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The articles are given
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CONTENTS

ORIGINAL RESEARCH

M. Nisa, S.A. Buzdar, F. Siddique, M.S. Ahmad, M. Akhtar, S. Nisar, A. Nazir, H. Ullah

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HARNESSING AI AND NATURAL THERAPEUTICS: COVID-19 DATA ASSESSMENT AND CURCUMIN'S ROLE IN MITIGATION

The main purpose of this work is to produce early finding /detection report for covid-19 by automated system using artificial intelligence techniques and drug development. This work comprises a proposed method for quantifying the features of textured Covid Images and Curcumin as an analyte for five various concentrations i.e. 0 mM, 10 mM, 20 mM, 30 mM and 40 mM. During data analysis using artificial intelligence and machine learning approaches, HRCT was found to be useful diagnostic tool. For the quantification and features extraction, statistical analytical methods were applied on normal and affected data (grey images) after discussion with expert radiologist. Total number of region of interests selected was 320. The proposed method accuracy for three classes COVID-19 mild cases, COVID-19 severe cases and normal cases were 94.4%, 96.6% and 98.4%. Sensitivity was 94.5%, 96.6% and 98.4% with respect to principal component analysis, linear discriminant analysis and nonlinear discriminant analysis. Clinical findings disclose the higher mortality rate, different severity levels and to identify the stages of virus attack. Curcumin can be used as drug to improve histopathological results.

Keywords: Covid-19, Texture analysis, Curcumin, Co-occurrence matrix

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Introduction: There was a huge viral attack, checked in December 2019, appeared in Wuhan, province Hubei China and firstly spread to the other regions of china and then to the worldwide [1]. This novel corona virus (COVID-19) was observed with some common symptoms in mild cases like fever, fatigue, dry cough, etc. and in serious cases, infections observed that can cause fatal pneumonia [2], dyspnea, and acute respiratory distress condition that lead to death [3]. According to literature survey COVID-19 can spread among humans by means of respiratory track [4-5]. It was observed that mortality ratio was low in children [6] and high in males and elderly persons [7]. The incubation period for COVID-19 varies based on different sources: WHO (The World Health Organization) reported duration for incubation period for corona virus 2-10 days while, NHC (China's National Health Commission) had announced the estimated incubation duration 10-14days. The CDC (United States) claimed 2-14days whereas DXY.cn, a top ranked Chinese online community for physicians and health care professionals, reported estimation 3-7 days can be up to 14 days. The effective way to reduce the strength of corona virus is proper isolation [1]. Today's basic necessity is to identify the early stage of COVID-19 (even before symptoms appear) with an automated report generation with collaboration of diagnostic imaging. Literature shows Texture analysis plays great role in segregating the pattern observed in medical images [8-9]. CT texture analysis is a prominent tool to investigate and identify human tissue features precisely to distinguish malignant and normal tissue images by applying different quantification methods [10].

COVID-19 is a disease that spreads through virus and triggers the Severe Acute Respiratory Syndrome (SARS). In December 2019 COVID-19 spreads in whole world with origin Wuhan, a city of China [11]. Many elucidations were conducted on genome of COVID-19 by scientists and made many drugs. Protease was selected for such drugs because it works when RNA of Covid-19 replicates [12]. Curcumin is one of the most prominent antiviral. Bisdemethoxycurcumin, desmethoxycurcumin and curcuminoid are three types of curcumin. It is a polyphenol [13]. Curcumin acts as anticancer, antidepressant, antioxidant, anti-inflammatory and antiviral in many biological phenomenon's [14]. Curcumin by the process of fibrosis during COVID-19 reverse the pathway of pulmonary system due to its biological targets like inflammatory response, inhibition and immunological properties [15]. We have discussed the biological components and parameters of blood of COVID-19 patient for 0 mm, 10 mm, 20 mm, 30 mm and 40 mm hematological under Curcumin analyte.

The infected CT images of COVID-19 showed similarity for chest tomographic configuration of ground glass opacities, consolidation with bilateral and marginal lung infections for SARS-CoV-19. The radiologist found similar symptoms in detecting abnormalities for viral pneumonia and SARS-CoV-19 Pneumonia [16].

There is limitation in chest CT findings due to its negative prognostic value at primary symptoms appearance [17]. Artificial intelligence (AI) is somehow performing better understanding in human imaging analysis as well as for identifying abnormalities [18]. According to literature survey Coronavirus belongs to one of the largest viruses group Nidovirales, which contains Coronaviridae, Arteriviridae, Mesoniviridae, and Roniviridae families [19]. The Coronavirinae comprise of nine families. These viruses firstly differentiate or grouped according to serology

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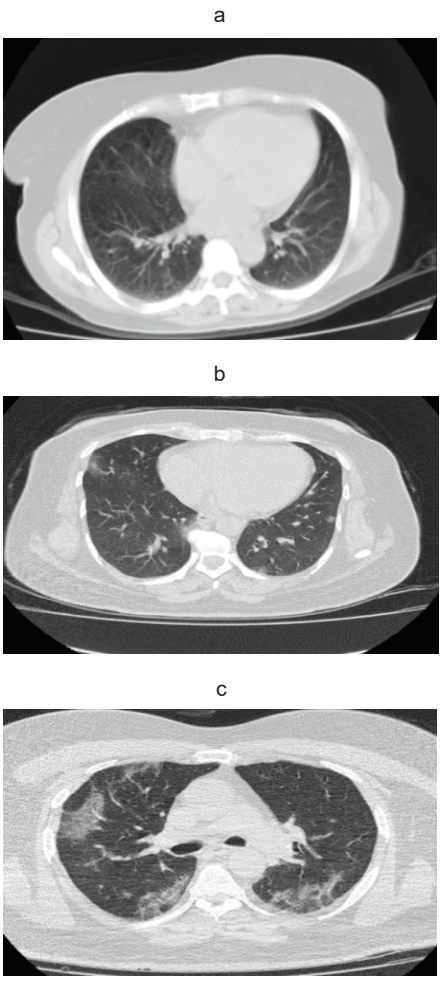

Fig. 1. High Resolution Computed tomography (HRCT) images of (a) normal and COVID-19 infected data (b) mild cases and (c) severe cases

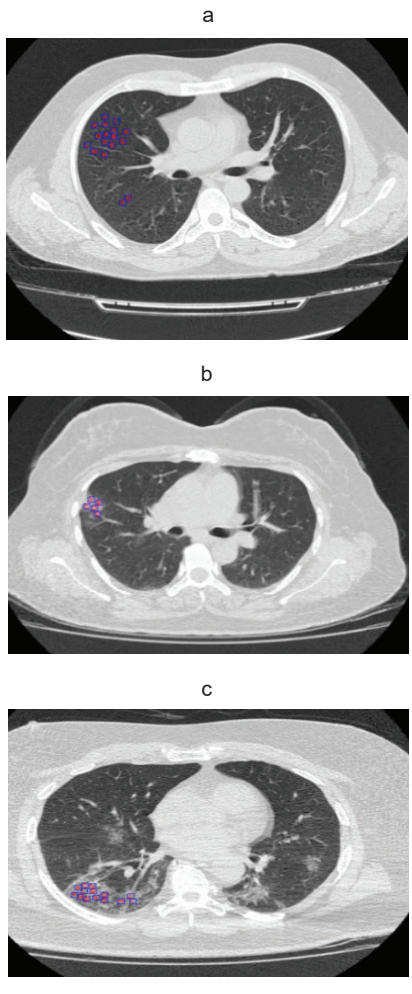

Fig. 2. ROI marked on HRCT images of the patients (a) normal (b) mild infected with covid (C) severe with coronavirus disease-2019. In case(c) GGO, consolidation and septal thickening appear that reveals the severity

but now they are classified by phylogenetic assembling. The Coronaviruses Alpha, Beta, Gamma and Delta are the four species arises from Coronavirinae family [20]. Lu et al [21] studied that a novel coronavirus (termed 2019-nCoV) detected during clinical sample investigations from viral pneumonia patients in Wuhan, China. 2019-nCoV has resemblance in pattern with the virus caused by SARS, epidemic 2003. A novel research on COVID-19 is also given by one of the academy of Medical Sciences in China described by Ren et al. They observed this research in five patients that was diagnosed with pneumonia due to viral as the major reason, later tested COVID-19 positive with the metagenomics observation of samples of patients of respiratory tract. Sequence findings showed that this virus is phylogenetically closest to the bat SARS-like CoV, but is in a different lineage, possessing. In addition, the amino acid sequence of this new CoV's preliminary receptor-binding domain (RBD) resembles that of SARS-CoV, implying that the same receptor could be used.

According to Wang et al [22], for the development to study and get rid of this dangerous and complex virus, scientific study is of critical importance. Many development and advance research, in field of medical, environmental and science, is needed to understand the clear view, growth and transfer of virus in body.

Rao *et al.* suggested that if online mobile based app is discovered to take sample, patient history, critical symptoms of COVID-19, it will save time and fast isolation is possible [23]. Even this data can be used for the basic screening and rapid detection of COVID-19 patients. With the help of artificial intelligence (AI), a statistical calculation can be achieved that will give good information according to risk factors like patients having no risks, patients having low risk, patients having medium risk factor and patients with severe risk. The patients with severe -risk factor detected may then be quarantined sooner, minimizing the probability of the virus spreading. It is very necessary to communicate with children and families in the hospitals. People may feel that there is no COVID-19 treatment, but we need to help them realize that it

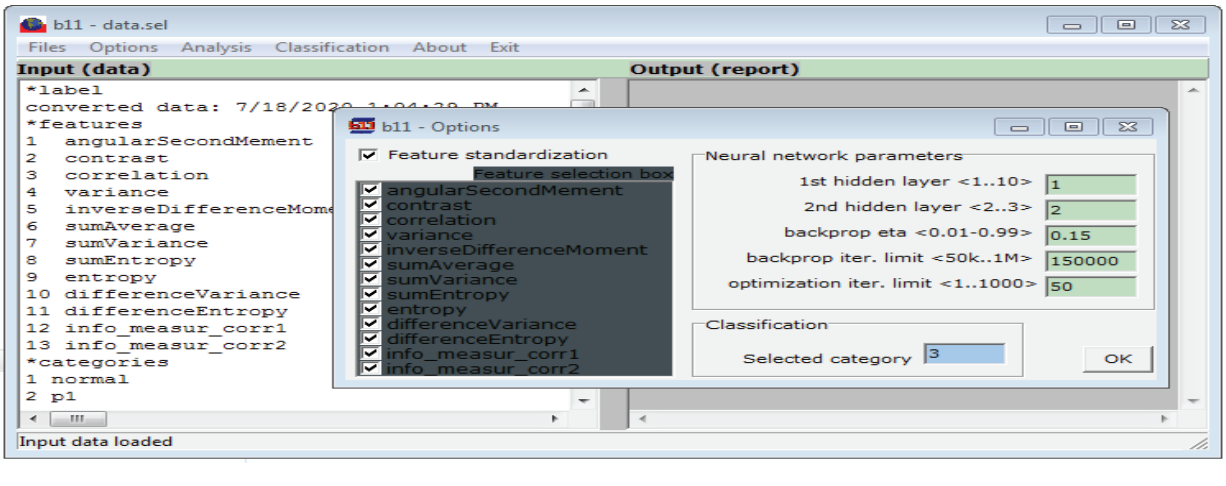

Fig. 3. Showing feature selection box using B11 software.

is likely that positive therapy is all that is required [6].

To estimate the transmission risk of COVID-19, a mathematical model was proposed to conclude that 6.47 could be the basic reproduction number. Wang et al. [24] proposed the following guidelines, based on the report findings (1) CT scan or x-ray scan of lung of each patient should be considered. In clinically suspected cases of quarantine, patients with traditional pulmonary signs should be included. Lung CT should be rechecked in 3 to 5 days for patients without apparent lung signs but with clinical symptoms, (2) as a requirement for admission to the quarantine ward, positive lung CT results instead of a positive nucleic acid test should be used. (3) CT exams should be performed every 5 to 7 days in hospitalized patients and a low-dose scan should be used. In short, clinicians and radiologists should recognize the importance of chest CT in the diagnosis and treatment of COVID-19, be familiar with the characteristics and diagnostic points of COVID-19 chest imaging, and improve contact within the radiology community, which is particularly important in the fight against COVID-19 [24].

Currently researchers are working on AI (Artificial Intelligence) to develop tools that can boost the potential of health care [18]. *Qanees et al.* developed FPAS-SA-ANFIS (flower pollination algorithm using the salp swarm algorithm) that was applied as a forecasting technique that has the ability to predict number of confirmed COVID-19 cases within ten days [25]. Srinivasa *et al.* suggested that deep learning algorithms can be implemented to identify early signs of COVID-19 viral infection [23].

Materials and methods. In this study, the data was collected from personal contacts for clinical aspects to characterize and differentiate normal and COVID-19 cases. Analysis was done with 20 normal cases versus 20 corona infected patients with mild state and 50 severe corona patients with HRCT images. Senior doctors and radiologist were consulted for the precise judgment and discussion of symptoms and clinical findings to strengthen proposed analysis results. The most common symptoms observed in mild cases were fever, cough, fatigue, myalgia (body aching) and poor appetite. Clinical findings were peripheral Ground Glass Opacity (GGO), Basal Consolidation, septal thickening and vascular dilation [26] etc. Recovery time was 10-15 days. Severe patients were observed with some complications due to diabetics, hypertensive, cardiac, smoker, high grade fever and shortness of breath. Some patients were treated with oxygen therapy. Pattern on HRCT was same Ground glass opacity, consolidation, septal thickening and vascular dilation with high grade. Recovery time examined 21 days to one month. Generally, age was one of the basic factors perceived in mortality rates.

Blood smear preparation: Blood smear method was used for preparation of slides of blood cells. Fixing and staining was used for WBCs and RBCs and for platelet cells PRP by centrifuge method at 50×10^6 rpm. Fixing is done by using Ethanol and staining by using field strain (A, B). Then images of these slides were captured by using microscope with lens of 40X for WBCs and RBCs. This was conducted at room temperature.

Feature Extraction: The digitization of texture features is done by feature extraction process in texture analysis methods. Texture variation, angles of direction and surface structure can be defined by these extracted features or parameters. Statistical analysis method, Co-occurrence matrix was used for computing Haralick texture features for each ROI. Features data was calculated from the region of interests was based on image intensity. A square matrix that keeps record of frequencies of occurrence of these gray levels in pairs relationships is known as co-occurrence matrix [27]. Its dimensions are independent to that of the image matrix [28].

