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Уважаемые читатели!

Представляем вашему вниманию очередной номер журнала, в котором собраны оригинальные исследования и аналитические материалы, отражающие актуальные направления современной медицины и общественного здравоохранения. Тематика выпуска охватывает широкий спектр вопросов — от молекулярно-генетических основ персонализированной терапии до социально значимых аспектов охраны здоровья женщин и детей.

Особое внимание в номере уделено вопросам **репродуктивного здоровья женщин** на разных этапах жизненного цикла. В представленных работах рассматриваются современные подходы к профилактике, ранней диагностике и персонализированному лечению онкологических заболеваний, включая анализ молекулярно-генетического профиля рака молочной железы и роли мутаций *BRCA*, а также результаты пилотного валидационного исследования по скринингу рака шейки матки методом самостоятельного забора образцов среди женщин в Казахстане. Дополняют данное направление исследования в области акушерства и перинатальной медицины, посвящённые оценке возможности вагинальных родов у женщин с рубцовыми изменениями матки как альтернативы повторному кесареву сечению, а также анализу эффективности длительного приёма фолиевой кислоты для профилактики преэклампсии у беременных с нарушениями и без нарушений фолатного цикла.

В выпуске также представлены исследования, посвящённые **кардиологическим и медико-генетическим аспектам диагностики** у пациентов различных возрастных групп. Рассматриваются особенности деформации миокарда по данным спекл-трекинг эхокардиографии у пациентов с сохранённой фракцией выброса, а также вопросы диагностики орфанных и врождённых заболеваний, включая результаты полноэкзомного секвенирования у детей с подозрением на синдром Альпорта и оценку КТ-ангиографических показателей при выявлении гипоплазии дуги аорты. Представленные данные способствуют углублению понимания патофизиологических механизмов заболеваний и совершенствованию клинической практики.

Не менее важным направлением является **оценка качества жизни пациентов и внедрение валидированных инструментов** в клиническую практику. В выпуске представлена работа по адаптации и оценке опросника качества жизни пациентов с гемофилией в Республике Казахстан, что имеет практическое значение для комплексного ведения пациентов и оценки эффективности терапии.

Отдельного внимания заслуживает статья, посвящённая **международному опыту гендерного образования медицинских работников** как инструменту профилактики гендерного насилия и возможностям его имплементации в Казахстане. Данная работа

подчёркивает междисциплинарный характер современной медицины и важность интеграции социальных и образовательных подходов в систему здравоохранения.

Редакция надеется, что материалы данного номера будут полезны практикующим врачам, исследователям, преподавателям и обучающимся, а также внесут вклад в развитие научной мысли и развитие доказательной медицины в Казахстане и за его пределами. Желаем вам интересного и плодотворного чтения.

С уважением,

Главный редактор

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The relation between hormonal changes and myocardial deformation parameters as determined by speckle-tracking echocardiography in women with preserved ejection fraction

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Abstract

In the era of technological modernization, new preventive and therapeutic strategies have been developed for cardiovascular diseases. Speckle tracking studies are no exception.

Study objective. To evaluate the values of speckle tracking echocardiography parameters in the diagnosis of left ventricular myocardial dysfunction in perimenopausal women.

Materials and methods. This study had a prospective design with a one-year follow-up period. The study included 150 female patients, aged 47 to 53 years, with known hormonal levels, corresponding to the perimenopausal period. The study was conducted at the Clinical Medical Center of the Presidential Administration of the Republic of Kazakhstan, Department of Functional Diagnostics. All tests were performed using IBM SPSS Statistics 20 (IBM, USA) with a 95% confidence level.

Study results. All 150 subjects underwent routine echocardiography, after which they were divided into two main groups: 90 women (60%) constituted the cohort of individuals with existing LV diastolic dysfunction, while the remaining 60 women, or 40%, were individuals without existing LV diastolic dysfunction. Speckle-tracking echocardiography was performed.

In the study, of the 90 patients with LV diastolic dysfunction based on routine echocardiography, 85 had basal segment systolic dysfunction. This constituted 94.5% of patients. In the remaining 5 patients (5.5%), no regressive changes in systole were detected. In the second cohort of sixty women with no LV diastolic dysfunction on routine cardiac ultrasound, only 50 (83.4%) had normal systolic function on the basal plane. The remaining 16.6% (10 patients) with normal diastolic function on routine echocardiography showed abnormal systole and pre-diastolic pathology on speckle-tracking echocardiography.

Conclusions. Routine echocardiography in our study demonstrated that it can often serve as a prognostic tool for the development of systolic myocardial dysfunction in individuals with existing left ventricular diastolic dysfunction. A direct correlation was found between the presence of decreased basal plane indices on speckle-tracking echocardiography. This means it is mandatory and recommended to implement speckle tracking in routine echocardiography as an informative predictor of future adverse cardiovascular events.

Keywords: speckle tracking echocardiography, left ventricular diastolic dysfunction, left atrium.

1. Introduction

Speckle tracking, a current echocardiographic study, is a popular and promising technique for assessing myocardial structural and functional changes. Its estimated global longitudinal myocardial strain is more sensitive to early changes in left ventricular contractility than ejection fraction and other parameters.

Attention is paid in detail to diastolic dysfunction, which has become increasingly important for assessing pathological conditions characterized by elevated left ventricular filling pressure without overt left ventricular (LV) dysfunction. In fact, assessment of diastolic function is recommended for every echocardiographic examination. Therefore, new indices have been investigated for sensitive and reliable quantitative assessment of diastolic dysfunction, particularly for the early diagnosis of cardiovascular events. Assessment of global left ventricular strain has demonstrated its role in the diagnostic and prognostic evaluation of cardiac pathologies [1]. The diagnostic capabilities of speckle-tracking echocardiography are reflected in the clinical guidelines of the European Society of Cardiology (2016–2018), the European Association of Cardiovascular Imaging (EACVI), and the American Society of Echocardiography (2016–2018). Currently, considerable attention is being paid to the use of speckle-tracking echocardiography in various cardiac pathologies, oncologic pathologies, and hormonal and metabolic disorders [2]. Importantly, speckle-tracking echocardiography can be used not only for diagnosis but also for assessing the prognosis of cardiovascular events [3].

According to the WHO, cardiac pathology is one of the most common non-specific diseases, accounting for 30% of all deaths.

Gender differences in cardiovascular diseases, particularly heart failure (HF), have been noted in several recent publications. Although sex differences in age-related cardiovascular changes are well described, little is known about how female menopause and sex hormones relate to myocardial mechanics and function [4].

Women's cardiovascular disease risk increases later in life, often coinciding with their menopausal transition. Previous studies have identified key changes associated with menopause, including changes in endogenous sex hormone levels, body fat distribution, and cardiometabolic health. Although the menopause transition is not formally recognized as a cardiovascular risk factor in guidelines, there are compelling adverse cardiometabolic changes that accompany midlife and menopause [5].

Taken together, these maladaptive changes at menopause are potentially associated with worsening myocardial function, i.e., greater left ventricular diastolic dysfunction [7,9], increased LV concentric remodeling [6,12], and altered cardiac strain indices [8,13], potentially making postmenopausal women susceptible to heart failure with preserved ejection fraction [14,18]. However, to date, no study has comprehensively examined the relationship between menopause, circulating estradiol levels, and left ventricular and left atrial myocardial strain indices. Previous studies have been relatively small and have not included comparisons between hormonal status and advanced echocardiographic techniques [9,10,14,18]. Therefore, we used a chamber-specific speckle tracking method to examine the relationship between menopause stages and cardiac geometry and mechanics (left atrium and left ventricle) in an asymptomatic population.

2. Methods

This study had a prospective design with a 12-month follow-up period. The study included 150 female patients, aged 47 to 53 years, with known hormonal levels, consistent with their perimenopausal stage. The study was conducted at the Functional Diagnostics Department of the Clinical Medical Center of the Presidential Administration of the Republic of Kazakhstan.

According to electrocardiography results, all study participants had sinus rhythm, with a heart rate of 60-90 bpm.

Exclusion criteria included congenital and acquired heart defects, coronary artery disease, atrial fibrillation, heart failure with an ejection fraction of less than 50%, chronic kidney disease, and liver and thyroid dysfunction.

Upon recruitment, all participants underwent a thorough medical history, laboratory data, electrocardiography, echocardiography with tissue Doppler, and speckle - tracking echocardiography. Hormonal status was determined by estradiol and follicle - stimulating hormone (FSH) levels, and obstetric gynecological examination was performed.

Left ventricular longitudinal strain was measured globally and regionally (basal, mid, and apical) in all patients using speckle-tracking echocardiography. Left atrial longitudinal strain was also assessed in all patients. Normal left ventricular speckle - tracking echocardiography was defined as ≤ - 18%, and for the left atrium, - 35%.

The study protocol was approved by the LEC of the NAO MUA in 2022, Protocol N 1. All subjects signed informed consent before inclusion in the study.

Echocardiographic examination

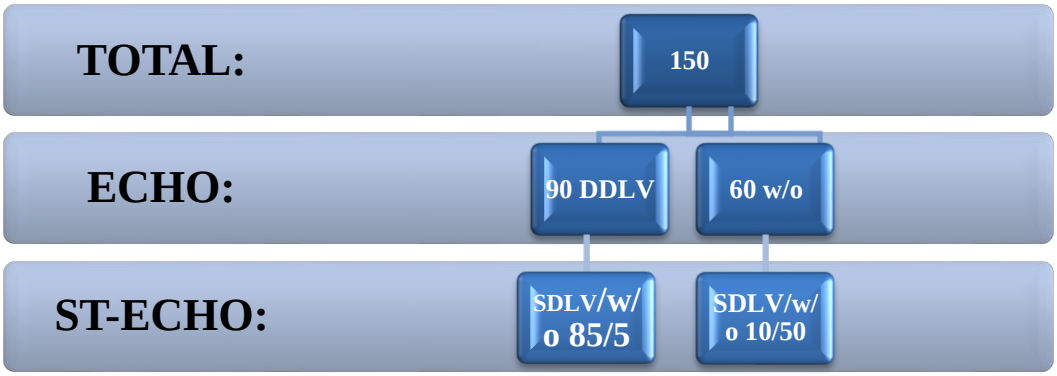
Full two-dimensional and Doppler echocardiography was performed by two experienced physicians at rest (GE Vivid E9 with a 1–5 MHz transducer) in accordance with the ASE guidelines. Left ventricular end-diastolic volume, left ventricular end-systolic volume, and ejection fraction were calculated from apical two- and four-chamber views using a modified Simpson method. Diastolic parameters, including mitral inflow velocity (E and A waves), mitral annular Doppler velocity (septal and lateral e'), left atrial volume index (LAVI), and peak tricuspid regurgitation velocity, were measured by averaging over three

consecutive cardiac cycles to assess diastolic function. Isovolumic relaxation time (IVRT) and myocardial performance index (MPI) were also measured using tissue Doppler. All patients then underwent echocardiography to assess longitudinal myocardial strain in 16 segments and determine the circulation type. Speckle-tracking echocardiography of the left atrium with determination of reservoir, conduit, and pump functions [7,9].

Statistical analysis

Results for quantitative variables with a normal distribution were expressed as mean ± standard deviation, while numerical variables with a non-normal distribution were expressed as median with interquartile range. Qualitative variables were presented as number and percentage. The Student's t-test and Mann-Whitney U-test were used to compare numerical variables with and without a normal distribution, respectively. In addition, the chi-square test was used to compare nominal variables. All tests were performed using IBM SPSS Statistics 20 (IBM, USA) with a 95% confidence level.

Diagram 1



3. Results

All 150 subjects underwent routine echocardiography, after which we divided them into two main groups: 90 women (60%) formed a cohort of individuals with existing LV diastolic dysfunction, the remaining 60 women were individuals without existing LV diastolic dysfunction. During the speckle tracking study in individuals with LVEDD according to the results of routine echocardiography, 85 out of 90 patients had a decrease in basal segment indices. This amounted to 94.5% of patients. In the remaining 5 patients (5.5%), regressive changes in myocardial dysfunction were not detected. In the second cohort of sixty women without LVEDD on routine echocardiography, only 50, or 83.4%, had no impairment in the reduction of speckle tracking echocardiography indices in the basal section. The remaining 16.6% (10 patients) with no changes in diastolic dysfunction on routine echocardiography showed decreased speckle-tracking echocardiography parameters (Tables 1 and 2).

Table 1 - Echocardiography parameters

Group statistics of routine echocardiography					
	Factor	**N**	**Mean**	**Standart deviation**	**Standard error of the mean**
E/e	DDLV	90	11.10	1.050	0.111
	w/o DDLV	60	6.78	0.666	0.086
LV MMI	DDLV	90	101.00	6.106	0.644
	w/o DDLV	60	83.75	5.488	0.709
RWT	DDLV	90	31.54	1.664	0.175
	w/o DDLV	60	25.70	1.522	0.196
SPAP	DDLV	90	36.96	1.669	0.176
	w/o DDLV	60	25.68	3.322	0.429
EF	DDLV	90	54.71	2.536	0.267
	w/o DDLV	60	60.77	2.205	0.285

Table 2 - ST-Echocardiography parameters

Group statistics of ST-Echocardiography					
	Factor	**N**	**Mean**	**Standart deviation**	**Standard error of the mean**
Global ST	DDLV	90	-16.89	0.827	0.087
	w/o DDLV	60	-20.07	1.572	0.203
LA ST	DDLV	90	-31.89	1.869	0.197
	w/o DDLV	60	-35.60	0.978	0.126

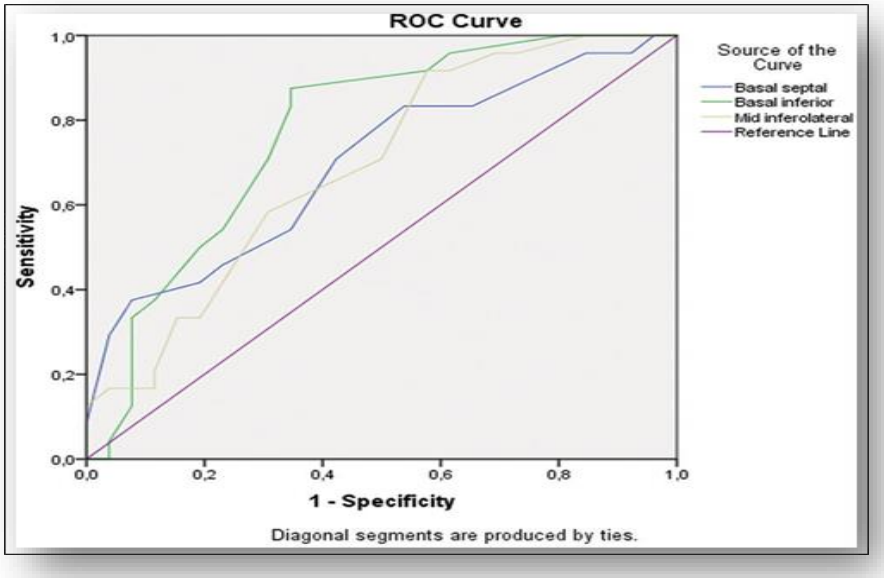


Figure 1 - ROC curve of the relationship between LV diastolic dysfunction and echocardiography segments by speckle tracking

According to Figure 1, the area under the receiver operating characteristic (ROC) curve for the correlation between the presence of left ventricular diastolic dysfunction and the basal septal segment of the left ventricle was 0.696 ± 0.075 (95% CI: 0.549–0.842, p = 0.018).

The cutoff value for the basal septal segment was -19.50. When the basal septal segment was equal to or greater than this value, a high risk of left ventricular diastolic dysfunction was predicted. The sensitivity and specificity of the method were 70.8% and 57.7%, respectively.

The area under the receiver operating characteristic (ROC) curve for the correlation between the presence of left ventricular diastolic dysfunction and the basal inferior segment was 0.772 ± 0.068 (95% CI: 0.639–0.904, p = 0.001). The cutoff value for the basal inferior segment was - 21.50. When the basal inferior segment was equal to or greater than this value, a high risk of left ventricular diastolic dysfunction was predicted. The sensitivity and specificity of the method were 87.5% and 65.4%, respectively. The area under the ROC curve for the correlation between the presence of LV diastolic dysfunction and the mid-lateral segment was AUC 0.692 ± 0.074 (95% CI: 0.547–0.838, p = 0.020). The cutoff value for the mid-lateral segment was - 20.50. When the mid-lateral segment was equal to or greater than this value, a high risk of left ventricular diastolic dysfunction was predicted. The sensitivity and specificity of the method were 70.8% and 50.0%, respectively. The area under the receiver operating characteristic (ROC) curve was 0.806 ± 0.065 (95% CI: 0.679-0.933, p < 0.001), indicating "very good" predictive performance of the model.

4. Discussion

According to the scientific article on the role of speckle-tracking echocardiography in the diagnosis and treatment of cardiovascular diseases by E.G. Nesukai and A.A. Danilenko, speckle-tracking echocardiography is a new technique for assessing myocardial function [15]. Global longitudinal strain is the most clinically used parameter in speckle-tracking echocardiography. Routine sonographic methods have a place in the diagnosis of existing clinical signs of pathology. This study examines left ventricular diastolic dysfunction as a model for assessing deformation, contractility, and other cardiac muscle functions, including left ventricular remodeling and hypertrophic processes. Atria involvement cannot be ruled out [11,12].

Relevant data continues to emerge due to the intensive use of speckle-tracking echocardiography in various patient groups with various pathologies [15,16]. For future guidelines and research, the question of supplementing left atrial data and a full examination of right ventricular function remains open, focusing on the usefulness of the results. In this study, using speckle tracking for a comprehensive assessment of myocardial function in an asymptomatic population, women had varying indicators of diastolic function. Female menopause and declining estradiol levels were associated with greater left ventricular remodeling combined with reduced left ventricular longitudinal strain. Furthermore, among postmenopausal women, decreased speckle tracking echocardiography parameters were independently associated with clinical outcomes. Taken together, these data contribute to our understanding of hormonal differences in heart failure and the predominance of postmenopausal women among heart failure patients with preserved LV function. Our findings of smaller LV dimensions, greater LV sphericity and concentricity, larger LA dimension, and worse LV diastolic function, despite better LV systolic function in women compared with men, are consistent with previous studies [15,16]. Our results extend previous data showing that, regardless of age and cardiovascular risk factors, female menopause is associated with greater LV and LA structural remodeling in tandem with a modest decrease in LV and LA longitudinal strain, despite preserved LVEF. Notably, while LV longitudinal function decreased, LV torsional function increased in postmenopausal women. Chinese American women in early menopause are at higher risk of cardiac remodeling compared with other ethnic

groups [20]. Menopause and a shorter reproductive period due to early menopause are proposed to be risk factors for the development of HF with EF in women [9,13,14,20]. Importantly, speckle tracking echocardiography is a highly sensitive and relatively afterload-independent measure of left atrial and left ventricular function, respectively. Our data suggest that strain indices and the LA stiffness index, with cutoff values of 31.6% and 18.2%, respectively, may be more sensitive for detecting subclinical kinetic changes, even when traditional left atrial (e.g., LA emptying fraction) and left ventricular (e.g., LV ejection fraction, or E/e') markers remain unchanged.

5. Conclusion

Routine echocardiography in our study demonstrated that it can often serve as a prognostic tool for the development of systolic myocardial dysfunction in individuals with pre-existing left ventricular diastolic dysfunction. A direct correlation was found between the presence of decreased basal layer indices on speckle tracking. This suggests that speckle tracking should be incorporated into routine echocardiography as an informative predictor of subsequent adverse cardiovascular events.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Conceptualization - D.G.A; Investigation - B.Z.A; Formal analysis - Z.N.S., B.Z.A; Writing - original draft - B.Z.A.; Writing - review and editing - Z.A.U., G.M.; Supervision - K.E.S., D.G.A. All authors have read and approved the final manuscript.

References

1. Lam, C. S., Arnott, C., Beale, A. L., Chandramouli, C., Hilfiker-Kleiner, D., Kaye, D. M., Voors, A. A. (2019). Sex differences in heart failure. *European heart journal*, *40*(47), 3859-3868c. https://doi.org/10.1093/eurheartj/ehz835

2. Santema, B. T., Ouwerkerk, W., Tromp, J., Sama, I. E., Ravera, A., Regitz-Zagrosek, V., Voors, A. A. (2019). Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *The Lancet*, *394*(10205), 1254-1263. https://doi.org/10.1016/S0140-6736(19)31792-1

3. Solomon, S. D., McMurray, J. J., Anand, I. S., Ge, J., Lam, C. S., Maggioni, A. P., Lefkowitz, M. P. (2019). Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *New England Journal of Medicine*, *381*(17), 1609-1620. https://doi.org/10.1056/nejmoa1908655

4. Treibel, T. A., Kozor, R., Fontana, M., Torlasco, C., Reant, P., Badiani, S., Moon, J. C. (2018). Sex dimorphism in the myocardial response to aortic stenosis. *JACC: Cardiovascular Imaging*, *11*(7), 962-973. https://doi.org/10.1016/j.jcmg.2017.08.025

5. Muka, T., Oliver-Williams, C., Kunutsor, S., Laven, J. S., Fauser, B. C., Chowdhury, R., Franco, O. H. (2016). Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA cardiology*, *1*(7), 767-776. https://doi.org/10.1001/jamacardio.2016.2415

6. El Khoudary, S. R., Wildman, R. P., Matthews, K., Thurston, R. C., Bromberger, J. T., Sutton-Tyrrell, K. (2012). Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. *Atherosclerosis*, *225*(1), 180-186. https://doi.org/10.1016/j.atherosclerosis.2012.07.025

7. Sun, Y., Liu, B., Snetselaar, L. G., Wallace, R. B., Caan, B. J., Rohan, T. E., Bao, W. (2019). Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. *JAMA network open*, *2*(7), e197337-e197337. https://doi.org/10.1001/jamanetworkopen.2019.7337

8. El Khoudary, S. R., Aggarwal, B., Beckie, T. M., Hodis, H. N., Johnson, A. E., Langer, R. D., American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. (2020). Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation*, *142*(25), e506-e532. https://doi.org/10.1161/CIR.0000000000000912

9. Sung, K. T., Chandramouli, C., Lo, C. I., Tsai, J. P., Lai, Y. H., Hsiao, C. C., Lam, C. S. (2022). Association of female menopause with atrioventricular mechanics and outcomes. *Frontiers in cardiovascular medicine*, *9*, 804336. https://doi.org/10.3389/fcvm.2022.804336

10. Duzenli, M. A., Ozdemir, K., Sokmen, A., Gezginc, K., Soylu, A., Celik, C., Tokac, M. (2010). The effects of hormone replacement therapy on myocardial performance in early postmenopausal women. *Climacteric*, *13*(2), 157-170. https://doi.org/10.3109/13697130902929567

11. Carrick-Ranson, G., Howden, E. J., Brazile, T. L., Levine, B. D., Reading, S. A. (2023). Effects of aging and endurance exercise training on cardiorespiratory fitness and cardiac structure and function in healthy midlife and older women. *Journal of Applied Physiology*, *135*(6), 1215-1235. https://doi.org/10.1152/japplphysiol.00798.2022

12. Keskin Kurt, R., Nacar, A. B., Güler, A., Silfeler, D. B., Buyukkaya, E., Karateke, A., Tanboga, I. H. (2014). Menopausal cardiomyopathy: Does it really exist? A case–control deformation imaging study. *Journal of Obstetrics and Gynaecology Research*, *40*(6), 1748-1753. https://doi.org/10.1111/jog.12368

13. Ebong, I. A., Wilson, M. D., Appiah, D., Michos, E. D., Racette, S. B., Villablanca, A., Bertoni, A. G. (2022). Relationship between age at menopause, obesity, and incident heart failure: the atherosclerosis risk in communities study. *Journal of the American Heart Association*, *11*(8), e024461. https://doi.org/10.1161/JAHA.121.024461

14. Hall, P. S., Nah, G., Howard, B. V., Lewis, C. E., Allison, M. A., Sarto, G. E., Parikh, N. I. (2017). Reproductive factors and incidence of heart failure hospitalization in the Women's Health Initiative. *Journal of the American College of Cardiology*, *69*(20), 2517-2526. https://doi.org/10.1016/j.jacc.2017.03.557

15. Lee, K. Y., Kim, H. L., Kim, K. J. (2023). Sex difference in the age-related decline of global longitudinal strain of left ventricle. *Scientific Reports*, *13*(1), 18441. https://doi.org/10.1038/s41598-023-42286-9

16. Yusifov, A., Woulfe, K. C., Bruns, D. R. (2022). Mechanisms and implications of sex differences in cardiac aging. *The journal of cardiovascular aging*, *2*, 20. https://doi.org/10.20517/jca.2022.01

17. Beaumont, A. J., Campbell, A. K., Unnithan, V. B., Oxborough, D., Grace, F., Knox, A., Sculthorpe, N. F. (2024). The influence of age and exercise training status on left ventricular systolic twist mechanics in Healthy Males—An Exploratory Study. *Journal of Cardiovascular Development and Disease*, *11*(10), 321. https://doi.org/10.3390/jcdd11100321

18. Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Voigt, J. U. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart Journal-Cardiovascular Imaging*, *16*(3), 233-271. https://doi.org/10.1093/ehjci/jev014

19. Stylianos Tzeis, M. D., Gerstenfeld, E. P., Jonathan Kalman, M. D., Saad, E. B., Shamloo, A. S., Andrade, J. G., Trines, S. A. (2024). 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. https://doi.org/10.1002/joa3.13082

20. Magnussen, C., Niiranen, T. J., Ojeda, F. M., Gianfagna, F., Blankenberg, S., Njølstad, I., Schnabel, R. B. (2017). Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation*, *136*(17), 1588-1597. https://doi.org/10.1161/circulationaha.117.028981

21. Ebong, I. A., Wilson, M. D., Appiah, D., Michos, E. D., Racette, S. B., Villablanca, A., Bertoni, A. G. (2022). Relationship between age at menopause, obesity, and incident heart failure: the atherosclerosis risk in communities study. *Journal of the American Heart Association*, *11*(8), e024461. https://doi.org/10.1161/JAHA.121.024461

22. De Gregorio, C., Marini, H., Alibrandi, A., Di Benedetto, A., Bitto, A., Adamo, E. B., Arcoraci, V. (2017). Genistein supplementation and cardiac function in postmenopausal women with metabolic syndrome: results from a pilot strain-echo study. *Nutrients*, *9*(6), 584. https://www.mdpi.com/2072-6643/9/6/584#

Аластау фракциясы сақталған әйелдердегі спекл-трекинг эхокардиографиясының деректері бойынша гормоналды өзгерістер мен миокард деформациясының параметрлері арасындағы байланыс

Дербисалина Г.А. [1], Бальмұхамедова Ж.А. [2], Маринскис Г., Жолдасбекова А.Ө. [4], Келімбердиева Э.С. [5], Землянская Н.С. [6]

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Түйіндеме

Технологиялық жаңғыру дәуірінде жүрек-қан тамырлары ауруларына қарсы жаңа профилактикалық және емдік стратегиялар жасалды. Дақты бақылау зерттеулері де ерекшелік емес.

Мақсаты. Перименопаузадағы әйелдерде сол жақ қарынша миокард дисфункциясын диагностикалауда дақты бақылау эхокардиографиясы параметрлерінің мәндерін бағалау.

Материалдар мен әдістер. Бұл зерттеу бір жылдық бақылау кезеңімен перспективалық дизайнға ие болды. Зерттеуге перименопауза кезеңіне сәйкес келетін белгілі гормоналды деңгейі бар, 47 жастан 53 жасқа дейінгі 150 әйел пациент қатысты. Зерттеу Қазақстан Республикасы Президенті Әкімшілігінің Медициналық орталығының функционалдық диагностика бөлімінде жүргізілді. Барлық сынақтар IBM SPSS Statistics 20 (IBM, АҚШ) көмегімен 95% сенімділік деңгейімен жүргізілді.

Зерттеу нәтижелері. Барлық 150 субъектіге жоспарлы эхокардиография жасалды, содан кейін біз оларды екі негізгі топқа бөлдік: 90 әйел (60%) сол жақ қарыншаның диастолалық дисфункциясы бар адамдардың когортасын құрады, ал қалған 60 әйел немесе 40% сол жақ қарыншаның диастолалық дисфункциясы жоқ адамдар болды. Дақтарды бақылау эхокардиографиясы жүргізілді.

Зерттеуде, әдеттегі эхокардиографияға негізделген сол жақ қарыншаның диастолалық дисфункциясы бар 90 науқастың 85-інде базальды сегменттің систолалық дисфункциясы болды. Бұл науқастардың 94,5%-ын құрады. Қалған 5 науқаста (5,5%) систолада регрессивті өзгерістер анықталмады. Әдеттегі жүрек ультрадыбысында сол жақ қарыншаның диастолалық дисфункциясы жоқ алпыс әйелден тұратын екінші когортада тек 50-інде (83,4%) базальды жазықтықта қалыпты систолалық функция болды. Әдеттегі

эхокардиографияда қалыпты диастолалық функциясы бар қалған 16,6%-да (10 науқас) дақтарды бақылау эхокардиографиясында қалыптан тыс систола және диастолалыққа дейінгі патология байқалды.

Қорытынды. Біздің зерттеуіміздегі әдеттегі эхокардиография сол жақ қарыншаның диастолалық дисфункциясы бар адамдарда систолалық миокард дисфункциясының дамуының болжамдық құралы ретінде қызмет ете алатынын көрсетті. Дақтарды бақылау эхокардиографиясында базальды жазықтық индекстерінің төмендеуі арасында тікелей корреляция анықталды. Бұл болашақтағы жағымсыз жүрек-қан тамырлары оқиғаларының ақпараттық болжаушысы ретінде күнделікті эхокардиографияда дақтарды бақылауды енгізу міндетті және ұсынылғанын білдіреді.

Түйін сөздер: дақтарды бақылау эхокардиографиясы, сол жақ қарыншаның диастолалық дисфункциясы, сол жақ жүрекше.

Связь гормональных изменений и параметров деформации миокарда по данным спекл-трекинг эхокардиографии у женщин с сохранной фракцией выброса

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Резюме

В эпоху модернизирования технологий были разработаны новые профилактические и терапевтические стратегии и для сердечно-сосудистых заболеваний. Спекл-трекинговое исследование тому не исключение.

Цель исследования. Оценить значения параметров спекл трекинг эхокардиографии при диагностике дисфункций миокарда левого желудочка у лиц женского пола в период перименопаузы.

Материалы и методы. Данное исследование имело проспективный дизайн с продолжительностью периода наблюдения в год. В исследовании участвовало 150 пациенток женского пола, в возрасте от 47 до 53 лет, с известным гормональным уровнем, в соответствии с переменопаузальным периодом. Исследование проводилось в Больница Медицинского Центра Управления Делами Президента Республики Казахстан, отделении функциональной диагностики. Все тесты проводились с использованием IBM SPSS Statistics 20 (IBM, США) с доверительной вероятностью 95%.

Результаты исследования. Всем 150 исследуемым было воспроизведено рутинное эхокардиографическое исследование, после которого мы разделили их на две основные группы: 90 женщин

(60%) составили когорту лиц с имеющейся диастолической дисфункцией ЛЖ, оставшиеся 60 женщин, а это 40%, явились лицами без имеющейся диастолической дисфункции ЛЖ. Произвели спекл-трекинг ЭХОКГ.

В ходе исследования у когорты лиц с наличием диастолической дисфункции ЛЖ по результатам рутинного ЭХОКГ, из 90 пациенток, у 85 пациенток имелась систолическая дисфункция базального сегмента. Это составило 94,5 % пациенток. У оставшихся 5 пациенток (5,5%) регрессивные изменения со стороны систолы выявлены не были. У второй когорты шестидесяти женщин с отсутствием диастолической дисфункции ЛЖ на рутинном узи сердца, лишь у 50 , а это 83,4%, систолическая функция на базальном срезе нарушена не была. Оставшиеся 16,6 % - 10 пациенток, без изменений диастолической функции на ЭХОКГ рутинном, выдали показатели нарушения систолы и пред диастолической патологии при исследовании на спекл-трекинг ЭХОКГ.

Выводы. Рутинный метод эхокардиографии в рамках нашего исследования показал, что он зачастую может выступать как прогностический метод развития систолической дисфункции миокарда у лиц, с уже имеющейся диастолической дисфункцией миокарда левого желудочка. Выявлена прямая связь наличия снижения показателей базальных слоев на спекл-трекинг. Это означает обязательным и рекомендованным внедрить спекл-трекинг к рутинному обследованию ЭХОКГ, как информативный метод-предиктор дальнейших неблагоприятных сердечно-сосудистых событий.

Ключевые слова: спекл-трекинг эхокардиография, диастолическая дисфункция миокарда левого желудочка, левое предсердие.

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Agreement between Z-score and an arch-to-ascending aorta ratio derived from CT angiography for detection of aortic arch hypoplasia

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Abstract

Background. Aortic arch hypoplasia (AAH) is an important congenital cardiovascular abnormality that requires accurate anatomical characterization for appropriate surgical planning. Computed tomography angiography (CTA) provides high-resolution measurements of the ascending aorta and transverse aortic arch; however, different diagnostic criteria may classify hypoplasia inconsistently.

Objective. This study aimed to compare the agreement between a Z-score-based definition of AAH and a ratio-based morphologic criterion derived from CTA measurements.

Methods. This retrospective study included 48 pediatric patients with clinically confirmed AAH who underwent CTA. The ascending aorta diameter, transverse aortic arch diameter, and the arch-to-ascending aorta (Arch/AAo) ratio were obtained from multiplanar reformatted CTA images. Hypoplasia was defined using two approaches: (1) Z-scores (≤ −2), and (2) a ratio-based criterion (Arch/AAo < 0.50). Summary statistics were computed for all measurements, and agreement between methods was assessed using percent agreement, Cohen's κ, and McNemar's test.

Results. The mean ascending aorta diameter was 0.95 ± 0.46 cm, the mean transverse arch diameter was 0.50 ± 0.27 cm, and the median Arch/AAo ratio was 0.50 (IQR 0.43-0.65). The Z-score method classified 47 of 48 patients (97.9%) as hypoplastic, whereas the ratio criterion identified 18 patients (37.5%) as hypoplastic. Agreement between methods was 44.2%, with a Cohen's κ of 0.03, indicating minimal concordance beyond chance. McNemar's test demonstrated significant disagreement between classifications ($\chi^2 = 22.04$).

Conclusion. The Z-score and Arch/AAo ratio methods differ substantially in how they classify AAH. While Z-scores incorporate normative size adjustment, the ratio criterion reflects anatomical proportionality and identifies a more selective subset of patients with marked transverse arch narrowing. Clinicians should recognize these methodological differences when assessing AAH and selecting criteria for diagnosis or surgical decision-making.

Keywords: aortic arch hypoplasia, congenital heart defects, computed tomography angiography, Z-score, aortic ratio, pediatric cardiovascular imaging, aortic measurements, diagnostic agreement.

1. Introduction

Congenital anomalies of the aortic arch are relatively uncommon and may coexist with other congenital cardiovascular disorders [1, 2]. In most cases, these anomalies are detected incidentally on imaging in otherwise asymptomatic patients [3]. An important exception occurs when the aberrant arch configuration forms a complete vascular ring, encircling the trachea and esophagus and potentially producing compressive symptoms [4].

Aortic arch hypoplasia (AAH) is defined by comparing the external diameter of each arch segment with that of the ascending aorta, which is assumed to represent normal caliber [5]. Based on established criteria, the proximal transverse arch is considered hypoplastic when its external diameter measures <60% of the ascending aorta (AAo), the distal transverse arch when <50% [6, 7], and the aortic isthmus when <40% of the AAo diameter [8]. AAH may occur as an isolated abnormality or in association with other aortic lesions that impede systemic outflow, such as coarctation and interruption of the aorta [9]. It may also coexist with intracardiac defects, including atrial septal defect, ventricular septal defect, or patent ductus arteriosus [10].

Computed tomography angiography (CTA) is a non-invasive imaging modality that enables accurate detection and characterization of aortic arch anomalies through high-resolution visualization of anatomical relationships, advanced post-processing techniques (Volume Rendering, Maximum Intensity Projection, and Multiplanar Reformation), and the ability to identify associated congenital abnormalities [11]. The high spatial resolution of CTA, combined with its capacity to evaluate extracardiac structures such as the great vessels, makes it the preferred modality for generating three-dimensional models in congenital heart disease [12, 13] *(Figure 1)*.

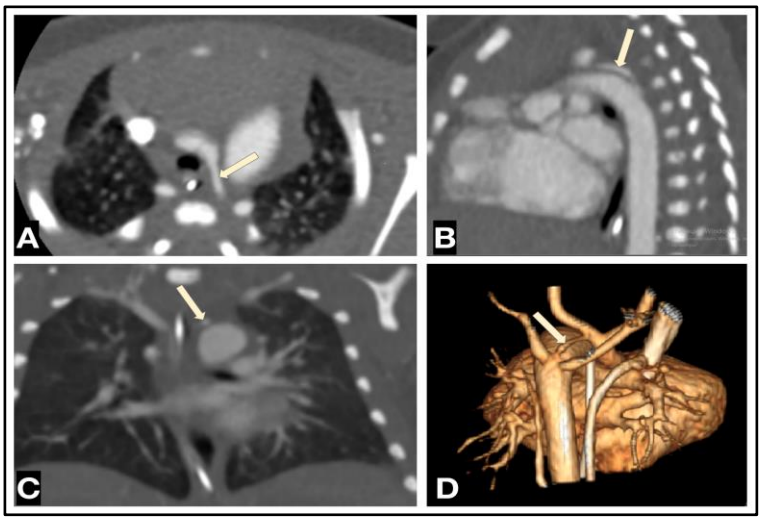

Figure 1 - CTA multiplanar images of a 5-day-old patient with AAH. (A) Axial plane, (B) sagittal plane, and (C) coronal plane demonstrate the narrowed transverse aortic arch, indicated by the yellow arrow. (D) Three-dimensional volume-rendered reconstruction provides an overview of the aortic arch anatomy, with the hypoplastic segment similarly highlighted

Despite the central role of CTA imaging in the evaluation of congenital aortic arch pathology, there is no consensus regarding the optimal criterion for defining AAH, and different measurement approaches may classify the same anatomy inconsistently. In particular, Z-score-based assessment [14, 15] and arch-to-ascending aorta (Arch/AAo) ratio-based morphological criteria are both used in clinical practice, yet their level of agreement has not been adequately examined. Therefore, this study aimed to compare these two commonly employed methods: Z-scores and the Arch/AAo diameter ratio using CTA-derived measurements in a cohort of patients with clinically confirmed AAH. By assessing the concordance between these approaches, we sought to clarify their diagnostic alignment and highlight potential implications for clinical evaluation and surgical planning.

2. Material and methods

Study design and population

This retrospective study included 48 consecutive pediatric patients with a confirmed clinical diagnosis of AAH who underwent CTA as part of their diagnostic evaluation at the Heart Center of the University Medical Center in Astana, Kazakhstan, between 2020 and 2023. Inclusion criteria were patients with available CTA imaging of sufficient quality to allow precise measurement of both the AAo and the aortic arch. Patients with incomplete CTA datasets, nondiagnostic image quality, or prior aortic surgery were excluded. All diagnoses were established by a multidisciplinary team consensus consisting of pediatric cardiologists, cardiothoracic surgeons, and radiologists.

Written informed consent was obtained from the legal representatives of pediatric patients for publication and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Heart

Center, University Medical Center, Astana, Kazakhstan (21 Jan 2022/No. 01-110/2022).

Imaging acquisition

CTA examinations were performed using a Siemens Somatom Definition AS 64-slice scanner. Prospective ECG gating was applied to minimize cardiac motion artifacts. Intravenous iodinated contrast medium (Ultravist 370; 1.5-2.0 mL/kg) was administered using a dual-head injector at an infusion rate of 0.5-2.0 mL/s. Bolus tracking was performed with the region of interest positioned in the AAo and an acquisition trigger threshold of 100 Hounsfield units. Axial images were reconstructed with a slice thickness of 0.6 mm and a reconstruction increment of 0.1 mm. Multiplanar reformations were generated using syngo.via (Siemens, Germany) to obtain measurements perpendicular to the vascular axis.

Aortic diameter measurements

Z-score method [14]: the Z-score value reported in the CTA report (Heart Center institutional pipeline) was used to determine hypoplasia. Hypoplasia is defined as $Z \leq -2$. Z-scores were calculated by the CTA reporting software, normalized to body surface area.

AAH was defined using the Arch/AAo diameter ratio:

$$\frac{Aortic\ \ arch\ \ diameter}{Ascending\ \ aorta\ \ diameter} < 0.5.$$

Aortic arch diameter/Ascending aorta diameter<0.5.

This threshold is consistent with established radiologic and surgical criteria for clinically significant transverse arch hypoplasia [15].

Statistical Analysis

Statistical analyses were performed using Stata version 18.0 (STATA, StataCorp, Texas, US). Continuous variables were summarized using mean, standard deviation (SD), median, and interquartile range (IQR). Categorical variables were expressed as counts and percentages, with comparisons conducted using the Chi-square or Fisher's exact test, as appropriate. Normality was assessed using the Shapiro-Wilk test. Agreement between the Z-score method and the ratio-based method was evaluated using overall percent agreement, Cohen's κ statistic, and McNemar's test based on a 2×2 contingency table. A p-value < 0.05 was considered statistically significant.

3. Results

Patient cohort

A total of 48 patients with clinically confirmed AAH were included. After cleaning and standardization of CTA measurements, complete aortic diameter data (AAo and aortic arch) were available in all analyzable cases, and these were used for the Arch/AAo ratio calculation. The distribution of CTA-derived diameters is presented in *Table 1*.

Table 1 - Descriptive statistics of aortic measurements

Measurement	Mean	SD	Median	IQR	Min	Max
AAo	0.946	0.458	0.80	0.70-1.00	0.40	3.00
Arch	0.497	0.269	0.40	0.385-0.50	0.18	1.70
Ratio	0.539	0.154	0.50	0.43-0.65	0.30	1.00
Z-score (CTA)	-4.149	1.748	-3.965	-4.752- -2.950	-9.40	-1.98

Arch-to-ascending aorta diameter ratio

The Arch/AAo ratio was calculated in all patients with complete aortic measurements. The distribution of ratio values *(Figure 1)* demonstrated substantial anatomical variability, with a subset of patients exhibiting markedly reduced ratios consistent with pronounced transverse arch narrowing. Histogram plots of the AAo diameter, transverse aortic arch diameter, and the resulting Arch/AAo ratio illustrate the variability within the cohort and highlight the morphological differences captured by this proportional metric.

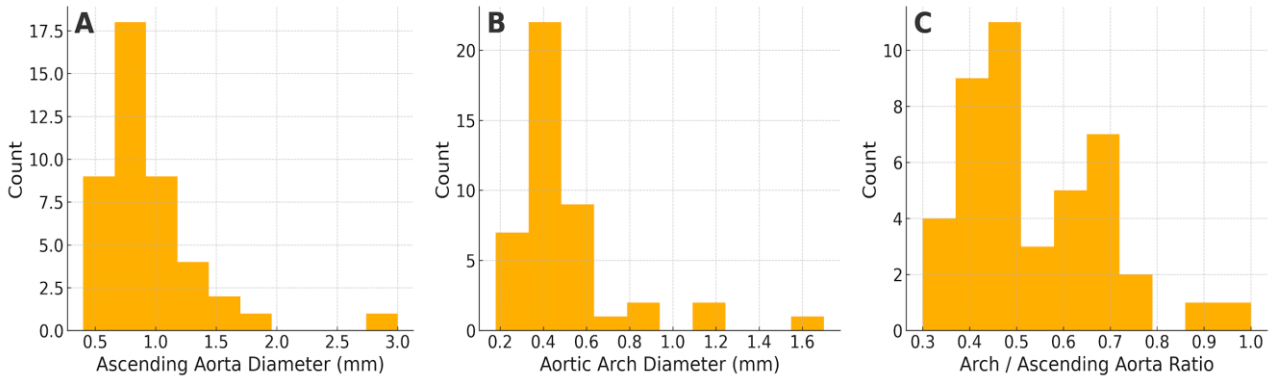

Figure 2 - Distribution of AAo, aortic arch, and Arch/AAo ratio measurements in the study cohort. The panel presents histograms of (A) AAo diameter, (B) transverse aortic arch diameter, and (C) the Arch/AAo ratio. All measurements were obtained from CTA in patients with complete aortic diameter data included in the final analysis

Agreement between the Z-score and the arch-to-ascending aorta ratio

An agreement analysis between the Z-score method and the ratio-based criterion was performed in all 48 patients *(Table 2)*. Using the <0.50 threshold, 18 patients were classified as hypoplastic by the ratio method. Based on available and clinically derived Z-score classifications, 47 patients were categorized as hypoplastic. The agreement analysis showed 18 concordant hypoplastic classifications and 25 discordant classifications, with one case classified as negative by both methods. Overall agreement was 44.2%. Cohen's κ was 0.03, and McNemar's test yielded a χ^2 value of 22.04.

Table 2 - Agreement between methods

Comparison	n concordant hypoplasia	n discordant	κ (95% CI)	McNemar p
Z-score vs Ratio	22	25	0.03	22.04

Associated cardiovascular anomalies

Chi-square and Fisher's exact tests were applied to assess the clinical characteristics of patients with AAH and their associated chromosomal and cardiovascular anomalies, which were diagnosed using echocardiography and CTA. The results of these analyses are presented in *Table 3*.

Table 3 - Clinical data of 48 patients with AAH and their associated cardiovascular anomalies

Characteristics	Options	Number (Percentage)
Imaging modalities	64-slice CTA	48 (100.0%)
	Echocardiography	48 (100.0%)
Aortic arch side	Left	46 (95.8%)
	Right	2 (4.2%)
Chromosome abnormalities	Down syndrome	2 (4.2%)
Combined cardiovascular anomalies	Ventricular septal defect	33 (68.8%)
	Atrial septal defect	21 (43.8%)
	Atrioventricular septal defect	5 (10.4%)
	Coarctation of the aorta	28 (58.3%)
	Patent ductus arteriosus	33 (68.8%)
	Patent foramen ovale	19 (39.6%)
	Aortopulmonary window	1 (2.1%)
	Transposition of the great arteries	8 (16.7%)
	Bicuspid aortic valve	7 (14.6%)
	Ebstein's anomaly	1 (2.1%)
	Taussig-Bing anomaly	3 (6.3%)
Myocardial hypertrophy	Left	8 (16.7%)
	Right	1 (2.1%)
	Both	1 (2.1%)

4. Discussion

The comparison between the ratio-based method and the Z-score classification demonstrated substantial variation in how each approach identifies AAH. The ratio method, which reflects the proportional relationship between the aortic arch and the AAo [17], classified a smaller proportion of patients as hypoplastic, whereas the Z-score method identified nearly all patients as hypoplastic. This resulted in a low level of agreement between the two approaches. Cohen's κ was near zero, indicating minimal concordance beyond chance, and McNemar's test showed significant directional disagreement *(Table 2)*, suggesting that the two methods categorize patients differently in a non-random manner.

