная частота фибрилляции и трепетания предсердий [10,18,79]. При этом отмечено,

что наличие предсердного фиброза у женщин этой возрастной группы, страдающих фибрилляцией предсердий, может значительно увеличить риск развития ишемической болезни сердца (ИБС), ишемических атак и даже летального исхода, по сравнению с их сверстниками мужского пола [3]. Результат исследования *Mieziene B. et al.* показал, что подростки и молодые люди, независимо от пола, имеют высокие показатели распространенности и заболеваемости ИБС. При этом, среди женщин в возрасте 30–39 лет отмечается высокий уровень заболеваемости ИБС по сравнению с другими возрастными группами [45].

Ряд авторов устновили, что наиболее высокие цифры заболеваемости и распространенности по показателям DALY наблюдаются среди лиц в возрасте 25-39 лет, при этом у данной возрастной группы регистрируются самые высокие уровни смертности от эндокардита. Кроме того, у женщин в возрасте 30-39 лет фиксируются высокие показатели смертности связаны с трепетанием и фибрилляцией предсердий [10,67,70]. *Ghosh M et al.* отмечают, что на неинфекционные заболевания (НИЗ) приходится около 60% и четверть этой нагрузки связано непосредственно с ССЗ [24]. В ряде исследований было выявлено, что основными детерминантами показателя DALY при ССЗ являются повышение систолического артериального давления (САД), увеличение индекса массы тела (ИМТ) и повышенный уровень холестерина липопротеинов низкой плотности (ЛПНП) [3, 18,40,57,65,82].

Несбалансированное питания и ожирение

Несмотря на то, что в последние десятилетия популярность здорового питания в мире возрастает [11,13,17,69], исследования, проведенные среди молодого населения Европы, выявили лишь 7-11% соблюдения рекомендуемого диетического питания, причем среди мужчин этот показатель значительно ниже (2%), чем среди женщин (14%) [45,67]. Еще более худшие результаты были получены в США, где среди молодого населения практически отсутствовала приверженность здоровому питанию [39].

Многие авторы отмечают, что несбалансированный рацион питания считается существенным фактором риска развития сердечно-сосудистых заболеваний (ССЗ) [13,21,24,38,47,72]. *Wang F et al.* выявил, что употребление пищи с высоким содержанием переработанных ингредиентов, сахара и трансжиров, а также недостаток фруктов, овощей, клетчатки, цельнозерновых продуктов и орехов, в сочетании с низкой физической активностью, ожирением, употреблением алкоголя, значительно увеличивает вероятность возникновения ССЗ [80].

Данный факт подтверждается аналогичными иследованиями, где мужчины с ожирением и любым типом метаболического расстройства имели более высокий риск сердечно-сосудистых заболеваний, инсульта и смертности от сердечно-сосудистых заболеваний (исключая инфакрт миокарда) по сравнению с лицами с нормальным индексом массы тела (ИМТ) и без метаболических расстройств. Женщины с ожирением и любым типом метаболического расстройства так же имели более высокий риск сердечно-сосудистых заболеваний и инсульта по сравнению с лицами с нормальным ИМТ и без метаболических расстройств [31,68].

Неправильное питание было связано с увеличением на 64 % всех случаев смерти от ССЗ среди лиц в возрасте 25-34 лет, причем наибольшая доля смертей приходится на лиц с избыточным потреблением подслащенных сахаром напитков и переработанного мяса [43]. Употребление этих продуктов в возрасте 9-16 лет привело к увеличению частоты развития гипертонии на 16% в 17-лет. [6]. Более того, приверженность нездоровому питанию ассоциировалась с повышенным уровнем провоспалительных маркеров, начиная с детства [12], и увеличением кардиометаболического риска на более поздних этапах жизни [11].

Высокое потребление хлеба, картофеля, сливочного масла, колбас, молока и кофе приводило к повышению уровня общего холестерина и холестерина липопротеинов низкой плотности (ЛПНП), аполипопротеина-В и С-реактивного белка [13,46]. Напротив, высокая приверженность средиземноморской диете снизила ИМТ и улучшила уровень глюкозы и АД у молодых мужчин [39,58]. По результатам авторов *Buckland G. et al. u Dai H. et al.,* здоровое питание, такие как DASH, флекситарианская диета и Нордическая диета, снижают риск развития преддиабета на 65% у молодого населения [11,17].

Результаты недавнего анализа молодой популяции, проведенного в рамках исследования CARDIA, показали, что общая богатая питательными веществами растительная диета, начиная с молодого возраста (18-30 лет), ассоциируется с более низким риском ССЗ в зрелом возрасте [42].

Стресс

Как отмечает *Mofatteh M. et al.,* стресс представляет собой естественное состояние тревоги или психоэмоционального напряжения, возникающее под воздействием различных обстоятельств. У молодых людей причины стресса часто связаны с семейным давлением, сложностями в учебе, финансовыми трудностями, низкой самооценкой и влиянием со стороны сверстников [47]. Эти факторы усиливают стрессовую нагрузку, что увеличивает риск сердечно-сосудистых заболеваний за счет активации автономной нервной системы и негативного влияния на функции сердечно-сосудистой системы. Под воздействием стресса усиливается активность симпатической нервной системы, что вызывает физиологические изменения, такие как учащение сердечного ритма, сужение сосудов, расширение артериальных сосудов и усиление сократимости сердечной мышцы, обусловленные воздействием на сердечно-сосудистую систему [75].

Экология

Согласно данным *Adekoya A et al.,* высокие показатели смертности обусловленные ССЗ в странах с низким и ниже среднего уровнем дохода, связаны с загрязнением воздуха внутри помещений, которое возникает вследствие использования твердого топлива. Этот фактор практически отсутствует в странах со средним и высоким доходом [1]. При этом, интересному заключению пришли *Kim S.R. et al.,* где снижение физической активности может привести к

последующему повышению риска сердечно-сосудистых заболеваний у молодых людей, подвергающихся воздействию низких или умеренных уровней загрязнения воздуха, тогда как значительное увеличение физической активности в условиях сильного загрязнения окружающей среды может неблагоприятно повлиять на сердечно-сосудистую систему [33].

Курение

Курение признано одним из ключевых факторов риска развития сердечно-сосудистых заболеваний (ССЗ) и остается основной предотвратимой причиной смертности, связанной с заболеваниями сердца [10,35]. В работах *Reidy K.J. et al.* отмечается связь между ростом популярности курения среди молодежи с увеличением частоты сердечно-сосудистых осложнений в этой возрастной группе [60]. В сигаретном дыме содержится множество токсичных соединений, включая никотин, цианистый водород, формальдегид, свинец, мышьяк, аммиак, радиоактивные элементы и бензол. По данным *Fa-Binefa M. et al. u Gallucci G. et al.* никотин оказывает стимулирующее воздействие на адренергическую систему, что приводит к повышению частоты сердечных сокращений, снижению чувствительности к инсулину, усилению сократительной способности миокарда и нарушению функции эндотелия [20,23]. Результаты исследований *Roy A et al.* указывают на то, что мужчины в большей степени подвержены воздействию большинства факторов риска, включая табакокурение, чем женщины [22,66].

Потребление табака среди молодого населениятесно связано с минимальным возрастом, установленным законом для покупки, и удваивается среди взрослых в возрасте 18-20 лет по сравнению с подростками. Исторически сложившаяся большая распространенность курения среди мужчин в настоящее время несколько снижается за счет роста числа курящих молодых женщин из стран Африки, Азии и Южной Америки [23,73].

Продольные исследования *Jee Y. et al.* среди молодой популяции показали причинно-следственную связь между курением и ССЗ независимо от уровня холестерина [29].

В работах *Fa-Binefa M. et al.* установлена линейная связь между возрастом начала курения и смертностью от ССЗ, когда каждый год позднего начало курения ассоциировался с 4-процентным снижением риска ССЗ [20].

Кроме того, пассивное курение в раннем возрасте ассоциировалось с такими факторами ССЗ, как эндотелиальная дисфункция, повышение АД, воспаление и интолерантность к глюкозе. Эти эффекты были еще более выражены у молодых женщин по сравнению с молодыми или пожилыми мужчинами [10]. Таким образом, несмотря на то, что молодые люди никогда не курили, у них значительно повышается риск развития ССЗ, если они подвергаются пассивному курению в детстве.

В то же время, по данным *Biery D. W. et al. u Fa-Binefa M. et al.* отказ от курения значительно улучшает прогноз ССЗ в молодой популяции [10,20], снижая риск смерти, связанной с курением, на 90%, и поэтому настоятельно рекомендуется для профилактики ССЗ.

Наркотические вещества

В последние годы случаи употребления наркотических веществ среди молодежи стали значительно учащаться. Это связано как с влиянием окружения, так и с желанием экспериментировать или со стремлением избежать реальности молодого поколения. Такой образ поведения привел к повышению риска развития сердечно-сосудистых заболеваний (ССЗ) [27,30]. Употребление наркотиков остается одной из ведущих предотвратимых причин возникновения ССЗ. По данным *Gill T et al. u Puri R et al.* наиболее часто употребляемыми наркотическими веществами в Индии являются каннабис, опиоиды (например, героин и морфин), кокаин, а также чарас и ганджа [26,59].

Как отмечает *Zhao L. et al.* стимуляция каннабиноидных рецепторов первого типа у человека может приводить к эндотелиальной дисфункции, которая играет ключевую роль в формировании атеросклероза и сердечно-сосудистых заболеваний [85]. Активация каннабиноидных рецепторов инициирует механизмы, препятствующие нормальной вазодилатации в эндотелиальных клетках [25].

Кокаин известен своей способностью вызывать спазмы коронарных артерий. У людей, употребляющих кокаин, коронарные артерии подвержены повышенному риску спазмов. Кроме того, употребление кокаина приводит к снижению коронарного кровотока, что ограничивает доступ кислорода к миокарду и одновременно увеличивает его кислородную потребность [30,34]. Действие кокаина связано с его функцией адренергического агониста, так как он блокирует реабсорбцию норадреналина, способствует высвобождению эпинефрина из надпочечников, а также угнетает работу натриевых каналов. Это, в свою очередь, снижает мембранный потенциал покоя, уменьшает амплитуду потенциала действия, но удлиняет его длительность [26].

Нарушение функции щитовидной железы

Jabbar A et al. установили, что изменения в уровнях гормонов щитовидной железы могут способствовать увеличению риска развития инфаркта миокарда и других сердечно-сосудистых заболеваний [28]. Нарушения функции щитовидной железы способны вызывать различные патологии сердечно-сосудистой системы [74]. Тиреоидные гормоны оказывают влияние на сердце, изменяя частоту сердечных сокращений (хронотропный эффект) и силу их сокращений (инотропный эффект). В нормальных физиологических условиях эти эффекты благоприятны, однако в определённых патологических состояниях они могут оказывать отрицательное воздействие на сердечно-сосудистую систему [28].

Как отмечает *Jabbar A. et al.* гормоны щитовидной железы снижают периферическое сосудистое сопротивление и увеличивают сердечный выброс, что приводит к уменьшению диастолического артериального давления за счёт снижения системного сосудистого сопротивления. Они также играют значительную роль в регуляции уровней липопротеинов высокой плотности (ЛПВП) и низкой плотности (ЛПНП) [28].

Дополнительные эффекты тиреоидных гормонов включают гипертрофию миокарда, усиление сердечного

выброса, увеличение силы и эффективности сокращений сердца. Эти гормоны оказывают как прямое воздействие на миокардиальные клетки, так и косвенное влияние на гемодинамические параметры и уровень потребления кислорода тканями [53].

Малоподвижный образ жизни

По сведениям *Nikitara K. et al.* отсутствие или недостаточный уровень физической активности представляет собой значимый фактор, влияющий на сокращение продолжительности жизни. На увеличение уровня физической активности влияют различные аспекты, включая индивидуальные, социальные и культурные причины. Современные реалии, такие как урбанизация, длительное время, проводимое за экранами устройств, недостаток мотивации или интереса к физическим упражнениям, являются ключевыми факторами.

Около трети молодого населения мира, за исключением Африки и Южной Азии, считается физически неактивным, в основном из-за чрезмерного просмотра телевизора (ТВ) [50]. По результатам исследования CARDIA, в возрасте 18 лет 80 % мужчин занимаются спортом, в то время как среди женщин этот показатель составлял лишь 40 %. Однако в период между 18 и 30 годами наблюдалось постепенное снижение физической активности, более выраженное у мужчин [48]. Объяснение этому можно найти в исследовании *Young Finns Study* (YFS), которое показало, что время просмотра телевизора увеличивается у мужчин в процессе старения, а у женщин наблюдается противоположная тенденция [36,84].

Согласно *Melo E. et al.* низкий уровень физической активности в сочетании с высококалорийным питанием, особенно среди молодежи, способствует увеличению случаев ожирения. Это состояние связано с метаболическими расстройствами, такими как нарушение обмена глюкозы, инсулинорезистентность, снижение кардиореспираторной функции, повышенное артериальное давление и рост индекса массы тела. Более того, гиподинамия приводит к ухудшению кровотока, что негативно отражается на функции сосудов и ассоциируется с повышенным риском развития сердечно-сосудистых заболеваний [42].

На основании данных CARDIA каждое снижение физической активности приводил к увеличению заболеваемости гипертонией на 2%, в то время как достижение максимально рекомендованного уровня физической активности, как оказалось, предотвращает развитие гипертонии [48,61].

В соответствии с этими результатами для снижения риска ССЗ во всех возрастных группах в настоящее время рекомендуется 150-300 мин умеренной физической активности или 75-150 мин интенсивной активности [80].

Эти сведения подчеркивают значимость изучения глобальных показателей распространенности и заболеваемости ССЗ, а также факторов риска у подростков и молодых людей, акцентируя необходимость неотложных мер, направленных на определение приоритетов, мобилизацию и распределение ресурсов для улучшения здравоохранения, общественного здоровья и проведения исследований, связанных со здоровьем молодежи на глобальном уровне. Ряд ранее проведенных исследований, включая работы *Song et al. u Feigin et al.,* сообщили о значительном глобальном бремени ССЗ в общей популяции, особенно среди лиц в возрасте от 18 до 90 лет [21,72]. В то же время, несмотря на снижение заболеваемости ССЗ у среднего и пожилого возраста в мировом масштабе, работа *Shi H et al.* показал стабильный рост распространенности и заболеваемости ССЗ среди молодого населения [70].

Социально-экономический фактор, конфликты

Многие исследования подчеркивают важность и эффективность мер, направленных на снижение нескольких факторов риска, для предотвращения сердечно-сосудистых заболеваний (ССЗ) в странах с низким и средним уровнем дохода [19, 44,49,54,78]. Также установлено, что в регионах Африки, Восточной Европы и Центральной Азии наблюдается наиболее быстрый рост заболеваемости и распространенности ССЗ по сравнению с другими частями мира [63]. Такие факторы, как частые военные конфликты и социально-экономические потрясения, значительно ограничивают доступ населения к медицинской помощи, включая подростков и молодых людей [14, 63,81]. В частности, страны Африки южнее Сахары сталкиваются с серьезными трудностями в борьбе с быстро растущей распространенностью и заболеваемостью ССЗ из-за нехватки финансирования, недостатка ресурсов и слабой системы здравоохранения [55].

Нарушение сна

Исходя из данных *McArdle N. et al.* за последние десятилетия все чаще обращает внимание распространенность и последствия нарушений сна среди молодых людей. В недавнем популяционном исследовании как минимум одно нарушение сна было обнаружено у 41,0% молодых женщин и 42,3% мужчин. Наиболее распространенным расстройством сна было обструктивное апноэ сна (ОСА) у мужчин (26,9%) и хроническая бессонница у женщин (19,3%) [41]. Исследования, проведенные в США и европейских странах, подтверждают эти результаты: в целом 30-35% молодого населения страдают от расстройств сна, причем в последние годы отмечается небольшой рост распространенности среди женщин [32,71].

Fernström M. et al. было установлено, что нарушения сна достоверно ассоциируются с более высоким ИМТ и содержанием жира в организме, инсулинорезистентностью и общим риском ССЗ у молодого населения[22].

По отчетам *Kianersi S. et al.* в настоящее время для достижения адекватной продолжительности сна 7-9 ч у молодого населения рекомендуется соблюдать гигиену сна и обращаться к специалисту при наличии проблемы. Поскольку нарушения сна в значительной степени связаны с психическими заболеваниями, курением и злоупотреблением психоактивными веществами у молодого населения [32], рекомендуется проводить терапию, направленную на преодоление этих факторов.

Хроническая болезнь почек

По сведениям *Pierce C.B. et al.* распространенность хронической болезни почек (ХБП) в мире составляет

примерно в 6% среди молодого населенияв возрасте до 40 лет с аналогичным распределением между полами, где в связи с нелинейной зависимостью скорости клубочковой фильтрации от возраста было разработано новое формула расчета для молодого населения[56].

Согласно *Reidy K.J et al.* в некоторых случаях генетический фон, например полиморфизмы APOL1 у африканцев связанных с атеросклеротической болезню сердца повышает риск ССЗ [62].

Более того, в исследовании *Bae E.H. et al.,* проведенном в корейской популяции молодого населенияв возрасте 20-39 лет, у лиц с повышенным риском ССЗ также чаще встречалось сопутствующее ожирение [9].

Исходя из данных *Lalayiannis A. D. et al.* у пациентов с болезнями почек в молодом возрасте с переходом в ХПН десятилетняя выживаемость составляет 79 %, при этом смертность от ХПН в 30 раз выше по сравнению с общей популяцией, где молодые люди на диализе имели по крайней мере один фактор ССЗ. Более того, в когорте пациентов с терминальной стадией почечной недостаточности в возрасте 20-30 лет около 19% смертей были связаны с сердечными заболеваниями [37].

Аутоиммунные и воспалительные заболевания

Системные и другие хронические воспалительные заболевания (ХВЗ) гораздо чаще встречаются у молодых женщин и повышают риск преждевременного развития атеросклеротической болезни сердца [37]. Недавний метаанализ 19 аутоиммунных заболеваний *Conrad N. et al.* показал, что относительный риск атеросклеротической болезни сердца был по меньшей мере на 50% выше у молодого населенияв возрасте до 45 лет по сравнению с более старшими подгруппами [15]. Более того, у молодого населения без традиционных фактор сердечно-сосудистого риска, но с ХВЗ, риск атеросклеротической болезни сердца был в 7 раз выше по сравнению с пациентами того же возраста без ХВЗ. Интересно, что в группе раннего инфаркт миокарда с ХВЗ было большинство женщин [83].

По исследованиям *Alfaddagh A. et al.* при отсутствии развившегося ХВЗ наличие слабовыраженное воспаление остается значимым фактором риска развития ССЗ, провоцирующим прогрессирование атеросклероза. В последнее время оно стало основным направлением медикаментозного лечения пациентов с прогрессироваными атеросклеротическими болезнями сердца [4], в то время как данные о первичной профилактике атеросклеротической болезни сердца ограничиваются противовоспалительным действием статинов у пожилых людей.

Выводы.

Рост заболеваемости и смертности от ССЗ в возрастной группе 18–44 лет за последние три десятилетия указывает на изменение возрастной структуры сердечно-сосудистых рисков. Повышение распространенности таких заболеваний, как ишемическая болезнь сердца, инсульт и эндокардит, особенно среди женщин в возрасте 30–39 лет, требует пересмотра подходов к профилактике и лечению данной патологии. Невзирая на успехи в области диагностики и терапии, ССЗ продолжают оказывать социально-экономическую тяжесть на систему здравоохранения, особенно в странах с низким и средним уровнем дохода.

Факторы риска, такие как гиподинамия, несбалансированное питание, курение, стресс и употребление наркотических веществ, оказывают значительное влияние на увеличение заболеваемости ССЗ среди молодежи. Особое внимание обращает женщины, у которых фибрилляция предсердий в сочетании с предсердным фиброзом значительно повышает риск ишемической болезни сердца и инсульта. При этом наибольшие показатели смертности и DALY наблюдаются в странах с низким социально-демографическим индексом, где слабая система здравоохранения и ограниченный доступ к медицинской помощи усугубляют ситуацию.

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ПРОГРАММА УПРАВЛЕНИЯ ЗАБОЛЕВАНИЕМ ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Резюме

Введение. По данным Всемирной организации здравоохранения, более 1,5 миллиарда взрослых во всем мире страдают от повышенного артериального давления, причем почти две трети из них проживают в странах с низким и средним уровнем дохода. Артериальная гипертензия затрагивает около 25–30% взрослого населения Казахстана, что соответствует среднемировым показателям. Однако смертность от сердечно-сосудистых заболеваний в Казахстане значительно выше по сравнению с Европейским Союзом и США.

Цель исследования. Оценить эффективность внедрения программы управления заболеваниями у пациентов с артериальной гипертензией в Казахстане и провести сравнительный анализ с другими странами.

Стратегия поиска. Проведён анализ данных государственных статистических сборников о здравоохранении Казахстана за период 2013–2025 гг, а также публикаций отечественных и зарубежных авторов. Поиск литературы проводился в базах данных PubMed, Google Scholar, Scopus, Web of Science и e-Library. В обзор включены первичные исследования (описательные и аналитические), вторичные исследования (метаанализы и систематические обзоры), клинические рекомендации, а также полнотекстовые публикации на русском и английском языках, опубликованные за последние 20 лет по программе управления заболеванием.

Результаты. В Казахстане по итогам 2019 года доля пациентов, достигших целевого уровня артериального давления (140/90 мм рт. ст.), увеличилась до 62,7%. Госпитализация, связанная с хронической сердечной недостаточностью, снизилась на 14,5%. Внедрение ПУЗ позволило снизить смертность от ССЗ на 6% за первый год реализации. Однако сохраняются вызовы, включая низкий уровень контроля давления, ограниченность профилактических программ и недостаточную доступность медицинской помощи в сельских регионах.

Выводы. Для достижения уровня развитых стран необходимы: разработка комплексной программы профилактики и лечения АГ; повышение приверженности пациентов лечению; внедрение телемедицины и унификация клинических подходов; усиление взаимодействия между пациентами и медицинскими работниками.

Ключевые слова: *артериальная гипертензия, программа управления заболеваниями, амбулаторная помощь, смертность.*

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Abstract

HYPERTENSION DISEASE MANAGEMENT PROGRAMS

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Introduction. According to the World Health Organization, more than 1.28 billion adults worldwide suffer from elevated blood pressure, with almost two-thirds residing in low- and middle-income countries. Hypertension affects approximately 25–

30% of the adult population in Kazakhstan, which is consistent with global averages. However, mortality from cardiovascular diseases in Kazakhstan is significantly higher compared to the European Union and the United States.

Aim. To evaluate the effectiveness of implementing a disease management program for patients with hypertension in Kazakhstan and conduct a comparative analysis with other countries.

Search strategy. The study analyzed data from Kazakhstan's state healthcare statistical reports for the period of 2013–2025, along with publications by both domestic and foreign researchers. A comprehensive literature search was conducted in databases such as PubMed, Google Scholar, Scopus, Web of Science, and e-Library. The review includes primary studies (descriptive and analytical), secondary studies (meta-analyses and systematic reviews), clinical recommendations, as well as full-text publications in Russian and English published over the past 20 years under the disease management program.

Results. In Kazakhstan, at the end of 2019, the share of patients who reached the target blood pressure level (140/90 mm rt. st.) increased to 62.7%. Hospitalization, associated with chronic heart failure, decreased by 14.5%. The implementation of the disease management program reduced CVD mortality by 6% in the first year of implementation. However, challenges remain, including low blood pressure control levels, limited preventive programs, and insufficient access to medical care in rural areas.

Conclusions. To achieve the level of developed countries, the following measures are necessary: the development of a comprehensive program for the prevention and treatment of hypertension; increasing patient adherence to treatment; the introduction of telemedicine and the unification of clinical approaches; and strengthening collaboration between patients and healthcare professionals.

Keywords: *hypertension, disease management program, outpatient care, mortality.*

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Түйіндеме

АРТЕРИЯЛЫҚ ГИПЕРТЕНЗИЯ КЕЗІНДЕ АУРУДЫ БАСҚАРУ БАҒДАРЛАМАСЫ

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Кіріспе. Дүниежүзілік денсаулық сақтау ұйымының мәліметі бойынша, әлемде 1,5 миллиардтан астам ересек адам жоғары қан қысымынан зардап шегеді, олардың шамамен үштен екісі табысы төмен және орташа елдерде тұрады. Қазақстанда артериялық гипертензия ересектердің шамамен 25–30%-ын қамтиды, бұл әлемдік орташа көрсеткішке сәйкес келеді. Алайда, Қазақстанда жүрек-қан тамырлары ауруларынан болатын өлім-жітім Еуропалық Одақпен және АҚШ-пен салыстырғанда айтарлықтай жоғары.

Зерттеу мақсаты. Қазақстандағы артериялық гипертензиямен ауыратын науқастар үшін ауруларды басқару бағдарламасының тиімділігін бағалау және басқа елдермен салыстырмалы талдау жүргізу.

Зерттеу стратегиясы. 2013–2025 жылдар аралығындағы Қазақстанның мемлекеттік денсаулық сақтау статистикалық жинақтарының деректері және отандық пен шетелдік авторлардың жарияланымдары талданды. Әдебиеттерді іздеу PubMed, Google Scholar, Scopus, Web of Science және e-Library дерекқорларында жүргізілді. Шолуға бастапқы зерттеулер (сипаттамалық және аналитикалық), қайталама зерттеулер (Мета-анализдер және жүйелі шолулар), клиникалық ұсыныстар, сондай-ақ соңғы 20 жылда ауруды басқару бағдарламасы бойынша жарияланған орыс және ағылшын тілдеріндегі толық мәтінді басылымдар кіреді.

Нәтижелер. Қазақстанда 2019 жылдың соңында қан қысымының мақсатты деңгейіне (140/90 мм рт. ст.) жеткен науқастардың үлесі 62,7%-ға дейін өсті. Созылмалы жүрек жеткіліксіздігімен байланысты ауруханаға жатқызу 14,5%-ға төмендеді. Ауруды басқару бағдарламасын енгізу жүрек-қан тамырлары ауруларынан болатын өлім-жітімді іске асырылған бірінші жылдың өзінде 6%-ға төмендетуге мүмкіндік берді. Дегенмен, әлі де төмен қан қысымын бақылау деңгейі, алдын-алу бағдарламаларының шектеулілігі және ауылдық өңірлерде медициналық көмектің қолжетімсіздігі сияқты мәселелер сақталады.

Қорытынды. Дамыған елдер деңгейіне жету үшін келесі шараларды жүзеге асыру қажет: артериялық гипертензияның алдын алу және емдеу бойынша кешенді бағдарламаны әзірлеу; пациенттердің емделуге деген

ұстанымын арттыру; телемедицинаны енгізу және клиникалық тәсілдерді біріктіру; науқастар мен медицина қызметкерлері арасындағы өзара әрекеттестікті күшейту.

Түйінді сөздер: *артериялық гипертензия, ауруларды басқару бағдарламасы, амбулаторлық көмек, өлім-жітім.*

Дәйексөз үшін: *Маркабаева А.М., Керимкулова А.С., Нурпеисова Р.Г., Зекенова Е.М., Умбетжанова А.Т., Кубекова С.Ж., Алдабекова Г.У.* Артериялық гипертензия кезінде ауруды басқару бағдарламасы // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 219-231. *doi 10.34689/SH.2024.27.1.025*

Актуальность

Артериальная гипертензия (АГ) является ведущей медицинской и социальной проблемой современности вследствие её широкой распространенности и тяжести осложнений.

Артериальная гипертензия (АГ) вносит основной вклад в структуру заболеваемости ССЗ и является причиной преждевременной смертности среди населения. [49,50,61,64]. Согласно данным Всемирной организации здравоохранения (ВОЗ), наибольшая доля смертности от неинфекционных заболеваний (НИЗ) приходится на сердечно-сосудистые заболевания (ССЗ). В 2021 году от этих заболеваний скончалось не менее 19 миллионов человек [9]. Уровень заболеваемости АГ остается высоким во многих странах [51,73,78].

Учитывая высокую распространенность АГ в нашей стране и ее роль в развитии осложнений, большое значение имеет изучение организации медицинской помощи больным АГ, в том числе после внедрения программы управления заболеванием (ПУЗ) больным с АГ включающая выявление на ранних стадиях заболевания, адекватную оценку врачами степени сердечно-сосудистого риска (ССР) и своевременное проведения профилактических мер [31].

Цель исследования. Оценить эффективность внедрения программы управления заболеваниями для пациентов с артериальной гипертензией в Казахстане и провести сравнительный анализ с другими странами.

Стратегия поиска.

Проведён анализ данных государственных статистических сборников о здравоохранении Казахстана за период 2013–2025 гг, а также публикаций отечественных и зарубежных авторов. Поиск литературы проводился в базах данных PubMed, Google Scholar, Scopus, Web of Science и e-Library. В обзор включены первичные исследования (описательные и аналитические), вторичные исследования (метаанализы и систематические обзоры), клинические рекомендации, а также полнотекстовые публикации на русском и английском языках, опубликованные за последние 20 лет по программе управления заболеванием.

Результаты поиска

Повышение качества медицинской помощи способствует увеличению продолжительности жизни, особенно в экономически развитых странах. Однако это также приводит к увеличению общего числа пациентов с гипертонией. В последние тридцать лет в результате глобального старения населения доля гипертонии в общей структуре заболеваемости растет, так как артериальное давление повышается с возрастом. В настоящее время АГ рассматривается как «болезнь цивилизации» [5,62].

Рекомендации 2024 года определяют гипертонию как офисное систолическое артериальное давление (АД) ≥ 140 мм рт. ст. или диастолическое АД ≥ 90 мм рт. ст. Для большинства взрослых, получающих лечение для снижения риска сердечно-сосудистых заболеваний, рекомендуется поддерживать систолическое АД в пределах 120–129 мм рт. ст., если лечение хорошо переносится [79].

Распространенность АГ

По всему миру у 1,5 миллиарда взрослых людей диагностировано повышенное артериальное давление, при этом около двух третей из них проживают в странах с низким и средним уровнем дохода [6, 12, 23, 63,77]. Уровень распространенности АГ варьируется в разных странах и регионах:

- Румыния: 50,2% среди мужчин и 41,1% среди женщин [59];
- Польша: 42,1% среди мужчин и 32,9% среди женщин (по данным исследования WOBASZ) [48];
- Чехия: 43,6% [52];
- Великобритания: 30%;
- США: 19,5% [72].
- Россия: 44% [26]

В Казахстане 25–30% взрослого населения страдают артериальной гипертензией [25, 24] что соответствует средним мировым показателям. Однако уровень смертности от сердечно-сосудистых заболеваний в стране существенно выше, чем в странах Европы и США. Это связано с низким уровнем профилактики, недостаточной доступностью качественной медицинской помощи в сельской местности и низкой приверженностью пациентов к лечению [84, 86].

АГ увеличивает риск инфаркта миокарда и инсульта в 3–4 раза, а также способствует развитию почечной недостаточности, деменции и других хронических осложнений [17, 32].

Одной из основных причин ограниченного контроля АГ является недостаточная информированность больных о наличии заболевания, недостаток знаний о мерах профилактики АГ, а также низкая приверженность пациентов соблюдению рекомендаций врача. Никакие современные технологии не помогут человеку, если он сам не заботится о своем здоровье, которое во многом определяется образом жизни. От образа жизни и эффективности системы здравоохранения здоровье человека зависит на 60%, причем, от образа жизни - в 4-5 раз больше, чем от функционирования системы здравоохранения. Одним из основных методов повышения приверженности лечению и здоровому образу жизни и эффективности терапии являются образовательные программы для

пациентов. Проведенные исследования показали аспекты клинической, медико-социальной и экономической эффективности Школ Здоровья [28].

ВОЗ рекомендует внедрение оценки общего сердечно-сосудистого риска на уровне первичной медицинской помощи. В рамках Повестки дня в области устойчивого развития до 2030 года неинфекционные заболевания определены как ключевой барьер для устойчивого развития. ВОЗ поставила цель сократить преждевременную смертность от НИЗ на одну треть к 2030 году за счет профилактики и улучшения лечения, что требует широкомасштабных национальных программ [86].

Пациенты с ССЗ представляют большую проблему для первичной медико-санитарной помощи, поскольку они связаны с высокими расходами на здравоохранение и плохим соблюдением лечения и рекомендаций [57, 65, 66, 69, 71].

При наличии НИЗ поставщики первичной медико-санитарной помощи сталкиваются с трудностями в применении руководств [10, 67] и в поддержании непрерывности ухода [27].

Экономический ущерб при АГ

В Казахстане отмечается рост расходов на лечение неинфекционных заболеваний. Эти затраты составляют 95–96% от общих расходов государства на здравоохранение, в то время как на профилактику приходится лишь 3%.

В России экономические потери в 2017 году от ССЗ составили 2,7 трлн рублей, что эквивалентно 3,2% ВВП за этот год. Тем временем в странах Европы доля затрат на профилактику составляет 19% [37].

По прогнозам, к 2030 году общие расходы США на лечение хронических заболеваний составят более 42 триллионов долларов, при этом медицинские расходы и потери производительности обойдутся в 8600 долларов на человека [43].

Вопрос о взаимосвязи смертности и уровня дохода остается дискуссионным. С одной стороны, при уровне валового внутреннего продукта на душу населения выше 10 000 долларов США неинфекционные заболевания становятся причиной 75% всех случаев смерти. В странах с низким и средним уровнем дохода смертность имеет выраженную зависимость от экономического статуса [18, 55]. Внутри одного государства также прослеживается связь между доходом и продолжительностью жизни: богатые люди живут дольше бедных. Например, в США разница в продолжительности жизни между самыми богатыми 5% населения и самыми бедными 5% составляет 25% в пользу первых [81].

Факторы риска АГ

Обращает внимание тенденция повышения распространенности ФР среди молодых людей, особенно ожирения, гиподинамии, неправильного питания, злоупотребления психоактивными веществами [7, 82].

В Казахстане отсутствуют полные данные о динамике распространенности факторов риска артериальной гипертензии. [30] Однако исследования, проведенные в разных странах с 1956 по 1970 годы, подтвердили, что прогностическая значимость факторов риска для смертности различается в зависимости от уровня экономического развития страны. Эти исследования показали, что среди населения наблюдаются различия в распространенности таких факторов, как:

- Курение [88]
- Дислипидемию [22, 46]
- Избыточную массу тела [22, 47, 73]
- Чрезмерное употребление алкоголя [73]
- Низкий уровень физической активности [40, 1]
- Неправильное питание (употребление насыщенных жиров и холестеринсодержащих продуктов) [74].

В России исследователи оценили влияние различных факторов на снижение смертности с помощью анализа Imrast. Было установлено, что в период с 2003 по 2006 год снижение смертности от сердечно-сосудистых заболеваний (ССЗ) на 59,6% было обусловлено снижением тяжести факторов риска, тогда как только 29,4% улучшение показателей смертности объяснялось лечебными мероприятиями. Среди факторов риска наибольшее влияние на снижение смертности оказало снижение среднего уровня артериального давления (АД) на 47,6%. Вторым по значимости фактором стало снижение среднего уровня холестерина в популяции (14,8%), а третьим – снижение распространенности ожирения (15,8%) [41].

Результаты Фрамингемского исследования, а также европейского проекта ВОЗ (The WHO's European Collaborative), направленного на снижение смертности от ССЗ, подтвердили эффективность здорового образа жизни и лечения пациентов из групп высокого риска. Улучшение качества оказания медицинской помощи, раннее выявление ССЗ, проведение санитарно-просветительной работы, повышение охвата диспансерным наблюдением, доступность кардиологической помощи позволяют значительно снизить сердечно-сосудистые риски среди различных европейских популяций [87].

Программы эффективного контроля при АГ

Профилактика заболеваний является одной из ключевых задач первичной медико-санитарной помощи (ПМСП) [20] и охватывает как инфекционные, так и хронические неинфекционные заболевания. Профилактические меры реализуются на индивидуальном, групповом и популяционном уровнях. Основным инструментом профилактики является диспансерное наблюдение за хроническими заболеваниями [4, 34]. Несмотря на ряд положительных аспектов диспансеризации, её эффективность остаётся недостаточной, особенно в её текущей форме. Врачи предоставляют пациентам рекомендации по их заболеванию, однако они не могут охватить все жизненные ситуации пациента. Успешное лечение всех хронических заболеваний в амбулаторных условиях невозможно без активного участия самого пациента. В связи с этим возникла необходимость в новых подходах к работе с населением, страдающим хроническими заболеваниями, что привело к разработке программы управления заболеваниями (ПУЗ) — нового метода профилактики [76].

Исследования, посвященные внедрению программ эффективного контроля хронических неинфекционных заболеваний на уровне первичной медицинской помощи, проводились по всему миру. Американская

кардиологическая ассоциация доказала эффективность самостоятельного управления заболеванием у пациентов с ишемической болезнью сердца, артериальной гипертензией и сердечной недостаточностью [58].

Интеграция программ профилактики и лечения хронических заболеваний на уровне первичной медико-санитарной помощи дает возможность улучшить уход за пациентами с хроническими заболеваниями непосредственно в том учреждении, где они получают комплексную медицинскую помощь, обеспечивая при этом непрерывность [45].