Grey level co-occurrence matrix is second order method that statistically measures grey level. It works with the linear spatial relationship between neighboring pixels and describes combinations with neighboring pixels exist in any direction at angle θ [10, 29-30]. The computed Haralick texture features are *Angular Second Moment*, Contrast, Correlation, Variance, Inverse Difference Moment, Sum Average, Sum, variance, Sum Entropy, Entropy, Difference Variance, Difference Entropy, Information Measures of Correlation I, and Information Measures of Correlation2.

Experimental Results. High Resolution Computed tomography (HRCT) was performed with patients using 64-slice Toshiba Medical System, X-ray high voltage generator, Model CXXG-012A, input was 3˜, 200V and 50/60 Hz. Maximum input power was 90kVA. The output was 120kV, 600mA, and 135kV, 530mA made in Japan.

Selection and construction of ROIs. Region of interests were defined or selected when image loaded on image processing software. In this research work system was defined region of interest with sizes 8 × 8, 16 × 16 and 32 × 32 window sizes. For the precision and accuracy 8 × 8 ROI was constructed. Multiple ROIs from patient's image were chosen to increase the number of number of samples from patient's data. Size of region of interest basically indicates the number of pixels under consideration. In this study the shape of the selected region of interest was square.

Feature Selection. In digital image total dimensions are proportional to the number of pixels exist in that pattern. In that sense it constructs large number of dimensions. For specific problems it is good to minimize the number of dimensions by making feature vector. That features are called the statistical parameters which describes the spatial interrelationship of different grey levels in neighboring pixels. Basically feature section or reduction makes sense in terms of grouping

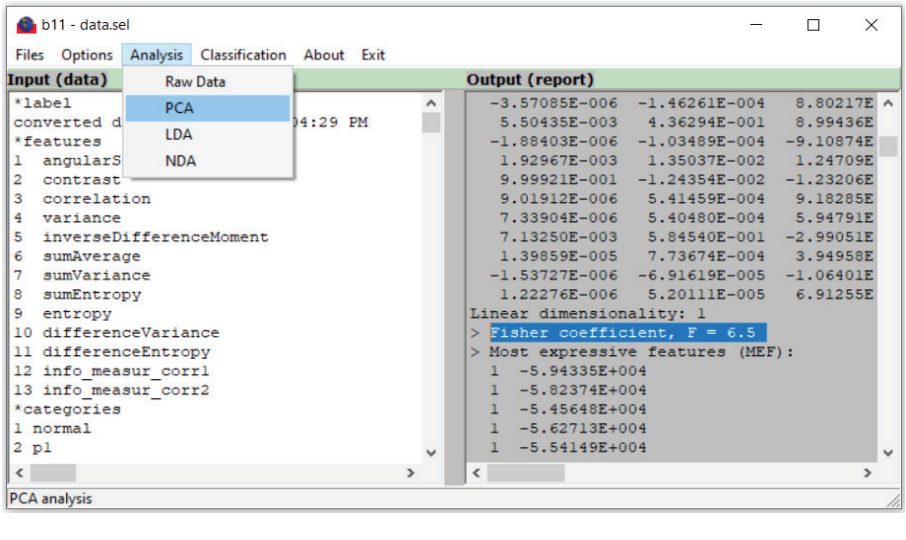

Fig. 4. showing analysis techniques using B11 software

Table 1

Features	pooled mean	pooled standard deviation
angular Second Moment	5.8036E-03	5.5229E-03
contrast	7.6720E+02	5.2918E+02
correlation	3.4903E-01	2.3780E-01
variance	5.3339E+02	3.6326E+02
inverse Difference Moment	1.0860E-01	1.2192E-01
sum Average	2.6590E+02	7.9759E+01
sum Variance	7.6099E+04	4.0695E+04
sum Entropy	4.2502E+00	5.8819E-01
entropy	5.5698E+00	5.8719E-01
difference Variance	6.2831E+02	4.4838E+02
difference Entropy	3.4639E+00	8.1990E-01
info_measur_corr1	-3.6850E-01	8.8901E-02
info_measur_corr2	9.3751E-01	7.8914E-02
Statistical Techniques	**Results**	
Principle component Analysis		
Linear dimensionality	5	
Fisher coefficient	11.6	
Feature vector standardization	yes	
1-NN classification of MEFs:		
Misclassified data vectors	18/320 [or 5.63%]	
Linear Discriminant analysis		
Linear separability	0.98	
LDA dimensionality	2	
Fisher coefficient	181	
Feature vector standardization	yes	
1-NN classification of MDFs:		
Misclassified data vectors	11/320 [or 3.44%]	
Nonlinear discriminant analysis		
Misclassified f. vectors	5/320 [or 1.56%]	
Fisher coefficient, F	50.4	
Feature vector standardized	yes	

or sorting to reduce irrelevant data and approach to accuracy. This feature selection process applied before the statistical techniques are applied on data [31].

Statistical Assessment / Data Processing Techniques. Statistical analysis was executed using Sante DICOM viewer (used to view images on impartial system), IrfanView 64 (that is pronounced for viewing and accomplishing trivial image's management. It simply works from changing file format to manipulation of digital images basic features), computer vision lab [32] (software designed for PhD work, used to compute different region of interest with 8 by 8, 16 by16, and 32 by 32 cursor size) and B11 [29] (a unit/software permits visualization of sample distribution and sorting the feature vectors. Furthermore, it provides tool for artificial neural network (ANN) and nonlinear supervised classification (1NN-1-nearest neighbor classifier). Statistical techniques executed in the B11 software encompass PCA (Principal component analysis), LDA (Linear discriminant analysis) and NDA (nonlinear discriminant analysis) [33-35].

Texture Analysis. Texture analysis is considered as the excellent tool in medical field like radiology. Homogenous and heterogeneous textures are pronounced in medical images for pointing the same and violent nature of lesions in the diagnostic imaging. To study diagnostic images, there is vital need to understand image pathology in detail. An image is

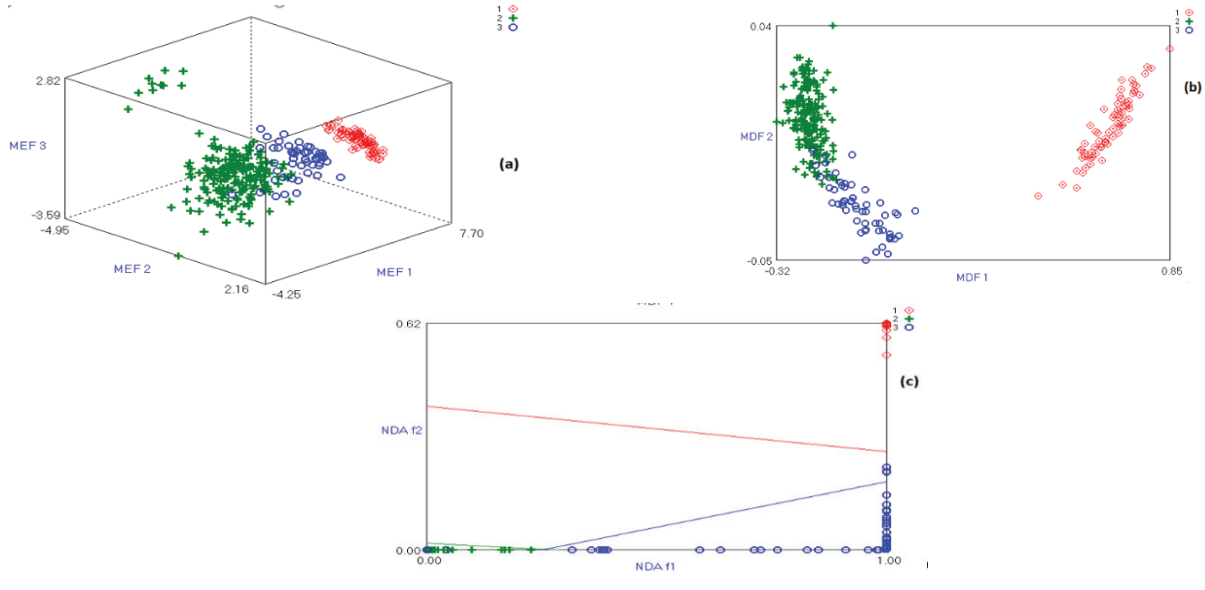

Fig. 5. Showing the distribution of texture features for ROI of dimensions 8 * 8 within normal (marked as red) and Covid (with severe cases marked as green) and with mild states (marked as blue) by (a) Principle Component Analysis in three dimensions, The longitudinal, lateral and vertical axis corresponds to most expressive features (MEFI, MEF2 and MEF3) (b) Linear Discriminant Analysis in two dimensions, The horizontal and vertical axis corresponds to the most Discriminative features in one linear dimension(MDF1 and MDF2) (c) Nonlinear Discriminant Analysis in two dimensions (NDAf1 and NDAf2).

collection of unit cell called pixel [36]. In latest research texture analysis has become the fundamental part of radiology to measure different parameters. As the images can be homogenous or heterogeneous (shows complicated pattern for crucial stages), for the quantification of heterogeneity, texture analysis is the essential tool that defines the texture information, that can predict routine stages and survival rates against diseases [32, 37]. The proposed method for this work figures out results from Haralick texture features using statistical techniques deduced from Co-occurrence matrix (GLCM). As single pixel intensity value variation does not provide enough information about texture behavior that's why second order statistics is used for pair of pixels.

Results showing Haralick texture features with pooled mean (p. mean) and pooled Standard deviation (p.std) and for all these features different statistical techniques Principle component analysis, Linear Discriminant analysis and Non-linear discriminant analysis presenting normalization, fisher Coefficients and misclassification rates (normal versus COVID-19 textured data) with feature vector standardization and 1NN classification of MEFs (Table 1).

(a) showing confusion matrix for classification using Principle component analysis (PCA) (b)Differentiation performance of normal versus covid (mild and severe cases) table showing the overall accuracy 94.4% with application of texture analysis method.TP, TN, FP and FN represent true positive, true negative, false positive and false negative respectively (Table 2).

(a) showing confusion matrix for classification using Linear discriminant analysis (LDA) (b) differentiation performance of normal versus covid (mild and severe cases) table showing the overall accuracy 96.6% with application of texture analysis method. TP, TN, FP and FN represent true positive, true negative, false positive and false negative respectively. (Table 3).

(a) showing confusion matrix for classification using Non discriminant analysis (NDA) (b) differentiation performance of normal versus covid (mild and severe cases) table showing the overall accuracy 98.4% with application of texture analysis method. TP, TN, FP and FN represent true positive, true negative, false positive and false negative respectively. (Table 4).

Microscopic Results. Deviations of blood components and parameters under five different concentrations of Curcumin i.e. 0 mM, 10 mM, 20 mM, 30 mM and 40 mM by using white light microscope of sample set (II) are shown below in figure 6.

Discussion. Figure 1 represents the overall workflow adopted in this research, illustrating the sequential steps involved in image acquisition, preprocessing, feature extraction, and classification. Initially, HRCT (High-Resolution Computed Tomography) or polarimetric images of patients were acquired and stored in a digital format. These images were then subjected to preprocessing operations, including noise reduction, contrast enhancement, and normalization, to ensure uniformity across all sam-

Table 2

a

PCA Analysis
TRUE Class

Predicted Class	Normal	Severe	Mild
Normal	71	0	0
Severe	0	186	10
Mild	0	8	45

b

PCA							
Class Name	TP	TN	FP	FN	Precision	Recall	F1-Score
Normal	71	249	0	0	1.000	1.000	1.000
Severe	186	116	10	8	0.949	0.959	0.954
Mild	45	257	8	10	0.849	0.818	0.833
Total	302		18	18	0.944	0.944	0.944

Table 3

a

LDA Analysis
TRUE Class

	Normal	Severe	Mild
Normal	71	0	0
Severe	0	190	7
Mild	0	4	48

b

LDA							
Class Name	TP	TN	FP	FN	Precision	Recall	F1-Score
Normal	71	249	0	0	1.000	1.000	1.000
Severe	190	119	7	4	0.964	0.979	0.972
Mild	48	261	4	7	0.923	0.873	0.897
Total	309		11	11	0.966	0.966	0.966

Table 4

a

NDA Analysis
TRUE Class

Predicted Class	Normal	Severe	Mild
Normal	71	0	0
Severe	0	194	5
Mild	0	0	50

b

NDA							
Class Name	TP	TN	FP	FN	Precision	Recall	F1-Score
Normal	71	249	0	0	1.000	1.000	1.000
Severe	194	121	5	0	0.975	1.000	0.987
Mild	50	265	0	5	1.000	0.909	0.952
Total	315		5	5	0.984	0.984	0.984

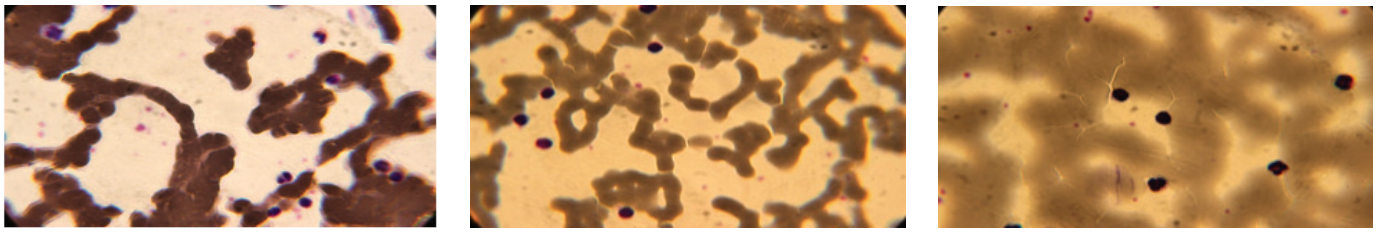

Fig. 6. Micrograph showing size and shape changes of WBCs fewer than five concentrations of Curcumin i.e. 0mM to 40mM under analyte (curcumin) at 40X.