These findings indicate that while CTA remains essential for evaluating aortic arch anatomy [18], notable methodological differences exist between the size-adjusted Z-score assessment and the morphology-based ratio criterion. The ratio method emphasizes structural disproportionality between aortic segments [19], while Z-scores rely on deviation from normative pediatric reference data [20]. As a result, the ratio approach appears to function as a more restrictive anatomical measure, identifying only those patients with pronounced narrowing of the transverse aortic arch.

The ratio has been widely adopted as a diagnostic criterion in prior research. Kiraly et al. identified an empiric threshold of 0.5 for differentiating normal from hypoplastic arches based on the distribution of Arch/AAo ratios. Most associated congenital anomalies were similarly distributed across both groups, except for atrial septal defect, which was consistently more frequent among patients with a hypoplastic arch [21]. In their case report describing endovascular treatment of recurrent aortic hypoplasia and coarctation in a 15-year-old patient, Rhodes et al. defined a hypoplastic aortic arch as an Arch/AAo diameter ratio of <0.5 [22]. Despite its widespread use, the definition and management of aortic hypoplasia, especially in relation to coarctation, remain areas of ongoing research and clinical debate [23-25].

This study has several limitations. Its retrospective design and the absence of standardized measurement acquisition may introduce selection and measurement bias. Z-scores were inconsistently documented and could not be recalculated from raw data, reducing uniformity in the reference standard. The relatively small cohort and the imbalance between hypoplastic and non-hypoplastic classifications also constrained the robustness of agreement statistics. Larger prospective studies with standardized measurements and recalculated Z-scores are needed to validate these findings.

5. Conclusion

This study evaluated two commonly used approaches for identifying AAH: Z-score assessment and a morphologic ratio-based criterion derived from CTA measurements. The ratio method identified a smaller subset of patients as having a hypoplastic arch, resulting in limited agreement with Z-score classification. These findings emphasize that the two methods reflect distinct aspects of aortic arch anatomy: Z-scores incorporate normative size adjustment, whereas the ratio criterion captures relative structural narrowing. When interpreting imaging findings or planning surgical management, clinicians should be aware of these methodological differences, as the selected definition may influence which patients are categorized as having clinically significant AAH. Further research incorporating standardized measurement protocols and larger cohorts may help refine the optimal approach for consistent and clinically meaningful identification of arch hypoplasia.

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Conflict of Interest

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

Author Contributions

Conceptualization: Moldakhanova Zh.A.; Methodology: Moldakhanova Zh.A.; Formal analysis and investigation: Nurmakhan Zh. ZH, Bastarbekova L.A.; Writing - original draft preparation: Moldakhanova Zh.A., Zholshybek N. ZH; Writing - review and editing: Dautov T.B., Zholshybek N. ZH; Visualization: Zh.S. Abdrakhmanova; Resources: Dautov T.B.; Supervision: Rakhimzhanova R.I.

References

1. Salzillo, C., La Verde, M., Imparato, A., Molitierno, R., Lucà, S., Pagliuca, F., Marzullo, A. (2024). Cardiovascular diseases in public health: Chromosomal abnormalities in congenital heart disease causing sudden cardiac death in children. *Medicina*, *60*(12), 1976. https://doi.org/10.3390/medicina60121976

2. Koplay, M., Seher, N. (2025). Computed tomography and magnetic resonance imaging findings in congenital cardiovascular anomalies. *Diagnostic and interventional radiology (Ankara, Turkey)*. https://doi.org/10.4274/dir.2025.252878

3. Молдаханова, Ж. А., Рахимжанова, Р. И., Даутов, Т. Б., Бастарбекова, Л. А., Калиев, Б. Б. (2023). Interrupted aortic arch in children: An in-depth look at etiology, embryological mechanisms, and morphology (a literature review). *Репродуктивная медицина (Центральная Азия)*, (3 (56)), 80-85. https://doi.org/10.37800/RM.3.2023.80-85

Moldaxanova, Zh. A., Raximzhanova, R. I., Dautov, T. B., Bastarbekova, L. A., Kaliev, B. B. (2023). Interrupted aortic arch in children: An in-depth look at etiology, embryological mechanisms, and morphology (a literature review). Reproduktivnaya medicina (Central`naya Aziya), (3 (56)), 80-85. https://doi.org/10.37800/RM.3.2023.80-85

4. Türkvatan, A., Büyükbayraktar, F. G., Ölçer, T., Cumhur, T. (2009). Congenital anomalies of the aortic arch: evaluation with the use of multidetector computed tomography. *Korean Journal of Radiology*, *10*(2), 176. https://doi.org/10.3348%2Fkjr.2009.10.2.176

5. Priya, S., Thomas, R., Nagpal, P., Sharma, A., Steigner, M. (2018). Congenital anomalies of the aortic arch. *Cardiovascular diagnosis and therapy*, *8*(Suppl 1), S26. https://doi.org/10.21037/cdt.2017.10.15

6. Singh, S., Hakim, F. A., Sharma, A., Roy, R. R., Panse, P. M., Chandrasekaran, K., ... & Mookadam, F. (2015). Hypoplasia, pseudocoarctation and coarctation of the aorta–a systematic review. *Heart, Lung and Circulation*, *24*(2), 110-118. https://doi.org/10.1016/j.hlc.2014.08.006

7. Fraund, S., Böning, A., Scheewe, J., Cremer, J. T. (2002). Antero-axillary access for hypoplastic aortic arch repair. *The Annals of thoracic surgery*, *73*(1), 278-280. https://doi.org/10.1016/S0003-4975(01)02861-2

8. Hanneman, K., Newman, B., Chan, F. (2017). Congenital variants and anomalies of the aortic arch. *Radiographics*, *37*(1), 32-51. https://doi.org/10.1148/rg.2017160033

9. Moldakhanova, Z., Rakhimzhanova, R., Dautov, T., Bastarbekova, L., Kaliyev, B., Almussina, A., Zholshybek, N. (2025). A comparative analysis of CT angiography and echocardiography in the evaluation of chest findings in patients with interrupted aortic arch. *Frontiers in Radiology*, *5*, 1616112. https://doi.org/10.3389/fradi.2025.1616112

10. Onalan, M. A., Temur, B., Aydın, S., Basgoze, S., Guzelmeric, F., Odemis, E., Erek, E. (2021). Management of aortic arch hypoplasia in neonates and infants. *Journal of Cardiac Surgery*, *36*(1), 124-133. https://doi.org/10.1111/jocs.15212

11. Baz, R. O., Refi, D., Scheau, C., Axelerad, A., Baz, R. A., Niscoveanu, C. (2024). CT Angiography for Aortic Arch Anomalies: Prevalence, Diagnostic Efficacy, and Illustrative Findings. *Diagnostics*, *14*(17), 1851. https://doi.org/10.3390/diagnostics14171851

12. Bae, S. B., Kang, E. J., Choo, K. S., Lee, J., Kim, S. H., Lim, K. J., Kwon, H. (2022). Aortic arch variants and anomalies: embryology, imaging findings, and clinical considerations. *Journal of cardiovascular imaging*, *30*(4), 231. https://doi.org/10.4250/jcvi.2022.0058

13. Bastarbekova, L., Rakhimzhanova, R., Dautov, T., Altenov, K., Moldakhanova, Z., Zholshybek, N. (2025). Selecting optimal imaging modalities for total anomalous pulmonary venous connection visualization. *Egyptian Journal of Radiology and Nuclear Medicine*, *56*(1), 177. https://doi.org/10.1186/s43055-025-01587-x

14. den Dekker, M. H., Slieker, M. G., Blank, A. C., Haas, F., Freund, M. W. (2013). Comparability of Z-score equations of cardiac structures in hypoplastic left heart complex. *Journal of the American Society of Echocardiography*, *26*(11), 1314-1321. https://doi.org/10.1016/j.echo.2013.07.022

15. Karamlou, T., Bernasconi, A., Jaeggi, E., Alhabshan, F., Williams, W. G., Van Arsdell, G. S., Caldarone, C. A. (2009). Factors associated with arch reintervention and growth of the aortic arch after coarctation repair in neonates weighing less than 2.5 kg. *The Journal of thoracic and cardiovascular surgery*, *137*(5), 1163-1167. https://doi.org/10.1016/j.jtcvs.2008.07.065

16. Siewers, R. D., Ettedgui, J., Pahl, E., Tallman, T., del Nido, P. J. (1991). Coarctation and hypoplasia of the aortic arch: will the arch grow? *The Ann. of thoracic surgery*, *52*(3), 608-613. https://doi.org/10.1016/0003-4975(91)90958-S

17. Brouwer, M. H. J., Cromme-Dijkhuis, A. H., Ebels, T., Eijgelaar, A. (1992). Growth of the hypoplastic aortic arch after simple coarctation resection and end-to-end anastomosis. *The Journal of Thoracic and Cardiovascular Surgery*, *104*(2), 426-433. https://doi.org/10.1016/S0022-5223(19)34799-3

18. Молдаханова, Ж. А., Рахимжанова, Р. И., Даутов, Т. Б., Бастарбекова, Л. А. (2024). Методы визуализации врожденных аномалии дуги аорты у детей. Преимущества и недостатки. *Астана медициналық журналы*, 58-63. https://doi.org/10.54500/2790-1203-2023-118-58-63

Moldaxanova, Zh. A., Raximzhanova, R. I., Dautov, T. B., Bastarbekova, L. A. (2024). Metody` vizualizacii vrozhdenny`x anomalii dugi aorty` u detej. Preimushhestva i nedostatki (Imaging methods for congenital aortic arch anomalies in children. Advantages and disadvantages) [in Russian]. Astana medicinaly`q zhurnaly`, 58-63. https://doi.org/10.54500/2790-1203-2023-118-58-63

19. Poirier, N. C., Van Arsdell, G. S., Brindle, M., Thyagarajan, G. K., Coles, J. G., Black, M. D., Williams, W. G. (1999). Surgical treatment of aortic arch hypoplasia in infants and children with biventricular hearts. *The Annals of thoracic surgery*, *68*(6), 2293-2297. https://doi.org/10.1016/S0003-4975(99)01144-3

20. De Backer, J., Muiño-Mosquera, L., Campens, L. (2022). How to measure the aorta in the setting of genetic aortic disease. *Age*, *1*, 20. https://biblio.ugent.be/publication/01GW1ZDGM3MWDAK3Z3PGXH0VXZ

21. Kiraly, L., Környei, L., Mogyorossy, G., Szatmari, A. (2005). Hypoplastic aortic arch in newborns rapidly adapts to post-coarctectomy circulatory conditions. *Heart*, *91*(2), 233-234. https://doi.org/10.1136/hrt.2003.029314

22. Rhodes, A. B., O'Donnell, S. D., Gillespie, D. L., Rasmussen, T. E., Johnson, C. A., Fox, C. J., Hagler, D. J. (2005). The endovascular management of recurrent aortic hypoplasia and coarctation in a 15-year-old male. *Journal of vascular surgery*, *41*(3), 531-534. https://doi.org/10.1016/j.jvs.2004.09.035

23. Margarint, I. M., Youssef, T., Robu, M., Rotaru, I., Popescu, A., Untaru, O., Vladareanu, R. (2024). The Management of Aortic Coarctation Associated with Hypoplastic Arches and Particular Arch Anatomies: A Literature Review. *Journal of Personalized Medicine*, *14*(7), 732. https://doi.org/10.3390/jpm14070732

24. Murtuza, B., Alsoufi, B. (2017, December). Current readings on surgery for the neonate with hypoplastic aortic arch. In *Seminars in Thoracic and Cardiovascular Surgery* (Vol. 29, No. 4, pp. 479-485). WB Saunders. https://doi.org/10.1053/j.semtcvs.2017.11.004

25. Huuskonen, A., Hui, L., Runeckles, K., Hui, W., Barron, D. J., Friedberg, M. K., Honjo, O. (2023). Growth of unrepaired hypoplastic proximal aortic arch and reintervention rate after aortic coarctation repair. *The Journal of Thoracic and Cardiovascular Surgery*, *165*(5), 1631-1640. https://doi.org/10.1016/j.jtcvs.2022.08.030

Қолқа доғасының гипоплазиясын анықтау үшін КТ-ангиография деректерінен алынған Z-көрсеткіш пен қолқа доғасының өрлемелі қолқаға қатынасының арасындағы келісімділік

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Түйіндеме

Кіріспе. Қолқа доғасының гипоплазиясы (ҚДГ) хирургиялық тактиканы дұрыс жоспарлау үшін дәл анатомиялық бағалауды талап ететін маңызды туа біткен жүрек-қантамыр аномалиясы болып табылады. Компьютерлік томография ангиографиясы (КТ-ангиография) өрлемелі қолқаның және көлденең қолқа доғасының өлшемдерін жоғары кеңістіктік айырымдылықпен анықтауға мүмкіндік береді; алайда әртүрлі диагностикалық критерийлер гипоплазияны әрқалай жіктеуі мүмкін.

Зерттеудің мақсаты. ҚДГ анықтауда қолданылатын КТ-ангиография деректерінен алынған Z-көрсеткішке негізделген тәсіл және арақатынасқа негізделген морфологиялық критерийдің өзара келісімділігін бағалау.

Әдістері. Бұл ретроспективті зерттеуге клиникалық түрде ҚДГ расталып КТ-ангиография жасалған 48 педиатриялық науқас енгізілді. КТ-ангиография суреттерінің көпкеңістікті реконструкциясынан өрлемелі қолқаның диаметрі, көлденең қолқа доғасының диаметрі және доға мен өрлемелі қолқаның арақатынасы (Arch/AAo) алынған. Гипоплазия екі тәсілмен анықталды: (1) Z-көрсеткіші ≤ –2 және (2) Arch/AAo қатынасы < 0,50. Барлық өлшемдер үшін сипаттамалық статистика жүргізілді, ал әдістер арасындағы келісімділік пайыздық сәйкестік, Коэн κ коэффициенті және Мак-Немар тестін қолдану арқылы бағаланды.

Нәтижесі. Өрлемелі қолқаның орташа диаметрі 0,95 ± 0,46 см, көлденең доғаның орташа диаметрі 0,50 ± 0,27 см, ал Arch/AAo қатынасының медианасы 0,50 (IQR 0,43–0,65) болды. Z-көрсеткіш тәсілі 48 науқастың 47-сін (97,9%) гипоплазия деп жіктесе, қатынас критерийі 18 науқасқа (37,5%) гипоплазия диагнозын қойды.

Әдістердің жалпы сәйкестігі 44,2% болды, ал Коэн к коэффициенті 0,03 құрап, кездейсоқ сәйкестіктен жоғары минималды келісімділікті көрсетті. Мак-Немар тесті жіктеулер арасында айтарлықтай айырмашылықты анықтады ($\chi^2 = 22,04$).

Қорытынды. Z-көрсеткішке және Arch/AAo қатынасына негізделген әдістер ҚДГ жіктелуінде айтарлықтай айырмашылық көрсетеді. Z-көрсеткіштері өлшемдердің қалыпты өлшемнен ауытқуын ескерсе, қатынас критерийі анатомиялық пропорцияны сипаттайды және көлденең доғаның айқын тарылуы бар науқастардың тар ауқымын анықтайды. ҚДГ-ны бағалау және диагностикалық не хирургиялық шешім қабылдау барысында клиницистер бұл әдістемелік айырмашылықтарды ескеруі тиіс.

Түйін сөздер: қолқа доғасының гипоплазиясы, туа біткен жүрек ақаулары, КТ-ангиография, Z-көрсеткіш, аорталық қатынас, педиатриялық жүрек-қантамыр визуализациясы, қолқа өлшемдері, диагностикалық келісімділік.

Согласованность между Z-оценкой и отношением диаметра дуги аорты к восходящей аорте, рассчитанным по данным КТ-ангиографии, для выявления гипоплазии дуги аорты

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Резюме

Введение. Гипоплазия дуги аорты (ГДА) является важной врождённой сердечно-сосудистой аномалией, требующей точной анатомической оценки для планирования хирургического вмешательства. Компьютерная томографическая ангиография (КТ-ангиография) обеспечивает высокое пространственное разрешение для измерения восходящей аорты и поперечной дуги аорты; однако применение различных диагностических критериев может приводить к неоднозначной классификации гипоплазии.

Цель исследования. Оценить согласованность между определением ГДА на основе Z-оценки и морфологическим критерием, основанным на соотношении диаметров, рассчитанным по данным КТ-ангиографии.

Методы. В ретроспективное исследование были включены 48 педиатрических пациентов с клинически подтверждённой ГДА, которым была выполнена КТ-ангиография. Из многоплоскостных реконструкций были получены параметры: диаметр восходящей аорты, диаметр поперечной дуги аорты и отношение дуги к восходящей аорте (Arch/AAo). Гипоплазия определялась двумя способами: (1) Z-показатель ≤ –2 и (2) критерий

отношения Arch/AAo < 0,50. Для всех измерений были рассчитаны описательные статистики, а согласованность методов оценивалась с использованием процента совпадений, коэффициента к Коэна и критерия Мак-Немара.

Результаты. Средний диаметр восходящей аорты составил 0,95 ± 0,46 см, средний диаметр поперечной дуги — 0,50 ± 0,27 см, а медиана отношения Arch/AAo — 0,50 (IQR 0,43–0,65). Метод Z-оценки классифицировал 47 из 48 пациентов (97,9%) как имеющих гипоплазию, тогда как критерий отношения выявил гипоплазию у 18 пациентов (37,5%). Общая согласованность методов составила 44,2%, а коэффициент к Коэна — 0,03, что свидетельствует о минимальном совпадении сверх уровня случайности. Критерий Мак-Немара показал существенные расхождения между классификациями ($\chi^2 = 22,04$).

Заключение. Методы, основанные на Z-показателях и отношении Arch/AAo, существенно различаются в классификации ГДА. Z-показатели учитывают отклонение размеров от нормативов, тогда как критерий отношения отражает анатомическую пропорциональность и выделяет более узкую подгруппу пациентов с выраженным сужением поперечной дуги. При оценке ГДА и выборе диагностического или хирургического подхода клиницистам следует учитывать эти методологические различия.

Ключевые слова: гипоплазия дуги аорты, врождённые пороки сердца, КТ-ангиография, Z-показатель, аортальное отношение, детская сердечно-сосудистая визуализация, измерения аорты, диагностическая согласованность.

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Childbirth in Women with a Uterine Scar – An Alternative to Repeat Cesarean Delivery

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Abstract

Vaginal birth after cesarean (VBAC) remains a relevant issue in modern obstetrics. In global practice, VBAC is recognized as a safe and effective method when patients are properly selected, which is confirmed by the recommendations of the World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG), and the Royal College of Obstetricians and Gynaecologists (RCOG). According to ACOG (2020), the success rate of vaginal birth after cesarean ranges from 60% to 80%. In Kazakhstan, this approach is still limited due to the cautious attitude of specialists and insufficient awareness among women.

Objective. To analyze childbirth outcomes among women with a uterine scar after cesarean section and determine the frequency of successful VBAC cases at the City Multidisciplinary Hospital (CMH) of Uralsk.

Materials and Methods. A retrospective study was conducted based on the analysis of medical records of women who delivered at the City Multidisciplinary Hospital (CMH) of Uralsk between 2021 and 2025. The study included patients with a uterine scar after a previous cesarean section. The obstetric and gynecological history, characteristics of pregnancy, indications for repeat cesarean delivery, birth outcomes, and neonatal conditions were evaluated.

Results. The total number of deliveries between January 2021 and April 2025 was 27,482, of which 4,553 (16.8%) were performed by cesarean section. Among all cesarean deliveries, 1,290 operations were performed on women who had a previous cesarean birth. Successful vaginal deliveries in women with a uterine scar accounted for 7.9% of all cases with one prior cesarean section. The main indications for repeat

cesarean delivery were lack of labor progression and signs of acute fetal hypoxia. Women who delivered vaginally had significantly less blood loss, faster postpartum recovery, and fewer complications.

Discussion. The obtained results are original and reflect the local context. Major challenges include the high level of caution among healthcare providers, limited experience with VBAC, and fear of complications. To improve childbirth management in women with a uterine scar, it is necessary to implement international protocols (ACOG, WHO), provide additional training for obstetricians, and increase patient awareness about the safety of VBAC.

Conclusions. Vaginal birth after cesarean is feasible and safe in a multidisciplinary hospital setting, provided that patients are carefully selected and antenatal and intrapartum monitoring are performed according to international recommendations. Successful VBAC reduces surgical risks, improves women's reproductive health, and decreases the number of repeat cesarean deliveries. Further research and adaptation of international protocols to the healthcare context of Kazakhstan are required.

Keywords: cesarean section, uterine scar, VBAC, vaginal delivery, obstetrics, Kazakhstan.

1. Introduction

The management of childbirth in women with a uterine scar has become one of the most widely discussed topics in obstetrics. Previously, pregnancy and childbirth after a cesarean section were mainly regarded as an unquestionable indication for repeat surgical intervention. Today, international clinical guidelines emphasize the possibility and safety of vaginal birth when patients are properly selected.

In developed countries, the practice of VBAC (vaginal birth after cesarean) is widely implemented. When appropriate clinical conditions are met, it allows for a significant reduction in the frequency of repeat surgeries and associated complications. International organizations such as the World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG), and the Royal College of Obstetricians and Gynecologists of the United Kingdom (RCOG) have developed guidelines regulating the management of childbirth in women with a uterine scar. According to ACOG (2020;2), successful vaginal birth after cesarean occurs in 60–80% of cases, confirming a high probability of favorable outcomes when modern intrapartum monitoring technologies and adequate labor management are applied. Similar data are presented in the RCOG guidelines, which note that VBAC is the preferred mode of delivery in the absence of absolute contraindications [1–3].

In European countries and the United States, «Trial of Labor After Cesarean» (TOLAC) protocols have been implemented, which include modern intrapartum monitoring methods and strict patient selection criteria. The key technologies ensuring the safety of this approach include:

- cardiotocographic monitoring (CTG) and fetal echocardiography for assessing fetal condition;
- the use of protocols for labor induction and augmentation in women with a uterine scar (for example, the use of amniotomy, oxytocin under strict monitoring);
- strategies to minimize unnecessary repeat cesarean sections, which help reduce the frequency of postoperative complications and preserve women's reproductive health.

In Kazakhstan, the management of childbirth in women with a uterine scar remains controversial. According to the Ministry of Health of the Republic of Kazakhstan (2022), the national cesarean section rate averages 30–35% of all deliveries. In the West Kazakhstan Region, the average rate of surgical deliveries in recent years has ranged between 32% and 38%, which is comparable to the figures reported in several Eastern European countries (for example, Poland — about 35%, Hungary — 33%), but significantly exceeds the values recommended by the World Health Organization (WHO) — 10–15% of all births [4–5].

The increase in the number of cesarean sections in Kazakhstan is associated with several factors: the rising age of primiparous women, the growing incidence of extragenital pathology, fear of complications from vaginal birth among both patients and medical staff, and the availability of modern diagnostic technologies that enable more frequent identification of indications for surgical intervention.

Domestic and international researchers note that an excessive increase in the number of surgical deliveries does not lead to a significant reduction in maternal or perinatal mortality but increases the risk of complications in subsequent pregnancies, including the formation of a uterine scar, abnormal placentation over the scar, and complications in subsequent deliveries. For this reason, in recent years, particular attention has been paid to the safe management of childbirth in women with a uterine scar and the expansion of TOLAC/VBAC practices (attempted and successful vaginal births after cesarean).

According to regional perinatal centers, the proportion of women permitted to undergo TOLAC in Kazakhstan remains low — no more than 10–12% of all patients with a uterine scar. This is explained by cautious clinical practice and the absence of standardized protocols for managing such deliveries. Nevertheless, successful VBAC cases in domestic clinics (including at the City Multidisciplinary Hospital of Uralsk, where the rate of vaginal birth after cesarean was approximately 4.5%) confirm the feasibility of further developing this practice with strict adherence to selection criteria, continuous monitoring, and readiness for emergency surgical intervention [6–7].

This approach not only reduces the rate of surgical interventions and associated complications but also contributes to improved postpartum quality of life for women, shorter hospitalization periods, and decreased burden on the healthcare system.

Objective of the study — to identify the characteristics and outcomes of childbirth in women with a uterine scar in the City Multidisciplinary Hospital of Uralsk and to determine possible ways to reduce the frequency of cesarean section in this patient group.

2. Materials and Methods

The study is a retrospective cohort study.

Research method: Analysis of medical records and obstetric histories of women who delivered at the City Multidisciplinary Hospital (CMH) of Uralsk from January 2021 to April 2025. Data were extracted from both paper and electronic delivery records, with confidentiality requirements strictly observed: identifying information (full name, address, Individual Identification Number) was excluded when forming the database. Data processing was conducted only on secure computers within the clinic.

The study included 102 women with a uterine scar following a previous cesarean section who delivered at CMH during the specified period. **Inclusion criteria** were the availability of a complete clinical history, data on the nature of the previous intervention, gestational age and delivery outcome, and the presence of a uterine scar after cesarean section. **Exclusion criteria** included missing key data and absolute contraindications to vaginal birth (placental abruption, antepartum hemorrhage, risk of uterine rupture, placenta previa, multiple uterine scars (with the exception of 2 cases with two uterine scars and 1 case with three uterine scars).

Key clinical outcomes analyzed included: successful vaginal birth after cesarean (VBAC), blood loss, neonatal status assessed by the Apgar score, and maternal and perinatal complications.

For statistical analysis, **SPSS Statistics v.27 (IBM)** was used. Continuous variables were described as mean ± standard deviation (Mean ± SD) for normally distributed data (Shapiro–Wilk test) or median and interquartile range (median (Me) and interquartile range (IQR)) for non-normal distributions. Categorical data were presented as percentages and absolute numbers (n, %).

Comparisons of continuous variables between two groups (VBAC and repeat cesarean) were performed using the Student's t-test for normally distributed data or the Mann–Whitney U test for non-normal distributions. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. To evaluate factors associated with VBAC success, multivariate logistic regression analysis was conducted with calculation of odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$ [6].

To minimize data entry errors, double-checking (validation) was performed on 10–15% of randomly selected medical records. Discrepancies were verified against the original documents. For incomplete data (<10% per variable), complete-case analysis was applied.

The study was approved by the Ethics Committee of the City Multidisciplinary Hospital of Uralsk. Due to the retrospective nature of the study, written informed consent was not required. All procedures adhered to the principles of the **Declaration of Helsinki** [8].

3. Results

The results of the study

The total sample included 102 women. The mean age of the patients was 31.73 ± 4.2 years, mean body mass index (BMI) was 28.87 kg/m², mean parity was 3.43, mean gestational age was 38.75 ± 1.0 weeks, mean neonatal weight was 3,357.37 ± 68.9 g, mean Apgar score was 8.73 ± 0.2 points, and mean blood loss was 235.78 ± 34.8 mL.

Analysis of the causes of previous cesarean sections revealed that the most frequent were malpresentation of the fetus — 34.68%, fetal distress — 20.4%, placental abruption and antepartum hemorrhage — 20.4%, cervical dystocia — 7.1%, asynclitic head insertion — 10.2%, myopia — 3.06%, symphysitis — 5.1%, other causes — 3.06%, and severe preeclampsia — 1.96% [8].

Among extragenital pathologies, insulin-dependent diabetes mellitus was observed in 0.98% of women, aplastic anemia in 0.98%, and coronavirus infection in 2.9%.

Out of the 102 women included in the study, 95 delivered at term (37 weeks or more), which accounted for 93.13%. Preterm births amounted to 7 cases (6.86%). Spontaneous onset of labor was observed in 93.88% of women with a uterine scar. Labor induction was performed in 6.12% of cases due to premature rupture of membranes. Polyhydramnios occurred in 1.96% of cases. Premature rupture of amniotic membranes was observed in 13.72%.

Placental location on the posterior uterine wall was observed in 56.1% of women, considered a more favorable condition for vaginal birth. In two cases (2.04%), vaginal birth occurred in women with two prior cesarean sections, and in one case (0.98%) in a woman with three uterine scars [9].

During labor, fetal heart activity was carefully monitored using cardiotocography (CTG). The condition of the mother and the progress of labor were assessed. In cases where there were concerns regarding possible uterine scar dehiscence or fetal distress, an emergency cesarean section was performed.

In 89.2% of cases, labor proceeded without complications. Various postpartum complications were observed in 10.78% of cases; among them, in 4 cases, due to placental attachment defects, manual removal of the placenta was required. Atonic postpartum hemorrhage was diagnosed in 5 women and was managed

conservatively. In 1 case, postpartum urinary retention due to bladder atony was observed. There were 3 vacuum-assisted deliveries, episiotomy was performed in 10 women, and in 1 case labor was complicated by chorioamnionitis [10].

Mean blood loss in VBAC was 210 ± 25.0 mL, compared to 500–1,000 mL in repeat cesarean sections. Women who gave birth vaginally had shorter hospital stays (on average 2–4 days), fewer purulent-septic complications, and a lower incidence of anemia. These findings are consistent with Russian authors, showing that vaginal birth after cesarean is associated with less blood loss, faster recovery, and lower frequency of postoperative complications.

Perinatal outcomes were satisfactory: 98 live births and 4 stillbirths (antenatal fetal death). Distribution of perinatal outcomes: live preterm — 4.08%, stillborn preterm — 3.06%, stillborn term — 1.02%.

4. Discussion

The results of this study confirm the feasibility and safety of vaginal birth in women with a uterine scar after cesarean section, provided that strict patient selection and adherence to modern obstetric protocols are ensured. In the present analysis, the success rate of VBAC was 89.2% (deliveries without the aforementioned complications), which is comparable to international data, where the success rate of vaginal birth after cesarean ranges from 60% to 80% (ACOG, 2020; RCOG, 2022) [11]. This indicates that, with appropriate patient selection, careful labor monitoring, and readiness for emergency surgical intervention, VBAC is a safe and effective alternative to repeat cesarean section.

The findings highlight the high potential for broader implementation of TOLAC/VBAC practices in obstetric care in Kazakhstan, which could reduce the rate of surgical deliveries, lower the risk of surgical complications, improve postpartum recovery, and decrease the burden on healthcare facilities.

When compared with global indicators, some differences were identified, likely due to organizational and staffing characteristics of the national healthcare system. In particular, physicians' caution toward VBAC is often linked to limited practical experience, the absence of clear national protocols, and fear of legal consequences in the event of complications. A significant portion of patients are insufficiently informed about the possibilities and benefits of VBAC, which also influences the choice of delivery method.

International experience demonstrates that the implementation of "Trial of Labor After Cesarean" (TOLAC) protocols, active training of medical personnel, and educating pregnant women about the safety of VBAC make it possible to increase the rate of successful vaginal births after cesarean delivery without an increase in complications. In this context, it is important that adapted versions of international guidelines from ACOG, WHO, and RCOG be gradually introduced in Kazakhstan, taking into account local conditions and the material and technical resources of medical institutions [12].

Thus, the results of this study confirm that, with qualified personnel, continuous monitoring of maternal and fetal condition, and readiness for emergency surgical intervention, VBAC can be considered a safe alternative to repeat cesarean section.

5. Conclusion

The experience of the maternity unit of the City Multidisciplinary Hospital of Uralsk confirms that, when clinical protocols are followed and appropriate labor management strategies are applied, the rate of successful VBAC (Vaginal Birth After Cesarean) can be comparable to international indicators.

Successful vaginal births after cesarean contribute to reducing the frequency of surgical

complications, decreasing blood loss, shortening the duration of hospitalization, and promoting a more favorable recovery of women's reproductive health. They help preserve the functional integrity of the uterus for subsequent pregnancies, which is important for the demographic and perinatal policy of Kazakhstan.

However, barriers remain that limit the widespread implementation of VBAC practice in the country. In this regard, further research is needed aimed at a systematic study of delivery outcomes with a uterine scar, as well as adaptation of international recommendations (ACOG, WHO, RCOG) to the conditions of the national healthcare system.

Implementation of such protocols and targeted training programs for obstetricians and gynecologists will help increase the safety level of childbirth, reduce the frequency of unjustified repeat cesarean sections, and improve the health indicators of mothers and newborns in Kazakhstan.

The purpose of the study was to analyze the features of labor management in women with a uterine scar and to assess the effectiveness and safety of VBAC (Vaginal Birth After Cesarean) practice in obstetric hospitals of Kazakhstan. The set goal was achieved: the analysis of clinical data, regulatory documents, and international recommendations confirmed that vaginal birth after cesarean is possible and safe when medical selection criteria and protocols are followed.

Thus, achieving the goal of the study confirmed the relevance and effectiveness of implementing VBAC practice in Kazakhstan. To further improve childbirth safety and reproductive indicators, it is recommended to:
continue the systematic study of delivery outcomes in women with a uterine scar;
develop and implement national clinical protocols adapted to Kazakhstan practice;
strengthen the training of obstetricians and gynecologists in VBAC management;
conduct informational and educational work among pregnant women.

Comprehensive implementation of these measures will help reduce the proportion of repeat cesarean sections, improve the quality of obstetric care, and strengthen the reproductive health of women in Kazakhstan.

Limitations of this study:

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References

1. World Health Organization (WHO). *WHO recommendations: non-clinical interventions to reduce unnecessary caesarean sections*. Geneva: World Health Organization; 2018.
Available from: https://www.who.int/publications/i/item/9789241550338

2. Obstetricians ACo, G. (2019). ACOG practice Bulletin No. 205: vaginal birth after cesarean delivery. *Obstet Gynecol*, *133*, e110-27.

3. Australian, R. (2005). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *The Australian and New Zealand journal of psychiatry*, *39*(1-2), 1-30. https://doi.org/10.1080/j.1440-1614.2005.01516.x

4. Demianczuk, N. N., Hunter, D. J., Taylor, D. W. (1982). Trial of labor after previous cesarean section: prognostic indicators of outcome. *American journal of obstetrics and gynecology*, *142*(6), 640-642. https://doi.org/10.1016/S0002-9378(16)32433-4

5. Betrán, A. P., Ye, J., Moller, A. B., Zhang, J., Gülmezoglu, A. M., Torloni, M. R. (2016). The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. *PloS one*, *11*(2), e0148343. https://doi.org/10.1371/journal.pone.0148343

6. Казахстан, Р. МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ КАЗАХСТАН.

7. Об утверждении стандарта организации оказания акушерско-гинекологической помощи в Республике Казахстан. Приказ Министра здравоохранения Республики Казахстан от 26 августа 2021 года № ҚР ДСМ-92. https://adilet.zan.kz/rus/docs/V2100024131

Ob utverzhdenii standarta organizacii okazaniya akushersko-ginekologicheskoj pomoshhi v Respublike Kazaxstan. Prikaz Ministra zdravooxraneniya Respubliki Kazaxstan ot 26 avgusta 2021 goda № ҚR DSM-92 https://adilet.zan.kz/rus/docs/V2100024131

8. World Medical Association. (2025). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *Jama*, *333*(1), 71-74. https://doi.org/10.1001/jama.2024.21972

9. Худоярова, Д. Р., Туракулова, Ш. Э., Шопулотова, З. А. (2024). РУБЕЦ НА МАТКЕ И ПОСЛЕДНИЕ ТЕНДЕНЦИИ В НАУКЕ. *Eurasian Journal of Medical and Natural Sciences*, *4*(8), 13-17. https://cyberleninka.ru/article/n/rubets-na-matke-i-poslednie-tendentsii-v-nauke

Xudoyarova, D. R., Turakulova, Sh. E`., & Shopulotova, Z. A. (2024). Rubecz na matke i poslednie tendencii v nauke (Uterine scar and latest trends in science) [in Russian]. *Eurasian Journal of Medical and Natural Sciences*, *4*(8), 13-17. https://cyberleninka.ru/article/n/rubets-na-matke-i-poslednie-tendentsii-v-nauke

10. Нестеров, В. Ф., и Мальгина, Г. Б. (2025). Современные аспекты родовспоможения пациенток с рубцом на матке после кесарева сечения (обзор литературы). Журнал материнского и детского благополучия, 2(4), 19-29. https://www.vestnikomm.ru/jour/article/view/78

Nesterov, V. F., i Mal`gina, G. B. (2025). Sovremenny`e aspekty` rodovspomozheniya pacientok s rubczom na matke posle kesareva secheniya (obzor literatury`) (Modern aspects of obstetric care for patients with a uterine scar after cesarean section (literature review)) [in Russian]. Zhurnal materinskogo i detskogo blagopoluchiya, 2(4), 19-29. https://www.vestnikomm.ru/jour/article/view/78

11. Guise, J. M., Eden, K., Emeis, C., Denman, M. A., Marshall, N., Fu, R. R., McDonagh, M. (2010). Vaginal birth after cesarean: new insights. *Evidence report/technology assessment*, (191), 1. https://www.ncbi.nlm.nih.gov/

12. Lundgren, I., van Limbeek, E., Vehvilainen-Julkunen, K., Nilsson, C. (2015). Clinicians' views of factors of importance for improving the rate of VBAC (vaginal birth after caesarean section): a qualitative study from countries with high VBAC rates. *BMC pregnancy and childbirth*, *15*(1), 196. https://doi.org/10.1186/s12884-015-0629-6

Алдыңғы кесарь тілігінен кейінгі босану: Балама тәсілдер

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Түйіндеме

Бұрынғы кесар тілігінен кейінгі табиғи босану (VBAC — *Vaginal Birth After Cesarean*) қазіргі акушериядағы өзекті мәселе болып табылады. Әлемдік тәжірибеде VBAC науқастарды дұрыс іріктеу жағдайында қауіпсіз және тиімді әдіс ретінде танылған. Бұл Дүниежүзілік денсаулық сақтау ұйымының (ДДҰ), Америка акушер-гинекологтар колледжінің (ACOG) және Ұлыбритания акушер-гинекологтар корольдік колледжінің (RCOG) ұсынымдарымен расталады. ACOG (2020) деректері бойынша кесар тілігінен кейінгі табиғи босанудың сәттілігі 60–80% аралығында. Қазақстанда бұл тәсіл әлі де шектеулі түрде қолданылады, бұл мамандардың сақ көзқарасымен және әйелдердің жеткіліксіз ақпараттандырылуымен байланысты.

Зерттеудің мақсаты. Кесар тілігі жасалғаннан кейін жатырда тыртық қалған әйелдердің босану нәтижелерін талдау және Орал қаласының Қалалық көпсалалы ауруханасы (ҚКА) жағдайында сәтті VBAC жиілігін анықтау.

Материалдар мен әдістер. 2021–2025 жылдар аралығында Орал қаласының Қалалық көпсалалы ауруханасында босанған әйелдердің медициналық карталарына ретроспективті талдау жүргізілді. Зерттеуге бұрын кесар тілігі жасалған жатыр тыртығы бар әйелдер енгізілді. Акушерлік-гинекологиялық анамнез, жүктіліктің ағымы, қайталама кесар тілігіне көрсеткіштер, босану нәтижелері және нәрестелердің жағдайы бағаланды.

Нәтижелер. 2021 жылдың қаңтарынан 2025 жылдың сәуіріне дейін барлығы 27 482 босану тіркелді, олардың ішінде 4 553 (16,8%) — кесар тілігі арқылы өтті. Операциялық босанулардың ішінде 1 290 әйелде бұрын бір кесар тілігі болған. Жатыр тыртығымен табиғи жолмен босанған әйелдер жалпы кесар тілігі жасалғандардың 7,9% құрады. Қайталама кесар тілігіне негізгі көрсеткіштер — босану әрекетінің прогресінің болмауы және ұрық гипоксиясының белгілері болды. Табиғи жолмен босанған әйелдерде қан жоғалту көлемі аз, босанудан кейінгі қалпына келу уақыты қысқа және асқынулар аз кездесті.

Талқылау. Алынған нәтижелер түпнұсқалы және жергілікті жағдайды көрсетеді. Негізгі мәселелер — мамандардың сақтығы, VBAC жүргізу тәжірибесінің жеткіліксіздігі және асқынулардан қорқу. Жатыр тыртығы бар әйелдердің босануын тиімді жүргізу үшін халықаралық хаттамаларды (ACOG, WHO) енгізу, акушер-гинеколог дәрігерлерін оқыту және әйелдерді VBAC қауіпсіздігі туралы ақпараттандыру қажет.

Қорытындылар. Жатырда тыртығы бар әйелдердің табиғи жолмен босануы көпсалалы стационар жағдайында науқастарды мұқият іріктеу және антенаталдық пен интранаталдық мониторинг жүргізу кезінде қауіпсіз және тиімді болып табылады. Сәтті VBAC хирургиялық қауіптерді азайтады, әйелдердің репродуктивтік денсаулығын жақсартады және қайталама кесар тіліктерінің санын төмендетеді. Қазақстан жағдайына бейімделген халықаралық хаттамаларды енгізу және осы бағыттағы қосымша зерттеулер жүргізу қажет.

Түйін сөздер: кесар тілігі, жатыр тыртығы, VBAC, табиғи босану, акушерия, Қазақстан.

Роды у женщин с рубцом на матке – альтернатива повторным оперативным родам

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Резюме

Роды через естественные родовые пути после ранее перенесенного кесарева сечения (VBAC — Vaginal Birth After Cesarean) представляют собой актуальную проблему современного акушерства. В мировой практике VBAC признан безопасным методом при правильном отборе пациенток, что подтверждается рекомендациями Всемирной организации здравоохранения (WHO)[1], Американского колледжа акушеров и гинекологов (ACOG)[2] и Королевского колледжа акушеров и гинекологов Великобритании (RCOG)[3]. Согласно данным ACOG (2020). Успешность родов через естественные пути после кесарева сечения составляет 60–80%. В Казахстане данный метод до сих пор применяется ограниченно, что обусловлено настороженностью специалистов и недостаточной информированностью женщин.

Цель исследования — провести анализ исходов родов у женщин с рубцом на матке после кесарева сечения и определить частоту успешных VBAC в условиях Городской многопрофильной больницы (ГМБ) г. Уральска.

Материалы и методы. Проведено ретроспективное исследование, включающее анализ историй родов женщин, родивших в Городской многопрофильной больницы (ГМБ) г. Уральска в период с 2021 по 2025 год. В исследование были включены пациентки с рубцом на матке после предыдущего кесарева сечения. Оценивались акушерско-гинекологический анамнез, особенности течения беременности, показания к повторному кесареву сечению, исходы родов и состояние новорождённых.

Результаты. Общее количество родов за период с января 2021 по апрель 2025 года составило 27 482. Из них путем операции кесарева сечения 4553 родов или 16,8%. Из общего количества оперативных родов 1290 операций проведены у женщин, имевших одни оперативные роды в анамнезе. Успешные роды через естественные пути с рубцом на матке составили 7,9% от общего числа родов с одним рубцом на матке после операции кесарева сечения. Основными показаниями к повторному кесареву сечению являлись отсутствие прогресса родовой деятельности, признаки острой гипоксии плода в родах. У женщин, родивших через естественные родовые пути, отмечалась меньшая кровопотеря, более быстрое восстановление после родов и меньшее количество послеродовых осложнений.

Обсуждение. Полученные результаты являются оригинальными. Выявлены локальные проблемы - высокая настороженность врачей, ограниченный опыт проведения VBAC и страх осложнений. Для повышения эффективности ведения родов у женщин с рубцом на матке необходимо внедрять международные протоколы (ACOG, WHO), организовывать обучение специалистов и повышать информированность пациенток о возможностях VBAC.

Выводы. Ведение родов с рубцом на матке возможно в условиях многопрофильного стационара при строгом отборе пациенток, антенатальном и интранатальном мониторинге и соблюдении международных рекомендаций. Успешные VBAC позволяют снизить операционные риски, улучшить репродуктивное здоровье женщин и сократить количество повторных оперативных вмешательств. Требуются дальнейшие исследования и адаптация международных протоколов для условий Казахстана.

Ключевые слова: кесарево сечение, рубец на матке, VBAC, естественные роды, акушерство, Казахстан.

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Cervical cancer screening using the self-sampling method among Kazakhstani women: A pilot validation study

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Abstract

Background. With the high rates of cervical cancer incidence and mortality in Kazakhstan and limited coverage of the national cytological cervical screening program, the alternative methods of screening need to be tested and implemented. This is a pilot study that aims to validate acceptance of the cervical self-sampling device for human papillomavirus (HPV) detection among Kazakhstani women and investigate their perceptions of the comfort, potential advantages, and barriers of the approach.

Methods. Two questionnaires and a self-sampling HPV test BGI Sentis was distributed among women attending outpatient gynecological facilities in Astana in January 2025 - June 2025. Ordinal logistic regression and non-parametric tests are used to find the relationships between sociodemographic and medical characteristics and attitudes of women.

Results. A total of 34 women were included in the final analysis. 61.8% of participants perceived the self-sampling test as easy to take, 82.4% as unpainful, and 58.9% as not unpleasant. Only 44.1% of respondents are sure they took the sample correctly. For their subsequent cervical cancer examination, 38.2% of respondents would choose the self-sampling method, 58.8% - a gynecologist-taken sample, 3% - a GP-taken sample.

Conclusions. Women in Kazakhstan accept HPV self-sampling devices as an efficient and comfortable way to increase coverage of cervical cancer screening. Despite their positive experience with the self-sampling device, participants prefer sampling done by a healthcare professional over self-sampling across the board, with no difference in age, marital status, number of children, or other factors. There could be social, cultural, and economic factors affecting women's preference for sampling by a doctor that need to be further investigated.

Keywords: cervical cancer, precancerous diseases of the cervix, self-collection of material.

1. Introduction

Cervical cancer is an abnormal growth of cells of the cervix, a lower part of the uterus that connects to the vagina (birth canal) [1]. In 2020, there were 604,000 new cases and 340,000 deaths detected worldwide due to cervical cancer. Cervical cancer was estimated to be the 4th most common cancer in women (6.5% of all new cancer cases) and the 8th most common cancer overall (3.1% of all new cancer cases) [2]. About 85% of cervical cancer deaths worldwide occur in developing countries, with the death rate 18 times greater in low- and middle-income countries compared with wealthier nations [3].

In Kazakhstan, in 2018, the crude incidence rate of cervical cancer was estimated to be 19.5, while the crude mortality rate was 6.4 per 100,000 women. Age-standardized incidence rate (ASIR) was 18.3 per 100,000 women [4]. In Kazakhstan, cervical cancer ranks second among cancers that affect women [5]. According to Igissinov, et.al. (2021), the ASIR of cervical cancer in Kazakhstan is at its highest at the ages of 45 to 64, with the average age of cervical cancer patients being 50.7 [4].