Анализ, проведённый Джоном П. Аллегранте и его коллегами, доказал, что самоуправление улучшает качество жизни и снижает потребление лекарств [43].

Исследование проведеннное в восьми первичных медицинских учреждениях в регионе Сагеней, Квебек, Канада показали положительные результаты интеграции программ профилактики и лечения хронических заболеваний в первичную медицинскую помощь, сосредоточенную на нескольких хронических состояниях для пациентов и для членов их семей. PR1MaC программа интеграции профилактических услуг способствовала тому, что некоторые пациенты стали более мотивированными и уверенными в себе, чтобы внести здоровые изменения в свою жизнь и изменить свои привычки. Пациенты начали худеть, придерживаясь более здорового питания, занимаясь физической активностью и возобновив наблюдение за своими хроническими заболеваниями [67].

Обучение в кабинете профилактики сердечно-сосудистых заболеваний и их осложнений для больных с АГ формирует активную жизненную позицию пациента в отношении заболевания, улучшает мотивацию к выполнению профилактических рекомендаций [44].

*Epstein R.S., Sherwood L.M. (*1996) определили термин "управление заболеваниями" как использование функциональных возможностей пациента в максимальной степени, предотвращение болезней, инвалидности и смертности, а также повышение эффективности системы здравоохранения [60]. Программа управления заболеваниями направлена на улучшение качества жизни людей с хроническими заболеваниями и снижение затрат на здравоохранение за счёт предотвращения или минимизации последствий заболеваний [30].

Управление болезнью считается одним из наиболее эффективных подходов к планированию и обеспечению охраны здоровья, получившим широкую международную поддержку. Этот метод признан структурированным и системным решением, способным устранить ряд проблем, с которыми столкнулась система медицинского обслуживания в последние годы.

Если пациент находится в центре системы здравоохранения, теория управления заболеваниями предполагает более эффективное использование ресурсов [86]. Пациенты должны активно участвовать в процессе лечения в качестве партнёров врача [33, 53, 70], получать полную информацию о своём состоянии, контролировать лечение и нести ответственность за управление своим здоровьем [19, 54].

Основные компоненты программы управления заболеваниями:

1. *Реестры и сегментация пациентов* — наличие реестров хронических заболеваний с соответствующими данными и персоналом, обладающим необходимыми навыками работы с ними. Цели и исходные данные определяются для каждого показателя. Реестры помогают отслеживать изменения в будущем. Пациентов можно распределять по группам на основании уровня контроля их заболеваний.

2. *Карты наблюдения пациентов* — одностраничный документ, содержащий ключевую информацию о пациенте: его здоровье, последние лабораторные показатели и проводимое лечение. Используется медицинским персоналом при каждом визите [29].

3. *Плановые приёмы* — направлены на повышение эффективности медицинской помощи и поддержку самоуправления пациента. Планирование и структурирование приёмов с использованием карты наблюдения является основной стратегией.

4. *Контрольные звонки пациентам* — интервал звонков определяется для каждой группы пациентов заранее. Система звонков позволяет выявлять пациентов, пропустивших приём, и разрабатывать стратегии их повторного вовлечения в процесс наблюдения.

5. *Групповые приёмы* — пациенты с определённым заболеванием приглашаются на приём, в ходе которого обсуждаются их медицинские потребности, проводится дополнительное обучение по их состоянию, а также создаются условия для обмена опытом. Это также позволяет медицинскому персоналу лучше контролировать состояние пациентов.

6. *Поддержка самоуправления* — направлена на поощрение активного участия пациента в управлении своим заболеванием, изменение образа жизни и повышение мотивации [15, 56].

Таким образом, программы управления заболеваниями рассматриваются как эффективная альтернатива диспансеризации. Они способствуют повышению вовлечённости пациентов, улучшению эффективности медицинской помощи и снижению заболеваемости и смертности [11, 83].

В целях привлечения граждан к совместной ответственности за управление своим здоровьем и хроническими заболеваниями Министерство здравоохранения Республики Казахстан запустило пилотные проекты ПУЗ в 2013 году в 7 поликлиниках Северо-Казахстанской и Павлодарской областей в рамках государственной программы "Денсаулық" на 2016-2019 годы. В 2016 году к проекту подключились ещё 5 медицинских организаций из Алматы, Астаны, Уральска, Костаная и Караганды [21].

Этапы внедрения программы управления заболеваниями:

1. *Выбор пациентов для участия в программе*. Основная задача сотрудников поликлиник — выявить пациентов, соответствующих критериям участия в ПУЗ. В программу включены пациенты с гипертонической болезнью II-III стадии (без тяжёлых сопутствующих заболеваний), пациенты с сахарным диабетом 2 типа (без тяжёлых осложнений) и пациенты с хронической сердечной недостаточностью, имеющие факторы риска.

2. *Анкетирование пациентов*. Опрос проводится для оценки осведомлённости населения о программе, выявления уровня мотивации к участию и определения ожиданий пациентов.

3. *Заключение соглашения.* Если пациент согласен участвовать в программе, ему объясняются преимущества ПУЗ, его права и обязанности. Между пациентом и медицинским учреждением подписывается соглашение, в котором прописаны их взаимные обязательства [33].

Программа направлена на снижение смертности от сердечно-сосудистых заболеваний за счёт совершенствования амбулаторно-поликлинической помощи и внедрения профилактических мероприятий [35] и позволяет пациентам, работая в сотрудничестве с медицинскими работниками, контролировать свое заболевание и предотвращать осложнения путем постоянного взаимодействия с мультидисциплинарной командой. В состав этой команды входят терапевт, профильный специалист, средний медицинский персонал, психолог, специалист по формированию здорового образа жизни и социальный работник.

В Казахстане программа охватывает гипертоническую болезнь, хроническую сердечную недостаточность и сахарный диабет 2 типа. Для этих заболеваний были разработаны электронные реестры, что позволяет регулярно отслеживать состояние пациентов. Любые отклонения от нормы оперативно фиксируются в системе, и междисциплинарная команда может незамедлительно принять корректирующие меры [68].

Основную роль в мониторинге пациентов играют участковые терапевты и врачи общей практики. Они выявляют ключевые факторы риска, разрабатывают индивидуальные программы снижения этих факторов, обучают пациентов основам самоуправления, следят за ведением дневников самоконтроля и анализируют данные о состоянии пациентов.

Электронные реестры настроены на отправку регулярных уведомлений о необходимости профилактических осмотров или сдачи анализов. Если ухудшение состояния пациента связано не с лечением, а с другими факторами, разрабатывается "Краткий план действий" с участием психолога, социального работника и ближайших родственников пациента. Этот план может включать снижение массы тела, отказ от вредных привычек и другие важные мероприятия. Масштаб поставленных целей определяется с учётом "Шкалы уверенности пациента в себе" [38].

Концепция мобильного приложения для пациентов с Программой управления заболеваниями (ПУЗ), разработанная специалистами Научно-исследовательского института кардиологии и внутренних болезней, дополнительно включила раздел "ПУЗ".

Также ПУЗ была усовершенствована и внедрена для опытного использования в мобильном приложении Damumed в рамках существующей шкалы SCORE. Шкала SCORE — это международная шкала, оценивающая уровень коронарного риска на ближайшие 10 лет [36]. Медицинский работник может оценить риск развития сердечно-сосудистых заболеваний у пациента и дать соответствующие рекомендации по управлению факторами риска. Под контролем медицинских работников для пациента должны быть определены целевые показатели артериального давления, уровня холестерина, глюкозы в крови, массы тела. Кроме того, пациенту может потребоваться прием лекарственных средств [13].

В мобильном приложении пациент может вводить свои данные (систолическое и диастолическое артериальное давление, вес, рост, частоту пульса, уровень глюкозы в крови и моче, международные единицы (ХЕ), хроническую сердечную недостаточность (ХСН). Эти данные затем будут отображаться для участкового врача в базе данных «ДамуМед». Также пациент может самостоятельно оценивать свое состояние в мобильном приложении, в результате чего автоматически будет определена соответствующая зона (зеленая, желтая или красная), и в зависимости от уровня риска он сможет получить рекомендации от врача.

В программу «ДамуМед» внедрено раздел «ПУЗ», где врачи могут планировать прием и отслеживать состояние пациента. Основной принцип теории управления заболеваниями заключается в том, что пациент является активным участником процесса лечения и центром системы здравоохранения, что способствует более эффективному использованию ресурсов здравоохранения [80].

Эффективность внеднерия ПУЗ

Внедрение ПУЗ в Республике Казахстан показало положительные результаты среди пациентов: у 62,7% пациентов с артериальной гипертензией удалось стабилизировать показатели артериального давления. Улучшился контроль артериального давления и регулярность приема гипотензивных препаратов. У 21,4% пациентов с АГ уровень липопротеидов низкой плотности (ЛПНП) снизился до целевого показателя <2,5 ммоль/л. По итогам 2018 года внедрение ПУЗ способствовало снижению смертности от сердечно-сосудистых заболеваний (ССЗ) на 4,3%, в том числе: от АГ — на 12%, от ишемической болезни сердца (ИБС) — на 4%, от острого инфаркта миокарда (ОИМ) — на 4,8%, от острого нарушения мозгового кровообращения (ОНМК) — на 8% [2].

Важную роль в реализации ПУЗ и повышении ее эффективности сыграли навыки самоуправления пациентов. Это способность человека с хроническим заболеванием контролировать симптомы, процесс лечения, физические и социальные последствия, а также снижать вероятность обострений заболевания, осложнений и потребности в стационарной и неотложной медицинской помощи путем изменения образа жизни [3].

По сравнению с развитыми системами здравоохранения США и Европы, где внедрены системные подходы к профилактике и контролю повышенного артериального давления, казахстанская система здравоохранения сталкивается со структурными и организационными проблемами [16].

Система здравоохранения США использует передовые технологии и инновационные подходы для управления АГ. В рамках программы Million Hearts Initiative была поставлена цель предотвратить 1 миллион инфарктов и инсультов путем внедрения скрининговых программ, обучения населения и использования мобильных приложений для контроля

давления. Успешные инициативы включают использование автоматизированных систем измерения артериального давления (например, Omron и Withings), интегрированных с электронными медицинскими картами пациентов, что повысило контроль артериальной гипертензии до 48% [42].

В Европе применяется комплексный междисциплинарный подход к управлению АГ, включающий программы раннего выявления, цифровую поддержку пациентов и интеграцию в систему первичной медико-санитарной помощи. В странах Северной Европы (Швеция, Финляндия) контроль артериального давления достигает 60%, что связано с высокой приверженностью пациентов к лечению и использованием современных технологий [58].

В России диспансеризация, включающая профилактические осмотры, способствует раннему выявлению заболевания. Однако, несмотря на высокий уровень выявления АГ, приверженность лечению остается низкой. Согласно исследованиям [60, 93], только 60% пациентов с диагнозом АГ регулярно посещают врача. Кроме того, в лечении часто применяются устаревшие препараты, что снижает эффективность терапии, а профилактические программы недостаточно интегрированы на уровне первичной медико-санитарной помощи. В работе Калинина показано сильная статистически значимая взаимосвязь между выявленной при диспансеризации АГ и алиментарно-зависимыми факторами риска, что определяет многофакторность профилактики и контроля АГ в первичном звене здравоохранения.

Результаты ПУЗ в РК

В период внедрения ПУЗ в Казахстане наблюдается положительная динамика среди пациентов с хроническими заболеваниями. По итогам 2019 года доля пациентов, достигших целевого уровня артериального давления (140/90 мм рт. ст.), увеличилась до 62,7%. Смертность от сердечно-сосудистых заболеваний снизилась на 6% по сравнению с 2015 годом. Госпитализация, связанная с хронической сердечной недостаточностью, снизилась на 14,5% [2, 11, 13]. Однако смертность от сердечно-сосудистых заболеваний в Казахстане остается высокой, что требует изучение причин данной проблемы и разработки мер по совершенствованию организации медицинской помощи пациентам с артериальной гипертензией на уровне первичной медико-санитарной помощи.

С целью определения проблем диспансеризации больных с артериальной гипертензией на первичном звене здравоохранения проведена экпертиза медицинских карт в базе комплексной медицинской информационной системе больных с АГ, состоящие на диспансерном учете у ВОП, где выявлены несоблюдения ВОП протокола лечения АГ и плана диспансерного наблюдения по ПУЗ. Результаты предварительной экпертизы медицинских карт указывают на актуальность организации ретроспективного исследования для изучения эффективности реализации ПУЗ у больных с АГ для выявления возможных медицинских и организационных причин.

Снижение эффективности ПУЗ в Казахстане связано низким уровенем контроля артериального давления, с низкой приверженностью к лечению и недостаточной мотивацией врачей первичной медико-санитарной помощи, недостаточное использование медицинских сестер в управлении артериальной гипертенщии и мало уделяется внимание на телемедицину. Также недостаточно профилактических программ, таких как: программы по снижению потребления соли и повышению физической активности.

Рекомендации по повышению эффективности ПУЗ в Республике Казахстан:

- Активное испозьзование телемедицины, мобильных приложений для контроля давления, интеграция данных в электронные медицинские регистры.

- Развитие роли медсестер: обучение медсестер управлению АГ.

Заключение

Последние исследования, опубликованные в базе данных PubMed, демонстрируют, что программы управления заболеванием при артериальной гипертензии приводят к значительному снижению артериального давления, уменьшению числа госпитализаций и снижению риска развития сердечно-сосудистых осложнений. Важным направлением является интеграция цифровых технологий, позволяющих осуществлять дистанционный мониторинг состояния пациентов, что обеспечивает своевременное вмешательство и корректировку лечебных мероприятий. Кроме того, усиление коммуникации между пациентами и медицинскими работниками, а также активное обучение пациентов принципам самоуправления и здорового образа жизни способствуют повышению приверженности режиму лечения и улучшению клинических показателей. Таким образом, дальнейшее развитие и адаптация программ управления заболеванием, с учетом современных цифровых решений и акцента на партнерском взаимодействии в системе здравоохранения, являются ключевыми факторами для дальнейшего снижения смертности и повышения качества жизни пациентов с артериальной гипертензией в Казахстане.

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ОРГАНИЗАЦИОННЫЕ АСПЕКТЫ УПРАВЛЕНИЯ РИСК-ОРИЕНТИРОВАННЫМИ ТЕХНОЛОГИЯМИ В ОРГАНИЗАЦИЯХ РОДОВСПОМОЖЕНИЯ

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Резюме

Введение. Управление эпидемиологическими рисками является важной задачей для медицинских организаций родовспоможения, так как они работают с высокорисковыми пациентками, включая беременных и новорожденных детей, которые более восприимчивы к инфекционным заболеваниям.

Цель. Анализ данных литературы по вопросу управления риск-ориентированными технологиями в организациях родовспоможения.

Стратегия поиска. Поиск публикаций по теме исследования проводился в базах данных e-Library, Cyberleninka, Google Академия, ResearchGate, Pubmed, Web of Science, Scopus. *Критериями включения являлись*: аналитические и описательные исследования, метаанализы и систематические обзоры, клинические руководства, монографии, а также данные отчетов и приказов, оригинальные полнотекстовые статьи на английском и русском языках, находящиеся в открытом доступе и содержащие статистически подтвержденные выводы. *Критерии исключения*: краткие отчеты, газетные статьи и личные сообщения. Глубина поиска составила 5-7 лет (2018-2024).

Результаты и выводы. Анализ литературных данных показал, что эффективное управление эпидемиологическими рисками и внедрение риск-ориентированных технологий являются ключевыми организационными мероприятиями для повышения эффективности работы организаций родовспоможения. Такие меры способствуют снижению заболеваемости ИСМП, что подчеркивает важность и актуальность данной проблемы для международных исследований. В период изменения подходов к оказанию медицинской помощи, система здравоохранения нуждается в трансформации с учетом эпохи цифровизации. Результаты межгосударственного поперечного исследования, с использованием анкетирования IPCAF, показало, что только 12,5% из 88 стран-участниц внедрили элементы всех основных компонентов, также имеют недостаточные знания, имеют медработники, в области профилактики инфекций и инфекционного контроля. Прохождение обучений, большой опыт работы могут способствовать улучшению в системе здравоохранения на всех уровнях оказания медицинской помощи. Рекомендуется сосредоточиться на разработке стратегий образовательных программ, повышении квалификации, организации научных конференций, практических семинаров и обучающих тренингов, внедрив комплексные программы непрерывного специализированного образования.

Ключевые слова: *инфекции, связанные с оказанием медицинской помощи, риски, организации родовспоможения, система оценки профилактики и контроля инфекций, опрос.*

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Abstract

ORGANIZATIONAL ASPECTS OF RISK-MANAGEMENT ORIENTED TECHNOLOGIES IN MATERNAL CARE ORGANIZATIONS

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Introduction. Epidemiological risk management is an important task for obstetrics medical organizations, as they work with high-risk patients, including pregnant women and newborn children, who are more susceptible to infectious diseases.

Aim. Analysis of Literature Data on Risk-Oriented Technology Management in Maternity Care Organizations

Search Strategy. The search for publications on the research topic was conducted in the following databases: e-Library, Cybereninka, Google Scholar, ResearchGate, PubMed, Web of Science, and Scopus. Inclusion criteria were: analytical and descriptive studies, meta-analyses and systematic reviews, clinical guidelines, monographs, as well as reports, official directives, and original full-text articles in English and Russian, available in open access and containing statistically validated findings. Exclusion criteria included: brief reports, newspaper articles, and personal communications. The search depth covered a period of 5–7 years (2018–2024).

Results and Conclusions. The analysis of literature data showed that epidemic risk management, risk-oriented technologies are the main organizational measures aimed at improving the efficiency, stabilization and reduction of morbidity on HICM in obstetrics organizations is an actual problem studied at the global level.

Thus, at this stage in the period of changing approaches to the provision of medical care, the health care system needs to be transformed to take into account the era of digitalization. The results of interstate cross-sectional study using IPCAF questionnaire showed that only 12.5% of 88 participating countries have implemented elements of all major components, also insufficient knowledge of health workers in the field of PIIC and ISMP. Training and experience can contribute to improvements in the health system at all levels of care. It is recommended to focus on developing strategies for educational programs, professional development, organizing scientific conferences, workshops and training sessions, and introducing comprehensive programs of continuous specialized education.

Key words: *healthcare-associated infections (HAIs), risks, obstetric organizations, Infection Prevention and Control Evaluation System (IPES), survey.*

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Түйіндеме

БОСАНДЫРУ ҰЙЫМДАРЫНДАҒЫ БАҒДАРЛАНҒАН ТЕХНОЛОГИЯЛАРДЫҢ ТӘУЕКЕЛІН БАСҚАРУДЫҢ ҰЙЫМДАСТЫРУШЫЛЫҚ АСПЕКТІЛЕРІ

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Кіріспе. Эпидемиологиялық тәуекелдерді басқару медициналық акушерлік ұйымдар үшін маңызды міндет болып табылады, өйткені олар қауіптілігі жоғары науқастармен, соның ішінде жұқпалы ауруларға бейім жүкті және жаңа туған нәрестелермен жұмыс істейді.

Мақсаты. Босандыру ұйымдарындағы тәуекелге бағдарланған технологияларды басқару мәселесі бойынша әдебиеттер деректерін талдау.

Іздеу стратегиясы.Зерттеу тақырыбы бойынша жарияланымдарды іздеу келесі дерекқорларда жүргізілді: e-Library, Cyberleninka, Google Академиясы, ResearchGate, PubMed, Web of Science, Scopus. Іріктеу критерийлері: аналитикалық және сипаттамалық зерттеулер, метаанализдер мен жүйелі шолулар, клиникалық нұсқаулықтар, монографиялар, сондай-ақ есептер мен бұйрықтар деректері, ағылшын және орыс тілдеріндегі ашық қолжетімділіктегі, статистикалық негізделген қорытындылары бар түпнұсқалық толық мәтінді мақалалар.Қоспау критерийлері: қысқаша есептер, газет мақалалары және жеке хат алмасулар.Іздеу терең дігі – соңғы 5–7 жылды қамтыды (2018–2024 жж.).

Нәтижелер және қорытындылар. Әдеби деректерді талдау эпидемиялық тәуекелдерді басқару және тәуекелге бағытталған технологиялар босандыру ұйымдарындағы жедел медициналық көмек көрсету жүйесінің

тиімділігін арттыруға, тұрақтандыруға және аурушаңдық деңгейін төмендетуге бағытталған негізгі ұйымдастыру шаралары жаһандық деңгейде зерттелетін өзекті мәселе екенін көрсетті.

Осылайша, осы кезеңде медициналық көмек көрсету тәсілдерінің өзгеруі кезеңінде денсаулық сақтау жүйесі цифрландыру дәуірін ескере отырып трансформацияны қажет етеді. IPCAF сауалнамасын қолданатын мемлекетаралық көлденең зерттеу нәтижелері 88 қатысушы елдің тек 12,5%-ы барлық негізгі компоненттердің элементтерін енгізгенін және медицина қызметкерлерінің білімі жеткіліксіз екенін көрсетті. Оқыту және үлкен жұмыс тәжірибесі денсаулық сақтаудың барлық деңгейлерінде денсаулық сақтау жүйесін жақсартуға көмектеседі. Үздіксіз мамандандырылған білім берудің кешенді бағдарламаларын енгізе отырып, білім беру бағдарламаларының стратегияларын әзірлеуге, біліктілікті арттыруға, ғылыми конференциялар, практикалық семинарлар мен тренингтер ұйымдастыруға баса назар аудару ұсынылады.

Түйінді сөздер: *медициналық көмекпен байланысты инфекциялар, тәуекелдер, акушерлік көмек, инфекциялардың алдын алу және бақылау жүйесін бағалау, сауалнама.*

Дәйексөз үшін: *Алдабекова Г.У., Мусина А.А., Камалбекова Г.М., Данбаева Ж.С., Хамидуллина З.Г., Оспанова А.Б., Исаева Е.И.* Босандыру ұйымдарындағы бағдарланған технологиялардың тәуекелін басқарудың ұйымдастырушылық аспектілері // Ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б. 232-249. *doi 10.34689/SH.2025.27.1.026*

Введение

На сегодняшний день управление эпидемиологическими рисками в медицинских организациях родовспоможения, является актуальным, особенно в свете последних глобальных пандемий, таких как COVID-19. Управление эпидемиологическими рисками является важной задачей для медицинских организаций родовспоможения, так как они работают с высокорисковыми пациентками, включая беременных и новорожденных детей, которые более восприимчивы к инфекционным заболеваниям. Более того, медицинские работники в этих учреждениях также подвергаются риску заражения инфекциями, так как им приходится работать в непосредственной близости с пациентами [16,43].

Множество эпидемиологических исследований показывает, что в международной практике «безопасность» пациентов занимает приоритетные позиции в политике здравоохранения и является основным компонентом качества медицинских услуг. Однако ни одна медицинская организация в любой стране не может полностью исключить риск возникновения инфекций, связанных с оказанием медицинской помощи (ИСМП).

В организациях родовспоможении пациентки с ИСМП – это наиболее тяжёлый контингент для последующего лечения и реабилитации, возникновению тяжелой клинического проявления и может в любой момент привести к грозным генерализованным осложнениям, таким как несостоятельность швов на матке, акушерский перитонит и сепсис [11,32]. Термин «инфекции, связанные с оказанием медицинской помощи» обозначает группу инфекций, возникших в результате изменения представлений о внутрибольничных инфекциях. ИСМП определяется как любое клинически выраженное инфекционное заболевание, которое развилось у пациента в процессе получения медицинской помощи, независимо от того, происходило ли это в стационаре, в амбулаторно-поликлинических условиях или на дому. Также это касается медицинских работников, которые заразились в ходе своей профессиональной деятельности. Система организации профилактики инфекций и инфекционного контроля (ПИИК) в отношении ИСМП является важным компонентом обеспечения безопасности и качества медицинских услуг [1]. В 1979 году Европейским бюро Всемирной организации здравоохранения (ВОЗ) было предложено первое определение: «Внутрибольничная инфекция (нозокомиальная, больничная, госпитальная) на сегодняшний день в эпохе цифровизации, изменении подходов медицинских технологий, организации оказании медицинской помощи обозначения термина «ВБИ» в системы здравоохранения, трансформировалось как ИСМП. В клинической практике термин ПИИК, наиболее часто используется как ИК «инфекционный контроль», однако ПИИК и ИК считаются синонимами.

Риск возникновения инфекций, связанных с оказанием медицинской помощи, представляет собой потенциальную и количественно измеримую вероятность инфицирования или развития инфекции как у пациентов, так и у медицинского персонала. Это также включает возможные осложнения, такие как заболеваемость, инвалидность, летальные исходы, а также экономические и другие виды ущерба. Для повышения эффективности мероприятий по контролю инфекций, связанных с медицинской помощью, необходимо внедрить в клиническую практику ряд мероприятий, направленных на: оптимизацию системы эпидемиологического надзора; использование современных перинатальных технологий; постоянный контроль состояния материально-технической базы и укомплектованности кадрами; профессиональную подготовку медицинских работников и их ответственность за качество оказания медицинской помощи женщинам; совершенствование лабораторной диагностики и мониторинга возбудителей; повышение эффективности дезинфекционных и стерилизационных мероприятий; разработку стратегии и тактики применения антибиотиков и химиопрепаратов; рационализацию основных принципов госпитальной гигиены; оценку экономической эффективности мероприятий по профилактике данной группы инфекций; развитие научных исследований в области гигиены, эпидемиологии и профилактики [2].

Следует отметить, что ключевым элементом в управлении риск-ориентированными технологиями ИСМП является установленный мониторинг, который

предоставляет значительное преимущество для повышения осведомленности о важности профилактики инфекций и контроля их распространения, а также для выявления рисков до их возникновения. Эффективное управление рисками, быстрая их идентификация, организация необходимых мер и активный обмен информацией между руководством, сотрудниками и пациентами являются важными аспектами, обеспечивающими успешную профилактику. Мониторинг охватывает следующие аспекты: своевременное выявление новых рисков и проведение анализа текущей ситуации.

Цель: анализ данных литературы по вопросу управления риск ориентированными технологиями в организациях родовспоможения.

Стратегия поиска. Поиск источников проводился в следующих базах данных: e-Library, Cyberleninka, Google Академия, ResearchGate, Pubmed, Web of Science, Scopus. *Критериями включения являлись:* аналитические и описательные исследования, метаанализы и систематические обзоры, клинические руководства, монографии, отчеты и приказы, оригинальные полнотекстовые статьи на английском и русском языках, находящиеся в открытом доступе и содержащие статистически подтвержденные выводы. Также были подробно изучены: Отчет о результатах ситуационного анализа основных компонентов программ профилактики инфекций и инфекционного контроля на уровне медицинских организаций в Республике Казахстан (Национальный центр общественного здравоохранения), нормативно правовые акты Министра здравоохранения Республики Казахстан № ҚР ДСМ-151 «Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по предупреждению инфекций, связанных с оказанием медицинской помощи» от 2 декабря 2022 года, зарегистрирован в Министерстве юстиции Республики Казахстан 2 декабря 2022 года № 30928. *Критерии исключения:* краткие отчеты, газетные статьи и личные сообщения. Глубина поиска составила преимущественно 5-7 лет (2018-2024), но были приняты для анализа и единичные работы, изданные в период с 2010 - 2006 годы, так как в них содержалась концептуальная информация, либо данные для сравнительного анализа.

Результаты поиска и их обсуждение.

Краткий обзор по управлению риск ориентированными технологиями в организациях родовспоможения.

Эффективное управление эпидемиологическими рисками в медицинских организациях родовспоможения имеет ключевое значение для защиты здоровья пациентов и медицинских работников, а также для обеспечения безопасной и эффективной медицинской помощи. Научное обоснование для такого управления можно найти во многих исследованиях и руководствах Всемирной организации здравоохранения (ВОЗ). Руководящие принципы ВОЗ по основным компонентам программ профилактики инфекций и инфекционного контроля охватывают как национальный уровень, так и уровень учреждений неотложной медицинской помощи [15,17]. Например, в рекомендациях ВОЗ по профилактике инфекций в родильных учреждениях отмечается, что меры по защите от инфекций должны включать строгое соблюдение гигиены рук, использование стерильных инструментов, применение мер по контролю инфекций и другие меры. Исследования действительно показывают, что строгие меры профилактики могут значительно снизить риск передачи инфекций, включая стрептококковую инфекцию группы В (GBS) во время беременности. *Sheriff A. Shazley и его коллеги* подтвердили, что 12% летальных исходов связаны с профилактикой GBS вовремя беременности. Это подчеркивает важность скрининга и лечения для предотвращения неонатальных инфекций, таких как сепсис, пневмония и менингит. Исследование, проведенное Национальным институтом здравоохранения (NIH) и Медицинской школой Вашингтонского университета, действительно показало, что использование антисептических растворов для очистки кожи перед родами может снизить риск инфекций родовых путей и гнойных осложнений. Это подчеркивает важность использования антисептиков в медицинской практике для улучшения исходов родов и снижения риска инфекций [44].

Кроме того, в обновленном Сборнике стратегий профилактики инфекций, связанных с оказанием медицинской помощи (США,2022), было показано, что применение системного подхода к управлению инфекционными рисками в медицинских учреждениях может значительно снизить инциденты инфекций [39].

Также стоит упомянуть руководство по управлению инфекционными рисками в родильных учреждениях, опубликованное Коллегией Акушеров и Гинекологов Великобритании. Это руководство содержит рекомендации по соблюдению гигиены рук, использованию стерильных инструментов, контролю инфекций и другим мерам для снижения риска передачи инфекций [18,31,35].

Необходимо отметить, что Республика Казахстан (далее РК) достиг значительных успехов в снижении материнской смертности благодаря внедрению эффективных перинатальных технологий (ЭПТ) и регионализации перинатальной помощи [7]. Эти меры позволили значительно улучшить качество экстренной помощи при неотложных акушерских состояниях, что способствовало снижению материнской смертности на 11,4%. Однако акушерский сепсис остается одной из основных причин материнской смертности, что требует дополнительного внимания. Для дальнейшего улучшения ситуации необходимо совершенствование системы профилактики и контроля инфекций, связанных с оказанием медицинской помощи. Это включает в себя: расширение применения современных перинатальных технологий для женщин с тяжелыми акушерскими осложнениями; обучение медицинского персонала и повышение их квалификации; усиление эпидемиологического надзора и мониторинга инфекций; внедрение комплексных программ по профилактике инфекций и инфекционному контролю. Эти меры помогут обеспечить высокий уровень качества и безопасности ухода на всех этапах родовспоможения.

Управления рисками (риск-менеджмент) является ключевым аспектом в решении данной проблемы, непрерывное эпидемиологическое наблюдение и эффективное функционирование системы инфекционного контроля, позволяет выявлять и оценивать вероятные риски, связанные с инвазивными лечебно-диагностическими вмешательствами. К таким рискам относятся: инъекции, трансфузии, установка сосудистых катетеров и катетеров мочевыводящих путей, забор крови, пункции, интубационные трубки, а также использование сложного технологического оборудования, такого как аппараты искусственной вентиляции легких и ингаляторы. Еще одним важным фактором является длительный период госпитализации (более 7 дней) при различных осложнениях, продолжительность родов, частота влагалищных исследований и неоднократные перемещения пациенток между отделениями по различным причинам. Гигиеническими факторами риска являются: недостаточное материально-техническое оснащение оборудованием, инструментарием, перевязочным материалом; недостаточный набор и площади помещений; перекрест технологических потоков; нарушения в работе приточно-вытяжной вентиляции; аварийные ситуации в водопроводной и канализационной системах; нехватка современных дезинфицирующих средств. К факторам риска также можно отнести: переполненность стационаров, нехватку врачей и среднего медицинского персонала; нарушение цикличности и порядка заполнения палат; несвоевременный перевод новорожденных в специализированные лечебные учреждения; а также задержку с выпиской родильниц и новорожденных [35].

Современные технологии, внедренные в учреждения родовспоможения, такие как семейно-ориентированные (партнерские) роды, индивидуальные родильные палаты, совместное пребывание матери и ребенка в послеродовом отделении, наблюдение за послеоперационным швом в формате «открытого ведения», ранняя активизация и выписка пациенток, направлены на обеспечение биологического разнообразия микрофлоры в больничной среде и создание условий для нормальных колонизационных процессов у пациентов. Эти технологии способствуют сохранению беременности и выхаживанию новорожденных, однако значительно увеличивают риск инфекционных осложнений. Часто возникающие осложнения в послеродовом периоде у родильниц в структуре гнойно-септических заболеваний наиболее часто регистрируются как маститы, нагноения послеоперационной раны после кесарева сечения и послеродовый эндометрит. Кроме того, наблюдается преобладание женщин с тяжелыми экстрагенитальными заболеваниями, такими как диабет, хронический пиелонефрит, сердечно-сосудистые заболевания, различные формы бесплодия, гормональные нарушения и хирургическая коррекция не вынашивания беременности, а также хронические вирусно-бактериальные инфекции различной локализации, что относит их к группе высокого риска развития инфекционных осложнений и требует особого внимания [20,42].

Инфекция, связанная с оказанием медицинской помощи - глобальная эпидемиологическая проблема.

Общеизвестно, что для всех систем здравоохранения инфекции, связанные с медицинскими процедурами (ИСМП), представляют собой глобальную эпидемиологическую проблему, оказывающую серьезное негативное влияние на ключевые аспекты здравоохранения и здоровье населения. Это включает в себя качество медицинской помощи, безопасность пациентов, устойчивость системы и доступность необходимых ресурсов. Согласно международным данным, даже в странах, где регулярно проводятся эпидемиологические исследования и принимаются серьезные меры контроля, полностью искоренить ИСМП невозможно. Более того, в тех местах, где профилактика и инфекционный контроль не реализованы должным образом, уровень ИСМП продолжает оставаться высоким. Особенно подвержены риску уязвимые группы пациентов, как беременные женщины, роженицы и родильницы в послеродовом и послеоперационном периодах, которые подвергаются различным инвазивным медицинским процедурам, таких как кесарево сечение, эпизиотомия, установка катетеров и мониторинг состояния плода. Инфицирование в период беременности может привести к преждевременным родам, внутриутробной инфекции плода, сепсису и другим серьезным осложнениям, угрожающим жизни как матери, так и ребенка. Таким образом, учреждения, занимающиеся родовспоможением, учитывая специфику деятельности, являются зонами повышенного риска распространения ИСМП, особенно учитывая серьезные последствия, которые могут возникнуть в случае инфицирования рожениц и новорожденных, что может привести к развитию эндометрита, мастита, послеродового сепсиса и других опасных состояний.

Следует подчеркнуть, что инфекции, связанные с оказанием медицинской помощи, являются многогранной проблемой из-за их широкого распространения и негативного влияния на здоровье пациентов, персонала и экономику государства. Эта проблема сохраняет свою актуальность на протяжении многих десятилетий, оказывая значительное воздействие на ключевые показатели качества и доступности медицинской помощи, включая уровень материнской и младенческой смертности. Несмотря на предпринятые усилия, частота ИСМП продолжает оставаться высокой, что связано с увеличением устойчивости патогенов к антибиотикам, антисептикам и дезинфектантам, а также с увеличением использования инвазивных технологий и повышением выживаемости пациентов с тяжелыми заболеваниями, которое сопровождается с ослабленной иммунной системой, неспособной эффективно бороться с инфекциями. Эпидемиологическая безопасность медицинских технологий и благоприятная среда микрофлоры, в которой предоставляются услуги, является важнейшей частью обеспечения качества медицинской помощи [13,21,24].

Профилактика инфекций, связанных с оказанием медицинской помощи (ИСМП), представляет собой одно из приоритетных направлений в обеспечении качества медицинской помощи в организациях родовспоможения,

поскольку ИСМП существенно усугубляет течение заболевания, приводя к развитию тяжёлых осложнений и увеличению риска неблагоприятных исходов. Всемирная организация здравоохранения (ВОЗ) выделяет ИСМП как одну из глобальных угроз безопасности пациентов, особенно уязвимыми к которой остаются беременные женщины и родильницы в послеродовом и послеоперационном периодах. Несмотря на то, что ИСМП могут казаться вторичными по значимости, они обладают выраженной клинической тяжестью, сопровождаясь такими осложнениями, как преждевременные роды, преждевременное излитие околоплодных вод, отслойка плаценты и гипертензивные расстройства, что в ряде случаев может привести к летальному исходу [2].

Профилактика данных осложнений требует системного и комплексного подхода. Обучение медицинского персонала современным стандартам инфекционного контроля, активное вовлечение его в реализацию профилактических мероприятий, соблюдение гигиены рук, использование антисептиков и постоянный мониторинг состояния пациенток — всё это входит в структуру эффективного управления рисками в организациях родовспоможения. Регулярные тренинги и повышение квалификации способствуют поддержанию высокой готовности персонала к предотвращению и быстрому реагированию на возможные инфекционные угрозы. Согласно данным Европейского центра профилактики и контроля заболеваний (ECDC), около 75% случаев материнской смертности обусловлены осложнениями беременности и родов, включая массивные кровотечения, инфекции, гипертензивные состояния, последствия родов и небезопасных абортов [22]. Особенно тревожным выглядит рост показателя материнской смертности, зафиксированный в 2020 году по данным ВОЗ, после рекордно низкого уровня в 2019 году. Это подчёркивает необходимость дальнейшего усиления мер по обеспечению инфекционной безопасности в организациях родовспоможения. В частности, ежегодно от ИСМП страдают около 1,4 миллиона пациенток, и риск инфицирования в развивающихся странах может быть до 20 раз выше, чем в экономически развитых [27].