Table 5

Abnormalities or improvement in cells and parameters values under Curcumin Concentrations

Sr. No.	Curcumin Concentration mM	No. of WBCs 10^3 /µL	No. of platelet 10^3 /µL	No. of RBCs 10^6/ µL	HGB g/dL	RDW %	PDW %	MCV fL	MPV fL	HCT %	PCT %
1	0 mM	2.85	178	4.05	10.2	15.4	18.9	92.4	8.2	37.3	0.24
2	10 mM	4.17	219.5	4.33	10.6	15.9	20.6	93.5	8.6	37.1	0.24
3	20 mM	4.99	245.7	4.41	10.5	15.7	20.1	94.1	8.0	39.2	0.20
4	30 mM	7.69	246	4.58	12.1	15.8	21.9	94.9	8.6	42.3	0.23
5	40 mM	10.47	280.9	4.89	14.3	16.4	22.3	96.6	8.5	44.6	0.25

ples. Subsequently, texture-based and statistical parameters were extracted from the processed images to quantify microstructural differences between normal and infected tissues. The extracted features were then analyzed using dimensionality reduction and classification techniques such as PCA, LDA, and NDA to distinguish between various stages of infection or disease severity. Thus, Figure 1 outlines the complete analytical pipeline—from raw image input to final diagnostic classification—demonstrating the systematic approach adopted in this study. Figure 2 depicts the selection of **Regions of Interest (ROIs)** on HRCT images of patients with varying degrees of COVID-19 infection. Subfigure **(a)** represents a normal lung image showing clear alveolar structures without visible abnormalities. Subfigure **(b)** shows a mildly infected case, where faint **ground-glass opacities (GGO)** are observed, indicating early inflammatory changes. Subfigure **(c)** illustrates a severely infected lung, where extensive **GGO**, **consolidation**, and **interlobular septal thickening** are evident, signifying advanced pulmonary involvement and severe tissue damage. The ROIs were marked as square windows of fixed size to capture specific texture patterns within each region, facilitating quantitative comparison of structural changes across infection stages. This figure demonstrates the rationale behind ROI selection and highlights the visual progression of COVID-19–related pathological features in HRCT imaging.

In the present study, total number of regions of interest selected for work was 320, in which normal were 71, mild 55 and severe 194. The pooled statistical evaluation of polarimetric texture features demonstrated clear distinctions between normal and pathological tissues. High contrast (7.67×10^2) and variance (5.33×10^2) indicated significant structural heterogeneity, while low angular second moment (5.80×10^{-3}) and inverse difference moment (0.108) reflected reduced uniformity. Elevated entropy (5.57) and sum entropy (4.25) values signified increased randomness and tissue disorganization associated with malignancy. Correlation parameters (0.349) and information measures (info_measure_corr1 = –0.368; info_measure_corr2 = 0.938) confirmed moderate pixel dependencies, highlighting disrupted microstructural patterns. Principal Component Analysis (PCA) achieved a Fisher coefficient of 11.6 with 5.63% misclassification, while Linear Discriminant Analysis (LDA) improved accuracy (3.44% error; Fisher = 181; separability = 0.98). The best classification was obtained using Nonlinear Discriminant Analysis (NDA), showing only 1.56% misclassification and Fisher coefficient of 50.4. Overall, nonlinear statistical mapping demonstrated superior tissue differentiation and strong diagnostic potential of polarimetric and textural parameters. Here the proposed work has done with ROI 8*8. As indicated in table 1, p. mean and p.std was derived from Haralick texture features. After setting feature vectors standardization, neural network parameters, and classifying categories, analysis was completed with PCA, LDA and NDA methods. In PCA model the linear dimensionality and fisher coefficient were 5 and 11.6 respectively.1-NN classification of MEFs shows the misclassification data vectors 5.63% and classification and overall accuracy for PCA module was 94.4% (as indicated in table 2) Figure 3(a) showing the distribution of texture features for ROIs for normal cases the isolated cluster is observed (red) with 100 % accuracy while other two clusters showed accuracy with some misclassification proportion. These disparities measured by means of other physical aspect ratio (symptoms of unhealthy conditions like smoking, hypertension and diabetes etc.). Figure 3(b) showing the distribution of texture features for normal, mild and severe ROIs there is three sequestered clusters, but Covid-infected was lineup in comparison with normal that showed the aggressive nature of disease even in mild or critical situation. In LDA model the linear separability was 0.98. LDA dimensionality was 2 and fisher coefficient was 181. During 1-NN classification of MDFs the misclassification rate was observed 3.44%. The overall accuracy perceived was 96.6%for LDA analysis (as shown in table 3). In NDA analysis fisher coefficient was 50.4 and misclassified f. vectors were 1.56%. The overall accuracy 98.4% was reported (as point out in table 4). Even though there was overlapping among some ROIs among mild and severe cases that showed the variation of infection rates due to already existed some dysfunctions of the body. While the analysis with normal cases was reported 100% for all methods PCA, LDA

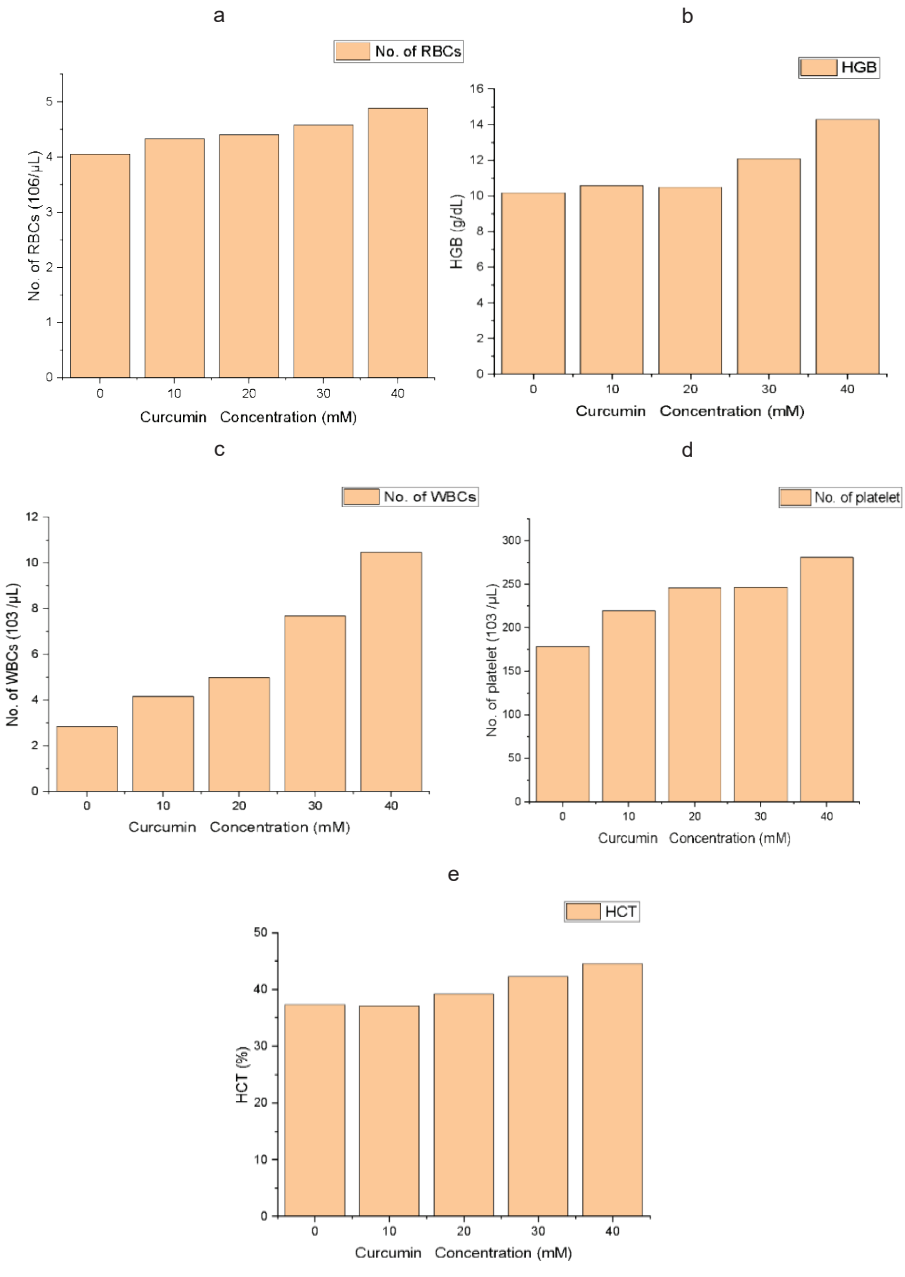

Fig. 7. Showing two dimensional graphical trends of (a) WBC (b) PLTs (C) RBCs (d) HGB and (e) HCT against 0 mM to 40 mM concentration of Curcumin Analyte with step size of 10 mM.

and NDA. Figure 3(c) discriminated the texture features properly due to contrast and correlation of the vectors.

In this proposed work different confusion matrices have drawn for the real assessment. These matrices are showing TP, TN, FP and FN (true positive, true negative, false positive and false negative) values with measurements of Precision, Recall, F1-score and accuracy (used equations are shown below [38].

Precision = TP/(TP+FP) (1)
Recall/ Sensitivity = TP/(TP+FN) (2)
*F1-score = (2*TP)/(2*TP+FP+FN)* (3)
Overall accuracy = Sum of TP/ Total number of ROI (4)

Accuracy (https://tech.labs.oliverwyman.com/blog/2019/10/17/accuracy-precision-recal-elixir/) is the sum of the diagonal divided by the total. Table 2(a) is showing the confusion matrix for PCA analysis, the TP (True positive) for normal was 71, TN (True negative) 249, FP (False positive) and FN (False negative) was 0. Value of Precision, recall and F1-score was 1 that shows excellent accuracy for normal ROIs for PCA. For severe cases/ samples/ ROIs the TP was 186 and TN 116 whereas FP and FN values were 10 and 8 respectively. Precision, recall and F1 score was less than 1 and 0.949, 0.959 and 0.954 respectively. For mild ROIs TP was 45 and TN, FP and FN was 257, 8 and 10 respectively. Measurements for precision with recall and F1 score was less than 1 and 0.849, 0.818 and 0.833 respectively. Table 2 (b) presenting the total TP= 302, FP and FN =18, total precision = recall = F1-score = 0.944. The overall accuracy calculated from the confusion matrix was 94.4%.

Table 3 presenting a confusion matrix for LDA analysis to differentiate between performance of normal versus covid (mild and critical) ROIs. Value of TP=71, TN = 249, FP=FN=0 and precision, recall and F-1 score approaches to 1, that shows the maximum accuracy. In case of severe category TP=190, TN= 119, FP=7, FN=4 and the values of the precision, recall and f1-score were 0.964, 0.979 and 0.972 respectively. For mild class TP=48, TN=261, FP=4, FN=7, precision= 0.923, recall=0.873, and F1-score was 0.897. LDA analysis showed more vibrant results as compared to PCA with total TP 309, FP=FN=11, overall precision was 0.966, recall 0.873 and F1-score 0.966 that disclosed the total accuracy 96.6%.

Confusion matrix for NDA method has drawn in Table 4 that delivers the descriptive information about textural features of different ROIs. In normal case like PCA and LDA precision was observed with excellent results with 100% TP and TN ratio. In severe class TP was 194, TN 121, FP and FN was reported with values 5 and 0 respectively. In this analysis value of precision was 0.975, Recall 0.909 and F1-score 0.952. In mild category the values for TP, TN, FP and FN were 50, 265, 0 and 5 respectively. Precision points to 1 whereas recall and F1-score were 0.909 and 0.952 respectively. NDA analysis presented more exciting results with entire accuracy of 98.4% and total precision was 0.984. Although the total TP values were 315 and FP, FN were 5, 5 respectively. It is concluded that Corona virus is an extremely spreadable among human beings and can cause moderate to prolonged effects that can be harmful [39]. Patients with mild state observed with ground glass opacity (GGO) and basal consolidation in common. GGO was the most common sign in either mild or severe patients. In critical situations lesions were scattered and finally infected the lungs and septal thickening and vascular dilation were found with pulmonary consolidation. These changes appear in the form of shortness of breath that takes time to recovery and enhance infection rate. This suggests that presented techniques have promising probability to identify the infection in early stages even on critical one. The visual assessment/ findings indicate that mortality rate can

be increased due to aging, or lesions present in lungs or liver [2-3, 40] or others. It is also cleared at this stage that HCRT texture analysis is a practically applicable tool for characterization and differentiation normal versus infected ROIs. In further recommendations that are a lot of work remaining on individual diseased organs infected with covid-19 that will help out to more commercialize this method in diagnostic units.

Also we have tried to explain the abnormalities / improvement in blood cells and parameters of Covid-19 patient blood with the help of hematology and microscopy after admixing Curcumin for inherent concentration i.e. 0 mM and for 10 mM, 20 mM, 30 Mm and 40 mM. Convicted covid-19 patient has highly effected immune system and blood coagulation system i.e. physiology of WBCs and Platelet cells are disturbed highly. Size and shape of WBCs is improved by the use of curcumin as we can see from figure 5 (a-e). Shape of RBCs changes from biconcave to spherical and spiked and their size also increases when we increase the concentration of Curcumin. Similarly, size and shape of Platelet cells is improved under curcumin from inherent to optimum value as shown in figure 6 (a-e). Count of WBCs goes on increasing gradually from 8.5**×**10^3/μL at inherent value to 8.94**×** 10^3/μL at optimum value as drawn in figure 7 (a). Basophil and lymphocytes illustrate drastic changes. Thus Curcumin improves the immune system of Covid-19 patient. Lymphocytes (natural germ killer) produce antibodies against the parts affected by either cancer or by virus. Their count increases from 2.23% to 4.74%. Basophil produces histamine (homeostasis factor) and heparin (an anticoagulant). Count of Basophil cells is also increased from 0.55% to 2.57% as we mix curcumin from inherent to optimum concentration. Rest types of WBCs remained unchanged. In covid-19 patient count of platelet cells goes on increasing from 178×10^3/μL at inherent value and reaches 280.9×10^3/μL at 40 mM concentration as drawn in figure 7(b). It can also be concluded that low count of platelet cells in diabetes can be improved by using curcumin. Count of RBCs in Covid-19 patients is not much affected just very slow gradual increase. HGB is the oxygen transportation pigment of Red colour present in our body. HGB level increases as we increase the concentration from 10.2 g/dL at inherent value up to14.4 g/dL at optimum value as drawn in figure 7(d). Respiratory system suffered a lot in covid-19 but Curcumin plays very vital role in restoring it by increasing the HGB level. Parameter like HCT which measures the proportion of RBCs in blood is increased from 37.3% to 44.6% as we increase the concentration of Curcumin. Parameters like MCV, MPV, RDW, PCT and PDW show little bit deviation at optimum value as we compare with value at inherent concentration. Thus, Curcumin showed a strong restorative effect on the hematological profile of COVID-19 patients. Increasing its concentration improved the morphology and count of WBCs, RBCs, and platelets**,** enhancing immune response, oxygen transport, and blood coagulation balance. Elevated HGB and HCT levels, along with increased lymphocyte and basophil counts, confirm curcumin's role in strengthening immunity and restoring normal blood physiology. Overall, curcumin demonstrates promising potential as a natural therapeutic agent for mitigating hematological disturbances caused by COVID-19 infection.