Human papillomavirus (HPV), a sexually transmitted infection, is the cause of cervical cancer in 99.7% of cases [6]. HPV is a double-stranded DNA virus belonging to the Papillomaviridae family of more than 200 types of viruses that affect skin basal epithelial cells or inner lining of tissues [7]. Other than cervical cancer, HPV can cause anal, oropharyngeal, penile, vaginal, and vulvar cancer [1]. Based on their correlation with cancer risk, HPVs can be classified as high-risk and low-risk. Low-risk HPV types, types 6, 11, 42, 43, and 44, can cause warts on or around the genitals, anus, mouth, or throat but don't cause cancer. High-risk HPV types, types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70, can cause several types of cancer [1,8]. HPV-16 and -18, specifically, account for over 50% and 10% of cervical cancer cases, respectively, and are considered the prevailing cause of cervical cancer [6].

As HPV is a sexually transmitted infection, the risk factors of cervical cancer include sexual activity factors, such as the age of first sexual contact, having several partners, and parity, and other health factors, such as smoking, long-term use of oral contraceptives, and co-infection with chlamydia, genital herpes, and human immunodeficiency virus infection (HIV) [6]. The majority sexually active people in the world will have come in contact with HPV at least once in their lifetime without experiencing any pathologies [7]. Worldwide, the prevalence of HPV 16/18 is equal to 3.9% in women with normal cytology, 25.8% with low-grade lesions, 51.9% with high-grade lesions, and 69.4% with cervical cancer. A large proportion of cervical cancer cases are caused by high-risk HPV types, which is proven by histology results in women with invasive cervical cancer that indicate the presence of HPV-16 and HPV-18 in 55.2% and 14.2% of cases, respectively [9]. The increased risk of HPV infection coincides with the highest metaplastic activity, which occurs at puberty and first pregnancy and drops after menopause. Sexually active young women aged 18-30 are the most exposed to HPV infection; then, there is a sharp decline in prevalence to the virus. Nonetheless,

women over 35 are significantly more likely to get cervical cancer, indicating that HPV infection starts earlier and eventually develops into cancer later in life [8].

There is no available data from the HPV Information Centre on the HPV burden in the general population of Kazakhstan yet. In Asia, the estimated prevalence of cervical HPV-16/18 infection at any one moment is 3.4% of women in the general population [5]. According to some limited studies, between 43.8% and 55.8% of the population of Kazakhstan is HPV positive. Still, the state of the epidemiology of HPV-related cancers in Kazakhstan is not well understood due to a lack of available data. Researchers can only infer the widespread nature of HPV from the high incidence and mortality rates of cervical cancer due to the absence of reliable data and HPV screening and low public awareness of the problem [10].

Cervical cancer can be prevented using primary and secondary prevention methods. Primary prevention involves the elimination of risk factors to prevent disease occurrence. In the case of cervical cancer, primary prevention includes HPV vaccination and sexual health education [11]. The first vaccine against HPV, Gardasil (Merck&Co, Pennsylvania), was licensed and approved by the US Food and Drug Administration in 2006. It protects against four HPV strains: 6, 11, 16, and 18 [6]. Additionally to Gardasil, three other HPV vaccines are in use: Gardasil-9, Cervarix, and Cecolin. Since the vaccine was first approved, more than 100 WHO member countries implemented it successfully [12].

Secondary prevention entails early diagnosis and treatment of the disease. Secondary methods for cervical cancer prevention include cervical cancer screening and HPV DNA tests [11]. The techniques for screening preinvasive disease include conventional cervical cytology, or Papanicolaou test (Pap-smear), liquid-based cytology, histological methods such as visual inspection using 3%-5% acetic acid (VIA) and Lugol's iodine (VILI), and HPV DNA testing [11,13]. Cervical cytology is the globally recommended cervical cancer screening method that has been shown to reduce the occurrence of invasive cervical cancer by up to 80% [11]. Pap-smear detects abnormal cell changes and precancers in the transformation zone of the cervix that can be treated before they turn into cancer [1]. The WHO suggests that women in general and women living with HIV should begin routine cervical cancer screening at ages 30 and 25, respectively. Where HPV DNA tests are unavailable, WHO suggests a screening interval of 3 years using VIA or cytology as primary tests [8].

Despite its immense contribution to cancer prevention, the Pap-smear test has limitations, namely low sensitivity and coverage. The sensitivity and specificity of Pap-smear in detecting cervical premalignant and malignant lesions are equal to 47.19% and 64.79%, respectively [14]. Inadequate samples constitute about 8% of cytology specimens received. There have been reports of false-negative rates as high as 20–30% [8]. Low sensitivity can be solved by co-testing - the approach of using cervical cytology together with HPV testing. A combination of the high sensitivity of HPV DNA testing and the high specificity of cytology can lengthen the screening interval for women who tested negative by both methods. The FDA authorized such a combined test in 2003 for primary screening use in low-risk women 30 years of age and older [11].

In 2020, the WHO officially launched the Global Strategy to Accelerate the Elimination of Cervical Cancer. By 2030, the Global Strategy aims "to vaccinate 90% of eligible girls against HPV, to screen 70% of eligible women at least twice in their lifetimes, and to effectively treat 90% of those with a positive screening test or a cervical lesion, including palliative care when needed" [13].

In Kazakhstan, women are screened for cervical cancer using the cervical cancer cytology, Papanicolaou test (Pap-test). The national cervical cancer screening program is covered by the Government and is available free of charge for all women aged 30-70 every 4 years in any gynecologic outpatient department. HPV testing is offered only on a self-pay basis and in big cities [15]. The use of only Pap-test as a screening method makes the cervical cancer prevention program in Kazakhstan less efficient than most developed countries, which employ co-testing [4]. Still, the introduction of a screening program in Kazakhstan has shown substantial results: in 2007, the percentage of women with an advanced stage upon diagnosis, or the neglect rate, was 26.7%. Since the

state cervical screening program was implemented in 2008, the neglect rate has fallen by half [4].

Overall, 4,460,320 women were screened for cervical cancer in Kazakhstan as of 2018. The coverage of cervical cancer screening was 45.9% in 2016 [16]. The present coverage does not meet the goals set by the WHO and the Ministry of Health of the Republic of Kazakhstan, which is to reach at least 70% of the population at risk [17]. According to Issa, et.al. (2021), the low screening coverage can be explained by low awareness about cervical cancer and the free screening program and the fact that participants regarded themselves either healthy or too young to attend screening. With these factors, other potential reasons for low screening coverage include a lack of practical resources such as sufficient medical facilities nearby or time to go to the screening, emotional barriers such as fear of the results, discomfort during the procedure, and distrust towards medical institutions [18].

Self-sampling devices for Human Papillomavirus (HPV) detection are used as a potential way to increase cervical cancer screening coverage. Patients use brushes or other devices to collect samples from the cervix by themselves. A possible benefit of self-sampling is the potential for reaching those at risk of developing cervical cancer who are unable to see a doctor for screening. The participation rates of self-sampled HPV tests are higher than in physician-collected tests [19]). According to Chao, et.al. (2018), for the detection of CIN2 (cervical intraepithelial neoplasia) or severe diagnosis, HPV self-sampled testing can attain diagnostic test accuracy comparable to that of clinician-sampled tests. In terms of ease of use, privacy, and physical and mental comfort (such as less pain, anxiety, and shame), self-sampled specimens are deemed acceptable [20]). Overall, self-sampling devices are considered an accurate, comfortable, and convenient method for HPV detection and cervical cancer prevention on a larger scale.

Aim: to validate acceptance of the cervical self-sampling device for HPV detection among Kazakhstani women and investigate their perceptions of the comfort, potential advantages, and barriers of the approach.

Hypothesis: Kazakhstani women accept self-sampling devices for HPV detection as an efficient and comfortable way to increase participation and coverage of cervical cancer screening, as compared to traditional methods administered by healthcare professionals.

2. Materials and Methods

Study design and participants

This is a cross-sectional study, which was conducted in the period of January 2025 – June 2025 in the outpatient gynecological facilities of Astana, Kazakhstan. A total of 34 women participated in the study, answered the demographic and topic-related questionnaires fully, and were included in the analysis.

Inclusion criteria

The study participants were selected from the general population based on age, health, and literacy. Women above 18 years were surveyed on the grounds of their ability to give informed consent. The study participants had to have an intact cervix with no prior surgeries done on the cervix, including a total hysterectomy. Participants had to be able to read, write, comprehend, and respond to survey questions. Women younger than 18, with no intact cervix, or those who cannot read, write, comprehend, and give valid answers in Russian, Kazakh, or English were excluded from participating in the study. Those who could not use the test due to menstruation or physiological concerns, or withdrawn consent after learning about the method of taking the sample, were also excluded from the study.

Study instruments

The primary instrument in the study were (1) BGI Sentis self-collection kit for HPV (Figure 1). The BGI HPV test combines self-sampling technology and genotyping assay to detect 14 high-risk HPV types, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 2 low-risk types - 6, 11. Study participants are presented with the BGI DNA sample storage card and a brush for sample collection and asked to take a sample themselves. Before taking a sample, participants get thorough written and verbal instructions on the use of the test.

Figure 1 - BGI Sentis self-sampling card for HPV contents: a) Sampling brush; b) DNA sample storage card

Two questionnaires were used in the study. The first survey collected data on the demographic and clinical characteristics of women. Sociodemographic data recorded were age, ethnicity, marital status, number of pregnancies, births, living children, and abortions. Clinical metrics such as height, body mass, age of menarche, menstrual function, age of start of sexual activity, gynecological disorders and surgeries endured, smoking status, contraceptive use, and oncological diseases in participants or their close relatives were also recorded. There was a section with questions regarding gynecologic screening tests - Pap-smear and vaginal microbiome test. The second questionnaire was adapted from De Pauw, et.al. (2021) [21] and adapted to investigate the acceptance of the self-sampling device among women in Kazakhstan. The questionnaire was modified to fit the context of Kazakhstan. All questions were translated into Kazakh and Russian languages (the official languages of the country) by independent trilingual translators. The survey was divided into two parts for women to answer: before and after using the self-sampling device. The first part focuses on the awareness of women on the topics of HPV and cervical cancer, preliminary preferences in methods of taking the test, and the potential benefits of self-sampling devices. Questions after taking the test evaluate the instructions attached to the test and the comfort and ease of use of the self-sampling test. Both parts included Likert scale questions and Yes/No, Agree/Disagree questions. Additionally, information about the participant's experience with the Pap-test is also requested.

Variables

Independent variables

In this research, the independent variables included sociodemographic characteristics such as age, BMI, education level, marital status, and number of living children. Age was categorized into two groups: 19-32 and 32-66 years. Ethnicity was categorized into 2 groups: Kazakh and other ethnicities. Education level was categorized as middle (high school), middle-specialized (college), and higher. Additionally, BMI (underweight, normal weight, overweight, obese), age of menarche (12≥, 13-15, 15<), number of abortions (none, 1, more than 1), and the use of contraceptives (yes, no) are all independent variables.

Outcome variable

The outcome variable was the preference of women for sampling methods for their next cervical cancer examination. Women chose between self-taken, a general practitioner-taken, and a gynecologist-taken sample. For the sake of statistical analysis, the options of

a GP and a gynecologist taking a cervical sample were combined as "health provider-taken samples".

Statistical analysis

Statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) software. All continuous variables were tested for normality of data distribution, revealing non-normal distribution for age, BMI, and age of menarche. The variables were described as median and interquartile range and non-parametric tests, Mann-Whitney U and Kruskal-Wallis tests, with a significance value of <0.05 were used to analyze the relationships between continuous and categorical variables. Pearson Chi-square test and Fisher's exact test with a significance value of <0.05 were used to analyze the relationships between nominal variables.

Ethical considerations

The study was approved by the Institutional Research Ethics Committee of Nazarbayev University (NU IREC) on 21 October 2022 (IREC Number: 621/03102022). Before inclusion in the study, all potential participants were informed about the aims, methods, risks, and benefits of the study. Written consent was obtained from participants after an explanation of the study's voluntary and anonymous nature.

3. Results

A total of 34 women aged 19 to 66 years agreed to participate in the study. Table 1 represents the socioeconomic characteristics of the participants. The median age of participants was 28.5 (21.25-41) years, with 19 participants aged 19-32 (55.9%) and 15 participants older than 32 (44.1%). Most participants were of Kazakh descent (94.1%). 67.6% of participants had a higher education. The majority of participants are married (52.9%) and have children: 41.2% have 1 to 3 children, and 20.6% have more than 4 children.

Table 1 - The socioeconomic characteristics of the participants (N = 34)

Variables	BGI sentis, N = 34 (%)
Age, Median	28.5 (21.25-41)
19-32	55.9 %
32<	44.1%
Ethnicity	
Kazakh	32 (94.1)
Other	2 (5.9)
Education	
Middle (high school)	7 (20.6)
Middle-specialized (college)	4 (11.8)
Higher	23 (67.6)
Marital status	
Married	18 (52.9)
Single	16 (47.1)

Table 2 depicts the health characteristics, especially related to gynecological examinations, of the participants. The median BMI of the women is 22.81 (19.54-27.11), which is within the normal range, with 11.8% within the underweight, 20.6% within the normal, 47.1% within the overweight, and 20.6% within the obese range.

The median age of menarche is 13 (13-14.75). Most participants have normal menstrual function (67.6%) and don't suffer from gynecological disorders (70.6%). The most common gynecological illnesses among the participants are uterine fibroids (11.8%) and ovarian cysts (11.8%). The majority of the respondents have not undergone any reproductive system surgeries (73.5%) and never had abortions (61.8%). 20.6% of respondents have never had sexual experience, while 11.8% had their first experience at the age of 18 or younger, 44.1% at 19-22 years, and 23.5% older than 22 years. Among the sexually active participants, 14 don't use any contraception (41.2% of all), 8 use IUDs (23.5%), and 5 use barrier contraception methods (14.7%). Most participants have not taken a Pap smear (79.4%). The majority of participants don't smoke (91.2%), have no oncological disorders (100%), and have no relatives who have oncological disorders (94.1%).

Table 2 - The health characteristics of the participants

Variables	Total N = 34 (%)
BMI, Median 22.81 (19.54-27.11)	
Underweight (18.5>)	4 (11.8%)
Normal weight (18.5-24.9)	7 (20.6%)
Overweight (25.0-29.9)	16 (47.1%)
Obese (30.0≤)	7 (20.6%)
Menarche age, Median 13 (13-14.75)	
12≥	4 (11.8%)
13-15	28 (82.3%)
15<	2 (5.9%)
Menstrual function	
Normal	23 (67.6%)
Abnormal	11 (32.3%)
Age of start of sexual activity	
Never	7 (20.6%)
18≥	4 (11.8%)
19-22	15 (44.1%)
22<	8 (23.5%)
Gynecological illnesses	
None	24 (70.6%)
Uterine fibroids	4 (11.8%)
Ovarian cyst	4 (11.8%)
Other	3 (8.8%)
Gynecological surgeries	
None	25 (73.5%)
C-section	3 (8.8%)
Other	6 (17.6%)
Abortions	
None	21 (61.8%)
1	9 (26.5%)
1<	4 (11.8%)

Pap-smear	
Performed	7 (20.6%)
None	27 (79.4%)

Figure 2 illustrates the participants' opinions regarding the BGI self-sampling HPV test before using it. The overwhelming majority believed that the self-sampling test is a good way to increase coverage of cervical cancer screening among women who do not go to a general practitioner or gynecologist for a Pap-smear (76.5%). 67.6% of the women believed that the self-taken sample is worse than that taken by a doctor. Most women claim that the self-sampling approach is suitable for women who have not undergone cervical cancer screening before (58.8%). When it comes to the possible preference of self-sample over going to the doctor's office, women were conflicted - 38.3% believe that most women will choose self-sampling over the sampling by a health professional, 35.3% disagree, and 26.5% are not sure.

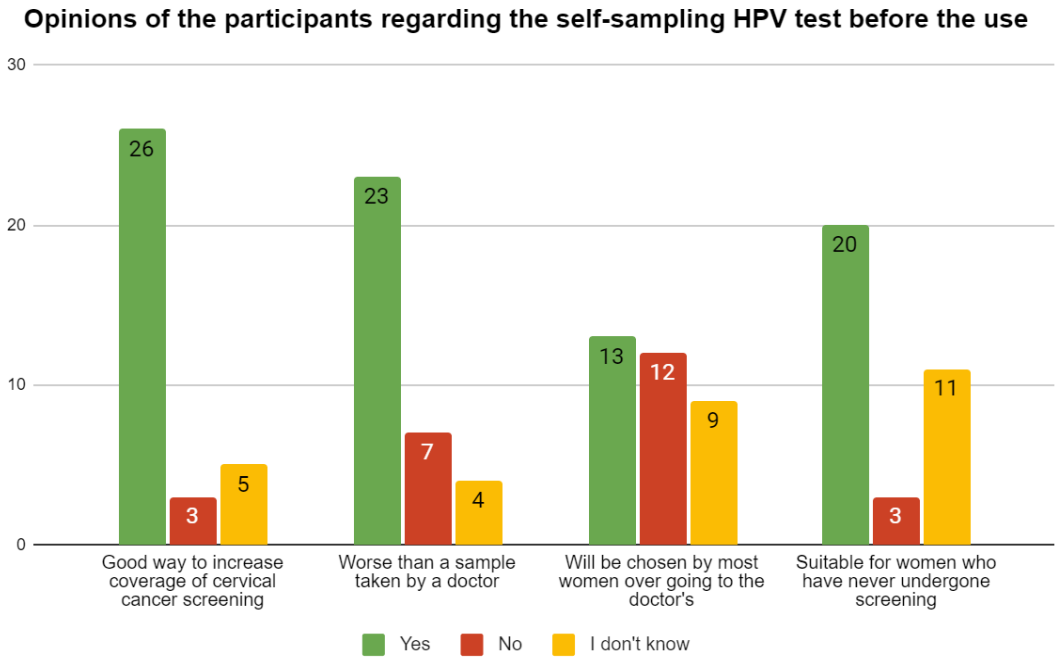

Figure 2 - Opinions of the participants regarding the self-sampling HPV test before the use (N=34). Yes (green bar); No (red bar); I don't know (yellow bar)

Figure 3 shows the participants' perceptions of their experiences with the BGI self-sampling HPV test after using it. The majority, 61.8%, perceived the test to be easy to take. 82.4% of the women disagreed with the statement that the test is painful, and 58.9% disagreed that it is unpleasant. 44.1% of respondents are sure they took the sample correctly, 29.4% partially agree, and 20.6% are not sure. Most women would recommend the procedure to their family and friends (64.7%). Finally, 41.2% of respondents are sure that self-sampling is an easier approach to cervical cancer screening than going to the doctor's office, while 29.4% of them fully disagree.

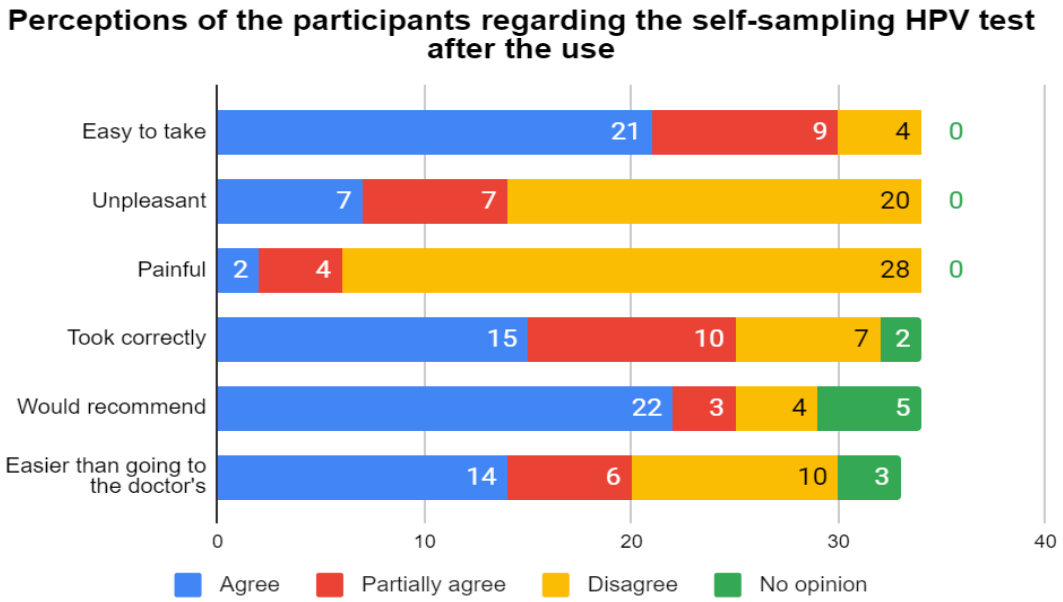

Figure 3 - Perceptions of the participants regarding the self-sampling HPV test after the use (N=34). Agree (blue bar); Partially agree (red bar); Disagree (yellow bar), No opinion (green bar)

In terms of the preferences in the sampling methods for their following cervical cancer examination, 38.2% of respondents would choose the self-sampling method; 58.8% would prefer a gynecologist to take a sample, while 3% would prefer a GP to take a sample for their subsequent cervical cancer examination.

4. Discussion

Cervical cancer remains the 2nd most common cancer in women in Kazakhstan (Bruni, et.al., 2023b) with the crude rate of incidence of CC of 19.5 and the crude mortality rate of 6.4 per 100,000 women in 2018 [4]. With the coverage of cervical cancer screening being as low as 45.9% in 2016 [16], the healthcare system of Kazakhstan needs to further reinforce the cervical cancer screening program. Determining the factors associated with acceptance of self-sampling HPV tests as a viable cervical cancer screening method would allow the technology to be implemented taking into account specific socioeconomic, cultural, and medical characteristics of the target audience. Up to now, there has been no research done on the perceptions of women on self-screening HPV tests, not only in Kazakhstan but in Central Asia overall. Thus, there is a need to validate the acceptance of the cervical self-sampling device for HPV detection among Kazakhstani women and investigate their perceptions of the comfort, potential advantages, and barriers of the approach.

Overall, the present study shows that most women in Kazakhstan believe that the self-sampling approach is a sufficient way to increase cervical cancer screening coverage, especially for women who have never undergone a Pap-test. After taking the test, most participants perceived it as not causing pain or discomfort and as easy to administer. They would recommend using the method for their friends and family. Still, there is a barrier for women to fully embrace the self-sampling approach. Some of the participants view the sample taken by themselves to be worse and less trustworthy than that taken by a medical professional.

Despite the positive feedback on the self-sampling device, most women still choose to have their sample taken by a gynecologist.

The results could be explained by the fact that the concept of self-sampling is new and unfamiliar in Kazakhstan for women of all ages, education levels, marital statuses, and any number of children. The lack of confidence in women in the sample quality could be due to the absence of similar methods of sampling in the country. Interestingly, the only factor that has a significant correlation with the preference for a sampling method is the use of contraceptives: those who use contraception were more likely to prefer a self-sampling device over a sample taken by a medical professional. The reason for this could be that women who use contraception are more likely to know about their health and HPV screening methods and be comfortable with administering tests on themselves.

The present research also sheds light on the awareness of women in Kazakhstan of cervical cancer, HPV, and HPV testing. Figure 5 shows that only half of the respondents know that HPV causes cervical cancer, which shows low levels of cervical cancer awareness among Kazakhstani women. This ignorance could be another reason for distrust towards the self-sampling device and preference for sampling done by a doctor. According to Issa, et.al. (2021) [17], low screening coverage in Kazakhstan can be attributed to low awareness about cervical cancer and the free screening program [18]. Similar reasons could affect the mixed reaction of women towards the self-sampling device. Future research could focus on health awareness, contraceptive use, and other factors and their role in the decision-making process of women who undergo or avoid screening.

There were some differences between the present study results and previous research conducted in other countries of the world. The study that built the framework of the present study, De Pauw, et.al. (2021), assesses attitudes and experiences associated with self-sampling among women enrolled in VALHUDES, a Belgian research comparing the clinical accuracy of HPV self-sampling tests and clinician-taken sample tests [21]. As the study is conducted in a high-income European country, Belgium, the results indicate higher acceptance, more apparent preference for the self-sampling method over a sample taken by a doctor, and more evident awareness of HPV and cervical cancer, compared to the present results. These observations can be explained by the fact that co-testing and alternative methods of cervical cancer screening were introduced sooner and in higher magnitude in high-income countries than in low- and middle-income countries. Furthermore, the increased awareness of HPV and cervical cancer in European countries may be attributed to the higher quality of health-related education and media coverage.

Results obtained in Kazakhstan, a middle-income country, could be compared to the results of other low- and middle-income countries (LMIC). The literature review of 50 articles from 26 countries performed by Kamath Mulki & Withers (2021) investigated the feasibility and acceptability of the self-sampling method in LMIC (countries of sub-Saharan Africa, Latin America/Caribbean, East Asia/Pacific, South Asia, Middle East/North Africa) [22]. According to the researchers, the HPV self-sampling method is an effective way to increase cervical cancer coverage in LMICs. Overall, participants reported that the HPV self-sampling method was easy to administer (75–97%, 18 studies), painless (60–90%, nine studies), and preferred over clinician-taken sampling (57–100%, 14 studies). The most crucial perceived benefits of self-sampling were the convenience of screening in the home environment, less shame and embarrassment, and less travel. However, some reviewed studies show that women had issues with the quality of self-sampling, privacy issues in sampling from home, and the need for assistance from health professionals with self-sampling.

Similarly, in the research from China, Zhao, et.al. (2019), among 1375 women, 86.55% perceived the self-sampling as convenient, 78.40% as not uncomfortable, 83.27% would choose self-sampling for cervical cancer screening again, and 85.82% were wary of inaccurate sampling [23]. In research by Qu, et.al. (2023), 27% of 862 surveyed Chinese women from the Jiangsu province favored clinician-sampling, 33% favored self-sampling, and 40% had no apparent preference [24]. Women with sufficient knowledge about HPV and prior positive

experience with HPV self-sampling were more accepting of self-sampling, compared to those who weren't aware of or exposed to it before. This further proves that awareness about HPV, cervical cancer, and the self-sampling approach produces higher acceptance for the self-sampling device. As China has a comparable economic state and some social and cultural characteristics to Kazakhstan, the results indicate the same experiences, attitudes, and worries in women in both countries. Both women in China and Kazakhstan, despite their positive experiences with the self-sampling device, worry about the accuracy of their sample and favor clinician-taken samples almost as much as samples taken by themselves.

The current study doesn't investigate the reasons for preference for a health professional-taken sampling, but they could be close to those obtained by Kamath Mulki & Withers (2021), Zhao, et.al. (2019), and Qu, et.al. (2023) [23,24]. Overall, the economic, social, and cultural context of the self-sampling approach among women in Kazakhstan needs to be further investigated in future research.

Study strengths and limitations

The present research is the first study to examine the attitudes of Kazakhstani women on cervical self-sampling, their comfort when using the device, and perceived advantages and disadvantages of the test compared to a professional-taken test. There are many strengths of the study. Firstly, the research inspects an innovative and unexplored approach to cervical cancer screening in Kazakhstan. As Kazakhstan has a crude incidence rate of cervical cancer of 19.5 and a crude mortality rate of 6.4 per 100,000 women [4], the study provides indispensable and relevant insight into the acceptability of the self-sampling approach among women. Considering the high risk and low coverage of cervical cancer screening in the country, the researchers raise an important issue that affects all women. The study evaluates the acceptance of the self-sampling approach based on various factors, including experience after taking the sample, perception of effectiveness for increasing cervical cancer screening coverage, preference over going to the doctor's office, and others. The research reveals important implications for further investigation on social, cultural, and economic factors affecting women's distrust of the self-sampling method.

Nevertheless, there are some limitations to the study. Firstly, the sample size was too low (N=34). Due to the low respondent count, statistical analysis results have shown an insignificant relationship between socioeconomic and medical characteristics and women's choice of sampling methods. For more comprehensive results, more participants need to be surveyed. The study was conducted in one outpatient facility in Astana, which makes the results less suitable to make general conclusions about all women in Kazakhstan. Further studies could be conducted in outpatient facilities in different cities and towns of Kazakhstan. Additionally, the study doesn't explore the reasons for choosing the self-sampling method, which could be explored next time.

Possible clinical implications. The results of the study could be used to successfully implement the self-sampling device in cervical cancer screening programs. Kazakhstan comes closer to implementing co-testing for cervical cancer screening. Therefore, the present research could be used as a testament to the need to raise reproductive health-related awareness among local women before introducing the self-sampling approach to broader audiences. The research also opens the opportunity to study the social, cultural, and economic factors, which are specific to Kazakhstan, that prevent successful implementation of cervical self-sampling methods.

5. Conclusion

The present study assesses the acceptance of the self-sampling HPV test among Kazakhstani women. Women in Kazakhstan accept self-sampling devices for Human Papillomavirus detection as an efficient and comfortable way to increase participation and coverage of cervical cancer screening. Despite their positive experience with the self-sampling device, participants prefer sampling done by a healthcare professional over

self-sampling across the board, with no difference in age, marital status, number of children, and other factors. There could be social, cultural, and economic factors affecting women's preference for sampling by a doctor that need to be further investigated.

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References

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *71*(3), 209-249. https://doi.org/10.3322/caac.21660

2. Zhang, S., Xu, H., Zhang, L., Qiao, Y. (2020). Cervical cancer: Epidemiology, risk factors and screening. *Chinese Journal of Cancer Research*, *32*(6), 720. https://doi.org/10.21147/j.issn.1000-9604.2020.06.05

3. Igissinov, N., Igissinova, G., Telmanova, Z., Bilyalova, Z., Kulmirzayeva, D., Kozhakhmetova, Z., Kuandykov, Y. (2021). New trends of cervical cancer incidence in Kazakhstan. *Asian Pacific journal of cancer prevention: APJCP*, *22*(4), 1295 https://doi.org/10.31557/APJCP.2021.22.4.1295

4. Papillomavirus, H. (2023). Related Cancers, Fact Sheet. *Saudi Arabia*.

5. Johnson, C. A., James, D., Marzan, A., Armaos, M. (2019, April). Cervical cancer: an overview of pathophysiology and management. In *Seminars in oncology nursing* (Vol. 35, No. 2, pp. 166-174). WB Saunders. https://doi.org/10.1016/j.soncn.2019.02.003

6. Kombe Kombe, A. J., Li, B., Zahid, A., Mengist, H. M., Bounda, G. A., Zhou, Y., Jin, T. (2021). Epidemiology and burden of human papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation. *Frontiers in public health*, *8*, 552028. https://doi.org/10.3389/fpubh.2020.552028

7. Kusakabe, M., Taguchi, A., Sone, K., Mori, M., Osuga, Y. (2023). Carcinogenesis and management of human papillomavirus-associated cervical cancer. *International Journal of Clinical Oncology*, *28*(8), 965-974. https://doi.org/10.1007/s10147-023-02337-7

8. Bruni, L., Albero, G., Serrano, B., Mena, M., Gómez, D., Muñoz, J. (2022). *Human papillomavirus and related diseases in the world. Summary Report. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre); 2023*.

9. Aimagambetova, G., & Azizan, A. (2018). Epidemiology of HPV infection and HPV-related cancers in Kazakhstan: a review. *Asian Pacific journal of cancer prevention: APJCP*, *19*(5), 1175. https://doi.org/10.22034/APJCP.2018.19.5.1175

10. Aggarwal, P. (2014). Cervical cancer: can it be prevented? *World journal of clinical oncology*, *5*(4), 775. https://doi.org/10.5306/wjco.v5.i4.775

11. Akhatova, A., Azizan, A., Atageldiyeva, K., Ashimkhanova, A., Marat, A., Iztleuov, Y., Suleimenova, A., Shamkeeva, S., Aimagambetova, G. (2022, November 11). Prophylactic Human Papillomavirus Vaccination: From the Origin to the Current State. Vaccines (Basel), 10(11):1912. https://doi.org/10.3390/vaccines10111912

12. World Health Organization. (2021). WHO recommends DNA testing as a first-choice screening method for cervical cancer prevention. *Geneva: WHO. Available online at: https://www.who. int/news/item/2021-dna-testing-for-cervical-cancer (Accessed August 11, 2024)*. https://doi.org/10.1200/jgo.18.65600

13. Najib, F. S., Hashemi, M., Shiravani, Z., Poordast, T., Sharifi, S., Askary, E. (2020). Diagnostic accuracy of cervical pap smear and colposcopy in detecting premalignant and malignant lesions of cervix. *Indian journal of surgical oncology*, *11*(3), 453-458. https://doi.org/10.1007/s13193-020-01118-2

14. Aimagambetova, G., Chan, C. K., Ukybassova, T., Imankulova, B., Balykov, A., Kongrtay, K., Azizan, A. (2021). Cervical cancer screening and prevention in Kazakhstan and Central Asia. *Journal of medical screening*, *28*(1), 48-50. https://doi.org/10.1177/0969141320902482

15. Kaidarova, D., Zhylkaidarova, A., Dushimova, Z., Bolatbekova, R. (2018). Screening for cervical cancer in Kazakhstan. https://doi.org/10.1200/jgo.18.65600

16. Issa, T., Babi, A., Azizan, A., Alibekova, R., Khan, S.A., Issanov, A., Chan, C.K., Aimagambetova, G. (2021, January-December). Factors associated with cervical cancer screening behaviour of women attending gynaecological clinics in Kazakhstan: A cross-sectional study. Womens Health (Lond), 17:17455065211004135. https://doi.org/10.1177/17455065211004135

17. Chorley, A. J., Marlow, L. A., Forster, A. S., Haddrell, J. B., Waller, J. (2017). Experiences of cervical screening and barriers to participation in the context of an organised programme: a systematic review and thematic synthesis. *Psycho-oncology*, *26*(2), 161-172. https://doi.org/10.1002/pon.4126

18. Chao, Y. S., Clark, M., Ford, C. (2018). HPV self-sampling for primary cervical cancer screening: a review of diagnostic test accuracy and clinical evidence.

19. Nishimura, H., Yeh, P. T., Oguntade, H., Kennedy, C. E., Narasimhan, M. (2021). HPV self-sampling for cervical cancer screening: a systematic review of values and preferences. *BMJ global health*, *6*(5). https://doi.org/10.1136/bmjgh-2020-003743

20. De Pauw, H., Donders, G., Weyers, S., De Sutter, P., Doyen, J., Tjalma, W. A., Arbyn, M. (2021). Cervical cancer screening using HPV tests on self-samples: attitudes and preferences of women participating in the VALHUDES study. *Archives of Public Health*, *79*(1), 155. https://doi.org/10.1186/s13690-021-00667-4

21. Kamath Mulki, A., Withers, M. (2021). Human Papilloma Virus self-sampling performance in low-and middle-income countries. *BMC women's health*, *21*(1), 12. https://doi.org/10.1186/s12905-020-01158-4

22. Zhao, Y., Liao, Q., Mi, X., Li, M. Z., Zhao, C., Cui, S. H., Wei, L. H. (2019). Survey of the acceptance status of HPV self-sampling screening in female population for cervical cancer. *Zhonghua fu chan ke za zhi*, *54*(5), 312-317. https://doi.org/10.3760/cma.j.issn.0529-567x.2019.05.005

23. Qu, S. X., Ni, Y. H., Qin, J. F., Chen, X. Y., Wu, W. L., Zhang, W. C. (2023). Experience and acceptability for HPV self-sampling among women in Jiangsu province, China: a cross-sectional survey. *Journal of Obstetrics and Gynaecology*, *43*(1), 2204942. https://doi.org/10.1080/01443615.2023.2204942

Қазақстандағы әйелдер арасында жатыр мойны обырын өздігінен жинау арқылы скрининг: Пилоттық валидациялық зерттеу

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Түйіндеме

Кіріспе. Қазақстанда жатыр мойны обырының аурушаңдығы мен өлім-жітім деңгейінің жоғары болуына, сондай-ақ жатыр мойны цитологиясының ұлттық скринингтік бағдарламасының шектеулі қамтылуына байланысты скринингтің баламалы әдістерін сынақтан өткізу және енгізу қажет.

Зерттеудің мақсаты. Бұл пилоттық зерттеу қазақстандық әйелдер арасында адам папилломасы вирусына (АПВ) жатыр мойны жағындыларын сынау үшін өздігінен сынама алу құрылғысының қолайлылығын растауға және олардың осы тәсілдің ыңғайлылығы, ықтимал артықшылықтары мен шектеулері туралы түсініктерін зерттеуге бағытталған.

Әдістері. 2025 жылдың қаңтары мен 2025 жылдың аусым аралығында Астанадағы амбулаторлық гинекологиялық емханаларға келген әйелдерге екі сауалнама және BGI Sentis сынағы берілді. Әлеуметтік-демографиялық және медициналық сипаттамалар арасындағы байланыстарды, сондай-ақ әйелдердің емдеуге деген көзқарасын анықтау үшін реттік логистикалық регрессия және параметрлік емес тесттер қолданылды.

Нәтижесі. Соңғы талдауға 34 әйел қатысты. Қатысушылардың 61,8%-ы жағындыны өздігінен жинауды жеңіл, 82,4%-ы ауыртпалықсыз, 58,9%-ы жағымды деп тапты. Респонденттердің тек 44,1%-ы жағындыны дұрыс жинағандарына сенімді. Жатыр мойны обырының кейінгі скринингі үшін респонденттердің 38,2%-ы жағындыны өздігінен жинауды, 58,8%-ы оны жинау үшін гинекологты және 3%-ы оны жинау үшін дәрігерді таңдайды.

Қорытынды. Қазақстандық әйелдер HPV тестілеуге арналған өзін-өзі жинау құрылғыларын жатыр мойны обырын скринингтік қамтуды арттырудың тиімді және ыңғайлы әдісі деп санайды. Өзін-өзі жинау құрылғыларының оң тәжірибесіне қарамастан, қатысушылар жасына, отбасылық жағдайына, балалар санына немесе басқа факторларға қарамастан, жағындыларды дәрігердің жинағанын қалайды. Әйелдердің жағындыларды дәрігерден алуды қалайтынына қосымша зерттеуді қажет ететін әлеуметтік, мәдени және экономикалық факторлар әсер етуі мүмкін.

Түйін сөздер: жатыр мойны обыры, жатыр мойнының ісік алды зақымдануы, өздігінен сынама алу.

Скрининг рака шейки матки методом самостоятельного забора образцов среди женщин в Казахстане: Пилотное валидационное исследование

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Резюме

Актуальность. В связи с высокими показателями заболеваемости раком шейки матки и смертности от него в Казахстане, а также ограниченным охватом населения национальной программой цитологического скрининга шейки матки, необходимо апробировать и внедрить альтернативные методы скрининга.

Цель. Данное пилотное исследование направлено на обоснование приемлемости устройства для самостоятельного взятия мазка с шейки матки для выявления вируса папилломы человека (ВПЧ) среди

казахстанских женщин и изучение их восприятия удобства, потенциальных преимуществ и ограничений данного подхода.

Методы. Женщинам, посещавшим амбулаторные гинекологические учреждения Астаны в период с января 2025 года по июнь 2025 года, были розданы две анкеты и тест на ВПЧ BGI Sentis. Для выявления взаимосвязей между социально-демографическими и медицинскими характеристиками, а также отношением женщин к лечению используются порядковая логистическая регрессия и непараметрические тесты.

Результаты. В окончательный анализ были включены 34 женщины. 61,8% участниц посчитали самостоятельный забор мазка простым, 82,4% – безболезненным, а 58,9% – не неприятным. Только 44,1% респондентов уверены, что взяли мазок правильно. Для последующего обследования на рак шейки матки 38,2% респонденток выбрали бы самостоятельный забор мазка, 58,8% – забор гинекологом, 3% – забор терапевтом.

Выводы. Женщины в Казахстане считают устройства для самостоятельного забора мазка на ВПЧ эффективным и удобным способом увеличения охвата скринингом рака шейки матки. Несмотря на положительный опыт использования устройства для самостоятельного забора мазка, участницы предпочитают забор мазка врачом, независимо от возраста, семейного положения, количества детей или других факторов. На предпочтение женщинами забора мазка врачом могут влиять социальные, культурные и экономические факторы, требующие дальнейшего изучения.

Ключевые слова: рак шейки матки, предраковые заболевания шейки матки, самостоятельный забор материала.

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Molecular-genetic profile of breast cancer: The role of BRCA mutations, germline and somatic alterations as a basis for personalized therapy

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Abstract

Breast cancer remains one of the most prevalent and socially significant malignancies among women worldwide. Advances in molecular biology and oncogenetics have substantially transformed approaches to the diagnosis, prognosis, and treatment of breast cancer, with a growing emphasis on personalized medicine. This review explores the molecular-genetic landscape of breast cancer, focusing on the distinctions between germline and somatic mutations, their clinical relevance, and their role in guiding individualized therapeutic strategies. The results of the literature review demonstrated that germline mutations - particularly in *BRCA1* and *BRCA2* - are strongly associated with hereditary breast cancer predisposition, influencing both risk assessment and preventive strategies. In contrast, somatic mutations, including alterations in *TP53*, *PIK3CA*, and *ESR1*, play a pivotal role in tumor behavior, treatment resistance, and disease progression. Moreover, integrative molecular profiling using next generation sequencing incorporates both germline and somatic mutation data provides a more accurate framework for clinical decision-making in personalized therapy. Studies have shown that patients with combined profiling benefit from more precise therapeutic targeting, including *PARP*

inhibitors, endocrine therapies, and immune checkpoint inhibitors. The integration of germline and somatic analyses represents a critical step in the realization of precision medicine, ultimately improving therapeutic outcomes and prognosis in breast cancer patients.

Keywords: breast cancer, BRCA1/2, germline somatic mutation, next-generation sequencing, precision medicine.

1. Introduction

The relevance of breast cancer as a public health issue

Breast cancer (BC) continues to be one of the most common and socially impactful forms of malignant neoplasms among women globally, posing a significant challenge to public health systems. According to global epidemiological data from 2022, the total number of newly diagnosed cancer cases reached approximately 20 million, with cancer-related mortality approaching 10 million cases. Among these, BC ranks as the most frequently diagnosed cancer in women, accounting for more than 2.29 million new cases annually, making it the leading oncological pathology in the female population worldwide (1). A similar epidemiological pattern is observed in the Republic of Kazakhstan, where breast cancer accounted for 26.4% of all female malignancies in 2023, ranking first among cancers affecting women (2).

Understanding the molecular-genetic basis of breast cancer is essential for accurate diagnosis, optimal therapeutic decision-making, and outcome prediction in the context of personalized medicine. Genetic analysis in breast cancer typically involves the study of germline (inherited) and somatic (acquired) mutations. Determining which type of mutation should be prioritized for clinical evaluation necessitates a comprehensive approach that considers clinical objectives, therapeutic options, and the broader framework of personalized oncology.

Drawing on current data and evolving clinical demands in personalized breast cancer care, we hypothesize that an integrated molecular-genetic profiling approach - simultaneously assessing both germline and somatic mutations, particularly in patients with a hereditary predisposition - outperforms isolated analyses in optimizing diagnostic, prognostic, and therapeutic strategies. We suggest that such an integrative method, which accounts for both the tumor's genetic architecture and hereditary risk factors, will facilitate more accurate selection of targeted therapies, improve the prediction of treatment response, and enable more effective patient stratification for preventive measures and genetic counseling. This, in turn, may significantly enhance the clinical effectiveness of personalized management in breast cancer. Accordingly, this review consolidates current data on the molecular-genetic characteristics of breast cancer, with particular emphasis on the clinical implications of germline versus somatic mutations, aiming to support evidence-based decision-making in the era of precision medicine.

2. Materials and Methods

This study is based on the analysis of scientific publications published between 2015 and 2025, with the aim of systematizing modern data on the molecular genetic characteristics of breast cancer, especially in the context of the differences between germline and somatic mutations and their role in personalized medicine. The main sources of information were the leading international scientific databases: PubMed, Scopus and

Web of Science, Google Scholar (Fig. 1). The search strategy included the use of the following keywords and their combinations: "breast cancer", "BRCA1/2", "germline mutations", "somatic mutations", "next generation sequencing" (NGS), "precision medicine". Filters were applied to select peer-reviewed publications in English. At the initial stage of the analysis, 327 publications were identified that met the search criteria. After assessment of abstracts, study design and methodological quality, taking into account the relevance and clinical significance of the presented data, 36 articles that fully met the goals and objectives of this review were included in the final analysis. The selected publications were classified according to the following areas: genetic aspects of breast cancer: the contribution of hereditary and acquired mutations, the role of germline and somatic mutations in breast cancer carcinogenesis: from hereditary predisposition to molecular heterogeneity, the significance of next-generation sequencing (NGS) technologies: in diagnostics, prognosis and choice of therapy; clinical relevance of the integration of germline and somatic profiling in the framework of personalized medicine and genetic counseling. The analysis was carried out taking into account the latest recommendations of NCCN, ESMO, ASCO and other specialized communities. This approach allowed us to conduct a comprehensive review of current knowledge, identify current areas of scientific research and highlight the importance of comprehensive molecular genetic analysis in breast cancer in the era of precision medicine.