По мнению ВОЗ, ситуация с инфекциями, связанными с оказанием медицинской помощи (ИСМП), остается недостаточно изученной, из-за сложностей в сборе достоверных данных на глобальном уровне [6].. Во многих ситуациях, от больниц до амбулаторных учреждений, ИСМП представляют собой скрытую проблему, которую ни одно учреждение, ни одна страна не смогли решить полностью. Кроме того, данные о распространенности ИСМП в учреждениях родовспоможения, ограничены, отмечено, что каждый 10000 живорождений приходится 70 женщин с подозрением или подтвержденной инфекцией, требующей стационарного лечения, в том числе 11 женщин с тяжелыми материнскими исходами. Рядом авторов было отмечено, что инфекция была основной причиной или сопутствующей причиной более чем половины материнских смертей во многих странах мира Европы, США, в том числе в Казахстане. Известно, что одна из десяти смертей, связанных с беременностью и родами, связана с сепсисом, при этом более 95% смертей вызваны материнским сепсисом в странах с низким и средним уровнем дохода [11].

Согласно статистическим данным, в Казахстане за 2023 год количество родов составило 384356, за 2022 год немногим больше 400198, из них оперативное родозрашение в 2023г 84590 (22%), в 2022 году составил 83381 (20,8%) следует отметить, количества операций кесарева сечения увеличилось, что приводит к частому возникновению ИСМП в сравнении с физиологическими родами.

Уровни распространенности инфекций, связанных с медицинской помощью (ИСМП), существенно недооценены. К примеру, количество выявленных случаев ИСМП в стране оказывается в 214 раз меньше международных показателей среди женщин в родах и в 157 раз ниже для новорожденных. Согласно данным за период с 2008 по 2018 годы в Республике Казахстан, количество случаев ИСМП колебалось от 298 до 516. Показатель, рассчитанный на 100 случаев госпитализации, варьировался от 0,009 до 0,021, несмотря на увеличение регистрации ИСМП в 2017-2018 годах. Однако в целом уровень заболеваемости ИСМП за данный период значительно уменьшился. В 2018 году в Казахстане было зафиксировано 484 случая ИСМП, а показатель заболеваемости на 100 случаев госпитализации составил 0, 018. Заболеваемость ИСМП в целом варьировалась от 0,7% до 1,0% [4].

Причины возникновения осложнений среди родильниц.

По Республике Казахстан 2023 года прослеживается тенденция роста ИСМП после кесарева сечения 71% в сравнении с физиологическими родами 34 случая 29% регистрировано, как осложнения, что вместе с тем, за время наблюдения возрос процент ИСМП с 0,21% в 2022г на 0,30 в 2023г, что заслуживает отдельного внимания. В то время среди родильниц после физиологических родов регистрировалась реже на 0,6%. В 2023 году эти показатели находились на уровне 0,3% и 0,2% соответственно [4].

По Республике Казахстан по структуре заболеваемости ИСМП среди родильниц, доля осложнений зафиксировано таким образом: послеродовый эндометрит 73% (85 сл.), осложнение послеоперационной раны, нагноение послеоперационного шва 16% (12 сл.), перитонит 4% (5 сл.), сепсис 3% (3 сл.), метроэндометрит 5% (6 сл.), гнойно септические осложнения (расхождения шва) 4% (5 сл.), гнойный мастит 0,85% (1 сл.)

Отдельно нужно сказать о причинах возникновения осложнений ИСМП, около половины из причин составляет: несоблюдение правил асептики и антисептики – 30%; почти одинаково, составляет нарушение правил обработки рук – 15% и нарушение правил дезинфекции и стерилизации – 10%; больше 1/3 из общих причин составил: экстрагенитальная патология, многоплодная беременность, тазовое предлежание плода, неправильное положение плода (поперечное, косое), преждевременные роды, гипертензивные состояния, врождённые пороки развития плода, многоводие, маловодие, осложнения беременности, социальные факторы, вредные привычки (курение, алкоголь, наркотики) – 45%.

Таким образом, при анализе полученных данных можно обозначить различия в распространенности ИСМП в Казахстане по сравнению с другими странами. Официально зарегистрированный уровень распространенности инфекций, связанных с медицинской практикой (ИСМП), в Казахстане значительно ниже, чем в странах с высокоразвитыми экономиками (в 422 раза) и в государствах с развивающейся экономикой (в 561 раз). К примеру, в высокоразвитых странах этот показатель составляет 7,6, а в развивающихся — 10,1. Подобные тенденции наблюдаются не только в Казахстане, но и в ряде других стран с похожими системами здравоохранения, особенно тех, где уделяется серьезное внимание на санитарно-гигиенического благополучия. В частности, в Российской Федерации, согласно официальной статистике за 2023 год, число случаев ИСМП оказалось на 2,6 раза ниже по сравнению с 2022 годом. В то же время, количество гнойно-септических инфекций среди родильниц за год составило 1944 случая, что немного выше, чем в 2022 году, когда было зарегистрировано 1749 случаев [3].

Несмотря на большое количество современных методов лечения, высокоэффективных антибактериальных и антисептических средств, проблема заболеваний ИСМП сохраняет свою актуальность в настоящий момент. Число пациентов, госпитализированных с ИСМП, неуклонно растет. По литературным данным, более чем на 53 тысяч операций, частота ИСМП колеблется от 1,51 до 27.8% [9].

Гигиена рук является одним из самых эффективных компонентов программы профилактики инфекций и инфекционного контроля. Строгое соблюдение правил обработки рук, и использование кожных антисептиков могут значительно снизить риск передачи инфекций. Основные меры включают: мытьё рук с мылом и водой в течение не менее 30 секунд; использование спиртосодержащих антисептиков для рук, особенно в медицинских учреждениях; обучение медицинского персонала правильным методам гигиены рук; регулярный мониторинг и контроль соблюдения гигиенических норм. Эти меры помогают предотвратить распространение инфекций и обеспечивают безопасность, как пациентов, так и медицинского персонала. Также, совершенствование компонентов программы ПИИК, направленными на оценку прогресса отдельных направлений, на информирование участников и содействие принятию решений в рамках программ, чтобы внешняя оценка эффективности по профилактике инфекции и инфекционного контроля проводилась с точки зрения ориентации на активное обучение, достижение качественного владения необходимыми навыками, а не на наказание, однако сложившиеся подходы (мониторинг, аудит) создают важный фактор к сокрытию ИСМП. Учитывая сложность и комплексность проблемы, выявленные недостатки снижают эффективность, вызывая негативный эффект. Системный подход при оценке реализации задач действительно требует разделения по уровням среди заинтересованных организаций. Это позволяет принимать эффективные решения, направленные на улучшение взаимоотношений между участниками системы профилактики и контроля инфекций (ПИИК), включая органы, осуществляющие внешний контроль, и медицинские организации. Внедрение подходов и инструментов для сбора, анализа и обмена достоверными данными по инфекциям, связанным с оказанием медицинской помощи (ИСМП), антибиотикорезистентности (АБР) и факторам риска, является ключевым элементом этого процесса. Это включает: систематический сбор данных о случаях ИСМП и АБР; анализ данных для выявления тенденций и факторов риска; обмен информацией между различными уровнями системы здравоохранения для принятия обоснованных решений; обучение и повышение квалификации медицинского персонала для эффективного использования этих данных. Эти меры помогут улучшить качество медицинской помощи и снизить риски, связанные с инфекциями и антибиотикорезистентностью [29].

В настоящее время оказание высококвалифицированного медицинского ухода зависит напрямую от компетентности практикующих врачей, что является следствием работы общей системы по повышению квалификации и профессиональной переподготовки, своевременной адаптации алгоритмов оказания медицинской помощи, неизменно, в свою очередь может спасти жизнь до, вовремя и после родов женщин и новорожденных.

Полученные результаты позволяют сделать следующие выводы: в разрезе медицинских работников в мероприятиях по повышению грамотности по ИСМП нуждаются средний медицинский персонал (акушеры отделение патологии беременных, послеродовое отделение). Выявленный уровень грамотности в области ИСМП требует незамедлительных мер по повышению грамотности путем внедрения реформ в области здравоохранения. Как известно, в целом перспективное развитие современной медицины в принципе невозможно без непрерывного медицинского образования, динамично охватывающего не только большинство научных дисциплин, но и многогранной спектр инновационных технологий. Обучение медицинского персонала по профилактике ИСМП – это постоянный процесс, который начинается еще во время учебы в бакалавриате и продолжается на протяжения всей их профессиональной карьеры. Результаты исследования показали, что медицинские работники с более большим опытом работы и прошедшие обучение по ИСМП (инфекциям, связанным с медицинской помощью), показали значительно более высокие баллы в опросниках, чем те специалисты, которые имели небольшой стаж работы и не проходили обучение. В Казахстанских медицинских университетах и колледжах были внедрены дисциплины, посвященные ИСМП, а также созданы курсы для повышения квалификации.

На наш взгляд, Всемирная организация здравоохранения (ВОЗ) разработала различные инструменты для продвижения программ по профилактики инфекций и инфекционному контролю, подчеркивая важность профессиональной подготовки специалистов здравоохранения и повышения осведомленности по этим вопросам. Это остается несомненно серьезной проблемой на пути оказания

качественной медицинской помощи. В 2019 году ВОЗ разработала и внедрила надежный инструмент IPCAF (Infection Prevention and Control Assessment Framework), что обозначает «Система оценки профилактики инфекции и инфекционного контроля» для практического применения в медицинских учреждениях. Этот инструмент представляет собой анкету с закрытыми вопросами и системой бальной оценки, снабженную полными пояснениями и сносками для каждого вопроса, что позволяет оценивать структуры и методы, необходимые для совместных оценок внешними экспертами, такими как Министерство здравоохранения, ВОЗ или другие заинтересованные стороны. Вопросники, использованные для проведения структурированных опросов, разрабатывались Колумбийском университетом, США (2018 г.).

Также можно рассматривать как диагностический механизм для выявления проблем и недостатков, соответствующих международным стандартам и требованиям, структурирована в соответствии с рекомендациями Руководства ВОЗ, охватывает восемь ключевых разделов: наличие программ ПИИК, методические указания, стандартные операционные процедуры по ПИИК, обучение и повышение квалификации персонала медицинских организаций, эпидемиологический надзор за ИСМП, мультимодальные стратегии, мониторинг и аудит методов ПИИК, а также инфраструктуру и оборудование для ПИИК в медицинских учреждениях. В общей сложности рассматривается 81 индикатор, сформулированный на основе фактических данных и мнений экспертов. Ответы на вопросы в этих разделах оцениваются, и на основе общего балла, полученного из суммарных ответов, учреждению присваивается один из четырех уровней внедрения ПИИК:

Недостаточный — реализация основных компонентов ПИИК недостаточна, требуются значительные улучшения.

Базовый — некоторые аспекты компонентов ПИИК существуют, но внедрены недостаточно, необходимы дополнительные действия для улучшения.

Средний — большинство аспектов внедрены надлежащим образом, необходимо продолжать повышать качество внедрения программы и разрабатывать долгосрочные планы для ее поддержания.

Высокий — все компоненты ПИИК полностью реализованы в соответствии с рекомендациями ВОЗ и соответствуют потребностям учреждения.

Максимальный балл по каждому разделу составляет 100 баллов, и по сумме всех баллов формируется общая оценка. IPCAF не предназначена для сравнительного анализа, так как медицинские учреждения могут различаться по коечному фонду, медицинской направленности и социально-экономическим условиям. В 2020–2021 годах было проведено межгосударственное исследование с использованием анкетирования IPCAF, которое показало, что только 12,5% из 88 стран-участниц полностью внедрили все основные компоненты ПИИК. Существует достаточное количество доказательств о преимуществе и пользе инструмента IPCAF. Этот метод может предотвратить до половины всех случаев ИСМП, способствует значительному снижению материнской смертности, риска реализации сепсиса. Анализ и оценка результатов анкетирования показывают высокую эффективность проведенного обучения, что подтверждается статистически значимым увеличением числа правильных ответов на заданные вопросы. Тем не менее, необходимо отметить, что существуют затруднения в усвоении некоторых теоретических знаний, что указывает на необходимость усиленной подготовки по определенным проблемным темам. Более того, устойчивое закрепление полученных знаний, умений и навыков возможно только при регулярном повторении, что требует проведения подобных курсов обучения на постоянной основе.

Azak E. и соавт. (2021) провели оценку внедрения основных компонентов IPCAF по профилактики и контроля инфекций в Турецких медицинских учреждениях. В исследовании приняли участие 68 медорганизаций, из них 85% составили многопрофильные стационары и 25% первичная санитарная помощь. Пятьдесят медицинских учреждений из 68 имели высокий уровень IPCAF (межквартильный размах) составил 668,8 баллов, самые низкие баллы 70 баллов набраны по компоненту: кадровое обеспечение, обучение и образование. Турецкие исследователи отметили, что обучение сотрудников по вопросам ИСМП и факторам риска не осуществляется должным образом и с необходимой частотой. Так, как подготовка специалистов по ПИИК, должно быть с поддержкой со стороны национальных профессиональных организаций, активно финансируемых государством. Следовательно, существующая ситуация требует вложения финансирования на обучения в области эпидемиологии, микробиологии, поэтому решение должно приниматься на государственном уровне [10].

Гигиена рук действительно является одним из наиболее важных компонентов профилактики инфекций в медицинских учреждениях. Однако эпидемиологический надзор за инфекциями, связанными с центральными катетерами, часто остается наименее развитым. Появление устойчивости к противомикробным препаратам (AMR) действительно усложняет лечение инфекций. Устойчивые бактерии могут распространяться среди восприимчивого населения, если нет эффективных программ по профилактике инфекций и инфекционному контролю. Это подтверждается исследованиями, проведенными в Индии и Пакистане, где также отмечены проблемы с инфекционным контролем и устойчивостью к антибиотикам. Внедрение комплексных программ по профилактике инфекций и обучению медицинского персонала, а также усиление эпидемиологического надзора, являются ключевыми шагами для улучшения ситуации. Эти меры помогут: повысить осведомленность медицинского персонала о важности профилактики инфекций; улучшить соблюдение гигиенических норм, таких как гигиена рук и использование антисептиков; снизить распространение устойчивых к антибиотикам бактерий; обеспечить своевременную диагностику и лечение инфекций;

усилить контроль за состоянием здоровья пациентов и условиями в медицинских учреждениях [28,33].

Harun M.G.D. и соавт. (2021) в целях улучшения деятельности области ПИИК, для изучения сильных и слабых сторон, также для обеспечения безопасности пациентов и медицинских работников, провели анкетирование используя инструмент оценки (IPCAF) в период с сентября по декабрь 2020 года в 11 многопрофильных стационарах Бангладеш. Общий средний балл IPCAF составил 355,0 из 800. Результаты опроса показали, что около 90% больниц не имели активной системы мониторинга и аудита отслеживания ИСМП, 55% недостаточную укомплектованность персоналом, 70% не имели достаточный запас антисептиков для гигиены рук, 30% емкости для утилизации медицинских отходов, что демонстрируют недостаточный уровень для обеспечения безопасности работников здравоохранения, пациентов и посетителей. В 60% стационарах нереализованным является обучение по эпидемиологическому надзору за ИСМП, также первичное обучения по ПИИК для сотрудников при поступлении на работу. Кадровое обеспечение, нехватка достаточного количества персонала, наличие сертифицированных специалистов, снижение рабочей нагрузки явилось важной проблемой по профилактике и контролю инфекций, связанных с оказанием медицинской помощи. Так же, авторы отметили, что факты недостаточной обеспеченности, недостаточного оснащения материалами обусловлены отсутствием отдельного бюджета на реализацию [26].

Aghdassi S.J.S. и соавт. (2021) оценили программу профилактики и контроля инфекций в австрийских больницах неотложной помощи с использованием системы оценки профилактики и контроля инфекций ВОЗ IPCAF с октября по декабрь 2018 года среди 65 больниц, было продемонстрированы возможности улучшения эффективной реализации мультимодальных стратегий и вовлечения профессиональных групп, общий балл IPCAF составил 620 (из возможного максимального балла 800). Из 65 изученных больниц 38 достигли продвинутого уровня ПИИК, а самые низкие оценки были по компоненту мультимодальные стратегий реализации мероприятий по ПИИК, а также по образованию и подготовке в области ПИИК, особенно в отношении кадрового обеспечения, образования и подготовки в области ПИИК. Около 26% (n = 17) больниц сообщили, что местная команда ПИИК не пользуется постоянной поддержкой со стороны комитета, также имеется и нехватка специалистов по ПИИК 23% (n = 15) больниц, 26% (n = 17) имело только одного специалиста на ≤250 коек [12].

Asgedom A.A. и соавт. (2021) было рассмотрено 13 полноформатных статей из Африки, Азии и Европы. Результаты показали, что существуют расхождения в значениях IPCAF от недостаточного до продвинутого уровня. Текущий обзор показывает продвинутый уровень IPCAF в странах со средним и высоким уровнем дохода. Страны с низким уровнем дохода показали более низкий балл IPCAF. Необходимо усиление потенциала по ПИИК и предоставить ресурсы по профилактике инфекций для предотвращения инфекций, связанных с оказанием медицинской помощи, с упором на страны с низким уровнем дохода. Меры профилактики и контроля ПИИК сообщаются о том, что они плохо реализуются во всем мире. Руководящие принципы дают ограниченное представление о сложностях внедрения в обычных системах здравоохранения, особенно тех, которые сталкиваются с существенными ограничениями ресурсов [13].

В другом исследовании, в Дакка, *Miah K.A. и его соавт. (2020) показали*, что возбудители инфекционных заболевании являются важной причиной госпитальной микрофлоры. В течение двух лет наблюдались 1055 пациентов, среди госпитализированных было зарегистрировано ИСМП 101 (84,6%) в хирургическом отделении: хирургическая раневая инфекция 26 (22,6%). Из 101 пациентов 44 (38,3%) были поражены *золотистым стафилококком*, за ним следовала *кишечная палочка* - 23 (20%). Результаты, этого исследовании показали, что не хватка доступа к базовой микробиологической обследовании, для диагностики ИСМП врачи чаще полагались на клинические симптомы [31].

В исследование *Saba Savyl и его соавт* (2019) действительно подчеркивает, что профилактика и контроль инфекций (IPCAF) являются игнорируемой областью в медицинских учреждениях Пакистана. Это представляет собой глобальную проблему общественного здравоохранения, связанную со значительной смертностью и заболеваемостью. Исследование показало, что в большинстве больниц Пакистана меры IPCAF недостаточно развиты, что требует значительных улучшений для обеспечения безопасности пациентов и медицинского персонала. Внедрение эффективных программ IPCAF и обучение медицинского персонала могут существенно снизить риски инфекций и улучшить общие результаты лечения Таким образом, в период с ноября по декабрь 2019 года в пяти государственных больницах Исламабада провели поперечное исследование опрос, согласно анкеты (IPCAF), с целью выяснения текущего состояния практики профилактики и контроля инфекций в государственных больницах, общий балл IPCAF составил менее 200, медианный балл 117,5 с межквартильным размахом 53,75, по программе ПИИК не выполнили даже 50% требуемых стандартов, одним из них является разработка и внедрение руководств по профилактике и контролю инфекций, обеспечение расходными материалами, обучение сотрудников по ПИИК. По мнению авторов, только таким образом можно обеспечить высокий уровень качества медицинской помощи, снижения ошибок и повышению безопасности [39].

Например, недавние исследование *Agill S. S. и его соавт*. (2018) посвященному системе наблюдения (ИТ технология) в качестве метода выявления ИСМП в послеоперационном периоде в течение 30 дней после кесарева сечения. Актуальность работы состоялась в том, что после выписки увеличилось количество пациентов (после кесарева сечения), диагностированных во время пребывания в стационаре, при повторной госпитализации, в случаях амбулаторного посещения. Мы пришли к выводу, что система наблюдения может выявлять ИСМП в послеоперационном периоде после выписки [30].

Аналогичное исследование, проведенное *Moro M.L. and Morsillo F.A* в регионе Эмилия-Романья в Италии, показало, что качества данных послеоперационных инфекциях в регистре выписки из стационара не подходит для наблюдения за ИСМП в послеоперационном периоде. В исследовании были включены 6158 пациентов из 36 государственных больниц. Данные проспективного региона сравнивались с данными из регионального регистра выписки из больницы с использованием различных классов кодов МКБ-9-КМ. Чувствительность базы данных выписки из больницы для послеоперационных хирургических инфекций составила 10%, когда использовались коды МКБ-9-КМ, напрямую указывающие на послеоперационные инфекционные осложнения. При добавлении неспецифических кодов послеоперационных осложнений, не обязательно инфекционного происхождения, чувствительность повышалось и достигала 21% [32].

Во всем мире инфекции, связанные с оказанием медицинской помощи (ИСМП), представляют собой серьезную проблему общественного здравоохранения. Они являются основной причиной роста заболеваемости и смертности пациентов и влекут за собой высокие затраты, повышенную потребность в передовой медицинской помощи, использование дорогих антибиотиков для лечения ИСМП, что может привести к появлению других устойчивых к противомикробным препаратам организмов. Работники здравоохранения врачи, средний медицинский персонал часто служат переносчиками ИСМП; и их роль требует серьезного рассмотрения при реализации стратегий инфекционного контроля для предотвращения ИСМП.

По данным исследования, проведённого Европейским центром профилактики и контроля заболеваний (ECDC), в отчёте «Опрос по точечной распространённости инфекций, связанных с оказанием медицинской помощи, и применению антимикробных препаратов в европейских больницах» представлены ключевые данные о заболеваемости ИСМП в странах Европы. Этот документ подчеркивает важность и необходимость внедрения эффективных методов мониторинга и контроля инфекций в медицинских учреждениях (European Centre for Disease Prevention and Control, 2023). [19].

Исследования, проведённые Bako B. и его коллегами, выявили факторы риска, способствующие одной из ведущих причин материнской смертности. Среди них – отсутствие предварительной госпитализации, роды на дому, травмы промежности, кесарево сечение и возраст матери младше 24 лет. Важным аспектом является повышение осведомленности населения о необходимости своевременной госпитализации, обеспечении квалифицированной медицинской помощи при родах и соблюдении асептики в родильных учреждениях. [14]. Кроме того, в исследованиях *Paul E и его соавт. (2020)* [35]., также *Pittet D и его соавт*. (20) были сосредоточены на знаниях и практики гигиены рук [36]. Причиной выбора родильного дома и детской больницы для проведения этого исследования было сообщение о высокой периодической распространенности до 19,2% заболеваемости (13,7 ИСМП на 1000 койко-дней) в последние годы.

Несмотря на то, что Центр по контролю инфекций Совета сотрудничества стран Персидского залива (ССЗ) был создан для регистрации темпов, тенденций, сопутствующих рисков по ИСМП и обеспечения применения методов и стратегий по снижению, неясно, соблюдаются ли протоколы контроля инфекций, установленные этим центром, во всех больницах третичного уровня в странах ССЗ. Постоянной проблемой, с которой сталкивается Королевство с 2012 года, являются вспышки инфекций, вызванных коронавирусом ближневосточного респираторного синдрома (MERS-CoV), а теперь и недавняя вспышка COVID-19 во всем мире.

Vicentini C. и его соавт. (2022) провели опрос IPCAF, в 42 государственных больницах неотложной помощи интенсивной терапии на северо-западе Италии региона Пьемонт. Медианный общий балл IPCAF составил 11/14 (межквартильный размах, IQR: 9,25–12). Мультимодальная стратегия с самым высоким уровнем приверженности включала образование и обучение, за которыми следовали коммуникация и напоминания. Стратегии с самым низким уровнем приверженности включали климат безопасности и культуру изменений, а также изменение системы. Общая распространенность HAI составила 8,06%. Была обнаружена слабая или умеренная обратная связь между баллом IPCAF и распространенностью HAI (Rho Спирмена -0,340, p 0,034). Никакой другой значимой корреляции обнаружено не было.Это исследование выявило высокий уровень самооценки общего внедрения мультимодальных стратегий для ПКИ в регионе. Результаты этого исследования свидетельствуют о релевантности мультимодального подхода и обоснованности оценки IPCAF при измерении программ ПКИ с точки зрения эффективности профилактики передачи ИСМП [45].

Tartari E. и его соавт. (2017) в исследовании, проведенном в больницах США, показало, что у 3,2% пациентов было одно или несколько ИСМП, что ежегодно в европейских учреждениях интенсивной терапии и длительного ухода регистрируется 8,9 млн случая [42]. Внедрение эффективных мер профилактики и контроля инфекций, способствует снижение от 35% до 55%. Всемирная организация здравоохранения (ВОЗ) отметила, что распространенность ИСМП была самой высокой в странах с низким/средним уровнем дохода, варьируясь от 5,7% до 19,1% и устойчивость к противомикробным препаратам (УПП) значительно влияют на качество и безопасность оказания медицинской помощи. Исследование точечной распространенности 2016–2017 гг. Европейского центра профилактики и контроля заболеваний, по предыдущим оценкам, показало, что в общей сложности из-за ИСМП на 100 000 человек населения теряется 501 год жизни с поправкой на инвалидность, при этом ежегодно умирает более 90 000 человек. В 2015 г. в Юго-Восточной Азии распространенность ИСМП оценивалась в 9%. В период с июня 2017 года по ноябрь 2018 года было проведено

многострановое поперечное исследование на основе полу структурированных интервью с национальными координаторами по ПИИК в министерствах здравоохранения или других правительственных организациях. В рамках данного исследования авторами целенаправленно были отобраны 140 государств-членов ВОЗ, подписавших обязательства в рамках Первой глобальной инициативы по безопасности пациентов «Чистая помощь — безопасная помощь», предусматривающей действия по снижению уровня ИСМП и повышению безопасности пациентов. Для обеспечения репрезентативности полученных данных был рассчитан размер стратифицированной выборки с учётом уровня дохода стран согласно классификациям ВОЗ и Всемирного банка. Расчет размера выборки был основан на общем количестве 140 стран, подписавших обязательство «Чистый уход — более безопасный уход», 95% доверительных интервалах (ДИ) и ожидаемой доле стран с программой ПИИК, которая, по оценкам, составляла ~50% на основе предыдущих отчетов. Был оценен идеальный размер выборки из 103 стран, и включал следующие пропорции по регионам ВОЗ: Западная часть Тихого океана, 10/14; Восточное Средиземноморье, 11/15; Юго-Восточная Азия, 4/6; Европа, 24/33; Африка, 28/38; и Америка, 25/34. Затем через ВОЗ и/или указанными органами здравоохранения их стран была им определена удобная выборка национальных координаторов для интервьюирования [42].

В исследовании *Tomczyk S. и соавт*. (2021) всего приняли участие 46 стран, 181 больница и 324 человека; 52 (16%) и 55 (17%) индивидуальных респондентов представляли страны с низким и ниже среднего уровнем дохода соответственно. 52% респондентов потратили менее 1 часа на заполнение IPCAF. В целом, наблюдалась адекватная внутренняя согласованность и высокий ICC (0,92, 95% доверительный интервал 0,89–0,94). Десять индивидуальных вопросов имели низкую надежность (ICC <0,4); они были рассмотрены для пересмотра в соответствии с отзывами об удобстве использования и мнением экспертов [43].

Stewardson A.J. и соавт. (2020) оценили систему обработки гигиены рук, среди медицинских работников, согласно инструменту HHSAF (тестирование) Всемирной организации здравоохранения [41]. 42 медицинских учреждения были протестированы, среди них 26 учреждений из 19 стран ответили с общими баллами в диапазоне от 35 до 480 (среднее значение 262), опрошенные из 23/26 выразили мнение, что тесты «просты в использовании» и «много полезной информации по гигиене рук». На решение тестов было выделено десять минут времени, из 41/42 получили удовлетворительные результаты, по итогу опроса, оценки варьировались от 0,54 до 0,86. Несмотря на положительные отклики, некоторые авторы утверждали, что необходимо акцентировать на практические навыки, являющиеся ключевым фактором при безопасном и компетентном уходе за пациентами [25,33].

Ehsan A и соавт. (2023) провели в государственных больницах Пенджаба анкетирование IPCAF в период с октября по апрель, выбраны 11 больниц государственного сектора (включая стационары и первичные медицинские учреждения). Общий средний балл составил 532,5 (IQR: 292,5-690) из 800. Каждая из четырех больниц набрала как «базовый», а остальные три «средний уровень». Для доступного донесения информации имелись руководства по различным темам профилактики, таким как утилизация медицинских отходов, зонирование помещении, программа гигиены рук. Охват специалистов для обучения по вопросам ПИИК составил 90%, из них 40% стационаров, 60% первичной медицинские учреждения. Среди многопрофильных стационаров лишь в 1 из 5 больниц имела специалиста по обучению ПИИК, а в 2 из 5 отсутствовало. Однако, другие аспекты, как мониторинг/аудит за ИСМП, антибиотикотерапия за возбудителями с множественной лекарственной устойчивостью не проводится, что требует совершенствования системы государственного сектора [20].

Supriadi I. и соавт. (2021) оценили уровень ПИИК с использованием инструмента IPCAF поперечное исследование, с июля по ноябрь 2021 года среди 355 индонезийских больницах. Общий средний балл IPCAF составил 620,0, набраны баллы по следующим уровням высокий 56,9%, средний 35,8%, базовый 7,0% и недостаточный 0,3%. Намного выше, чем из Германии, Австрии, Индии, где средние баллы составили 365,0-532,0 соответственно [40].

Проведённый анализ системы контроля и профилактики инфекций, связанных с оказанием медицинской помощи (ИСМП), в Республике Казахстан показал, что действующая система носит фрагментарный характер и не соответствует современным международным стандартам. Из шести компонентов системы профилактики инфекций и инфекционного контроля (ПИИК), рекомендованных Всемирной организацией здравоохранения (ВОЗ), в стране реализованы лишь базовые элементы, что составляет всего 17,9% от целевого уровня. Уровень реализации по отдельным направлениям варьируется: от 11% по компоненту мониторинга, аудита и обратной связи, до 23% по применению многокомпонентных стратегий. Согласно отчёту о результатах ситуационного анализа ключевых компонентов ПИИК в медицинских организациях Республики Казахстан за 2022 год, даже те элементы, которые формально считаются внедрёнными, на практике реализуются частично или формально, без должного эффекта [5].

Таким образом, данные, полученные в результате самооценки с использованием инструмента IPCAF, свидетельствуют о том, что в Казахстане отсутствует значительное число критически важных характеристик, присущих полноценной, комплексной системе ПИИК — особенно в организациях, оказывающих акушерскую помощь, где высокий риск инфекционных осложнений требует особенно тщательного контроля. [23]

Ученые мира пришли к единому мнению, что признанным эффективным методом поддержания и улучшения качества, своевременного выявления, предупреждения ИСМП неизменно требуют обширный круг знаний и высокий уровень подготовки во всех областях не только медицины, но и в многогранной

спектре инновационных технологии, своевременной адаптации различных международных правовых актов ориентированное на внедрение, направленное в поддержку ПИИК и мониторинге ИСМП.

Разработка алгоритма действия медицинского работника направленных на снижение риска распространения ИСМП.

За последние несколько лет ряд реформ в современных условиях развития здравоохранения привели к усовершенствованию разработки соответствующих внутренних правил, руководств которое содержит основные аспекты и детальное описание процедур, внутренние правила для конкретных клинических ситуации, инструменты оценок, программ, стандарты оперативных процедур (далее СОП), алгоритмы, схемы действии медицинских работников направленные на ПИИК и ИСМП по организации родовспоможении. В таблице1 представлены перечень рабочих документов в организации родовспоможении, направленных на снижение риска распространения ИСМП с позиции доказательной медицины (Таблица 1)

Таблица 1.

Перечень рабочих документов в организации родовспоможении Республики Казахстан, направленных на снижение риска распространения ИСМП с позиции доказательной медицины.

(Table1. List of working documents in the organization of obstetric care in the Republic of Kazakhstan, aimed at reducing the risk of the spread of HAIs from the perspective of evidence-based medicine).

№	Стандарты операционных процедур (СОП)	Внутренние правила	Алгоритмы действия медицинского работника
1	Гигиена рук «Обработка рук при проведении различных медицинских манипуляций»	Программа гигиены рук. Обучение медработников по вопросам гигиены рук	Алгоритм «Европейский стандарт обработки рук»
2	Схема утилизации, сбора, транспортировки, утилизации медицинских отходов классов А, Б, В, Г, Д.	Правила по классификации медицинских отходов, согласно Базельской конвенции.	Алгоритм утилизации медицинских отходов в отделениях. Алгоритм движения, сбора и транспортировки медицинских отходов, вывоза медицинских отходов класса «Б» и «В» с помещения временного хранения.
3	Дезинфекция и стерилизация ИМН (инструменты медицинского назначения)	Универсальные меры предосторожности при возможном контакте с биологическими жидкостями, правила по оценке рисков возникновения инфекций.	Алгоритмы обработки, дезинфекции и стерилизации для различных видов медицинских изделий и устройств; обработки кварцевых ламп
4	Применения лекарственных средств.	Программа обучения медработников по вопросам инъекционной безопасности	Алгоритм забора крови для лабораторного анализа
5	Управление опасными материалами. Снижение рисков последствий розлива опасных химических и дезинфицирующих средств.	Программа приготовления рабочих растворов, техника безопасности при работе, применение и сроки хранения дезинфицирующих средств.	Алгоритм оказания первой помощи при отравлении дезинфицирующими средствами
6	Обеспечение защиты и безопасности медицинских работников.	Правила проведения обязательных медицинских осмотров для ЛМК (личные медицинские книжки).	Алгоритм доставки биологических материалов в отделение лабораторной диагностики.
7	Обращение с бельем и спец.одеждой.	Правила работы машиниста по стирке белья в прачечном отделении	Алгоритм работы прачечной, сортировка, хранения.
8	Перечень документальной базы, регламентирующей раздел ПИИК в соответствии с санитарными правилами и нормами.	Программа обучения по ПИИК, ИСМП. План обучающих семинаров, вводный и периодический инструктаж, тренинги с врачами, средним и младшим медицинским персоналом. План аттестации врачей и средних медицинских работников на знание ПИИК.	Алгоритм «Виды обработки рук» Алгоритм «Гигиеническая обработка рук» Алгоритм «Хирургическая обработка рук» Алгоритм «Социальный уровень обработки рук»
9	Действия медицинского работника при розливе биологических жидкостей.	Стандартные меры предосторожности, профилактика порезов, аварийные ситуации	Алгоритм «Действие медицинского работника в случае прокола или пореза кожных покровов (аварийный случай)»
10	Санитарно-дезинфекционный режим по уборке и дезинфекции.	Маркерная диагностика и вакцинация сотрудников против Вирусного гепатита В	Алгоритм проведения уборки (генеральная, текущая, заключительная обработка) обеззараживания и хранения уборочного инвентаря
11	Оповещение в случае выявления больного с подозрением на карантинную и особо опасную инфекцию.	Правила при изоляции. Перечень эпидемиологических показаний пациентов, подлежащих изоляции	Алгоритм надевания и снятия СИЗ (средств индивидуальной защиты) ПЧК (противочумного костюма)

12	Эпидемиологический контроль проведения комплекса профилактических и противоэпидемических, санитарно-гигиенических мероприятий.	Памятка по санитарному минимуму, правила по обработке посуды, проведения уборок для раздаточного помещения, пищеблока.	Алгоритм при выявлении инфекционного заболевания, передающегося воздушно-капельным и контактно-бытовым путем
13	Противоэпидемиологические меры по профилактике инфекции, имеющие эпидемическое значение (грипп, туберкулез и др)	Гигиена дыхания и этикет кашля	Алгоритм сбора мокроты, временного хранения, транспортировки мокроты
14	Профилактика инфекции послеоперационной раны.	Правила рационального использования антибактериальных препаратов.	Алгоритм изоляции при выявлении инфекционных заболевании.
15	Противоэпидемиологические меры по профилактике инфекции (вирусные гепатиты В, С, ВИЧ-инфекция, грипп)	Профилактика катетер-ассоциированных инфекций кровотока.	Алгоритм проведения постконтактной профилактики.
16	Эпидемиологическая диагностика ИСМП	Программа по ПИИК (документ, описывающий политику, цели и стратегии по вопросам ПИИК)	Алгоритм передачи экстренного извещения, при выявлении ИСМП.

Помимо рабочих документов, представленных в таблице 1, имеются основные документы, направленные на снижение риска распространения ИСМП, действующие утвержденные санитарные правила МЗ РК, которые регламентируются на законодательном уровне.

Таблица 2.

Перечень доступных действующих нормативно правовых документов, санитарных правил для использования в клинической практике.

(Table 2. List of available current regulatory documents and sanitary rules for use in clinical practice).