Conclusion. This study has total 320 ROIs, with normal 71; mild 55 and severe 194 by using after setting feature vectors standardization, neural network parameters, and classifying categories, analysis was completed with PCA, LDA and NDA methods. The results show an excellent accuracy for normal ROIs for **PCA** with TP=71, TN=249, FP and FN was 0 and precision value=1. Severe cases for PCA with TP=186, TN=116, FP=10and FN=8 and precision value <1 while Mild cases for PCA with TP=45, TN=257, FP=8and FN=10 and precision value <1. The overall accuracy calculated from the confusion matrix was **94.4%**. For **LDA** analysis of normal ROIs TP=71, TN = 249, FP=FN=0 and precision approaches to 1,. In case of severe category TP=190, TN= 119, FP=7, FN=4 and the values of the precision <1. For mild class TP=48, TN=261, FP=4, FN=7, precision <1. LDA analysis showed more vibrant results as compared to PCA that disclosed the total accuracy **96.6%**. For **NDA** in normal case like PCA and LDA precision was observed with excellent results with 100% TP and TN ratio. NDA analysis presented more exciting results with entire accuracy of **98.4%**. It is concluded that Corona virus is an extremely spreadable among human beings and can cause moderate to prolonged effects that can be harmful and Curcumin has the potential as one of the most prominent, less expensive, homeopathic antiviral for improvement of blood cells and parameters in Covid-19 patient.

Declarations. Formal consent was not required, as the study used archived, anonymized diagnostic samples and CT data without patient contact or intervention, in accordance with institutional ethical guidelines.

Competing interests: The authors declare that they have no competing interests

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HISTOLOGIC CHANGES OF THE PLACENTA IN CHRONIC SUBCOMPENSATED PLACENTAL INSUFFICIENCY IN WOMEN WITH COVID-19 OF MODERATE SEVERITY IN THE SECOND AND THIRD TRIMESTERS OF PREGNANCY

Introduction. COVID-19 in pregnant women is associated with inflammatory damage to the placenta, leading to impaired uteroplacental and fetal-placental circulation and the development of chronic placental insufficiency. Objective. To perform histologic study of placental tissues in women with chronic subcompensated placental insufficiency associated with COVID-19 of moderate severity. **Materials and methods.** Placentas from women who developed chronic subcompensated placental insufficiency against the background of moderate COVID-19 in the second and third trimesters of pregnancy (main group, n = 40). The control group consisted of placentas from women not infected with SARS-CoV-2 (n = 20). Histological study and morphometric analysis of placenta slice preparations were performed. **Results.** Histologic study of placenta from women of the main group revealed the following uncharacteristic specific signs of viral tissue damage: decidual vasculopathy, lymphoplasmacytic infiltration, thrombi in the venous vessels of the stem villi, villitis and intervillusitis, deposition of intervillous fibrinoid, hyperplasia of syncytiotrophoblast and chorangiosis. Morphometric analysis showed an increase in the proportion of perivorsinchal fibrin and capillaries in terminal villi, and a decrease in the density of syncytiotrophoblast membranes. In addition, an increase in the number of syncytial nodules and intermediate immature villi, as well as capillary bleeding in intermediate and terminal villi were found. **Conclusion.** The moderately severe course of COVID-19 in the second and third trimesters of pregnancy is associated with structural changes in the placenta, which, with insufficient efficiency of compensatory and adaptive mechanisms, is one of the causes of the development of chronic subcompensated placental insufficiency.

Keywords: pregnancy, COVID- 19, chronic subcompensated placental insufficiency, placental histology, morphometry.

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Introduction. Pregnancy is accompanied by physiologic restructuring of immune, endocrine and hemostatic regulation, which makes the placenta vulnerable to systemic inflammation and microcirculatory disturbances in COVID-19 [2, 3, 15]. Against this background, infection in the second and third trimesters of pregnancy is associated with remodeling of the intervillous space and villous tree of the placenta due to systemic inflammatory response, endothelial dysfunction and hypercoagulability, which is manifested by a complex of signs of maternal and/or fetal vascular malperfusion [5]. Morphological signs of maternal vascular insufficiency in COVID-19 include decidual vasculopathy with hypertrophy of the vascular wall, increased fibrin deposition and thrombosis in the intervillous space, accelerated maturation of villi with increased formation of syncytial nodules, signs of distal hypoplasia of villi, formation of retroplacental hematomas and infarcts of villi. Changes in fetal blood flow are manifested as chorangiosis, thrombosis of the choroidal plate, avascular villi, and perivorhinal fibrin deposition. In addition, some cases show signs of marked chorioamnionitis and umbilical cord vasculitis, as well as chronic inflammation in the form of lymphohistiocytic intervillusitis and villitis [6, 7, 8, 11]. At the same time, specific pathomorphologic changes characteristic of the moderate course of COVID-19 have not been established. Even with confirmed virosemia, the detectable spectrum of morphologic changes often coincides with abnormalities observed in other obstetric pathologies [4, 9]. However, there is evidence in the literature that in some cases of moderate and severe course, there is a characteristic phenotype of placentitis associated with SARS-CoV-2, represented by the triad: chronic or subacute intervillusitis, diffuse fibrin deposition in the intervillous space and necrosis of syncytiotrophoblast [12]. These changes, according to the authors, are associated with placental insufficiency, intrauterine fetal death, and unfavorable perinatal outcomes [14]. To correctly interpret structural changes in the placenta, many researchers rely on the Amsterdam Placental Workshop Group recommendations of 2014, which standardize protocols for material collection, terminology and diagnostic criteria for maternal and/or fetal malperfusion, as well as take into account the nature of inflammatory damage and the presence of thrombi in the vascular lumen [10, 13]. We believe that the above emphasizes the relevance of our study.

Purpose of the study: to perform histological study of placental tissues in women with chronic subcompensated placental insufficiency associated with COVID-19 of moderate severity in the second and third trimesters of pregnancy.

Materials and methods of research

We studied 40 placentas from women with chronic subcompensated placental insufficiency who underwent COVID-19 of moderate severity in the second and third trimesters of pregnancy (main group) and 20 placentas from women not infected with SARS-CoV-2 (control group). All women were delivered at 38-40 weeks of gestation. Retrospectively, to confirm subcompensated placental insufficiency, screening ultrasound examinations in the third trimester of pregnancy were analyzed (medical records of pregnant women, women in labor and delivery receiving inpatient medical care (Form N 096/1u-20), individual medical records of pregnant women and women in labor and delivery (Form N 111/u-20)).

Inclusion criteria for the main group: spontaneous singleton pregnancy; age 20-35 years; moderately severe course of COVID-19 in the second and third trimesters of pregnancy, confirmed clinically and laboratory by polymerase chain reaction; chronic subcompensated placental insufficiency; informed consent for the study.

Inclusion criteria for the control group: spontaneous singleton pregnancy uncomplicated by COVID-19 and other infectious and inflammatory diseases; age 20-35 years; informed consent for the study.

Exclusion criteria: multiple pregnancy; pregnancy after IVF; anemic syndrome; cardiovascular diseases; exacerbation of chronic non-infectious diseases; presence of chronic nonspecific lung diseases; presence of specific diseases of the bronchopulmonary system; genital anomalies; gestational diabetes mellitus; presence of sexually transmitted infections; presence of hormonal support with gestagens; smoking; alcohol consumption during pregnancy; patients' refusal to be tested

Material was collected in the period 2022-2023 on the basis of the maternity department of the State Autonomous Health Care Institution of the Amur Region "Blagoveshchensk City Clinical Hospital" (Blagoveshchensk). Histological studies were performed in the scientific laboratory of the mechanisms of etiopathogenesis and restorative processes of the respiratory system in nonspecific lung diseases of the Federal State Budgetary Scientific Institution "Far Eastern Scientific Center of Physiology and Pathology of Respiration" (Blagoveshchensk). The study was performed taking into account the ethical principles of the Declaration of Helsinki of the World Medical Association and was approved by the local ethical committee at the DNC FPD (Protocol No. 148, 15.11.2023).

For histologic analysis, sections from the central, paracentral and marginal parts of the placenta (up to 6 samples) were taken immediately after delivery. Samples were fixed in 10% neutral formalin solution, pH 7.2-7.4 (HistoSafe, BioVitrum, Russia) at room temperature for 48 hours. After that, they were washed in water and dehydrated in a series of alcohols according to the generally accepted method. Slices up to 3 μm thick were made from the obtained blocks on a Thermo Fisher Scientific HM 325 rotary microtome (USA). Sections were stained with hematoxylin and eosin [1]. Microscopic studies were performed using a digital microscope MEIJI MT 4300L (Japan) at magnification ×100, ×200, ×400.

Morphometric measurements were performed on digital images of slices using Aperio ImageScope software (Leica Biosystems, USA), with preliminary scale calibration using Micron micrometer scale (Russia). Each measurement was performed in five fields of view. Quantitative values were indicated in terms of 1 mm2, fractional values in %. We evaluated: the proportion of fibrin in the intervillous space (%), the number of terminal villi with 5 or more capillaries (%), the number of full blood capillaries in terminal villi (%) and vessels of intermediate villi (%), the proportion of intermediate immature villi (%), the number of syncytiocapillary membranes in terminal villi (per 1 mm2), syncytial nodules (per 1 mm2), as well as desquamation of syncytiotrophoblast on the scale: 0 – absent, 1 –partial, 2 – total.

Statistical analysis was performed using GraphPad Prism, version 9.0 (GraphPad Software, San Diego, CA, USA). The normality of data distribution was assessed using the Shapiro-Wilk criterion. In pairwise comparisons of quantitative data in independent groups, Student's t-test was used in case of normal distribution of the trait or Mann-Whitney U-test when the distribution did not follow the law of normal distribution. Quantitative data are presented as median (Me) and interquartile range (Q25%-Q75%). Differences were considered statistically significant at a significance level of $p<0.05$.

Results and discussion. The results of histologic examination of placenta preparations of the main group are presented in figure 1.

Histologic signs of basal deciduitis infiltration of basal decidual tissue with lymphocytes and plasma cells – were detected quite often in the decidual laminae (fig. 1A). At the same time in the vessels of the stem villi there were signs of moderate or pronounced vasculitis, and in some cases thrombi in the lumen of the veins were detected (fig. 1B, C). The presence of combined inflammatory vascular lesions and thrombus formation indicates the involvement of the maternal part of the placenta in the general pathomorphologic process of placental hemodynamic disorders. This combination is an objective morphologic criterion of blood flow disturbance in the maternal placental vessels (maternal vascular malperfusion).

In addition, the villitis (mixed infiltration of the stroma of intermediate and terminal villi with lymphocytes, macrophages and single plasma cells) and intervillusitis (lymphohistiocytic infiltration of the intervillous space), expansion of the intervillous space, as well as fibrin deposition with the formation of fibrin "bridges" between the villi were noted in the villous tree (fig. 1D, E). The presence of villitis and intervillusitis may indicate an inflammatory lesion of the villous tree and intervillous space with the involvement of cells of innate and adaptive immunity, which is consistent with our previous work [2]. Fibrin deposition in the intervarsinal space is interpreted as a sign of chronic maternal hypoperfusion and syncytiotrophoblast damage [14].

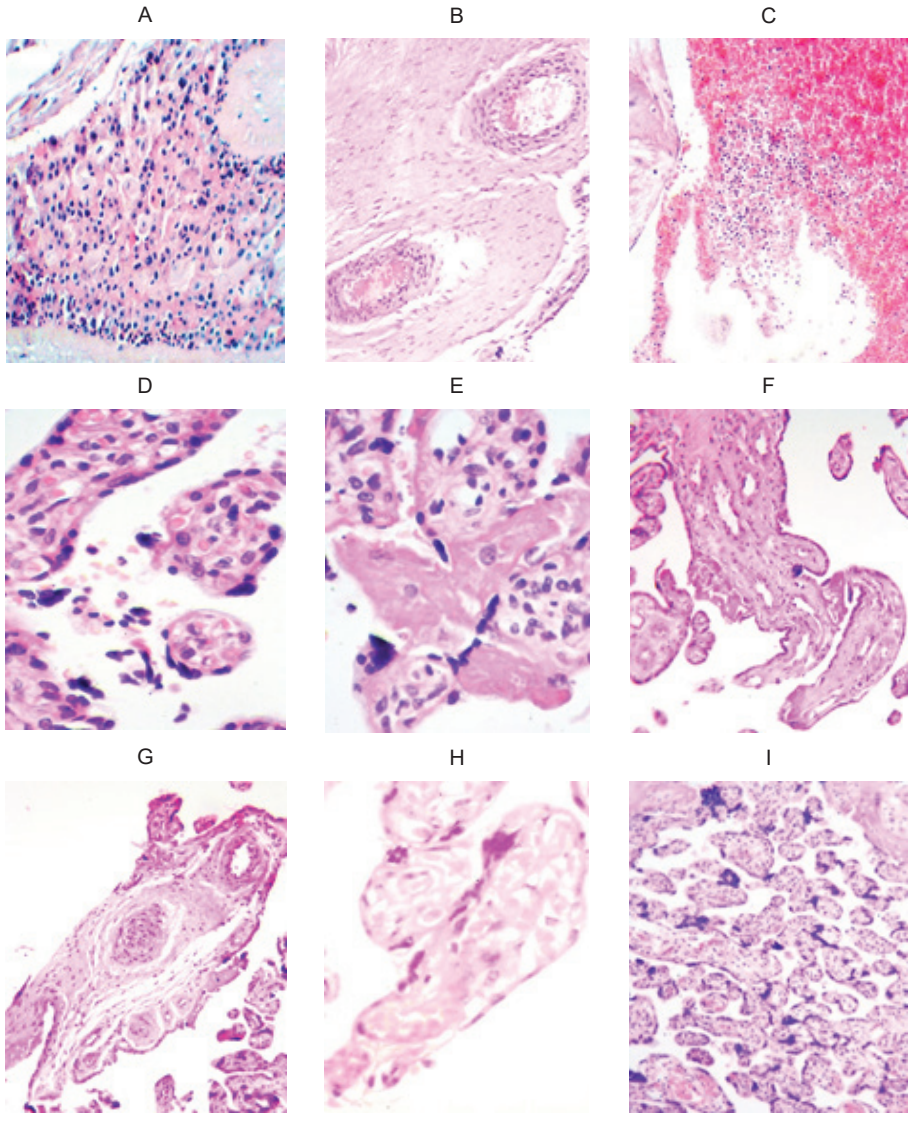
It can be concluded that the totality of the detected disorders is the result of a decrease in the effective surface area of syncytiotrophoblast, which limits the metabolic processes between mother and fetus [16]. This was confirmed by the presence of foci of necrosis of stem and intermediate villi (fig. 1F), and arterial wall fibrosis with partial obliteration of the arterial lumen (fig. 1G). In addition, chorangiosis of intermediate and terminal villi was also encountered (fig. 1H), hyperplasia of syncytiotrophoblast and increase in the number of syncytial nodules (fig. 1I), which also indicated circulatory and involutional-dystrophic changes in the placenta.