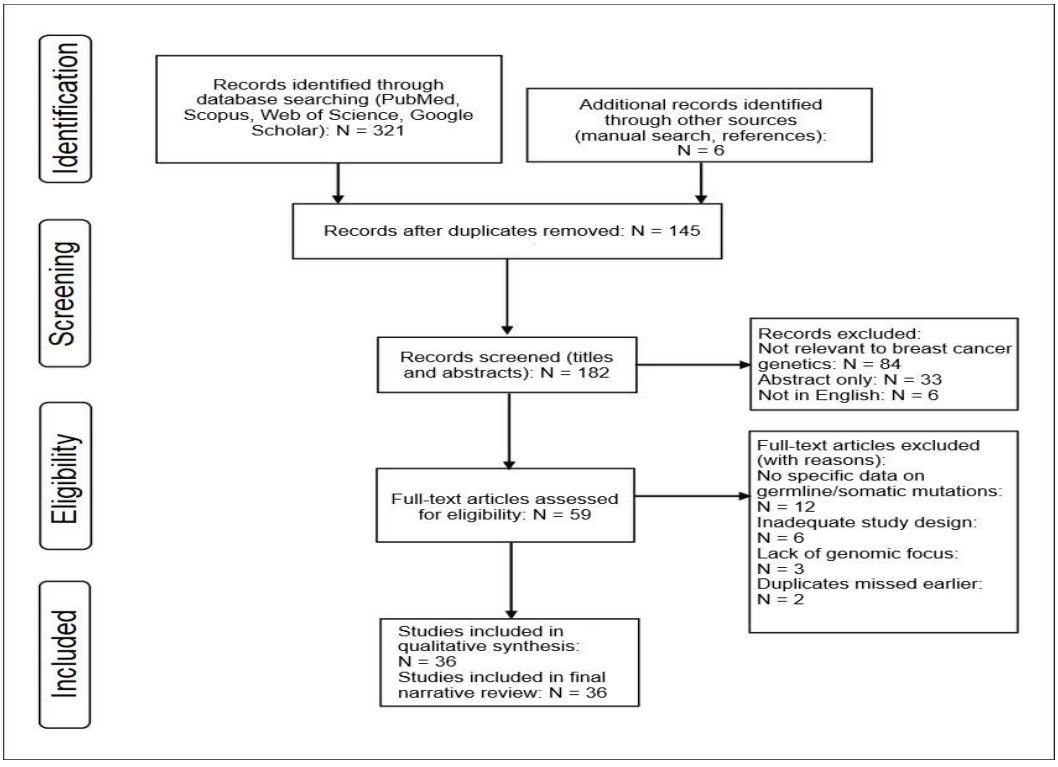

Figure 1 - Flow diagram

3. Results

The genetic nature of breast cancer: the role of germline and somatic mutations

Cancer is fundamentally a genetic disease, arising from alterations in genes that regulate cell growth and proliferation. These genetic aberrations may be inherited from parents (germline mutations) or may occur spontaneously during an individual's lifetime as a result of environmental and endogenous factors. Over

several decades, basic research has elucidated the mechanisms of cellular transformation and identified key driver mutations responsible for uncontrolled cell division and tumorigenesis (3).

In contemporary oncology, molecular-genetic profiling has become an integral component of comprehensive cancer diagnostics and therapy. Advances in molecular biology and cancer genetics have significantly expanded our ability to identify molecular biomarkers with substantial predictive and prognostic value. Genetic aberrations, particularly mutations, play a central role in oncogenesis. These mutations disrupt normal cellular functions, promoting unregulated proliferation, resistance to apoptosis, and metastatic potential (4). However, the identification of such mutations also offers a unique opportunity to distinguish malignant cells from normal tissues, which is critical for both diagnosis and the development of targeted therapeutic strategies. A profound understanding of the molecular and genetic mechanisms underlying malignancies, especially in the context of breast cancer (BC), forms the foundation for personalized molecular-targeted treatment approaches (5).

Genetic alterations associated with cancer can be transmitted through the germline and are responsible for approximately 5–10% of all breast cancer cases, significantly increasing the risk of malignancy. In breast cancer specifically, germline mutations, particularly in *BRCA1*/2 genes, play a pivotal role in the development of hereditary forms of the disease. In contrast, the majority of cases (90–95%) are considered sporadic, arising de novo and lacking familial inheritance patterns (6). Extensive studies of proto-oncogenes and tumor suppressor genes, as well as point mutations, have contributed significantly to our understanding of cancer pathogenesis. Proto-oncogenes, which normally regulate cell growth and differentiation, can become oncogenic through mutation or overexpression, resulting in loss of cell cycle control and malignant transformation. Conversely, tumor suppressor genes, which are responsible for cell cycle regulation and apoptosis, contribute to tumor development when inactivated or dysfunctional (7). The response of breast cancer patients to anti-cancer therapies is known to vary widely. This heterogeneity is driven by individual differences in the molecular pathogenesis of tumors, shaped by a diverse spectrum of driver gene mutations that initiate and sustain carcinogenesis. Studies of the molecular characteristics of breast tumors have revealed significant genetic heterogeneity and clonal evolution during disease progression. Elucidating the molecular profiles of tumor cells, particularly those associated with specific mutations, opens new avenues for improving therapeutic outcomes and survival (8).

Genetic testing can be applied in patients with a confirmed diagnosis of breast cancer to guide the selection of individualized targeted therapies. Furthermore, in patients under the age of 50 diagnosed with breast cancer, the identification of hereditary cancer syndromes can significantly influence both treatment and preventive strategies (9). Among unaffected individuals with a family history of cancer, the detection of germline predispositions allows for timely preventive interventions and early cancer detection. The variability in treatment response among patients is explained by molecular heterogeneity and the presence of diverse driver mutations, and their identification enables not only the discrimination of malignant from normal cells but also the rational application of precision-targeted therapies. Moreover, detecting either germline or somatic mutations facilitates the selection of specific targeted agents that directly interfere with aberrant signaling pathways driving tumor growth (10).

Therefore, given the molecular heterogeneity of breast cancer, modern approaches no longer prioritize either germline or somatic mutations in isolation. Instead, emphasis is placed on comprehensive molecular-genetic profiling. An integrative analysis of both mutation types - often utilizing next-generation sequencing (NGS) - provides the most complete representation of the tumor's genetic landscape and hereditary risk factors. This enables oncologists to make well-informed decisions that enhance diagnostic accuracy, optimize treatment strategies, and improve clinical outcomes for patients with breast cancer.

The role of germline mutations in the development of hereditary breast cancer

Hereditary cancer comprises a heterogeneous group of malignancies driven by germline mutations in one or more genes, inherited from a parent and present in all somatic cells of the body. These mutations typically affect genes critical for maintaining genomic stability, regulating the cell cycle, mediating DNA repair, or suppressing tumor development. In contrast to sporadic cancers, where mutations are acquired somatically during an individual's lifetime, germline mutations are inherited and often follow an autosomal dominant pattern, resulting in a 50% probability of transmission of the mutant allele to offspring. Although the presence of germline mutations significantly increases the risk of cancer development, it does not in itself guarantee tumor formation. This is explained by the concept of incomplete penetrance, which postulates that disease manifestation requires additional somatic mutations - the so-called "second hits" - that impair the function of the remaining wild-type allele or affect other tumor suppressor genes (11).

The most well-known and extensively studied genes implicated in hereditary breast cancer are *BRCA1* and *BRCA2*. Both are inherited in an autosomal dominant manner and play a key role in the homologous recombination repair of DNA double-strand breaks. Mutations in these genes disrupt the synthesis of functional proteins, leading to impaired DNA repair and accumulation of genetic damage that promotes malignant transformation (12). Carriers of *BRCA1*/2 mutations face a markedly increased lifetime risk of developing breast cancer. Moreover, *BRCA*-associated tumors are frequently characterized by a triple-negative molecular phenotype - lacking expression of estrogen receptors (ER), progesterone receptors (PR), and *HER2/neu* - which is associated with a more aggressive clinical course and limited options for targeted therapy. It has also been shown that mutation carriers tend to develop cancer at a younger age, which underlines the need for proactive clinical surveillance. Asymptomatic individuals with *BRCA1*/2 mutations should undergo regular monitoring and be considered for inclusion in personalized prevention and early detection programs (13).

Commonly identified pathogenic variants include *BRCA1 (185delAG, 5382ins*C*)* and *BRCA2 (617delT, 997del5)* mutations, which result in loss of gene function through frameshift-induced protein truncationгенов (14). Beyond *BRCA1*/2, several other genes have been implicated in hereditary breast cancer, including *MLH1, MSH2, TP53, CHEK2, PALB2, PTEN, NBN, ATM, BRIP1, RAD50, BLM*, and *FGFR2*, all of which are involved in cell cycle control, apoptosis, and DNA repair. This highlights the genetic heterogeneity underlying hereditary breast cancer syndromes. (15).

Accurate identification of germline mutations, along with assessment of their functional significance and population prevalence, is of critical importance for risk stratification, prognostic evaluation, and the selection of clinical management strategies. Given the high degree of molecular and clinical heterogeneity, the interpretation of mutational profiles necessitates an integrated approach involving molecular-genetic testing, genetic counseling, and personalized strategies for surveillance and therapy.

Somatic mutations and their role in carcinogenesis: molecular heterogeneity

Somatic mutations arise in post-zygotic somatic cells and, unlike germline mutations, are not heritable. These genetic alterations are confined to the affected cells and their clonal descendants, creating a genetic mosaicism within the organism. Although some somatic mutations are a consequence of physiological aging, their accumulation plays a critical role in the molecular pathogenesis of numerous diseases, particularly malignant neoplasms (16) .

It is now well established that somatic mutations constitute the genetic basis of the vast majority of sporadic cancers, which account for approximately 90% of all oncological cases. These mutations accumulate over a person's lifetime. While many are functionally neutral, a subset can disrupt critical cellular processes such as proliferation, apoptosis, and replication, thereby initiating oncogenesis. The principal molecular targets of somatic mutations in carcinogenesis are proto-oncogenes and tumor suppressor genes. When mutated, proto-

oncogenes can convert into oncogenes, acquiring the capacity to promote uncontrolled cell growth, invasion, and metastasis. One of the most studied oncogenes in breast cancer is *HER2/neu (ERBB2)*, a member of the epidermal growth factor receptor family. Its overexpression is associated with a poor prognosis and aggressive clinical behavior. Among the most frequently mutated genes in breast cancer, significant alterations are found in *TP53*, *PIK3CA*, *AKT1*, *GATA3*, *CDH1*, *MAP3K1*, *PTEN*, *ERBB2 (HER2)*, and *RB1* (17).

TP53 mutations are predominantly found in triple-negative breast cancers (TNBC) and are linked to a high level of genomic instability and malignant potential (18). In contrast, *PIK3CA* mutations are more common in hormone receptor-positive tumors (ER+/*HER2*−) and are generally associated with a favorable prognosis (19). CDH1 mutations result in the loss of E-cadherin function, impairing cell–cell adhesion and promoting invasive growth, particularly in lobular carcinoma. *ERBB2 (HER2)* amplification serves as a key biomarker for selecting patients for anti-*HER2* targeted therapies, including trastuzumab, pertuzumab, and T-DM1. *AKT1* mutations, such as *E17K*, activate the *PI3K/AKT* signaling pathway, conferring resistance to anti-estrogen therapy (20). Mutations in *MAP3K1* and *GATA3* frequently occur in luminal A/B subtypes and are generally associated with hormone receptor-positive phenotypes. Furthermore, *ESR1* mutations are most commonly observed in patients with metastatic or recurrent breast cancer who have previously received hormone therapy, particularly aromatase inhibitors. These mutations are rare in primary tumors, highlighting their acquired nature and possible selection under therapeutic pressure (21).

The immunogenic aspects of the somatic mutational profile also warrant attention - particularly *PD-L1* (programmed death-ligand 1) expression, which can be upregulated as a result of various somatic rearrangements and mutations (22). *PD-L1* expression is notably enriched in triple-negative breast cancers (TNBC), particularly those harboring *TP53* mutations, a high tumor mutational burden (TMB), and tumor-infiltrating lymphocytes (TILs) (23). Such tumors may be responsive to immune checkpoint inhibitors targeting *PD-1/PD-L1*, such as atezolizumab and pembrolizumab (24). Additionally, rare but clinically significant mutations in *MSH6*, *MLH1*, and *POLE*, associated with microsatellite instability (MSI) and a hypermutated phenotype, are also reported to confer enhanced immunotherapy sensitivity (25).

The detection and molecular characterization of somatic mutations are of paramount importance in modern oncology, particularly in breast cancer. These mutations are the driving force behind the majority of sporadic tumors and contribute to the genetic heterogeneity that underlies differences in tumor behavior, aggressiveness, and therapeutic response. Precise identification of somatic alterations - including driver mutations, gene amplifications, translocations, and immune-related markers such as *PD-L1* - enables patient stratification, disease prognostication, and the selection of individualized targeted and immunotherapies. As molecular diagnostic technologies rapidly evolve, the role of somatic mutation profiling continues to expand, becoming an indispensable element in the implementation of precision oncology.

Next-generation sequencing (NGS) in personalized breast cancer diagnostics

Contemporary molecular oncogenetics possesses a broad arsenal of highly sensitive and specific methods for detecting genetic alterations that play a pivotal role in oncogenesis. These methods enable the effective identification of both somatic mutations - occurring directly within tumor cells and serving as key drivers of malignant transformation - and germline mutations inherited from parents, which determine constitutional cancer predisposition (26). In routine clinical practice, somatic mutation analysis commonly relies on tumor tissue samples, most frequently formalin-fixed paraffin-embedded blocks obtained via biopsy or surgical resection. DNA extraction from these preserved samples permits subsequent sequencing or other molecular testing. In contrast, germline mutation detection is standardized through DNA analysis extracted from peripheral blood, since these mutations are present in all nucleated cells of the body. The application of advanced methods such as NGS enables comprehensive and high-throughput genomic profiling, allowing simultaneous analysis of numerous genes and

the detection of a wide mutation spectrum - an essential requirement for personalized oncology (27).

This technology, regarded as the "gold standard" in molecular diagnostics of malignancies, permits detailed examination of nucleotide sequences in both DNA and RNA, providing integrative predictive, prognostic, and diagnostic information necessary for personalized patient management (28). Unlike conventional molecular methods, NGS facilitates parallel sequencing of thousands of fragments, significantly accelerating genome decoding and enabling the detection of rare or low-frequency mutations.

At the international level, leading clinical guidelines - including those from NCCN, ESMO, and ASCO - now incorporate NGS into diagnostic and therapeutic algorithms for various cancers, including breast cancer (29). NGS is particularly valuable when triaging patients for targeted therapy. Large-scale studies have shown that NGS usage is associated with improved clinical outcomes: patients who underwent sequencing and received tumor profile - guided treatment demonstrated higher progression-free survival (PFS) and overall survival (OS) compared to those who did not receive molecular stratification. Например, в исследовании Kato et al. (2020) таргетированное лечение, основанное на результатах For example, in the study by Kato et al. (2020), targeted therapy based on NGS results and evaluated by a multidisciplinary tumor board resulted in statistically significant improvements in both PFS (HR = 0.63; 95% CI: 0.50–0.80; P < 0.001) and OS (HR = 0.67; 95% CI: 0.50–0.90; P = 0.007) (30).

Additionally, the size of the sequencing panel influences diagnostic yield. In the study by Kopetz et al. (2019), the use of an expanded NGS panel identified at least one previously undetected activating oncogene mutation in 41% of patients, of whom 19% received personalized therapy - associated with a significant improvement in overall survival (P = 0.017) (31). Similarly, the systematic review by Gibbs et al. (2023) demonstrated that in the majority of included publications, the application of NGS and targeted treatments led to improved clinical outcomes across various tumor types, including breast cancer (32).

Thus, whole-genome sequencing utilizing NGS technologies has become an indispensable component of modern oncogenetic diagnostics. It enables the detection of a broad spectrum of clinically relevant mutations and the assessment of immune target expression. Given the genetic heterogeneity of tumors - particularly in breast cancer - implementing NGS facilitates more accurate patient stratification, therapy response prediction, and treatment optimization. The integration of this technology into routine clinical practice significantly enhances the capabilities of personalized medicine and improves overall oncological treatment effectiveness.

Clinical significance of germline and somatic mutations in breast cancer

The identification of germline and somatic mutations in breast cancer holds substantial clinical importance and should be conducted in alignment with therapeutic goals, disease stage, and a personalized approach. In many cases, the detection of germline mutations - such as *BRCA1* and *BRCA2* - is essential at the time of initial diagnosis to assess hereditary cancer risk and to inform prophylactic or targeted interventions. However, as the disease progresses or therapy resistance develops, the clinical priority shifts toward re-evaluating the tumor's molecular profile to detect both *BRCA1*/2 and newly acquired somatic mutations, which reflect subclonal evolution and guide subsequent therapeutic decisions (33).

The crucial role of early germline *BRCA1*/2 mutation testing is underpinned by a combination of factors suggestive of hereditary predisposition. These include early-onset breast cancer, which significantly increases the likelihood of harboring pathogenic variants in predisposition genes (34). Special attention is given to patients with triple-negative breast cancer (TNBC) diagnosed at a young age, as this subtype is statistically more frequently associated with germline *BRCA1* mutations. A strong family history, including breast, ovarian, pancreatic, or prostate cancer in first-degree relatives, serves as a strong indicator for preventive genetic screening (35). Beyond individual clinical features, demographic and ethnic characteristics also play a critical role in determining the appropriateness of *BRCA1*/2 genetic testing. Due to the heterogeneity of

tumor biology and population-specific genetic variations, extended genetic screening is warranted in many countries - even in the absence of early-onset disease or a clear family history. The identification of *BRCA1*/2 mutation carriers not only allows for precise risk stratification of the index patient but also provides essential information for at-risk relatives, supporting cascade testing and the implementation of individualized surveillance and prophylactic strategies, including risk-reducing mastectomy and salpingo-oophorectomy (36).

In the context of metastatic disease and therapeutic resistance, the assessment of somatic mutations becomes paramount, complementing data on germline predisposition. Unlike inherited alterations, somatic mutations arise de novo in tumor cells during carcinogenesis and clonal evolution. These mutations are not heritable and reflect the specific molecular profile of a tumor at a given point in its progression. Modern approaches to the treatment of metastatic breast cancer increasingly rely on the principles of precision oncology, whereby therapeutic selection is contingent upon the identification of actionable driver mutations that dictate drug sensitivity or resistance. Comprehensive genomic profiling methods, such as next-generation sequencing (NGS), enable the detection of a wide range of clinically relevant somatic alterations in genes beyond *BRCA* - including PIK3CA, *ESR1*, *ERBB2*, *TP53*, and others - thus providing a foundation for treatment personalization (37).

As the disease advances or resistance emerges, dynamic monitoring of somatic mutations becomes an indispensable clinical tool. Under therapeutic pressure, tumors may acquire new mutations or exhibit clonal selection of pre-existing resistant subpopulations. In such scenarios, re-biopsy of tumor tissue - or increasingly, liquid biopsy via analysis of circulating tumor DNA (ctDNA) in plasma - enables real-time monitoring of molecular evolution. For example, *ESR1* mutations serve as biomarkers of resistance to endocrine therapy and may indicate the need for *CDK4/6* inhibitors or alternative treatments. Similarly, somatic mutations in DNA repair genes, such as *BRCA1*/2 or others involved in homologous recombination, may confer sensitivity to *PARP* inhibitors - even in the absence of inherited mutations - when acquired de novo in the tumor (38).

In summary, the comprehensive assessment of both germline and somatic mutations constitutes a cornerstone of modern oncology. Germline mutations inform hereditary risk assessment, guide familial testing strategies, and influence systemic treatment choices, including the use of *PARP* inhibitors in adjuvant and metastatic settings. Somatic mutations, by contrast, are critical for adapting treatment to the evolving molecular landscape of the tumor, particularly in the metastatic setting, where the timely identification of resistance mechanisms enables switching to more effective targeted therapies. The synthesis of data derived from both germline and somatic analyses facilitates the design of individualized treatment regimens tailored to the unique biological characteristics of each patient's tumor, ultimately improving therapeutic efficacy and clinical outcomes.

4. Discussion

The conducted literature analysis emphasized the important role of both germline and somatic mutations in the pathogenesis and clinical course of breast cancer. Particular attention is paid to mutations in the *BRCA1* and *BRCA2* genes, whose inherited pathogenic variants are associated with a high risk of breast cancer development and have a significant impact on the choice of therapy. Impaired mechanisms of DNA repair by homologous recombination caused by defects in these genes determines high sensitivity of tumors to *PARP* inhibitors and other agents inducing DNA damage. On the other hand, somatic mutations that occur sporadically during life significantly contribute to the molecular heterogeneity of breast cancer. In particular, variations in the *TP53*, *PIK3CA*, *AKT1*, *ESR1* and *GATA3* genes are associated with tumor aggressiveness, resistance to therapy and variability of the clinical course. These mutations can serve as both prognostic and

predictive biomarkers, especially when choosing targeted or hormonal drugs. The heterogeneity of somatic mutations necessitates molecular profiling of each tumor to justify the therapeutic strategy.

An integrated approach combining the analysis of germline and somatic changes using next-generation sequencing technologies has demonstrated high efficiency in the diagnosis and treatment of breast cancer. Integration of data on the patient's genetic background and tumor characteristics allows for more accurate risk stratification, determination of sensitivity to treatment, and prediction of outcomes. This is especially valuable for patients with a family history or "BRCAness" phenotype, in which tumors exhibit sensitivity to the same drugs as in BRCA-associated breast cancer, despite the absence of germline mutations.

At the same time, significant gaps in current knowledge have been identified. The interactions between different somatic mutations and their impact on clinical resistance, as well as the relationship between germline mutations in less studied genes (*PALB2*, *CHEK2*, *ATM*) and the molecular phenotype of the tumor, are insufficiently studied. The number of studies analyzing the combined effect of germline and somatic mutations on the choice of therapy, especially in the context of using combination treatment regimens, is limited. Approaches to interpreting variants of uncertain clinical significance are poorly developed, which complicates decision-making in clinical practice. The lack of uniform protocols for integrating NGS results into breast cancer treatment also remains an obstacle to the widespread implementation of precision medicine. Thus, the need for further research aimed at studying the interactions between different types of mutations and their clinical significance remains extremely relevant. This will improve genetic testing strategies, increase the accuracy of prognosis and move towards truly personalized treatment of breast cancer.

5. Conclusion

This review summarizes current knowledge on the molecular pathology of breast cancer, with a particular focus on germline and somatic mutations and an emphasis on the clinical relevance of *BRCA1* and *BRCA2*. Advances in molecular diagnostics have enabled the identification of oncogenic mutations not only in patients with breast cancer but also in healthy individuals, which is critically important for the personalization of diagnosis, treatment, and prevention strategies. The detection of *BRCA* mutations significantly enhances clinical disease management by informing the development of targeted therapeutic approaches and supporting genetic counseling and surveillance programs for mutation carriers. A clear distinction between germline mutations, which confer inherited predisposition, and somatic mutations, which act as drivers of sporadic tumor development, is of fundamental importance for understanding pathogenesis and selecting the appropriate clinical management strategy. Contemporary high-throughput sequencing technologies facilitate comprehensive analysis of both mutation types, forming the basis of personalized cancer care. An individualized approach to the assessment of both germline and somatic mutations is particularly valuable. In the presence of factors suggestive of hereditary cancer, comprehensive genetic testing - encompassing both inherited and acquired alterations - is advisable. Such an approach offers a more complete understanding of tumor biology and enables the optimization of therapeutic strategies tailored to the specific molecular features of each patient's disease.

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References

1. Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *74*(3), 229-263. https://doi.org/10.3322/caac.21834

2. Carbone, M., Arron, S. T., Beutler, B., Bononi, A., Cavenee, W., Cleaver, J. E., Yang, H. (2020). Tumour predisposition and cancer syndromes as models to study gene–environment interactions. *Nature Reviews Cancer*, *20*(9), 533-549. https://doi.org/10.1038/s41568-020-0265-y

3. Kontomanolis, E. N., Koutras, A., Syllaios, A., Schizas, D., Mastoraki, A., Garmpis, N., Fasoulakis, Z. (2020). Role of oncogenes and tumor-suppressor genes in carcinogenesis: a review. *Anticancer research*, *40*(11), 6009-6015. https://doi.org/10.21873/anticanres.14622

4. Feng, Y., Spezia, M., Huang, S., Yuan, C., Zeng, Z., Zhang, L., Ren, G. (2018). Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes & diseases*, *5*(2), 77-106. https://doi.org/10.1016/j.gendis.2018.05.001

5. Tempfer, C. B., Reymond, M. A. (2016). Sporadic cancers. In *The Molecular Basis of Human Cancer* (pp. 323-334). New York, NY: Springer New York. https://doi.org/10.1007/978-1-59745-458-2_21

6. Velez, A. M. A., Howard, M. S. (2015). Tumor-suppressor genes, cell cycle regulatory checkpoints, and the skin. *North American Journal of Medical Sciences*, *7*(5), 176. https://pmc.ncbi.nlm.nih.gov/articles/PMC4462812/

7. Xiong, X., Zheng, L. W., Ding, Y., Chen, Y. F., Cai, Y. W., Wang, L. P., Yu, K. D. (2025). Breast cancer: pathogenesis and treatments. *Signal transduction and targeted therapy*, *10*(1), 49. https://www.nature.com/articles/s41392-024-02108-4

9. Shah, R., Rosso, K., Nathanson, S. D. (2014). Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World journal of clinical oncology*, *5*(3), 283. https://doi.org/10.5306/wjco.v5.i3.283

10. Santarpia, L., Bottai, G., Kelly, C. M., Győrffy, B., Székely, B., Pusztai, L. (2016). Deciphering and targeting oncogenic mutations and pathways in breast cancer. *The oncologist*, *21*(9), 1063-1078. https://doi.org/10.1634/theoncologist.2015-0369

11. Garutti, M., Foffano, L., Mazzeo, R., Michelotti, A., Da Ros, L., Viel, A., Puglisi, F. (2023). Hereditary cancer syndromes: a comprehensive review with a visual tool. *Genes*, *14*(5), 1025. https://doi.org/10.3390/genes14051025

12. Ismail, T., Alzneika, S., Riguene, E., Al-Maraghi, S., Alabdulrazzak, A., Al-Khal, N., Nomikos, M. (2024). BRCA1 and its vulnerable C-terminal BRCT domain: structure, function, genetic mutations and links to diagnosis and treatment of breast and ovarian cancer. *Pharmaceuticals*, *17*(3), 333. https://doi.org/10.3390/ph17030333

13. Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M. J., Gilbert, F., ESMO Guidelines Committee. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Annals of Oncology*, *27*, v103-v110. https://doi.org/10.1093/annonc/mdw327

14. Abou-El-Naga, A., Shaban, A., Ghazy, H., Elsaid, A., Elshazli, R., Settin, A. (2018). Frequency of BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations in Egyptian women with breast cancer compared to healthy controls. *Meta Gene*, *15*, 35-41. https://doi.org/10.1016/j.mgene.2017.11.002

15. Pal, M., Das, D., Pandey, M. (2024). Understanding genetic variations associated with familial breast cancer. *World Journal of Surgical Oncology*, *22*(1), 271. https://doi.org/10.1186/s12957-024-03553-9

16. Zhang, L., Vijg, J. (2018). Somatic mutagenesis in mammals and its implications for human disease and aging. *Annual review of genetics*, *52*(1), 397-419. https://doi.org/10.1146/annurev-genet-120417-031501

17. Beňačka, R., Szabóová, D., Guľašová, Z., Hertelyová, Z., Radoňák, J. (2022). Classic and new markers in diagnostics and classification of breast cancer. *Cancers*, *14*(21), 5444. https://www.mdpi.com/2072-6694/14/21/5444#

18. Mitri, Z. I., Abuhadra, N., Goodyear, S. M., Hobbs, E. A., Kaempf, A., Thompson, A. M., Moulder, S. L. (2022). Impact of TP53 mutations in triple negative breast cancer. *npj Precision Oncology*, *6*(1), 64. https://doi.org/10.1038/s41698-022-00303-6

19. Araki, K., Miyoshi, Y. (2018). Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer. *Breast cancer*, *25*(4), 392-401. https://doi.org/10.1007/s12282-017-0812-x

20. Ruan, Y., Chen, L., Xie, D., Luo, T., Xu, Y., Ye, T., Wu, X. (2022). Mechanisms of cell adhesion molecules in endocrine-related cancers: a concise outlook. *Frontiers in endocrinology*, *13*, 865436. https://doi.org/10.3389/fendo.2022.865436

21. Desmedt, C., Pingitore, J., Rothé, F., Marchio, C., Clatot, F., Rouas, G., Sotiriou, C. (2019). ESR1 mutations in metastatic lobular breast cancer patients. *NPJ breast cancer*, *5*(1), 9. https://doi.org/10.1038/s41523-019-0104-z

22. Angelico, G., Broggi, G., Tinnirello, G., Puzzo, L., Vecchio, G. M., Salvatorelli, L., Caltabiano, R. (2023). Tumor infiltrating lymphocytes (TILS) and PD-L1 expression in breast cancer: a review of current evidence and prognostic implications from pathologist's perspective. *Cancers*, *15*(18), 4479. https://doi.org/10.3390/cancers15184479

23. Lotfinejad, P., Asghari Jafarabadi, M., Abdoli Shadbad, M., Kazemi, T., Pashazadeh, F., Sandoghchian Shotorbani, S., Baradaran, B. (2020). Prognostic role and clinical significance of tumor-infiltrating lymphocyte (TIL) and programmed death ligand 1 (PD-L1) expression in triple-negative breast cancer (TNBC): a systematic review and meta-analysis study. *Diagnostics*, *10*(9), 704. https://www.mdpi.com/2075-4418/10/9/704#

24. Bertucci, F., Gonçalves, A. (2017). Immunotherapy in breast cancer: the emerging role of PD-1 and PD-L1. *Current oncology reports*, *19*(10), 64. https://doi.org/10.1007/s11912-017-0627-0

25. Voutsadakis, I. A. (2020). High tumor mutation burden and other immunotherapy response predictors in breast cancers: associations and therapeutic opportunities. *Targeted oncology*, *15*(1), 127-138. https://doi.org/10.1007/s11523-019-00689-7

26. Casolino, R., Beer, P. A., Chakravarty, D., Davis, M. B., Malapelle, U., Mazzarella, L., Biankin, A. V. (2024). Interpreting and integrating genomic tests results in clinical cancer care: Overview and practical guidance. *CA: a cancer journal for clinicians*, *74*(3), 264-285. https://doi.org/10.3322/caac.21825

27. Satam, H., Joshi, K., Mangrolia, U., Waghoo, S., Zaidi, G., Rawool, S., Malonia, S. K. (2023). Next-generation sequencing technology: current trends and advancements. *Biology*, *12*(7), 997. https://www.mdpi.com/2079-7737/12/7/997#

28. Satam, H., Joshi, K., Mangrolia, U., Waghoo, S., Zaidi, G., Rawool, S., Malonia, S. K. (2024). Correction: Satam et al. Next-generation sequencing technology: Current trends and advancements. Biology 2023, 12, 997. *Biology*, *13*(5), 286. https://www.mdpi.com/2079-7737/13/5/286#

29. Cardoso, F., Paluch-Shimon, S., Schumacher-Wulf, E., Matos, L., Gelmon, K., Aapro, M. S., Bajpai, J., Barrios, C. H., Bergh, J., Bergsten-Nordström, E., Biganzoli, L., Cardoso, M. J., Carey, L. A., Chavez-MacGregor, M., Chidebe, R., Cortés, J., Curigliano, G., Dent, R. A., El Saghir, N. S., Winer, E. P. (2024). 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *The Breast*, *76*, 103756. https://doi.org/10.1016/j.breast.2024.103756

30. Kato, S., Kim, K. H., Lim, H. J., Boichard, A., Nikanjam, M., Weihe, E., Kurzrock, R. (2020). Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nature communications*, *11*(1), 4965. https://doi.org/10.1038/s41467-020-18613-3

31. Kopetz, S., Mills Shaw, K. R., Lee, J. J., Zhang, J., Litzenburger, B., Holla, V., Broaddus, R. R. (2019). Use of a targeted exome next-generation sequencing panel offers therapeutic opportunity and clinical benefit in a subset of patients with advanced cancers. *JCO Precision Oncology*, *3*, 1-14. https://doi.org/10.1200/PO.18.00213

32. Gibbs, S. N., Peneva, D., Cuyun Carter, G., Palomares, M. R., Thakkar, S., Hall, D. W., Yermilov, I. (2023). Comprehensive review on the clinical impact of next-generation sequencing tests for the management of advanced cancer. *JCO precision oncology*, *7*, e2200715. https://doi.org/10.1200/PO.22.00715

33. Godet, I., Gilkes, D. M. (2017). BRCA1 and BRCA2 mutations and treatment strategies for breast cancer. *Integrative cancer science and therapeutics*, *4*(1), 10-15761. https://doi.org/10.15761/ICST.1000228

34. Abdel-Razeq, H., Al-Omari, A., Zahran, F., Arun, B. (2018). Germline BRCA1/BRCA2 mutations among high risk breast cancer patients in Jordan. *BMC cancer*, *18*(1), 152. https://doi.org/10.1186/s12885-018-4079-1

35. Pederson, H. J., Narod, S. A. (2024). Commentary: Why is genetic testing underutilized worldwide? The case for hereditary breast cancer. *BJC reports*, *2*(1), 73. https://doi.org/10.1038/s44276-024-00099-x

36. Morgan, O., Belda, R., Schnur, J., Montgomery, G., Parmar, S., Chirivella, I., Cano, A. (2024). Prophylactic mastectomy and bilateral salpingo-oophorectomy in patients with breast cancer: a systematic review of postsurgical sexual function and menopausal hormone therapy symptom mitigation. *Sexual medicine reviews*, *12*(1), 3-13. https://doi.org/10.1093/sxmrev/qead020

37. Virga, A., Gianni, C., Palleschi, M., Angeli, D., Merloni, F., Maltoni, R., Bravaccini, S. (2024). A Novel AKT1, ERBB2, ESR1, KRAS, PIK3CA, and TP53 NGS assay: a non-invasive tool to monitor resistance mechanisms to hormonal therapy and CDK4/6 Inhibitors. *Biomedicines*, *12*(10), 2183. https://doi.org/10.3390/biomedicines12102183

38. Crucitta, S., Ruglioni, M., Lorenzini, G., Bargagna, I., Luculli, G. I., Albanese, I., Del Re, M. (2023). CDK4/6 inhibitors overcome endocrine ESR1 mutation-related resistance in metastatic breast cancer patients. *Cancers*, *15*(4), 1306. https://doi.org/10.3390/cancers15041306

Сүт безі қатерлі ісігінің молекулярлық-генетикалық профилі: BRCA мутацияларының рөлі, дербестендірілген емнің негізі ретінде герминальді және соматикалық альтерациялар

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Түйіндеме

Сүт безі қатерлі ісігі бүкіл әлемде әйелдер арасында ең таралған және әлеуметтік маңызды қатерлі ісіктердің бірі болып қала береді. Молекулярлық биология мен онкогенетикадағы жетістіктер сүт безі обырын диагностикалауға, болжауға және емдеуге деген көзқарастарды түбегейлі өзгертті, дербестендірілген медицинаға көбірек көңіл бөледі. Бұл шолу сүт безі қатерлі ісігінің молекулярлық-генетикалық ландшафтын зерттейді, герминальді және соматикалық мутациялар арасындағы айырмашылықтарға, олардың клиникалық маңыздылығына және жеке терапиялық стратегияларды басқарудағы рөліне назар аударады. Әдебиеттерді шолу нәтижелері герминальді мутациялары, әсіресе *BRCA1* және *BRCA2* - сүт безі обырының тұқым қуалайтын бейімділігімен тығыз байланысты екенін көрсетті, бұл тәуекелді бағалауға да, алдын алу стратегияларына да әсер етеді. Керісінше, соматикалық мутациялар, соның ішінде *TP53*, *PIK3CA* және *ESR1* өзгерістері ісіктің ерекшелігінде, емдеуге төзімділікте және аурудың өршуінде маңызды рөл атқарады. Сонымен қатар, толық геномды секвенирлеу арқылы анықталған герминальді және соматикалық мутация деректерін қамтитын интегративті молекулалық профильдеу дербестендірілген терапияда клиникалық шешім қабылдау үшін дәлірек негізді қамтамасыз етеді. Зерттеулер біріктірілген профильді емделушілер *PARP* тежегіштерін, эндокриндік терапияны және иммундық бақылау нүктесі ингибиторларын қоса, дәлірек терапевтік мақсатты тағайындаудан пайда көретінін көрсетті. Герминальді және соматикалық талдаулардың интеграциясы сүт безі қатерлі ісігімен ауыратын науқастарда терапевтік нәтижелер мен болжамды жақсартатын нақтыланған медицинаны жүзеге асырудағы маңызды қадам болып табылады.

Түйін сөздер: сүт безі қатерлі ісігі, BRCA1/2, герминальді соматикалық мутация, толық геномды секвенирлеу, нақтыланған медицина.

Молекулярно-генетический профиль рака молочной железы: Роль мутаций *BRCA*, герминальные и соматические альтерации как основа персонализированной терапии

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Резюме

Рак молочной железы остается одним из самых распространенных и социально значимых злокачественных заболеваний среди женщин во всем мире. Достижения молекулярной биологии и онкогенетики существенно изменили подходы к диагностике, прогнозированию и лечению рака молочной

железы, при этом все большее внимание уделяется персонализированной медицине. В данном обзоре рассматривается молекулярно-генетический ландшафт рака молочной железы с акцентом на различия между герминальными и соматическими мутациями, их клиническое значение и роль в определении индивидуальных терапевтических стратегий. Результаты обзора литературы показали, что герминальные мутации, особенно в генах *BRCA1* и *BRCA2,* тесно связаны с наследственной предрасположенностью к раку молочной железы, влияя как на оценку риска, так и на профилактические стратегии. Напротив, соматические мутации, включая изменения в генах *TP53, PIK3CA* и *ESR1,* играют ключевую роль в поведении опухоли, резистентности к лечению и прогрессировании заболевания. Более того, интегративное молекулярное профилирование с использованием секвенирования нового поколения, включающее данные как о герминальных, так и о соматических мутациях, обеспечивает более точную основу для принятия клинических решений при персонализированной терапии. Исследования показали, что пациенты с комбинированным профилированием получают преимущества от более точного терапевтического воздействия, включая ингибиторы *PARP*, эндокринную терапию и ингибиторы иммунных контрольных точек. Интеграция герминального и соматического анализа представляет собой критически важный шаг на пути к реализации прецизионной медицины, в конечном итоге улучшая результаты лечения и прогноз у пациентов с раком молочной железы.

Ключевые слова: рак молочной железы, *BRCA1/2*, герминальная соматическая мутация, секвенирование нового поколения, прецизионная медицина.

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Effectiveness of long-term folic acid supplementation for the prevention of preeclampsia in pregnant women with and without folate cycle disorders

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Abstract

Introduction. Preeclampsia remains one of the leading causes of maternal and perinatal morbidity worldwide. Accumulated evidence indicates that disturbances in folate metabolism and elevated homocysteine levels may contribute to the development of hypertensive disorders of pregnancy. This study evaluated the effectiveness of long-term folic acid supplementation for the prevention of preeclampsia in pregnant women with and without polymorphisms in folate cycle genes.

Methods. A single-center randomized controlled study included 320 women in the control group (folic acid intake until 12 weeks of gestation) and 894 women in the main group (folic acid intake throughout pregnancy). The main group was stratified by dosage: 400 μg, 800 μg, and 1200 μg. Clinical, biochemical, and genetic assessments were performed, including measurement of homocysteine levels and

genotyping of MTHFR, MTR, and MTRR polymorphisms. Pregnancy outcomes and the incidence of hypertensive complications were compared between groups.

Results. Long-term folic acid supplementation was associated with a lower overall incidence of hypertensive disorders of pregnancy compared with the control group (RR 1.43; p = 0.038). The incidence of preeclampsia was 1.67 times lower in the main group, indicating a favorable trend. No significant differences in blood pressure dynamics or perinatal outcomes were found among groups receiving different folic acid doses. Homocysteine levels were significantly higher in all women who subsequently developed preeclampsia, regardless of folic acid dosage. Genotype distribution demonstrated population-specific frequencies of MTHFR and MTR polymorphisms; however, no clear dose–response relationship was observed.

Conclusion. Long-term folic acid supplementation reduces the risk of hypertensive disorders of pregnancy, including a tendency toward a decreased incidence of preeclampsia, and is safe at all studied doses. The potential benefit is particularly relevant for populations with a high prevalence of genetic variants affecting folate metabolism. Further multicenter randomized studies are required to determine the optimal dosage and duration of supplementation.

Keywords: preeclampsia, folate cycle, folic acid.

1. Introduction

Preeclampsia is one of the serious and potentially life-threatening pregnancy-related conditions that lead to numerous maternal and fetal complications [1], and its prevalence is increasing in developed countries [2]. The global trend toward delayed childbearing in high-income countries contributes to the rise in risk factors associated with preeclampsia, such as advanced maternal age, obesity, insulin resistance, and the accumulation of comorbid somatic conditions [2]. Inadequate or absent prenatal care partly explains the high prevalence of preeclampsia in developing countries [1–3].

Despite significant progress in understanding the preeclampsia pathogenesis, effective methods of primary prevention remain limited. The exact etiological factors of preeclampsia are still unclear. However, it is believed that two critical mechanisms play a major role in the pathogenesis of preeclampsia: abnormal placentation, followed by the development of a maternal-placental syndrome associated with an excess of anti-angiogenic factors [1,2,4,5,6]. These well-established hypotheses conceptualizing preeclampsia as a placental disorder contribute to understanding and appropriate management of the complications associated with the condition.

Recent research continues to identify factors that may reduce the risk of developing preeclampsia [6]. Numerous studies have been conducted to explore possible approaches to prevent and manage preeclampsia [1,3,7–9]. Growing evidence indicates that disturbances in folic acid metabolism and elevated homocysteine levels may contribute to the development of hypertensive disorders during pregnancy, including preeclampsia [8–10]. One such potential protective factor is folic acid supplementation, traditionally prescribed during preconception and the first trimester for the prevention of neural tube defects [9]. In recent years, researchers have increasingly focused on the possible role of long-term folic acid supplementation in reducing the likelihood of hypertensive pregnancy complications, including preeclampsia. Potential mechanisms linking folate deficiency and hyperhomocysteinemia with preeclampsia include endothelial dysfunction, oxidative

stress, and impaired DNA methylation, all of which may lead to vascular dysregulation and placental perfusion abnormalities [9,10]. Many studies confirm that folic acid supplementation can help reduce elevated levels of homocysteine in the blood [8,12–18]. However, the relationship between folic acid intake and reduced risk of preeclampsia has produced conflicting findings, and the recommended doses vary widely [7,8,19–24]. Whether folic acid supplementation during pregnancy can reduce the risk of preeclampsia remains unclear [7].

The mechanisms underlying the proposed protective effect of folic acid are not fully understood; its involvement in the regulation of endothelial function, homocysteine metabolism, and antioxidant protection has been suggested. Given the clinical importance of the problem and accessibility of the intervention, investigating the role of folic acid in preeclampsia prevention presents significant scientific and practical interest.

The present study aims to evaluate the effectiveness of long-term folic acid supplementation in reducing the risk of preeclampsia among pregnant women with and without folate-metabolism impairments.

Hypothesis: Long-term folic acid supplementation lowers the risk of developing preeclampsia in pregnant women with and without folate-metabolism disorders.

2. Materials and research methods

Design: a single-center, randomized controlled trial.

Study Material: the study included 320 pregnant women in the control group, who received folic acid from the moment pregnancy was confirmed until 12 weeks of gestation for the prevention of congenital fetal malformations, and 894 pregnant women in the study group, who received folic acid throughout the entire duration of pregnancy. The study group was stratified according to folic-acid dosage: 400 mcg (n = 332), 800 mcg (n = 257), and 1200 mcg (n = 305).

The sample size for the randomized controlled trial was calculated according to the standard formula [20]. The sample size for the nested cohort was determined using the Epi Info statistical software (CDC, USA), based on previously published data on the frequency of polymorphisms in the MTHFR (C677T, A1298C), MTRR (G66A), and MTR (G2756A) genes among pregnant women in the Kazakh population [21]. The calculation was based on the lowest frequency polymorphism among those under study, specifically MTR (rs1805087), with a prevalence of 17.9%, and considering the prevalence of preeclampsia (PE) of 5.5% in the population of 18,000 pregnant women in Aktobe. Allowing for a 30% attrition rate, the required sample size was determined to be 536 pregnant women.

Participant selection and randomization method: a stratified sampling method was applied to form the study groups, based on the presence or absence of established risk factors for PE, in accordance with recommendations from previous research [22].

Inclusion Criteria: Kazakh ethnicity; age ≥18 years; ultrasound-confirmed singleton intrauterine pregnancy; gestational age up to 14 weeks at enrollment; written informed consent; and adherence to the study protocol.

The clinical component of the study was conducted in city polyclinics, at the Regional Perinatal Center of Aktobe, and at Kargalinsk City Hospital.

The laboratory component was conducted at the Scientific and Practical Center of West Kazakhstan Marat Ospanov Medical University and at INVITRO-Kazakhstan.

A complete blood count with platelet count was performed using the MEK-7300K automated hematology analyzer (Nihon Kohden Corporation, Japan, series 2845). Biochemical measurements, including bilirubin levels and cytolytic enzyme activity (ALT and AST), were performed using the Respons-910 biochemical analyzer (Germany).

Proteinuria was assessed using either a single urine sample and/or a 24-hour urine collection, analyzed

on the Uriscan Optima analyzer (YD Diagnostics, South Korea).

Homocysteine levels were measured using an immunochemiluminescent assay (ICLA) on the automated IMMULITE® 2000 XPi analyzer (Siemens, Germany) with Immulite® 2000 Homocysteine reagents (Siemens, Germany). The determination of homocysteine concentration (Hcy) in serum or EDTA-stabilized plasma was performed according to the immunochemiluminescent method using the IMMULITE® 2000 XPi analyzer (Siemens Healthcare Diagnostics, Germany).

The analytical method is based on competitive binding between endogenous homocysteine in the patient's sample and an enzyme-labeled methylated derivative of homocysteine for a limited number of specific antibodies immobilized on a solid phase. After binding and washing of unbound components, a substrate for alkaline phosphatase is added, which produces a chemiluminescent signal detected by the analyzer's photometer. The intensity of the emitted signal is inversely proportional to the concentration of homocysteine in the sample.

Samples were processed in EDTA-stabilized plasma or in serum obtained after centrifugation at 3000 rpm for 10 minutes. Storage conditions were as follows: at +2°C to +8°C for no more than 48 hours; at −20°C for up to 3 months. Frozen samples were thawed at room temperature and mixed before analysis. Repeated freeze-thaw cycles were not permitted. The analysis utilized the Siemens IMMULITE® 2000 Homocysteine Assay Kit, which includes a solid phase with immobilized anti-Hcy antibodies, an enzyme conjugate (alkaline phosphatase–homocysteine), calibrators (2–50 μmol/L), control materials (low and high levels), and the chemiluminescent substrate. Prepared samples, calibrators, and controls were loaded into the designated positions of the IMMULITE® 2000 XPi analyzer, which automatically performed sample pipetting, incubation, washing, substrate addition, and chemiluminescent signal measurement.

Genotyping of Folate Metabolism Gene Polymorphisms: venous blood (2.0 ml) was collected by venipuncture into K2-EDTA tubes (EcoPharm International, Kazakhstan). DNA extraction was performed using the PROBA-RS-GENETIKA reagent kit (DNA-Technology, Russia). DNA concentration was measured using the NanoDrop Lite spectrophotometer (USA), where a minimum DNA concentration of at least 1.0 ng/ml per PCR tube was required, corresponding to Ct ≤ 32.0 on the VK detection channel (Sy5). Molecular genetic analysis was performed using real-time polymerase chain reaction (Real-Time PCR) on the DTprime 4 instrument (DNA-Technology, Russia), with determination of genotypes for the polymorphisms under study: MTHFR (C677T, A1298C), MTRR (G66A), and MTR (G2756A). Ready-to-use primers were used: MTHFR 677 C>T (Ala222Val), MTHFR 1298 A>C (Glu429Ala), MTR 2756 A>G (Asp919Gly), and MTRR 66 A>G (IIe22Met) (DNA-Technology, Russia).