№	Номер и дата выпуска приказов	Наименование приказов Министерства здравоохранения Республики Казахстан
1	№ 360-VI ЗРК. от 07.07.2020г.	Кодекс «О здоровье народа и системе здравоохранения»
2	№ 122-VII ЗРК. от 21 мая 2022 года	Закон Республики Казахстан «О биологической безопасности Республики Казахстан».
3	№ 59 от 01.06. 2020г О внесении изменении № ҚР ДСМ-2 от 05.01 2021 года	Правила оказания государственной услуги "Выдача лицензии на медицинскую деятельность".
4	№110 от 05.10.2022г	Об утверждении методики управления биологическими рисками
5	№196 от 25.10.2020г	Об утверждении Правил выдачи, учета и ведения личных медицинских книжек
6	№ 62 от 21.07.2021г	Санитарно-эпидемиологические требования к хранению, транспортировке и использованию иммунологических лекарственных препаратов (иммунобиологических лекарственных препаратов)»
7	№92 от 26.08.2021г	Об утверждении стандарта организации оказания акушерско-гинекологической помощи в Республике Казахстан
8	№19 от 16.02. 2021г	Правила хранения и транспортировки лекарственных средств и медицинских изделий
9	№ 68 от 29.07.2022г	Санитарно-эпидемиологические требования к организации и проведению дезинфекции, дезинсекции и дератизации"
10	№ 96 от 11.08.2020г обнов. *28.01.2022*	«Санитарно-эпидемиологические требования к объектам здравоохранения»
11	№151 от 02.12.2022г	«Санитарно-профилактических мероприятий по предупреждению Санитарных правил «Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических инфекций, связанных с оказанием медицинской помощи»
12	№ 62 от 07.04. 2023г	«Санитарно-эпидемиологические требования к производственному контролю»
13	№95 от 01.09. 2021г.	«Санитарно-эпидемиологические требования к дезинфекции систем вентиляции и кондиционирования воздуха»
14	№175 от 30.10. 2020г	Об утверждении форм учетной документации в области здравоохранения
15	№ 153 от 26.10.2020г	Об утверждении правил предоставления в государственный орган в сфере санитарно-эпидемиологического благополучия населения информации (экстренного извещения) о случаях инфекционных заболеваний, отравлений
16	№ 111 от 05.10.2022г	«Сан-эпид требования к организации и проведению сан-противоэпид мероприятия по предупреждению острых кишечных инфекций

17	№331 от 25.12.2020г	«Санитарно-эпидемиологические требования к сбору, использованию, применению, обезвреживанию, транспортировке, хранению и захоронению отходов производства и потребления"
18	№114 от 12.11.2021г	«Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по предупреждению особо опасных инфекционных заболеваний" (*Бешенство, Сибирская язва, Туляремия, Конго-Крымская геморрагическая лихорадка, Геморрагическая лихорадка с почечным синдромом, Листериоз, Лептоспироз, бруцеллез)*
19	№116 от 14.12.2021г	«Санитарно-эпидемиологические требования к организации и проведению сан-противоэпид мероприятий по предупреждению особо опасных инфекционных заболеваний» (*чума, холера*)
20	№118 от 08.10.2020г	Об утверждении состава аптечки для оказания первой помощи
21	№ 47 от 27.05.2021г	«Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий при острых респираторных вирусных инфекциях, гриппе и их осложнениях (пневмонии), менингококковой инфекции, коронавирусной инфекции COVID-19, ветряной оспе и скарлатине»,
22	№44 от 16.05. 2022г.	"Сан-эпид требования к организации и проведению сан-противоэпид и сан-проф мероприятий по предупреждению паразитарных заболеваний
23	№211 от 27.11.2020г	Правила обязательного конфиденциального медицинского обследования на наличие ВИЧ-инфекции лиц по клиническим и эпидемиологическим показаниям»
24	№204 от 25.11.2020г	Об утверждении правил добровольного анонимного и (или) конфиденциального медицинского обследования и консультирования по вопросам ВИЧ-инфекции в рамках гарантированного объема бесплатной медицинской помощи в государственных организациях здравоохранения, осуществляющих деятельность в сфере профилактики ВИЧ-инфекции
25	№137 от 19.10.2020г	Об утверждении правил проведения мероприятий по профилактике ВИЧ-инфекции
26	№44 от 26.05.2021г.	Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по вирусным гепатитам и ВИЧ-инфекции
27	№214 от 30.11.2020г	Правила проведения мероприятий по профилактике туберкулеза
28	№29 от28.03.2022г	Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по предупреждению инфекционных заболеваний (туберкулез)»
29	№107 от 23.09. 2020г	Об утверждении Правил проведения медицинского обследования с целью признания лица больным заразной формой туберкулеза
30	№158 от 05.01.2020г	Стандарта организации оказания населению медицинской помощи при туберкулезе

Выводы

В ходе анализа установлено, что организация родовспоможения в структуре многопрофильных стационаров демонстрирует как схожие подходы, так и существенные различия. Эти различия, как правило, обусловлены уровнем материнской и перинатальной заболеваемости, который напрямую влияет на вероятность развития тяжёлых неблагоприятных исходов. Данный фактор требует индивидуализированного подхода к управлению рисками и внедрения специализированных клинических решений в рамках каждой конкретной медицинской организации.

В первую очередь для обеспечения безопасности своевременной качественной медицинской помощи в организациях родовспоможении необходима НПА, основанная на доказательственной медицине. Нынешнем основном НПА, в котором отображены критерии для принятия клинических решений для точной оценки ИСМП, риски возникновении осложнений, направленные на выяснение причин, (приказ Министра здравоохранения Республики Казахстан № ҚР ДСМ-151. Об утверждении Санитарных правил "Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по предупреждению инфекций, связанных с оказанием медицинской помощи" от 2 декабря 2022 года, зарегистрирован в Министерстве юстиции Республики Казахстан 2 декабря 2022 года № 30928) испытываются сложности в условиях повседневной клинической практики, а именно по главе 2, пункту 6: подлежат учету как ИСМП, инфекционные осложнения, связанные с оказанием акушерско – гинекологической помощи – в течение тридцати календарных дней, после выписки.

Согласно, исследовании *Адамян Л.В. и др.,* (2016г), осложнения в послеродовом периоде приходилось 50-60%, эти данные говорят о наличии инфекции у матери на догоспитальном этапе, часто у родильниц после оперативного родоразрешения развивается с большей интенсивностью, поэтому они входят в группу повышенного риска по ИСМП.

Несмотря на противоречивые мнения по поводу применение пункта 6 по учету, что осложнения, выявленные до 30 дней после выписки, регистрируется как ИСМП, необходимо понимать, что приказ 151 единственный НПА, предлагаемый для организации родовспоможения. На данном этапе, отсутствует нормативный правовой акт по организации родовспоможении.

Таблица 3.

Положительные стороны и пункты, требующие пересмотра нормативных правовых актов.

Table 3. Positive aspects and points requiring revision of regulatory legal acts.

Правила и требования, утвержденные приказами МЗ РК	Положительные стороны	Пункты, требующие пересмотра
Об утверждении Санитарных правил "Санитарно-эпидемиологические требования к организации и проведению санитарно-противоэпидемических, санитарно-профилактических мероприятий по предупреждению инфекций, связанных с оказанием медицинской помощи" Приказ Министра здравоохранения Республики Казахстан от 2 декабря 2022 года № ҚР ДСМ-151. Зарегистрирован в Министерстве юстиции Республики Казахстан 2 декабря 2022 года № 30928.	Четко распределены виды ИСМП, углубленное описание критерии, соответствует современным научным-обоснованным определениям: 1) Инфекции в области хирургического вмешательства, 2) Первичные инфекции кровотока (кровяного русла), 3) Внутрибольничная пневмония, 4) Инфекции мочевыводящих путей, 5) Инфекции суставов и костей, 6) Инфекции сердечно-сосудистой системы, 7) Инфекции центральной нервной системы, 8) Инфекции глаз, уха, горла, носа и полости рта, 9) Инфекции органов пищеварительной системы, 10) Инфекции нижних дыхательных путей (исключая пневмонию),	Основное обсуждаемое требование в приказе, глава 2, пункт 6: подлежат учету как ИСМП, инфекционные осложнения, связанные с оказанием акушерско – гинекологической помощи – в течение тридцати календарных дней, после выписки. Согласно, исследованию Адамян Л.В. и др, (2016г), на осложнение послеродового периода приходилось 50-60%, эти данные говорят о наличии инфекции у матери на догоспитальном этапе, часто у родильниц послеоперативного родоразрешения развивается с большей интенсивностью, поэтому входят в группу повышенного риска.
	Уделено достаточное внимание на алгоритм обработки рук, также изучено регламент надевания перчаток. 1) Гигиеническая обработки рук сотрудников медицинских организаций 2) Мытье рук мылом и водой без применения антисептиков 3) Обработка рук с применением антисептика 4) Хирургическая дезинфекция рук	Существует необходимость терминологической правки, применение изначального понятия, так как на повседневной рабочей рутине, до сих пор придается большой приоритет обозначению «социальная», «гигиеническая», «хирургическая» обработка рук, чем ее восприятие в данном приказе.
	Разработаны основополагающие инструкция, обоснованной практикой, которые включают как исследовательские, так и клинические аспекты по бактериологическому контролю.	Отсутствует методика определения чувствительности микрофлоры к антисептикам и дезинфектантам.

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Данный материал не был опубликован в других изданиях и не находится на рассмотрении в других издательствах.

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THE ROLE OF BIOCHEMICAL MARKERS IN BONE METABOLISM IN CHILDREN AND ADOLESCENTS. LITERATURE REVIEW

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Abstract

Background. Skeletal health is of paramount importance during childhood and adolescence, as it directly influences growth, development, and overall quality of life. Individuals who do not achieve optimal bone mass during these critical periods are at risk of developing osteoporosis, even if they do not experience accelerated bone loss in adulthood.

In recent years, biochemical markers have become valuable tools for assessing bone metabolism and turnover. However, interpreting these results remains challenging, as measurements fluctuate based on factors such as age, pubertal stage, growth rate, mineral accumulation, hormonal regulation, nutritional status, circadian and diurnal variations, tissue specificity, and the sensitivity and specificity of analytical methods. Serum markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and the C- and N-terminal propeptides of type I collagen. Urinary markers of bone resorption include degradation products of type I collagen such as pyridinoline (PYD), deoxypyridinoline (D-PYD), and the C- and N-terminal telopeptides of type I collagen (CTX and NTX).Therefore, it is essential to establish reference values that account for age and sex in each pediatric population, considering their specific climatic conditions and lifestyle factors.

Aim. To analyze the literature on the role of bone turnover markers and their reference values in children.

Search Strategy: A systematic search was conducted in the PubMed and Google Scholar databases using the following keywords: "bone metabolism markers," "osteopenic syndrome in children," "osteoporosis diagnosis," "C-terminal telopeptide," and "reference values of bone metabolism markers." The search was limited to studies published in English over the past 10 years. 40 sources were reviewed.

Discussion. An analysis of the literature indicates that quantitative values of osteocalcin, C-terminal telopeptide of type I collagen, N-terminal propeptide of type I procollagen, and alkaline phosphatase in the blood of healthy children and adolescents from different countries vary considerably and exhibit gender-specific differences.

Conclusion. A review of the literature underscores the importance of assessing bone metabolism markers in pediatric populations. Age-specific reference intervals for these markers, taking into account ethnic, gender, and geographic variations, are clinically significant for evaluating bone metabolism in children and adolescents.

Keywords: *"bone metabolism markers", "osteopenic syndrome in children", "osteoporosis diagnosis", "C-terminal telopeptide", "reference values of bone metabolism markers".*

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Резюме

РОЛЬ БИОХИМИЧЕСКИХ МАРКЕРОВ В КОСТНОМ ОБМЕНЕ У ДЕТЕЙ И ПОДРОСТКОВ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Здоровье скелета имеет первостепенное значение в детском и подростковом возрасте, поскольку оно напрямую влияет на рост, развитие и общее качество жизни. Люди, которые не достигают адекватной костной массы в детстве и подростковом возрасте, подвержены риску развития остеопороза, даже если у них не происходит ускоренной потери костной массы во взрослом возрасте. В последние годы биохимические маркеры стали ценным инструментом для оценки костного метаболизма и костного обмена. Однако интерпретация результатов затруднена, поскольку такие измерения колеблются в зависимости от возраста, стадии полового созревания, скорости роста, накопления минералов, гормональной регуляции, статуса питания, циркадных колебаний, суточных колебаний и специфичности костной ткани, а также чувствительности и специфичности анализов. Сывороточные маркеры формирования костной ткани включают костную щелочную фосфатазу, остеокальцин и С- и N-концевые пропептиды коллагена I типа. Маркеры резорбции кости в моче включают продукты распада коллагена I типа, такие как пиридиновые сшивки (пиридинолин [PYR], дезоксипиридинолин [D-PYR]) и С- и N-телопептиды коллагена I типа (CTx и NTx). Таким образом, для каждой детской популяции, проживающей в определенном климате и с похожим образом жизни, должны быть получены референсные значения с учетом возраста и пола.

Цель. Анализ литературных источников о роли маркеров костного обмена и их референсных значении у детей.

Стратегия поиска. Проведен систематический поиск в базах PubMed, Google Scolar по ключевым словам: «маркеры костного метаболизма», «остеопенический синдром у детей», «диагностика остеопороза», «С концевой телопептид», «референсные значения маркеров костного метаболизма». Этот поиск был ограничен англоязычными исследованиями, опубликованными с 2015 по 2024 гг. Изучено 40 источников.

Обсуждение. Анализ публикаций показал, что количественные значения гормона остеокальцина, С-концевого телопептида коллагена I типа, N-концевого пропептида проколлагена типа I и щелочной фосфатазы в крови у здоровых детей и подростков из разных стран имели неравнозначные значения и гендерные различия.

Выводы. Анализ литературных источников показывает важность определения маркеров костного метаболизма у детей и подростков. Возрастные интервалы этих маркеров в детской популяции с учетом этнического, гендерного и географического распределения клинически значимы при оценке костного метаболизма.

Ключевые слова: *«маркеры костного метаболизма», «остеопенический синдром у детей», «диагностика остеопороза», «С концевой телопептид», «референсные значения маркеров костного метаболизма».*

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Түйіндеме

БАЛАЛАР МЕН ЖАСӨСПІРІМДЕРДЕГІ СҮЙЕК АЛМАСУЫНДАҒЫ БИОХИМИЯЛЫҚ МАРКЕРЛАРДЫҢ РӨЛІ. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе. Қаңқа саулығы балалық және жасөспірімдік шақта өте маңызды, өйткені ол өсуге, дамуға және жалпы өмір сапасына тікелей әсер етеді. Балалық және жасөспірім кезінде сүйек массасына жете алмайтын адамдарда остеопороздың даму қаупі бар, тіпті егер олар ересек жаста сүйек массасының жоғалуын тездетпесе де. Соңғы жылдары биохимиялық маркерлер сүйек метаболизмі мен сүйек алмасуын бағалаудың құнды құралына айналды. Дегенмен, нәтижелерді түсіндіру қиын, өйткені мұндай өлшемдер жасына, жыныстық жетілу кезеңіне, өсу жылдамдығына, минералдардың жиналуына, гормоналды реттеуге, тамақтану күйіне, циркадттық ауытқуларға, күнделікті өзгерістерге және сүйек ерекшелігіне, сондай-ақ талдаулардың сезімталдығы мен ерекшелігіне байланысты өзгереді. Сүйек түзілуінің сарысулық маркерлеріне сүйек сілтілі фосфатаза, остеокальцин және С - және N-терминал коллаген I типті пропептидтер жатады. Зәрдегі сүйек резорбциясының маркерлеріне пиридиндік айқаспалы байланыстар (пиридинолин [PYR], дезоксипиридинолин [D-PYR]) және I типті коллаген С - және N-телопептидтер (CTx және NTx) сияқты I типті коллагеннің ыдырау өнімдері жатады. Осылайша, белгілі бір климатта өмір сүретін және өмір салты ұқсас әрбір балалар популяциясы үшін жас пен жынысты ескере отырып, референстік мәндер алынуы керек.

Мақсаты. Сүйек алмасу маркерлерінің рөлі және олардың балалардағы референстік мәні туралы әдеби дереккөздерді талдау.

Іздеу стратегиясы. PubMed, Google Scolar деректер қорында "сүйек метаболизмінің маркерлері", "балалардағы остеопениялық синдром", "остеопороз диагностикасы", "телопептид ұшы", "сүйек метаболизмінің маркерлерінің

анықтамалық мәндері" түйін сөздері бойынша жүйелі іздеу жүргізілді. Ізденіс 2015 жылдан 2024 жылға дейін жарияланған шет тіліндегі зерттеулермен шектелді. 40 дереккөз зерттелді.

Талқылау. Жарияланымдарды талдау әр түрлі елдердің дені сау балалары мен жасөспірімдеріндегі остеокальцин, I типті коллагеннің С-терминалды телопептидінің, проколлагеннің I типті N-терминалды пропептидінің және қандағы сілтілі фосфатазаның сандық мәндері бірдей емес мәндер мен гендерлік айырмашылықтарға ие екенін көрсетті.

Қорытынды. Әдеби дереккөздерді талдау балалар мен жасөспірімдердегі сүйек метаболизмінің маркерлерін анықтаудың маңыздылығын көрсетеді. Этникалық, гендерлік және географиялық таралуын ескере отырып, балалар популяциясындағы осы маркерлердің жас аралықтары сүйек метаболизмін бағалауда клиникалық маңызды.

Түйінді сөздер: *"сүйек метаболизмінің маркерлері", "балалардағы остеопениялық синдром", "остеопороз диагностикасы", "телопептид ұшы", "сүйек метаболизмінің маркерлерінің анықтамалық мәндері".*

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Introduction

Skeletal health is critical during childhood and adolescence, as it directly affects growth, development, and overall quality of life. Optimal bone development and maintenance require a precise balance between bone formation and resorption [22]. Two processes—remodeling and modeling—underlie the development and maintenance of the skeletal system. Bone modeling is responsible for growth and mechanically induced adaptation of the bone. [32]. Bone remodeling, a continuous process of old bone resorption followed by new bone formation, plays a fundamental role in preserving skeletal integrity, strength, and mineralization [15]. The primary molecular mechanisms underlying reduced bone mineral density are believed to involve increased osteoclast activity, decreased osteoblast activity, or both—resulting in an imbalance in the bone remodeling process characterized by accelerated bone resorption and impaired bone formation [20].

Peak bone mass attained during adolescence and the rate of bone loss in adulthood are key determinants of future osteoporosis risk [2,30]. In addition, the level of peak bone mass reached in adolescence directly influences the likelihood of pathological fractures and osteoporosis later in life [9, 13]. Disruptions in bone metabolism can lead to growth delays and various skeletal disorders, including osteoporosis and fractures [15, 27]. In pediatric populations, bone mineral content is commonly used to assess bone deficiencies and fracture risk [8, 35]. Bone health is evaluated through various methods, with dual-energy X-ray absorptiometry (DXA) recognized as the gold standard for bone density assessment [19, 21] In recent years, biochemical markers have become valuable tools for assessing bone metabolism and turnover [10]. Serum markers of bone formation include bone-specific alkaline phosphatase, osteocalcin, and the C- and N-terminal propeptides of type I collagen. Urinary markers of bone resorption include degradation products of type I collagen, such as pyridinoline (PYD), deoxypyridinoline (D-PYD), and the C- and N-terminal telopeptides of type I collagen (CTX and NTX) [16]. The assessment of biochemical markers of bone metabolism enables evaluation of bone status, determination of the rate of bone turnover and the extent of spontaneous bone loss, monitoring of osteoporosis treatment with antiresorptive agents, and prediction of fracture risk [17]. Several studies have demonstrated that bone turnover markers (BTMs) may provide information on fracture risk independently of bone mineral density (BMD); thus, incorporating them into risk assessment algorithms may enhance the prediction of fractures [33].

Bone metabolism markers are a group of biological molecules produced during bone tissue renewal and its regulatory processes, including bone matrix proteins, enzymes, and hormones. Compared to radiological methods, marker-based assessments may provide a more accurate reflection of bone metabolism [5, 29]. Osteoid production by osteoblasts is reflected in the formation of non-collagenous markers—such as bone-specific alkaline phosphatase (BALP) and osteocalcin (OC)—as well as collagenous markers, including the N-terminal propeptide of type I procollagen (PINP). Type I collagen is the most abundant collagen in connective tissue, with its highest synthesis occurring in bones, where it constitutes the majority of the organic bone matrix. Its precursor, type I procollagen, is synthesized by osteoblasts, and its terminal propeptides are cleaved extracellularly. Bone resorption, which involves the degradation of the organic bone matrix following enzymatic digestion, is assessed using resorption markers, such as degradation fragments of type I collagen—N- and C-terminal telopeptides of type I collagen (NTX and CTX)—as well as the release of tartrate-resistant acid phosphatase type 5b (TRAcP5b) [16, 24]. Laboratory analysis of bone turnover markers is non-invasive, sensitive, and rapid, making it useful not only for evaluating overall bone metabolism but also for monitoring the treatment of osteopenic conditions [34]. By measuring bone metabolism markers, clinicians can assess the overall metabolic state of bones and track dynamic changes in systemic bone tissue [12].

In children, bone turnover markers can be valuable for diagnosing and managing skeletal disorders; however, challenges in interpreting results may arise. The results obtained using different methods are not identical, with the discrepancies being particularly pronounced for β-CTX assays at higher concentrations typically observed in children, which necessitates method-specific reference intervals [7]. Compared to adults, children exhibit elevated levels of bone markers due to the rapid skeletal growth rate and high bone turnover. The selection of markers for assessing bone metabolism is based on several criteria, including bone specificity, clinical efficacy, biological and analytical variability, broad availability, potential for methodological standardization, sample processing requirements, stability, and measurement environment [24]. However, the interpretation of results is complicated by the

influence of multiple factors, such as age, pubertal stage, growth velocity, mineral accumulation, hormonal regulation, nutritional status, circadian and daily variations, bone tissue specificity, and the sensitivity and specificity of assays [31].

The use of discrete age strata allows for easy implementation into standard laboratory information systems. However, continuous reference intervals may be preferable, particularly when test results exhibit rapid changes with age [25]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) recommend serum P1NP and CTX-1 as the preferred markers for bone formation and resorption, respectively, for fracture risk assessment and osteoporosis treatment monitoring [36].

Thus, for each pediatric population residing in a specific climate and sharing a similar lifestyle, reference values should be established based on age and sex. These reference values must be derived after validating the relationships between bone formation and turnover markers, accounting for age- and sex-related differences in subjects with similar lifestyles within the same geographic regions [40]. The onset and progression of osteoporosis is closely associated with factors regulating bone remodeling, such as calcium, vitamin D, estrogen, and parathyroid hormone (PTH). Vitamin D plays a crucial role in the bone remodeling process as it is involved in calcium homeostasis, which is essential for maintaining bone health. It enhances the absorption of dietary calcium in the intestines, reduces calcium loss in urine, and mobilizes calcium stored in the skeleton [18]. Vitamin D levels are an important factor in determining bone health. A deficiency of active vitamin D metabolites severely impacts the calcification of osteoid, leading to rickets in children and adolescents or osteomalacia in adults. It has been proven that skeletal manifestations of vitamin D deficiency are linked to a secondary contributing factor: hyperparathyroidism. This results in increased bone remodeling turnover, changes in calcium and phosphate metabolism, and consequently, an increased risk of osteopenia and osteoporosis [1]. In vitamin D deficiency, parathyroid hormone (PTH) is activated, playing a central role in the regulation of calcium-phosphate metabolism and its elevation in response to low serum calcium levels. Chronic hypersecretion of PTH most often leads to bone resorption [11].

In Kazakhstan, the assessment of bone metabolism markers in pediatric populations remains limited in clinical practice. We identified only two domestic publications that investigated infants under one year of age, with no published studies on children older than one year or adolescents [38, 39]. Therefore, the present literature review is highly relevant to address this gap.

This review aims to analyze the literature on the role of bone turnover markers and their reference values in children.

Search Strategy:

A systematic search was conducted in the electronic databases PubMed and Google Scholar using the following keywords: "bone metabolism markers," "osteopenic syndrome in children," "osteoporosis diagnosis," "C-terminal telopeptide," and "reference values of bone metabolism markers." The search was limited to studies published in English over the past 10 years.

Inclusion Criteria: studies were included in the review if they met the following criteria: (1) data on the use of bone metabolism markers in somatically healthy children and adolescents; (2) information on the role of bone metabolism markers in pediatric populations; (3) studies published in English; (4) diagnostic studies assessing the early detection of reduced bone mineral density; (5) research evaluating the diagnostic role of bone metabolism markers.

Exclusion Criteria: the following studies were excluded: (1) research focusing on adult populations with bone disorders; (2) articles without full-text availability; (3) studies with low methodological quality, such as case reports and case series; (4) publications in languages other than English, (5) studies that did not assess bone metabolism markers.

A total of 40 sources were reviewed, describing the role of bone turnover markers in healthy children and adolescentsand their association with various pathologies. However, only five studies met our inclusion criteria.

Ethical Statement: This literature review was based on previously published studies; therefore, ethical committee approval and patient consent were not required.

Discussion

In the analysis of the selected studies, we examined the levels of osteocalcin, C-terminal telopeptide of type I collagen (CTX-I), N-terminal propeptide of type I procollagen (PINP), and alkaline phosphatase in the blood of healthy children and adolescents from Poland, Korea, China, Portugal, and Italy.

A study conducted by Gajewska J et al. (2024) examined 355 healthy children and adolescents from Poland with normal weight (46.5% girls) aged 1 to 18 years. Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry (DXA), and bone turnover marker concentrations were measured using immunoassay methods.

The study findings revealed significant variations in bone marker levels among adolescents, with notable gender differences:

- Median alkaline phosphatase (BALP) levels at ages 14–15.9 and 16–18 years were significantly higher in boys than in girls ($p < 0.001$; $p = 0.022$, respectively).
- Median osteocalcin (OC) levels at ages 12–13.9, 14–15.9, and 16–18 years were higher in boys than in girls ($p = 0.019$; $p = 0.010$; $p = 0.018$, respectively).
- Median C-terminal telopeptide of type I collagen (CTX-I) levels at ages 14–15.9 years were higher in boys than in girls ($p = 0.004$).

Statistically significant positive correlations were observed across the entire study population, as well as in gender-specific subgroups:

- CTX-I and osteocalcin levels ($r = 0.664$, $p < 0.001$; $r = 0.687$, $p < 0.001$; $r = 0.645$, $p < 0.001$, respectively).
- CTX-I and alkaline phosphatase levels ($r = 0.207$, $p < 0.001$; $r = 0.256$, $p = 0.001$; $r = 0.173$, $p = 0.017$, respectively).
- Osteocalcin and alkaline phosphatase levels, both in the total study group and in the female subgroup ($r = 0.170$, $p = 0.001$; $r = 0.219$, $p = 0.005$, respectively) [14].

In 2019, Choi JS et al. conducted a study to assess the association between N-terminal propeptide of type I procollagen (P1NP) and osteocalcin with age and sex in a cohort of healthy Korean children and adolescents.

The study included 580 participants (290 boys and 290 girls), aged 0–18 years, recruited from outpatient clinics in Korea. Significant age-related changes in bone turnover markers were observed in both sexes ($p < 0.001$), along with notable differences between boys and girls ($p < 0.05$).

• P1NP levels were highest during the first year of life, after which they gradually declined, with some fluctuations leading up to puberty.

• In boys, P1NP levels tended to rise during puberty, whereas in girls, they showed a steady decline with age.

• Unlike P1NP, osteocalcin did not exhibit a distinct postnatal peak. Instead, its levels increased with age in both sexes, peaking at 11–13 years in boys and 9–12 years in girls.

• A significant positive correlation was found between serum P1NP and osteocalcin levels ($r = 0.467$, $p < 0.001$) [6].

Table 1.

Reference values of bone metabolism markers in children and adolescents.

№	Author, year of publication	Country	Total sample, age	OC[1] ng/mL	CTX-1[2] ng/mL	P1NP[3] µg/L	(BALP)[4] U/L	*P**
1	Gajewska J., 2024 [1]	Poland	355(0-18)	83.2 (52.6-114.4)	1.70 (1.19-2.12)	-	112.1 (87.9-132.5)	< 0.004
2	Choi J.S., 2019 [22]	South Korea	290 (0-18)	67.3–108.8	-	519.6–1966,9	-	< 0.001
3	Zhang Y., 2023 [33]	China	661(0-16)	-	-	61–1399	-	< 0.001
4	Monjardino T., 2019 [44]	Portugal	395 (7)	51.3 – 133.8	0.470-1.690	-	159 - 439	< 0.002
5	Brescia, 2024 [5]	Italy	202(1-14лет)	25.33-190.07	0.48-2.86	-	22.32-163.54	< 0.05
6	Larsen J.B., 2021 [6]	Northern Europs	420(2-18 years)	-	-	18-62 15-75	-	< 0.001

[1] OC- Osteocalcin, [3] P1NP -N-terminal propeptide of type I procollagen,
[2] CTX-1- C-terminal telopeptide of type I collagen, [4] BALP - Alkaline phosphatase.

According to a 2023 study by *Zhang Y. et al.,* a total of 366 boys and 295 girls aged 0–16 years from Southwest China participated in the research. The participants were categorized into three age groups: preschool (boys and girls aged 0–6 years), prepubertal (boys aged 6–12 years and girls aged 6–10 years), and adolescent (boys aged 12–16 years and girls aged 10–16 years). The study found that P1NP levels in boys decreased with age until the prepubertal stage, after which they began to rise. Significant differences in P1NP levels were observed between the preschool and adolescent groups ($p < 0.001$ and $p = 0.007$, respectively). Meanwhile, levels of C-terminal telopeptide of type I collagen (CTX-I) and N-terminal mid-fragment of osteocalcin increased with age in boys. Statistically significant differences in these markers were noted between the preschool and prepubertal stages ($p < 0.001$ and $p = 0.006$, respectively), between the preschool and adolescent stages ($p < 0.001$ for both markers), and between the prepubertal and adolescent stages ($p < 0.001$ for both markers) [37].

In a 2019 study, *Monjardino T. et al.* highlighted that single-time-point measurements of bone metabolism markers have limited utility in describing anthropometric growth and overall bone health in generally healthy prepubertal children. The study evaluated 395 seven-year-old children from a Portuguese cohort. When comparing BMI groups, the researchers observed that overweight children had significantly higher alkaline phosphatase concentrations than those with normal weight ($p = 0.002$). However, no differences in serum osteocalcin and C-terminal telopeptide (CTX) concentrations were detected across BMI groups or weight gain trajectories. Furthermore, CTX showed no correlation with any bone parameters measured via DXA [28].

Brescia et al. in a 2024 study assessed reference intervals for bone metabolism markers in Italian children and adolescents. The study included a total of 202 participants aged 1 to 18 years. Significant differences ($p < 0.05$) were found in median alkaline phosphatase concentrations, with higher levels in the 13–18 age group compared to the 1–6 and 7–12 age groups. Additionally, notable sex-based differences ($p < 0.05$) were observed in alkaline phosphatase levels, particularly within the 13–18 age group. The study also reported significant variations ($p < 0.05$) in median CTX concentrations, with higher levels in the 13–18 age group compared to younger age groups. Furthermore, CTX concentrations differed significantly ($p < 0.05$) between males and females, with particularly strong statistical significance in the 13–18 age group ($p < 0.0001$) [4].

Bayer, M. (2014) investigated the relationships between bone formation markers, bone turnover markers, and variables such as age, gender, and pubertal stage in a cohort (n = 439) of healthy children and adolescents of European descent. The highest levels of PINP were observed during the first year of life. No postnatal peak for OC was found; however, its levels remained higher than the reference interval for adults throughout childhood. OC reached its peak during the pubertal growth spurt, at the second to third stages of Tanner breast development in girls and at the second to third stages of Tanner genital development in boys. PINP peaked during the second to third stages of Tanner breast development in girls and at the third stage of Tanner genital development in boys [3].

Larsen J.B. et al. (2021) in their study determined the serum level of PIIINP, which were analyzed in healthy blood donors aged 19–67 years (n = 240) and children aged 2–18 years (n = 420). PIIINP levels were influenced by age but not gender. The following reference intervals were established: 2–10 years, 18–62 µg/L; 11–18 years, 15–75 µg/L; 19–39 years, 15–55 µg/L; 40–67 years, 14–31 µg/L. In conclusion, age-specific reference intervals for PIIINP using the MAGLUMI 800 CLIA were indicated in a large Danish cohort. These results may be useful for other laboratories wishing to set up PIIINP on the same platform and may provide improved recommendations for clinicians [23].

The role of vitamin D in bone metabolism is well-established in both children and adults. In their study, *Marwaha et al.* (2019) investigated the status of bone markers in children with vitamin D deficiency across four schools in India. The study included 468 children and adolescents. These participants, with preserved samples taken before and after supplement intake, along with available anthropometric data,

serum biochemistry, 25-hydroxyvitamin D, and parathyroid hormone levels, were evaluated for markers of bone formation (aminoterminal propeptide of type 1 procollagen [P1NP]) and resorption (β-crosslaps [CTx]). Following supplementation, a significant reduction in serum P1NP levels (from 691 ± 233 ng/mL to 640 ± 259 ng/mL, P < 0.001) and CTx levels (from 1.67 ± 0.53 ng/mL to 1.39 ± 0.51 ng/mL, P < 0.001) was observed. While reductions in both P1NP and CTx levels were noted in both boys and girls, the effect was more pronounced for serum CTx levels compared to P1NP levels across all three supplement intake groups and vitamin D deficiency (VDD) categories [26].

Conclusion. This review highlights the importance of assessing bone metabolism markers in children and adolescents. Establishing age-specific reference intervals for these markers, considering ethnic and geographic variations, can be clinically valuable in evaluating bone metabolism. The determination of reference ranges for osteocalcin, C- and N-terminal procollagen type I propeptides, and alkaline phosphatase as biochemical markers of bone formation is essential for their clinical application in pediatric practice.

Conflict of Interest. *The authors declare no conflicts of interest. Additionally, no part of this article has been previously published or is under consideration by other publishers.*

Author Contributions. *As this is a review article, all authors contributed to the literature search using separate methodologies, and the decision to exclude certain materials was made collectively.*

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ЭРАДИКАЦИОННАЯ ТЕРАПИЯ HELICOBACTER PYLORI

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Резюме

Актуальность. Helicobacter pylori – бактерия, вызывающая хронический активный гастрит, пептическую язвенную болезнь, желудочную аденокарциному, МАЛТ-лимфому, атрофический гастрит. В последние годы в мире развилась устойчивость Helicobacter pylori к различным антибиотикам, что требует изучения вопроса и разработки новых схем терапии.)

Цель: анализ современных подходов к эрадикационной терапии *Helicobacter pylori по данным современной литературы.*

Стратегия поиска. Поиск научной литературы проводился в базах данных PubMed, Scopus, Web of Science и Cochrane Library за период с 2014 по 2024 год. Использовались следующие ключевые слова и комбинации: *"Helicobacter pylori"*, *"eradication"*, *"treatment strategies"*, *"antibiotic resistance"*, *"triple therapy"*, *"quadruple therapy"*, *"bismuth-based therapy"*, *"sequential therapy"*, *"vonoprazan"*, *"probiotics and H. pylori"*, *"guidelines for H. pylori eradication"*. Дополнительно был проведён ручной поиск литературы. Предпочтение отдавалось оригинальным исследованиям, систематическим обзорам, клиническим рекомендациям и метаанализам, опубликованным на английском и русском языках. Для анализа были отобраны 81 источник.

Результаты и выводы. Золотым стандартом диагностики Helicobacter pylori среди неивазивных методик, являются такие как: 13 С дыхательный уреазный тест, выявление антигена Helicobacter pylori в кале. Данные тесты позволяют оценить и эффективность проведенной антихеликобактерной эрадикационной терапии. Для эрадикации Helicobacter pylori предложена тройная и квадротерапия, основанные на использовании больших доз ИПП, двух антибиотиков и препарата висмута. В схемы эрадикации введены калий конкурентные блокаторы протонной помпы, самые мощные кислотосупрессорные препараты.

Несмотря на наличие многочисленных схем терапии, уровень успешной эрадикации *H. pylori* остаётся ниже оптимального и остаётся важной задачей гастроэнтерологии, особенно в связи с её ролью в развитии язвенной болезни, рака желудка и других патологий. Растущая антибиотикорезистентность требует индивидуального подхода к выбору схемы лечения, предпочтения более эффективным и адаптированным стратегиям — таким как квадротерапия с висмутом или схемы с вонопразаном. Будущее лечения связано с персонализированной медициной, разработкой новых молекул и улучшением диагностики резистентных штаммов. Необходима дальнейшая международная координация для мониторинга резистентности и оптимизации клинических рекомендаций.

Ключевые слова: *Helicobacter pylori, эрадикационная терапия, ингибиторы протонной помпы, калий конкурентные блокаторы протонной помпы*

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Abstract

ERADICATION THERAPY FOR HELICOBACTER PYLORI

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Relevance. *Helicobacter pylori* is a bacterium that causes chronic active gastritis, peptic ulcer disease, gastric adenocarcinoma, MALT lymphoma, and atrophic gastritis. In recent years, antibiotic resistance of *Helicobacter pylori* has become widespread globally, necessitating further investigation and the development of new therapeutic regimens.

Objective: To analyze current approaches to *Helicobacter pylori* eradication therapy based on modern literature.