Comparative analysis of morphometric parameters of placenta of the main and control groups is presented in the table.

The placentas of the main group showed an increase in the proportion of fibrin in the intervillous space by 2.85 times ($p<0.001$) compared to the control group. The number of capillaries in terminal villi was also increased by 1.99 times ($p<0.001$). At the same time, the density of syncytiocapillary membranes decreased by 1.34 times ($p<0.001$) compared to the control group. Reduced contact zones of syncytiotrophoblast with the capillary network in the presence of hypervascularization of villi may indicate fetal blood flow disturbance.

The indicators characterizing the maturation of the villous tree in the placentas of the main group also underwent changes. An increase in the number of intermediate immature villi by 1.63 times ($p<0.001$) was detected, indicating morphological immaturity of the villous tree and decreased blood flow velocity. There was also an increase in the number of syncytial nodules by 2.09 times ($p<0.001$) compared to the control group, which may be a sign of preplacental hypoxia and changes in placental villi.

The increase in the indices of full blood



Histologic changes in the placenta from women of the main group: A – basal deciduitis with lymphoplasmacytic infiltration. Hematoxylin and eosin, magnification ×200. B – lymphocyte infiltration of stem villous vessels (vasculitis). Hematoxylin and eosin, magnification ×200. C – thrombus with admixture of endotheliocytes, lymphocytes in the lumen of the stem villous vein. Hematoxylin and eosin, magnification ×200. D – infiltration of the stroma of intermediate and terminal villi by lymphocytes, macrophages and single plasma cells (villitis), lymphohistiocytic infiltration of the intervillous space with a single accumulation of erythrocytes (intervillusitis). Hematoxylin and eosin, magnification ×400. E – perivorsinc fibrin with formation of fibrin "bridges" between intermediate and terminal villi. Hematoxylin and eosin, magnification ×400. F – focal necrosis of the stroma of stem and intermediate villi. Hematoxylin and eosin, magnification ×100. G – arterial wall fibrosis with partial obliteration of the lumen. Hematoxylin and eosin, magnification ×200. H – increased number of vessels (capillaries) in the stroma of intermediate and terminal villi (chorangiosis). Hematoxylin and eosin, magnification ×400. I – hyperplasia of syncytiotrophoblast and increased number of syncytial nodules. Hematoxylin and eosin, magnification ×100.

flow of terminal and intermediate villi, respectively, 1.36 times (p<0.001) and 1.54 times (p<0.001) compared to the control group was also noteworthy. It is likely that placental vascular hypertension is also a sign of changes in the microcirculatory system of mother–placenta–fetus.

An additional criterion of villous damage was desquamation of syncytiotrophoblast, the severity of which was higher in the main group (p<0.001) compared to the control group.

Conclusion. Summarizing our results, we can conclude that COVID-19 of moderate severity in the second and third trimesters of pregnancy causes structural placental abnormalities, which, when compensation mechanisms fail, often lead to the development of chronic subcompensated placental insufficiency. The main morphologic criteria of placental abnormalities in COVID-19 include decidual vasculopathy, perivascular inflammation with thrombus formation in the lumen of stem villous veins, villitis, intervillusitis, syncytiotrophoblast hyperplasia, and chorangiosis. Morphometric analysis showed an increase in the number of fibrinoid masses in the intervillous space, the number of capillaries in terminal villi, the number of full-blooded capillaries in terminal villi and vessels of intermediate villi, a decrease in the density of syncytiotrophoblast membranes, and an increase in the number of syncytial nodules.

The results obtained are not definitive and require further studies to investigate the morphologic features of the placenta at different severity and timing of SARS-CoV-2 infection during pregnancy.

Conflict of interest. The authors declare no conflict of interest in the submitted article.

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Morphometric indices of the placenta

Indicators	Main group (n=40)	Control group (n=20)	p
Fibrin in the intervillous space.	46.8 (40.8; 60.5)	16.4 (10.6; 26.5)	<0.001
Terminal villi with 5 or more capillaries	50.6 (37.7; 60.7)	25.4 (16.3; 37.1)	<0.001
Syncytial nodules	18.6 (15.8; 21.7)	8.9 (7.2; 11.7)	<0.001
Syncytiocapillary membranes	39.4 (34.8; 44.5)	52.8 (48.8; 57.7)	<0.001
Full blood capillaries in terminal villi	1.9 (1.6; 2.2)	1.4 (1.2; 1.7)	<0.001
Full blood vessels in intermediate villi	2.0 (1.8; 2.4)	1.3 (0.9; 1.7)	<0.001
Intermediate immature villi	42.9 (29.5; 53.0)	26.3 (18.7; 38.3)	<0.001
Desquamation of syncytiotrophoblast	1.0 (1.0; 2.0)	0.0 (0.0; 1.0)	<0.001

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УДК 616.12-008.46-06

A.S. Ankudinov, J. T.- B. Galsanova, A.L.- N. Zhamyandabayeva

CHARACTERISTICS OF LABORATORY PARAMETERS AND MORPHOFUNCTIONAL PARAMETERS OF ECHOCARDIOGRAPHY OF PATIENTS WITH CHRONIC HEART FAILURE ON THE BACKGROUND OF CHEMOTHERAPY FOR BREAST CANCER IN THE REPUBLIC OF BURYATIA

A study of echocardiographic parameters of the myocardium in patients with chronic heart failure (CHF) undergoing chemotherapy for breast cancer was conducted. The level of C-reactive protein (CRP) was assessed, and possible associations of chemotherapy with echocardiography parameters were evaluated. In the study group, statistically significant associations of CRP were found with such indicators as the blood flow rate in the late diastole caused by atrial contraction, the level of systolic pressure in the pulmonary artery and the left ventricular ejection fraction. Significant differences in these parameters were revealed compared with patients with CHF without cancer.

Keywords: chronic heart failure, breast malignancy, C-reactive protein, chemotherapy, diastolic dysfunction

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Introduction. Patients with chronic heart failure (CHF) have an increased risk of cardiotoxic effects during cancer treatment. To date, there are two types of cardiotoxicity: irreversible – this type of cardiotoxicity is characteristic of the use of anthracycline antibiotics and chemotherapy. The irreversible effect is characterized by a violation of the contractile function of the myocardium due to the death of cardiomyocytes. Reversible – damage to mitochondria and proteins responsible for myocardial contraction [5, 6, 10]. Anthracyclines, trastuzumab, alkylating agents, antimetabolites, tyrosine kinase inhibitors, angiogenesis inhibitors, checkpoint inhibitors, and proteasome inhibitors have the most pronounced cardiotoxic effects [9, 12]. The detailed mechanisms of the development and progression of CHF against the background of antitumor therapy are being actively studied. Known factors include activation of inflammatory cytokines, oxidative stress, mitochondrial damage, free radical production, and destruction of DNA and cardiomyocyte membranes [16]. Echocardiography is the leading technique for changes in myocardial contractility in patients with CHF on the background of chemotherapy. However, the changes obtained are morphological and, as a rule, may not change significantly at the initial stage of neoplasm therapy. Immunological markers are actively discussed, but they may not be available due to technical and economic reasons. From the point of view of practical healthcare, the use of routine methods is an urgent task, especially important for patients living in remote areas of the Russian Federation. Natriuretic peptides, troponins, and C-reactive protein (CRP) are one of the most accessible prognostic markers for patients with CHF on the background of chemotherapy. The most accessible marker in outpatient settings is CRP, which has both diagnostic properties in oncological pathology and is also associated with the progression of heart failure [11].

The aim: study was to conduct a comparative analysis of morphofunctional parameters and laboratory parameters of patients with CHF on the background

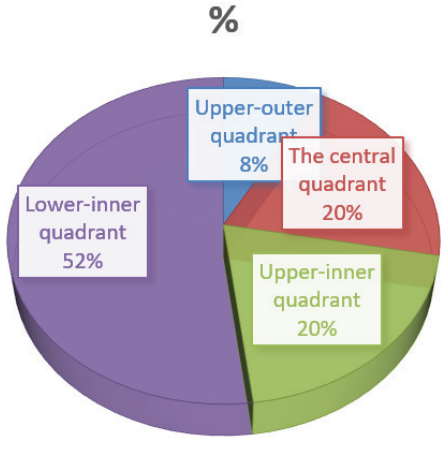

Fig. 1. Characteristics of anatomical localization of breast cancer

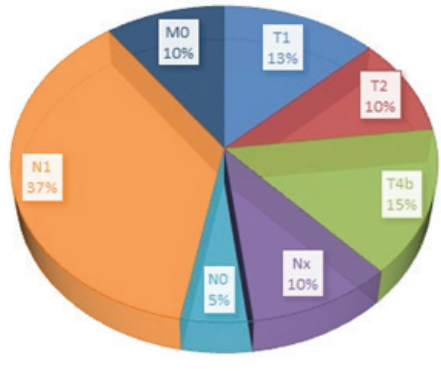

Fig. 2. Distribution of patients according to the classification of Tumor Nodulus Metastasis

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Table 1

List of medications used for chemotherapy

Drug	% of application
Pertuzumab 11	11
Anastrozole 25	25
Paclitaxel 9	9
Paclitaxel+carboplatin 24	24
Zoledronic acid+anastrozole 5	5
Doxorubicin+ cyclophosphamide 14	14
Goserelin+triptorelin+ buserelin 12	12

of chemotherapy for breast cancer and to search for possible associations of chemotherapy with the above parameters.

Materials and methods of research. The study design is a single-stage cohort study. The examined subjects are patients suffering from CHF, ischemic etiology, undergoing routine examination in a polyclinic. The study group consisted of patients with CHF, confirmed on the basis of laboratory and instrumental studies (N–terminal natriuretic peptide, transthoracic echocardiography) with a preserved left ventricular ejection fraction (LVEF) of 50% or more and moderately reduced LVEF (from 41 to 49%) undergoing chemotherapy for breast cancer (Fig. 1) The comparison group consisted of 20 patients with CHF without cancer. Exclusion criteria: CHF with reduced LVEF (40% or less); terminal cancer (multiple metastases, cachexia); intolerance to chemotherapy; surgical treatment of malignant neoplasm; refusal to participate in the study.

The average age of the participants was 64.66 (61.0-69.00) and 67.66 (60-70) years, respectively (p=0.001). The distribution of the studied group of patients according to the classification of Tumor Nodulus Metastasis (TNM) is shown in fig. 2.

The list of drugs used for chemotherapy is presented in Table 2.

There were no statistically significant differences in the frequency of chemotherapy courses. CHF treatment was carried out taking into account modern clinical recommendations and included modern groups of drugs: ace inhibitors, ARA-2, beta blockers, statins.

A comparative assessment of laboratory parameters and parameters of

Table 2

Comparative analysis of laboratory parameters

CHF				CHF with cancer			p
Parametrs	Median	Q1	Q3	Median	Q1	Q3	
ALT, Unit/l	18.49	11.21	21.08	17.63	14.29	18.33	0.530
AST, Unit/l	20.47	13.5	46.26	20.36	15.43	21.04	0.672
Total protein g/l	73.3	68.51	74.2	68.8	65.23	76.83	0.380
Total bilirubin mmol/l	12.56	8.5	13.25	11.51	5.39	12.7	0.781
Glucose, mmol/l	5.67	5.26	6.32	5.45	4.5	5.7	0.234
Iron, mmol/l	12.4	10.9	13.4	11.2	10.4	12.3	0.493
Creatinine, mmol/l	94.70	77	102.03	76.99	66.7	88.21	0.008
Uric acid, mmol/l	354.6	280.69	343.12	332.07	302.54	365.89	0.354
Urea, mmol/l	7.2	5.04	9.4	4.37	3.59	5.35	0.001
LDL, mmol/l	2.04	1.85	2.96	2.6	2.4	2.9	0.365
Total cholesterol, mmol/l	4.76	3.76	5.5	5.37	4.66	6.14	0.011
HDL, mmol/l	1.72	1.38	2.1	1.29	1.07	1.5	0.001
GFR, ml/min/1.73 m^2	83.07	75.24	88.71	87.64	84.5	97.36	0.395
CRP, mg/l	2.29	1.11	4.45	18.45	12.3	23.6	0.001
Red blood cells, 10-12/l	4.36	3.91	4.9	4.43	4.18	4.58	0.727
Hematocrit, 10^9/l	38.63	37.2	43.8	49.58	35.4	42.3	0.345
Hemoglobin, g/l	114	105	144	131.76	118	143	0.045
White blood cells, 10^9/l	5.98	4.82	7.13	5.77	3.9	7.49	0.071
Lymphocytes, %	26.4	2.83	36.1	29.96	24.3	36	0.042
Monocytes, %	6.5	5.1	6.9	10.31	6.7	10.2	0.040
ESR, mm/hr	16	5.6	36	21.42	11	28	0.021
Neutrophils, 10^9/l	48.7	46	57	51.08	45.2	55	0.971
Platelets, 10^9/l	232	119	526	253.6	198.6	286	0.672
Basophils, 10^9/l	0.4	0.1	1.9	0.28	0	0.3	0.037
Eosinophils, 10^9/l	0.51	0.1	5	0.7	0.2	3.6	0.230

Note. ALT – alanine aminotransferase, AST – aspartate aminotransferase, LDL – low-density lipoproteins, HDL – high-density lipoproteins, GFR – glomerular filtration rate, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate.