Blood Collection and Genomic DNA Isolation: For the analysis, after overnight fasting, 5.0 milliliters of peripheral blood samples were obtained from each of the study subjects in EDTA-containing tubes. Genomic DNA was extracted from the cell pellet in whole blood using the Promega Wizard® Genomic DNA Purification Kit following a standard method according to the producer's instructions. The real-time polymerase chain reaction (RT-PCR) using CFX-96 Real-Time System (Singapore) and Vector Best (Russia) reagents with specific primers for PCR were used to perform the analysis for detection of the MTR A2756G, MTRR A66G, and MTHFR C677T genotypes. The following RT-PCR cycle parameters were followed: 94 ◦C for 2 min, then 35 cycles of amplification (94 ◦C 30 s, 60 ◦C 30 s, and 72◦ 30 s). The final elongation step of 10 min, 72 ◦C, and 5 mL of the reaction product were analyzed in a 1.5% agarose gel. The normal, heterozygous, and homozygous mutant genotype profiles of each of the genes were identified.

Statistical analysis. Statistical analysis and data visualization were performed using the R statistical computing environment, version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were presented as absolute and relative frequencies for categorical variables, and as medians with interquartile ranges (1st–3rd quartiles) for continuous variables with asymmetric distributions. Assessment of normality for continuous variables was

conducted using the Shapiro–Wilk test, evaluation of the skewness coefficient (where an absolute value >1.96 was considered indicative of significant deviation from normality), and visual inspection of histograms and quantile–quantile (Q–Q) plots.

Compliance of observed genotype frequencies with theoretical Hardy–Weinberg equilibrium was assessed using Pearson's χ^2 test and the inbreeding coefficient (f).

Comparisons between two groups for quantitative variables were performed using the Mann–Whitney U test, whereas comparisons among three or more groups were conducted using the Kruskal–Wallis test, with post-hoc pairwise analyses performed using Dunn's test. Group comparisons for categorical variables were conducted using Pearson's χ^2 test and Fisher's exact test when the minimum expected frequency in contingency table cells was <5. The Holm correction was applied to adjust for multiple pairwise comparisons. Relative risk (RR) with corresponding 95% confidence intervals (95% CI) was used to assess the strength of association between binary outcomes and potential predictors. For the analysis of changes in quantitative and binary outcomes across repeated measurements, generalized estimating equations (GEE) were employed, including models with interaction terms between gestational-age indicators and group assignment.

Stepwise predictor selection for inclusion in the prognostic model was performed using the Akaike Information Criterion (AIC). Selected predictors were incorporated into a multivariable logistic regression model without interaction terms. Model performance was evaluated using Nagelkerke's pseudo-R^2, Somers' Dxy coefficient, and the concordance index (C-index, AUC). Additionally, metrics corrected for potential overfitting were obtained using non-parametric bootstrapping (B = 1000). The optimal threshold probability for classification was determined using Youden's J-statistic, followed by calculation of predictive accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), all with corresponding 95% CI.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all participants prior to sample collection. Ethical approval was granted by the Local Bioethics Committee of the West-Kazakhstan Medical University (Minutes No. 7, dated 03 March 2025). Throughout the study, the investigators adhered to established principles of biomedical research ethics and scientific integrity. No personally identifiable information was accessible to the research team at any stage of the study.

3. Results

The mean age of pregnant women in the main and control groups was 30.2 ± 5.7 and 29.4 ± 4.9 years, respectively, with no statistically significant differences identified between them ($p < 0.001$; see Table 1 in the appendix). There were no statistically significant differences between the groups with respect to body weight ($p = 0.83$); the mean body weight of all examined participants was 58.7 ± 8.9 kg and 58.8 ± 8.7 kg, respectively. The average body mass index (BMI) was 22.5 ± 3.2 and 22.6 ± 3.1 kg/m², indicating the absence of such risk factors for preeclampsia as obesity or excessive body weight. No significant intergroup differences were detected in social status ($p = 0.994$), family history, or personal medical history, including arterial hypertension, diabetes mellitus, cholecystitis, or prior surgical interventions, which might influence the development of preeclampsia. A positive family history of malignant neoplasms of various localizations was observed only among participants receiving the 800-mcg folic acid dose ($p = 0.01$).

Comparative analysis of gynecological and obstetric histories revealed that women in the main study group exhibited a tendency toward a higher age at sexual debut ($p = 0.059$). The prevalence of cervical erosion was significantly higher among participants in the control group ($p < 0.001$), whereas uterine fibroids were observed only among participants in the main group ($p = 0.076$) (see table in the appendix). Therefore, no statistically

significant differences were identified between the main and control groups regarding major demographic or medical history characteristics that could influence the outcomes of the study. Comparative analysis of systolic blood pressure (SBP) dynamics throughout pregnancy demonstrated no statistically significant differences between the groups (p = 0.522) (Table 1).

Table 1 - Dynamics of systolic blood pressure in the study groups

Gestational age	Control group	Study group			p[1]
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	103,7 (±7,8) 100 (100; 110)	103,2 (±7,9) 100 (100; 110)	104,5 (±7,5) 110 (100; 110)	103,6 (±7,7) 100 (100; 110)	0,216
14-20 weeks	104,5 (±8,3) 110 (100; 110)	103,8 (±8,3) 100 (100; 110)	105,2 (±8,4) 110 (100; 110)	104,6 (±8,6) 110 (100; 110)	0,251
20-24 weeks	105 (±8,6) 105 (100; 110)	104,1 (±8,9) 100 (100; 110)	105,3 (±9) 105 (100; 110)	105,2 (±8,8) 105 (100; 110)	0,289
24-30 weeks	105,6 (±8,7) 110 (100; 110)	104,2 (±9,1) 100 (100; 110)	106,4 (±8,6) 110 (100; 110)	105,1 (±9) 110 (100; 110)	**0,031**
30-34 weeks	107,8 (±11,3) 110 (100; 110)	106,8 (±9,8) 110 (100; 110)	107,8 (±10,2) 110 (100; 110)	106,1 (±9,5) 110 (100; 110)	0,112
34-38 weeks	111,6 (±13,4) 110 (100; 120)	110,8 (±13,6) 110 (100; 120)	110,9 (±12,2) 110 (100; 120)	109,4 (±11,4) 110 (100; 115)	0,183
40-42 weeks	113,8 (±11,6) 110 (110; 120)	114 (±10,8) 110 (110; 120)	114 (±10,9) 110 (110; 120)	113,7 (±10,4) 110 (110; 120)	0,989
p[2]	**<0,001**	**<0,001**	**<0,001**	**<0,001**	–

Note: p[1] - ; p[2] -

In all groups, a statistically significant increase in SBP was observed as the pregnancy period increased, especially in the later stages (Table 2).

Table 2 - Results of comparative analysis of the dynamics of SBP in the study groups

Group	Comparison	14-20 weeks	20-24 weeks	24-30 weeks	30-34 weeks	34-38 weeks	40-42 weeks
Control group	vs. baseline period	0,359	0,066	0,003	<0,001	<0,001	<0,001
	vs. preceding period	0,422	0,870	0,668	0,001	<0,001	0,072
400 mcg	vs. baseline period	0,53	0,231	0,212	<0,001	<0,001	<0,001
	vs. preceding period	0,617	0,978	>0,999	<0,001	<0,001	0,001
800 mcg	vs. baseline period	0,460	0,473	0,004	<0,001	<0,001	<0,001
	vs. preceding period	0,539	>0,999	0,161	0,081	<0,001	0,003
1200 mcg	vs. baseline period	0,105	0,006	0,013	<0,001	<0,001	<0,001
	vs. preceding period	0,119	0,672	>0,999	0,234	<0,001	<0,001

At 24-30 weeks, the group of patients taking 400 mcg of folic acid showed a statistically significantly lower SBP level compared to the group of patients taking 800 mcg of folic acid (p=0.023) (Table 4).

Pairwise comparisons of the other groups revealed no statistically significant differences.

A comparative analysis of diastolic blood pressure between the study groups revealed no statistically significant differences between the groups in pregnancy dynamics (p=0.383) (see table in the appendix).

All study groups showed a statistically significant increase in DBP with increasing gestational age (p<0.001), most pronounced in the second half of the gestational period (Table 3).

Table 3 - Results of comparative analysis of the dynamics of DBP in the study groups

Group	Comparison	14-20 weeks	20-24 weeks	24-30 weeks	30-34 weeks	34-38 weeks	40-42 weeks
Control group	vs. baseline period	0,568	0,01	<0,001	<0,001	<0,001	<0,001
	vs. preceding period	–	0,184	0,65	0,059	<0,001	0,014
400 mcg	vs. baseline period	0,841	0,460	0,003	0,001	<0,001	<0,001
	vs. preceding period	–	0,958	0,103	0,968	<0,001	<0,001
800 mcg	vs. baseline period	0,101	0,355	0,001	<0,001	<0,001	<0,001
	vs. preceding period	–	>0,999	0,149	0,37	<0,001	<0,001
1200 mcg	vs. baseline period	0,988	0,209	0,021	0,016	<0,001	<0,001
	vs. preceding period	–	0,024	0,811	>0,999	<0,001	<0,001

No statistically significant differences were found between the groups in terms of proteinuria dynamics during pregnancy (p=0.285). However, a statistically significant increase in the frequency of proteinuria was noted in the control group and in the group of participants taking folic acid in doses of 400 mcg and 1200 mcg (p<0.001 and p<0.028).

Table 4 - Dynamics of proteinuria frequency in the study groups

Gestational age	Control group	Study group			p^1
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
14-20 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
20-24 weeks	0/306 (0%)	0/331 (0%)	0/255 (0%)	0/304 (0%)	–
24-30 weeks	0/305 (0%)	0/330 (0%)	0/253 (0%)	0/304 (0%)	–
30-34 weeks	2/306 (0,7%)	0/330 (0%)	1/254 (0,4%)	0/304 (0%)	0,389
34-38 weeks	7/306 (2,3%)	10/330 (3%)	4/254 (1,6%)	2/304 (0,7%)	0,083
40-42 weeks	6/295 (2%)	9/323 (2,8%)	4/252 (1,6%)	5/299 (1,7%)	0,754
p^2	0,133	<0,001	0,218	0,028	–

Note: p^1 - differences between the control and main groups; p^2 - differences in the same group between the previous and subsequent indicator.

The incidence of general (non-hypertensive) pregnancy complications (such as anemia and threatened miscarriage) was 18.1% in the control group and 19.2% in the study group, which did not have a statistically significant difference (P=0.82). The highest incidence of general pregnancy complications in both groups occurred in the second trimester due to an increase in anemia.

A comparative analysis of all pregnancy complications, including hypertensive conditions, revealed a trend toward a higher incidence of pregnancy complications among patients in the control group (RR=1.07 [95% CI: 0.99; 1.15], p=0.076). The incidence of hypertensive conditions (arterial hypertension without proteinuria, proteinuria without hypertension, preeclampsia, arterial hypertension with proteinuria) in the study group was 9.6%, and did not differ significantly from the control group (P=0.038). The incidence of preeclampsia was 1.67 [95% CI: 0.94; 3.28] times significantly lower in the study group compared to the control group (p=0.077).

The overall incidence of hypertensive conditions during pregnancy among patients in the study group was statistically significantly 1.43 [95% CI: 1.02; 2.53] times lower (p=0.038) than in the control group.

Table 5 - Features of the course of pregnancy in the study groups

Variables	**Control group n=306**	**Study group n=894**	**p**
Pregnancy complications	160(52,2%)	388 (43,4%)	0,076
I trimester	14 (4,4%)	39 (4,4%)	0,876
II trimester	24 (7,5%)	76 (8,5%)	0,719
III trimester	20 (6,25%)	56 (6,3%)	0,866
Pregnancy-induced hypertension	12 (3,75%)	24 (2,7%)	0,274
Preeclampsia	15 (4,68%)	25 (2,8%)	0,077
Pregnancy-induced proteinuria	17 (5,3%)	37 (4,1%)	0,302
Total hypertensive disorders	44 (13,75%)	86(9,6%)	0,038

The results of the comparative analysis of the study groups in terms of the characteristics of the pregnancy course (Table 6) showed that general pregnancy complications were slightly more common among the participants taking 1200 mcg folate compared to the control group (OR=1.13 [95% CI: 1.01; 1.27], p=0.028, Figure 7); other pairwise intergroup comparisons revealed no statistically significant differences in the incidence of pregnancy complications. No statistically significant differences were found between the groups in terms of the incidence of arterial hypertension and preeclampsia (p=0.565 and 0.237, respectively); however, a trend towards a higher incidence of proteinuria was found among the control group participants who did not take folic acid (p=0.06).

Table 6 - Complications during pregnancy depending on the dose of folic acid taken

Variables	Control group (n=306)	Study group (n=894)			p
		400 mcg (n=332)	**800 mcg** (n=257)	**1200 mcg** (n=305)	
Pregnancy complications	160(52,2%)	97(29,2%)	83(32,2%)	77 (25,2%)	**0,025**
I trimester	14 (4,6%)	14 (4,2%)	10 (3,9%)	15 (4,9%)	0,94
II trimester	24 (7,8%)	30 (9%)	23 (8,9%)	23 (7,5%)	0,876
III trimester	20 (6,5%)	14 (4,2%)	23 (8,9%)	19 (6,2%)	0,139
Pregnancy-induced hypertension	12 (3,9%)	8 (2,4%)	9 (3,5%)	7 (2,3%)	0,565
Preeclampsia	15 (4,9%)	10 (3%)	9 (3,5%)	6 (2,0%)	0,237
Pregnancy-induced proteinuria	17 (5,6%)	21 (6,3%)	9 (3,5%)	7 (2,3%)	**0,06**

There were no statistically significant differences in platelet levels (p=0.363) between the control group and the groups of patients taking folic acid at doses of 400, 800, and 1200 mcg (see table in the appendix).

There were no statistically significant differences between the groups of patients taking folic acid in terms of AST (p=0.841) and ALT (p=0.931) levels.

The concentration of serum homocysteine levels in the first trimester of pregnancy in the control group was statistically comparable with pregnant women with further folic acid intake at dosages of 400, 800, and 1200 mcg in both pregnant women with further development of preeclampsia and non-preeclampsia cases Table 7. However, we found that in all cases of further development of preeclampsia, serum homocysteine concentrations in all groups were significantly higher in comparison with pregnant women without developing preeclampsia during pregnancy Table 7.

Thus, at the start of the folic acid supplementation study, pregnant women had no differences in serum homocysteine concentrations.

Table 7 - Serum homocysteine concentrations in the first trimester of pregnancy depends on the development of preeclampsia

		Control group n=306	Folic acid supplementation groups			p-value
			FA 400 n=334	**FA 800 n=259**	**FA 1200 n=305**	
HCY concentrations, umol/L, Me (25-75IQR)	PE	13.1 (9.1-15.6)	14.7 (12.2-20.2)	15.5 (14.6-18.8)	16.9 (11.5-23.8)	0.704[1]
	non-PE	5,9 (5.4-6.7)	6.0 (4.9-7.5)	5.8 (4.9-7.4)	6.0 (4.9-7.3)	0.05[1]
p-value		< 0.0001[2]	< 0.0001[2]	< 0.0001[2]	< 0.0001[2]	

[1] - Kruskal-Wallis ANOVA test; [2] - Mann-Whitney U Test

HCY – homocysteine; PE - preeclampsia

Analysis of the condition of the fetus in the study groups (Table 8) did not show statistically significant differences between the groups with respect to the anthropometric characteristics of newborns and assessment according to the Apgar scale at the 1st (p=0.675) and 5th (p=0.695) minutes.

Table 8 - Fetal condition in the study groups

Variables	Control group	Study group			p
		400 mcg	800 mcg	1200 mcg	
Body weight (g)	3450 (3120; 3750)	3440 (3100; 3720)	3470 (3100; 3704)	3400 (3094; 3720)	0,506
Body length (cm)	54 (52; 56)	53 (52; 55)	54 (52; 56)	53 (51; 55)	0,313
Apgar score					
at 1 minute	9 (8; 9)	9 (8; 9)	9 (8; 9)	9 (9; 9)	0,675
2 points	1/306 (0,3%)	0/331 (0%)	2/254 (0,8%)	2/303 (0,7%)	
3 points	–	–	–	–	
4 points	–	–	–	–	
5 points	2/306 (0,7%)	1/331 (0,3%)	0/254 (0%)	0/303 (0%)	
6 points	10/306 (3,3%)	9/331 (2,7%)	6/254 (2,4%)	6/303 (2%)	
7 points	23/306 (7,5%)	21/331 (6,3%)	17/254 (6,7%)	22/303 (7,3%)	
8 points	47/306 (15,4%)	59/331 (17,8%)	45/254 (17,7%)	41/303 (13,5%)	
9 points	223/306 (72,9%)	241/331 (72,8%)	184/254 (72,4%)	232/303 (76,6%)	
at 5 minutes	10 (9; 10)	10 (9; 10)	10 (9; 10)	10 (10; 10)	0,695
6 points	2/306 (0,7%)	0/331 (0%)	2/254 (0,8%)	2/303 (0,7%)	
7 points	7/306 (2,3%)	8/331 (2,4%)	6/254 (2,4%)	5/303 (1,7%)	
8 points	23/306 (7,5%)	21/331 (6,3%)	14/254 (5,5%)	21/303 (6,9%)	
9 points	51/306 (16,7%)	61/331 (18,4%)	48/254 (18,9%)	43/303 (14,2%)	
10 points	223/306 (72,9%)	241/331 (72,8%)	184/254 (72,4%)	232/303 (76,6%)	
Congenital malformation	5/306 (1,6%)	4/331 (1,2%)	2/255 (0,8%)	1/304 (0,3%)	0,408
Transfer to the acute renal failure/intensive care unit	19/306 (6,2%)	19/331 (5,7%)	10/255 (3,9%)	15/304 (4,9%)	0,64

Table 9 and Figures 1, 2, 3 present the results of genotyping of patients in the main group in relation to polymorphic loci of the MTR, MTRR, and MTHFR genes. The analysis of the correspondence between the observed genotype frequency at the studied loci and the theoretical one determined by the Hardy-Weinberg equilibrium in relation to the polymorphic loci rs1801394 of the MTRR gene (f= -0.008, χ^2=0.013, p=0.909) and rs1801131 of the

MTHFR gene (f=0.078, χ^2=3.08, p=0.079) did not reveal any significant deviation of the observed frequencies from the theoretical ones; the distribution of genotypes at the polymorphic loci rs1805087 of the MTR gene (f=0.19, χ^2=17.74, p<0.001) and rs1801133 of the MTHFR gene (f=0.161, χ^2=13.603, p<0.001) was statistically significant deviated from the theoretical distribution (Figure 1).

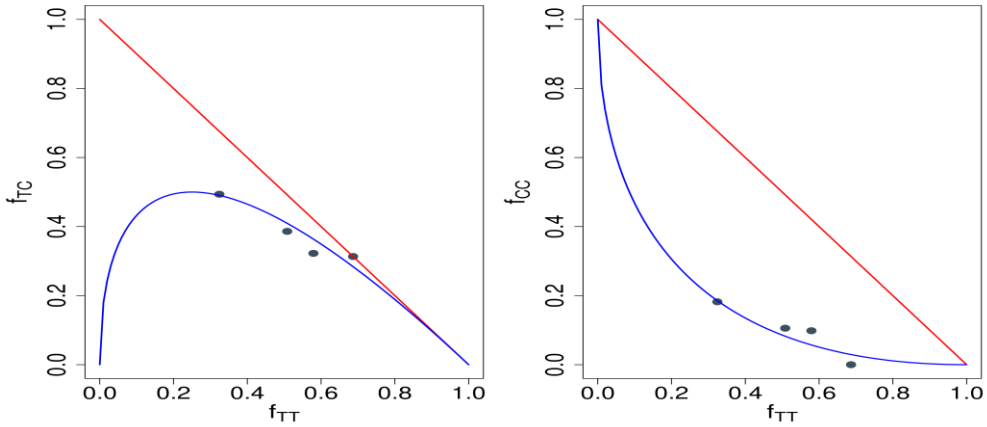


Figure 1 - Correspondence between the observed genotype frequency at the studied loci and the theoretical frequency determined by the Hardy-Weinberg equilibrium (B is the minor allele)

A comparative analysis revealed a lower proportion of CC homozygotes in the group of patients receiving 1200 mcg folate compared to those receiving 400 (p=0.005) or 800 mcg (p=0.144). Table 8 presents a multivariate model developed using stepwise selection of predictors with exclusion based on the Akaike information criterion (AIC) to predict the likelihood of developing obstetric complications among patients receiving folate.

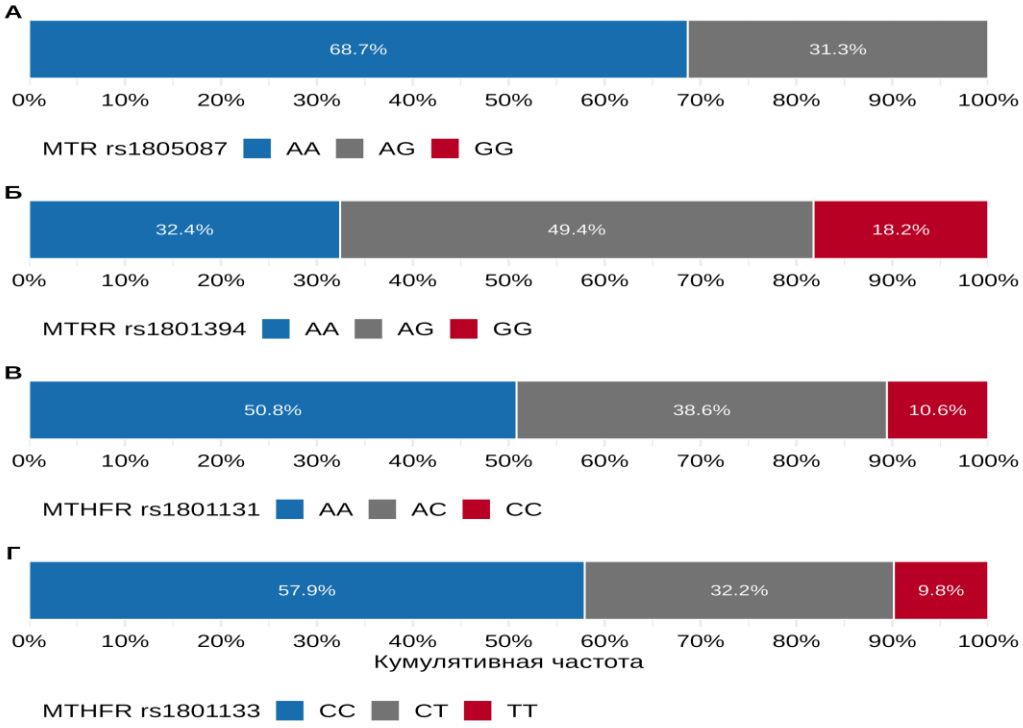
The resulting model was characterized by a Nigelkerke pseudo-R^2 value of 0.03, Sommers' D_{XY} coefficient of 0.14 (adjusted value - 0.1), and AUC of 0.58 [95% CI: 0.53; 0.63] (adjusted value - 0.55) (Figures 2 and 3). Based on the model coefficients, a prognostic nomogram was developed to assess the likelihood of developing obstetric complications among patients taking folates (Figure 4).

Table 9 - Genotyping results

Locus	All patients (n=549)	400 mcg (n=199)	800 mcg (n=162)	1200 mcg (n=188)	p
MTR rs1805087					0,671
AA	377 (68,7%)	140 (70,4%)	107 (66%)	130 (69,1%)	
AG	172 (31,3%)	59 (29,6%)	55 (34%)	58 (30,9%)	
MTRR rs1801394					0,12
AA	178 (32,4%)	62 (31,2%)	44 (27,2%)	72 (38,3%)	
AG	271 (49,4%)	105 (52,8%)	81 (50%)	85 (45,2%)	
GG	100 (18,2%)	32 (16,1%)	37 (22,8%)	31 (16,5%)	
-/G	371 (67,6%)	137 (68,8%)	118 (72,8%)	116 (61,7%)	0,076
MTHFR rs1801131					0,499

AA	279 (50,8%)	106 (53,3%)	86 (53,1%)	87 (46,3%)	
AC	212 (38,6%)	73 (36,7%)	57 (35,2%)	82 (43,6%)	
CC	58 (10,6%)	20 (10,1%)	19 (11,7%)	19 (10,1%)	
-/C	270 (49,2%)	93 (46,7%)	76 (46,9%)	101 (53,7%)	0,307
MTHFR rs1801133					0,01
CC	318 (57,9%)	125 (62,8%)	96 (59,3%)	97 (51,6%)	
CT	177 (32,2%)	50 (25,1%)	49 (30,2%)	78 (41,5%)	
TT	54 (9,8%)	24 (12,1%)	17 (10,5%)	13 (6,9%)	
-/T	231 (42,1%)	74 (37,2%)	66 (40,7%)	91 (48,4%)	0,076

Figure 2 - Results of genotyping of polymorphic loci rs1805087 of the MTR gene (A), rs1801394 of the MTRR gene (B), rs1801131 (C) and rs1801133 (D) of the MTHFR gene



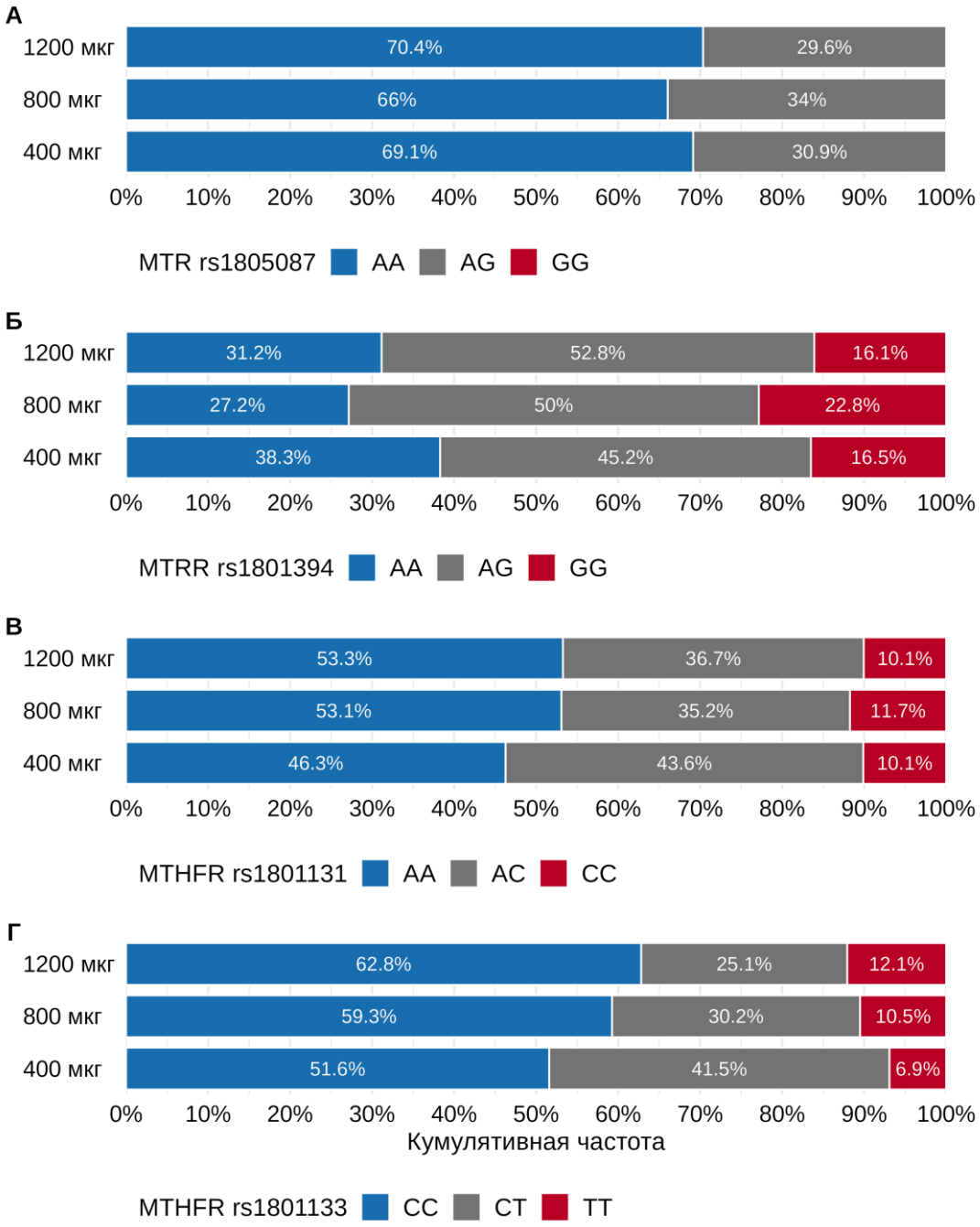


Figure 3 - Results of genotyping of polymorphic loci rs1805087 of the MTR gene (A), rs1801394 of the MTRR gene (B), rs1801131 (C) and rs1801133 (D) of the MTHFR gene in the study groups

Using a 25% cutoff for the predicted probability of developing obstetric complications among folate-supplemented patients, the resulting model had 49.2% [95% CI: 44.9; 53.4] predictive accuracy, 75.9% [95% CI: 68.5; 82.4] sensitivity, and 38.4% [95% CI: 33.5; 43.4] specificity. The positive predictive value was 33.2% [95% CI: 28.4; 38.4], and the negative predictive value was 79.8% [95% CI: 73.3; 85.3] (Table 9).

Table 10 - Coefficients in the resulting model for predicting the likelihood of developing complications during childbirth among patients taking folates

Predictor	β SE)	OR	95% CI	p	VIF
Intercept	-1,53 (0,25)	–	–	–	–
Genotype at MTHFR rs1801133					
CC	0	1	–	–	–
CT	0,49 (0,21)	1,64	1,07; 2,50	0,022	1,17
TT	0,3 (0,36)	1,34	0,65; 2,69	0,412	1,27
Carrier of C allele at MTHFR rs1801131	0,33 (0,21)	1,39	0,92; 2,12	0,115	1,23
Carrier of G allele at MTRR rs1801394	0,38 (0,21)	1,46	0,97; 2,22	0,072	1,01

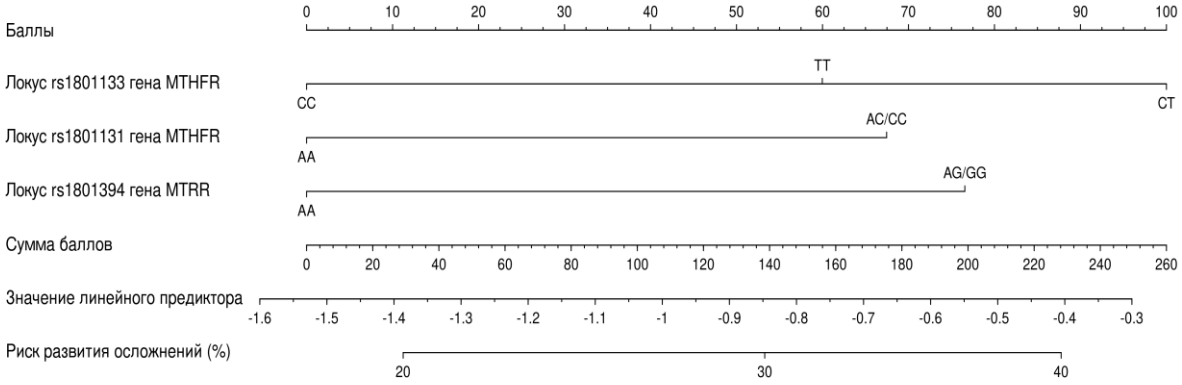


Figure 4 - Nomogram for predicting the likelihood of developing obstetric complications among patients taking folate. To estimate the likelihood of developing obstetric complications, it is necessary to determine the score corresponding to the predictor value by lowering the normal to the appropriate scale. Then, it is necessary to find the sum of the scores and, by lowering the normal to the appropriate scale, find the estimate of the linear predictor value (the logarithm of the odds of the event) and the likelihood of developing obstetric complications

4. Discussion of Study Results

This study evaluated the effectiveness of long-term folic acid supplementation at different doses (400, 800, and 1200 mcg) for the prevention of preeclampsia in pregnant women and examined its relationship with folate metabolism markers and pregnancy outcomes. The study results show a trend toward reduced preeclampsia incidence in the group taking folic acid overall, with no statistically significant differences in the primary outcomes between the dosage groups. Some differences were noted in the frequency of overall complications and homocysteine levels. These observations partially align with and partially differ from previously published.

Results from the large international randomized FACT trial demonstrated that high doses of folic acid (4 mg/day) after the first trimester do not prevent the development of preeclampsia in high-risk women [1]. This is consistent with our data, where significant

preeclampsia prevention from high (compared to low) doses was not observed.

Some meta-analyses and reviews have shown conflicting results: some studies reported a positive effect of folic acid or folate-containing multivitamins in reducing the risk of hypertensive disorders of pregnancy, whereas other reviews and meta-analyses did not support a significant impact of folate therapy on preeclampsia risk. Our findings—absence of a pronounced clinical effect when comparing doses—align with recent systematic reviews highlighting the ambiguity of existing data and the need for further high-quality research [27-33].

Several recent studies have noted associations between polymorphisms in folate metabolism genes (specifically MTHFR C677T and A1298C) and increased risk of preeclampsia, as well as imbalances in angiogenic markers. Our study considered the frequency of these polymorphisms in the local Kazakh population, which is important for interpreting responses to folate therapy since genetic background can modify both folate metabolism and clinical response. These observations are consistent with studies in other populations, including a Tunisian cohort and broader analyses of variant population frequencies [27].

Possible Reasons for Discrepancies and Agreements

1. Dose and timing of therapy: differences in study design (folic acid doses, timing of initiation, and duration) complicate direct comparison. FACT used a dose of 4 mg in late pregnancy, whereas our study examined lower therapeutic doses throughout pregnancy, including the periconceptional period, which may explain partial differences in results.

2. Population structure and genetic background: population differences in the frequency of folate metabolism gene polymorphisms (e.g., MTHFR) and baseline prevalence of folate deficiency/hyperhomocysteinemia may influence the observed effect size of supplementation. Our data from the Kazakh population emphasize the importance of accounting for genetic and epidemiological characteristics.

3. Methodological differences and study power: our results should be interpreted in the context of a randomized design with an adequate sample size for primary comparisons; however, the potential influence of confounders and effect sizes approaching statistical significance for some outcomes (e.g., reduced preeclampsia incidence in the main group, $p \approx 0.077$) warrant cautious interpretation and confirmation in future studies.

Clinical Significance and Recommendations for Future Research

Our data confirm that routine high-dose folic acid supplementation solely for preeclampsia prevention lacks strong evidence, although periconceptional folate intake remains standard for neural tube defect prevention. Further studies are needed to:

- Stratify risks considering genetic profiles (polymorphisms of MTHFR, MTRR, etc.);
- Compare the effect of folate monotherapy versus complex multivitamin regimens;
- Investigate potential biomarkers (homocysteine levels, sFlt-1/PlGF) as predictors of therapy response.

The results demonstrate consistency with large randomized studies and partial alignment with some meta-analyses: folic acid remains an important nutrient during pregnancy, but its role in primary preeclampsia prevention is uncertain and likely depends on dose, timing, and population genetics.

In this study, we analyzed the effectiveness of long-term folic acid supplementation in preventing preeclampsia among pregnant women with and without folate cycle disorders. The results showed a trend toward reduced hypertensive disorders and preeclampsia among participants taking folic acid throughout pregnancy compared to the control group. Although some differences did not reach statistical significance, the overall risk of pregnancy complications was lower in women receiving folic acid.

Dose comparisons indicated that 800 mcg was associated with a relatively low incidence of hypertensive complications, while 1200 mcg showed no significant advantage over lower doses. This aligns with previous studies highlighting the effectiveness of moderate folic

acid doses without additional benefits from higher doses. Proteinuria analysis also showed a trend toward reduced frequency in groups with long-term folic acid intake, particularly in late pregnancy. However, these differences were mostly not statistically significant, likely due to sample size and population heterogeneity. Importantly, long-term folate supplementation did not negatively affect laboratory parameters (platelet count, ALT, AST), confirming the safety of this intervention. Observed differences in homocysteine levels support the role of folate metabolism in hypertensive pregnancy complications.

Comparison with the literature shows consistency with systematic reviews and meta-analyses emphasizing folic acid's role in reducing the risk of gestational hypertension and preeclampsia, especially in women with folate metabolism gene polymorphisms (MTHFR, MTRR, MTR). However, variability in results depending on dose and duration of supplementation persists, similar to our findings. Practical significance long-term folic acid supplementation may be considered an accessible, safe, and relatively inexpensive strategy for preeclampsia prevention in clinical practice. This is especially relevant in regions with high prevalence of folate cycle gene polymorphisms and limited access to specialized prevention. Thus, these results can inform clinical guidelines for managing pregnant women, including those at high risk for hypertensive complications, indicating the level of evidence.

The findings demonstrate reduced risk of hypertensive complications and preeclampsia among women taking long-term folic acid, consistent with systematic reviews and meta-analyses. Literature indicates that folic acid improves endothelial function, lowers homocysteine levels, and may reduce the likelihood of gestational hypertension. However, as in our study, many studies show conflicting results regarding doses and duration, underscoring the need for further clinical trials.

Given conflicting data and limited statistical significance of some results, additional multicenter randomized studies are needed to clarify optimal folate doses and duration in pregnant women.

Practical Implications

Long-term folate supplementation is an accessible, safe, and cost-effective method for preventing pregnancy complications. Implementing this strategy is particularly important in populations with high prevalence of folate metabolism gene polymorphisms. Routine long-term folic acid use may reduce preeclampsia incidence and thereby improve perinatal outcomes.

Study Limitations

The study has several limitations. First, not all differences reached statistical significance, possibly due to limited sample size and population heterogeneity. Second, additional factors such as diet, physical activity, or comorbidities cannot be excluded. Third, the study was conducted in a single region, limiting generalizability. These factors should be considered when interpreting results and planning future research. Inclusion of only one population (Central Asian) may limit generalizability. There may also be limitations regarding follow-up duration and monitoring of concomitant nutrient status (particularly vitamins B12 and B6).

5. Conclusion

Long-term folic acid supplementation may be considered a promising method for preeclampsia prevention, particularly in women with folate metabolism disorders. Multicenter randomized trials are needed to determine optimal doses and duration of therapy.

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Author Contributions.

Conceptualization: Tusupkaliev A.B.; Methodology: Gaiday A.N.; Data curation: Urazova U.M.; Formal analysis: Dinets A.V.; Resources: Ayazbaeva L.K.; Writing – original draft: *Kaldygulova L.K.;* Writing – review & editing: A.A., Gaiday A.N.; Project administration: Tusupkaliev A.B..

All authors have read and approved the final version of the manuscript.

References

1. Ives, C. W., Sinkey, R., Rajapreyar, I., Tita, A. T., Oparil, S. (2020). Preeclampsia—pathophysiology and clinical presentations: JACC state-of-the-art review. *Journal of the American College of Cardiology*, *76*(14), 1690-1702. https://www.jacc.org/doi/abs/10.1016/j.jacc.2020.08.014
2. Phipps, E., Prasanna, D., Brima, W., Jim, B. (2016). Preeclampsia: updates in pathogenesis, definitions, and guidelines. *Clinical Journal of the American Society of Nephrology*, *11*(6), 1102-1113. https://doi.org/10.2215/CJN.12081115
3. Espinoza, J., Vidaeff, A., Pettker, C. M., & Simhan, H. (2020). Gestational hypertension and preeclampsia. *Obstetrics and gynecology*, *135*(6), E237-E260.
4. El-Sayed, A. A. (2017). Preeclampsia: A review of the pathogenesis and possible management strategies based on its pathophysiological derangements. *Taiwanese Journal of Obstetrics and Gynecology*, *56*(5), 593-598. https://doi.org/10.1016/j.tjog.2017.08.004
5. Rana, S., Lemoine, E., Granger, J. P., & Karumanchi, S. A. (2019). Preeclampsia: pathophysiology, challenges, and perspectives. *Circulation research*, *124*(7), 1094-1112. https://doi.org/10.1161/CIRCRESAHA.118.313276
6. Hua, X., Zhang, J., Guo, Y., Shen, M., Gaudet, L., Janoudi, G., Wen, S. W. (2016). Effect of folic acid supplementation during pregnancy on gestational hypertension/preeclampsia: A systematic review and meta-analysis. *Hypertension in Pregnancy*, *35*(4), 447-460. https://doi.org/10.1080/10641955.2016.1183673
7. Liu, C., Liu, C., Wang, Q., Zhang, Z. (2018). Supplementation of folic acid in pregnancy and the risk of preeclampsia and gestational hypertension: a meta-analysis. *Archives of gynecology and obstetrics*, *298*(4), 697-704. https://doi.org/10.1007/s00404-018-4823-4
8. Ferrazzi, E., Tiso, G., & Di Martino, D. (2020). Folic acid versus 5-methyl tetrahydrofolate supplementation in pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *253*, 312-319. https://doi.org/10.1016/j.ejogrb.2020.06.012
9. Kaldygulova, L., Ukybassova, T., Aimagambetova, G., Gaiday, A., & Tussupkaliyev, A. (2023). Biological role of folic acid in pregnancy and possible therapeutic application for the prevention of preeclampsia. *Biomedicines*, *11*(2), 272. https://doi.org/10.3390/biomedicines11020272
10. Kaldygulova, L., Yerdessov, S., Ukybassova, T., Kim, Y., Ayaganov, D., & Gaiday, A. (2024). Polymorphism of Folate Metabolism Genes among Ethnic Kazakh Women with Preeclampsia in Kazakhstan: A Descriptive Study. *Biology*, *13*(9), 648. https://www.mdpi.com/2079-7737/13/9/648#
11. Hauspurg, A., Countouris, M. E., & Catov, J. M. (2019). Hypertensive disorders of pregnancy and future maternal health: how can the evidence guide postpartum management?. *Current hypertension reports*, *21*(12), 96. https://doi.org/10.1007/s11906-019-0999-7
12. Sanchez, S. E., Zhang, C., Rene Malinow, M., Ware-Jauregui, S., Larrabure, G., Williams, M. A. (2001). Plasma folate, vitamin B12, and homocyst (e) ine concentrations in preeclamptic and normotensive Peruvian women. *American journal of epidemiology*, *153*(5), 474-480. https://doi.org/10.1093/aje/153.5.474
13. Vollset, S. E., Refsum, H., Irgens, L. M., Emblem, B. M., Tverdal, A., Gjessing, H. K., Ueland, P. M. (2000). Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine

study. *The American journal of clinical nutrition*, *71*(4), 962-968. https://doi.org/10.1093/ajcn/71.4.962

14. Manizheh, S. M., Mandana, S., Hassan, A., Amir, G. H., Mahlisha, K. S., Morteza, G. (2009). Comparison study on the effect of prenatal administration of high dose and low dose folic acid. *Saudi medical journal*, *30*(1), 88-97. https://www.ncbi.nlm.nih.gov/

15. Shahbazian, N., Jafari, R. M., Haghnia, S. (2016). The evaluation of serum homocysteine, folic acid, and vitamin B12 in patients complicated with preeclampsia. *Electronic physician*, *8*(10), 3057. https://doi.org/10.19082/3057

16. Dai, C., Fei, Y., Li, J., Shi, Y., Yang, X. (2021). A novel review of homocysteine and pregnancy complications. *BioMed research international*, *2021*(1), 6652231. https://doi.org/10.1155/2021/6652231

17. Liew, S. C., & Gupta, E. D. (2015). Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. *European journal of medical genetics*, *58*(1), 1-10. https://doi.org/10.1016/j.ejmg.2014.10.004

18. Akilzhanova, A., Takamura, N., Kusano, Y., Karazhanova, L., Yamashita, S., Saito, H., Aoyagi, K. (2008). Association between C677T/MTHFR genotype and homocysteine concentration in a Kazakh population. *Asia Pacific journal of clinical nutrition*, *17*(2), 325-9. https://apjcn.qdu.edu.cn/17_2_15.pdf

19. Hiraoka, M., Kagawa, Y. (2017). Genetic polymorphisms and folate status. *Congenital anomalies*, *57*(5), 142-149. https://doi.org/10.1111/cga.12232

20. Razbekova, M., Issanov, A., Chan, M. Y., Chan, R., Yerezhepov, D., Kozhamkulov, U., Chan, C. K. (2021). Genetic factors associated with obesity risks in a Kazakhstani population. *BMJ Nutrition, Prevention & Health*, *4*(1), 90. https://doi.org/10.1136/bmjnph-2020-000139

21. Kindler, H. L. (2008). Systemic treatments for mesothelioma: standard and novel. *Current treatment options in oncology*, *9*(2), 171-179. https://doi.org/10.1007/s11864-008-0071-3

22. Wen, S. W., White, R. R., Rybak, N., Gaudet, L. M., Robson, S., Hague, W., Walker, M. C. (2018). Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *bmj*, *362*. https://doi.org/10.1136/bmj.k3478

23. De Ocampo, M. P., Araneta, M. R. G., Macera, C. A., Alcaraz, J. E., Moore, T. R., Chambers, C. D. (2018). Folic acid supplement use and the risk of gestational hypertension and preeclampsia. *Women and Birth*, *31*(2), e77-e83. https://doi.org/10.1016/j.wombi.2017.08.128

24. Catov, J. M., Bodnar, L. M., Olsen, J., Olsen, S., Nohr, E. A. (2011). Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National Birth Cohort. *The American journal of clinical nutrition*, *94*(3), 906-912. https://doi.org/10.3945/ajcn.111.012393

25. Hassan, A. G. M., & Shehata, N. A. (2015). Comparison between the roles of low-dose aspirin and folic acid in preventing preeclampsia among high-risk women screened by uterine artery Doppler at 22–24 weeks of gestation: a randomized–controlled trial. *Journal of Evidence-Based Women's Health Journal Society*, *5*(3), 111-117. https://doi.org/10.1097/01.EBX.0000466601.40481.95