Search strategy. A literature search was conducted in the PubMed, Scopus, Web of Science, and Cochrane Library databases for the period from 2014 to 2024. The following keywords and combinations were used: "Helicobacter pylori", "eradication", "treatment strategies", "antibiotic resistance", "triple therapy", "quadruple therapy", "bismuth-based therapy", "sequential therapy", "vonoprazan", "probiotics and H. pylori", "guidelines for H. pylori eradication". Additionally, a manual search of the literature was performed. Preference was given to original studies, systematic reviews, clinical guidelines, and meta-analyses published in English and Russian. A total of 81 sources were selected for analysis.

Results and conclusions. Among non-invasive diagnostic methods, the ^{13}C-urea breath test and stool antigen detection for *Helicobacter pylori* are considered the gold standards. These tests also help assess the effectiveness of eradication therapy. Triple and quadruple therapy regimens have been proposed for *Helicobacter pylori* eradication, typically involving high doses of proton pump inhibitors (PPIs), two antibiotics, and a bismuth compound. More recently, potassium-competitive acid blockers (P-CABs), the most potent acid-suppressing agents, have been incorporated into treatment regimens.

Despite the variety of treatment protocols available, the success rate of *H. pylori* eradication remains suboptimal and continues to be a pressing challenge in gastroenterology, especially given the bacterium's role in the pathogenesis of peptic ulcer disease, gastric cancer, and other conditions. The rise in antibiotic resistance necessitates an individualized approach to therapy selection, with a preference for more effective and locally adapted strategies such as bismuth-based quadruple therapy or vonoprazan-containing regimens. The future of *H. pylori* treatment lies in personalized medicine, the development of new molecules, and improved diagnostics for resistant strains. Continued international coordination is essential for monitoring resistance and optimizing clinical guidelines.

Keywords: Helicobacter pylori*, eradication therapy, proton pump inhibitors, potassium-competitive acid blockers.*

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Түйіндеме

HELICOBACTER PYLORI ЖОЮҒА БАҒЫТТАЛҒАН ТЕРАПИЯ

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Өзектілігі. *Helicobacter pylori* — бұл созылмалы белсенді гастрит, пептикалық ойық жара ауруы, асқазан аденокарциномасы, MALT-лимфома және атрофиялық гастритке себеп болатын бактерия. Соңғы жылдары әлем бойынша *Helicobacter pylori*-дің әртүрлі антибиотиктерге төзімділігі артты, бұл мәселені тереңірек зерттеуді және жаңа емдеу сызбаларын әзірлеуді талап етеді.

Мақсаты: Қазіргі заманғы әдебиеттер деректері бойынша *Helicobacter pylori*-ді эрадикациялау терапиясына қатысты заманауи тәсілдерді талдау.

Іздеу стратегиясы. Ғылыми әдебиеттерді іздеу 2014–2024 жылдар аралығында PubMed, Scopus, Web of Science және Cochrane Library дерекқорларында жүргізілді. Келесі негізгі сөздер мен тіркестер қолданылды: "Helicobacter pylori", "eradication", "treatment strategies", "antibiotic resistance", "triple therapy", "quadruple therapy", "bismuth-based therapy", "sequential therapy", "vonoprazan", "probiotics and H. pylori", "guidelines for H. pylori eradication". Қосымша қолмен іздеу де жүргізілді. Артықшылық ағылшын және орыс тілдерінде жарияланған түпнұсқалық зерттеулерге, жүйелі шолуларға, клиникалық ұсынымдар мен метаанализдерге берілді. Талдау үшін барлығы 81 дереккөз іріктеліп алынды.

Нәтижелері мен қорытындылары. *Helicobacter pylori*-ді анықтаудың инвазивті емес әдістері ішінде ^{13}C тыныс уреаза сынамасы мен нәжістегі антигенді анықтау "алтын стандарт" болып есептеледі. Бұл сынақтар жүргізілген эрадикациялық терапияның тиімділігін бағалауға да мүмкіндік береді. *Helicobacter pylori*-ді жою үшін ИПП-ның (протондық помпа тежегіштері) жоғары дозалары, екі антибиотик және висмут препаратын қамтитын үштік және төрттік терапиялар ұсынылған. Эрадикациялық сызбаларға сонымен қатар қышқылдықты ең жоғары басатын дәрілер — калийге бәсекелес протондық помпа блокаторлары енгізілді.

Терапия сызбаларының көптігіне қарамастан, *H. pylori*-ді жоюдың табыстылық деңгейі әлі де оңтайлы емес және гастроэнтерологияның маңызды мәселесі болып қала береді, әсіресе бұл бактерияның ойық жара, асқазан обыры және басқа да патологиялардың дамуындағы рөліне байланысты. Антибиотиктерге төзімділіктің өсуі емдеу сызбаларын таңдауда жекелей тәсілді қажет етеді, тиімді әрі бейімделген стратегияларға — мысалы, висмутпен төрттік терапия немесе вонопразанмен емдеу сызбаларына басымдық берілуі керек. Болашақ емдеу бағыттары дербестендірілген медицинамен, жаңа молекулаларды әзірлеумен және төзімді штамдарды анықтайтын диагностика әдістерін жетілдірумен байланысты. Төзімділікті бақылау және клиникалық ұсынымдарды оңтайландыру үшін халықаралық үйлестіруді жалғастыру қажет.

Түйінді сөздер: *Helicobacter pylori*, *эрадикациялық терапия, протон помпасының тежегіштері, калийге бәсекелес протондық помпа блокаторлары.*

Дәйексөз үшін:

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Введение

Helicobacter pylori – человеческий патоген, передающийся от человека к человеку, вызывающий хронический активный гастрит у колонизируемых субъектов. Инфицирование приводит к развитию пептической язвенной болезни, желудочной аденокарциноме, МАЛТ-лимфоме, атрофическому гастриту [45, 46, 67].

Helicobacter pylori является фактором риска рака желудка. Свыше миллиона случаев рака желудка в 2020 году были связаны с болезнями, вызванными Helicobacter pylori, в связи с чем рекомендуется лечение инфекции независимо от симптоматики [57,69,78,79].

Киотский консенсус предложил ввести в классификацию Helicobacter pylori как этиологический фактор гастрита и рассматривать хронический гастрит как инфекционное заболевание, в настоящий момент Helicobacter pylori введен в Международную классификацию болезней (МКБ) 11 пересмотра [40, 42, 68].

Тестирование на Helicobacter pylori и эрадикационная терапия показана пациентам с язвенной болезнью, с хронической диспепсией, пациентам, длительно принимающих НПП, с раком желудка, МАЛТ лимфомой, при железо-дефицитной анемии, идиопатической тромбоцитопенической пурпуре, В 12 дефицитной анемии [14, 42, 52].

Успешная эрадикация H. pylori - начальная терапия MALT лимфомы приводит в 70-80% случаев к длительной ремиссии и является стандартом лечения [34, 58].

В последние годы возникли новые вызовы в эрадикационной терапии Helicobacter pylori (HP), среди них - развившаяся резистентность Helicobacter pylori к прежним схемам эрадикационной терапии, что потребовало модификации существующих режимов терапии Helicobacter pylori, изложенных в Маастрихт 6, Флорентийского консенсуса по лечению инфекции Helicobacter pylori [7, 46].

Стратегия поиска. Поиск научной литературы проводился в базах данных **PubMed**, **Scopus**, **Web of Science** и **Cochrane Library** за период с **2015 по 2024 год**. Использовались следующие ключевые слова и комбинации: *"Helicobacter pylori"*, *"eradication"*, *"treatment strategies"*, *"antibiotic resistance"*, *"triple therapy"*, *"quadruple therapy"*, *"bismuth-based therapy"*, *"sequential therapy"*, *"vonoprazan"*, *"probiotics and H. pylori"*, *"guidelines for H. pylori eradication"*.

Дополнительно был проведён ручной поиск по спискам литературы в ключевых публикациях и метаанализах. В обзор включались статьи, опубликованные на английском и русском языках, соответствующие критериям оригинальных исследований, систематических обзоров, клинических рекомендаций и метаанализов

Результаты и обсуждение.

Эпидемиология Helicobacter pylori

Helicobacter pylori выявляется во многих странах, треть взрослого населения инфицирована на юге Европейского континента и в Южной Америке. В Азии инфицировано около половины населения. Helicobacter pylori диагностируют у эмигрантов, однако в последние десятилетия выявлено снижение инфицированности Helicobacter pylori среди молодого поколения, что приведет к снижению инфицированности в последующую декаду. Плохие социально-экономические условия в детстве являются факторами риска для заболеваемости. Недостаточно изучены пути передачи, иногда бывают рецидивы после успешной эрадикации [8, 15, 77].

На земле инфицировано 4,4 миллиарда человек, от 18,9 до 87,7%, больше всего инфицированных в Африке (70,1%) и в Южной Америке (69,4%) [32].

В Казахстане в 1997 году Helicobacter pylori выявлен у 67% пациентов с язвенной болезнью желудка и у 89,8% с язвенной болезнью 12-перстной кишки [5].

В 2006 году *Нургалиевой Б.К.* была изучена инфицированность Helicobacter pylori у алматинских подростков, 60 % подростков с хроническим гастритом были инфицированы Helicobacter pylori и 85,7% случаев язвенной болезни у подростков были ассоциированы с Helicobacter pylori [6].

Пути передачи Helicobacter pylori не до конца изучены, инфекция передается от человека к человеку или через окружающую среду [35, 39, 64].

Передача инфекции от человека к человеку бывает горизонтальной и вертикальной, вертикальный путь передачи инфекции от родителей к детям внутри семьи, горизонтальный путь передачи инфекции, когда инфицируются вне семьи [60].

Инфицирование внутри семьи объясняется близким контактом, одним социо-экономическим уровнем, генетической предрасположенностью к инфекции и подверженности одному источнику заражения [35, 39, 55, 61].

Пути передачи инфекции фекально – оральный, изо рта в рот, гастро-оральный [15,72].

Возможно инфицирование через воду, продукты, через молоко, мясо, овощи [81].

Диагностика Helicobacter Pylori

Клинические рекомендации рекомендуют диагностические тесты для Helicobacter Pylori при язвенной болезни, при хронической диспепсии, при гастропатии, вызванной применением нестероидных противовоспалительных препаратов, при предраковых желудочных повреждениях, при раке желудка, при мальт-лимфоме, при положительном семейном анамнезе по раку желудка, при язвенной болезни, у пациентов с хеликобактерной инфекцией, с В -12 дефицитной анемией [18, 20, 44, 45, 47, 59, 62, 65, 67, 69, 73].

Для диагностических тестов используются инвазивные тесты, к золотому стандарту относится гистологическое исследование, быстрый уреазный тест, культуральный метод, полимеразная цепная реакция, к неинвазивным методам относятся [13] С дыхательный уреазный тест, тест для выявления антигена

Helicobacter pylori в стуле, выявление антител к Helicobacter pylori в сыворотке, моче и слюне [21, 24, 26, 36, 38, 63, 75, 76].

[13] **С дыхательный уреазный тест** – неинвазиный тест, рекомендован после проведения эрадикационной терапии. Чувствительность теста 96%, специфичность 93%. Пациенту назначают мочевину, меченную ^{13}C

перорально, после процесса гидролизации мочевины уреазой бактерии Helicobacter pylori, меченный углекислый газ определяют в выдыхаемом воздухе.

Существуют 2 разновидности теста для выявления **антигена Helicobacter pylori в кале**, антиген определяется с помощью моноклональных и поликлональных антител. Чувствительность моноклонального теста 94%, поликлонального 83%, специфичность обоих тестов сопоставима 96 и 97%. Тест рекомендован для оценки проведенной эрадикационной терапии [36].

Серологические тесты недорогие, неинвазивные, в сыворотке определяют Ig G к Helicobacter pylori , титр антител повышается через 3 недели после инфицирования Helicobacter pylori и сохраняется в течение 6-12 месяцев после проведенной эрадикации. Чувствительность и специфичность тестов низкая 85% и 79 % [43, 75].

Наибольшей специфичностью и чувствительностью отличаются **инвазивные тесты** для диагностики Helicobacter pylori. Золотым стандартом считается выявление Helicobacter pylori в гистологическом препарате, чувствительность и специфичность теста 95 и 99% [38].

Быстрый уреазный тест заключается в погружении биоптатов в среду, содержащей мочевину и pH индикатор. Уреаза Helicobacter pylori конвертирует мочевину в аммиак, что увеличивает pH, что проявляется в изменении цвета pH индикатора. Чувствительность этого теста колеблется от 85 до 95%, специфичность от 95 до 100% [75, 76]

Чувствительность культурального **метода диагностики** Helicobacter pylori колеблется от 85 до 95%, специфичность достигает 100% [75, 76].

Helicobacter pylori выявляется ПЦР в желудочном соке, в биоптате из желудка, стуле и слюне. Чувствительность этого теста 100% и специфичность 98%. Вышеуказанные тесты используются для диагностики Helicobacter pylori и оценки результатов эрадикационной терапии [75, 76].

Эрадикационная терапия

Цель лечения Helicobacter pylori достигнуть эрадикацию (уничтожение) бактерии. Эрадикация Helicobacter pylori — режим терапии, направленный на элиминацию Helicobacter pylori в слизистой оболочке желудка с целью заживления язв и других повреждений слизистой.

Приемлемой эрадикационной терапией Helicobacter pylori считается режим, когда достигается 80% уничтожения Helicobacter pylori, заживление язвенного дефекта или гастрита, длительностью терапии не должна превышать 14 суток, побочные эффекты не должны превышать 10—15 % [8].

Группа по изучению Helicobacter pylori организовала конференции для выработки рекомендаций к проведению эрадикационной терапии, первая конференция, проведенная в городе Маастрихте в 1996 году, дала название последующим рекомендациям от Маастрихта 1 до Маастрихта 6 [3,4].

Современные методы этиотропной терапии хеликобактериоза, изложенные еще в 4 Маастрихтском соглашении [7], предусматривают использование широкого спектра антибактериальных препаратов разных фармакологических групп – нитрофураны (фуразолидон), нитроимидазол (метронидазол, нитромидазол), антибиотики (тетрациклин, кларитромицин, азитромицин, левофлоксацин, рифабутин, амоксициллин). Предложенные 3-х и 4-х компонентные схемы эрадикационной терапии первой и второй линии, содержащие в своем составе наряду с антибактериальными препаратами ингибиторы протонной помпы (ИПП), препараты висмута. При этом длительность эрадикационной терапии рекомендуется до 14 суток [7, 10].

Во всех схемах используются антисекреторные препараты, ингибиторы протонной помпы или новая группа препаратов, калий конкурентные блокаторы протонной помпы [52].

Ингибиторы протонной помпы необратиомо связывают и подавляют H+K+атфазу в париетальных клетках, за счет чего подавляют секрецию соляной кислоты. В эрадикационных схемах рекомендованы высокие дозы ингибиторов протонной помпы до 80 мг омепразола в сутки, что эффективнее низких доз [74].

Калий конкурентные блокаторы протонной помпы обратимо связывают ионы калия и блокируют H+ K+ АТФазу, ингибируя кислотную секрецию, препараты действуют очень быстро и эффективны с первой дозы. На фармацевтическом рынке выпущены ревапразан, вонопразан, тегопразан. 10 мг вонопразана эквивалентно 60 мг омепразола [11, 30].

Вонопразон в 350 раз мощнее, чем ингибитор протонной помпы ланзопразол, благодаря способности аккумулировать в слизистой тела желудка, особенно, в париетальных клетках [56].

В феврале 2015 г, вонопразон впервые появился на рынке в Японии для лечения кислотных заболеваний и в дополнение к эрадикационной терапии Helicobacter pylori. В мае 2022 года Управление по санитарному надзору и качеством пищевых продуктов и медикаментов США одобрило вонопразан в комбинации с амоксициллином и кларитромицином для лечения Helicobacter pylori. Исследования показали, что тройная терапия вонопразона с амоксициллином и кларитромицином достигает 90% эрадикации [11].

Вонопразон метабилизируется несколькими изоформами цитохрома P450 (CYP) CYP3A4, в меньшей степени CYP3A5, CYP2B6, CYP2C19, CYP2C9 and CYP2D6. Сульфо - и глюкоронозил –трансферазы участвуют в метаболизме вонопразона [11].

Антибактериальные препараты, в том числе амоксициллин, применяются 1000 мг 2 раза в сутки, в рекомендованных суточных дозах (2000/сут) в сочетании с кларитромицином (500 мг 2 раза) или джозамицином (1000 мг 2 раза в день) или нитроксазидом (400 мг 2 раза в день) в течение 14 дней [69].

Во всех эрадикационных схемах предложено применение амоксициллина, несмотря на то, что во всех странах растет антибиотикорезистентность Helicobacter pylori к клартитромицину, метронидазолу, тетрациклину, хинолону, макролидам [48], однако не описано устойчивости Helicobacter pylori к амоксициллину.

В течение 30 лет амоксициллин входит в различные эрадикационные схемы, несмотря на это Helicobacter pylori не смог адаптироваться к воздействию пенициллина [31].

Антибиотик амоксициллин относится к группе полусинтетических пенициллинов широкого спектра действия. Амоксициллин бактерициден в отношении аэробных грамположительных бактерий: Staphylococcus spp. (за исключением штаммов, продуцирующих пенициллиназу), Streptococcus spp.; аэробных грамотрицательных бактерий: Neisseria gonorrhoeae, Neisseria meningitidis, Escherichia coli, Shigella spp., Salmonella spp., Klebsiella spp. Амоксициллин активен в отношении аэробных грамположительных бактерий, в комбинации с метронидазолом активен в отношении Helicobacter pylori [1,10], данная комбинация тормозит развитие устойчивости к метронидазолу бактерии Helicobacter pylori.

При пероральном приеме амоксициллин всасывается из желудочно-кишечного тракта и не разрушается в кислой среде желудка. Максимальная концентрация препарата в крови достигается через 1-2 ч. При в/в, в/м введении и пероральном приеме в плазме достигаются сходные концентрации препарата. Амоксициллин широко распределяется в тканях и жидкостях организма, сообщается о высоких концентрациях амоксициллина в печени [1, 10].

Около 60% дозы выводится в неизмененном виде с мочой путем клубочковой фильтрации и канальцевой секреции. Некоторое количество амоксициллина определяется в кале [10].

Амоксициллин выпускается в капсулах в дозе 250 мг, 500 мг, в таблетках – в дозе 250 мг, 500 мг, 1000 мг, в диспергируемых таблетках 125 мг, 250 мг, 500 мг, 750 мг, 1000 мг [1, 10].

Общепринятая стандартная расфасовка антибактериальных препаратов (в том числе амоксициллина) обеспечивает поступление per os лекарственного средства в организм, но создает суммарно крайне непродолжительный по времени и ограниченный по кратности (2 раза в сутки) непосредственный прямой контакт с инфекционным агентом Helicobacter pylori в местах его обитания. В 2022 году *Нургалиевой Б.К., Енокяном С.Г., Искаковым Б.С.* предложена контурная ячейковая упаковка для максимального длительного прямого контакта антибактериального препарата – амоксициллина с инфекционным агентом – Helicobacter pylori в местах сосредоточения последнего – в желудке [2].

Режимы эрадикации Helicobacter pylori подбирались эмпирически, учитывалась резистентность Helicobacter pylori, доступность препаратов, до сих пор ведутся поиски оптимальной эрадикационной терапии [8,9].

Предложено несколько типов эрадикации – тройная терапия, квадритерапия с висмутом, квадротерапия без висмута, терапия с левофлоксацином, с висмутом и левофлоксацином, терапия второй линии, терапия третьей линии.

Трехкомпонентная эрадикационная терапия Helicobacter pylori включает комбинации больших доз ингибитора протонной помпы с кларитромицином и метронидазолом, (тинидазол) или комбинацию больших доз ингибитора протонной помпы с кларитромицином и амоксициллином.

В регионах с высокой резистентностью к кларитромицину рекомендована 14 дневная терапия с препаратами висмута в качестве первой линии [51].

Двухнедельная трехкомпонентная эрадикационная терапия доказала свою эффективность в сравнении с однонедельной эрадикационной терапией. *Jiaofeng Wang с соавторами* (2015) пролечили 267 пациентов с хеликобактерной инфекцией в течение 14 и 7 дней, двухнедельная эрадикационная терапия позволили достичь более высокого процента эрадикации в сравнении с семидневной эрадикационной терапией (95% и 81%) [33].

Проведенное в Испании многоцентровое исследование OPTRICON выявило 82,3 % эрадикации при 14 дневном трехкомпонентном курсе [51].

Последовательная антибиотикотерапия Helicobacter pylori состоит из комбинации ингибитора протонной помпы с амоксициллином в течение 5-7 дней, затем назначением второго антибиотика. Последовательная терапия улучшает результат эрадикации за счет ослабления клеточных стенок при лечении амоксициллином, что позволит использовать более высокие концентрации кларитромицина. Хотя данный режим может вызвать и устойчивость микроорганизма. *Nyssen O. со соавторами* выявила эффективность последовательной терапии в сравнении со стандартной тройной эрадикационной терапии Helicobacter pylori у пациентов с устойчивостью к кларитромицину. Однако этот режим эрадикации и стандартная трехкомпонентная терапия не позволили достичь эффективной эрадикации, чем эмпирический подбор антибиотика после определения чувствительности [37,54].

Предложены различные варианты тройной терапии комбинация ИПП и двух антибиотиков, амоксициллина (2000мг в сутки) и кларитромицина (1000 мг в сутки), амоксициллина (2000 мг в стуки) и джозамицина (2000 мг в сутки) или нифуратела (800 мг в сутки), амоксициллина и метронидазола, амоксициллина и левофлоксацина. Левофлоксацин ипользуется во второй линии терапии, однако, в последнее время пишут о резистентности Helicobacter pylori к левофлоксацину в 37%. Во второй линии терапии комбинация с левофлоксацином позволяет достичь эрадикации от 78 до 92% [23, 28, 38, 41, 53].

При назначении квадротерапии к трехкомпонентной терапии добавляют препараты висмута в дозе 480 мг, квадротерапия позволяет повысить эффективность эрадикации до 80%.

Терапия первой линии основана на использовании кларитромицина, амоксициллина и метронидазола в течение 14 дней, эффективность терапии 80-85% [18, 19, 45].

Терапия второй линии основана на квадротерапии (ИПП, препараты висмута, метронидазол и тетрациклин) в течение 14 дней. Эта схема может использоваться как терапия первой линии[18, 19, 45].

Терапия третьей линии комбинация ИПП, амоксициллина и леваофлоксацина в течение 14 дней.

Рекомендуются более высокие дозы левофлоксацина 500 мг дважды в день[18, 19, 45].

Терапия четвертой линии состоит из ИПП с ампициллином и рифабутином. Длительность терапии от 10 до 14 дней. В США комбинированная таблетка омепразола, амоксициллина и рифабутина производится с 2019 года [29, 71].

Резистентность к эрадикационной терапии

Неудачи в эрадикации Helicobacter pylori объясняются устойчивостью к антибиотикам. Резистентность к антибиотикам увеличилась в последние 20 лет, что объясняется широким потреблением антибиотиков населением [13, 49].

Антибиотик, к которому in vitro у Helicobacter pylori выявлена резистентность, включается в режим эрадикации. Проведенное исследование показало, что когда ин витро есть устойчивость к кларитромицину или лефлоксацину, неудача эрадикации увеличивается в 7 раз. Устойчивость к нитроимидазолу ин витро имеет меньший клинический эффект, увеличивая неудачу эрадикации в 2.5 раза [62].

Доминанатный молекулярный механизм, ответственный за устойчивость H. Pylori, к клартромицину выявлен в одной из трех мутаций в 23S рибосомальной единице, к левофлоксацину (мутации ДКН гиразе в А локусе), к амоксициллину (мутации в пенициллин связанном белке), к тетрациклину (мутации в про B, beta единице гене полимеразы РНК) [27].

Устойчивость к нитроимидазолу – более сложный механизм, это связано с мутацией в rdxA, в гене, кодирующем нитроредуктазу, которая активирует нитроимидазол (например, метронидазол), из состояния пролекарство. Сложность мутации в гене rdxA и возможная синергия с другими окислительными реакциями, связанными с генами Helicobacter pylori, исключает тестирование молекул на мутацию для определения устойчивости. Это объясняет низкую ценность определение устойчивости к метронидазолу ин витро [66].

Проведенный мета-анализ, основанный на обследовании 50 000 пациентов, из 45 стран, выявил, что первичная резистентность к кларитромицину колеблется от 10 до 34%, к левофлоксацину - от 11 до 30%, к метронидазолу - от 23 до 56%. После неудачной эрадикации H. Pylori (вторичная резистентность) увеличивается к кларитромицину от 15 до 67%, к левофлоксацину от 30 до 65%, к метронидазолу от 30 до 65%. Однако выявлена низкая резистентность H. Pylori (менее чем у 5 % штаммов) к амоксициллину 1-2% [25, 29, 66].

Отсутствие приверженности терапии у пациентов может способствовать неудаче эрадикации. Исследования подтвердили, что приверженность эрадикационной терапии более 60% и 90% способствует успешной эрадикации H. Pylori. Люди могут пропускать прием препаратов из-за сложности проглотить большую таблетку, из-за побочных эффектов и плохой коммуникации с работниками здравоохранения и отсутствием понимания для чего предписано данное лечение [16].

Генетические особенности объясняют рефрактерность эрадикационной терапии, полиморфизм влияет на CYP2C19, IL-1B and MDR1, что соответствует успешной эрадикации. H. Pylori чувствителен к антибиотикам, когда интрагастральный pH колеблется от 6 до 8, оптимальный pH для для репликации H. Pylori. Некоторым антибиотикам, таким как кларитромицин и амоксициллин, требуется супрессия выработки интрагастральной кислоты для максимальной эффективности [22].

Учитывая, что часто встречаются фенотипы CYP2C19, нужен эмпирический выбор стратегии, подавляющий секрецию соляной кислоты, для эрадикации H. Pylori потребует более высоких ингибиторов протонной помпы (ИПП), использование ингибиторов следующего поколения, более эффективных и выбор мощных, чем ИПП кислотосупрессоров, таких как вонопразан [66].

Не к генетическим факторам, влияющим на неуспешность эрадикации, относятся возраст, курение. У курящих пациентов вдвое выше резистентность H. Pylori, чем не у курящих. Курение увеличивает кислотную секрецию, нарушает слизистую секрецию и кровоток желудка, что снижает доставку антибиотика [70].

Также резистентность H. Pylori объясняется генетической разнообразностью микроорганизмов, эти механизмы включают уклонение от ответа организма хозяина, повреждением желудочной среды, увеличением бактериальной нагрузки, вирулентностью, с последующим повреждением гистопатологии желудка, устойчивостью к антимикробным средствам [17, 50].

Алгоритм лечения зависит от наличия и отсутствия аллергии на пенициллин. Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США рекомендуют в случае неудачи эрадикационной квадротерапии, основанной на использовании висмута, использовать тройную терапию, основанной на левофлоксацине и на рифабутине с высокими дозами ИПП и амоксициллином, или альтернативную квадротерапию с висмутом, в качестве второй линии. В связи с ростом устойчивости к левофлоксацину, левофлоксацин не может быть назначен до тех пор, пока не будет установлена чувствительность, это же правило распространяется на кларитромицин [18].

Резистентность к рифабутину и амоксициллину в составе тройной терапии очень редка. Недавние исследования показывают, что добавление рифабутина к высоким дозам амоксициллину и ИПП, улучшает процент эрадикации значительно. Длительное лечение высокими дозами в течение 14 дней более эффективно для лечения рефрактерной H. Pylori – ассоциированной инфекцией [18].

В течение десятилетий бактерии и вирулентные антигены такие как UreB, VacA, CagA, and HspA используются для создания цельных вакцин, векторных, субъединичных вакцин, вакцин нуклеиновой кислоты, эпитопов. 3 фаза исследования, проведенная в Китае (дети, 4464), заключила, что эффективность оральной рекомбинатной вакцины H. Pylori достигла 71,8% в первый год и снизилась до 55% во второй год [80].

В дальнейшем необходимы исследования по изучению эффективности антихеликобактерных вакцин.

Заключение

Helicobacter pylori ассоциирован с хроническим гастритом, язвенной болезнью, раком желудка, MALT лимфомой. Для выявления Helicobacter pylori рекомендованы инвазивные и неивазивные методы диагностики, к золотому стандарту отнесены 13 С дыхательный уреазный тест, выявление антигена Helicobacter pylori в кале, гистологический метод.

Для эрадикационной терапии Helicobacter pylori предложены 4 линии тройной и квадротерапии, основанной на использовании больших доз ИПП, двух антибиотиков и препарата висмута.

В последние годы развилась резистентность Helicobacter pylori к различным антибиотикам, что привело к проблемам эрадикации. Безуспешная эрадикация связана с генетическими особенностями, полиморфизмом цитохромов и интерлейкинов, вирулентностью штаммов Helicobacter pylori, отсутствием приверженности к лечению, поведенческими рисками.

В новых схемах эрадикации предложено использование калий конкурентных блокаторов протонной помпы, которые в 350 раз мощнее ИПП. При резистентности Helicobacter pylori к антибиотикам, рекомендовано определение чувствительности. В последнее десятилетие разрабатывается вакцина против Helicobacter pylori. Разработка вакцины является перспективным направлением для предотвращения развития Helicobacter pylori ассоциированных заболеваний.

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CLINICAL CASE: POSTSTREPTOCOCCAL ARTHRITIS ASSOCIATED WITH COVID-19

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Abstract

Introduction: Poststreptococcal arthritis associated with COVID-19 is a rare but severe inflammatory condition that arises following a prior COVID-19 infection, contributing to complications of a preceding streptococcal infection. It serves as an example of how COVID-19 may precede and trigger autoimmune diseases. In recent years, there has been an increase in cases associated with infections linked to COVID-19, highlighting the importance of studying the long-term health consequences of the pandemic and the rising incidence of infectious disorders.

The purpose of the study: To draw the attention of rheumatologists, general practitioners, and infectious disease specialists to the risks of developing autoimmune diseases following COVID-19 infection, as well as to emphasize the importance of early diagnosis, prevention, and comprehensive management of COVID-19 to minimize long-term complications, including autoimmune disorders.

Materials and Methods: To diagnose this condition, patient anamnesis and clinical-laboratory data were collected. Additionally, a review of global publications from the last five years was conducted, examining the role of COVID-19 as a precursor to autoimmune diseases and a predictor of complications from various infectious diseases that may lead to autoimmune pathology.

Results: Based on anamnesis, clinical and laboratory, instrumental data a diagnosis of poststreptococcal arthritis associated with COVID-19 was established. The investigation results confirmed the presence of an inflammatory (streptococcal) process related to a previous COVID-19 infection, suggesting a possible link between past infection and the development of an autoimmune disorder.

Conclusions: COVID-19 causes a cytokine storm, leading to a decrease in T-lymphocyte levels, suppression of cellular immunity, and increased susceptibility to other infections. In this clinical case, poststreptococcal arthritis developed in a patient with laboratory-confirmed immune alterations following COVID-19. This case underscores the importance of primary and secondary prevention of infectious diseases, as well as the necessity of monitoring the immune status of patients who have recovered from COVID-19 to ensure timely detection and treatment of potential autoimmune complications.

Keywords: *COVID-19, poststreptococcal arthritis, autoimmune diseases.*

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Резюме

КЛИНИЧЕСКИЙ СЛУЧАЙ: ПОСТСТРЕПТОКОККОВЫЙ АРТРИТ АССОЦИИРОВАННЫЙ С COVID-19

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Введение: Постстрептококковый артрит, ассоциированный с COVID-19, представлет собой редкое воспалительное заболевание суставов, появляющееся на фоне предшествующей инфекции COVID-19, что привело в свою очередь к осложнению перенесённой стрептококковой инфекции. Данный момент показывает один из примеров того, что COVID-19 может быть предиктором аутоиммунных заболеваний. После пандемии за последние годы прослеживается уровень роста случаев инфекций, аутоиммунных заболеваний, связанных с COVID-19, что демонстрирует значимость изучения и наблюдения долгосрочных следствий.

Цель: Привлечь внимания ревматологов, врачей общей практики и инфекционистов к рискам развития аутоиммунных заболеваний на фоне перенесенной инфекции COVID-19, а также акцентировать важность ранней диагностики, профилактики и комплексного лечения COVID-19 с целью минимизации продолжительных осложнений, включая аутоиммунные расстройства.

Материалы и методы: Для диагностики данной патологии были собраны анамнестические и клинико-лабораторные данные пациента. Проведен обзор мировых публикаций за последние 5 лет, в которых рассматривается роль COVID-19 как предиктора аутоиммунных заболеваний и осложнений разнобразных инфекционных заболеваний, которые могут привести к развитию аутоиммунной патологии.

Результаты: На основании анамнеза, клинико-лабораторных и инструментальных данных был поставлен диагноз: постстрептококковый артрит, ассоциированный с COVID-19. Результаты обследования подтвердили наличие воспалительного процесса (стрептококкового), связанного с перенесенной инфекцией COVID-19, что показывает вероятную связь между перенесенной инфекцией и развитием аутоиммунного расстройства.

Выводы: COVID-19 вызывает цитокиновый шторм, что в свою очередь приводит к снижению уровня Т-лимфоцитов, угнетению клеточного иммунитета и повышенной восприимчивости к другим инфекциям. В данном клиническом случае на фоне перенесенного COVID-19 и снижения иммунной активности у пациента развился постстрептококковый артрит. Этот случай показывает важность первичной и вторичной профилактики инфекционных заболеваний, также необходимость мониторинга иммунного статуса пациентов, перенёсших COVID-19, для своевременного выявления и лечения возможных аутоиммунных осложнений.

Ключевые слова: *COVID-19, постстрептококковый артрит, аутоимунные заболевания.*

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Түйіндеме

КЛИНИКАЛЫҚ ЖАҒДАЙ: COVID-19- АССОЦИРЛЕНГЕН СТРЕПТОКОККТАН КЕЙІНГІ АРТРИТ

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Кіріспе: COVID-19-бен ассоцирленген стрептококктан кейінгі артрит, COVID-19 инфекциясы аясында стрептококк инфекциясының асқынуына алып келген, сирек кездесетін буындардың қабынулық ауруы. Осы клиникалық жағдай COVID-19 аутоиммунды аурулардың ізашарлығының бір мысалы. Пандемиядан кейінгі соңғы жылдар инфекциялардың, сондай-ақ COVID-19-мен байланысты аутоиммунды аурулардың өсуі байқалды, бұл өз кезегінде COVID-19-дың ұзақ мерзімді салдарларын зерттеу мен бақылаудың өзектілігін көрсетеді.

Зерттеудің мақсаты: COVID-19 инфекциясы аясында аутоиммунды аурулардың даму қауіптілігіне ревматологтардың, жалпы тәжірибелік дәрігерлердің, инфекционистердің назарын аудары, сондай-ақ COVID-19 нәтижесінде қалыптасатын ұзақ мерзімді асқынулар және аутоиммунды бұзылыстрады азайту мақсатында, COVID-19-дың ерте диагностикасына, профилактикасына, кешенді еміне аса жоғары мән беру қажет.

Материалдар мен әдістер: Осы патологияны диагностикалау үшін науқастың анамнездік және клиникалық-зертханалық деректері жиналды. Сондай-ақ, соңғы 5-жылдық әлемдік COVID-19 аутоиммунды аурулардың ізашары және аутоиммунды патологияның дамуына әкелуі мүмкін әртүрлі жұқпалы аурулардың асқынуларының болжаушысы рөлін қарастырылған соңғы 5-жылдағы әлемдік басылымдарға шолу жасалды.

Нәтижелер: Анамнезді, клиникалық-зертханалық және аспаптық деректерді бағалау негізінде COVID-19-бен аасоцирленген стрептококктан кейінгі артрит диагнозы қойылды. Зерттеулер нәтижелері COVID-19 инфекциясымен байланысты қабыну процесінің (стрептококктық) болуын растады, бұл бастан өткерген инфекция мен аутоиммундық бұзылыстың дамуы арасындағы ықтимал байланысты көрсетеді.

Қорытындылар: COVID-19 Т-лимфоциттер деңгейінің төмендеуіне, жасушалық иммунитеттің тежелуіне және басқа инфекцияларға сезімталдықтың жоғарылауына алып келетін «цитокиндік дауылды» тудырады. Осы клиникалық жағдайда COVID-19 және иммундық белсенділіктің төмендеуі аясында науқаста стрептококктан кейінгі артрит дамыды. Бұл жағдай жұқпалы аурулардың бірінішілік және екіншілік профилактикасының маңыздылығын, сонымен қатар COVID-19-ды басынан өткерген науқастардың иммундық жағдайын бақылау арқылы аутоиммунды асқынулардың уақытылы анықталуы мен емінің қажеттілігін көрсетеді.

Түйінді сөздер: *COVID-19, стрептококктан кейінгі артрит, аутоиммунды аурулар.*

Дәйексөз үшін:

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Introduction

Post-streptococcal arthritis is an inflammatory joint disease that develops after a streptococcal infection, most often after pharyngitis or tonsillitis caused by group A streptococcus (Streptococcus pyogenes). The development of the disease is associated with the body's immune response to streptococcal antigen, which leads to the formation of autoantibodies and activation of inflammatory processes in the joints. Clinically, PSA is manifested by pain and swelling in one or more large joints, such as the knee and ankle, and is usually self-limiting, disappearing after a few weeks [1,8,10,6].