Table 3

Comparative analysis of echocardiography parameters

CHF				CHF with cancer			p
Параметр	Median	Q1	Q3	Median	Q1	Q3	
ФВЛЖ	46.7	45.0	48.6	44.03	40.4	46.2	0.241
КДР	5.09	4.8	5.4	5.02	4.6	5.2	0.671
КСР	3.3	3	3.6	3.37	3.2	3.7	0.907
ТМЖП	1.25	1.1	1.4	1.21	1.1	1.3	0.461
Объем ЛП	14.79	11.2	16.8	12.6	10.56	14.43	0.232
Объем ПП	14.4	11.5	14.06	11.8	10.2	13.2	0.270
ЧСС	67.91	62	73	69.08	65	75	0.719

Note. LVEF - left ventricular ejection fraction, CDR - final diastolic size, DAC - final systolic size, LVEF - thickness of the interventricular septum, LP - left atrium, PP - right atrium, HR - heart rate.

transthoracic echocardiography was performed.

Statistical processing of the material was performed taking into account modern SAMPLE criteria. The correspondence of the data to the Gaussian distribution was evaluated using the Kolmogorov–Smirnov criterion. The values were presented in medians indicating the upper and lower quartiles (25th and 75th percentiles). The statistical significance of the differences between the averages was assessed using the Mann–Whitney criterion (U). The associations of the studied features and their characteristics were evaluated using logistic regression analysis. The statistical hypothesis was tested and the level of statistical significance was determined at a value of $p < 0.05$ [3].

Results and discussion. A comparative analysis of laboratory parameters revealed statistically significant differences in creatinine, urea, lipidogram and some indicators of the general blood test (Table 3).

Probably, the differences obtained are due to the presence of an oncological process and side effects caused by chemotherapy. There was also a significantly increased level of CRP in the group of patients with CHF and oncopathology. The echocardiography parameters were evaluated (Table 4).

Statistically significant differences in blood flow velocity during late diastole caused by atrial contraction were obtained between the studied groups (Fig. 3) and the level of systolic pressure in the pulmonary artery (Fig. 4).

Multivariate regression analysis revealed statistically significant associations between CRP levels and chemotherapy with echocardiography. The results of the analysis in the group of patients with CHF and oncology are presented in Table 5.

Conclusion. The study of the features of the course of CHF against the background of oncological pathologies, as well as the effects of chemotherapy, is an urgent task of modern cardiology. To date, the identification of signs of decompensation of heart failure in the pre-symptomatic stages is a primary task. In the conducted study, statistically significant differences in CRP levels were obtained with a significantly higher marker level in the group of patients with oncological diseases. It is worth noting that the results obtained are not a new scientific finding, since it is already known that this marker increases in patients with

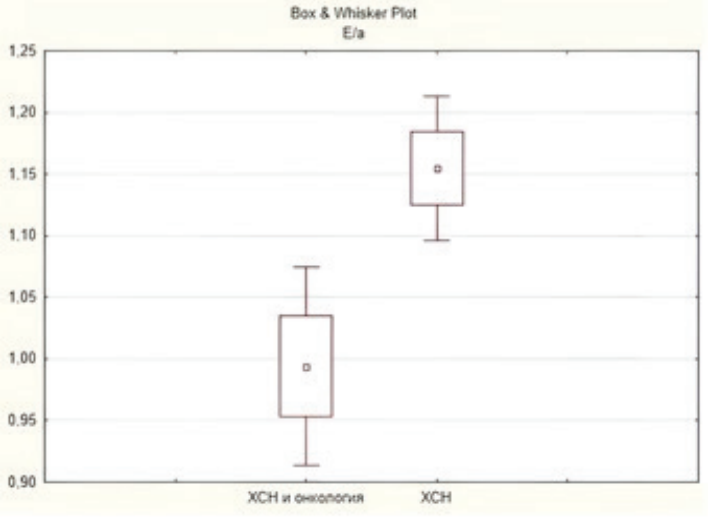

Fig. 3. Indices of blood flow velocity during late diastole induced by atrial contraction

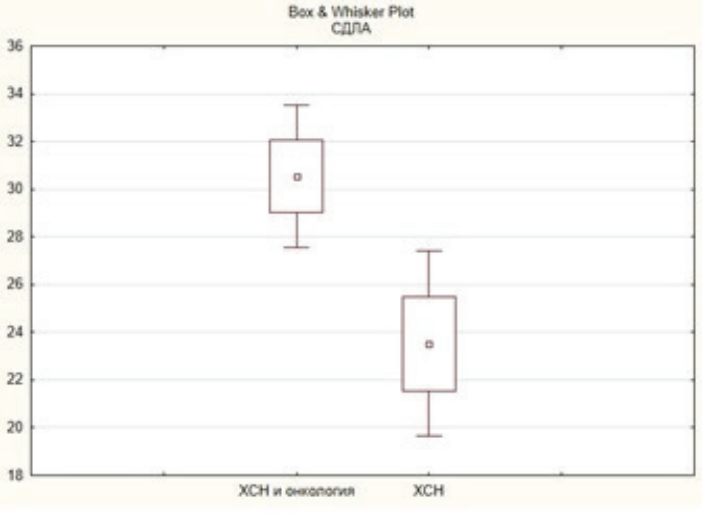

Fig. 4. Comparative analysis of systolic pressure in the pulmonary artery

Table 4

Multifactorial regression analysis with CRP levels and chemotherapy with echocardiography indicators

	R	R^2	beta	f	p
ФВЛЖ	0.129	0.016756	-0.034993	0.32380	0.576000
КДР	0.310	0.096409	0.048852	2.02721	0.170719
КСР	0.027	0.000760	-0.051832	0.01445	0.905583
ТМЖП	0.182	0.033386	-0.017488	0.65625	0.427918
Объем ЛП	0.414	0.171935	0.128353	3.94507	0.061627
Объем ПП	0.303	0.092075	0.044289	1.92683	0.181169
E/A	0.184	0.034022	-0.016819	0.66918	0.423478
СДЛА	0.535	0.286771	0.249232	7.63939	0.012355
ЧСС	0.689	0.475763	0.448171	17.24312	0.000541

malignant neoplasms [14]. It is also worth noting that CRP is associated with both the onset and course of heart failure and has a prognostic role in its development, which subsequently increases the risk of sudden cardiac death [10].

According to literature sources, patients receiving chemotherapeutic treatment in the presence of CHF, as a rule, have pronounced clinical symptoms of cardiotoxicity and morphofunctional changes in the myocardium [1]. However, our study revealed statistically significant differences only in such indicators as the blood flow rate in the late diastole caused by atrial contraction and the level of systolic pressure in the pulmonary artery, with poorer values in the group of patients with CHF and cancer. At the same time, the LVEF indicators did not differ between the groups. Thus, it should be noted that such patients, given the absence of pronounced differences in CHF symptoms and LVEF parameters, may not come under the close attention of a cardiologist. However, the association of CRP with echocardiography parameters and the differences in the above indicators probably indicate an increased risk of heart failure progression. This conclusion is consistent with the opinion of experts dealing with this problem [13]. The data obtained may indicate more pronounced changes in indicators of diastolic myocardial dysfunction and pulmonary hypertension, which may potentially indicate an increased risk of heart failure progression during treatment of malignant neoplasms.

Thus, against the background of chemotherapy for breast cancer, patients with CHF experience some significant changes reflecting a deterioration in diastolic dysfunction. It should be noted that in the regression analysis, due to the small size of the study group, it was not possible to study the effect of individual drugs on the course of heart failure, which probably requires additional research.

The authors declare that there is no conflict of interest.

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УДК 616.8

A.V. Krylov, N.I. Pavlova, S.K. Kononova, A.A. Bochurov

POLYMORPHISM OF THE SEROTONERGIC SYSTEM (5-HTTLPR) IN PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 1: A COMPARATIVE ANALYSIS USING THE MODEL OF AN ISOLATED YAKUT POPULATION

Spinocerebellar ataxia type 1 (SCA1) is a severe neurodegenerative disorder accompanied by motor and psycho-emotional disturbances. One of the factors potentially influencing the mental state of patients is the 5-HTTLPR polymorphism of the serotonin transporter gene SLC6A4. This study included 206 individuals of Yakut origin: 57 patients with confirmed SCA1 and 149 healthy controls. DNA was extracted from whole blood and PCR genotyping of the 5-HTTLPR locus was performed; genotype and allele frequencies were compared using the χ^2 test and odds ratios (OR) with 95% confidence intervals (CI) were calculated. The distribution of genotypes (LL, SL, SS) and alleles (L, S) was similar in patients and controls, with no significant differences observed (χ^2 , p=0.610). The OR for S allele carriers was 1.201 (95% CI 0.690–2.092), indicating no reliable association between the 5-HTTLPR polymorphism and the presence of SCA1. However, the overall Yakut sample demonstrated a high frequency of the short S allele and the SS genotype. These findings suggest that allele and genotype frequencies of 5-HTTLPR do not differ significantly between patients and healthy individuals (p>0.05). However, the high prevalence of the S allele and SS genotype in both groups may contribute to psycho-emotional vulnerability in the context of a severe disease course. Further studies are required to clarify the role of 5-HTTLPR in the development of depressive and anxiety disorders in patients with SCA1.

Keywords: spinocerebellar ataxia 1; 5-HTTLPR; SLC6A4; SCA1; psychogenetics

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Introduction. Neurodegenerative diseases (NDDs) are a growing medical and social problem on a global scale. They are of particular importance in regions with isolated gene pools, such as the Republic of Sakha (Yakutia), where a high incidence of hereditary diseases is recorded [2, 14]. Among them, a key place is occupied by spinocerebellar ataxia type 1 (SCA1), a progressive autosomal dominant disorder caused by a CAG expansion in the *ATXN1* gene, leading to dysfunction of the cerebellum and brainstem, and subsequent disability [2, 16].

Patients with SCA1 suffer not only from movement disorders but also from severe cognitive and psychoemotional impairments, including depression, anxiety, and emotional lability. These symptoms significantly reduce quality of life and complicate rehabilitation measures. Studying the factors modulating these conditions is an important task in clinical neurogenetics [15].

One of the factors influencing the psycho-emotional state - in particular, **a predisposition to depressive and anxiety disorders** is the 5-HTTLPR polymorphism in the serotonin transporter gene *SLC6A4*. The short allele (S) of this polymorphism is associated with reduced expression of the transport protein and increased sensitivity to stress and depression [3]. According to *Gyurak A. et al.,* the SS genotype promotes enhanced perception of negative stimuli and adverse emotional reactions. Furthermore, studies on various cohort samples indicate that carriers of the SS allele are more likely to develop anxiety and affective disorders in the presence of adverse life events [6].

In recent years, extensive data has accumulated on the involvement of the 5-HTTLPR polymorphism of the *SLC6A4 gene* in modulating the risk of developing depression and anxiety. For example, a review by *Fratelli et al. (2020)* noted that the S allele of the 5-HTTLPR polymorphism is more common in patients with depressive disorder [5]. Similar findings have been obtained in cohorts of patients with Parkinson's disease (PD). Thus, A study by *Wang et al. (2019)* showed that carriage of the SS genotype for 5-HTTLPR is associated with an increased risk of depression in patients with PD, while the LL genotype, on the contrary, has some protective effect role [18]. These results are consistent with the hypothesis that reduced expression of the serotonin transporter (SS genotype) increases susceptibility to stress and mental disorders.

Research also focuses on psychoemotional disorders in patients with neurodegenerative ataxic syndromes. *Lin et al. (2024)* described a wide range of **psychoemotional and cognitive symptoms** in autosomal dominant spinocerebellar ataxias: depression and anxiety are often found in these patients. Similarly, a cross-sectional study in Thai patients with SCA revealed a high prevalence of depression (27.3%) and its close relationship with stress levels [11]. These studies highlight the need to consider psychiatric symptoms in neurodegenerative ataxias. Furthermore, *Karamazovova et al. (2023)* showed that patients with SCA and Friedreich's disease often experience depressive and anxiety symptoms

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in combination with cognitive impairment and apathy [8].

5-HTTLPR polymorphism of the *SLC6A4* gene, affecting serotonergic neurotransmission, is considered an important factor in the genetic predisposition to depressive and anxiety disorders. Its distribution in the Yakut population has been previously described, but associations with psychoemotional vulnerability in SCA type 1 have not been studied to date [1]. Given the high frequency of the SS genotype of the gene *SLC6A4* in Asian groups [1] and the severe clinical course of SCA1, caused not only by motor but also affective disorders, it seems relevant to assess the possible modifying role of this polymorphism.

The aim of the study was to study the distribution of 5-HTTLPR polymorphism in Yakut patients with confirmed SCA1 type compared to the control group, and to discuss the possible relationship between genotypes and psychoemotional vulnerability.

Materials and methods. The work was carried out with written informed consent from all participants, protocol the study was approved by the local biomedical ethics committee of the Yakutsk Scientific Center for Complex Medical Problems (Yakutsk, protocol No. 62 dated November 22, 2024). The survey program covered socio-demographic parameters (including health status, bad habits, marital status, and hereditary diseases) along with anthropometric measurements.

To detect mutations in genes ***ATXN1*** (SCA type 1) and ***SLC6A4*** DNA samples from patients from the biomaterial collection of the Yakut Scientific Center for Complex Medical Problems and the Yakutia Genome Research Institute (registration number USU_507512) were used. All patients consulted a geneticist at the Medical and Genetic Center of the Republican Hospital No. 1 of the National Center of Medicine (MGC RH No. 1 NCM) and underwent inpatient treatment at the hospital of the FSBSI Yakut Scientific Center for Complex Medical Problems (YSC CMP). The experimental part of the work on identifying the expansion of CAG repeats in the gene ***ATXN1*** and **INS/DEL** in the gene ***SLC6A4*** The study was conducted in the Hereditary Pathology Laboratory of the Molecular Genetics Department of the YSC CMP. The total sample size was 206 people, of whom 57 (29 women, 28 men) aged 30 to 85 years had SCA1. The control group consisted of 149 people (120 women, 29 men) of Yakut ethnicity without neurological or mental illnesses.