26. Zitouni, H., Chayeb, V., Raguema, N., Gannoun, M. B. A., Bendhaher, S., Zouari, I., Almawi, W. Y. (2025). Association of MTHFR C677T and A1298C variants with preeclampsia risk and angiogenic imbalance in Tunisian women. *Pregnancy Hypertension*, *39*, 101187. https://doi.org/10.1016/j.preghy.2025.101187

27. Bulloch, R. E., Lovell, A. L., Jordan, V. M., McCowan, L. M., Thompson, J. M., & Wall, C. R. (2018). Maternal folic acid supplementation for the prevention of preeclampsia: a systematic review and meta-analysis. *Paediatric and perinatal epidemiology*, *32*(4), 346-357. https://doi.org/10.1111/ppe.12476

28. Liu, C., Liu, C., Wang, Q., Zhang, Z. (2018). Supplementation of folic acid in pregnancy and the risk of preeclampsia and gestational hypertension: a meta-analysis. *Archives of gynecology and obstetrics*, *298*(4), 697-704. https://doi.org/10.1007/s00404-018-4823-4

29. Hu, Y., Wang, A., & Yi, K. (2023). MTHFR A1298C Polymorphism and Risk of Preeclampsia: A Meta-

Analysis. *Clinical and Experimental Obstetrics & Gynecology*, *50*(12), 266. https://doi.org/10.31083/j.ceog5012266

30. Gu, C., Wu, W., Lai, K., Li, H., Wu, L., Lu, W., Luo, M. (2023). Maternal pre-pregnancy BMI, MTHFR polymorphisms, and the risk of adverse pregnancy outcomes in pregnant women from South China: a retrospective cohort study. *BMC Pregnancy and Childbirth*, *23*(1), 295. https://doi.org/10.1186/s12884-023-05605-6

31. Cui, H., Zhang, N., An, J., Zeng, X., Zhao, Y., Sun, X., Wang, H. (2024). Maternal folic acid supplementation to prevent preeclampsia: a systematic review and meta-analysis. *Complementary Therapies in Medicine*, *82*, 103052. https://doi.org/10.1016/j.ctim.2024.103052

32. Wen, S. W., White, R. R., Rybak, N., Gaudet, L. M., Robson, S., Hague, W., Walker, M. C. (2018). Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *bmj*, *362*. https://doi.org/10.1136/bmj.k3478

Appendix

Demographic and anamnestic characteristics of the study and control groups

Characteristic	**Control group (n=320)**	**Main group (n=894)**	**p**
Age (years)	29,4 (±4,9) 29 (26; 31)	30,2 (±5,7) 30 (26; 34)	<0,067
Height	161,4 (±5,7) 161 (158; 165)	161,6 (±5,4) 161,5 (158; 165)	0,732
Weight (kg)	58,8 (±8,7) 58 (52; 64)	58,7 (±8,9) 58 (52; 64)	0,83
BMI (kg/m²)	22,6 (±3,1) 22,2 (20,4; 24,1)	22,5 (±3,2) 22 (20,2; 24,2)	0,529
Social status			0,994
Employed	150 (49%)	438 (49%)	
Unemployed	156 (51%)	456 (51%)	
Family history	20 (6,5%)	66 (7,4%)	0,62
Hypertension	12 (3,9%)	34 (3,8%)	0,926
Diabetes mellitus	8 (2,6%)	29 (3,2%)	0,582
Thyroid disease	0 (0%)	3 (0,3%)	0,575
Past medical history			
Appendicitis	44 (14,4%)	97 (10,9%)	0,098
Hepatitis A	12 (3,9%)	22 (2,5%)	0,184
Chickenpox	9 (2,9%)	24 (2,7%)	0,813
Urinary tract infections	2 (0,7%)	2 (0,2%)	0,27
Calculous cholecystitis	1 (0,3%)	1 (0,1%)	0,445
Surgical interventions in history	61 (19,9%)	146 (16,3%)	0,15
Chronic gynecological diseases	23 (7,5%)	57 (6,4%)	0,49

Features of the gynecological and obstetric history of the study participants

Characteristic	Control group	Main group	p
Age at menarche (years)	13 (13; 14)	13 (13; 14)	0,813
Age at onset of sexual activity (years)	21,2 (±2,6) 21 (20; 22)	21,6 (±2,9) 21 (20; 22)	0,059
Irregular menstruation	9 (2,9%)	28 (3,1%)	0,868
Gynecological diseases	69 (22,5%)	159 (17,8%)	0,067
Cervical erosion	64 (20,9%)	99 (11,1%)	<0,001
Ovarian cyst	1 (0,3%)	12 (1,3%)	0,203
Endometrial polyp	1 (0,3%)	11 (1,2%)	0,315
PCOS (Polycystic Ovary Syndrome)	1 (0,3%)	10 (1,1%)	0,307
Uterine fibroids	0 (0%)	11 (1,2%)	0,076
STIs (Sexually Transmitted Infections)	0 (0%)	5 (0,6%)	0,337
History of pregnancies	209 (68,3%)	601 (67,2%)	0,729
History of deliveries	196 (64,1%)	564 (63,1%)	0,762
History of abortions	62 (20,3%)	148 (16,6%)	0,141
History of miscarriages/stillbirth	44 (14,4%)	147 (16,4%)	0,394
Gestational age (weeks)	12 (11; 12)	12 (11; 13)	0,409

Dynamics of diastolic blood pressure in the study groups

Gestational age	Control group	Main group			p¹
		400 mcg	800 mcg	1200 mcg	
10-14 weeks	65,5 (±6,6) 60 (60; 70)	65,6 (±7,3) 70 (60; 70)	66,2 (±5,8) 70 (60; 70)	66,1 (±7,2) 70 (60; 70)	0,48
14-20 weeks	66,1 (±6,5) 70 (60; 70)	66 (±6,8) 65 (60; 70)	67,1 (±6,7) 70 (60; 70)	65,9 (±6,3) 70 (60; 70)	0,131
20-24 weeks	66,9 (±6,6) 70 (60; 70)	66,3 (±6,7) 70 (60; 70)	67 (±7) 70 (60; 70)	67 (±6,9) 70 (60; 70)	0,484
24-30 weeks	67,5 (±6,5) 70 (60; 70)	67,3 (±6,5) 70 (60; 70)	68 (±6,7) 70 (60; 70)	67,5 (±6,7) 70 (60; 70)	0,584
30-34 weeks	68,7 (±8,4) 70 (60; 70)	67,5 (±7,6) 70 (60; 70)	68,8 (±7,6) 70 (60; 70)	67,6 (±6,5) 70 (60; 70)	0,059
34-38 weeks	71,8 (±9,3) 70 (65; 80)	71,3 (±9,2) 70 (60; 80)	71,6 (±8,1) 70 (70; 80)	70,3 (±8,4) 70 (60; 80)	0,157
40-42 weeks	73,8 (±8,4) 70 (70; 80)	74,5 (±8,4) 70 (70; 80)	74,7 (±8,8) 70 (70; 80)	73,9 (±7) 70 (70; 80)	0,624
p²	**<0,001**	**<0,001**	**<0,001**	**<0,001**	–

Note: p¹ - ; p² -

Results of the study of individual laboratory blood parameters in pregnant women of the study groups

Parameters	Control group	Main group			p
		400 mcg	800 mcg	1200 mcg	
Platelets (×10⁹/L)	227,5 (200; 264)	230 (208; 272)	230 (202; 263)	230 (203; 269)	0,363
ALT (U/L)	–	12 (12; 18)	12 (8; 18)	13 (8,6; 18)	0,841
AST (U/L)	–	23 (20; 29)	23 (20; 29,1)	24 (19; 29,1)	0,931
Homocysteine (μmol/L)	5,7 (4,6; 7)	6 (5; 7,6)	5,9 (5; 7,6)	6 (5; 7,3)	**0,02**

Фолий циклінің бұзылуы бар және онсыз жүкті әйелдерде преэклампсияның алдын алу үшін ұзақ мерзімді фолий қышқылын енгізудің тиімділігі

Калдыгулова Л. [1], Уразова У. [2], Тусупкалиев А. [3], Гайдай А. [4], Аязбаева Л. [5], Динец А. [6]

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Түйіндеме

Кіріспе. Преэклампсия бүкіл әлемде ана мен ұрық аурушаңдығының жетекші себептерінің бірі болып қала береді. Жинақталған деректер фолат алмасуының бұзылыстары мен гомоцистеин деңгейінің жоғарылауы жүктілік кезіндегі гипертензиялық асқынулардың дамуына ықпал етуі мүмкін екенін көрсетеді. Бұл зерттеуде фолаттық цикл гендерінің полиморфизмдері бар және жоқ жүкті әйелдерде преэклампсияның алдын алу үшін фолий қышқылын ұзақ уақыт қолданудың тиімділігі бағаланды.

Әдістері. Бір орталықты рандомизацияланған бақыланатын зерттеуге бақылау тобына 320 әйел (фолий қышқылын жүктіліктің 12 аптасына дейін қабылдаған) және негізгі топқа 894 әйел (фолий қышқылын жүктілік бойы қабылдаған) енгізілді. Негізгі топ дозалар бойынша стратификацияланды: 400 мкг, 800 мкг және 1200 мкг. Клиникалық, биохимиялық және генетикалық зерттеулер жүргізілді, оның ішінде гомоцистеин деңгейін анықтау және MTHFR, MTR және MTRR полиморфизмдерінің генотиптелуі қамтылды. Жүктілік нәтижелері мен гипертензиялық асқынулардың жиілігі топтар арасында салыстырылды.

Нәтижелері. Фолий қышқылын ұзақ уақыт қабылдау бақылау тобымен салыстырғанда жүктілік кезіндегі гипертензиялық бұзылыстардың жалпы жиілігінің төмендеуімен байланысты болды (RR 1,43; p=0,038).

Негізгі топта преэклампсияның жиілігі 1,67 есе төмен болды, бұл қолайлы үрдісті көрсетеді. Фолий қышқылының әртүрлі дозаларын қабылдаған топтар арасында артериялық қысым динамикасы мен перинаталдық нәтижелер бойынша айтарлықтай айырмашылықтар анықталған жоқ. Кейін преэклампсия дамыған барлық әйелдерде гомоцистеин деңгейі фолий қышқылының дозасына тәуелсіз түрде айтарлықтай жоғары болды. Генотиптердің таралуы MTHFR және MTR полиморфизмдерінің популяцияға тән жиіліктерін көрсетті, алайда «доза–әсер» айқын байланысы анықталмады.

Қорытынды. Фолий қышқылын ұзақ уақыт қолдану жүктілік кезіндегі гипертензиялық асқынулардың, соның ішінде преэклампсия жиілігінің төмендеу үрдісін қоса алғанда, даму қаупін азайтады және барлық зерттелген дозаларда қауіпсіз болып табылады. Оның әлеуетті пайдасы фолат алмасуына жауапты генетикалық варианттардың таралуы жоғары популяциялар үшін ерекше маңызды. Оңтайлы доза мен қабылдау ұзақтығын анықтау үшін көп орталықты рандомизацияланған зерттеулер қажет.

Түйін сөздер: преэклампсия, фолий циклі, фолий қышқылы.

Эффективность длительного приема фолиевой кислоты для профилактики преэклампсии у беременных с и без нарушения фолатного цикла

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Резюме

Введение. Преэклампсия остаётся одной из ведущих причин материнской и перинатальной заболеваемости во всём мире. Накопленные данные свидетельствуют о том, что нарушения фолатного обмена и повышенный уровень гомоцистеина могут способствовать развитию гипертензивных осложнений беременности. В данном исследовании оценивалась эффективность длительного приёма фолиевой кислоты для профилактики преэклампсии у беременных женщин с наличием и отсутствием полиморфизмов генов фолатного цикла.

Методы. В одноцентровое рандомизированное контролируемое исследование были включены 320 женщин в контрольной группе (приём фолиевой кислоты до 12 недель беременности) и 894 женщины в основной группе (приём фолиевой кислоты на протяжении всей беременности). Основная группа была стратифицирована по дозам: 400 мкг, 800 мкг и 1200 мкг. Проводились клинические, биохимические и генетические исследования, включая определение уровня гомоцистеина и генотипирование полиморфизмов

MTHFR, MTR и MTRR. Показатели исходов беременности и частота гипертензивных осложнений сравнивались между группами.

Результаты. Длительный приём фолиевой кислоты ассоциировался с более низкой общей частотой гипертензивных осложнений беременности по сравнению с контрольной группой (RR 1,43; p=0,038). Частота преэклампсии была в 1,67 раза ниже в основной группе, что отражает благоприятную тенденцию. Значимых различий в динамике артериального давления и перинатальных исходах между группами с различными дозами фолиевой кислоты выявлено не было. Уровень гомоцистеина был достоверно выше у всех женщин, у которых в дальнейшем развилась преэклампсия, независимо от дозы фолиевой кислоты. Распределение генотипов продемонстрировало популяционно-специфические частоты полиморфизмов MTHFR и MTR, однако чёткой зависимости «доза–эффект» выявлено не было.

Заключение. Длительный приём фолиевой кислоты снижает риск развития гипертензивных осложнений беременности, включая тенденцию к снижению частоты преэклампсии, и является безопасным во всех изученных дозах. Потенциальная польза особенно значима для популяций с высокой распространённостью генетических вариантов фолатного обмена. Для определения оптимальной дозы и продолжительности приёма необходимы дальнейшие многоцентровые рандомизированные исследования.

Ключевые слова: преэклампсия, фолатный цикл, фолиевая кислота.

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Генетические особенности у детей с подозрением на синдром Альпорта: Результаты полноэкзомного секвенирования

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Резюме

Введение. Синдром Альпорта является редким мультисистемным заболеванием, вызванным мутациями в генах COL4A3, COL4A4, COL4A5. Актуальность изучения синдрома Альпорта обусловлена его высокой частотой среди наследственных заболеваний почек, чрезвычайной генетической и фенотипической гетерогенностью, сложностью интерпретации клинических и генетических методов диагностики, наличием значимых популяционных различий в частоте и спектре специфичных мутаций.

Целью настоящего исследования является анализ данных полноэкзомного секвенирования у пациентов с клинико-лабораторным подозрением на синдром Альпорта для характеристики спектра выявляемых генетических вариантов, вызываемых данное заболевание

Методы. Выделение геномной ДНК из образцов крови от пациентов с предполагаемым синдромом Альпорта. Проведено полноэкзомное секвенирование образцов, а также биоинформатическая и статистическая обработка данных секвенирования.

Результаты. Выявлена ранее неописанная мутация в интронной области гена COL4A5 c.1588-2A>G, вероятно ассоциированная с синдромом Альпорта.

Выводы. Исследование подчеркивает значимость генетических исследований синдрома Альпорта, и важность изучение интронных областей генов COL4A3, COL4A4, COL4A5.

Ключевые слова: синдром Альпорта, Х-сцепленный синдром Альпорта, полноэкзомное секвенирование, корреляция генотипа и фенотипа, нарушения сплайсинга.

1. Введение

Синдром Альпорта (наследственный нефрит, МКБ-10 - Q87.8) является редким мультисистемным заболеванием, вызванным мутациями в генах COL4A3, COL4A4, COL4A5, кодирующих α3-, α4-, α5-цепей коллагена IV типа. Основными клиническими симптомами синдрома Альпорта (СА) являются: прогрессирующая нефропатия, приводящая к развитию тяжелой почечной недостаточности (ПН), а также, сопутствующие глазные аномалии и сенсоневральная глухота [1]. Впервые синдром был описан в 1927 году английским врачом Alport, A.C [2] в статье о связи болезни почек и наследственной глухоты в одной британской семье.

Согласно результатам полноэкзомного секвенирования (WES) при хронической болезни почек, мутации в генах COL4A3, COL4A4, COL4A5 обнаружены у 30% пациентов, что делает синдром Альпорта вторым по распространенности наследственным заболеванием почек после поликистозной болезни почек - 31% случаев [3]. Кроме того, у пациентов с фокально-сегментарным гломерулосклерозом (ФСГ) было выявлено значительное число мутаций в генах COL4A3, COL4A4, COL4A5, что подтверждает высокий генетический вклад этих мутаций в развитие заболеваний почек [4,5,6].

Синдром Альпорта характеризуется фенотипической и генетической гетерогенностью, что затрудняет его раннюю диагностику и своевременное назначение нефропротективной терапии, что обусловливает неблагоприятный прогноз заболевания. Синдром Альпорта – это генетически и фенотипически гетерогенное заболевание гломерулярных, кохлеарных и глазных базальных мембран, возникающее в результате мутаций в генах коллагена IV - COL4A3, COL4A4 и COL4A5 [6,7,8]. Как показано в таблице 1, данный синдром может передаваться как сцепленное с Х-хромосомой (OMIM301050), аутосомно-рецессивное (OMIM 203780), аутосомно-доминантное (OMIM 104200) или дигенное (обычно с патогенным вариантом в каждом из COL4A3 и COL4A4 заболевание [9,10]. При дигенном наследовании передача мутаций может происходить в двух локусах, что приводит к неменделевским моделям наследования и более высокой фенотипической гетерогенности синдром Альпорта в этих семьях [10,11].

Таблица 1 - Классификация синдрома Альпорта по типам наследования и ассоциированным генам [12,13]

Наследование	Вовлеченный ген	Генетический статус
Х-сцепленное	COL4A5	Гемизигота (мужчины) Гетерозигота (женщины)
Аутосомное	COL4A3 или COL4A4	Рецессивное (гомозигота или компаунд гетерозигота)

Дигенное	COL4A3, COL4A4, и COL4A5	Варианты COL4A3 и COL4A4 в trans положении (рецессивное) Варианты COL4A3 и COL4A4 в cis положении (доминантное) Варианты в COL4A5 и в COL4A3 или COL4A4 (неменделевское)
Не установлено	-	клинические, генеалогические и гистологические данные с большой долей вероятности указывают на синдром Альпорта, но генетические данные не подтверждают его.

Гетерогенность локуса, широкий спектр мутаций - миссенс, нонсенс, сплайсинговые, сдвиг рамки считывания, крупные делеции и дупликации в ассоциированных генах приводят к гетерогенности клинического фенотипа (фенотипическая гетерогенность), что создает дополнительные трудности при ранней диагностике и затрудняет проведение своевременной эффективной терапии. [14,15,16].

Помимо генетической и фенотипической гетерогенности, одной из основных трудностей в клиническом изучении заболевания является его дифференциальная тяжесть течения в зависимости от пола. Синдром Альпорта может быть вызван гомозиготными или сложными гетерозиготными мутациями COL4A3 или COL4A4, или гемизиготностью по одному дефектному аллелю COL4A5 у мужчин [9,15] при аутосомно-рецессивном и Х-сцепленном типе наследования. В отличие от известных менделевских наследуемых заболеваний, даже гетерозиготность патогенной мутации любого из генов COL4A3, COL4A4 или COL4A5 может иметь клинические проявления в виде микроскопической гематурии, истончения базальных мембран клубочков и риск развития ПН. Поэтому выявленные гетерозиготные носители также, как и все пациенты с синдромом Альпорта, требуют постоянного медицинского наблюдения [17].

Генетический анализ дает возможность ранней диагностики и своевременной нефропротективной терапии, позволяет прогнозировать течение болезни и развитие ПН, провести каскадное обследование членов семьи и семейное медико-генетическое консультирование, а также определить возможность родственного донорства при необходимости трансплантации почек. Согласно рекомендациям международных экспертов, которыми были пересмотрены критерии, алгоритм диагностики и тактика ведения пациентов, анализом первой линии для пациентов с изолированной гломерулярной гематурией и соответствующей клинической картиной, семейным анамнезом является генетическое тестирование [13,18,19].

Как представлено в базе Alport Variant Database: https://alportdatabase.org [20], в настоящее время описано около 3000 мутаций в генах COL4A3, COL4A4 и COL4A5, из них 60 % приходится на долю гена COL4A5, включая около 1200 редких мутаций, абсолютное большинство из которых являются патогенными [20]. У мужчин с Х-сцепленным СА установлена четкая зависимость фенотипических проявлений болезни от типа и локализации мутации в гене COL4A5. Генетические варианты, обуславливающие преждевременную терминацию синтеза белка (большие перестройки, нонсенс мутации и сдвиг рамки считывания), ассоциируются с развитием ПН уже на второй декаде жизни (ювенильная форма СА); при миссенс-вариантах, как правило, отмечается благоприятный прогноз (взрослая форма СА), пациенты с мутациями, затрагивающими сайты сплайсинга, имеют промежуточный фенотип [18,21]. У женщин зависимость клинических проявлений СА от генотипа менее очевидна, что обусловлено случайной лайонизацией одной из Х-хромосом и, как следствие, мозаичным синтезом α5-цепи коллагена подоцитами [22].

Для гена COL4A5 описано большее число патогенных мутаций, чем для COL4A3 и COL4A4 , и они в 60% являются миссенс-мутациями, в 10% - нонсенс-мутациями, в 10% - каноническими сайтами

сплайсинга и в 20% - сдвигами рамки считывания [23]. Интересно, что из всех патогенных мутаций в гене COL4A5 только 12 были отнесены к частым с преобладанием в отдельных географических регионах мира. Например, вариант COL4A5 p.Gly624Asp, обусловленный глициновой заменой в коллагеновом домене гена, является самым распространенным в Центральной и Западной Европе (39 % семей с миссенс-вариантами) [24]. Показано, что COL4A5 p.Gly624Asp обуславливает относительно благоприятное течение нефропатии с более поздним развитием ПН по сравнению с другими миссенс-вариантами [15,25].

В целом, Х-сцепленный СА характеризуется более тяжелой клинической картиной у мужчин с прогрессирующим течением нефропатии, приводящей к развитию ПН на второй - третьей декаде жизни, и наличием нейро-сенсорной тугоухости у 50% пациентов. Женщины с этой формой СА имеют более мягкую клиническую картину, у 20 % - изолированная гематурия, у 75 % - гематурия с протеинурией, почечная недостаточность и нейросенсорная тугоухость развиваются после 55 лет у 42% пациенток [19,23]. Эти результаты доказали, что термин «носительство» не должен использоваться у женщин с гемизиготными мутациями в гене COL4A5 потому, что пациентки СА с гемизиготными вариантами в COL4A5 требуют строгого диспансерного наблюдения, назначения нефропротективной терапии и не должны рассматриваться в качестве потенциальных родственных доноров.

Клинические проявления и прогноз пациентов с аутосомно-рецессивным СА не зависят от пола и соответствуют таковым у мужчин с Х-сцепленным вариантом болезни [19]. Аутосомно-доминантная форма СА характеризуется наиболее благоприятным течением: как правило, экстраренальные проявления отсутствуют, почечная недостаточность развивается у 20–30 % пациентов обычно после 60 лет [26]. Следует помнить, что наличие гетерозиготных мутаций COL4A3 или COL4A4 у пациентов с Х-сцепленным СА ухудшает прогноз заболевания [21,32].

Актуальность. Проведенные генетические исследования СА немногочисленны и подчас противоречивы, что связано не только с чрезвычайной генетической и клинической гетерогенностью СА, но и определенными методологическими погрешностями: отсутствием региональных регистров, небольшим объёмом выборок, использованием различных диагностических критериев, сложностью и доступностью диагностики. В казахской популяции частота СА, структура мутаций COL4A3, COL4A4 и COL4A5, вклад различных типов наследования не изучены, что диктует необходимость проведения широкомасштабных популяционных исследований для оказания своевременной и эффективной медицинской помощи пациентам с СА в РК.

Целью настоящего исследования является анализ данных полноэкзомного секвенирования у пациентов с клинико-лабораторным подозрением на синдром Альпорта для характеристики спектра выявляемых генетических вариантов, вызываемых данное заболевание.

2. Материалы и методы

2.1 Рекрутинг пациентов

Рекрутинг пациентов проводился на базе ТОО «Центр молекулярных исследований» с участием врачей: детский эндокринолог, нефролог и медицинский генетик. Проведен рекрутинг 4 пациентов с предполагаемым диагнозом синдром Альпорта. Рекрутинг включал интервью пациентов, анализ имеющейся медицинской документации, лабораторных и инструментальных исследований. Проведено медико-генетическое консультирование семей пациентов с СА.

Все участники были полностью информированы об их включении в исследование, и было получено информированное согласие от взрослых участников и законных представителей несовершеннолетних пациентов. Данная рукопись не содержит идентифицирующей информации. Данное исследование было одобрено этическим комитетом Национального центра биотехнологии (№ 5/14.05.2024, Астана, Казахстан) и проведено в соответствии с принципами, изложенными в Хельсинкской декларации.

2.2 Выделение ДНК

Забор периферической крови проводился в одноразовые стерильные вакуумные пробирки AVATUBE объемом 9 мл с K2ЭДТА и, согласно договору, биоматериал был отправлен для проведения генетического исследования в ТОО «Национальный центр биотехнологий». Геномную ДНК из цельной крови выделяли, используя коммерческий набор для выделения геномной ДНК из цельной крови GeneJET, фирмы Thermo Fisher Scientific, согласно инструкции производителя.

2.3 Измерение концентрации ДНК

Точную концентрацию ДНК измеряли на флуориметре Qubit 2, используя коммерческий набор Qubit dsDNA BR Assay kit фирмы Invitrogen, согласно инструкции производителя.

Степень деградации ДНК оценивали с помощью флуоресцентной детекции на приборе 4150 TapeStation System (Agilent).

2.4 Полноэкзомное секвенирование

Для подготовки стандартных библиотек для секвенирования экзомов использовался набор SureSelect V6-Post (Agilent Technologies, Санта-Клара, Калифорния, США) для построения парно-концевой (paired-end) библиотеки секвенирования на платформе Illumina, при использовании 1 мкг геномной ДНК в качестве исходного материала. Полное экзомное секвенирование (Whole-Exome Sequencing, WES) проводилось на платформе NovaSeq 6000 (Illumina Inc., Сан-Диего, Калифорния, США) в соответствии с инструкциями производителя. Услуга по экзомному секвенированию былы проведена в компании «Macrogen».

2.5 Биоинформатический и статистический анализ

Биоинформатическая обработка данных секвенирования проводилась по стандартному аналитическому конвейеру с использованием современных инструментов анализа данных высокопроизводительного секвенирования.

Файлы базового вызова (base calling files), представленные в двоичном формате, были преобразованы в формат FASTQ с использованием пакета bcl2fastq v2.20.0 (Illumina). Парно-концевые (paired-end) последовательности, полученные на платформе NovaSeq, были выровнены с человеческим референтным геномом с помощью программы выравнивания BWA (версия 0.7.17; https://sourceforge.net/projects/bio-bwa/). В качестве референтного генома использовалась сборка hg38 из базы UCSC (оригинальная сборка GRCh38 от NCBI, декабрь 2013 г.). Дублированные прочтения были удалены с использованием Picard-tools (версия 2.18.2-SNAPSHOT).

Генетические варианты идентифицировались с помощью Genome Analysis Toolkit (GATK v4.0.5.1) (https://gatk.broadinstitute.org/hc/en-us) — программного пакета, предназначенного для анализа данных высокопроизводительного секвенирования. Отфильтрованные варианты были аннотированы с использованием программы SnpEff (версия 4.3t, 24 ноября 2017 г.; https://sourceforge.net/projects/snpeff/files/snpEff_v4_3s_core.zip/download) и дополнительно отфильтрованы с применением баз данных dbSNP и проекта 1000 Genomes. Итоговые данные были сохранены в формате VCF. Для дополнительной аннотации и функциональной интерпретации вариантов использовались собственный (in-house) программный инструмент и SnpEff с привлечением дополнительных баз данных: ESP6500, ClinVar, dbNSFP и рекомендаций ACMG.

3. Результаты

3.1 Клинические исследования пациентов

Данное исследование проведено на группе из четырех пациентов из Казахстана с подозрением на синдром Альпорта. Клинические характеристики представлены в таблице 2.

Таблица 2 - Клинические характеристики пациентов с синдромом Альпорта

Симптомы	**Пациент 1**	**Пациент 2 - родной брат пациента 1**	**Пациент 3**	**Пациент 4**
Пол	женский	мужской	мужской	женский
Возраст исследования	8 *лет*	13 *лет*	7 *лет*	13 *лет*
Возраст начала заболевания	6 *лет*	1,5 *лет*	7 *лет*	7 *лет*
Наследственная отягощенность	Родные сибсы, имеют родного дядю по материнской линии с аналогичным заболеванием		Родной дядя со стороны матери болен аналогичным заболеванием	Мама – ХПН1, получает диализ
Первичные симптомы	микрогематурия (эритроциты 10-15 в зр), протеинурия (белок-0,33г/*л*)	микрогематурия (25-30 в п/з) во время обструктивного бронхита. С 3 *лет* - макрогематурия Протеинурия – белок – 2,3г/*л*	макрогематурия (эритр в большом кол-ве), протеинурия до 0,33–0,44 г/*л*,	макрогематурия – (эр. 30-40 в п.зр) протеинурия (белок 0,3 г/*л*), Отеки на лице и ногах
Направительный диагноз:	Наследственный нефрит. Хроническая болезнь почек G1A2	Наследственная нефропатия, не классифицированная в других рубриках,	Нефритический синдром. Наследственный нефрит	Хронический нефритический синдром, ХБП1
Заключительный диагноз	Наследственная нефропатия. Синдром Альпорта. Х-сцепленный вариант	Наследственная нефропатия. Синдром Альпорта. Х-сцепленный вариант	Нефритический синдром.	Хронический нефритический синдром. Мембрано пролиферативный гломерулонефрит с умеренным фиброзом и лимфоцитарной инфильтрацией
ДНК анализ	Секвенирование экзома: гемизиготная мутация в 23 интроне гена COL4A5 с Х-	Секвенирование экзома: гемизиготная мутация в 23 интроне гена COL4A5 с Х-	Секвенирование экзома	Секвенирование экзома

	сцепленным синдромом Альпорта, тип1	сцепленным синдромом Альпорта, тип1		
Нарушения функции почек				
Гематурия	+	+	+	+
Протеинурия	+	+	+	+
Нейросенсорная тугоухость	Не отмечено	Не отмечено	Не отмечено	Не отмечено
Нарушения органов зрения	Не отмечено	Ангиопатия сетчатки.	Не отмечено	Не отмечено
УЗИ почек	уплотнение стенок ЧЛС почек с обеих сторон	Не выявлено	Двусторонний нефроптоз, уплотнение стенок ЧЛС почек и каликоэктазия с обеих сторон.	Не выявлено
Биопсия почек	Фокальный глобальный и сегментарный гломерулосклероз. Интерстициальный фиброз и атрофия канальцев 1 ст. Электронная микроскопия: Картина соответствует врожденной/наследственной патологии коллагена IV типа	Фокальный глобальный и сегментарный гломерулосклероз. Интерстициальный фиброз и атрофия канальцев 1 ст. Электронная микроскопия: Картина соответствует врожденной/наследственной патологии коллагена IV типа	Не проводилась	морфологические признаки мембранопролиферативного гломерулонефрита с умеренным фиброзом и лимфоцитарной инфиль-трацией в межуточной ткани (фокальный склероз – 85,2%, гиалиноз и склероз – 14,8%).
Общий анализ крови	гемоглобин-131 г/л; эритроциты-4,93х10*12/л; тромбоциты-365х10*9/л; лейкоциты-6,71 х10*9/л; СОЭ –4 мм/час.	гемоглобин-123 г/л; эритроциты-4,36х10*12/л; тромбоциты-341х10*9/л; лейкоциты-7,71 х10*9/л; СОЭ –10мм/час.	Лейкоциты – 6,08 х10*9/л; эритроциты - 4.8х10*12/л; гемоглобин 132 г/л; тромбоциты – 277х10*9/л; СОЭ – 25мм/час;	Нет данных
Анализ мочи	Цвет с/ж; прозрачная; удельный вес-1003; pH – 6.5; белок- 0; лейкоциты – 2 в мкл; эритроциты - 80 в мкл;	белок - 2,0, эритроциты- 40 в мкл., белок- 2,31 г/л, эритроциты- 15-20 в п/з, лейкоциты- 8-12 в п/з. Цвет-мясных помоев. Удельный вес-1002; pH – 7,0;	Цвет – с/ж, прозрачная; отн. плотность – 1030; белок - 0,264г/л; Лейкоциты - в большом количестве; Эритроциты	Нет данных

			неизм. - 10-15; Реакция (Ph) - кислая	
Биохимический анализ крови	Общий белок - 61 г/л; АЛТ – 10.6 U/l; АСТ – 21 U/l; мочевина –3.5 ммоль/л; креатинин – 44.7 ммоль/л; Глюкоза – 4,5 ммоль/л; билирубин - 4,8мкмоль/л.	Общий белок - 49 г/л; АЛТ – 7,6 U/l; АСТ – 19,6 U/l; мочевина –8,2 ммоль/л; креатинин – 69 ммоль/л; Глюкоза – 4,6 ммоль/л; билирубин -3мкмоль/л Креатинин — 46,8 мкмоль/л,	АСТ- 44.0; общий белок - 65.0; общий билирубин - 11,2; альбумин - 39; общий холестерин - 3,3; глюкоза - 3.9; креатининн - 34.3; мочевина - 3.53 (АЛаТ) - 16.0	Общий белок 60-48г/л, альбумин 40-28г/л, холестерин 2,4-9,79ммоль/л. АНА, АНЦА в норме, АСЛО 56 МЕ/л, С3 0,1(0,9-1,7), С4 0,23 (05-0,9).
Белок в суточной моче	Белок - 0,2475 г/с; 1,32 г/с.	Белок -0,528г/л. 0,436 гр/л; 1,815г/с	Белок - 2,31 г/с	Белок -0,231г/с
СКФ по Шварцу	СКФ -129мл/мин/1,73м2	СКФ -82 мл/мин/1,73 м2; 47 мл/мин/1,73 м2	Не определяли	СКФ 96мл/мин/1,73м2
ПН	Не отмечено	ХБП1 стадии с 12 лет	Не отмечено	Не отмечено

3.2 Анализ результатов полногеномного секвенирования

Основная сводная статистика необработанных данных о последовательностях, полученных из исследуемых образцов, представлена в таблице 3.

Таблица 3 - Статистика fastq данных

Название образца	Общий выход (п.н.)	Всего прочтений	GC (%)	AT (%)	Q20 (%)	Q30 (%)
Пациент 1	8,086,480,954	53,552,854	50.79	49.21	98.89	95.87
Пациент 2	8,012,671,852	53,064,052	50.45	49.55	98.98	96.03
Пациент 3	6,162,256,244	40,809,644	49.06	50.94	98.66	95.0
Пациент 4	8,033,747,224	53,203,624	51.23	48.77	98.62	95.25

Общий выход (bp) — общее количество секвенированных оснований; GC (%) — содержание GC; AT (%) — содержание AT; Q20 (%) — доля оснований с оценкой качества Phred выше 20; Q30 (%) — доля оснований с оценкой качества Phred выше 30.

Подробные показатели выравнивания для каждого образца, глубина, процент покрытия и показатели вариантов для всех образцов приведены в Таблице 4.

Таблица 4 - Количество прочтений, покрытие и статистика вариантов по образцам

Название образца	Пациент 1	Пациент 2	Пациент 3	Пациент 4
Всего прочтений	53,552,760	53,063,934	40,809,512	53,203,364
Средняя длина прочтения (п.н.)	146.55	149.28	144.35	140.18

Количество целевых генотипов (≥1×)	36,378,510	36,432,945	36,442,503	36,374,396
% Покрытие целевых регионов (≥10×)	99.7	99.8	99.9	99.6
% Покрытие целевых регионов (≥30×)	99.4	99.2	98.1	99.0
% Покрытие целевых регионов (≥50×)	97.2	95.4	84.2	93.8
Количество SNP	76,465	76,926	75,985	73,377
Миссенс-варианты	11,838	11,758	11,965	11,551
Приобретенный стоп-локус	106	117	112	99
Потерянный стоп-локус	26	24	23	18
Количество индел мутаций	14,789	15,127	14,304	13,522
Варианты со сдвигом рамки считывания	261	256	282	284
% найдено в dbSNP151	99.4	99.3	99.3	99.3

В результате фильтрации данных в генах COL4A5, COL4A4, COL4A6, COL4A3 были выявлены мутации, представленные в таблицах 5-8.

Таблица 5 - Мутации в генах COL4A5, COL4A4, COL4A3 и COL4A6, обнаруженные у пациента 1

хромосома	**генотип**	**зиготность**	**тип мутации**	**название гена**	**HGVS.c**	**HGVS.p**	**dbSNP156_ID**	**CLINVAR_CLNSIG**	**CLINVAR_CLNDN**
2	C	HET	миссенс	COL4A3	c.127G>C	p.Gly43Arg	rs13424243	Benign	Autosomal_recessive_Alport_syndrome|Alport_syndrome|Autosomal_dominant_Alport_syndrome|not_specified|not_provided
2	C	HOM	миссенс	COL4A3	c.422T>C	p.Leu141Pro	rs10178458	Benign	not_specified|Autosomal_dominant_Alport_syndrome|Autosomal_recessive_Alport_syndrome|not_provided|Alport_syndrome
2	G	HOM	миссенс	COL4A3	c.485A>G	p.Glu162Gly	rs6436669	Benign	Autosomal_dominant_Alport_syndrome|Alport_syndrome|not_provided|not_specified|Autosomal_recessive_Alport_syndrome
2	T	HET	миссенс	COL4A3	c.976G>T	p.Asp326Tyr	rs55703767	Benign	not_specified|Autosomal_recessive_Alport_syndrome|not_provided|Alport_syndrome|Autosomal_dominant_Alport_syndrome
2	T	HET	миссенс	COL4A3	c.1721C>T	p.Pro574Leu	rs28381984	Benign	not_specified|Autosomal_recessive_Alport_syndrome|Alport_syndrome|not_provided
X	T	HET	миссенс	COL4A6	c.2707G>A	p.Ala903Thr	rs138246637	Uncertain_significance	not_provided|not_specified
X	G	HET	миссенс	COL4A6	c.1360T>C	p.Ser454Pro	rs1042065	Benign	Hearing_loss,_X-linked_6|not_provided|not_specified

X	CCTT	HET	вставка в консервативную рамку считывания	COL4A6	c.1971_1972insAAG	p.Glu657_Val658insLys	rs146680910	Benign	Hearing_loss, X-linked_6
X	G	HET	акцептор сплайсинга	COL4A5	c.1588-2A>G	-	-	-	-

HET-гетерозигота, HOM-гомозигота.

Таблица 6 - Мутации в генах COL4A5, COL4A4, COL4A3 и COL4A6, обнаруженные у пациента 2

хромосома	**генотип**	**зиготность**	**тип мутации**	**название гена**	**HGVS.c**	**HGVS.p**	**dbSNP156_ID**	**CLINVAR_CLNSIG**	**CLINVAR_CLNDN**
2	C	HET	**миссенс**	COL4A3	c.127G>C	p.Gly43Arg	rs13424243	Benign	Autosomal_recessive_Alport_syndrome|Alport_syndrome|Autosomal_dominant_Alport_syndrome|not_specified|not_provided
2	C	HOM	**миссенс**	COL4A3	c.422T>C	p.Gly43Arg	rs10178458	Benign	not_specified|Autosomal_dominant_Alport_syndrome|Autosomal_recessive_Alport_syndrome|not_provided|Alport_syndrome
2	G	HOM	**миссенс**	COL4A3	c.485A>G	p.Glu162Gly	rs6436669	Benign	Autosomal_dominant_Alport_syndrome|Alport_syndrome|not_provided|not_specified|Autosomal_recessive_Alport_syndrome
2	T	HET	**миссенс**	COL4A3	c.976G>T	p.Asp326Tyr	rs55703767	Benign	not_specified|Autosomal_recessive_Alport_syndrome|not_provided|Alport_syndrome|Autosomal_dominant_Alport_syndrome
2	T	HET	**миссенс**	COL4A3	c.1721C>T	p.Pro574Leu	rs28381984	Benign	not_specified|Autosomal_recessive_Alport_syndrome|Alport_syndrome|not_provided
X	G	HET	**splice_acceptor_variant&intron_variant**	COL4A5	c.1588-2A>G	-	-	-	-

Таблица 7 - Мутации в генах COL4A5, COL4A4, COL4A3 и COL4A6, обнаруженные у пациента 3

хромосома	генотип	зиготность	тип мутации	название гена	HGVS.c	HGVS.p	dbSNP156_ID	CLINVAR_CLNSIG	CLINVAR_CLNDN
2	G	HET	**миссенс**	COL4A4	c.4207T>C	p.Ser1403Pro	rs3752895	Benign	MedGen:CN169374|MedGen:C3661900|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63|MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919
2	T	HET	**миссенс**	COL4A4	c.3979G>A	p.Val1327Met	rs2229813	Benign/Likely_benign	MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919|MONDO:MONDO:0010520,MedGen:C4746986,OMIM:301050,Orphanet:63,Orphanet:88917|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63|MedGen:CN169374|MedGen:C3661900
2	A	HET	**миссенс**	COL4A4	c.3011C>T	p.Pro1004Leu	rs1800517	Benign	MedGen:CN169374|MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63|MedGen:C3661900
2	A	HOM	**миссенс**	COL4A4	c.1444C>T	p.Pro482Ser	rs2229814	Benign	MedGen:CN169374|MedGen:C3661900|MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63
2	A	HET	**миссенс**	COL4A4	c.289C>T	p.Arg97Cys	rs202096172	Conflicting_classifications_of_pathogenicity	.|MedGen:C3661900
2	C	HET	**миссенс**	COL4A3	c.422T>C	p.Leu141Pro	rs10178458	Benign	MedGen:CN169374|MONDO:MONDO:0007086,MedGen:C5882663,OMIM:104200,Orphanet:63,Orphanet:88918|MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919|MedGen:C3661900|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63
2	G	HET	**миссенс**	COL4A3	c.485A>G	p.Glu162Gly	rs6436669	Benign	MONDO:MONDO:0007086,MedGen:C5882663,OMIM:104200,Orphanet:63,Orphanet:88918|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63|MedGen:C3661900|MedGen:CN169374|MONDO:MO

									NDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919
2	T	HET	**миссенс**	COL4A3	c.1721C>T	p.Pro574Leu	rs28381984	Benign	MedGen:CN169374|MONDO:MONDO:0008762,MedGen:C4746745,OMIM:203780,Orphanet:63,Orphanet:88919|MONDO:MONDO:0018965,MedGen:C1567741,OMIM:PS301050,Orphanet:63|MedGen:C3661900

Таблица 8 - Мутации в генах COL4A5, COL4A4, COL4A3 и COL4A6, обнаруженные у пациента 4

хромосома	**генотип**	**зиготность**	**тип мутации**	**название гена**	**HGVS.c**	**HGVS.p**	**dbSNP156_ID**	**CLINVAR_CLNSIG**	**CLINVAR_CLNDN**
2	G	HET	**миссенс**	COL4A4	c.4207T>C	p.Ser1403Pro	rs3752895	Benign	not_specified|not_provided|Alport_syndrome|Autosomal_recessive_Alport_syndrome
2	T	HET	**миссенс**	COL4A4	c.3979G>A	p.Val1327Met	rs2229813	Benign/Likely_benign	Autosomal_recessive_Alport_syndrome|X-linked_Alport_syndrome|Alport_syndrome|not_specified|not_provided
2	C	HET	**миссенс**	COL4A3	c.422T>C	p.Leu141Pro	rs1017 8458	Benign	not_specified|Autosomal_dominant_Alport_syndrome|Autosomal_recessive_Alport_syndrome|not_provided|Alport_syndrome
2	G	HET	**миссенс**	COL4A3	c.485A>G	p.Glu162Gly	rs6436669	Benign	Autosomal_dominant_Alport_syndrome|Alport_syndrome|not_provided|not_specified|Autosomal_recessive_Alport_syndrome
2	T	HET	**миссенс**	COL4A3	c.1721C>T	p.Pro574Leu	rs2838 1984	Benign	not_specified|Autosomal_recessive_Alport_syndrome|Alport_syndrome|not_provided
X	G	HET	**миссенс**	COL4A6	c.1360T>C	p.Ser454Pro	rs1042065	Benign	Hearing_loss,_X-linked_6|not_provided|not_specified
X	CCTT	HET	**Вставка в консервативную рамку считывания**	COL4A6	c.1971_1972insAAG	p.Glu657_Val658insLys	rs1466 80910	Benign	Hearing_loss,_X-linked_6

Таким образом, из таблиц 5-8 видно, что в основном выявленны мутации, характеризующиеся как доброкачественные (Benign)

4. Заключение

Клинические симптомы четырех обследованных пациентов с синдромом Альпорта представлены в таблице 2. Пациент 1 и пациент 2 являлись родными сибсами. Средний возраст обследуемых пациентов составил 10,25 лет. Распределение возраста появления первых симптомов СА варьировал от 1,5 до 7 лет, что соответствует известным литературным данным о более тяжелой клинической картине у мальчиков (пациент 2) при Х-сцепленной форме СА. У родной сестры заболевание СА проявилось в 6 лет.

Все пациенты имели отягощенный семейный анамнез. Пациенты 1,2 и 3 имели родного дядю по материнской линии с аналогичным заболеванием, что свидетельствует о возможном Х-сцепленном наследовании. У пациентки 4 – мама имеет ХПН и в течение многих лет находится на постоянном гемодиализе, что предполагает аутосомно-доминантную форму СА.

У всех пациентов первыми симптомами заболевания явились микрогематурия – 10-20 в п/зрения, которая быстро прогрессировала до макрогематурии – 40-50 в п/зрения, в двух случаях – пациент 2 и 3. Вторым основным диагностическим симптомом явилась протеинурия, содержание белка в моче варьировало от 0,30 г/л у пациента 4, до 2,3 г/л у пациента 2 с клинически более тяжелой Х-сцепленной формой СА.

Помимо основных симптомов – гематурии и протеинурии проведен анализ наличия возможных сопутствующих проявлений СА. Нейросенсорная тугоухость и нарушения органов зрения, помимо неспецифичного симптома ангиопатии сетчатки у пациента 2, не было обнаружено у всех 4 пациентов. Это связано с тем, что согласно международным руководствам по диагностике и лечению СА, нарушения слуха и зрения возникают в более позднем подростковом или взрослом возрасте. Двум старшим пациентам исполнилось 13 лет, что предполагает развитие этих симптомов в дальнейшей жизни.

Характерные изменения почек были выявлены у двух (50%) пациентов 1 -уплотнение стенок чашечно-лоханочной системы почек с обеих сторон. У пациента 3 - двусторонний нефроптоз, уплотнение стенок чашечно-лоханочной системы почек и каликоэктазия с обеих сторон.