The relationship between infections like COVID-19 and the emergence of autoimmune disorders has drawn the attention of the medical community in recent years. The SARS-CoV-2 virus causes coronavirus infection (COVID-19), which can cause damage to many organs and systems and range in clinical manifestation from asymptomatic to severe. Pathogenetically, COVID-19 causes endothelopathy, systemic inflammatory responses, and hyperactivity of the coagulation cascade, which can result in organ failure and micro- and macrothrombosis [2,3,4,11,12,5,13].

Recent research suggests that COVID-19 may be linked to the development of infectious diseases, including arthritis, after a streptococcal infection. Although there are studies on poststreptococcal arthritis, they don't look at how it relates to SARS-CoV-2. Poststreptococcal arthritis linked to COVID-19 is an uncommon clinical condition that has not received enough attention and requires more research, including thorough diagnostic evaluation and elucidation [8,2,9,3,4,11,5,7].

In this paper, we describe a case of PSA in a patient who had been infected with COVID-19, which apparently served as a trigger factor for the activation of inflammatory processes, followed by the development of persistent arthritis [2,9,4,12,7].

Details of the patient:

On November 8, 2024, a 37-year-old male patient named R. complained of upper and lower extremity joint pain, lower limb muscle pain, morning stiffness that lasted for up to two hours, nodular skin eruptions on the lower extremities (mostly on the thigh and varying in size), fatigue, fever up to 38.5°C, sweating, and weakness.

Patient History:

The patient was under the care of dermatologists since July 2024 for hidradenitis, which initially responded well to treatment. In August, he received a three-day course of antibiotics (Spiramycin 3 million IU once daily) for purulent tonsillitis, but he discontinued the medication prematurely. The patient claims that discomfort and swelling started to occur in August following a skin injury (following shaving) in the left axillary area, which led to a repeated visit to the dermatologist. After applying disinfectant ointments, the condition improved. Painful, tiny, reddish-tinted nodules first emerged on the left leg in September 2024. But it wasn't until October 2024 that the patient sought a rheumatologist's advice and had more tests: ASLO = 1404.83 U/ml, RF = 9.39 UI/ml, and CRP = 10.74 mg/L. Despite taking acyclovir, ibuprofen, and diclofenac as part of the suggested treatment, no improvement was seen. Then things got worse: the erythema got worse and the temperature rose to 37.5°C. The patient was therefore reassessed by a rheumatologist in October 2024 and given antibiotic medication, which did not result in a favorable outcome. Over time, the condition further deteriorated, with the onset of pain in all joints, an increase in erythema size, prompting another rheumatology consultation. A preliminary diagnosis of Erythema Nodosum? was made. Nonsteroidal anti-inflammatory drugs (NSAIDs), methylprednisolone pulse therapy at a dose of 250 mg × 3, and medicine that improve peripheral vascular system microcirculation were all part of the treatment plan, although they had little impact. Joint condition worsened, limiting movement, skin eruptions grew, and new painful erythematous lesions developed despite the continued medication. Additionally, the patient experienced crusting, nasal congestion, and axillary and cervical lymph node enlargement. When D-dimer levels reached 2700 ng/mL, the patient had to be admitted to the therapeutic unit. Further examinations revealed positive PCR for Epstein-Barr virus, positive ELISA for Epstein-Barr virus NA-IgG (2.133), CMV IgG (2.932), and SARS-CoV-2 IgG/IgM (223 AU/mL). A consilium was conducted with the participation of a therapist, hematologist, and infectious disease specialist, resulting in the diagnosis of reactive arthritis, cutaneous anginitis, long COVID-19, chronic Epstein-Barr virus infection, and chronic cytomegalovirus infection. Suspicion of lymphogranulomatosis, lymph node disease, viral infections, and possibly a special form of systemic vasculitis. Recommended: lymph node biopsy, antibiotic therapy (received three times) without positive effect. The patient was then consulted by an oncologist with suspicion of systemic vasculitis, who recommended a follow-up consultation with a rheumatologist. As a result, the patient was hospitalized in the Center for Internal Medicine of KazNMU named after S.D. Asfendiyarov in the somatic department (rheumatology profile) for verifying diagnosis and treatment planning.

Based on the medical history of the patient:

There were no chronic illnesses found. Any prior procedures or injuries are denied by the patient. Additionally, he rejects sexually transmitted infections, viral hepatitis, and tuberculosis. No noteworthy family medical history exists. The only noted harmful habit is smoking—up to one pack of cigarettes per day. No past infusions of blood. The patient has a history of chronic herpes infection, with frequent exacerbations manifesting as herpes labialis (cold sores on the lips).

Epidemiological history:

The patient and his spouse reside in a private home. He visited Turkey in August. He visited hot springs just before being unwell, when he became hypothermic, which might have been a contributing role to the worsening of his health.

Physical examination:

The patient's general condition was assessed as moderately severe, attributed to joint pain, overall pain syndrome, and signs of intoxication. Consciousness is clear, and he responds appropriately to questions. At the time of examination, body temperature was 37.1°C. Height: 189 cm, weight: 86 kg, BMI: 24.08 kg/m² (within normal range). Skin: On the right shin and forearms, there are hyperpigmented reddish rashes with subcutaneous induration of various sizes, painless, with periodic localized temperature increases over the erythema. On the dorsal

surface of the right hand and right foot, there are erythematous rashes with calloused edges, also painless. Lymph nodes: Enlargement of cervical and axillary lymph nodes on both sides, non-confluent, with the left axillary node being more prominent. Muscle tenderness in the lower extremities upon palpation.

Musculoskeletal System: Palpation reveals pain in the elbows, shoulders, knees, and ankle joints, though they are externally non-deformed. Grip strength is preserved in both hands. The palmar test and lateral compression test at the MCP, PIP, and wrist joints are negative. The elbow, shoulder, knee, and ankle joints appear normal externally. Crepitus is noted in the knees upon palpation. Range of motion is not restricted.

Respiratory System*:* It is free to breathe through the nose. The chest moves symmetrically during respiration and has a normal shape without deformities. Vocal fremitus is symmetrically transmitted. Percussion reveals normal lung sounds across all fields, and lung borders are within normal limits. Auscultation detects vesicular breathing without rales. Respiratory rate: 17 breaths per minute.

Cardiovascular System: The heart and peripheral vessels appear normal. Borders of relative cardiac dullness: right at the sternal edge 4th intercostal space, left 1 cm outside the midclavicular line, and upper at the 3rd intercostal space. The apical impulse is localized. Heart sounds are muffled but rhythmic. Heart rate: 78 bpm. Blood pressure: 120/70 mmHg.

Digestive System: The tongue is coated with a whitish plaque. The abdomen is of normal size, soft and painless upon palpation. The liver is at the costal margin. The spleen is not palpable. Bowel movements are regular, well-formed, and without pathological impurities.

Urinary System: There is no apparent change in the kidney area. Murphy's percussion test is negative bilaterally. Urination is free and painless.

Table 1.

Laboratory data. On admission to the hospital.

Test	Laboratory Findings
CBC dated 07.11.2024	Hemoglobin: 98 g/L (decreased), Erythrocytes: 3.35 × 10^6/L (decreased), Hematocrit: 29.2% (decreased), WBC: 17.59 × 10^9/L (elevated), Neutrophils: 77.6%, Basophils: 0.1%, Eosinophils: 0.2%, Lymphocytes: 14.3%, Monocytes: 7.8%, Platelets: 548 × 10^9/L (elevated), ESR: 97 mm/h. **An increased ESR, leukocytosis, mild anemia, thrombocytosis**
General urinalysis dated 07.11.2024	Color – yellow, transparent; Specific gravity – 1.030 (elevated); pH – 6.0; Protein – 0.1 g/L; Glucose – negative; Ketone bodies – negative; Bilirubin – negative; Urobilinogen – negative; Nitrites – negative; Leukocytes – negative; Blood – 0.3 mg/L; Ascorbic acid – 20 mg/dL. Microscopic examination: Squamous epithelium: <1 per field of view Transitional epithelium: 1 per field of view Renal epithelium: 0 per field of view Leukocytes: 2 per field of view Unchanged erythrocytes: 1 per field of view Granular casts: 0 per field of view Hyaline casts: 0 per field of view Mucus: +++ Phosphates: negative Oxalates: negative Urates: negative Bacteria: negative Fungi: negative Uric acid crystals: negative Notes: Parameters are within normal limits. Total urine protein – 0.36 g/day (within normal limits).
Biochemical blood analysis dated 06.11.2024.	**ALT - 74 U/L,** AST - 11 U/L, total bilirubin - 5.2 µmol/L, urea - 4.9 mmol/L, glucose - 5.9 mmol/L, creatinine - 70 µmol/L, CPK - 16 U/L (decreased), CPK-MB fraction - 17 U/L, LDH - 203 U/L, **CRP - 239.67 mg/L.** **Notes: Elevated ALT and CRP, decreased CPK**.
ASLO, RF, Ferritin dated 06.11.2024	**ASO: 1348 IU/L (elevated).** RF from 05.11.2024: 10.71 IU/mL. Calcium: 2.04 mmol/L. **Ferritin: 943.73 mg/L (elevated).**
Protein fractions dated 24.10.2024.	**Total protein - 50.2 g/L (decreased),** albumin - 41.8%, alpha1-globulin - 11.1%, alpha2-globulin - 18.7% (increased), beta-globulin - 5.6%, beta2-globulin - 6%, gamma-globulins - 16.8%, albumin/globulin ratio - 0.72 (decreased), M-gradient - 0%. Notes: Hypoproteinemia, dysproteinemia.
Coagulogram dated 05.11.2024.	APTT - 26.5 sec, **D-dimer - 2419 ng/mL** (increased), TT - 17.0 sec, fibrinogen - 8.44 g/L (increased), TT - 14.5 sec (increased), PI - 62.6%, INR - 1.28 (normal), **D-dimer elevated.**
Tumor markers dated 22.10.2024: Immunoblot dated 06.11.2024.	In normal range Negative
ELISA for quantitative determination of IgG/IgM antibodies to SARS-CoV-2 from 23.10.2024.	**223 AU/ml - positive.**
Bacterial culture from throat swab for microbiota dated 02.10.2024.	Dermacoccus nishinomiyaensis - 10^5 CFU/mL. Streptococcus parasanguinis - 10^5 CFU/mL.

Table 2.

Visual diagnostics data: On admission to the hospital.

Methods	Results
Chest X-Ray in 2 projections	No focal or infiltrative changes were detected in the chest organs based on the X-ray findings.
ECG	Sinus rhythm, ventricular contraction rate of 85 bpm, horizontal position of the electrical axis. Diffuse myocardial changes.
Soft tissue MRI	Conclusion: MRI signs of moderate hyperplasia of the right lobe of the thyroid gland.
Color Doppler mapping and pulsed-Doppler imaging of the lower limb vessels.	No hemodynamic disturbances in the lower limb vessels were detected.
MRI of the nasal cavity and paranasal sinuses.	CT signs of a polyp in the left maxillary sinus, to be differentiated from a cyst with mucinous content. Mucosal hyperplasia of the right maxillary sinus, ethmoid air cells, and sphenoid sinus.
Color Doppler mapping and pulsed-Doppler imaging of the brachiocephalic vessels.	No hemodynamic disturbances in the lower limb vessels were detected.
CT scan of the abdominal organs with bolus contrast injection using an automatic injector.	No convincing data on pathological formations in the abdominal cavity and retroperitoneal space were detected on CT scanning. Hepatosplenomegaly.
CT scan of the pelvic organs with bolus contrast injection using an automatic injector.	At the time of the study, no convincing CT data indicating pathological formations in the pelvis were detected. CT findings suggest a formation in the roof of the left acetabulum, with an aneurysmal bone cyst not excluded.
Assessment of renal blood flow based on color Doppler mapping. Assessment of renal blood flow based on color Doppler mapping.	No hemodynamic disturbances in the renal vessels were detected.

A specialist medical board consilium was conducted, establishing the diagnosis of post-streptococcal arthritis associated with COVID-19 was established. Pathogenetic therapy was prescribed, including glucocorticosteroids (methylprednisolone 20 mg per day), hydroxychloroquine 400 mg per day as a baseline therapy, a five-day course of antibiotics, immunomodulatory therapy (intravenous human immunoglobulin, Octagam, Bioven, three doses), protein preparations (albumin, three doses), and anticoagulant therapy (nadroparin calcium 0.4 mg subcutaneously).

Table 3.

Clinical and laboratory parameters at discharge.

Test	Results
CBC dated 15.11.2024.	**HGB - 109 г/л**; RBC - 3.46 10*12/l; CI - 0.95 -; HCT - 31.1%; MCV - 89.8 fL; MCH - 31.4 pg; MCHC - 35.2 g/dL; **PLT - 435 10*9/l;** PCT - 0.378%; **WBC - 10.37 10*9/l;** RDW-SD - 50.4 fL; RDW-CV - 15.1%; MPV - 8 fL; PDW - 15.5%; **%NEUT - 68.6%;** NEUT - 7.11 10*9/l; %EOS - 0.2%; EOS - 0.02 10*9/l; %BAS - 0.6%; BASO - 0.06 10*9/l; %MON - 4.9%; MONO - 0.52 10*9/l; %LYM - 25.7%; LYMPH - 2.66 10*9/l, **ESR - 45 mm/hour**; Note: Mild anemia, leukocytosis, neutrophilia, thrombocytosis. A trend toward a decrease in leukocytes, neutrophils, platelets, and ESR.
Biochemical blood analysis dated 15.11.2024.	Total protein - 71.9 g/L, ASO - 649 (trend towards decrease, initial level 1348 IU/mL), CRP - 18.2 mg/L increased (trend towards decrease, initial level 239.67 mg/L).
Coagulogram dated 14.11.2024.	APTT - 28.1 sec, INR - 1.15, Prothrombin time - 12.5 sec, Prothrombin index - 79%, Thrombin time - 36.2 sec increased, Fibrinogen - 4.8 increased. Note: Increased thrombin time and fibrinogen.
D-dimer dated 15.11.2024.	D-dimer 718 ng/mL (normal: 0.00–680.00) increased (trend towards decrease, initial level - **2419 ng/mL**).
Ferritin dated 15.11.2024.	581 mg/l (trend towards decrease, initial level - **943.73 mg/L**).

Throughout the ongoing therapy

Improvements have been observed throughout the course of the treatment, including the lack of intoxication and joint and pain disorders. The stiffness in the morning has gone, and sleep is peaceful. The general state of wellbeing has improved. Overall state: satisfactory. In an active posture. The mercury was 36.4°C. Breathing through the nose is free. There is no enlargement of the peripheral lymph nodes. Hyperpigmented brownish eruptions on the right shin and forearms have shrunk in size; they are palpably painless and do not cause a localized

rise in temperature. The oral mucosa is clean and the throat is quiet. No rales, vesicular breathing. Heart sounds are rhythmic and somewhat muffled. The BP is 110/80 mmHg. 81 bpm is the pulse rate. Soft and painless is the abdomen. Murphy's percussion test is negative bilaterally. The patient is discharged for further follow-up and treatment in outpatient settings at the place of residence. Recommendations are given.

Upon discharge, the following treatment is recommended: continuation of glucocorticosteroid therapy with methylprednisolone at 20 mg per day, maintenance therapy with hydroxychloroquine at 400 mg per day, bicillin-5 (benzylpenicillin) at 1.5 million IU once every two weeks until ASLO levels normalize, and clopidogrel at 75 mg per day until D-dimer levels normalize.

Discussion

Given the circumstances of the pandemic, this clinical case of post-streptococcal arthritis linked to COVID-19 poses a unique but noteworthy diagnostic difficulty. Due to several overlapping features, including symptoms of both post-COVID disorders and relapses of chronic infections, such as cytomegalovirus, Epstein-Barr virus, staphylococcal and streptococcal infections, the case demonstrates the difficulty of diagnosis [2,3,4,11,5].

Along with growing joint pain, signs of intoxication and inflammation, and symptoms indicative of chronic viral infections, the patient's overall health gradually declined. Since these symptoms are non-specific and can be linked to a number of illnesses, such as autoimmune diseases, viral infections, and inflammatory processes, they can make diagnosis more difficult. In this instance, prompt anamnesis collection and clinical evaluation were crucial in establishing a connection between the onset of post-streptococcal arthritis and the previous COVID-19 infection [8,9,3,10,4,12,6,7].

Comprehensive diagnostics, which include clinical and laboratory data, should receive special emphasis. In addition to confirming the existence of an active inflammatory process, the correlation of laboratory results such as CRP, ASLO, ferritin, D-dimer, and other indicators of inflammation and hypercoagulation also assisted in ruling out other potential diagnoses, such as sepsis or thrombosis. This emphasizes how crucial laboratory testing is for early detection and differential diagnosis, especially when it comes to COVID-19-related problems [1,10,6].

The diagnostic difficulty also stems from the fact that SARS-CoV-2 infection can result in post-COVID syndrome, which is characterized by a variety of long-term symptoms that continue after the acute phase of the illness. Similar to other autoimmune disorders linked to joint inflammation, arthritis in this instance most likely developed as a result of immunological dysregulation brought on by the prior COVID-19 infection, indicating a potential interplay between viral and infectious processes [2,9,3,4,11,12,7].

Conclusion

The correlation between COVID-19 and PSA emphasizes the necessity of closely monitoring patients who have recovered from the virus, particularly if joint symptom is present. The idea of an excessive immune response and the possible emergence of autoimmune illnesses in response to viral infections are also supported by this instance, highlighting the need for additional study to elucidate pathogenic pathways and create the best possible diagnostic and therapeutic approaches.

The significance of a thorough approach in the diagnosis and treatment of patients with post-COVID sequelae, especially uncommon inflammatory joint disorders, is thus underscored by this clinical example. It also emphasizes how important it is to raise doctors' knowledge of possible COVID-19 problems [4,7,13].

Study Limitations: *The single-center nature of the study may limit its generalizability, and the absence of long-term follow-up data restricts the assessment of post-discharge outcomes.*

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SYSTEMIC RETINOIDS IN THE MANAGEMENT OF MODERATE TO-SEVERE ACNE: A CLINICAL CASE STUDY

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Abstract

Introduction: Acne vulgaris is a multifactorial inflammatory disorder affecting about 9% of the global population, most commonly in those aged 20–29 years. Its pathogenesis involves follicular hyperkeratinization, sebaceous hyperactivity, and immune activation, leading to inflammation and scarring, requiring targeted treatments like retinoids.

The **aim** of this study is to assess the clinical effectiveness of acnekutan in managing severe acne.

Materials and Methods: A retrospective case review was conducted using medical records from the dermatovenerology department of City Hospital No. 2, Abai region. The patient's condition was monitored in the CMIS from 2024 to 2025, following clinical guidelines approved by the Ministry of Health of Kazakhstan. Signed informed consent was obtained from both the clinic administration and the patient for publication.

Results: After transitioning a patient with severe acne to isotretinoin, a significant clinical improvement was observed. The treatment effectively reduced inflammatory lesions and prevented the formation of new acne elements. Clinical studies have demonstrated that acnekutan targets multiple pathogenic mechanisms of acne and enhances patients' quality of life. In our study, the patient experienced side effects such as skin dryness and a temporary increase in transaminase levels, consistent with global research findings.

Conclusion: Isotretinoin remains the preferred treatment for severe acne, ensuring high efficacy and prolonged remission. Careful monitoring and individualized dosing are essential for optimal patient management. Future research should focus on dosing optimization, combination therapies, and treatment resistance mechanisms.

Keywords: *acne, isotretinoin, retinoids, inflammation, clinical case.*

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Резюме

СИСТЕМНЫЕ РЕТИНОИДЫ В ЛЕЧЕНИИ СРЕДНЕТЯЖЕЛЫХ И ТЯЖЕЛЫХ ФОРМ АКНЕ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Введение: Обыкновенные угри - это многофакторное воспалительное заболевание, которым страдают около 9% населения земного шара, чаще всего в возрасте 20-29 лет. Его патогенез включает в себя гиперкератинизацию фолликулов, гиперактивность сальных желез и активацию иммунитета, что приводит к воспалению и образованию рубцов, требующих целенаправленного лечения, такого как системные ретиноиды.

Цель: оценить клиническую эффективность акнекутана в лечении тяжелой формы акне.

Материалы и методы: был проведен ретроспективный анализ случая на основе медицинской документации дерматовенерологического отделения Городской больницы №2 УЗ области Абай. Состояние пациента отслеживалось в медицинской информационной системе КМИС в период с 2024 по 2025 год в соответствии с клиническими рекомендациями, утвержденными Министерством здравоохранения Республики Казахстан и соблюдением этических норм.

Результаты: после перевода пациента с тяжелым акне на изотретиноин отмечено значительное клиническое улучшение. Препарат эффективно уменьшал воспалительные элементы и предотвращал появление новых высыпаний. Клинические исследования подтверждают, что акнекутан воздействует на основные звенья патогенеза акне и способствует улучшению качества жизни пациентов. В нашем исследовании пациент испытывал побочные эффекты, включая сухость кожи и временное повышение уровня трансаминаз, что соответствует данным мировых исследований.

Заключение: Изотретиноин остается предпочтительным методом лечения тяжелой формы акне, обеспечивая высокую эффективность и длительную ремиссию. Важную роль играет тщательный мониторинг побочных эффектов и индивидуальный подбор дозировки. Перспективы дальнейших исследований включают оптимизацию режимов дозирования, оценку комбинированной терапии и изучение механизмов устойчивости к лечению.

Ключевые слова: *угревая болезнь, изотретиноин, ретиноиды, воспаление, клинический случай.*

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Түйіндеме

БЕЗЕУДІҢ ОРТАША ЖӘНЕ АУЫР ТҮРЛЕРІН ЕМДЕУДЕГІ ЖҮЙЕЛІК РЕТИНОИДТАР: КЛИНИКАЛЫҚ ЖАҒДАЙ

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Кіріспе: кәдімгі безеу-бұл жер шарының шамамен 9% әсер ететін көп факторлы қабыну ауруы, көбінесе 20-29 жаста. Оның патогенезі фолликулалардың гиперкератинизациясын, май бездерінің шамадан тыс белсенділігін және иммунитетті белсендіруді қамтиды, нәтижесінде қабыну және жүйелі ретиноидтар сияқты мақсатты емдеуді қажет ететін тыртықтар пайда болады.

Зерттеудің мақсаты: безеудің ауыр түрін емдеудегі акнекутанның клиникалық тиімділігін бағалау.

Материалдар мен әдістер: Абай облысының № 2 ДСБ Қалалық ауруханасының дерматовенерологиялық бөлімшесінің медициналық құжаттамасы негізінде жағдайға ретроспективті талдау жүргізілді. Пациенттің жағдайы Қазақстан Республикасы Денсаулық сақтау министрлігі бекіткен клиникалық ұсынымдарға және этикалық нормалардың сақталуына сәйкес 2024-2025 жылдар аралығында ҚМИС медициналық ақпараттық жүйесінде бақыланды.

Нәтижелер: ауыр безеумен ауыратын науқасты изотретиноинге ауыстырғаннан кейін айтарлықтай клиникалық жақсару байқалды. Препарат қабыну элементтерін тиімді түрде азайтып, жаңа бөртпелердің пайда болуына жол бермеді. Клиникалық зерттеулер акнекутанның безеу патогенезінің негізгі буындарына әсер ететінін және пациенттердің өмір сүру сапасын жақсартуға ықпал ететінін растайды. Біздің зерттеуімізде пациент жанама әсерлерді, соның ішінде құрғақ теріні және трансаминазалардың уақытша жоғарылауын бастан кешірді, бұл әлемдік зерттеулерге сәйкес келеді.

Қорытынды: изотретиноин жоғары тиімділік пен ұзақ мерзімді ремиссияны қамтамасыз ететін ауыр безеуді емдеудің таңдаулы әдісі болып қала береді. Жанама әсерлерді мұқият бақылау және дозаны жеке таңдау маңызды рөл атқарады. Әрі қарайғы зерттеулердің болашағы дозалау режимдерін оңтайландыруды, аралас терапияны бағалауды және емдеуге төзімділік механизмдерін зерттеуді қамтиды.

***Түйінді сөздер**: безеу ауруы, изотретиноин, ретиноидтар, қабыну, клиникалық жағдай.*

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Background

Acne vulgaris is a polymorphic, multifactorial dermatological disorder primarily driven by inflammation of the pilosebaceous unit [6]. Epidemiological data indicate that approximately 9% of the global population is affected, with 80–85% of cases occurring in individuals aged 12 to 24 years [25]. In recent years, a growing body of research has highlighted a shift in the age distribution of acne, with an increasing prevalence among individuals aged 20–29 years [5]. Given its primary localization on the face and trunk, acne can significantly impair patients' quality of life, negatively affecting self-esteem and contributing to the development of anxiety and depressive disorders [3].

The classification of acne is based on disease severity, which is determined by the number and type of inflammatory lesions, including papules, pustules, and nodules [2]. The etiology and pathogenesis of acne involve a complex interplay of intrinsic and extrinsic factors, ultimately resulting in chronic inflammation [29]. One of the earliest pathogenic events is follicular hyperkeratinization, characterized by excessive proliferation and impaired desquamation of keratinocytes, the superficial skin cells. This dysregulated keratinization leads to the accumulation of keratinocytes within the sebaceous gland ducts, culminating in follicular obstruction and the formation of comedones - the primary lesions of acne [8]. Another key pathogenic mechanism is sebaceous gland hyperactivity, which leads to increased sebum production. Sebum, a lipid-rich substance that prevents skin dryness, is regulated by androgens. Elevated androgen levels stimulate sebaceous gland hypertrophy and excessive sebum secretion, which in turn contributes to follicular occlusion and provides a nutrient-rich environment for *Cutibacterium acnes* proliferation. *C. acnes* produces lipases that hydrolyze triglycerides in sebum into free fatty acids, which exert a pro-inflammatory effect on keratinocytes and activate the immune response [12].

Beyond direct lipid metabolism, *C. acnes* also triggers innate immune activation, promoting the secretion of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α). The recruitment of immune cells - including neutrophils, macrophages, and lymphocytes - into the affected follicular unit further amplifies local inflammation. This process ultimately weakens the follicular wall, leading to rupture and extrusion of its contents into the surrounding dermis. The resultant inflammatory cascade contributes to the formation of nodules and cysts, which are frequently associated with post-inflammatory scarring [32]. Acne inflammation can be exacerbated by both endogenous and exogenous factors [14]. Endogenous contributors include hormonal fluctuations, particularly elevated androgen levels, which stimulate sebaceous gland hypertrophy and increase sebum production. Exogenous factors, such as inadequate skincare, the use of comedogenic cosmetics, mechanical irritation, and environmental pollutants, may further exacerbate inflammatory processes [4].

A thorough understanding of these pathogenic mechanisms is essential for selecting an appropriate and effective therapeutic strategy. Retinoids, derivatives of vitamin A, are among the few pharmacological agents capable of targeting multiple pathways in acne pathogenesis [9]. These compounds modulate epidermal turnover, normalize keratinocyte differentiation, and reduce hyperkeratinization, thereby preventing microcomedone formation. Additionally, retinoids interact with nuclear receptors, including retinoic acid receptors (RARs) and retinoid X receptors (RXRs), altering gene expression and counteracting follicular occlusion. Moreover, retinoids exhibit potent anti-inflammatory properties, making them effective in treating inflammatory acne lesions. They also modulate sebum production, reducing its secretion and preventing follicular obstruction [24].

First-line medications for the treatment of acne include retinoids (e.g., tretinoin, adapalene), as well as benzoyl peroxide and azelaic acid, which are used as topical therapy. In more severe cases, systemic agents such as oral antibiotics, hormonal therapy, and isotretinoin are prescribed in combination with topical treatment [13]. The U.S. Food and Drug Administration (FDA) has approved isotretinoin for the treatment of moderate to severe acne vulgaris that is resistant to other therapeutic options [26].

Objective of the study: to evaluate the clinical efficacy of acnekutan in the treatment of patients with severe acne.

Materials and Methods:

A retrospective case review was conducted using a patient's medical records from the dermatovenerology department of City Hospital No. 2, which is part of the Abai region's Health Department. From 2024 to 2025, the patient's condition was tracked by the comprehensive medical information system (CMIS). The diagnostic and therapeutic interventions followed the clinical recommendations approved by the Republic of Kazakhstan's Ministry of Health (Order No. 24, dated June 29, 2017). Both the clinic administration and the patient provided signed informed consent to publish treatment outcomes.

Case description.

Patient A., 18 years old, presented with complaints of persistent eruptions on the face, chest, and back, associated with tenderness, inflammation, and residual scarring and hyperpigmentation. The patient reported excessive skin oiliness, occasional pruritus, and psychological discomfort.

Medical history. The initial onset of acne occurred at the age of 14, characterized by moderate inflammatory lesions. By the age of 16, the condition had worsened, with the development of deep, painful nodules and cysts prone to suppuration and scarring. Previous treatments included topical agents (benzoyl peroxide, azelaic acid, and antibiotics) and systemic therapy (doxycycline), but these provided limited efficacy.

Life history. The patient was born at term and experienced normal growth and development. There is no history of chronic diseases or severe infections. The allergic history is unremarkable. The patient's diet is irregular, with a preference for fast food. No harmful habits were reported.

Physical examination.

General condition satisfactory, height 176 cm, weight 71 kg (normosthenic body type). Lymph nodes not enlarged. Respiratory system vesicular breath sounds, no rales. Cardiovascular system heart sounds muffled but rhythmic. Abdomen soft, non-tender. Bowel and urinary function unremarkable. Edema absent.

Status localis:

The skin of the face, upper back, and chest exhibited erythema with pronounced seborrhea. Numerous inflammatory lesions were observed, including nodules, cystic formations (up to 1 cm), papules, and pustules. Post-inflammatory hyperpigmentation and atrophic scars were noted on the cheeks and forehead. Open and closed comedones were present, along with signs of post-inflammatory skin thickening in affected areas.

Laboratory findings.

Complete blood count (05.02.2024): hemoglobin: 142 g/L, erythrocytes 4.5×10^{12}/L, leukocytes 5.1×10^{9}/L, lymphocytes 20%, monocytes 4%, eosinophils 3%, band neutrophils 3%, segmented neutrophils 72%, ESR 10 mm/h. Conclusion: Mild signs of inflammation. Blood test for syphilis (RW, 05.02.2024) negative. Urinalysis (05.02.2024): color straw yellow, pH acidic, specific gravity 1014, transparency, protein negative, glucose negative, epithelial cells 1–2 per field of view, leukocytes negative, bacteria negative. Conclusion: no pathology. Biochemical blood analysis (05.02.2024): total protein 87 g/L, urea 8.6 mmol/L, creatinine 84 μmol/L, bilirubin 14.80 μmol/L, cholesterol 4.13 mmol/L, glucose 4.3 mmol/L, AST 18.10 U/L, ALT 14.30 U/L, Conclusion: no pathology. Hormonal panel (12.02.2024): (TSH, Free T4, Testosterone, DHEA-S) within normal limits. Microbiological examination for demodicosis and fungal infection: negative.

Clinical Diagnosis: Severe Acne. Post-acne (atrophic scars, hyperpigmentation).

Treatment Plan and Management: Systemic therapy: isotretinoin (acnekutan) initiated at 0.5 mg/kg/day, with a gradual increase to 1 mg/kg/day. The total treatment duration is planned for 5–6 months, with mandatory monitoring of liver function and lipid levels every four weeks. Adjunctive skin care: Hydrating skincare with hypoallergenic creams to restore the hydrolipidic barrier. Use of broad-spectrum sunscreen (SPF 50+). Avoidance of aggressive cosmetic procedures (chemical peels, mechanical extractions, laser treatments). Dietary modifications: Reduction of fatty and spicy foods. Increased intake of protein and vegetables.

Follow-up visits: monthly assessments to evaluate treatment efficacy and adjust the dosage if necessary. Treatment outcomes are presented in Figure 1.

Discussion.

Isotretinoin is one of the most effective drugs for the treatment of severe acne, as confirmed by numerous clinical studies [7]. The results of our study demonstrated the high efficacy of isotretinoin in a patient with severe acne. The patient exhibited a significant reduction in inflammatory lesions, decreased sebum production, and an overall improvement in skin condition. These findings are consistent with the study by Layton et al. (2021), in which 80% of patients receiving isotretinoin at a dose of 0.5–1 mg/kg/day for 20–24 weeks achieved significant clinical improvement [20]. Furthermore, *Zaenglein et al.* (2018) reported that isotretinoin outperforms conventional treatment regimens, including antibiotics and topical retinoids, both in terms of efficacy and remission duration [31]. Similar conclusions were drawn in a meta-analysis by Huang et al. (2020), which reported a significant reduction in acne recurrence following isotretinoin treatment compared to antibiotic therapy [15]. Major clinical studies on the use of retinoids in acne therapy are summarized in Table 1.

Despite its high efficacy, isotretinoin therapy is associated with several adverse effects, including skin and mucosal dryness, dyspeptic disorders, and potential elevations in liver enzyme and blood lipid levels [27]. In our study, the patient experienced adverse effects such as skin dryness and transient elevation of transaminase levels, which aligns with the findings of Kaur et al. (2019), where similar side effects were observed in 70–80% of patients [17].

Isotretinoin is highly teratogenic, making its use strictly contraindicated during pregnancy. It is essential to thoroughly inform patients about the associated risks and the necessity of reliable contraception during treatment and for at least one month after its completion [1].

Another important aspect is the risk of recurrence after treatment discontinuation. In a study by Dréno et al. (2019), 20% of patients experienced a relapse within the first year after isotretinoin withdrawal, highlighting the need for individualized dosage selection and treatment duration [10].

Figure 1. Patient status localis Before and After treatment.

Table 1. **The key studies of the last decade highlighting the efficacy of retinoids in acne treatment**

Authors (Year of publication)	Publication Type	Retinoid type	Acne Type	Significance
Tan J. et al. (2016) [29]	Systematic Review	Oral	Severe inflammatory acne	Widely regarded as increasing remission potential
Zaenglein A.L. et al. (2016) [31]	Clinical guideline	Topical	Mild acne	A topical retinoid alone or in combination with antibiotic and/or BPO* is first-line therapy
Leyden J. et al. (2017) [22]	Review	Topical	Noninflammatory and inflammatory acne	Topical retinoids should be considered the foundation of acne therapy
Thiboutot D.M.et al. (2018) [30]	Clinical recommendations	Topical	Inflammatory and/or comedonal acne	A topical retinoid plus BPO* is first-line therapy
Kolli S.S. et al. (2019) [18]	Systematic review	Topical	Acne vulgaris	Should be used in combination with BPO* to optimize results in patients
Leung A.K. et al. (2021) [21]	Review	Topical/Systemic	- Mild-to-moderate acne vulgaris - Moderate-to-severe acne	- Topical retinoids are the drugs of choice - Systemic retinoids for refractory acne to topical therapies
Latter G. et al. (2021) [19]	Review	Topical/Systemic	- Mild-to-moderate acne vulgaris - Severe acne	- Topical retinoid as a first-line treatment - Oral retinoid for severe cystic acne
Eichenfield D.Z. et al. (2021) [11]	Review	Topical/Systemic	- Mild-to-moderate acne vulgaris - Severe acne	- Topical retinoids are first-line therapies - Systemic retinoids for severe cases
Mavranezouli I. et al. (2022) [23]	Systematic review and network meta-analysis	Systemic	Moderate-to-severe acne	Oral pharmacological – isotretinoin of total cumulative dose ≥ 120 mg kg−1 per single course
Huang C.Y. et al. (2023) [16]	Network Meta-Analysis	Systemic	Acne vulgaris	Oral isotretinoin is more effective than triple therapies containing a topical retinoid, BPO*, and an antibiotic

***BPO – benzoyl peroxide**

Conclusion.

Thus, isotretinoin remains the treatment of choice for severe acne, providing high clinical efficacy and prolonged remission. However, the need for side effect monitoring and individualized dosing underscores the importance of a comprehensive approach to patient management. Future research directions include optimizing dosing regimens, evaluating combination therapies, and investigating the molecular mechanisms underlying treatment resistance.

Conflict of Interest. *The authors declare that they have no conflict of interest.*

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ВАРИАНТ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ СИНОВИАЛЬНОЙ САРКОМЫ МЯГКИХ ТКАНЕЙ ЛИЦА

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Резюме

Введение. Саркомы составляют 1–2,5% всех злокачественных опухолей и характеризуются агрессивным ростом и высокой смертностью. Они могут возникать в различных органах, включая лицо. Лечение сарком включает хирургическое вмешательство, лучевую и химиотерапию. Радикальная резекция с сохранением функциональности и внешнего вида является приоритетным методом лечения.

Цель исследования. Описать редкий клинический случай бифазной синовиальной саркомы щеки, диагностированной после неоднократных операций, и проанализировать эффективность хирургического лечения.

Методы. Проведен анализ клинического случая пациента с рецидивирующей опухолью щеки, включающий клинико-рентгенологические, гистологические и иммуногистохимические исследования. Выполнена хирургическая резекция опухоли с пластикой дефекта.