For molecular genetic analysis, DNA was extracted from whole blood using a commercial Newteryx DNA extraction kit (Yakutsk, Russia) according to the manufacturer's instructions. DNA concentration in each sample was determined using a spectrophotometer. **Implen NanoPhotometer** (Germany).

For gene analysis ***ATXN1*** Polymerase chain reaction (PCR) was used. The diagnosis of SCA1 was established in a proband with a characteristic clinical picture and an abnormal expansion of CAG triplets in the gene ***ATXN1***, identified through molecular genetic testing. Patients typically have 39 or more CAG repeats (more than 316 nucleotide pairs) (see Figure 1).

Figure 1. Electropherogram of the *ATXN 1* gene region in 4% agarose gel for detection of CAG repeat expansion.

Note. 1, 2, 4, 11, 12, 13, 14 – length of CAG repeats of PCR amplification within 212 – 316 nucleotide pairs; 3, 5, 6, 7, 8, 9 and 10 – length of CAG repeats of PCR amplification is more than 316 nucleotide pairs; M – Step100 marker; bp – nucleotide pairs.

Amplification of a gene region ***ATXN1*** **PCR**, containing a polymorphic region, was performed using primers manufactured by Lumiprob RUS LLC (Moscow). The reaction mixture included: forward and reverse primers (1 µl each), DreamTaq PCR Master Mix (2×) — 12.5 µl, deionized water — 9.5 µl, DNA — 1 µl.

Polymorphism Analysis **5-HTTLPR (44-BP INS/DEL)** gene ***SLC6A4*** was also carried out by the PCR method. Amplification of the gene region containing the polymorphic variant was carried out similarly using primers from Lumiprobe RUS LLC. The composition of the reaction mixture: forward and reverse primers, 1 µl each, buffer - 2.5 µl, betaine - 5 µl, dNTPs - 4 µl, Taq polymerase - 0.25 µl, deionized water - 10.25 µl, DNA - 1 µl. The amplification conditions are presented in Table 1. Interpretation of the genotyping results was performed on the basis of different band templates for the genotypes SS - 376 bp; SL - 420 bp, 376 bp; LL - 420 bp (Figure 2).

Table 1. Conditions for performing PCR analysis

Note. The table shows the forward (F) and reverse (R) primers used to amplify regions of *the ATXN1* and *SLC6A4* genes. For the *ATXN1 gene,* the amplification length varies depending on the number of CAG repeats (≥212 bp). For the 5-HTTLPR locus of the *SLC6A4* gene, two amplification lengths are presented: L is the long allele (419 bp), S is the short allele (376 bp). The annealing temperature was selected individually for each primer set.

Figure 2. Electropherogram of *the SLC6A4* gene region in 4% agarose gel.

Note. 1, 2, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 18, 19 – SS genotype; 3, 8, 13 and 14 – SL genotype; 5 – LL genotype; M – Step 100 marker; bp – nucleotide pairs.

Statistical analysis of the obtained research results was performed using the program "Office Microsoft Excel 2010". Correspondence of the genotype distribution to the expected values of the Hardy-Weinberg equilibrium and comparison of the frequencies of allelic variants/genotypes were performed using the χ (chi-square) test by the Pearson method for 2x2 contingency tables, calculating the odds ratio (OR), 95% confidence interval (95% CI). Differences were considered statistically significant at $p < 0.05$.

Results. Table 2 presents the distribution of genotypes (LL, SL, SS) and alleles (L, S) of the 5-HTTLPR polymorphism of the *SLC6A4 gene* in patients with SCA1 and a control group of healthy Yakuts. Comparison of the total sample of patients with SCA1 (n=57) and the control group without signs of neurodegenerative diseases (NDD) revealed no statistically significant differences in the frequency of genotypes and alleles (χ^2, p=0.610).

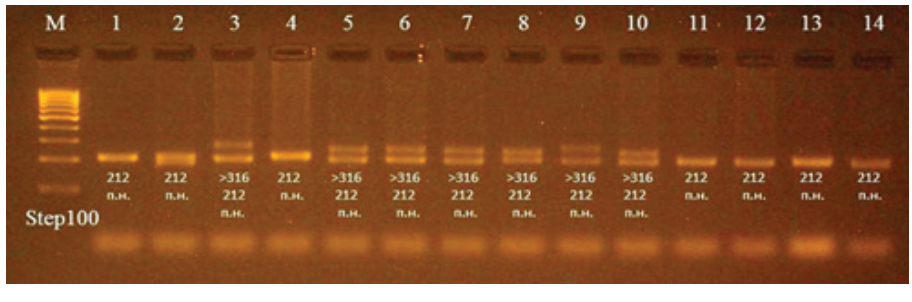

Fig. 1. Electropherogram of the ATXN 1 gene region in 4% agarose gel for detection of CAG repeat expansion.
Note. 1, 2, 4, 11, 12, 13, 14 – length of CAG repeats of PCR amplification within 212 – 316 nucleotide pairs; 3, 5, 6, 7, 8, 9 and 10 – length of CAG repeats of PCR amplification is more than 316 nucleotide pairs; M – Step100 marker; bp – nucleotide pairs

Table 1

Conditions for performing PCR analysis

Gene	Primer sequence	Length of n.p.	Annealing temperature
ATXN1	F:5'-CAACATGGGCAGTCTGAG-3'	212< n.p.	60 °C
	R:5'-AACTGGAAATGTGGACGTAC-3'		
SLC6A4	F:5'-GGACCGCAAGGTGGGCGGGA-3'	L – 419 n.p. S – 376 n.p.	62 °C
	R:5'-ATGCCAGCACCTAACCCCTAATGT-3'		

Note. The table shows the forward (F) and reverse (R) primers used to amplify regions of the ATXN1 and SLC6A4 genes. For the ATXN1 gene, the amplification length varies depending on the number of CAG repeats (≥212 n.p.). For the 5-HTTLPR locus of the SLC6A4 gene, two amplification lengths are presented: L is the long allele (419 n.p.), S is the short allele (376 n.p.). The annealing temperature was selected individually for each primer set

Fig. 2. Electropherogram of the SLC6A4 gene region in 4% agarose gel.
Note. 1, 2, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 18, 19 – SS genotype; 3, 8, 13 and 14 – SL genotype; 5 – LL genotype; M – Step 100 marker; bp – nucleotide pairs

Table 2

Frequency of 5-HTTLPR genotypes and alleles of the SLC6A4 gene in patients with SCA1 and control subjects of the Yakut population

Study groups	LL	SL	SS	L	S	OR (CI 95%)	p
Group without NDD	5.7	32.3	62.0	21.8	78.2	1.201 (0.690–2.092)	0.610
Patients with SCA1	5.7	26.4	67.9	18.9	81.1		
Men without NDD	8.1	24.3	67.6	20.3	79.7	0.885 (0.466–1.683)	0.832
Women without NDD	5.0	34.7	60.3	22.3	77.7		
Male patients with SCA1	4.0	28.0	68.0	18.0	82.0	0.898 (0.338–2.386)	0.974
Male patients with SCA1	7.1	25.0	67.9	19.6	80.4		

Note. The table presents the percentage values of the frequencies of the LL. SL. SS genotypes and the L and S alleles of the 5-HTTLPR polymorphism of the SLC6A4 gene in the study groups. OR is the odds ratio (Odds Ratio) for carriage of the S-allele; CI — 95% confidence interval; p — the value of the level of statistical significance according to the χ^2 criterion. Values of $p < 0.05$ are considered statistically significant. Discrepancies between the sum of percentage values are possible due to rounding

The calculated odds ratio (OR) for carriage of the S allele was 1.201 with a 95% confidence interval of 0.690–2.092, indicating the absence of a significant association between this polymorphism and the presence of SCA1 in the study cohort.

Table 2. Frequency of 5-HTTLPR genotypes and alleles of the *SLC6A4 gene* in patients with SCA1 and control subjects of the Yakut population

Note. The table presents the percentage values of the frequencies of the LL, SL, SS genotypes and the L and S alleles of the 5-HTTLPR polymorphism of the *SLC6A4 gene* in the study groups. OR is the odds ratio (Odds Ratio) for carriage of the S-allele; CI — 95% confidence interval; p — the value of the level of statistical significance according to the χ^2 criterion. Values of $p < 0.05$ are considered statistically significant. Discrepancies between the sum of percentage values are possible due to rounding.

No statistically significant differences were found in the analysis of gender subgroups. In men with SCA1, the proportion of the SS genotype was 68.0%, while in men without NDD it was 67.6%. In women with SCA1, the frequency of the SS genotype was 67.9%, while in healthy women it was 60.3%. The S allele was the most common in all subgroups: from 77.7% in healthy women to 82.0% in men with SCA1. However, none of the differences reached statistical significance: p -values for the subgroups were 0.832 (men) and 0.974 (women), and the calculated odds ratios ranged from 0.885 to 0.898 with wide confidence intervals including unity.

Thus, the frequencies of the LL, SL, and SS genotypes, as well as the L and S alleles, were similar in the patient and control groups. In all comparisons, p values exceeded the threshold for statistical significance ($p>0.05$), and the odds ratios did not indicate a significant risk associated with the presence of the S allele. These data confirm the absence of a statistically significant association between the 5-HTTLPR polymorphism and the presence of SCA1 in the Yakut population.

Discussion. The obtained results did not reveal a statistically significant difference in the frequency of genotypes and alleles of the 5-HTTLPR polymorphism of the *SLC6A4 gene* between patients with SCA1 and healthy control subjects of the Yakut population ($p>0.05$). This is consistent with the statement that the Yakut population is characterized by a high frequency of carriage of the S-allele and SS-genotype [1], regardless of the presence of a neurodegenerative disease.

However, given that the short S allele is associated with reduced expression of the serotonin transporter and increased reactivity to stress and depression [3, 9], its prevalence in patients with SCA1 may be considered a potential **psycho-emotional status modifier** in the context of a progressive incurable disease. Neuroimaging studies and meta-analysis of data have shown that carriage of the SS genotype is associated with increased activity of the amygdala when exposed to negative stimuli and greater vulnerability to affective disorders [9, 10].

It is important to take into account that patients with SCA1 often experience depressive and anxiety disorders; according to some data, the incidence of depression among patients with SCA1 can reach 25% [15]. These disorders are interpreted as part of the cerebellar cognitive-affective syndrome, caused by cerebellar degeneration and involvement of frontolimbic circuits [13].

However, the role of the S-allele cannot be viewed as unambiguously negative. The review by *Homberg and Lesch (2011)* emphasizes that increased sensitivity to emotional stimuli in carriers of the SS genotype may also have adaptive potential, contributing to greater attention and cognitive flexibility in conditions of uncertainty [7]. A number of studies have described associations between the S-allele and indicators of cognitive functions. Thus, in the study by *Volf et al. (2015)*, a link was found between the SS genotype and higher IQ scores in a sample from Novosibirsk, although the authors emphasize that this association may reflect both biological and socio-cultural factors. Other studies indicate correlations between the S-allele and more productive divergent thinking and cognitive flexibility [17]. Thus, the high frequency of the S-allele in the Yakut population can be seen as a reflection of an evolutionary compromise: on the one hand, vulnerability to stress, on the other, advantages in certain cognitive domains.

Of particular interest are studies devoted to motor functions. *Savostyanov et al. (2021)* showed that carriers of the SS genotype exhibit higher levels of personal anxiety, but at the same time, they demonstrate better motor self-control (based on premotor potentials), especially in samples with a predominantly Mongoloid ethnic component (Yakuts, Tuvans) [12]. These results suggest that in patients with SCA1, for whom motor impairments are a key symptom, the presence of the SS genotype may not only enhance psychoemotional vulnerability but also potentially partially compensate for some aspects of motor deficit.

Thus, the widespread distribution of the S-allele and SS-genotype in the Yakut population can be viewed in two ways: as a risk factor for the development of depressive and anxiety states against the background of a severe neurodegenerative process (SCA1), and simultaneously as a possible protective element against motor control disorders. This "duality" of genetic effects is consistent with the concept of evolutionary compromise [7]. A challenge in effectively reducing comorbid anxiety and depressive symptoms during the maintenance treatment of patients with SCA1 in the Yakut population may be the high prevalence of the S-allele, which is associated with adverse reactions to treatment with selective serotonin reuptake inhibitors (SSRIs) [4]. Further clinical and neurophysiological studies aimed at identifying the modifying role of 5-HTTLPR in SCA1 are needed for definitive verification of these hypotheses.

Conclusion. In the Yakut sample studied, no statistically significant differences were found in the frequency of 5-HTTLPR alleles and genotypes between patients with SCA1 and the control group. However, the high prevalence of the S allele in both groups suggests its possible role as a vulnerability factor to psychoemotional disorders in SCA1. Given the association of the SS genotype with depression and anxiety, its presence may enhance adverse reactions to disease-related stress. Further research is needed to assess the impact of this polymorphism on patients' mental health.

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CLINICAL AND MORPHOLOGICAL FEATURES OF THE PLACENTA IN EXTREMELY AND DEEPLY PREMATURE INFANTS

Placenta is a connecting link between mother and fetus. The article is devoted to the problem of identifying pathological changes in the placenta for the diagnosis of various clinical conditions in a premature extremely immature child. The continuous sampling method examined 131 afterbirth (96 afterbirth of extremely premature infants with a gestational age of less than 28 full weeks and 35 afterbirth of premature infants from 28 to 32 weeks of gestation). A comparative analysis of the main morphometric parameters of the placenta was performed; the presence of inflammatory diseases of the placenta (chorioamnionitis; deciduitis; placentitis; funiculitis, villousitis, phlebitis of umbilical cord vessels); the presence of acute placental circulatory disorders, chronic decompensated placental insufficiency. The results obtained for each of the latter were entered into a common database and subjected to statistical processing. When comparing the main clinical and morphometric parameters of live and stillborn babies at gestation from 22 to 32 weeks, a significant difference was found in fetal weight, gestation period, placenta mass and umbilical cord mass. An intrauterine infection, manifested by villousitis and deciduitis, increases the probability of stillbirth by 3.3 times at 22 to 28 weeks of gestation. The presence of placental involution increases the risk of stillbirth by 17.3 times. Histological examination of the placenta is an important step in diagnosing the causes of stillbirth at 22 to 32 weeks of gestation.