Одним из важнейших критериев постановки диагноза СА является инвазивный метод – биопсия ткани почек, которая была проведена 3 (75%) пациентам 1,2 и 4. Картина была характерной для СА и позволяла поставить этот диагноз на основании гистологических нарушений. У родных сибсов - пациентов 1 и 2 был описан фокальный глобальный и сегментарный гломерулосклероз. Интерстициальный фиброз и атрофия канальцев 1 ст. Электронная микроскопия выявила картину врожденной/наследственной патологии коллагена IV типа. У пациента 4 при биопсии ткани почек обнаружены морфологические признаки мембрано-пролиферативного гломерулонефрита с умеренным фиброзом и лимфоцитарной инфильтрацией в межуточной ткани (фокальный склероз – 85,2%, гиалиноз и склероз – 14,8%). Полученные результаты подтверждают высокую диагностическую значимость гистологических исследований ткани почек для ранней постановки диагноза СА.

Как представлено в таблице 2, общий и биохимический анализ крови у всех пациентов не показал специфичных отклонений. В то время, как общий анализ мочи продемонстрировал повышение белка и эритроцитов, в суточной моче содержание белка колебалось от 0,23 до 2,31 г/сутки, что подтверждало патологически высокий уровень протеинурии при СА.

Скорость клубочковой фильтрации (СКФ) определялась по формуле Шварца

рСКФ = kxH/CCr, где k = 0,0414 х возраст (количество лет) + 0,3018; Н – рост (см); CCr –

концентрация креатинина в сыворотке крови (мг/дл). Нормальная скорость клубочковой фильтрации (СКФ) для большинства взрослых — более 90 мл/мин/1,73 м². Диапазон 60-89 мл/мин/1,73 м² считается легким снижением функции почек, а более низкие показатели свидетельствуют о прогрессирующем нарушении работы почек. У детей в возрасте от 1 до 14 лет нормальное значение СКФ составляет от 70 до 140 мл/мин/1,73 м2. СКФ по Шварцу была измерена у пациентов 1,2 и 4, при этом, снижение фильтрационной функции почек до 47 мл/мин/1,73 м2 отмечено у пациента 2 с наиболее тяжелой клинической картиной СА из всех обследованных. У этого же пациента 2 имеется ХПН 1 степени.

В результате анализа данных полноэкзомного секвенирования у пациентов 1-4 не было обнаружено патогенных и вероятно патогенных мутаций в экзонных областях генов COL4A5, COL4A4, COL4A3 и COL4A6, которые классифицируются базами даннынных ClinVar и ACMG.

Однако у пациентов 1 и 2 была выявлена мутация в 23 интроне гена COL4A5 (chrX:108597375A>G), приводящая к нарушению канонического сайта сплайсинга (c. 1588-2A>G, NM_033380.2). В базе данных LOVD характеризуется как патогенная мутация [33] и базе CLINVAR как приводящая к аномальной структуре белка [34], однако не найдено публикаций в рецензируемых изданиях, содержащих функционального исследования именно данного варианта в COL4A5. Выявленная мутация упоминается лишь в сообщении, опубликованном в сборнике «Asian Journal of Pediatric Nephrology» в 2023 году, однако данный материал не содержит полных экспериментальных данных, в связи с чем не может рассматриваться как достоверный источник [35]. Также в статье Horinouchi et al. описана схожая мутация c.1588–1G>A в интроне 23. Данная мутация приводила к устранению сайта акцептора сплайсинга интрона 23 и активации нового сайта сплайсинга на один нуклеотид ниже по течению [36]. На основании совокупности имеющихся сведений мутацию c.1588-2A>G гена COL4A5 следует рассматривать как патогенную, вероятно приводящей к Х-сцепленному синдрому Альпорта, но требующей дополнительных функциональных исследований.

5. Выводы

Проведенный анализ медицинской документации, семейного анамнеза, оценки тяжести заболевания и диагностической значимости клинических симптомов показал, что генетическая диагностика имеет первостепенное значение для подтверждения диагноза и прогноза клинического течения синдрома Альпорта. Исследование подчеркивает значимость генетических исследований синдрома Альпорта, и важность изучение интронных областей генов COL4A3, COL4A4, COL4A5.

Конфликт интересов. Конфликт интересов отсутствует.

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Литература

1. Yamamura, T., Nozu, K., Fu, X. J., Nozu, Y., Ye, M. J., Shono, A., Iijima, K. (2017). Natural history and genotype–phenotype correlation in female X-linked Alport syndrome. *Kidney international reports*, *2*(5), 850-855. https://doi.org/10.1016/j.ekir.2017.04.011

2. Alport, A. C. (1927). Hereditary familial congenital haemorrhagic nephritis. *British medical journal*, *1*(3454), 504. https://doi.org/10.1136/bmj.1.3454.504

3. Groopman, E. E., Marasa, M., Cameron-Christie, S., Petrovski, S., Aggarwal, V. S., Milo-Rasouly, H., Gharavi, A. G. (2019). Diagnostic utility of exome sequencing for kidney disease. *New England Journal of Medicine*, *380*(2), 142-151. https://doi.org/10.1056/NEJMoa1806891

4. Gross, O., Friede, T., Hilgers, R., Görlitz, A., Gavénis, K., Ahmed, R., & Dürr, U. (2012). Safety and efficacy of the ACE-inhibitor Ramipril in Alport Syndrome: the double-blind, randomized, placebo-controlled, multicenter phase III EARLY PRO-TECT Alport trial in pediatric patients. *International Scholarly Research Notices*, *2012*(1), 436046. https://doi.org/10.5402/2012/436046

5. Inoue, Y., Nishio, H., Shirakawa, T., Nakanishi, K., Nakamura, H., Sumino, K., Yoshikawa, N. (1999). Detection of mutations in the COL4A5 gene in over 90% of male patients with X-linked Alport's syndrome by RT-PCR and direct sequencing. *American journal of kidney diseases*, *34*(5), 854-862. https://doi.org/10.1016/S0272-6386(99)70042-9

6. Nozu, K., Nakanishi, K., Abe, Y., Udagawa, T., Okada, S., Okamoto, T., Iijima, K. (2019). A review of clinical characteristics and genetic backgrounds in Alport syndrome. *Clinical and experimental nephrology*, *23*(2), 158-168. https://doi.org/10.1007/s10157-018-1629-4

7. Kashtan, C. E. (2021). Alport syndrome: achieving early diagnosis and treatment. *American Journal of Kidney Diseases*, *77*(2), 272-279. https://doi.org/10.1053/j.ajkd.2020.03.026

8. Kashtan, C E. (1998). Alport syndrome and thin glomerular basement membrane disease. *Journal of the American Society of Nephrology*, 9(9), 1736-1750. https://doi.org/10.1681/ASN.V991736

9. Savige, J., Ariani, F., Mari, F., Bruttini, M., Renieri, A., Gross, O., Storey, H. (2019). Expert consensus guidelines for the genetic diagnosis of Alport syndrome. *Pediatric Nephrology*, *34*(7), 1175-1189. https://doi.org/10.1007/s00467-018-3985-4

10. Fallerini, C., Baldassarri, M., Trevisson, E., Morbidoni, V., La Manna, A., Lazzarin, R., Ariani, F. (2017). Alport syndrome: impact of digenic inheritance in patients management. *Clinical genetics*, *92*(1), 34-44. https://doi.org/10.1111/cge.12919

11. Chugh, K. S., Sakhuja, V., Agarwal, A., Jha, V., Joshi, K., Datta, B. N., Gupta, K. L. (1993). Hereditary nephritis (Alport's syndrome)—clinical profile and inheritance in 28 kindreds. *Nephrology Dialysis Transplantation*, *8*(8), 690-695. https://doi.org/10.1093/ndt/8.8.690

12. Xiao, T., Zhang, J., Liu, L., & Zhang, B. (2024). Genetic diagnosis of Alport syndrome in 16 Chinese families. *Molecular Genetics & Genomic Medicine*, 12(3), e2406. https://doi.org/10.1002/mgg3.2406

13. Kashtan, C. E., Ding, J., Garosi, G., Heidet, L., Massella, L., Nakanishi, K., Gross, O. (2018). Alport syndrome: a unified classification of genetic disorders of collagen IV α345: a position paper of the Alport Syndrome Classification Working Group. *Kidney international*, *93*(5), 1045-1051. https://doi.org/10.1016/j.kint.2017.12.018

14. Jais, J. P., Knebelmann, B., Giatras, I., De Marchi, M. A. R. I. O., Rizzoni, G., Renieri, A., Gubler, M. C. (2000). X-linked Alport syndrome: natural history in 195 families and genotype-phenotype correlations in males. *Journal of the American Society of Nephrology*, *11*(4), 649-657. https://doi.org/10.1681/ASN.V114649

15. Nozu, K., Vorechovsky, I., Kaito, H., Fu, X. J., Nakanishi, K., Hashimura, Y., Iijima, K. (2014). X-linked Alport syndrome caused by splicing mutations in COL4A5. *Clinical Journal of the American Society of Nephrology*, *9*(11), 1958-1964.https://doi.org/10.2215/CJN.04140414

16. Kamiyoshi, N., Nozu, K., Fu, X. J., Morisada, N., Nozu, Y., Ye, M. J., Iijima, K. (2016). Genetic, clinical, and pathologic backgrounds of patients with autosomal dominant Alport syndrome. *Clinical Journal of the American Society of Nephrology*, *11*(8), 1441-1449. https://doi.org/10.2215/CJN.01000116

17. Pierides, A., Voskarides, K., Athanasiou, Y., Ioannou, K., Damianou, L., Arsali, M., Deltas, C. (2009). Clinico-pathological correlations in 127 patients in 11 large pedigrees, segregating one of three heterozygous mutations in the COL4A3/COL4A4 genes associated with familial haematuria and significant late progression to proteinuria and chronic kidney disease from focal segmental glomerulosclerosis. *Nephrology Dialysis Transplantation*, *24*(9), 2721-2729. https://doi.org/10.1093/ndt/gfp158

18. Savige, J., Storey, H., Watson, E., Hertz, J. M., Deltas, C., Renieri, A., Lipska-Ziętkiewicz, B. S. (2024). Correction: Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria. *European Journal of Human Genetics*, *32*, 132-132. https://doi.org/10.1038/s41431-023-01288-x

19. Zhang, Y., Ding, J., Zhang, H., Yao, Y., Xiao, H., Wang, S., & Wang, F. (2019). Effect of heterozygous pathogenic COL4A3 or COL4A4 variants on patients with X-linked Alport syndrome. *Molecular Genetics & Genomic Medicine*, *7*(5), e647. https://doi.org/10.1002/mgg3.647

20. Crockett, D. K., Pont-Kingdon, G., Gedge, F., Sumner, K., Seamons, R., & Lyon, E. (2010). The Alport syndrome COL4A5 variant database. *Human Mutation*, 31(8), E1652–E1657. https://doi.org/10.1002/humu.21312

21. Wood, A. R., Hernandez, D. G., Nalls, M. A., Yaghootkar, H., Gibbs, J. R., Harries, L. W., Frayling, T. M. (2011). Allelic heterogeneity and more detailed analyses of known loci explain additional phenotypic variation and reveal complex patterns of association. *Human molecular genetics*, *20*(20), 4082-4092. https://doi.org/10.1093/hmg/ddr328

22. Ahmed, F., Kamae, K. K., Jones, D. J., DeAngelis, M. M., Hageman, G. S., Gregory, M. C., & Bernstein, P. S. (2013). Temporal macular thinning associated with X-linked Alport syndrome. *JAMA ophthalmology*, *131*(6), 777-782. https://doi.org/10.1001/jamaophthalmol.2013.1452

23. Savige, J., Storey, H., Il Cheong, H., Gyung Kang, H., Park, E., Hilbert, P., Nagel, M. (2016). X-linked and autosomal recessive Alport syndrome: pathogenic variant features and further genotype-phenotype correlations. *PLoS One*, *11*(9), e0161802. https://doi.org/10.1371/journal.pone.0161802

24. Nozu, K., Nakanishi, K., Abe, Y., Udagawa, T., Okada, S., Okamoto, T., Iijima, K. (2019). A review of clinical characteristics and genetic backgrounds in Alport syndrome. *Clinical and experimental nephrology*, *23*(2), 158-168. https://doi.org/10.1007/s10157-018-1629-4

25. Hertz, J. M., Thomassen, M., Storey, H., Flinter, F. (2012). Clinical utility gene card for: Alport syndrome. *European Journal of Human Genetics*, *20*(6), 713-713. https://doi.org/10.1038/ejhg.2011.237

26. Żurowska, A. M., Bielska, O., Daca-Roszak, P., Jankowski, M., Szczepańska, M., Roszkowska-Bjanid, D., ... & Lipska-Ziętkiewicz, B. S. (2021). Mild X-linked Alport syndrome due to the COL4A5 G624D variant originating in the Middle Ages is predominant in Central/East Europe and causes kidney failure in midlife. *Kidney International*, *99*(6), 1451-1458. https://doi.org/10.1016/j.kint.2020.10.040

27. Zallocchi, M., Johnson, B. M., Meehan, D. T., Delimont, D., Cosgrove, D. (2013). α1β1 integrin/Rac1-dependent mesangial invasion of glomerular capillaries in Alport syndrome. *The American journal of pathology*, *183*(4), 1269-1280. https://doi.org/10.1016/j.ajpath.2013.06.015

28. Voskarides K., Pierides A., Deltas C. COL4A3/COL4A4 mutations and kidney disease: insights into pathogenesis and treatment. Nephrology Dialysis Transplantation. 2008; 23(9):2722–2726. https://doi.org/10.1681/ASN.2007040444

29. Hashimura Y., Nozu K., Kaito H. et al. Milder clinical course in COL4A5 hypomorphic variants: implications for variant classification. Clinical and Experimental Nephrology. 2014; 18(3):446–454. https://doi.org/10.1038/ki.2013.479

30. Savige J., Dagher H., Bogdanovic R. et al. Thin basement membrane nephropathy. Kidney International. 2003; 64(4):1169–1178. https://doi.org/10.1046/j.1523-1755.2003.00234.x

31. Global Variome shared LOVD. Website. Available from URL: https://databases.lovd.nl/shared/genes

32. ClinVar Genomic variation as it relates to human health. Website. Available from URL:https://www.ncbi.nlm.nih.gov/clinvar/variation/4463839/

33. Lu D., Shi L., Wu L. et al. A novel mutation in COL4A5 gene was found in a family with Alport syndrome in Western China. Abstracts of the Asian Congress of Pediatric Nephrology 2023. Asian Journal of Pediatric Nephrology. 2023; 6(2):73–184.

34. Horinouchi T., Nozu K., Yamamura T., Minamikawa S., Omori T., Nakanishi K., Fujimura J., Ashida A., Kitamura M., Kawano M., Shimabukuro W., Kitabayashi C., Imafuku A., Tamagaki K., Kamei K., Okamoto K., Fujinaga S., Oka M., Igarashi T., Iijima K. Detection of splicing abnormalities and genotype–phenotype correlation in X-linked Alport syndrome. Journal of the American Society of Nephrology. 2018; 29(8):2244–2254. https://doi.org/10.1681/asn.2018030228

35. Oka M., Nozu K., Kaito H., Fu X.J., Nakanishi K., Hashimura Y., et al. Natural history of genetically proven autosomal recessive Alport syndrome. Pediatric Nephrology. 2014;29(9):1535–1544. https://doi.org/10.1007/s00467-014-2797-4

36. Global Variome shared LOVD. Website. Available from URL: https://databases.lovd.nl/shared/variants/0000352597#00024106

37. ClinVar Genomic variation as it relates to human health. Website. Available from URL:https://www.ncbi.nlm.nih.gov/clinvar/variation/4463839/

38. Lu D., Shi L., Wu L. et al. A novel mutation in COL4A5 gene was found in a family with Alport syndrome in Western China. Abstracts of the Asian Congress of Pediatric Nephrology 2023. Asian Journal of Pediatric Nephrology. 2023; 6(2):73–184. https://doi.org/10.4103/ajpn.ajpn_14_23

39. Horinouchi T., Nozu K., Yamamura T., Minamikawa S., Omori T., Nakanishi K., Fujimura J., Ashida A., Kitamura M., Kawano M., Shimabukuro W., Kitabayashi C., Imafuku A., Tamagaki K., Kamei K., Okamoto K., Fujinaga S., Oka M., Igarashi T., Iijima K. Detection of splicing abnormalities and genotype–phenotype correlation in X-linked Alport syndrome. Journal of the American Society of Nephrology. 2018; 29(8):2244–2254. https://doi.org/10.1681/asn.2018030228

Альпорт синдромына күдікті балалардағы генетикалық ерекшеліктер: Толық экзомалық реттілік нәтижелері

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Түйіндеме

Кіріспе. Альпорт синдромы COL4A3, COL4A4, COL4A5 гендеріндегі мутациялардан туындаған сирек кездесетін көп жүйелі ауру. Альпорт синдромы зерттеудің өзектілігі оның тұқым қуалайтын бүйрек аурулары арасындағы жоғары жиілігіне, ерекше генетикалық және фенотиптік гетерогенділігіне, диагностиканың клиникалық және генетикалық әдістерін түсіндірудің күрделілігіне, спецификалық мутациялардың жиілігі мен спектрінде маңызды популяциялық айырмашылықтардың болуына байланысты.

Зерттеу мақсаты толық экзомалық реттілік диагностикалық маңыздылығын, анықталған генетикалық нұсқалар спектрінің сипаттамасын бағалау және молекулалық-генетикалық диагностиканың тиімділігіне әсер ететін факторларды анықтау үшін альпорт синдромына клиникалық және зертханалық күдікті пациенттердегі толық экзомалық реттілік деректерін талдау болып табылады.

Әдістері. Альпорт синдромы бар науқастардың қан үлгілерінен геномдық ДНҚ-ны оқшаулау. Үлгілердің толық экзомдық реттілігі, сондай-ақ секвенирлеу деректерін биоинформатикалық және статистикалық өңдеу жүргізілді.

Нәтижелер. COL4A5 генінің интрондық аймағында бұрын сипатталмаған мутация анықталды, c.1588-2A>G, мүмкін Альпорт синдромымен байланысты.

Қорытындылар. Зерттеу Альпорт синдромының популяциялық-генетикалық зерттеулерінің маңыздылығын көрсетеді және COL4A3, COL4A4, COL4A5 гендерінің интрондық аймақтарын зерттеу әсіресе маңызды.

Түйін сөздер: Альпорт синдромы, Альпорт Х-байланысты синдромы, толық экзомалық реттілік, генотип пен фенотиптің корреляциясы, сплайсингтің бұзылуы.

Genetic Features in Children with Suspected Alport Syndrome: Results of Whole-Exome Sequencing

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Abstract

Introduction. Alport syndrome is a rare multisystem disorder caused by mutations in the COL4A3, COL4A4, and COL4A5 genes. The relevance of studying Alport syndrome is due to its high frequency among inherited kidney diseases, its extreme genetic and phenotypic heterogeneity, the difficulty interpreting clinical and genetic diagnostic methods, and the presence of significant population differences in the frequency and spectrum of specific mutations.

The aim of this study is to analyze whole-exome sequencing data in patients with clinical and laboratory suspicion of Alport syndrome to assess the diagnostic value of WES, characterize the spectrum of detected genetic variants, and identify factors influencing the effectiveness of molecular genetic diagnostics.

Methods. Genomic DNA was isolated from blood samples of patients with suspected Alport syndrome. Whole-exome sequencing of the samples was performed, along with bioinformatic and statistical processing of the sequencing data.

Results. A previously undescribed mutation in the intronic region of the COL4A5 gene, c.1588-2A>G, was identified, likely associated with Alport syndrome.

Conclusions. This study highlights the importance of population genetic studies of Alport syndrome, particularly the study of the intronic regions of the COL4A3, COL4A4, and COL4A5 genes.

Keywords: Alport syndrome, X-linked Alport syndrome, whole-exome sequencing, genotype-phenotype correlation, splicing disorders.

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Adaptation and Evaluation of a Quality of Life Questionnaire for Patients with Hemophilia in the Republic of Kazakhstan

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Abstract

Introduction. Hemophilia is a chronic inherited disorder that substantially affects patients' physical, emotional, and social functioning. In the context of modern therapeutic approaches, health-related quality of life is regarded as an important patient-centered outcome. Objective assessment of these parameters requires validated disease-specific instruments adapted to the linguistic and cultural characteristics of the target population.

Objective. To perform the linguistic adaptation and psychometric validation of the Russian-language version of the A36Hemofilia-QoL questionnaire for use in adult patients with hemophilia in the Republic of Kazakhstan.

Methods. A methodological study was conducted using a standardized forward–backward translation procedure, expert review, and pilot testing. The study included 30 adult patients with mild, moderate, or severe hemophilia A or B. Internal consistency was assessed using Cronbach's alpha for the total scale and individual domains. Construct validity was evaluated by exploratory factor analysis with oblique rotation. Statistical analysis was performed using IBM SPSS Statistics version 28.0.

Results. The Russian-language version of the questionnaire demonstrated conceptual equivalence to the original instrument and good acceptability among patients. High or acceptable levels of internal consistency were observed for several

subscales, while lower Cronbach's alpha values were identified in certain domains, which may be attributable to the clinical heterogeneity of the sample and the pilot nature of the study. Exploratory factor analysis generally confirmed a satisfactory factor structure reflecting the physical, functional, emotional, and social dimensions of quality of life in patients with hemophilia.

Conclusion. The Russian-language version of the A36Hemophilia Quality of Life questionnaire appears to be a promising disease-specific instrument for assessing quality of life in adult patients with hemophilia in the Republic of Kazakhstan. Further studies with larger sample sizes are required to fully confirm its psychometric properties.

Keywords: hemophilia, quality of life, questionnaire, validation, A36Hemophilia-QoL.

1. Introduction

Hemophilia is a hereditary disorder of the hemostatic system characterized by a deficiency of coagulation factors VIII or IX and accompanied by a tendency to spontaneous or post-traumatic bleeding [1]. Despite significant progress in treatment due to the introduction of prophylactic replacement therapy, recombinant factors and non-factor drugs, hemophilia remains a chronic disease requiring lifelong medical supervision and having a significant impact on the physical, emotional and social well-being of the patient [2,3]. In older patients, especially those with a long history of the disease, chronic arthropathies, pain syndrome, limited mobility and difficulties in social adaptation often develop, which makes the assessment of quality of life a key component of comprehensive management [4].

One of the key clinical outcome measures in the management of hemophilia today is the assessment of quality of life, which allows an objective evaluation of the impact of the disease and the effectiveness of ongoing therapy [5]. Among standardized disease-specific instruments for patients with hemophilia, the A36Hemofilia-QoL questionnaire is widely used and was developed to assess the physical, psychological, and social aspects of life in individuals with hemophilia [6].

In international practice, both general (SF-36, EQ-5D) and specialized questionnaires, in particular Haem-A-QoL, are used to assess the quality of life of patients with hemophilia [7-9]. Universal instruments allow for internosological comparisons, but have limited sensitivity to the clinical features of hemophilia. The specialized questionnaire A36Hemofilia-QoL has a more comprehensive structure, as in addition to emotional and social aspects it provides a detailed assessment of physical functioning, joint involvement, pain, as well as treatment satisfaction and treatment-related difficulties. This ensures a more accurate reflection of the impact of the disease and therapy on the daily lives of patients with hemophilia and enhances the clinical relevance of the instrument. However, for the appropriate use of any questionnaire in a specific country, a process of cultural adaptation and psychometric validation is required, taking into account the linguistic, cultural, and clinical characteristics of the target population.

At present, there are no validated instruments in Kazakhstan that allow for a comprehensive assessment of the quality of life of adult patients with hemophilia in the Russian language while taking into account the specific characteristics of disease course in this population. This limits opportunities for conducting clinical and epidemiological studies, analyzing the effectiveness of different therapeutic strategies, and developing recommendations to improve the organization of medical care. The adaptation and validation of the

A36Hemofilia-QoL questionnaire will make it possible to standardize the assessment of quality of life, improve the quality of patient management, and expand the scientific research potential in the field of hemophilia.

The aim of the present study was to perform the linguistic adaptation and psychometric validation of the Russian-language version of the A36Hemofilia-QoL questionnaire for use in adult patients with hemophilia in the Republic of Kazakhstan.

2. Materials and methods

This methodological study was aimed at the translation, cultural adaptation, and validation of the disease-specific A36Hemofilia-QoL questionnaire designed to assess the quality of life of adult patients with hemophilia.

The A36Hemofilia-QoL questionnaire is a disease-specific instrument for assessing the quality of life of adult patients with hemophilia and consists of 36 items grouped into nine thematic domains (subscales) that reflect the key clinical, functional, and psychosocial aspects of the disease.

The structure of the questionnaire includes the following subscales: physical health (8 items), daily activities (4 items), joint damage (3 items), pain (2 items), treatment satisfaction (2 items), treatment-related difficulties (4 items), emotional functioning (5 items), mental health (3 items), and interpersonal relationships and social activity (5 items).

Translation and adaptation were conducted to enable the use of this instrument within the healthcare system of the Republic of Kazakhstan. The translation process followed established methodological criteria and included forward translation, reconciliation, back-translation, expert committee review, and pilot testing [10].

At the first stage, the original English version of the questionnaire was independently translated into Russian by two professional bilingual translators. Both translators were native Russian speakers, fluent in English, and had experience in translating medical and scientific texts.

Before commencing the work, the translators were provided with background materials, including the consent form, a description of the study objectives, characteristics of the target population, the intended mode of questionnaire administration, as well as clarifications of key terms and concepts used in the questionnaire items.

At the second stage, a meeting involving the translators and members of the research team was held, during which the forward translation versions were compared and reconciled. The primary focus was on achieving conceptual equivalence of the wording rather than literal correspondence. As a result of the discussion, a reconciled forward translation version was produced.

The reconciled Russian version was then back-translated into English by two independent translators who had not participated in the previous stages and had no access to the original questionnaire. The purpose of the back-translation was to identify potential semantic and conceptual discrepancies.

The research team conducted a comparative analysis of the original English version and the results of the back-translation. Any discrepancies identified were discussed jointly with the translators, after which the necessary revisions were made to the text. As a result, a preliminary Russian-language version of the A36Hemofilia-QoL questionnaire was developed.

The preliminary version of the questionnaire was pilot-tested in medical institutions providing care to patients with hemophilia. A sample of 30 adult patients was formed for the pilot testing. Inclusion criteria were age 18 years or older, a confirmed diagnosis of hemophilia A or B of mild, moderate, or severe severity, and written informed consent to participate in the study. No restrictions on treatment regimens were applied. Exclusion criteria included the presence of severe concomitant somatic or psychiatric disorders significantly affecting quality of life; acute bleeding episodes or hospitalization at the time of assessment; and

cognitive impairments preventing accurate completion of the questionnaires.

Each participant was assigned a unique code known only to the researcher, ensuring data confidentiality. The questionnaire was accompanied by a cover letter explaining the objectives of the study, the voluntary nature of participation, and guarantees of anonymity. Completed questionnaires were collected over a three-week period.

Statistical data analysis was performed using IBM SPSS Statistics software, version 28.0 (IBM Corp., USA). Quantitative variables are presented as mean values and standard deviations.

The reliability of the Russian-language version of the A36Hemofilia-QoL questionnaire was assessed by analyzing internal consistency using Cronbach's α coefficient for the total scale and individual subscales [11]. Values of $\alpha \geq 0.70$ were considered indicative of acceptable internal consistency, with the interpretation of results taking into account the number of items in each subscale and the pilot nature of the study.

Construct validity of the questionnaire was assessed using factor analysis. Prior to factor analysis, data suitability was evaluated using the Kaiser–Meyer–Olkin (KMO) measure and Bartlett's test of sphericity. The principal component method was used for factor extraction, and factor rotation was performed using oblique Oblimin rotation with Kaiser normalization, given the expected correlations among quality-of-life domains.

To assess relationships between questionnaire domains, correlation analysis was performed using Spearman's correlation coefficient, due to the ordinal nature of the response scale and the potential deviation of the variables from a normal distribution. The level of statistical significance was set at $p < 0.05$.

3. Results and discussion

Across all stages of the linguistic adaptation process, no significant semantic discrepancies were identified between the original and the Russian-language versions of the questionnaire. The expert committee noted good conceptual equivalence of the wording and its consistency with the clinical realities of patients with hemophilia.

According to the results of the pilot testing, the majority of respondents reported that the questionnaire items were clear and easy to understand. No significant difficulties were identified during completion of the questionnaire. The mean completion time was 12.5 minutes, indicating that the instrument is feasible and acceptable for both clinical and research use.

A total of 30 respondents participated in the pilot testing. The mean age of the participants was 37.57 ± 9.08 years, ranging from 22 to 57 years. All respondents were male. Half of the participants (n = 15) had completed higher education (bachelor's degree). Secondary vocational education (college or technical school) was reported by 10 patients (33.3%), incomplete higher education by 3 participants (10.0%), and general secondary education (11 years of schooling) by 2 patients (6.7%).

The assessment of internal consistency of the Russian-language version of the A36Hemofilia-QoL questionnaire revealed heterogeneous reliability indices across individual subscales (Table 1). High Cronbach's α coefficients were obtained for the domains "Daily Activities" ($\alpha = 0.90$), "Interpersonal Relationships and Social Activity" ($\alpha = 0.93$), and "Emotional Functioning" ($\alpha = 0.85$), indicating high internal consistency of the items within these subscales.

The "Treatment Satisfaction" subscale demonstrated an acceptable level of internal consistency ($\alpha = 0.74$). Moderate Cronbach's α values were observed for the "Mental Health" domain ($\alpha = 0.64$), which may be attributable to the small number of items and the variability of psychological characteristics among patients with a chronic disease.

Low Cronbach's α coefficients were identified for the "Physical Health" ($\alpha = 0.48$) and "Treatment-Related

Difficulties" (α=0.42) subscales, which may reflect clinical heterogeneity of disease manifestations and differences in individual treatment experiences within the study sample. For the "Joint Damage" subscale, a negative Cronbach's α value was obtained, indicating extremely low variability of responses and homogeneity of clinical characteristics in the examined sample rather than deficiencies in the translation or the structure of the questionnaire.

Table 1 - Factor loadings of items of the Russian-language version of the A36Hemofilia-QoL questionnaire

Questionnaire item	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**Number of items**	**Cronbach's α**
Physical Health (PH)									8	0,48
PH_Q1					–0,78					
PH_Q2	0,47				0,42					
PH _Q3			0,83							
PH_Q4					–0,32					
PH_Q5										
PH_Q6								0,84		
PH _Q7	0,56									
PH_B8								0,91		
Daily Activities (DA)									4	0,90
DA_Q1					–0,46					
DA_Q2	0,40				–0,61					
DA_Q3	0,63				–0,44					
DA_Q4	0,74									
Joint Damage (JD)									3	-1,22
JD_Q1					–0,88					
JD_Q2						0,88				
JD_Q3							0,46			
Pain (P)									2	-
P_Q1					–0,80					
P_Q2				0,57	–0,35					
Treatment Satisfaction (TS)									2	0,74
TS_Q1						–0,71				
TS_Q2								0,42		
Treatment-Related Difficulties (TRD)									4	0,42
TRD_Q1		0,78								
TRD_Q2		0,82								
TRD_Q3							0,94			
TRD_Q4		0,61								
Emotional Functioning (EF)									5	0,85
EF_Q1				0,94						
EF_Q2				0,53						

EF_Q3				0,45						
EF_Q4				0,45						
EF_Q5				0,70						
Mental Health (MH)									3	0,64
MH_Q1				0,92						
MH_Q2				0,92						
MH_Q3		0,80								
Interpersonal Relationships and Social Activity (IRSA)									5	0,93
IRSA_Q1	0,92									
IRSA_Q2	0,62									
IRSA_Q3	0,72									
IRSA_Q4	0,83									
IRSA_Q5	0,84									

Prior to conducting exploratory factor analysis, data suitability was confirmed by measures of sampling adequacy. The Kaiser–Meyer–Olkin (KMO) value indicated acceptable factorability of the data matrix, and Bartlett's test of sphericity was statistically significant ($p < 0.05$), supporting the appropriateness of applying factor analysis.

Exploratory factor analysis performed using the principal component method with oblique Oblimin rotation and Kaiser normalization identified eight factors with eigenvalues greater than 1. The cumulative proportion of explained variance was 81.45%, which represents a high value for quality-of-life questionnaires. Analysis of the scree plot further supported the appropriateness of an eight-factor structure.

The extracted communalities ranged from 0.63 to 0.95, indicating adequate representation of all items within the factor model and no need for item exclusion. Most items demonstrated factor loadings ≥ 0.40 on their respective factors and formed logically interpretable components reflecting the physical, functional, emotional, and social aspects of quality of life in patients with hemophilia.

Some items exhibited cross-loadings across factors, which is expected for clinical questionnaires assessing interrelated aspects of a chronic disease. Given their clinical relevance and satisfactory communality values, all items were retained in the questionnaire structure.

Correlation analysis of the factors revealed moderate associations between several components ($|r| \leq 0.41$), supporting the appropriateness of using oblique rotation and reflecting the multidimensional nature of quality of life in patients with hemophilia.

Discussion. In the present study, linguistic adaptation and preliminary psychometric validation of the Russian-language version of the A36Hemofilia-QoL questionnaire were performed to assess the quality of life of adult patients with hemophilia in the Republic of Kazakhstan. The obtained results indicate conceptual equivalence between the translated and original versions and support the acceptability of the instrument for use in both clinical and research settings.

The translation and cultural adaptation procedure was conducted in accordance with internationally recognized guidelines, including forward and back translation, expert review, and pilot testing. The absence of significant semantic discrepancies and the positive evaluation of item clarity by patients indicate the adequacy of the Russian-language version and its consistency with the clinical realities of the target population.

The analysis of internal consistency revealed heterogeneous reliability indices across individual questionnaire subscales. High Cronbach's α values obtained for the "Daily Activities," "Emotional Functioning," and "Interpersonal Relationships and

Social Activity" domains are comparable to those reported for the original version of the questionnaire and its international adaptations, and they confirm the stability of measurement of functional and psychosocial aspects of quality of life in patients with hemophilia. The acceptable reliability level of the "Treatment Satisfaction" subscale indicates its suitability for assessing patients' subjective perceptions of therapy.

At the same time, the lower Cronbach's α values observed for the "Physical Health" and "Treatment-Related Difficulties" domains may reflect clinical heterogeneity of disease manifestations, differences in hemophilia severity, treatment regimens, and individual patient experiences. Similar findings have been reported in previous psychometric studies of disease-specific questionnaires in chronic conditions and do not necessarily indicate shortcomings of the instrument, particularly in the context of a limited sample size.

Exploratory factor analysis overall confirmed satisfactory construct validity of the Russian-language version of the questionnaire. The extracted eight-factor structure accounted for a substantial proportion of the total variance and was clinically interpretable, reflecting the key physical, functional, emotional, and social aspects of quality of life in patients with hemophilia. The presence of cross-loadings for some items is expected in clinical questionnaires assessing interrelated components of a chronic disease and did not warrant item exclusion at this stage of the study.

The limitations of the study include the absence of an assessment of test–retest reliability of the questionnaire. This analysis was not performed due to the cross-sectional nature of the assessment and the limited number of participants.

Overall, the study results indicate the promise of the Russian-language version of the A36Hemofilia-QoL questionnaire as a disease-specific instrument for assessing the quality of life of adult patients with hemophilia in the Republic of Kazakhstan and provide a foundation for further research and the implementation of standardized patient-reported outcome assessment in clinical practice.

4. Conclusion

This study performed the linguistic adaptation and preliminary psychometric validation of the Russian-language version of the A36Hemofilia-QoL questionnaire for adult patients with hemophilia in the Republic of Kazakhstan. The Russian version demonstrated conceptual equivalence to the original instrument and good acceptability among patients. Reliability analysis and exploratory factor analysis generally confirmed satisfactory psychometric properties of the questionnaire, while indicating that certain subscales require further verification. The findings support the need for future studies with larger samples to provide definitive confirmation of the questionnaire's validity.

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References

1. Konkle B.A., Nakaya Fletcher S. Hemophilia A. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 2000 Sep 21 [updated 2025 Aug 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1404/

2. Liu, Z., Feng, J., Fang, Y., Cheng, Y., Li, S. (2023). Barriers to prophylactic treatment among patients with haemophilia A in Shandong Province, China: a qualitative study. *Orphanet Journal of Rare Diseases*, *18*(1), 226. https://doi.org/10.1186/s13023-023-02838-8

3. Marchesini, E., Morfini, M., Valentino, L. (2021). Recent advances in the treatment of hemophilia: a review. *Biologics: Targets and Therapy*, 221-235. https://doi.org/10.2147/BTT.S252580

4. Torres-Ortuño, A., Cid-Sabatel, R., Barbero, J., García-Dasí, M. (2017). Life experience of the adult and ageing patient with haemophilia. Practical aspects for psychological support. *Vox Sanguinis*, *112*(4), 301-309. https://doi.org/10.1111/vox.12501

5. Benemei, S., Boni, L., Castaman, G. (2024). Outcome measures in hemophilia: current and future perspectives. *Expert Review of Hematology*, *17*(7), 329-340. https://doi.org/10.1080/17474086.2024.2365929

6. Remor, E., Arranz, P., Quintana, M., Villar, A., Jimenez-Yuste, V., Diaz, J. L., Hemofilia-QoL Project Group. (2005). Psychometric field study of the new haemophilia quality of life questionnaire for adults: the 'Hemofilia-QoL'. *Haemophilia*, *11*(6), 603-610. https://doi.org/10.1111/j.1365-2516.2005.01144.x

7. Xu, R. H., Dong, D., Luo, N., Wong, E. L. Y., Yang, R., Liu, J., Zhang, S. (2022). Mapping the Haem-A-QoL to the EQ-5D-5L in patients with hemophilia. *Quality of Life Research*, *31*(5), 1533-1544. https://doi.org/10.1007/s11136-021-03051-5

8. Von Mackensen, S., Bullinger, M., Haemo-QoL Group. (2004). Development and testing of an instrument to assess the Quality of Life of Children with Haemophilia in Europe (Haemo-QoL). *Haemophilia*, *10*, 17-25. https://doi.org/10.1111/j.1355-0691.2004.00875.x

9. Guran, C., Ioniţă, H. M., Haţegan, M. G., Ioniţă, I., Trăilă, A., Ilie, A. M. (2022). A Perspective on the Quality of Life of Hemophilia A Patients in Romania—A Study on 100 Patients. *Journal of Vascular Diseases*, *1*(2), 105-112. https://doi.org/10.3390/jvd1020012

10. Cruchinho, P., López-Franco, M. D., Capelas, M. L., Almeida, S., Bennett, P. M., Miranda da Silva, M., Gaspar, F. (2024). Translation, cross-cultural adaptation, and validation of measurement instruments: A practical guideline for novice researchers. *Journal of Multidisciplinary Healthcare*, 2701-2728. https://doi.org/10.2147/JMDH.S419714

11. Adamson, K. A., Prion, S. (2013). Reliability: measuring internal consistency using Cronbach's α. *Clinical simulation in Nursing*, *9*(5), e179-e180. https://doi.org/10.1016/j.ecns.2012.12.001

Гемофилиямен ауыратын пациенттердің өмір сапасын бағалау сауалнамасын Қазақстан Республикасында бейімдеу және бағалау

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Түйіндеме

Кіріспе. Гемофилия-пациенттердің физикалық, эмоционалдық және әлеуметтік жұмысына айтарлықтай әсер ететін созылмалы тұқым қуалайтын ауру болып табылады. Қазіргі терапия жағдайында өмір сапасын бағалау маңызды пациентке бағытталған нәтиже ретінде қарастырылады. Осы көрсеткіштерді объективті бағалау үшін мақсатты популяцияның тілдік және мәдени ерекшеліктеріне бейімделген валидацияланған нозологиялық-спецификалық құралдар қажет.

Зерттеудің мақсаты. Қазақстан Республикасында гемофилиямен ауыратын ересек пациенттерде қолдануға арналған A36 Hemofilia Quality of Life сауалнамасының орыс тіліндегі нұсқасын лингвистикалық бейімдеу және психометриялық валидациялау жүргізу.

Әдістері. Тікелей және кері аударма, сараптамалық бағалау және пилоттық тестілеу рәсімдерін пайдалана отырып әдіснамалық зерттеу жүргізілді. Зерттеуге Гемофилиямен ауыратын 30 ересек пациент кіреді. Зерттеуге жеңіл, орташа немесе ауыр дәрежедегі А немесе В гемофилиясы бар 30 ересек пациент қатысты Ішкі келісу жалпы шкала мен жекелеген домендер үшін альфа Кронбах коэффициентін пайдалана отырып бағаланды. Құрылымдық жарамдылық көлбеу айналмалы эксплораторлық факторлық талдау әдісімен талданды. Деректерді статистикалық өңдеу IBM SPSS Statistics 28.0 нұсқасының бағдарламалық жасақтамасын қолдану арқылы жүзеге асырылды.

Нәтижесі. Сауалнаманың орыс тіліндегі нұсқасы түпнұсқаға тұжырымдамалық эквиваленттілікті және пациенттер үшін жақсы қабылдауды көрсетті. Бірқатар ішкі шкалалар үшін ішкі келісімділіктің жоғары немесе қолайлы көрсеткіштері алынды, ал жекелеген домендер бойынша іріктеменің клиникалық гетерогенділігіне және зерттеудің пилоттық сипатына байланысты болатын Кронбах альфа коэффициентінің төмен мәндері анықталды. Эксплораторлық факторлық талдау Гемофилиямен ауыратын науқастардың өмір сапасының физикалық, функционалдық, эмоционалдық және әлеуметтік аспектілерін көрсететін сауалнаманың жалпы қанағаттанарлық факторлық құрылымын растады.

Қорытынды. A36hemofilia Quality of Life сауалнамасының орыс тіліндегі нұсқасы Қазақстан Республикасында Гемофилиямен ауыратын ересек пациенттердің өмір сүру сапасын бағалаудың перспективалы мамандандырылған құралы болып табылады. Құралдың психометриялық қасиеттерін түпкілікті растау үшін кеңейтілген үлгідегі қосымша зерттеулер қажет.

Түйін сөздер: гемофилия, өмір сапасы, сауалнама, валидация, A36Hemofilia-QoL.

Оценка и адаптация опросника для оценки качества жизни пациентов с гемофилией в Республике Казахстан

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Резюме

Введение. Гемофилия является хроническим наследственным заболеванием, существенно влияющим на физическое, эмоциональное и социальное функционирование пациентов. В условиях современной терапии оценка качества жизни рассматривается как важный пациент-ориентированный исход. Для объективной оценки данных показателей необходимы валидированные нозологически-специфические инструменты, адаптированные к языковым и культурным особенностям целевой популяции.

Цель исследования. Проведение лингвистической адаптации и психометрической валидации русскоязычной версии опросника A36Hemofilia Quality of Life для использования у взрослых пациентов с гемофилией в Республике Казахстан

Методы. Проведено методологическое исследование с использованием процедуры прямого и обратного перевода, экспертной оценки и пилотного тестирования. В исследование включены 30 взрослых пациентов с гемофилией. В исследование были включены 30 взрослых пациентов с гемофилией А или В лёгкой, средней или тяжёлой степени. Внутренняя согласованность оценивалась с использованием коэффициента альфа Кронбаха для общей шкалы и отдельных доменов. Конструктивная валидность анализировалась методом эксплораторного факторного анализа с наклонным вращением. Статистическая обработка данных проводилась с использованием программного обеспечения IBM SPSS Statistics версии 28.0.

Результаты. Русскоязычная версия опросника продемонстрировала концептуальную эквивалентность оригиналу и хорошую приемлемость для пациентов. Для ряда подшкал были получены высокие или приемлемые показатели внутренней согласованности, тогда как по отдельным доменам выявлены низкие значения коэффициента альфа Кронбаха, что может быть связано с клинической гетерогенностью выборки и пилотным характером исследования. Эксплораторный факторный анализ подтвердил в целом удовлетворительную факторную структуру опросника, отражающую физические, функциональные, эмоциональные и социальные аспекты качества жизни пациентов с гемофилией.

Выводы. Русскоязычная версия опросника A36Hemofilia Quality of Life является перспективным специализированным инструментом для оценки качества жизни взрослых пациентов с гемофилией в Республике Казахстан. Для окончательного подтверждения психометрических свойств инструмента необходимы дальнейшие исследования с расширенной выборкой.

Ключевые слова: гемофилия, качество жизни, опросник, валидация, A36Hemofilia-QoL.

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International Experience in Gender Education for Medical Professionals as a Tool to Combat Gender-Based Violence: Implementation Opportunities in Kazakhstan

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Abstract

In the introduction, gender-based violence is examined as one of the most pressing public health and human rights challenges of the twenty-first century, associated with substantial physical, psychological, reproductive, and social consequences for women. The health-care system occupies a critical position in responding to this problem, as women exposed to violence frequently seek medical care for both acute injuries and chronic health conditions. Consequently, medical professionals are uniquely positioned to identify violence, provide first-line support, and facilitate access to appropriate services. However, this potential can only be realized if health-care providers possess adequate knowledge, skills, and professional attitudes, which are not systematically embedded in medical education curricula in many countries, including the Republic of Kazakhstan.

The object of this study is the system of training medical professionals to respond to gender-based violence in international and national contexts. The objective of the study is to systematically analyze international evidence on educational programs designed to prepare medical professionals to respond to gender-based violence, to assess their effectiveness, and to evaluate the relevance and adaptability of evidence-based models for integration into the medical education system of Kazakhstan.

The study employed an analytical design based on a scoping review approach. Publications indexed in major international bibliographic databases, as well as reports, guidelines, and training materials produced by international organizations, were reviewed. A total of twenty-six sources describing educational interventions for medical students and health-care professionals were included in the analysis. In

addition, national survey data on violence against women, forensic medical statistics, regional sociological studies, and publicly available medical curricula were examined to characterize the Kazakhstan context.

The results demonstrate that the most effective training programs share several common characteristics. These include multidimensional content addressing gender-based violence as a public health and human rights issue, the use of interactive and experiential pedagogical methods such as simulations, standardized patients, and case-based learning, and institutional integration into existing medical education structures. Such programs are consistently associated with improvements in knowledge, professional attitudes, and readiness to respond to violence, as well as with increased screening and documentation in clinical practice. Analysis of the Kazakhstan context reveals a high prevalence and low disclosure of gender-based violence, alongside fragmented educational coverage and limited institutional training capacity.

In conclusion, the findings indicate that integrating gender-based violence response training into medical education represents an evidence-based and strategically important direction for strengthening the capacity of the health-care system in the Republic of Kazakhstan. Adaptation of internationally validated models, combined with contextual sensitivity and institutional support, may contribute to more effective and sustainable health sector responses to gender-based violence.