Результаты. Представлен вариант хирургического лечения синовиальной саркомы мягких тканей лица распространившейся в ретромаксиллярную и подвисочную области, с использованием челюстно-лицевого доступа по Лауэрс-Балону, позволяющий рассчитывать на радикальное удаление опухоли с сохранением более нормальных контуров лица. Гистологический анализ подтвердил диагноз бифазной синовиальной саркомы. Операция позволила удалить опухоль с сохранением кожных покровов. Послеоперационный период прошел без осложнений.

Выводы. Дифференциальная диагностика сарком требует комплексного подхода. Радикальная резекция с последующей пластикой эффективна при лечении саркомы щеки, обеспечивая удовлетворительный функциональный и косметический результат.

Ключевые слова: *Саркома мягких тканей челюстно-лицевой области (ЧЛО), хирургическое лечение злокачественных опухолей (ЧЛО), компьютерная томография (КТ) опухолей ЧЛО.*

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Abstract

OPTION FOR SURGICAL TREATMENT OF SYNOVIAL SARCOMA OF FACIAL SOFT TISSUES

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Introduction. Sarcomas account for 1–2.5% of all malignant tumors and are characterized by aggressive growth and high mortality. They can occur in various organs, including the face. Treatment of sarcomas includes surgery, radiation and chemotherapy. Radical resection with preservation of functionality and appearance is a priority treatment method.

Objective. To describe a rare clinical case of biphasic synovial sarcoma of the cheek diagnosed after multiple surgeries and to analyze the effectiveness of surgical treatment.

Methods. An analysis of the clinical case of a patient with a recurrent cheek tumor was performed, including clinical, radiological, histological and immunohistochemical studies. Surgical resection of the tumor with defect plastic surgery was performed.

Results. A variant of surgical treatment of synovial sarcoma of facial soft tissues that has spread to the retromaxillary and infratemporal regions is presented, using the maxillofacial approach according to Lauers-Balon, which allows to count on radical removal of the tumor while preserving more normal facial contours. Histological analysis confirmed the diagnosis of biphasic synovial sarcoma. The operation allowed to remove the tumor while preserving the skin. The postoperative period passed without complications.

Conclusions. Differential diagnostics of sarcomas requires a comprehensive approach. Radical resection with subsequent plastic surgery is effective in the treatment of cheek sarcoma, providing a satisfactory functional and cosmetic result.

Keywords: *Soft tissue sarcoma of the maxillofacial region (MFR), surgical treatment of malignant tumors (MFR), computed tomography (CT) of MFR tumors.*

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Түйіндеме

БЕТТІҢ ЖҰМСАҚ ТІНДЕРІНІҢ СИНОВИАЛЬДЫ САРКОМАСЫН ХИРУРГИЯЛЫҚ ЕМДЕУ НҰСҚАСЫ

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Кіріспе. Саркомалар барлық қатерлі ісіктердің 1-2,5% құрайды және агрессивті өсумен және жоғары өліммен сипатталады. Олар әртүрлі органдарда, соның ішінде бетінде пайда болуы мүмкін. Саркоманы емдеу хирургияны, сәулеленуді және химиотерапияны қамтиды. Функционалдылығы мен сыртқы түрін сақтай отырып, радикалды резекция емдеудің басым әдісі болып табылады.

Зерттеудің мақсаты. Қайталанатын операциялардан кейін диагноз қойылған жақтың екі фазалы синовиальды саркомасының сирек кездесетін клиникалық жағдайын сипаттау және хирургиялық емнің тиімділігін талдау.

Әдістері. Клиникалық, радиологиялық, гистологиялық және иммуногистохимиялық зерттеулерді қоса алғанда, бетінің қайталанатын ісігі бар науқастың клиникалық жағдайы талданды. Ақаудың пластикалық операциясымен ісіктің хирургиялық резекциясы жасалды.

Нәтижелер. Беттің жұмсақ тіндерінің синовиальды саркомасының ретромаксилярлық және инфратемпоральды аймақтарға тараған хирургиялық емінің нұсқасы беттің қалыпты контурын сақтай отырып, ісіктерді түбегейлі жоюға мүмкіндік беретін Lauwers-Ballon жақ-бет тәсілін қолдану арқылы ұсынылған. Гистологиялық талдау екі фазалы синовиальды саркома диагнозын растады. Операция теріні сақтай отырып, ісіктерді алып тастауға мүмкіндік берді. Операциядан кейінгі кезең асқынусыз өтті.

Қорытындылар. Саркоманың дифференциалды диагностикасы кешенді тәсілді қажет етеді. Радикалды резекциядан кейін пластикалық хирургия қанағаттанарлық функционалды және косметикалық нәтиже беретін щек саркомасын емдеуде тиімді.

Түйінді сөздер: *Жақ-бет аймағының жұмсақ тінінің саркомасы (МФ), қатерлі ісіктерді хирургиялық емдеу (МФ), жақ-бет аймағының ісіктерінің компьютерлік томографиясы (КТ).*

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Введение

В структуре злокачественных опухолей саркомы составляют от 1 %, до 2,5% по различным данным, что относит их к редким [17]. Они очень опасны из-за агрессивности развития болезни и высокой смертности. Характеризуются быстрым ростом и склонностью к метастазированию [4, 15].

Встречаются в любых органах тела, ногах, плечах, туловище, реже на голове, шее от 5 до 9% случаев [17].

Формы и варианты сарком разнообразны, насчитывают несколько десятков, в зависимости от ткани, от которой они исходят [1].

В большинстве случаев лечение сарком комбинированное, включает хирургическое, лучевое и химиотерапию [7]. На выбор метода лечения влияет размер и расположение опухоли, степень злокачественности, а также распространенность процесса. Хирургия, как единственный метод лечения, может применяться только в том случае, если опухоль высокодифференцированная и возможно ее радикальное удаление.

Хирургическая резекция первичной опухоли является приоритетным компонентом лечения практически всех пациентов с саркомами мягких тканей. Резекция должна проводиться с захватом тканей, выходящих за пределы псевдокапсулы опухоли, если таковая есть, до достижения визуально здоровой, не вовлеченной в процесс ткани. В случаях хирургического лечения саркомы мягких тканей ЧЛО дополнительным условием является сохранение не только функциональных возможностей, но и нормальных контуров лица.

Клинический случай

Пациент Б., 28 лет, поступил в клинику с диагнозом: Рак кожи правой щечной области pT2N0M0 St II. Состояние после операции и лучевой терапии.

Из анамнеза известно, что в 2009 г. оперирован по поводу рака кожи правой щеки. В связи с рецидивом заболевания в декабре 2022г. повторно оперирован, произведено широкое иссечение опухоли кожи щеки. Гистология иссеченной опухоли - плоскоклеточная карцинома с изъязвлением, G3. В январе 2023г. в послеоперационном периоде получил курс близкофокусной лучевой терапии СОД 40Гр.

В мае 2024г в связи с повторным ростом опухоли обратился в Национальный центр онкологии в г.Астана.

При осмотре: На коже правой половины лица, в области щеки послеоперационные рубцы. Лицо несколько одутловато из-за наличия в толще мягких тканей щеки, под скуловым отростком, опухоли округлой-овальной формы, тугоэластической консистенции, размерами до 4,5х5,5см. При осмотре ротовой полости, на внутренней, щечной ее поверхности обширная, овально-округлая опухоль, распространяющаяся в ретромаксиллярную область и подвисочную ямку, задний отдел твердого неба, с распадом и некротической поверхностью. Альвеолярный отросток трех крайних зубов верхней челюсти также вовлечены в опухолевый процесс.

КТ-исследование

В поверхностной части жевательной мышцы справа определяется гиперваскулярное образование с четкими неровными контурами, размером около 4,2х3,1х5,2 см, плотностью до +48 ед. Х., с деструкцией медиальной стенки правой гайморовой пазухи, ветви правой нижней челюсти, височного отростка и альвеолярной дуги верхней челюсти справа. Обнаружены элементы остеолизиса костных стенок и незавершенного остеолизиса в опухолевой ткани. Сосудисто-нервный пучок шеи справа остается интактным. Шейные лимфоузлы справа увеличены до 1,0 см.

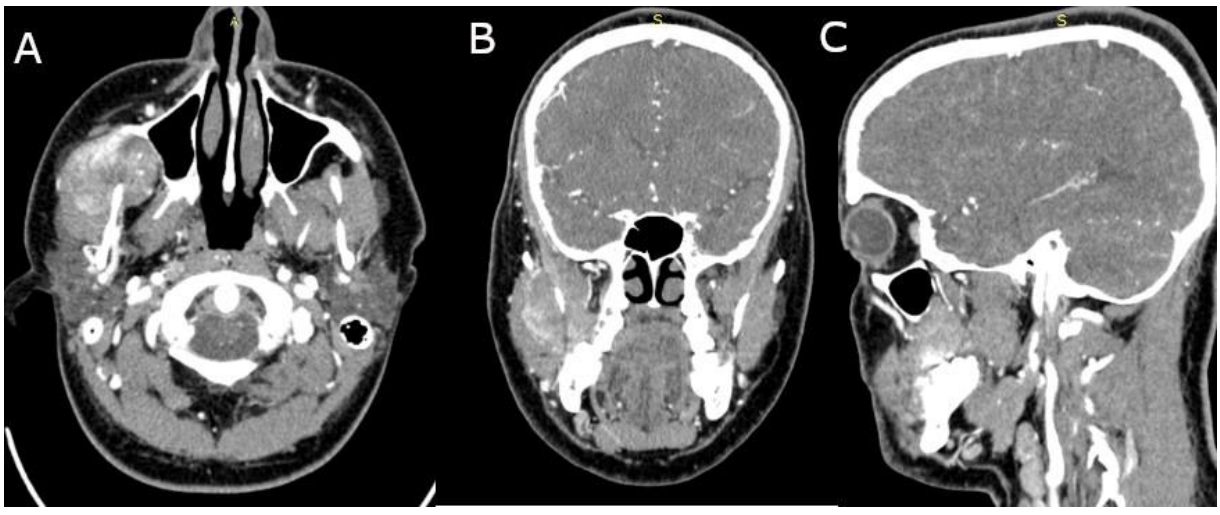

Рисунок 1. Компьютерная томография больного Б. /
(Figure 1. Computed tomography of patient B).

Пересмотр гистологических препаратов, ранее выполненной операции в 2022г, выявил несоответствие морфологии плоскоклеточной карциномы. Наличие двухкомпонентного строения опухоли вызвало предположение вероятности бифазной синовиальной саркомы.

Гистологическое исследование: В препаратах (№39810-13) выявлен двухкомпонентный опухолевый рост, представленный плотными скоплениями веретеновидных клеток, формирующих пучки и широкие поля, а также мономорфные эпителиальные клетки, образующие железистоподобные структуры. В просвете мелких железистых структур содержится эозинофильно

окрашенное вещество. Опухолевые клетки демонстрируют митотическую активность. В интратуморозной строме обнаружены гемангиоперицитомаподобные участки с образованием щелей, очаговый фиброз и кровоизлияния. В краевых отделах имеются элементы жировой и поперечнополосатой мышечной ткани.

Предоперационная оценка: В предоперационном периоде была проведена детальная оценка общего состояния пациента и тщательный анализ КТ для определения топографии опухоли, ее распространенности и границ. Анализ показал локализацию опухоли в тканях щеки, подвисочной и ретромаксиллярной областях, с разрушением скулового и венечного отростков нижней челюсти, альвеолярного отростка верхней челюсти и твердого неба в задних отделах, с наличием дефекта задней стеки верхне-челюстной пазухи. Это не исключало возможность образования дефекта кожи и мягких тканей щеки, а также дефекта задней стенки верхнечелюстной пазухи в ходе предстоящей операции. Учитывая такую локализацию, был рассмотрен вариант иссечения опухоли через доступ Лауэрс-Балона, как наиболее подходящий, а также возможные варианты пластического закрытия дефектов

Операция. 24 июля 2024 года была проведена операция по удалению опухоли мягких тканей щеки справа, распространившейся в ретромаксиллярное и подвисочное пространства, с доступом по Лауэрс-Балону, с лимфодиссекцией и пластикой послеоперационной полости (Рисунок 2).

Рисунок 2. Этап операции иссечения опухоли ретромаксиллярной области / *(Figure 2. Stage of tumor excision surgery in the retromaxillary region).*

Разрез был выполнен, начиная от середины нижней губы и продолжаясь вниз и вправо вдоль дуги нижней челюсти, отступая на 2 см до переднего края кивательной мышцы. Кожно-подкожный лоскут был откинут в сторону. При этом опухоль на щеке обнажилась и стала более обозрима. Это позволило произвести мобилизацию и иссечение опухоли по ее окружности по боковой стенке верхне-челюстной пазухи и кверху до скулового отростка. При этом обнаружено что опухоль вдавлена в заднюю стенку пазухи и лизировала ее, но осталась в пределах слизистой оболочки пазухи. Обнаружено вовлечение в опухолевый процесс верхней части венечного отростка нижней челюсти и сверху средней части скулового отростка, альвеолярного отростка верхней челюсти в задних отделах. При мобилизации опухоли на нижней ее поверхности, иссечена часть m.masseter спаянная с опухолью. После мобилизации опухоль иссечена единым блоком вместе с костными образованиями верней челюсти отростка нижней челюсти и скулового отростка. В ходе иссечения опухоли удалось сохранить кожу над опухолью, так как экспресс гистологический анализ краев резекции был отрицательный. После ревизии и иссечения остатков тканей подозрительных на опухолевую, операционная полость заполнена жировой тканью, взятой с передней брюшной стенки.

Послеоперационное течение прошло без осложнений. Жировая ткань в послеоперационной полости начала гранулировать, что позволило сделать пересадку расщепленного кожного лоскута.

После повторной операции в условиях ТОО «ННОЦ» резецированный макропрепарат был исследован гистологическим и иммуногистохимическим методами.

Гистологически опухоль имела двухфазное строение. Опухолевый рост представлен плотными скоплениями веретеновидных клеток, формирующих пучки и складывающиеся в широкие поля, а также содержит различное количество мономорфных эпителиальных клеток, образующих железистые эпителиальные структуры и тяжи. В просвете отдельных мелких желез содержится эозинофильно окрашенное вещество. В интратумарозной строме прослеживается гемангиоперицитарный сосудистый рисунок с образованием щелей. По краю опухоли видны элементы костной ткани, отграниченные от опухоли соединительнотканной прослойкой. В части фрагментов по поверхности имеется эпидермис с выраженными дистрофическими изменениями, участками изъязвления, кровоизлияниями, в дерме густая смешанноклеточная воспалительная инфильтрация с разрастанием сосудов грануляционного типа.

В восемнадцати обнаруженных лимфоузлах метастатического опухолевого роста не выявлено (рисунки 3, 4).

Для верификации гистогенеза опухоли было выполнено ИГХ-исследование: выявлена экспрессия маркеров TLE1, Anti-PanKeratin, виментин, Bcl-2, CD 56. Отсутствие окрашивания опухолевой ткани на такие маркеры как CK5/6, P63, CD99, SOX10, S100, CD34, S.M. Myosin, Myogenin, Chromogranin, Synaptophysin, AR-m (рисунки 5, 6, 7).

Окрашивание виментином свидетельствовало в пользу мезенхимального происхождения опухоли, на основании сильной диффузной экспрессии TLE1, Bcl-2, Anti-PanKeratin, CD 56, в сочетании с высоким индексом пролиферативной активности и характерной морфологической картиной, был выставлен диагноз бифазной синовиальной саркомы. ICD-O code: 9040/3.

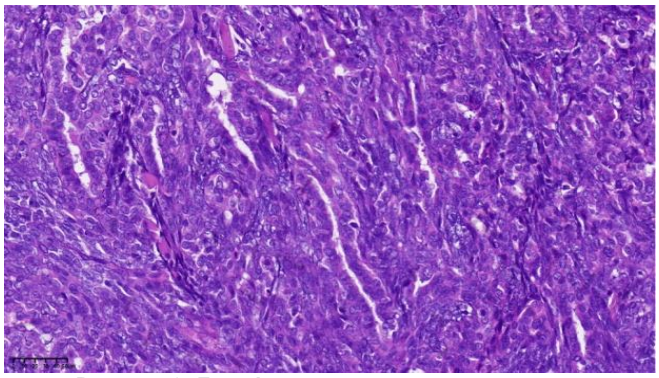

Рисунок 3. Двухфазная опухоль, состоящая из веретеноклеточного и эпителиального компонентов. Эпителиальный компонент формирует железистые структуры. H&E x20

(Figure 3. Biphasic tumor consisting of spindle cell and epithelial components. The epithelial component forms glandular structures. H&E, ×20.)

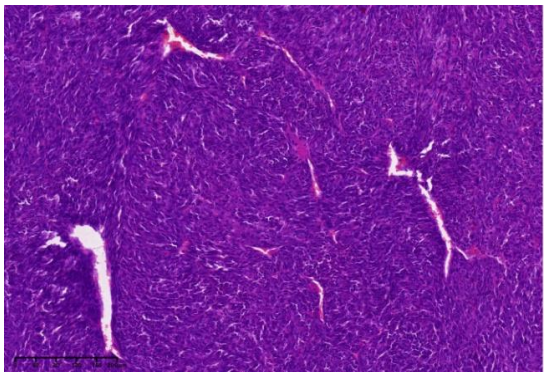

Рисунок 4. Компонент опухоли с коралловидным (гемангиопericитарным) разветвленным сосудистым рисунком. H&E x20/

(Figure 4. Tumor component with a coral-like (hemangiopericytic) branched vascular pattern. H&E, ×20.)

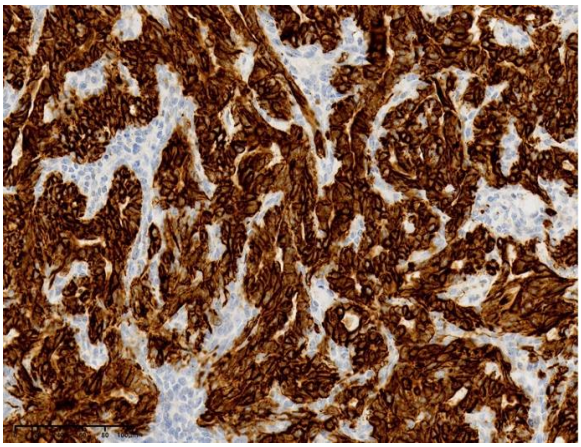

Рисунок 5. ИГХ-исследование. Anti-Pan Keratin - сильная диффузная цитоплазматическая и мембранная экспрессия в эпителиальном компоненте опухолевой ткани, отсутствие экспрессии в веретеноклеточном компоненте. X10 /

(Figure 5. IHC study. Anti-Pan Keratin – strong diffuse cytoplasmic and membranous expression in the epithelial component of the tumor tissue, with no expression in the spindle cell component. ×10).

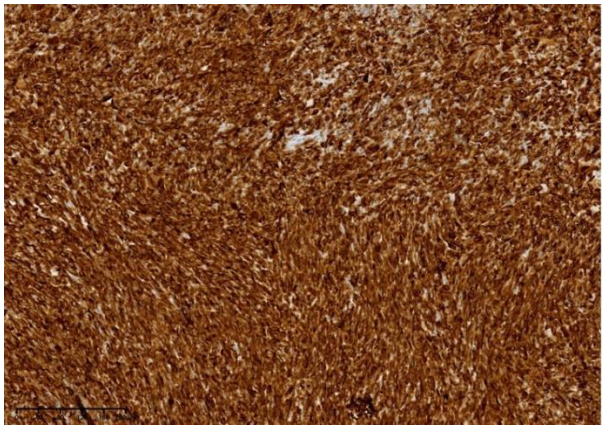

Рисунок 7. ИГХ-исследование. Vimentin - сильная диффузная цитоплазматическая экспрессия в опухолевой ткани. X10 /

(Figure 7. IHC study. Vimentin – strong diffuse cytoplasmic expression in the tumor tissue. ×10).

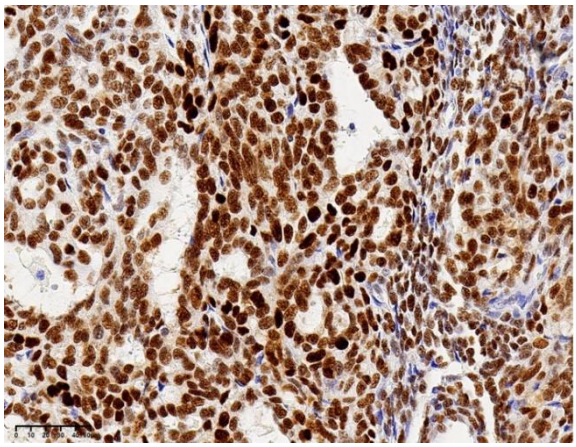

Рисунок 6. ИГХ-исследование. TLE1- сильная диффузная ядерная экспрессия в опухолевой ткани. X10 /

(Figure 6. IHC study. TLE1 – strong diffuse nuclear expression in the tumor tissue. ×10).

После проведения патогистологического и иммуногистохимического исследования операционного материала был установлен окончательный Диагноз: Саркома мягких тканей правой щеки T2N0M0 StII. Состояние после операции от 10.2022г - лучевой терапии от 17.02.23г.40Гр. Продолженный рост 12.2023г. Состояние после операции от 24.07.2024г.

Таким образом, пересмотр гистологического исследования, с учетом высокой вероятности саркомы, анализ КТ исследования, позволил сделать выбор для удаления опухоли через челюстно-лицевой доступ по Лауэрс-Балону, как наиболее оптимальный для радикального удаления опухоли. Он обеспечил хороший визуальный контроль операционного поля и дал возможность мобилизовать опухоль мягких тканей щеки, подвисочной и ретромаксиллярной областей и удалить его единым блоком вместе с костными элементами верхней и нижней челюсти. Выполненные в ходе операции отрицательные результаты краев резекции позволяют рассчитывать на радикальность удаление опухоли. Такой доступ позволил, в комбинации с пластическими компонентами операции, сохранить более приемлемые контуры лица.

Обсуждение. Синовиальная саркома лица — редкая злокачественная опухоль, составляющая менее 10% всех синовиальных сарком, ежегодно регистрируется от 800 до 1000 случаев [12]. Как отмечают *Soomers V. и др.* (2020), из-за отсутствия характерных клинических проявлений синовиальная саркома часто диагностируется на поздних стадиях, что ухудшает прогноз заболевания [18, 2].

Ранняя диагностика синовиальной саркомы представляет собой значительный вызов, поскольку ее клинические проявления неспецифичны и могут имитировать доброкачественные образования, такие как плевроморфная аденома или шваннома [3]. В данном случае диагноз был установлен только после биопсии и иммуногистохимического исследования [8, 14]. В соответствии с данными *Wang Y. и др.* (2018), ключевыми маркерами, используемыми для подтверждения диагноза синовиальной саркомы, являются EMA, CK и TLE1 [19, 13].

Как утверждают *Indrajanu I.N. и др.* (2024), хирургическое вмешательство с максимально возможным удалением опухоли остается основным методом лечения синовиальной саркомы [9, 10]. В данном случае была выполнена радикальная резекция новообразования с пластикой дефекта местным кожным лоскутом, что позволило сохранить эстетическую и функциональную целостность лица. Подход, использованный в этом клиническом случае, соответствует рекомендациям European Society for Medical Oncology (ESMO) по лечению сарком мягких тканей, согласно которым радикальная резекция с негативными хирургическими краями является основным фактором, определяющим выживаемость [11].

Роль адъювантной терапии в лечении синовиальной саркомы остается дискуссионной. Некоторые авторы, такие как *Scheer M. и др.* (2023), утверждают, что лучевая терапия снижает риск местного рецидива, особенно при наличии положительных хирургических краев [16]. Другие исследования, включая работу *Xu G. и др.* (2021), не выявили значительного увеличения общей выживаемости при применении химиотерапии [20]. В данном случае пациент не получал адъювантного лечения, что, возможно, связано с локализованным характером опухоли и радикальным удалением.

Как отмечают *El Beaino M. и др.* (2019), прогноз при синовиальной саркоме зависит от множества факторов, включая размер опухоли, степень дифференцировки и наличие метастазов [5]. Пятилетняя выживаемость пациентов заболевания составляет 50–60% [12]. Однако высокий риск рецидива остается серьезной проблемой. Исследование *Ferrari A. и др.* (2024) показало, что первый рецидив возникал в период от 3 до 132 месяцев после первоначального диагноза (медиана - 18 месяцев) и носил локальный характер в 34% случаев, был метастатическим в 54% и сочетал оба варианта в 12%. Лечение рецидива включало хирургическое вмешательство в 56% случаев, лучевую терапию в 34% и системную терапию в 88%. Вторую линию медикаментозного лечения получили 36 пациентов, из которых 32 проходили химиотерапию (по 10 различным схемам), а 4 - таргетную терапию. Эти данные подчеркивают высокий риск рецидива и необходимость тщательного динамического наблюдения, позволяющего своевременно корректировать тактику лечения [6].

Выводы. В ходе пересмотра гистологии и исследования макропрепарата было выявлено, что изначально поставленный диагноз плоскоклеточной карциномы был ошибочен. Патоморфологическое исследование подтвердило наличие синовиальной саркомы, что существенно меняет тактику лечения и прогноз для пациента

Изменение диагноза подчеркивает важность точной диагностики в онкологии и необходимость комплексного подхода к анализу тканей, включая значимость гистологических и визуализирующих методов для уточнения характера опухоли

С учетом нового диагноза синовиальной саркомы, был произведен пересмотр схемы лечения, включая возможные изменения в хирургической стратегии и наблюдении за пациентом.

Выбор для удаления опухоли через челюстно-лицевой доступ по Лауэрс-Балону обеспечил хороший визуальный контроль операционного поля и дал возможность на радикальность удаление опухоли.

Вклад авторов: *все авторы в равной мере принимали участие в написании статьи.*

Конфликт интересов: *конфликт интересов не заявлен.*

Сведения о публикации: *статья не была опубликована ранее в других журналах и не находится на рассмотрении в других издательствах.*

Финансирование публикации: *данная работа не получала никакой финансовой поддержки.*

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ПОЛНАЯ ТРАНСПОЗИЦИЯ ОРГАНОВ (SITUS VISCERUM INVERSUS TOTALIS) НА ПРИМЕРЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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Резюме

Актуальность: полная транспозиция органов (situs viscerum inversus totalis) среди населения земного шара встречается очень редко и знание особенностей анатомии пациента имеет большое значение, как в диагностике, так и в лечении торакальных и абдоминальных хирургических заболеваний.

Цель исследования: продемонстрировать значимость методов лучевой диагностики (на примере мгнитно-резонансной томографии) в первичной диагностике различных вариантов situs viscerum inversus totalis органов грудной клетки и брюшной полости. Так же проиллюстрировать значимость методов лучевой диагностики в выборе и определении метода и объема оперативного вмешательства при возникновении хирургической патологии органов грудной клетки и брюшной полости, сопровождающимися различными вариантами situs viscerum inversus totalis.

Методы исследования: данное исследование является обсервационным.

Обсуждение: проведение магнитно-резонансной томографии позволило выявить наличие у пациента наличие декстрокардии и полного зеркального расположения внутренних органов.

Выводы: таким образом, у больных с декстрокардией с высокой степенью вероятности имеют место и другие аномалии органов. Заболевания органов грудной клетки и органов брюшной полости в сочетании с декстрокардией должны рассматриваться, как показания к проведению магнитно-резонансной томографии органов грудной клетки и брюшной полости с применением контрастных веществ.

Ключевые слова: *Магнитно-резонансная томография, декстрокардия, зеркальное расположение органов.*

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Abstract

COMPLETE ORGAN TRANSPOSITION (SITUS VISCERUM INVERSUS TOTALIS) A CLINICAL CASE STUDY

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Relevance: a complete transposition of the organs (situs viscerum inversus totalis) is very rare condition among the world population. The knowledge of the patient's anatomy has great importance in the diagnosis and treatment of the thoracic and abdominal surgical diseases.

Objective of the study: to demonstrate the significance of the diagnostic radiology methods (in the example of magnetic resonance tomography) in the primary diagnosis of various variants of the situs viscerum inversus totalis of the thoracic and abdominal cavity organs. Also, to illustrate the consequential methods of the diagnostic radiology in the choice and

determination method and volume of surgical intervention at the occurrence of surgical pathology of thoracic and abdominal cavity organs, accompanied by multiple variants of situs viscerum inversus totalis.

Research methods: Observational study.

Discussion: magnetic resonance imaging revealed the presence of dextrocardia and complete mirror-image arrangement of the internal organs in the patient.

Conclusions: consequently, the patients with dextrocardia can be occurred the other organ abnormalities with strong possibility. Diseases of the chest and abdominal organs in combination with dextrocardia should be considered as indications for magnetic resonance imaging of the chest and abdominal organs using contrast agents.

Keywords: *Magnetic resonance imaging, dextrocardia, mirror position of organs.*

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Түйіндеме

ОРГАНДАРДЫҢ ТОЛЫҚ ТРАНСПОЗИЦИЯСЫ (SITUS VISCERUM INVERSUS TOTALIS) КЛИНИКАЛЫҚ ЖАҒДАЙ МЫСАЛЫНДА

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Өзектілігі: ағзалардың толық транспозициясы (situs viscerum inversus totalis) дүние жүзі тұрғындары арасында өте сирек кездеседі және науқастың анатомиясын білу кеуде және құрсақ қуысының хирургиялық ауруларын диагностикалауда да, емдеуде де үлкен маңызға ие.

Зерттеудің мақсаты: кеуде және құрсақ қуысындағы situs viscerum inversus totalis түрінің әртүрлі нұсқаларының алғашқы диагностикасында сәулелік диагностикалық әдістердің (мысалы, магнитті- резонансты томография) маңыздылығын көрсету. Сондай-ақ situs viscerum inversus totalis әртүрлі нұсқаларымен жүретін кеуде және құрсақ қуысы мүшелерінің хирургиялық патологиясы кезінде хирургиялық араласу әдісі мен көлемін таңдау және анықтауда сәулелік диагностикалық әдістердің маңыздылығын көрсету.

Зерттеу әдістері: Бұл зерттеу бақылау болып табылады.

Талқылау: Магнитті-резонансты томография науқаста декстрокардия және ішкі ағзалардың толық айнадай орналасуы анықталды.

Қорытынды: Осылайша, декстрокардиямен ауыратын науқастарда басқа органдардың ауытқулары болуы ықтимал. Кеуде және іш қуысы мүшелерінің декстрокардиямен біріктірілген ауруларын контраст агенттерін қолдану арқылы кеуде және іш қуысы мүшелерінің магнитті-резонансты томографияны көрсеткіштер ретінде қарастырған жөн.

Түйінді сөздер: *Магнитті резонансты томография, декстрокардия, мүшелердің айна орналасуы.*

Дәйексөз үшін:

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Актуальность

В литературе первая публикация (1606 год) о неправильном расположении сердца и сосудов в грудной полости принадлежит перу Иеронима Фабриция (итальянский хирург и анатом). *Марк Аурелио Северино* в 1643 году при описании пациента с зеркальным расположением внутренних органов грудной клетки использовал термин «декстрокардия». [6, 9].

Мэтью Бейли через 100 лет в своей публикации привел описание больного, у которого была полная транспозиция всех органов грудной клетки и брюшной полости в зеркальном изображении [6, 9].

На текущий момент под термином «декстрокардия» принято понимать редко встречающуюся врожденную аномалию развития сердечно-сосудистой системы, при которой сердце располагается в грудной клетке справа. При этом все входящие и исходящие сосуды сердца располагаются зеркально своему типичному расположению [2,6].

Было установлено путем различных генетических исследований, что декстрокардия чаще всего ассоциируется с мутацией генов Pitxz, ACVR2, ZIC3Shh, HAND и было доказано наличие аутосомно-рецессивного типа наследования данного заболевания.

Согласно исследованиям, мутации практически всегда происходят в первом триместре беременности, когда идет закладка всех органов и систем организма.

Частота указанных аномалий достигает 1,5-5% среди всех врожденных пороков сердца и, как правило, сочетается с транспозицией магистральных сосудов [2, 6, 8, 11, 12].

В 54% случаев встречается правосформированное праворасположенное сердце (изолированная декстрокардия) и в 33% случаев отмечается наличие левосформированного праворасположенное сердце («зеркальная декстрокардия»).

В первом варианте взаиморасположение остальных органов и систем, а также общая топография органов брюшной полости соответствует норме, во втором варианте отмечается полное обратное расположение всех органов и систем (situs inversus) [6, 8].

В зависимости от анатомического расположения внутренних органов можно выделить:

– **situs inversus cordis** – простая декстрокардия, при этой форме зеркально расположено только сердце, встречается довольно редко;

– **situs viscerum inversus partialis** – сердце, а так же органы пищеварительной или дыхательной системы располагаются зеркально;

– **situs viscerum inversus totalis** – все внутренние органы и системы расположены зеркально [3, 6].

По состоянию на текущий момент выявлены и изучены разнообразные варианты транспозиций внутренних органов и систем по отношению к их нормальной анатомической локализации, что имеет огромное практическое значение, особенно при планировании каких-либо оперативных вмешательств [5].

Полная транспозиции внутренних органов и систем наблюдается очень редко, по данным разных авторов – от 1:5 000 до 1:20 000 человек [1, 15, 17].

Из всех форм декстрокардий, приведенных выше, чаще всего встречается вариант это – situs inversus cordis. По данным *О.Э. Луцевич и соавторов* [3], которыми был проведен анализ более 10 000 компьютерных томографических исследований был выявлен единственный случай situs inversus totalis и три клинических наблюдения декстрокардии. В большинстве случаев наблюдения транспозиция внутренних органов брюшной полости и грудной клетки связана с различными типами аномалий развития внутренних органов и систем [5, 16].

Сочетание декстрокардии и вариантов *situs viscerum inversus totalis* органов брюшной полости, а также их врождённых аномалий, сказывается на клинике как абдоминальных хирургических заболеваний, а также клинике и течения заболеваний органов грудной клетки. В случае выявления показаний к оперативному лечению с подозрением на онкологическую патологию требуется нестандартное планирование операции [5].

В клинической практике при обследовании пациентов с зеркальным расположением внутренних органов имеется большая вероятность анатомической дезориентировки, что может повлечь постановку неправильного диагноза и выбор некорректного метода лечения заболевания [5, 7].

H. Blegen в своих работах описывает определенные сложности в диагностики и выявлении situs viscerum inversus totalis. Им был проведен ретроспективный анализ 144 пролеченных случаев, где из 144 пациентам было выполнено 158 различных хирургических вмешательств на органах брюшной полости грудной клетки. При выявлении у пациента признаков situs viscerum inversus totalis, неверный диагноз был поставлен у 45% пациентов, в результате чего некорректный хирургический доступ был проведен в 31% наблюдений [5, 9].

При подозрении на наличие различных вариантов situs inversus органов брюшной полости, а так же, для уточнения клинического диагноза и определения хирургического доступа применяются различные методы лучевой диагностики, такие как магнитно-резонансная томография и компьютерная томография [4].

Цель исследования: продемонстрировать значимость методов лучевой диагностики (на примере магнитно-резонансной томографии) в первичной диагностике различных вариантов situs viscerum inversus totalis органов грудной клетки и брюшной полости. Так же проиллюстрировать значимость методов лучевой диагностики в выборе и определении метода и объема оперативного вмешательства при возникновении хирургической патологии органов грудной клетки и брюшной полости, сопровождающимися различными вариантами situs viscerum inversus totalis.

Методы исследования: Данное исследование является обсервационным, дополнительная статистическая обработка данных не проводилась.

Обследование пациента проводилась на магнитно-резонансном томографе фирмы «Siemens», с напряженностью магнитного поля 1,5 Тесла, с использованием T1 и T2-взвешенных изображениях в аксиальных, коронарных и сагиттальных проекциях, последовательности T2-tirm, T2-fs в аксиальной проекции, T2-haste в коронарной и сагиттальной проекции, режим МР-холангиографии, DWI со значением b-фактора 0, 500, 1000, с построением ADC карт.

Динамическое контрастирование проводилось с использованием парамагнитного контрастного вещества «Гадовист» на постконтрастных T1-взвешенных изображениях в аксиальных, коронарных и сагиттальных проекциях.

Клинический случай.

В Центр ядерной медицины и онкологии города Семей обратился пациент Р. 1986 года рождения, с целью дообследования для исключения онкологического процесса.

При проведении магнитно-резонансного томографического исследования было выявлено зеркальное расположение внутренних органов брюшной полости и грудной клетки (рис. 1 - 6).

Печень в размерах не увеличена, контуры печени ровные, четкие. Правая доля печени расположена в левой половине брюшной полости, внутрипеченочные протоки не расширены.

Воротная вена располагается в левой половине брюшной полости, селезеночная вена располагается в правой половине брюшной полости, не расширены.