Key words: gender-based violence, domestic violence, medical education, health personnel, professional training, public health.

1. Introduction

Gender-based violence constitutes one of the most significant public health challenges of the twenty-first century, affecting approximately one in three women worldwide over the course of their lifetime, according to estimates by the World Health Organization. This phenomenon extends far beyond individual tragedies, representing a systemic violation of human rights with profound consequences for physical and mental health, social well-being, and economic development at the levels of families, communities, and entire nations. The medico-social consequences of gender-based violence encompass a wide spectrum of acute and chronic conditions, including traumatic injuries of varying severity, sexually transmitted infections and HIV, unintended pregnancies and unsafe abortions, chronic pelvic pain and gynecological disorders, post-traumatic stress disorder, depression, anxiety disorders, substance use disorders, and an increased risk of suicidal behavior. The World Health Organization emphasizes that differences in health outcomes between women and men result from a "combination of biological characteristics and socially constructed roles, norms, and power relations" [1, p. 5].

In the context of the Republic of Kazakhstan, the problem of gender-based violence acquires particular relevance, as evidenced by national surveys, forensic medical studies, and regional sociological research. These data indicate a substantial prevalence of various forms of violence against women, high levels of underreporting, and a pronounced gap between the scale of the problem and the use of institutional support services. Sociocultural norms, stigma, fear of consequences, and limited awareness of available services create a complex environment in which violence frequently remains

concealed, despite regular interactions between survivors and the healthcare system.

Healthcare professionals occupy a unique position at the intersection of health care and social protection and, in many cases, represent the first—and sometimes the only—professional point of contact for women experiencing violence. International studies demonstrate that such patients seek medical care not only for acute injuries, but also for chronic somatic conditions, reproductive health problems, and psychoemotional disorders. Consequently, the healthcare system possesses substantial potential for early identification, initial support, and referral of women subjected to violence, provided that healthcare professionals have the requisite knowledge, skills, and professional attitudes.

However, the realization of this potential in many countries is constrained by insufficient integration of a gender perspective and violence response training within medical education curricula. Research indicates that, in the absence of targeted training, healthcare professionals often experience difficulties initiating conversations about violence, fear causing harm to patients, lack confidence in interpreting disclosed information, and frequently do not have clear algorithms for subsequent action. Preliminary analytical reviews and expert assessments suggest that these challenges are also characteristic of the Kazakhstani context, where preparation of healthcare professionals to respond to gender-based violence remains fragmented and unsystematic.

International experience over the past two decades demonstrates that structured gender education for healthcare professionals constitutes an evidence-based strategy for improving the identification, documentation, and response to cases of violence. Programs implemented in the United States, Canada, Australia, countries of the European Union, South Asia, and Africa indicate that integrating a gender perspective into existing disciplines, employing interactive and experiential learning methods, developing communication and empathy skills, and providing training on clinical protocols and intersectoral referral pathways contribute to increased preparedness of healthcare professionals and to meaningful transformations in clinical practice. Leading international organizations, including the World Health Organization, have consistently promoted the integration of gender and human rights dimensions into both pre-service and in-service training of health personnel.

In Kazakhstan, the importance of this issue is further reinforced by institutional changes in the field of prevention and response to domestic violence, the expansion of the role of healthcare professionals in case documentation and intersectoral collaboration, and ongoing discussions regarding international commitments related to the protection of women's rights. Under these conditions, a systematic analysis of international experience in gender education for healthcare professionals and an assessment of the possibilities for its adaptation to the national context acquire particular scientific and practical significance.

The objective of this study is to systematically analyze international experience with gender education programs for healthcare professionals as a tool for addressing gender-based violence, to assess the effectiveness of different models and approaches, to identify key success factors and implementation barriers, and to determine the potential and strategies for adapting evidence-based educational models to the system of medical education and healthcare practice in the Republic of Kazakhstan.

2. Materials and methods

This study was conducted as a narrative review with elements of a scoping review and aimed to systematically synthesize international experience in integrating training for healthcare professionals on responding to gender-based violence, as well as to assess the feasibility of adapting identified approaches to the system of medical education in the Republic of Kazakhstan. The methodological framework of the

review was guided by the PRISMA recommendations for scoping reviews.

A comprehensive literature search was performed in the international bibliographic databases PubMed, Scopus, and Web of Science, as well as among publications and policy documents issued by international organizations, including the World Health Organization and the United Nations Population Fund. In addition, grey literature was examined, comprising program descriptions, evaluation reports, and other non–peer-reviewed materials relevant to the topic. The search was conducted without language restrictions.

Eligibility criteria included publications describing educational programs or training interventions for healthcare professionals or medical students focused on the identification and management of cases of gender-based violence and reporting educational, attitudinal, or practice-related outcomes. A total of twenty-six sources were included in the final analysis, representing nine countries and regional contexts, as well as global guidelines and evidence syntheses.

To examine the Kazakhstani context, data from national surveys on violence against women, forensic medical statistics, regional sociological studies, and regulatory documents were analyzed, together with publicly available curricula and course descriptions from medical universities. Data analysis followed a descriptive and synthetic approach and was aimed at identifying recurring educational models and key components of effective training programs.

The study relied exclusively on the analysis of published and publicly accessible sources and did not involve the collection of primary data. Accordingly, separate ethical approval was not required.

3. Results

3.1. Analysis of successful programs from different regions of the world

An international review of training programs for healthcare professionals on responding to violence against women, including studies from countries with well-developed healthcare systems, shows that the most effective models combine short lecture-based components with interactive methods (role-playing, simulation scenarios, work with standardized patients), rely on clearly defined clinical protocols and intersectoral algorithms, and are embedded within existing systems of training and accreditation for healthcare professionals.

A systematic review by N. Kalra and colleagues [2], including 19 studies from high- and middle-income countries (the United States, Australia, Iran, Mexico, Turkey, and the Netherlands), demonstrated that structured educational interventions for healthcare professionals (lecture modules combined with role-playing, simulations, and work with standardized patients) lead to significant improvements in attitudes, knowledge about intimate partner violence, and self-assessed readiness to respond among physicians and nurses working in primary care and hospital settings. In a number of studies included in the review, practice-related outcomes were also assessed: following the implementation of programs based on clinical algorithms and intersectoral pathways (safeguarding/domestic abuse pathways), the frequency of routine screening for violence and documentation of cases in medical records increased compared to baseline levels. This indicates real changes in the clinical behavior of healthcare professionals and confirms the potential of such programs to strengthen the systemic role of the healthcare sector in responding to gender-based violence.

In the United States, a range of training programs for healthcare professionals on responding to intimate partner violence has emerged in recent years, combining face-to-face training, simulations, and electronic learning. One example is the mPOWERED Electronic Learning System, a structured online course for nurses and other clinicians aimed at developing knowledge, confidence, and practical skills in screening, empathetic inquiry, and referral of women experiencing violence to specialized services [3]. The study showed that completion of the

module led to a significant increase in subjective preparedness and willingness to discuss violence with patients, as well as improvements in knowledge of response protocols and algorithms. Additional programs in the United States include short introductory sessions on screening and counseling, residency curricula involving experts from shelters, and the use of standardized female patients to practice communication scenarios. Taken together, these approaches contribute to the integration of responses to intimate partner violence into routine clinical practice across different levels of healthcare delivery.

In Canada, the EDUCATE program (Education in Domestic Violence for Residents and Clinicians Across Toronto East), developed at the University of Toronto and implemented in three affiliated hospitals, represents a strategically important example of the systematic integration of responses to intimate partner violence into obstetrics and gynecology residency training [4]. The program demonstrates that a targeted 12-hour educational intervention, distributed over the course of one year and based on the Prochaska–DiClemente stages-of-change model, a trauma-informed approach, and the CanMEDS competency framework, can not only expand knowledge and skills but also sustainably transform the clinical behavior of future specialists. The high level of interactivity of the program (standardized patients, role-play of scenarios, analysis of video recordings, collaboration with multidisciplinary teams and shelters) enabled residents not merely to "know about the problem," but to learn how to conduct difficult conversations safely and empathetically, plan subsequent steps, and document cases in ways that genuinely enhance the protection of women. The significance of EDUCATE is underscored by the fact that statistically significant improvements in knowledge and readiness to respond were maintained 12 months after completion of the training, and participants reported that the program helped them overcome feelings of helplessness when encountering violence and provided concrete tools for clinical practice. Thus, EDUCATE illustrates that well-designed training can bridge the critical gap between the rhetoric of the "role of healthcare in combating violence" and the actual competencies of frontline physicians.

While North American programs demonstrate the potential of deeply integrated and institutionally supported curricula, in the Asia–Pacific region attention is increasingly shifting toward adapting similar models to the conditions of countries with limited resources and pronounced sociocultural barriers.

In Australia, the Healthy Relationships Training program has been developed and implemented within the WEAVE project, targeting general practitioners. A pre–post analysis conducted by Felicity Young and colleagues (2024) showed that participation in this program led to significant increases in knowledge, practical skills, and confidence among physicians in counseling women experiencing intimate partner violence, including the ability to raise the topic of violence, provide supportive counseling, and discuss options for seeking help [5]. The training includes interactive components and work with clinical scenarios adapted to the Australian context, and the authors emphasize that integration of this training into general practice education is a key condition for sustainable changes in clinical practice.

In Aotearoa (New Zealand), the "Atawhai" initiative has been developed as a primary healthcare provider–led response to family violence, integrating culturally safe practices and Māori worldviews on well-being and healing. Thus, the program demonstrates that training of healthcare professionals can simultaneously strengthen clinical competencies and support the rights of Indigenous peoples when it is originally designed with consideration of local knowledge systems and values [6]. In the Pacific region, the Pasifika Veilomani pilot online project, which involved healthcare workers from nine island states, showed that even under significant technical constraints, a distance-learning format can increase professionals' confidence in working with gender-based and family violence and stimulate critical reflection on their own practice, opening important opportunities for scaling up training in resource-limited and geographically isolated contexts [7].

In the European Union, the research and innovation project IMPRODOVA (Improving Frontline

Responses to High Impact Domestic Violence) is being implemented with the participation of a group of experienced researchers and practitioners from eight countries: Austria, Finland, France, Germany, Hungary, Portugal, Slovenia, and the United Kingdom (Scotland) [8]. The project aims to propose comprehensive solutions for combating high-impact domestic violence based on in-depth empirical research on how police and other frontline professionals (including healthcare and social workers) respond to domestic violence in European countries. Within the framework of the project, specialized training modules have been developed for different medical specialties (gynecology/obstetrics, emergency medicine, dentistry, pediatrics). The program includes medical assessment, documentation of evidence, and discipline-specific competencies. Such differentiated approaches allow adaptation of content to the specific clinical situations encountered by different categories of healthcare professionals.

In Spain, a specialized 10-hour training program was developed for emergency and urgent care professionals, aimed at increasing their readiness to work with cases of gender-based violence. The course is built around problem-oriented video materials that simulate real clinical situations and includes discussion of scenarios, analysis of typical errors, and practice of algorithms for identification, initial support, documentation, and referral of survivors. The format combines online components with face-to-face interactive elements, making it possible to adapt training to the demanding schedules of emergency service workers without reducing the depth of content.

The effectiveness of this program was evaluated in a quasi-experimental study by Adánez-Martínez et al. (2025), comparing indicators before and after participation in the training. The authors showed that, following the course, healthcare professionals demonstrated substantial improvements in knowledge of the signs and dynamics of gender-based violence, awareness of existing protocols, confidence in their own skills in managing such cases, and subjective readiness to raise the issue of violence with patients and accurately document information in medical records. The study emphasizes that even a relatively brief but contextually tailored program can significantly improve the quality of the healthcare system's response to gender-based violence in one of its most critical segments [9].

Ukraine, operating under conditions of armed conflict, adapted the WHO Global Guidelines on the clinical management of rape to the national context with technical support from the World Health Organization. Within this initiative, 443 primary healthcare workers were trained, revealing substantial gaps in knowledge of legal protocols, awareness of available resources, and understanding of best practices in organizing services for survivors of sexual violence [10]. This experience demonstrates that even in the context of an acute humanitarian crisis, systematic training of healthcare professionals remains a critically important element of the response to gender-based and sexual violence and can be effectively implemented in parallel with the provision of emergency care.

On the African continent, training programs for healthcare professionals and other specialists on gender-based and domestic violence are developing under conditions of simultaneously high needs and limited resources, making the region's experience particularly illustrative for countries facing similar challenges.

In Kenya, multiyear intersectoral training programs (2012–2018) were implemented, involving medical, legal, and law enforcement professionals and using standardized patients and objective structured clinical examinations (OSCEs) as key tools for assessing competencies [11]. This indicates that training was structured not only around lectures, but also around practical rehearsal of scenarios with "patient-actors," allowing evaluation of how professionals actually ask questions, respond to disclosures of violence, document information, and interact with other services. This approach is important in that it brings training closer to real practice and simultaneously establishes a shared language and algorithms across different sectors—healthcare, police, and the judicial system.

In Tanzania, studies have shown that without specially designed training programs, healthcare professionals face serious limitations in identifying and managing cases of domestic violence [12]. These

limitations include not only a lack of knowledge about indicators of violence and response algorithms, but also uncertainty, fear of "harming" the patient by asking inappropriate questions, and lack of clarity regarding where and how to refer survivors. These deficits are particularly critical in contexts with high HIV prevalence among women, where gender-based violence acts as an additional stressor, undermining treatment adherence, exacerbating mental health problems, and increasing the risk of revictimization. Under such conditions, systematic training of healthcare professionals becomes not merely "desirable," but a structural component of effective HIV and reproductive health programs.

In Nigeria, the Ipas program plays an important role, targeting humanitarian workers and medical personnel working with women and girls who have experienced sexual violence in contexts of conflict, displacement, and humanitarian crises [13]. The training includes not only the fundamentals of trauma-informed care and ethics in working with survivors, but also highly specific clinical competencies, such as techniques for safe abortion, postabortion care, infection prevention, and psychological support. This is critically important in contexts where sexual violence coincides with limited access to reproductive health services and high levels of stigma, and where any error by a healthcare professional may exacerbate trauma or place a woman at additional risk.

In Burkina Faso, where a substantial proportion of the population lives in conditions of forced displacement, studies have identified multiple barriers to providing care for survivors of gender-based violence, ranging from geographic inaccessibility of services and shortages of trained personnel to fear of reprisals, distrust of institutions, and cultural norms that inhibit disclosure [14]. These findings underscore that training for humanitarian contexts cannot be limited to general lectures on women's rights; rather, programs are needed that are adapted to the realities of camps and temporary settlements, take into account linguistic, cultural, and gender dynamics, and build bridges among healthcare providers, nongovernmental organizations, community leaders, and international organizations. Such a comprehensive, context-sensitive approach to training becomes a key condition for ensuring that systems of care are not merely formal, but genuinely accessible and safe for survivors of violence.

Following the analysis of African initiatives implemented under conditions of conflict, humanitarian crises, and limited resources, it is particularly instructive to turn to the experience of South Asian countries, where efforts have been made to institutionalize training within national hospitals and global clinical guidelines. The "Gender in Medical Education" (GME) project, implemented between 2007 and 2012 in the state of Maharashtra, became one of the largest initiatives to integrate a gender perspective into medical education in low- and middle-income countries, covering seven medical colleges [15]. Its key feature was the embedding of gender content into existing disciplines (obstetrics and gynecology, public health, internal medicine, psychiatry, forensic medicine), rather than the creation of a separate course, which enhanced the sustainability and scalability of changes. Curricula were reviewed for stereotypes and "blind spots," and modules were enriched with topics such as violence during pregnancy, reproductive rights, and social determinants of health. The pedagogical approach relied on interactive methods and faculty development, and evaluation using the Gender Attitude Scale showed statistically significant improvements in students' gender attitudes across all disciplines ($p<0.05$), increased recognition of gender-based violence as a health issue, and greater readiness to raise this topic in clinical practice when institutional support was available.

In addition, a five-day cascade training program based on the WHO guideline "Caring for Women Subjected to Violence," adapted to the Indian context, was implemented in three tertiary-level hospitals in India. Trained facilitators subsequently trained medical staff in the identification and management of cases of violence. The study demonstrated that such training substantially improved healthcare professionals' understanding of violence against women as a health issue, increased levels of empathy, and enhanced interpersonal communication skills and supportive interactions with patients [16].

Among regional studies from low- and middle-income countries, the HERA project (Healthcare Responding to Violence and Abuse), implemented in

Brazil, Nepal, Sri Lanka, and the occupied Palestinian territories (Table 1), deserves particular attention. Research conducted by the London School of Hygiene and Tropical Medicine describes a multicenter intervention aimed at improving the healthcare system's response to domestic violence in low- and middle-income countries. The intervention included training healthcare professionals to identify and respond to cases of domestic violence, with an emphasis on a woman-centered and structurally integrated approach. Key outcomes included improved detection of domestic violence cases and enhanced professional expertise, with healthcare workers reporting increased confidence, readiness to identify, support, and refer survivors of violence. The training focused on developing empathy, nonjudgmental inquiry techniques, skills in first-line support, and subsequent case management. The project also involved the development of new detection and referral protocols, and training materials were adapted to the specific context of each country.

Table 1 - Changes in Detection of Gender-Based Violence Following Implementation of HERA and Comparable Healthcare Training Initiatives

Country	Key Outcomes of HERA and Similar Initiatives	Increase in Detection	Features of Change
Brazil	Significant improvement in the identification of cases of violence; introduction of new protocols and empathy training	+78%	Development of new training materials; expansion of the program to various regions
Nepal	Substantial increase in detection; introduction of structured approaches and new support methods	+100%	Adaptation of training to pandemic conditions; enhanced confidence of healthcare professionals
Sri Lanka	Improved skills in identification and support for victims of domestic violence; updated referral protocols	+69%	Practical integration into the healthcare system; training of multidisciplinary teams

The HERA project data demonstrate impressive results across different countries: in Brazil, the detection of cases of violence increased by 78%, in Nepal by 100%, and in Sri Lanka by 69% [17]. These findings clearly illustrate the potential of structured educational programs for healthcare professionals in the context of developing countries.

Alongside national programs, global training packages play an important role in setting standards for preparing healthcare workers to respond to gender-based violence. The UNFPA MGBViE (Managing Gender-Based Violence in Emergencies) project offers a three-phase training model (e-learning, a 7–8-day face-to-face training, and subsequent mentoring), designed for humanitarian settings and available in four languages, which ensures broad applicability across regions. The WHO/PAHO course Response to Violence Against Women and Girls and the WHO clinical guideline Caring for women subjected to violence serve as the foundation for national training programs, providing standardized modules on screening, first-line support, clinical management, and referral of survivors, including specialized courses on the clinical management of rape in humanitarian contexts. Taken together, these resources form a global framework that countries can draw upon when developing and adapting their own training programs for healthcare professionals.

Thus, the analysis of international experience demonstrates the existence of several core models of

gender education for healthcare professionals, adapted to local contexts.

3.2 The Kazakhstan Context

To analyze the Kazakhstan context, data from national surveys on violence against women, forensic medical statistics, regional sociological studies, as well as regulatory and programmatic documents in the fields of healthcare and medical education were used. The data obtained make it possible to characterize the scale of gender-based violence (GBV), the level of its institutional detection, and the current state of readiness of the healthcare system.

The results of the National Sample Survey on Violence against Women (n = 14,342; age 18–75 years) indicate a significant prevalence of various forms of GBV in the Republic of Kazakhstan [18]. According to the survey data, 17% of women who had ever been in an intimate partnership experienced physical or sexual violence by an intimate partner during their lifetime; 21% reported psychological violence, and 7% reported economic control by a partner. Marked regional variability was observed: in certain regions, the lifetime prevalence of physical and/or sexual violence reaches 19–31%. Forensic medical data summarized by Mussabekova et al. for the period 2019–2022 complement the survey findings and indicate pronounced gender asymmetry among victims of domestic violence, with women accounting for 77.9–91% of all registered survivors [19]. At the same time, approximately 78% of cases are recurrent, reflecting the chronic nature of violence.

Despite the high prevalence of GBV, the level of institutional help-seeking remains extremely low. According to the national survey, only 1.1% of women who experienced violence sought help from law enforcement agencies, while 51% did not disclose their experience to anyone [18]. These indicators point to high latency of gender-based violence and limited visibility of the problem in official statistics. Regional studies confirm this trend and allow for a more detailed understanding of barriers to help-seeking. In a study conducted in Turkistan Region (n = 24,621), the main barriers were fear of possible consequences (58.4%), feelings of shame and social stigmatization (46.9%), and distrust in the effectiveness of the institutional support system (34.1%) [20]. More than half of respondents indicated insufficient awareness of available support services; in rural areas, the level of awareness was below 40%, and willingness to seek help even when information was available did not exceed 8.6%.

Analysis of available data indicates that women experiencing GBV regularly interact with the healthcare system for various clinical reasons, including visits related to acute injuries, chronic somatic conditions, reproductive health disorders, and psycho-emotional disturbances. Under conditions of high latency, medical institutions often become the only institutional point of contact for survivors, even when the formal reason for seeking care is not directly related to a violent episode.

In recent years, institutional steps aimed at formalizing the medical response to gender-based violence have been recorded in Kazakhstan. In 2020, the first clinical protocol for the provision of medical care to patients affected by gender-based violence was approved, regulating procedures for identification, initial assessment, management, and documentation of cases in medical organizations [21]. The protocol was developed based on World Health Organization recommendations and adapted to the structure of the national healthcare system. An additional component was the implementation of an online course for primary healthcare workers, developed by the Ministry of Health of the Republic of Kazakhstan in collaboration with UNFPA. The course is available in Kazakh and Russian and is aimed at developing basic knowledge and skills for providing medical care to GBV survivors; by 2021, more than 40 healthcare workers from Shymkent and Turkistan Region had completed the training. Taken together, these initiatives demonstrate the existence of individual mechanisms for introducing training; however, their coverage remains limited.

An analysis of medical university curricula, based on a review of publicly available study plans, course descriptions, and national textbooks, revealed fragmented inclusion of GBV-related content in core medical disciplines. In obstetrics and gynecology, violence is mentioned mainly in the context of injuries during pregnancy, without systematic consideration of

prevalence, identification, and comprehensive clinical response. In forensic medicine, primary attention is paid to documentation of bodily injuries from a legal perspective, while clinical and psychosocial aspects of support are minimally represented. Disciplines such as public health, psychiatry, and internal medicine generally do not integrate GBV content, despite its proven impact on mental health and chronic somatic conditions. Additionally, some educational materials contain elements of gender bias, including stereotypical representations of gender roles and elements of victim blaming. According to preliminary studies and expert surveys, medical students and practicing physicians report insufficient preparedness to work with GBV cases, difficulties in initiating relevant questions, and uncertainty regarding further clinical actions after disclosure of violence.

Separate pilot initiatives indicate the potential of innovative solutions in the prevention of gender-based violence. For example, the UMAI-WINGS project implemented in 2024 demonstrated a 23% reduction in the prevalence of psychological violence among study participants [22]. At the same time, such initiatives have not yet been integrated into the system of medical education and clinical practice at the institutional level.

Overall, the results characterize the Kazakhstan context as a combination of high prevalence and latency of gender-based violence, limited institutional detection, and fragmented educational readiness of the healthcare system to respond.

3.3 Key Components of Effective Cender Education Programs for Healthcare Professionals

The synthesis of the gender education programs for healthcare professionals included in the review made it possible to identify a recurring set of components associated with positive educational outcomes. Despite differences in geographic, institutional, and sociocultural contexts, most of the analyzed initiatives demonstrated similar structural and pedagogical characteristics, allowing them to be considered common elements of effective educational models.

Across all programs that demonstrated significant improvements in knowledge, attitudes, and readiness to respond to gender-based violence, the training content was multidimensional in nature. It combined conceptual understandings of gender-based violence as a public health and human rights issue, epidemiological data on the prevalence and forms of violence, clinical aspects of case identification and management, ethical and legal frameworks for care provision, as well as elements of reflection on professional attitudes and potential biases. This approach ensured simultaneous influence on the cognitive, affective, and behavioral levels of healthcare professional training.

Pedagogical analysis of the included programs showed that initiatives based on interactive and experiential learning methods were consistently associated with more pronounced educational effects compared with programs relying predominantly on lecture-based formats. In most effective interventions, a similar set of pedagogical practices was employed, including work with standardized patients, role-playing and simulation of clinical scenarios, analysis of clinical cases, small-group discussions, structured reflective assignments, the use of multimedia materials, and elements of community engagement. As schematically presented in Figure 1, these methods formed a coherent cluster of experiential learning aimed at developing communication and empathy skills and increasing healthcare professionals' confidence in initiating and conducting sensitive conversations about gender-based violence with patients.

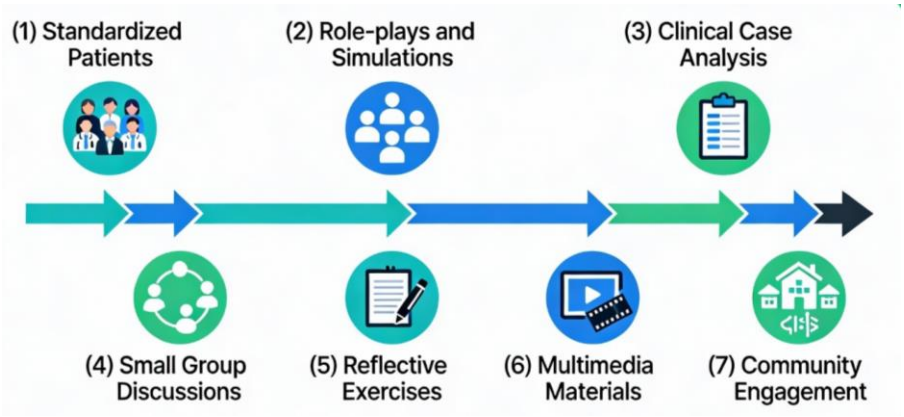

Figure 1 - Interactive and Experiential Pedagogical Methods Most Commonly Used in Effective Gender Education Programs for Healthcare Professionals

Organizational analysis showed that sustained educational effects were more often observed in programs integrated into existing curricula and clinical training, rather than those implemented as fragmented or elective courses. The integration of gender-related content into core medical disciplines made it possible to demonstrate its relevance across different areas of clinical practice and reduced the risk of marginalizing the topic. An additional factor contributing to sustainability was the presence of institutional support, including the involvement of program leadership, faculty development, and the availability of clinical protocols and algorithms that facilitate the application of acquired knowledge in practice.

Many of the analyzed programs highlighted the importance of multidisciplinary and intersectoral collaboration. Effective training models included cooperation between healthcare professionals and social services, non-governmental organizations, psychologists, and legal professionals, which broadened healthcare providers' understanding of the ecosystem of support for survivors of violence and contributed to the development of realistic referral skills to available support resources.

Finally, the analysis showed that programs adapted to the local sociocultural context generally demonstrated higher acceptability and participant engagement. Such adaptation included the use of local epidemiological data, clinical vignettes reflecting the context of a specific country or region, and consideration of cultural norms and barriers influencing disclosure of violence and help-seeking behaviors.

Taken together, the results of the synthesis indicate that the effectiveness of gender education for healthcare professionals is determined not by individual components in isolation, but by a combination of content-related, pedagogical, and organizational elements implemented in an institutionally supported and contextually adapted manner.

4. Discussion

The results of the present review study confirm that structured gender education for healthcare professionals represents a reproducible and evidence-based strategy for strengthening the role of the healthcare system in responding to gender-based violence. The analysis of programs implemented across diverse geographic and sociocultural contexts demonstrates consistent patterns of improvement in knowledge, professional attitudes, and subjective readiness of healthcare professionals to identify and manage cases of violence. Despite variations in format, duration, and institutional settings, effective initiatives are characterized by a similar combination of content-related, pedagogical, and organizational elements.

The findings are consistent with the results of the systematic review by Kalra et al., which showed that structured educational interventions are associated with significant improvements in healthcare workers' knowledge and attitudes, and in some studies with increased rates of routine screening and documentation of violence. Similarly, in North American and European programs, including EDUCATE and the IMPRODOVA project, the integration of training into clinical education with an emphasis on practical skill development and the use of clinical algorithms emerged as a key factor of effectiveness. These data support the conclusion that training embedded in the professional context and supported by institutional mechanisms has a higher potential for sustainable change than fragmented or elective courses.

The results of the pedagogical analysis are particularly important, as they highlight the advantages of interactive and experiential learning methods. The use of simulation scenarios, standardized patients, role-playing, and clinical case analysis enables the development not only of cognitive knowledge but also of communication and empathy skills that are essential for addressing the sensitive and highly stigmatized issue of violence. These conclusions are consistent with evidence from the EDUCATE and HERA programs, as well as from intersectoral initiatives in Africa, where experiential approaches were identified as a key mechanism for transforming clinical behavior rather than merely increasing awareness.

Evidence from studies conducted in low- and middle-income countries, as well as in humanitarian and crisis settings, further complements the overall picture and points to the high adaptability of educational models. Experience from India, African countries, and the HERA project demonstrates that even in resource-constrained environments, training healthcare professionals can lead to increased detection of violence and greater professional confidence, provided that the content is contextually adapted and referral pathways are available. These findings extend the applicability of the present review and confirm that the effectiveness of gender education is determined not by the level of available resources, but by the quality of integration and contextual relevance of the intervention.

At the same time, the analysis reveals substantial limitations in the existing evidence base. The majority of included studies focus on proximal educational outcomes—knowledge, attitudes, and self-assessed readiness—while data on actual changes in clinical practice and, in particular, on patient-level outcomes remain limited. This gap reflects methodological and ethical challenges in evaluating educational interventions in the field of gender-based violence, including the need for longitudinal follow-up, the use of objective measurement methods, and the protection of vulnerable populations. Therefore, the effectiveness of programs should be interpreted with the understanding that improved healthcare worker competencies constitute a necessary but insufficient condition for achieving systemic impacts on levels of violence and women's well-being.

The findings related to the Kazakhstani context underscore the relevance of the conclusions drawn from the international review. The high prevalence and latency of gender-based violence, combined with the limited educational preparedness of the healthcare system, create a situation in which medical institutions often serve as the only institutional point of contact for survivors. Despite the existence of a clinical protocol and isolated training initiatives, the fragmented integration of gender-based violence topics into medical education constrains the healthcare system's capacity for identification and first-line support. In this context, the international models identified in this study provide a relevant foundation for the further development of healthcare professional training in Kazakhstan.

A key strength of this study lies in the use of a scoping review design, which enabled the inclusion of a broad range of sources, including peer-reviewed publications, policy documents, and grey literature, as well as the comparison of international educational models with empirical data from the Kazakhstani context. Nevertheless, the results should be interpreted in light of limitations related to the heterogeneity of methodological quality among included studies and the predominance of

self-reported measures in assessing educational outcomes.

Overall, the discussion highlights that gender education for healthcare professionals should be viewed as a structural component of the healthcare system, whose effectiveness depends on the interplay of content-related, pedagogical, and organizational factors. The findings provide a basis for further research aimed at evaluating the impact of educational programs on clinical practice and patient outcomes, as well as at analyzing the conditions necessary to ensure the sustainability and scalability of such interventions in national contexts.

Implications for Integrating Training on Responses to Gender-Based Violence in Kazakhstan

The findings of this study have direct implications for the development of healthcare professional training in the Republic of Kazakhstan. The combination of a high prevalence and marked latency of gender-based violence, documented in national and regional studies, with the limited educational preparedness of the healthcare system indicates a structural gap between public health needs and current clinical response capacities. In this context, the international experience analyzed in the present study allows for the identification of principles that may be relevant for adaptation within the Kazakhstani system of medical education.

First, the results underscore the appropriateness of integrating training on responses to gender-based violence into existing medical disciplines and stages of medical education rather than introducing it in isolation as optional or elective courses. Such integration enhances the sustainability of educational initiatives and demonstrates the clinical relevance of a gender perspective across medical specialties, including obstetrics and gynecology, psychiatry, internal medicine, and primary health care.

Second, international evidence highlights the importance of moving beyond predominantly lecture-based formats toward interactive and experiential learning methods aimed at developing communication and empathy skills. In the Kazakhstani context, this implies a phased adaptation of such methods, taking into account resource constraints and the need for targeted faculty development.

Third, the findings indicate that educational interventions are most effective when supported by institutional commitment and aligned with clinical protocols and referral pathways. In Kazakhstan, this suggests that the integration of training should be accompanied by systematic efforts to enhance healthcare professionals' awareness of available support services and the practical functioning of intersectoral collaboration mechanisms.

Overall, the implications of this study point to the need to conceptualize training on responses to gender-based violence as a systemic component of healthcare system development rather than as a standalone educational initiative. Further research and pilot programs may contribute to refining optimal integration models that are aligned with national priorities and institutional conditions.

5. Conclusions

The systematic analysis of international experience in gender education for healthcare professionals achieved the objective of the study and demonstrated that the integration of training on responses to gender-based violence constitutes an evidence-based strategy for enhancing the healthcare system's preparedness to identify and manage violence against women. The results of the review indicate that the most effective educational programs are characterized by a combination of multidimensional content, interactive pedagogical approaches, and institutional integration into existing medical education systems, as evidenced by improvements in knowledge, professional attitudes, and readiness to respond among healthcare professionals across diverse countries and contexts. The analysis of data from Kazakhstan revealed that, despite the high prevalence and latency of gender-based violence, the healthcare system of the Republic of Kazakhstan currently exhibits limited educational readiness for a systematic response, reflected in the fragmented

inclusion of this topic in medical curricula and the restricted scope of training initiatives. The comparison of international models with the national context supports a qualified conclusion regarding the substantial potential for adapting evidence-based educational approaches, taking into account the institutional, sociocultural, and resource conditions of Kazakhstan. The findings confirm that training healthcare professionals to respond to gender-based violence should be regarded as a systemic component of healthcare development, and further research is required to assess its impact on clinical practice and outcomes for women who have experienced violence.

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References

1. WHO, G. M. C. (2006). integrating gender into the curricula for health professionals. Department of Gender. *Women and Health (GWH), World Health Organization*.

2. Kalra, N., Hooker, L., Reisenhofer, S., Di Tanna, G. L., García-Moreno, C. (2021). Training healthcare providers to respond to intimate partner violence against women. *Cochrane Database of Systematic Reviews*, (5). https://doi.org/10.1002/14651858.CD012423.pub2

3. Hughes, C., Musselman, E. A., Walsh, L., Mariscal, T., Warner, S., Hintze, A., Tran, J. (2020). The mPOWERED electronic learning system for intimate partner violence education: mixed methods usability study. *JMIR nursing*, *3*(1), e15828. https://doi.org/10.2196/15828

4. EDUCATE Investigators. (2020). Assessing readiness to manage intimate partner violence 12 months after completion of an educational program in fracture clinics: a pretest–posttest study. *Canadian Medical Association Open Access Journal*, *8*(4), E731-E736. https://doi.org/10.9778/cmajo.20200031

5. Young, F., Hameed, M., Hooker, L., Taft, A., Hegarty, K. (2024). Training Australian general practitioners to counsel women experiencing intimate partner abuse (WEAVE): a pre-post training analysis. *BMC primary care*, *25*(1), 93. https://doi.org/10.1186/s12875-024-02337-0

6. Gear, C., Koziol-McLain, J., Eppel, E., Rolleston, A., Timutimu, N., Ahomiro, H., Isham, C. (2024). 'Atawhai': a primary care provider-led response to family violence in Aotearoa New Zealand. *Archives of public health*, *82*(1), 74. https://doi.org/10.1186/s13690-024-01309-1

7. Chang, O., Ryan, B., Rokoduru, A., Hill, A., Hataogo, S., Naidu, V. (2022). The Pasifika Veilomani Project: a pilot online training programme for healthcare workers in managing gender-based violence and family violence and sharing experiences. *Australasian psychiatry*, *30*(6), 762-767. https://doi.org/10.1177/10398562211045090

8. IMPRODOVA. (n.d.). *Improving frontline responses to high impact domestic violence*. https://www.improdova.eu/index.php

9. Adánez-Martínez, M. G., Pérez-Cánovas, C., Leal-Costa, C., Ferrer, M. B. C., Díaz-Agea, J. L., & Ruiz, I. J. (2025, April). Efectividad de un programa de formación dirigido al abordaje de la violencia de género en profesionales de urgencias y emergencias: Estudio cuasi-experimental. In *Anales del sistema sanitario de Navarra* (Vol. 48, No. 1, p. e1111). https://doi.org/10.23938/ASSN.1111

10. World Health Organization. (2023). *Improving the health system response to violence against women: Report of a WHO/Europe expert meeting, Copenhagen, Denmark, 21–22 June 2022*. https://www.who.int/

11. Albezreh, S., Anastario, M., Ulibarrí, B. J., Naimer, K., Johnson, K., McHale, T., Nelson, B. D. (2022). Multiyear, multisectoral training program in Kenya to enhance medical–legal processes in response to sexual and gender-based violence. *Violence against women*, *28*(14), 3311-3330. https://doi.org/10.1177/10778012221099984

12. Matoy, L. S., Tarimo, F. S., Kosia, E. M., Mkunda, J. J., Weisser, M., Mtenga, S. (2024). Healthcare Workers' Experiences and Challenges in Managing Gender-Based Violence Among HIV-Positive Women Living in Southern, Tanzania: A Qualitative Study. *HIV/AIDS-Research and Palliative Care*, 275-287. https://doi.org/10.2147/HIV.S438672

13. Ipas Nigeria. (2025). *Training helps improve abortion and contraceptive care*. Website. [Cited 22 MAY, 2025]. Available from URL: https:// https://www.ipas.org/news/abortion-contraceptive-humanitarian-nigeria/

14. Bayoulou, S., Ngangue, P., Kaboré, S. S., Nteungue, B. A. K., Pafadnam, Y., Yopa, D. S., Kiki, G. M. (2024). Barriers influencing the care of survivors of gender-based violence in the context of forced displacement in Kaya, Burkina Faso: a qualitative study. *medRxiv*, 2024-04. https://doi.org/10.1101/2024.04.01.24305078

15. Neetha, N., & Thresia, C. U. (2025). Agency through Devalued Work: The case of Health Care Workers in Palliative Care in Kerala. *JOURNAL ON LABOUR*, 33. https://www.bollettinoadapt.it/wp-content/uploads/2025/09/CLLRA-Journal-2.pdf#page=34

16. Healthcare providers' perceptions and experiences of training in care of women subjected to violence. (2023). *International Journal of Environmental Research and Public Health*, 20(2), Article 1030. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9966429/

17. *Intervention improves healthcare response to domestic violence in low- and middle-income countries*. Website. [Cited 27 November, 2024]. Available from URL: https:// https://www.lshtm.ac.uk/newsevents/news/2024/intervention-improves-healthcare-response-domestic-violence-LMICs

18. United Nations Population Fund. (2017). *Violence against women survey: Kazakhstan*. https://kazakhstan.unfpa.org/

19. Mussabekova, S. A., Mkhitaryan, X. E., & Abdikadirova, K. R. (2024). Domestic violence in Kazakhstan: Forensic-medical and medical-social aspects. *Forensic science international: reports*, *9*, 100356. https://doi.org/10.1016/j.fsir.2024.100356

20. Esimbekovna, O. A., Orazbekovna, N. G., Valentinovna, G. M., Muratkhanovna, U. N. (2025). DOMESTIC VIOLENCE AS A PUBLIC HEALTH CHALLENGE: RESULTS OF A MASS SOCIOLOGICAL STUDY IN TURKISTAN REGION. *Наука и здравоохранение*, *27*(3), 64-69. https://cyberleninka.ru/article/n/domestic-violence-as-a-public-health-challenge-results-of-a-mass-sociological-study-in-turkistan-region

21. United Nations Population Fund. (2020). *Clinical protocol for diagnosis and treatment of gender-based violence*. UNFPA Kazakhstan. https://kazakhstan.unfpa.org/sites/default/files/pub-pdf/Clinical_protocol_GBV.pdf

22. Terlikbayeva, A., Primbetova, S., Gatanaga, O. S., Chang, M., Rozental, Y., Nurkatova, M., Gilbert, L. (2025). UMAI-WINGS: Evaluating the Effectiveness of Implementing mHealth Intimate Partner Violence Prevention Intervention in Reducing Intimate Partner Violence Among Women from Key Affected Populations in Kazakhstan Using a Community-Based Approach. *Behavioral Sciences*, *15*(5), 641. https://doi.org/10.3390/bs15050641

Гендерлік зорлық-зомбылықпен күрестегі құрал ретінде медицина қызметкерлерін гендерлік оқыту жөніндегі халықаралық тәжірибе: Қазақстанда іске асыру мүмкіндіктері

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Түйіндеме

Кіріспеде гендерлік негіздегі зорлық-зомбылық жиырма бірінші ғасырдағы қоғамдық денсаулық сақтау мен адам құқықтары саласындағы ең өзекті мәселелердің бірі ретінде қарастырылады. Бұл құбылыс әйелдердің физикалық, психикалық, репродуктивтік және әлеуметтік әл-ауқатына ұзақ мерзімді жағымсыз әсер етеді. Денсаулық сақтау жүйесі зорлық-зомбылықтан зардап шеккен әйелдермен өзара әрекеттесудің негізгі институционалдық кеңістігі болып табылады, себебі олар медициналық ұйымдарға жарақаттармен қатар созылмалы соматикалық және психоэмоционалдық шағымдармен жиі жүгінеді. Осыған байланысты медициналық қызметкерлер зорлық-зомбылықты ерте анықтау, бастапқы қолдау көрсету және тиісті қызметтерге бағыттау тұрғысынан маңызды рөл атқарады. Алайда бұл рөлді тиімді жүзеге асыру үшін арнайы білім мен дағдылар қажет, ал олар көптеген елдерде, соның ішінде Қазақстан Республикасында, медициналық білім беру жүйесіне жүйелі түрде енгізілмеген.

Зерттеудің объектісі халықаралық және ұлттық контексте медициналық қызметкерлерді гендерлік негіздегі зорлық-зомбылыққа жауап беруге даярлау жүйесі болып табылады. Зерттеудің мақсаты медициналық қызметкерлерге арналған білім беру бағдарламалары бойынша халықаралық тәжірибені жүйелі түрде талдау, олардың тиімділігін бағалау және дәлелді модельдерді Қазақстанның медициналық білім беру жүйесіне бейімдеу мүмкіндіктерін анықтау болып табылады.

Зерттеуде scoping review элементтері бар шолу-талдау әдістемесі қолданылды. Халықаралық библиографиялық дерекқорларда жарияланған ғылыми еңбектер, халықаралық ұйымдардың баяндамалары мен нұсқаулықтары талданды. Медициналық студенттер мен практик-мамандарға арналған білім беру интервенцияларын сипаттайтын жиырма алты дереккөз іріктелді. Сонымен қатар Қазақстандағы әйелдерге қатысты зорлық-зомбылық жөніндегі ұлттық сауалнамалар, сот-медициналық статистика және медициналық жоғары оқу орындарының ашық оқу жоспарлары пайдаланылды.

Нәтижелер тиімді бағдарламалардың ортақ сипаттамаларын анықтады. Оларға мазмұнның көпқырлылығы, интерактивті және тәжірибелік оқыту әдістерін қолдану, сондай-ақ білім беру құрылымдарына институционалдық тұрғыда интеграциялану жатады. Мұндай бағдарламалар білім деңгейінің, кәсіби ұстанымдардың және зорлық-зомбылыққа жауап беруге дайындықтың артуымен байланысты. Қазақстандық контекст талдау гендерлік негіздегі зорлық-зомбылықтың кең таралуы мен жасырын сипаты жағдайында білім беру дайындығының жеткіліксіз екенін көрсетті.

Қорытындылай келе, халықаралық дәлелдерге негізделген гендерлік негіздегі зорлық-зомбылыққа жауап беру даярлығын медициналық білім беру жүйесіне енгізу Қазақстан Республикасында денсаулық сақтау жүйесінің әлеуетін нығайтудың перспективалы бағыты болып табылады.

Түйін сөздер: гендерлік негіздегі зорлық-зомбылық, тұрмыстық зорлық-зомбылық, медициналық білім беру, медицина қызметкерлері, кәсіби даярлық, қоғамдық денсаулық сақтау.

Международный опыт гендерного образования медицинских работников как инструмент борьбы с гендерным насилием: Возможности имплементации в Казахстане

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Резюме

Во введении рассматривается гендерно-обусловленное насилие как одна из наиболее значимых проблем общественного здравоохранения и прав человека в современном мире. Оно сопровождается тяжелыми и долгосрочными последствиями для физического, психического и репродуктивного здоровья женщин, а также для их социального благополучия. Система здравоохранения занимает особое место в реагировании на данную проблему, поскольку женщины, пережившие насилие, нередко обращаются за медицинской помощью по самым разным поводам, не всегда напрямую связанным с насильственным эпизодом. В этой связи медицинские работники являются ключевыми субъектами раннего выявления и первичной поддержки пострадавших. Вместе с тем реализация этого потенциала требует наличия специализированных компетенций, которые во многих странах, включая Республику Казахстан, остаются фрагментарно представленными в системе медицинского образования.

Объектом исследования является система подготовки медицинских работников к реагированию на гендерно-обусловленное насилие в международном и национальном контексте. Цель исследования заключается в систематическом анализе международного опыта образовательных программ для медицинских работников, оценке их эффективности и выявлении возможностей адаптации доказательных моделей для системы медицинского образования Казахстана.

В исследовании применена методология обзорного анализа с элементами scoping review. Были проанализированы публикации из международных научных баз данных, документы международных организаций, а также программные и нормативные материалы. В итоговый анализ включены двадцать шесть источников, описывающих образовательные интервенции для медицинских студентов и практикующих специалистов. Дополнительно использованы данные национальных обследований по насилию в отношении женщин, судебно-медицинская статистика и открытые учебные планы медицинских вузов Казахстана.

Результаты исследования показывают, что наиболее эффективные программы подготовки медицинских работников характеризуются сочетанием мультидимензионального содержания, интерактивных педагогических методов и институциональной интеграции в существующие образовательные структуры. Использование симуляций, стандартизированных пациентов и анализа клинических случаев связано с улучшением знаний, профессиональных установок и готовности к реагированию на гендерно-обусловленное насилие. Анализ казахстанского контекста выявил значительный разрыв между масштабами и латентностью проблемы и уровнем образовательной готовности системы здравоохранения.

В заключение делается вывод о том, что интеграция подготовки медицинских работников по реагированию на гендерно-обусловленное насилие является обоснованным и перспективным направлением развития медицинского образования и укрепления потенциала системы здравоохранения Республики Казахстан.

Ключевые слова: гендерное насилие, домашнее насилие, медицинское образование, медицинские работники, профессиональная подготовка, общественное здравоохранение.