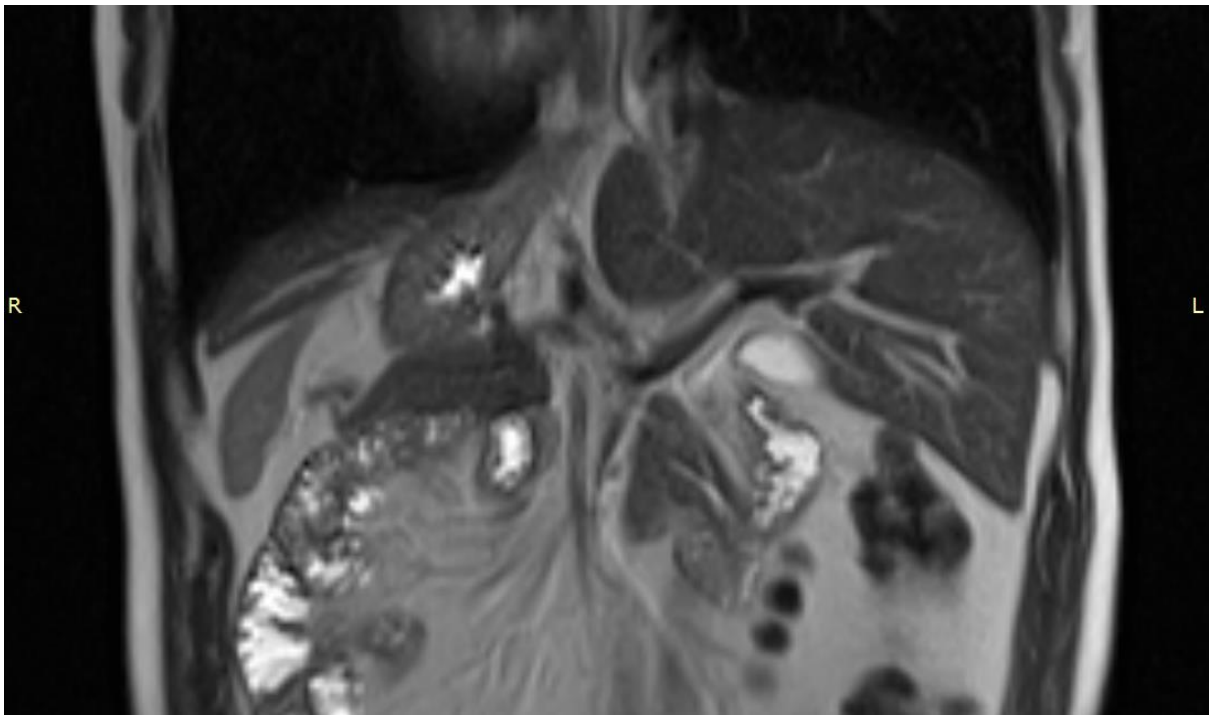

Рисунок 1. МРТ-срез в коронарной проекции.
Четко видна левостороння локализация печени и правосторонняя локализация селезенки.
(Figure 1. MRI slice in coronal view.
The left-sided localization of the liver and the right-sided localization of the spleen are clearly visible).

Желчный пузырь располагается в левой половине брюшной полости, по нижнему краю печени, содержимое его однородное, стенки его уплотнены. Холедох расположен в левых отделах брюшной полости, отмечается симптом «седиментации желчи», в средних отделах изгибается, в терминальных отделах конически сужается.

Головка поджелудочной железы расположена в левых отделах брюшной полости, тело и хвост соответственно в правых отделах, размеры поджелудочной железы не увеличены, внутреннее строение не изменено, вирсунгов проток не расширен.

Селезенка расположена в правых отделах брюшной полости, контуры ее ровные, чёткие, размеры селезенки не увеличены, структура однородная.

Обе почки имеют нормальное расположение и размеры. В проекции средней трети левой почки определяется кистоподобное образование с четкими ровным контурами, размером до 7мм. Толщина и структура почечной паренхимы не изменена, корковый и мозговой слои почек дифференцируются, демаркация между ними отчетливая. Почечные синусы несколько расширены.

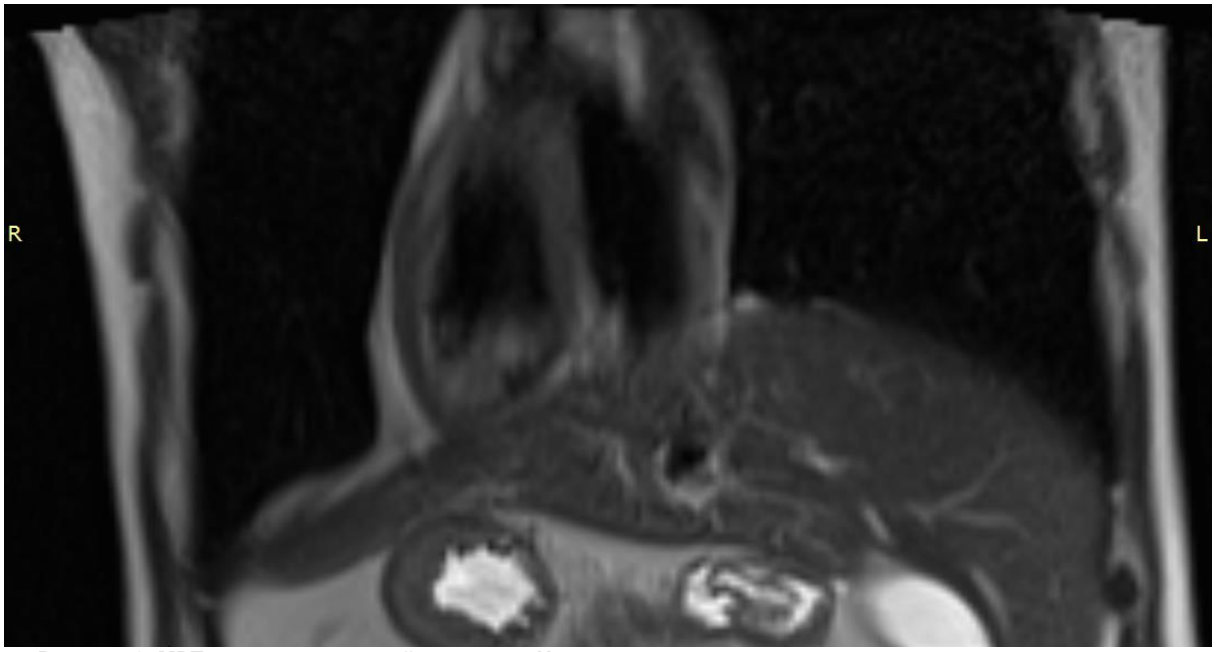

Рисунок 2. МРТ-срез в коронарной проекции. Четко определяется правосторонняя локализация сердца.
(Figure 2. MRI slice in coronary view. Right-sided localization of the heart is clearly defined.).

Оба надпочечника расположены типично. Структура обоих надпочечника однородная, диаметр ножек не превышает 4-5мм (норма не более 10 мм), капсула надпочечника сохранена. Околопочечная клетчатка несколько инфильтрирована.

На захваченных сканах органов грудной клетки определяется расположение сердца в правой половине грудной клетки.

Рисунок 3. МРТ-срез в аксиальной проекции.
Определяется левостороннее расположение печени, желчного пузыря и правосторонне расположение селезенки.
(Figure 3. MRI slice in axial view.
The left-sided location of the liver, gallbladder and the right-sided location of the spleen are determined).

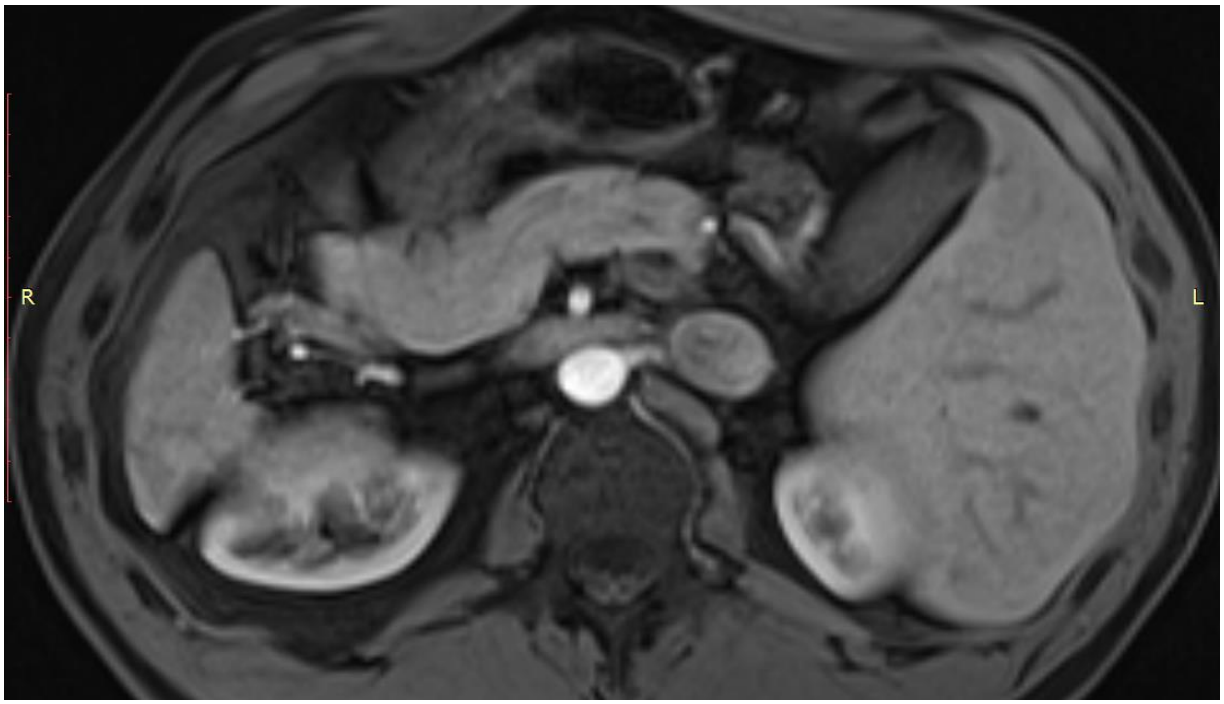

Рисунок 4. МРТ-срез в аксиальной проекции с контрастом.
Определяется левостороннее расположение печени, желчного пузыря и правосторонне расположение селезенки, а также тела и хвоста поджелудочной железы.
(Figure 4. MRI slice in axial view with contrast.
The left-sided location of the liver, gallbladder and the right-sided location of the spleen, as well as the body and tail of the pancreas are determined.).

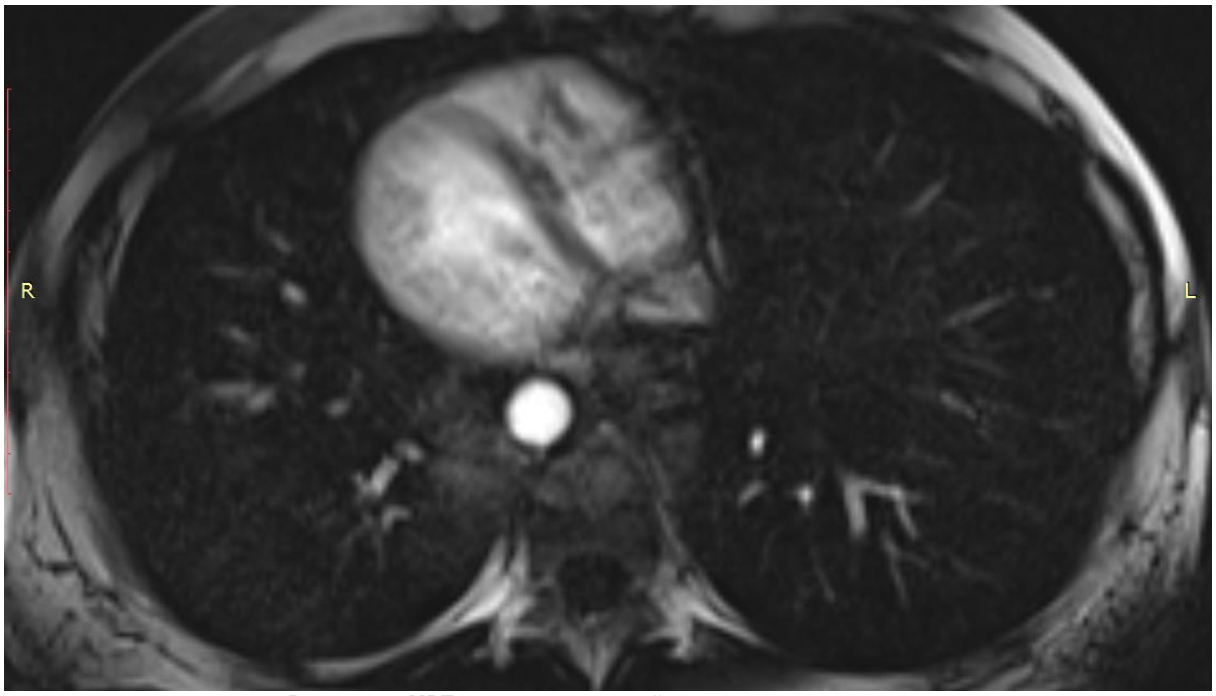

Рисунок 5. МРТ-срез в аксиальной проекции с контрастом.
Визуализируется правостороннее расположение всех полостей сердца.
(Figure 5. MRI slice in axial view with contrast. The right-sided arrangement of all heart cavities is visualized.).

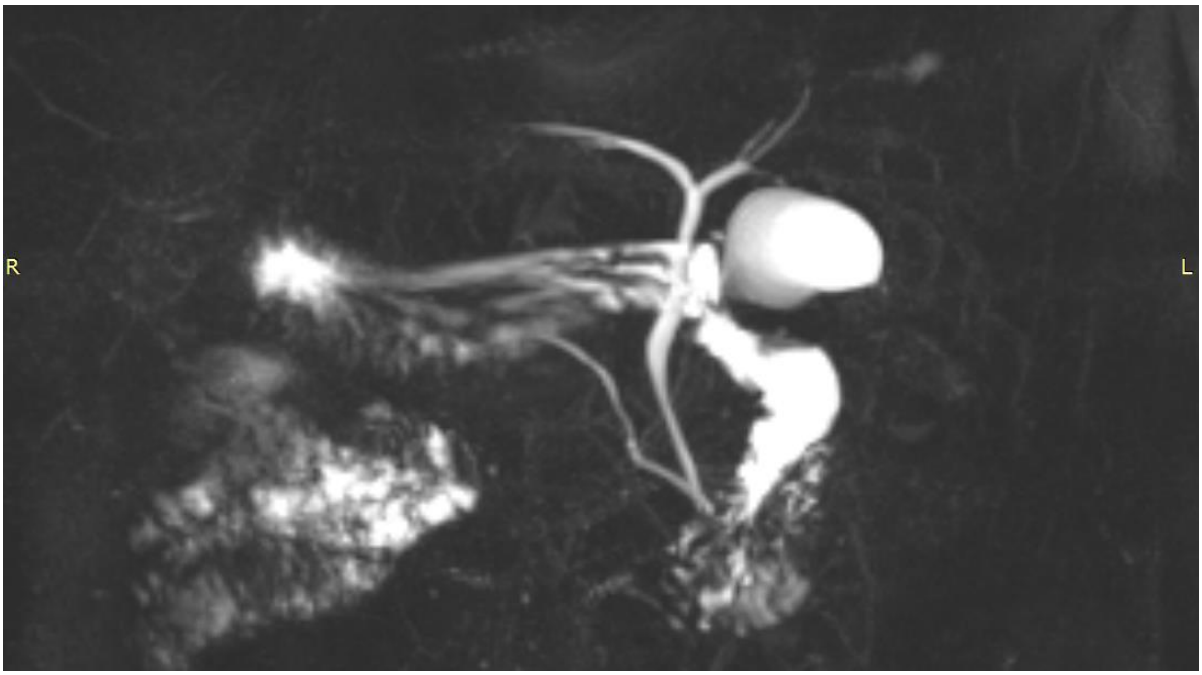

Рисунок 6. МР-холангиография.
Визуализируется полное зеркальное расположение внутрипеченочных и внепеченочных желчных протоков, а также вирсунгового протока.
(Figure 6. MR cholangiography.
A complete mirror image of the intrahepatic and extrahepatic bile ducts, as well as the Wirsung duct, is visualized).

Таким образом, опираясь на результаты магнитно-резонансного исследования, у пациента было выявлено полное зеркальное расположение органов брюшной полости и правостороннее расположение сердца (situs viscerum inversus totalis). Данных за злокачественный онкологический процесс на момент исследования не определяется. Отмечается наличие простой кисты левой почки. Кроме полного зеркального расположения органов (situs viscerum inversus totalis) у пациента отмечаются признаки застоя желчи и изгиб общего желчного протока, что в будущем может явиться причиной развития желчекаменной болезни и необходимости проведения оперативного вмешательства.

Обсуждение

Под термином «Situs viscerum inversus totalis» принято понимать правостороннее расположение сердца и основных внутренних органов и систем [12, 14, 20].

Декстрокардия (истинное зеркальное расположение сердца) чаще всего сочетается с situs viscerum inversus totalis. При этом аорта направляется вверх по противоположной стороне грудной клетки. Такое расположение сердца и аорты может приводить к нарушению нормальной функции органов грудной клетки, так как само сердце находится справа, и все камеры сердца расположены ассиметрично. Так же при situs viscerum inversus totalis все артерии, вены и органы брюшной полости расположены зеркально.

В настоящее время situs viscerum inversus totalis всё ещё не имеет чётких и признанных причин. Учитывая частую связь между нетипичным расположением органов и другими необычными врождёнными аномалиями, в одном из исследований была выдвинута гипотеза о приобретённой этиологии, возникающей в результате внутриутробного повреждения, нарушающего нормальный процесс дифференцировки клеток и ориентации формирующего эмбриобласта [18, 21].

Такая анатомическая особенность может осложнить диагностический процесс и диагностические или лечебные процедуры, особенно инвазивные. В силу редкости подобных случаев, практикующие врачи - в частности, гастроэнтерологи, радиологи и хирурги - обычно не имеют достаточного опыта работы с такими пациентами [18].

Выводы

Таким образом, у больных с декстрокардией с высокой степенью вероятности имеют место и другие аномалии органов. Любая патология при транспозиции органов грудной клетки и органов брюшной полости (situs viscerum inversus totalis) в сочетании с декстрокардией должны рассматриваться, как показания к проведению магнитно-резонансной томографии органов грудной клетки и органов брюшной полости с применением контрастных веществ.

Магнитно-резонансная томография является одним из важнейших методов первичного выявления различных патологических состояний и аномалий развития внутренних органов, в том числе и при полной транспозиции внутренних органов (situs viscerum inversus totalis), что позволяет выбрать у данных пациентов, подходящий хирургический доступ и определить соответствующую тактику оперативного вмешательства при наличии у пациента хирургической патологии органов брюшной полости и забрюшинного пространства.

Конфликт интересов. *Мы заявляем об отсутствии конфликта интересов.*

Вклад авторов

Кузнецова Т.В. – проведение и интерпретация МРТ исследования, подготовка иллюстраций для статьи;

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Мадиева М.Р., Рахимбеков А.В. – итоговая подготовка и редактирование текста статьи, ответственный за переписку.

Заявляем, что данный материал ранее не публиковался и не находится на рассмотрении в других издательствах.

Финансирование: *Отсутствует.*

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Содержание

ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

Jumabayeva A., Kaibullayeva J., Kaisina A., Nugmanova B., Zhumadilova Z., Botabayeva A., Ualiyeva A., Pashimov M., Kambarova G., Omarova K., Muratbekova A., Balabek A., Yergaliyeva A., Reshidova T., Saktagan A., Kassymova T., Mutaliyeva G., Anuar A., Kudaibergenova Sh. 7-16
Midterm results of the observational non-interventional clinical study "Evaluation of the effectiveness of the carnitine orotate and biphenyldimethyldicarboxylate complex in the pathogenetic therapy of metabolic-associated fatty liver disease: a prospective cohort study»

Nussupova R.R., Pack L.A., Mussazhanova Zh.B., Bolatov A.K., Zhakupov A.K., Muldakhmetov M.S., 17-25
Genetic Analysis of TP53 and CTNNB1 Mutations in Pediatric Medulloblastoma: A Study from Kazakhstan

Adilgazyuly Sh., Bulegenov T., Mussakhanova A., Altybayeva Zh., Medeulova A., Tokenova Zh., Urazalina N.M. 26-31
Assessment of the quality of life of patients with lung cancer in the Abay region

Тулеуханов С.Т., Зинченко В.П., Қайрат Б.Қ., Тусупбекова Г.А., Малибаева А.Е. 32-39
Эпилепсиялық белсенділік кезінде пароксизмальды деполяризациялық ығысу кластерлерінің құрылымына Kv7 тұқымдас калий каналдарының ингибиторлары мен активаторларының әсерін зерттеу

Petrova Y.V., Ivanova R.L., Goremykina M.V., Serikova T.K., Karakanova A.B., Bakytova A.B., Seitkhan D.S., Nogayeva M.G. 40-48
Quality of life and adherence to therapy in patient with rheumatoid arthritis

Kastey R., Faizullina K., Turganova M., Zhexenova A., Vaičiulis V., Akhtayeva N. 49-55
Study of Hospitalized Cases Associated with Acute Cerebrovascular Accidents

Калимолдина Г.К., Муздубаева Ж.Е., Ботабаева А.С., Оразалина А.С., Каскабаева А.Ш., Жумадилова З.К. 56-65
Эндотелиальная дисфункция при неспецифическом язвенном колите и возможности её коррекции при лечении

Ibekenov O.T., Baymakhanov A.N., Berkinbay A.B., Zheldibaev Ye.M., Duisebekov M.K., Esenbekov N.B., Zhorayev T.S. 66-74
Non-varicose bleeding from the upper gastrointestinal tract

Алимбаева А.Р., Дюсекенова Г.К., Тайоразова Г.Б., Латышев Д.Ю., Лобанов Ю.Ф., Дорохов Н.А., Скударнов Е.В., Болденкова И.Ю., Аильбаева Н.М., Токтамыс Д.Р. 75-81
Частота рецидивов гастроэзофагеальной рефлюксной болезни у детей школьного возраста

Мазмұны

БІРТУМА ЗЕРТТЕУЛЕР

Джумабаева А.Е., Кайбуллаева Д.А., Қайсина Ә.А., Нугманова Б.Т., Жумадилова З.К., Ботабаева А.С., Уалиева А.Е., Пашимов М.О., Камбарова Г.А., Омарова К.С., Муратбекова А.К., Балабек А.Н., Ергалиева А.А., Решидова Т.А., Сақтаған А.Е., Касымова Т.В., Муталиева Г.С., Ануар А.Д., Кудайбергенова Ш.Н. 7-16
Бақылаулық интервенциясыз клиникалық зерттеудің аралық нәтижелері «карнитин оротаты мен бифенилдиметилдикарбоксилат кешенін метаболизммен байланысты майлы бауыр ауруының патогенетикалық терапиясында қолдану тиімділігін бағалау: проспективті когорттық зерттеу»

Нусупова Р.Р., Пак Л.А., Мусажанова Ж.Б., Болатов А.К., Жакупов А.К., Мулдахметов М.С. 17-25
TP53 және CTNNB1 мутацияларының балалардағы медуллобластомасында генетикалық талдауы: Қазақстанда зерттеу

Әділғазыұлы Ш., Булегенов Т., Мусаханова А., Алтыбаева Ж., Медеулова А., Токенова Ж., Уразалина Н.М. 26-31
Абай өңіріндегі өкпе обыры бар науқастардың өмір сүру сапасын бағалау

Тулеуханов С.Т., Зинченко В.П., Қайрат Б.Қ., Тусупбекова Г.А., Малибаева А.Е. 32-39
Эпилепсиялық белсенділік кезінде пароксизмальды деполяризациялық ығысу кластерлерінің құрылымына Kv7 тұқымдас калий каналдарының ингибиторлары мен активаторларының әсерін зерттеу

Петрова Ю.В., Иванова Р.Л., Горемыкина М.В., Серикова Т.К., Караканова А.Б., Бакытова А.Б., Сейтхан Д.С., Ногаева М.Г. 40-48
Ревматоидты артритпен ауыратын науқастардың өмір сапасы және терапияға бейімділігі

Кастей Р., Файзуллина К., Турганова М., Жексенова А., Вайчюлис В., Ахтаева Н. 49-55
Жедел цереброваскулярлық бұзылулармен байланысты ауруханаға жатқызылған жағдайларды

Калимолдина Г.К., Муздубаева Ж.Е., Ботабаева А.С., Оразалина А.С., Каскабаева А.Ш., Жумадилова З.К. 56-65
Неспецификалық ойық жаралы колит кезіндегі эндотелий дисфункциясы және оны емдеу кезінде түзету мүмкіндіктері

Ибекенов О.Т., Баймаханов А.Н., Беркінбай А.Б., Желдібаев Е.М., Дүйсебеков М.Қ., Есенбеков Н.Б., Жораев Т.С. 66-74
Жоғарғы асқазан-ішек жолдарынан варикозды емес қан кету

Алимбаева А.Р., Дюсекенова Г.К., Тайоразова Г.Б., Латышев Д.Ю., Лобанов Ю.Ф., Дорохов Н.А., Скударнов Е.В., Болденкова И.Ю., Аильбаева Н.М., Токтамыс Д.Р. 75-81
Мектеп жасындағы балаларда гастроэзофагеальді рефлюкс ауруының қайталану жиілігі

Баймуханова М.С., Нургалиева Б.К., Ногаева М.Г., Костинов М.П.
Уровень заболеваемости сахарным диабетом 2 типа и хроническим вирусным гепатитом С на 2023 год в городе Алматы **82-88**

Maukayeva S.B., Kudaibergenova N.K., Merimgaliyeva A.K., Agybayeva A.M., Abzalkhanova G.T., Orazalina A.S., Yurkovskaya O.A., Goremykina M.V., Zeinolla K.A., Akhmetova A.K.
Analysis of the microflora on dates of the bacteriological laboratory **89-99**

Mukasheva G.D., Maukayeva S.B., Kudaibergenova N.K., Shabdarbayeva D.M., Berikuly D., Orazalina A.S., Apbassova S.A., Zhanibekova A., Kalkaman A., Akhmetova A.K.
Analysis of medical students' knowledge about HIV infection **100-106**

Sultanbekova B.M., Raushanova A., Akhtayeva N., Alekenova N., Nurbaulina E., Abilov T.
Perceptions of work processes and organizational dynamics in hospital gynecology departments **107-115**

Танышева Г.А., Берикханова К.Е., Шегенов Г.А., Нурмагамбетова Д.М., Билялова Г.Т., Советова С.Д., Саркучикова Г.Ж.
Иммунологические изменения при лечении антифосфолипидного синдрома у беременных **116-122**

Toleuov E.A., Moldagaliyev T.M., Seksenbayev N.Zh., Akkuzinova K.F., Zhamaliyeva L.M., Bubeliene D., Muzafarov R., Tleubayeva Sh., Malsova B.K.
Suicide across different age groups **123-129**

Moldagasimova A.B., Tussupbekova D.M., Sharipova A.T., Rysbekova R.K.
Experience of project work to identify anxiety as a possible factor in teenage suicide and its prevention among schoolchildren in Almaty **130-136**

АКТУАЛЬНАЯ ТЕМА - COVID-19

Shakirova A.A., Toktabayeva B.Zh., Orazalina A.S., Abyldazinova A.Zh., Amrenova K.Sh., Abayeva K.D., Zangaliyeva G.M.
The condition of the vascular endothelium in children with COVID-19 and broncho-obstructive syndrome **137-145**

Ayazbekov A., Taskynova G., Oshibayeva A., Taubekova M., Tanysheva G.
Long-term consequences of coronavirus infection (SARS-COV-2) in women of childbearing age **146-156**

ОБЗОР ЛИТЕРАТУРЫ

Yerketayeva A.Kh., Mussazhanova Zh.B., Kozykenova Zh.Y., Pak L.A., Dushimova Z.D., Toktabayeva B.Zh., Zhazykbayeva L.K., Rakhmankulova A.M.
The Impact of gene mutations in Thyroid Cancer: A review **157-166**

Doszhanov I.A., Nurdinov N.S., Abilov T.S., Sadykova K.Zh., Nuskabayeva G.O., Zharkynbekova N.A., Oshibayeva A.E., Aimakhanov M.S.
Exploring the Role of miRNA's in drug-resistant epilepsy: a literature review **167-173**

Баймуханова М.С., Нургалиева Б.К., Ногаева М.Г., Костинов М.П.
Алматы қаласында 2023 жылға 2 типті қант диабеті және созылмалы вирусты С гепатиті ауруының деңгейі

Маукаева С.Б., Кудайбергенова Н.К., Меримгалиева А.К., Агыбаева А.М., Абзалханова Г.Т., Оразалина А.С., Юрковская О.А., Горемыкина М.В., Зейнолла К.А., Ахметова А.К.
Бактериологиялық зертхананың мәліметтері бойынша микрофлораны талдау

Мукашева Г.Д., Маукаева С.Б., Кудайбергенова Н.К., Шабдарбаева Д.М., Берікұлы Д., Оразалина А.С., Апбасова С.А., Жәнібекова А., Қалқаман А., Ахметова А.К.
Медициналық студенттердің ВИЧ инфекциясы туралы білімін талдау

Султанбекова Б.М., Раушанова А., Ахтаева Н., Алекенова Н., Нурбаулина Э., Абилов Т.
Гинекологиялық бөлімшелерде жұмыс үдерістері мен ұйымдық динамиканы қабылдау

Танышева Г.А., Берикханова К.Е., Шегенов Г.А., Нурмагамбетова Д.М., Билялова Г.Т., Советова С.Д., Саркучикова Г.Ж.
Жүкті әйелдердегі антифосфолипидті синдромды емдеудегі иммунологиялық өзгерістер

Төлеуов Е.Ә., Молдагалиев Т.М., Сексенбаев Н.Ж., Аккузинова К.Ф., Жамалиева Л.М., Бубелиене Д., Музафаров Р.Х., Тлеубаева Ш.М., Мэлсова Б.К.
Әртүрлі жас топтарындағы суицид

Молдагасимова А.Б., Тусупбекова Д.М., Шарипова А.Т., Рысбекова Р.К.
Алматы қаласының оқушылары арасында жасөспірімдер суицидінің ықтимал факторы ретінде мазасыздықты анықтау және оның алдын алу бойынша жобалық жұмыс тәжірибес

COVID-19 - ӨЗЕКТІ ТАҚЫРЫП

Шакирова А.А., Токтабаева Б.Ж., Оразалина А.С., Абылгазинова А.Ж., Амренова К.Ш., Абаева К.Д., Жангалиева Г.М.
COVID-19 және бронхообструктивті синдромы бар балаларда тамыр эндотелиінің жағдайы

Аязбеков А., Таскынова Г., Ошибаева А., Таубекова М., Танышева Г.
Фертильді жастағы әйелдердегі коронавирустық инфекцияның (SARS-COV-2) ұзақ мерзімді салдары

ӘДЕБИЕТТІК ШОЛУ

Еркетаева А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Пак Л.А., Душимова З.Д., Токтабаева Б.Ж., Жазыкбаева Л.К., Рахманкулова А.М.
Қалқанша безінің қатерлі ісігіндегі генінің мутациясының рөлі. Әдебиеттік шолу

Досжанов И.А., Нурдинов Н.С., Абилов Т.С., Садыкова К.Ж., Нускабаева Г.О., Жаркынбекова Н.А., Ошибаева А.Е., Аймаханов М.С.
Дәріге төзімді эпилепсияда микроРНҚ-лардың рөлін зерттеу. Әдебиеттік шолу

Shotpakova A.K., Rakhmanov S.B., Abilov T.S., Zhumabay N.A.
Modern view on the morphofunction of the heart and intracardiac nervous structures
Almussina A.K., Rakhimzhanova R.I., Dautov T.B., Ganiyeva A.A.
Radiological methods in the diagnosis of atrioventricular septal defect
Ganiyeva A.A., Rakhimzhanova R.I., Dautov T.B., Abdrakhmanova Zh.S., Almussina A.K., Gani A.B., Duisebayeva N.A., Imangeldina M.S., Bektybayeva N.M.
Modern approaches to the diagnosis, surgical correction, and long-term monitoring of patients with common arterial trunk
Ерназаров А.А., Ошибаева А.Е., Нускабаева Г.О., Кырыкбаева С.С., Кемельбеков К.С., Аймагамбетова А.О., Дуйсенбаева Б.С.
Анализ факторов риска сердечно-сосудистых заболеваний у молодежи. Обзор литературы
Маркабаева А.М., Керимкулова А.С., Нурпеисова Р.Г., Зекенова Е.М., Умбетжанова А.Т., Кубекова С.Ж., Алдабекова Г.У.
Программа управления заболеванием при артериальной гипертензии
Алдабекова Г.У., Мусина А.А., Камалбекова Г.М., Данбаева Ж.С., Хамидуллина З.Г., Оспанова А.Б., Исаева Е.И.
Организационные аспекты управления риск ориентированных технологий в организациях родовспоможения
Madiyeva M., Kaskabayeva A., Rymbayeva T., Kanapiyanova G., Bersimbekova G., Aubakirov A., Beisenova A.
The Role of Biochemical Markers in Bone Metabolism in Children and Adolescents. Literature review
Нургалиева Б.К.
Эрадикационная терапия Helicobacter pylori

КЛИНИЧЕСКИЙ СЛУЧАЙ

Nogayeva M.G., Atasheva A.A., Omargali K.S., Nurgalieva B.K.
Clinical case: poststreptococcal arthritis associated with COVID-19
Kussainova A.A., Akhmetova A.K., Zhunussova D.K., Yurkovskaya O.A., Dyusseneva D.K., Adilgozhina S.M., Shamshudinov T.M., Bolekbayeva A.Y., Kassym L.T.
Systemic retinoids in the management of moderate-to-severe acne: a clinical case study
Шалабаев Б.Д., Бейбіт Ә.Б., Нуржанов А.А., Ганиева Е.Д., Сапаев М.Н., Манатова А.М., Куаныш Ж.М., Жарлыганова Д.С.
Вариант хирургического лечения синовиальной саркомы мягких тканей лица
Кузнецова Т.В., Парфенов А.В., Сурова А.Ж., Бекетова Б.Б., Мадиева М.Р., Раисов Д.Т., Рахимбеков А.В.
Полная транспозиция органов (Situs Viscerum Inversus Totalis) на примере клинического случая

174-184 Шотпақова А.Қ., Рахманов С.Б., Абилов Т.С., Жұмабай Н.А.
Жүрек және оның жүйке құрылымдарының морфофункциясы туралы заманауи көзқарас
185-195 Альмусина А.К., Рахимжанова Р.И., Даутов Т.Б., Ганиева А.А.
Атриовентрикулярлық септальды ақауды бағалауда сәулелік диагностика әдістері
196-207 Ганиева А.А., Рахимжанова Р.И., Даутов Т.Б., Абдрахманова Ж.С., Альмусина А.К., Гани А.Б., Дуйсебаева Н.А., Имангелдина М.С., Бектыбаева Н.М.
Туа біткен жалпы трункус артериозы бар науқастардың диагностикасының, хирургиялық түзеуінің және ұзақ мерзімді бақылауының заманауи тәсілдері
208-218 Ерназаров А.А., Ошибаева А.Е., Нускабаева Г.О., Кырыкбаева С.С., Кемельбеков К.С., Аймагамбетова А.О., Дуйсенбаева Б.С.
Жастардағы жүрек-қан тамырлары ауруларының қауіп факторларын зерттеу. Әдебиеттік шолу
219-231 Маркабаева А.М., Керимкулова А.С., Нурпеисова Р.Г., Зекенова Е.М., Умбетжанова А.Т., Кубекова С.Ж., Алдабекова Г.У.
Артериялық гипертензия кезінде ауруды басқару бағдарламасы
232-249 Алдабекова Г.У., Мусина А.А., Камалбекова Г.М., Данбаева Ж.С., Хамидуллина З.Г., Оспанова А.Б., Исаева Е.И.
Босандыру ұйымдарындағы бағдарланған технологиялардың тәуекелін басқарудың ұйымдастырушылық аспектілері
250-256 Мадиева М., Каскабаева А., Рымбаева Т., Канапиянова Г., Берсимбекова Г., Аубакиров А., Бейсенова А.
Балалар мен жасөспірімдердегі сүйек алмасуындағы биохимиялық маркерлардың рөлі. Әдебиеттік шолу
257-266 Nurgaliyeva B.K.
Eradication Therapy for Helicobacter pylori

КЛИНИКАЛЫҚ ЖАҒДАЙ

267-273 Ногаева М.Г., Аташева А.А., Омарғали Қ.С., Нургалиева Б.К.
Клиникалық жағдай: COVID-19- ассоцирленген стрептококктан кейінгі артрит
274-280 Кусаинова А.А., Ахметова А.К., Жунусова Д.К., Юрковская О.А., Дюсенева Д.К., Адильгожина С.М., Шамшудинов Т.М., Болекбаева А.Е., Касым Л.Т.
Безеудің орташа және ауыр түрлерін емдеудегі жүйелік ретиноидтар: клиникалық жағдай
281-287 Шалабаев Б.Д., Бейбіт Ә.Б., Нуржанов А.А., Ганиева Е.Д., Сапаев М.Н., Манатова А.М., Куаныш Ж.М., Жарлыганова Д.С.
Беттің жұмсақ тіндерінің синовиальды саркомасын хирургиялық емдеудің нұсқасы
288-295 Кузнецова Т.В., Парфенов А.В., Сурова А.Ж., Бекетова Б.Б., Мадиева М.Р., Раисов Д.Т., Рахимбеков А.В.
Толық орган транспозициясы (Situs Viscerum Inversus Totalis): клиникалық жағдай мысалында

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