Keywords: placenta, extreme immaturity, premature, stillbirth, intrauterine infection, involution

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Introduction. The placenta plays an important role in fetal development and function, being a link between the mother and the fetus, providing nutrition and gas exchange for the fetus, participating in the removal of metabolic products [10], determining fetal growth. Placental weight and neonatal body weight are highly correlated [13], changes in placental function can be biological predictors of the child's health. Gross morphological and histopathological features of the placenta are associated with adverse fetal outcomes, therefore, placental biomarkers can be used to predict outcomes due to the fact that the impact can be subclinical and invisible to the clinician, which is important for prognosis [7].

Many pregnancy complications are associated with abnormal placental development in the first trimester, the most dramatic are preeclampsia, fetal growth restriction, unexplained stillbirth, placental abruption and premature birth [14].

One of the important problems of perinatology is the infectious factor: thus, chorioamnionitis, confirmed histologically and clinically, or infection of the amniotic cavity are associated with a higher probability of early and late sepsis in premature infants [5, 9], is an independent risk factor for the development of IVH in premature infants [11]. The frequency of chorioamnionitis in premature infants aged 21 to 37 weeks of pregnancy was 18.7%, while in full-term infants it was only 3.9% [8].

Detection of pathological changes in the placenta may be important for the diagnosis of various clinical conditions in a premature extremely immature child [9].

The purpose of the study is to identify the clinical and morphological features of the placenta in liveborn and stillborn extremely and deeply premature infants.

Materials and methods. A continuous sampling method was used to study all placentas of premature babies born alive and stillborn in Khabarovsk from January 2020 to December 2023. A total of 131 placentas were studied (96 placentas of extremely premature babies with a gestational age of less than 28 completed weeks and 35 placentas of premature babies from 28 to 32 weeks of gestation).

Inclusion criteria are placentas of premature babies, gestational age less than 28 and more than 32 weeks, availability of complete primary medical records.

Exclusion criterion are congenital malformations incompatible with life leading to stillbirth.

The source of information was the data of medical documentation: N 097-1 / y-97 "History of the development of the newborn" and form N 003 / y "Medical record of a patient receiving medical care in inpatient settings, in a day hospital." The pathological examination was carried out according to a single protocol, within 24 hours from the moment of birth of the placenta, in the pathological department of the KGBUZ "Perinatal Center named after G.S. Postol", a morphological study of the placenta and an overview histological study were carried out. The mass of the placenta in grams was determined on the electronic scale "Sasha". Excision of pieces of tissue for an overview histological study was carried out in the central,

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paracentral, marginal and pathologically altered parts of the placenta, as well as the umbilical cord and extraplacental membranes. The obtained material was fixed in 10% neutral formalin after standard paraffin wiring. The overview histological examination was carried out in accordance with the methodological recommendations "Rules for conducting pathological and anatomical studies of the placenta" [3], which provide for an assessment of the maturity of the villous chorion, diagnosis of disorders of the uteroplacental and fetoplacental blood circulation, as well as an assessment of compensatory processes and a statement of placental insufficiency with clarification of the form and stage of the same. The morphofunctional assessment of the placenta was carried out by a pathologist according to the order (N82 of April 29, 1994) [4]. A macroscopic description of the placenta and a study of micropreparations (Leica TP1020, Germany) were carried out using a Nikoneclipse E200 light microscope (Japan), which included data on the mass, shape, size and structure of the placenta, characteristics of the umbilical cord, fetal membranes, a description of the structural components of the placenta, membranes, the presence of involutional-dystrophic changes, as well as the calculation of the placental-fetal coefficient (PFC). The nature of fetoplacental insufficiency was assessed by the duration of its course and the degree of compensation according to the classification adopted in obstetrics [1].

The following parameters were compared: placenta weight, length, width and thickness; umbilical cord weight, thickness and number of vessels; fetal membrane weight; placental-fetal coefficient (PFC); membranous-placental coefficient (MPC); child's body weight; gestational age; presence of inflammatory placental diseases (chorioamnionitis; deciduitis; placentitis; funiculitis, villusitis, phlebitis of umbilical cord vessels); presence of acute placental circulatory disorder, chronic decompensated placental insufficiency. The fetal-placental coefficient (PPC) serves as an objective morphological indicator of the circulatory-metabolic balance of the fetoplacental system and, under conditions of normal pregnancy, fluctuates within the range of 0.11–0.14. Exceeding this indicator indicates compensatory hyperplasia of placental tissue, which is typical for the compensated stage of chronic placental insufficiency. A decrease in the IPC is associated with chronic subcompensated and decompensated placental insufficiency, the development of intrauterine hypoxia, intrauterine growth retardation, and a high risk of intrauterine fetal death.

IPC is an integral indicator of the drainage function of the placenta, which largely corrects the volume and composition of the amniotic fluid. The normal level of IPC is 0.10–0.13 and increases as the filtration properties of the fetal membranes deteriorate, reaching maximum values (0.18–0.22) in severe forms of ascending bacterial infection of the placenta, occurring with exudative choriodeciduititis [2].

The results obtained for each placenta were entered into a common database and subjected to statistical processing. The description of quantitative indicators is performed indicating the median (Me), minimum and maximum values (min; max). Comparison of quantitative indicators in the comparison groups was performed using the Mann-Whitney test and Fisher's point test. Correlation analysis was performed using the Spearman rank correlation method. To assess the relationship between the studied factors and outcomes in the comparison groups, the odds ratio (OR) with the calculation of the confidence interval (95% CI) was used. Statistical analysis of the study results was performed using the statistical programs STATISTICA, version 12.0 (StatSoft Inc., USA), IBM SPSS Statistics 20. The level of statistical significance when testing the null hypothesis was considered to be p <0.05. The study was approved by the local ethics committee at the Far Eastern State Medical Univer-

Table 1

Comparative clinical and morphological characteristics of the study groups

Indicators	Gestation period up to 28 weeks, n=96	Gestation period 28-32 weeks, n=35	r
Live births, abs, %	67 (69.8)	30 (85.7)	-
Stillbirths, abs, %	29 (30.2)	5 (14.3)	-
Placenta weight, g Me (min ; max)	191.5 (90.0-616.0)	240.0 (80.0-655.0)	p<0.05
Placenta length, cm Me (min ; max)	14.0 (10.0-24.0)	15.0 (10.0-23.0)	p>0.05
Placenta width, cm Me (min; ma x)	12.0 (6.0-18.0)	12.0 (7.5-18.0)	p>0.05
Placenta thickness, cm Me (min ; ma x)	1.5 (0.4-5.0)	1.5 (0.8-2.5)	p>0.05
Baby's weight at birth, g Me (min; max)	710 (370-1490)	1120 (430-1640)	p<0.01
Gestation period, Me (min; max)	25 нед. (22 нед. - 27 нед. 6 дн.)	28 нед. (28 нед. - 32 нед.)	p<0.01
Umbilical cord weight, g Me (min; max)	19.0 (4.7-76.0)	28.0 (8.0-59.0)	p<0.05
Thickness of the umbilical cord, cm	1.5 (0.5-2.0)	1.3 (0.7-2.0)	p>0.05
Number of umbilical vessels Me (min; max)	3 (3-3)	3 (3-3)	p>0.05
Shell weight, g Me (min; max)	20.0 (2.0-80.0)	27.0 (8.0-66.0)	p>0.05
Placental-fetal coefficient, conventional unit Me (min; max)	0.31 (0.1-1.05)	0.21 (0.13-0.47)	p>0.05
Membranous-placental coefficient, conventional unit Me (min; max)	0.11 (0.02-0.61)	0.12 (0.03-0.39)	p>0.05

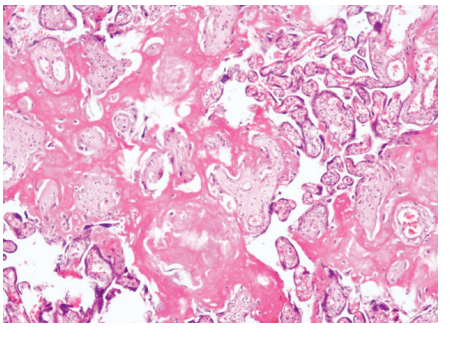

Fig. 1. Placenta x 10. Fibrinoid necrosis of chorionic villi - histological picture of chronic decompensated insufficiency

sity of the Ministry of Health of the Russian Federation (protocol No. 2 dated 16/05/2024).

In the first group of premature infants born in very early preterm labor at a gestation period of less than 28 weeks, 67 children (69.8%) were born alive; 29 fetuses (30.2%) were stillborn. In the second group, represented by children with a gestation period of 28-32 weeks, the majority (30 children) were born alive (85.7%), 5 children (14.3%) were stillborn.

The median placenta weight in the first group was 191.5 grams, in the second group, naturally, the median was higher and amounted to 240.0 grams. A statistically significant difference was found between the placenta weight, the umbilical cord weight, the gestational age and the body weight of the child (Table 1).

When comparing live and stillborn children born at 22-28 weeks of gestation, a significant difference was noted only in fetal body weight: in live births, the IBW was 800 grams, while the IBW in stillborns was 497 grams ($p<0.05$). In the group of live and stillborn children with a gestation period of 28-32 weeks, statistically significant differences in the analyzed characteristics were not found ($p>0.05$).

There are no significant differences between stillborn and live births at 22-28 weeks, as well as live and stillborn children at 28-32 weeks of gestation in either acute placental circulatory disorder or chronic decompensated placental insufficiency (Figure 1).

When analyzing the correlation relationships between stillbirths and the analyzed characteristics, a direct relationship of medium strength was established between stillbirths and the value of the AUC ($r = 0.51$; $p < 0.05$); the frequency of implantation failure ($r = 0.55$; $p < 0.05$) and placental involution ($r = 0.60$; $p < 0.05$) in stillbirths born at 22 to 28 weeks of gestation. No other significant relationships of medium and high strength were found with this method of statistical processing (Table 2).

When determining the odds ratio (Table 3), there is an increased relationship between placental involution and stillbirth at 22-28 weeks of gestation (OR 17.26 (1.97-150.70)). There is a relationship between deciduitis OR 3.95 (1.43-10.93) and willusitis OR 2.52 (1.03-6.14) with stillbirth of children up to 28 weeks of gestation (Figure 2).

The simultaneous presence of deciduitis and villousitis increased the incidence of stillbirth by 3 times (OR = 3.24, 95% CI (1.28 - 8.18)). However, many inflammatory diseases of the placenta (placentitis, chorioamnionitis) were equally characteristic of both live and stillbirths at 22-32 weeks of gestation (Figure 3).

R.K. Kersonsky and co-authors found that in extremely premature stillbirths, delayed maturation of the villi and a decrease in the number of nucleated erythrocytes were observed, indicating a lesser role of hypoxia as a cause of death in this group [6].

Disruption of blood circulation between the fetus and the mother is a common cause of stillbirth. The fetal vascular lesions observed in the placenta likely result from impaired fetal blood flow, which may be caused by fetal heart failure, umbilical cord occlusion, or hypercoagulability leading to venous congestion and venous thrombosis [12]. Previously referred to as uteroplacental insufficiency, maternal vascular perfusion is a consequence of inadequate extravillous trophoblast invasion and spiral artery remodeling

Table 2

Correlations between the studied factors and stillbirth

Indicators	Stillbirth Gestation period up to 28 weeks	Stillbirth Gestation period 28-32 weeks
Weight placenta, g	0.14 p<0.05	0.32 p<0.05
Length placenta, cm	0.23 p<0.05	0.29 p<0.05
Width of the placenta, cm	0.05 p<0.05	0.28 p<0.05
Thickness placenta, cm	0.35 p<0.05	0.33 p<0.05
Baby's weight at birth, g	-0.056 p>0.05	0.30 p<0.05
Term gestation	-0.04 p<0.05	-0.615 p<0.05
Weight umbilical cords, gr	0.06 p<0.05	0.15 p<0.05
Thickness umbilical cord, cm	0.13 p<0.05	0.16 p<0.05
Weight shells, gr	0.08 p>0.05	0.33 p<0.05
Placental-fetal coefficient, conventional unit	0.51 p<0.05	0.31 p<0.05
Membranous-placental coefficient, conventional unit	0.165 p<0.05	0.25 p<0.05
Swelling Vartanova well	0.38 p<0.05	-0.54 p>0.05
Deciduitis	0.46 p<0.05	0.36 p<0.05
Funiculitis	0.41 p<0.05	-0.40 p>0.05
Placentitis	0.05 p<0.05	-0.48 p>0.05
Chorioamnionitis	0.23 p<0.05	0.10 p<0.05
Villusite	0.40 p<0.05	0.60 p>0.05
Phlebitis vessels umbilical cord	0.49 p<0.05	0.45 p<0.05
Hypoplasia placenta	0.36 p<0.05	0.55 p>0.05
Involution placenta	0.60 p<0.05	0.23 p>0.05
Spicy violation placental blood circulation	0.38 p<0.05	0.54 p>0.05
Violation implantation	0.55 p<0.05	0.59 p>0.05

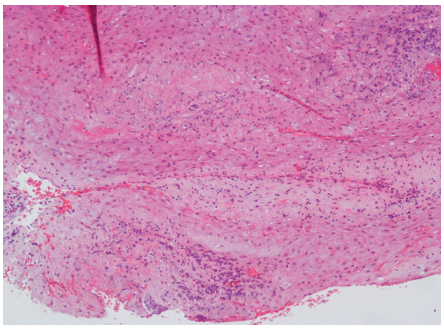

Fig. 2. Placenta x 10. Lymphocytic necrotic deciduitis

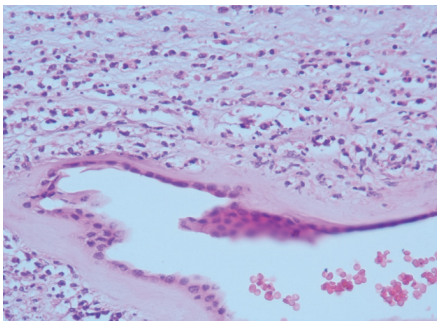

Fig. 3. Placenta x 40. Lymphocytic amnionitis

[15]. Inflammatory and molecular changes in the placenta have also been found in pregnancies complicated by stillbirth. Dysregulation of maternal immune function is also a consequence of impaired extravillous trophoblast invasion [15].

Conclusions. When comparing the main clinical and morphometric parameters of the placentas of live and stillborn babies at a gestation period of 22 to 32 weeks, a reliable difference was found only in fetal weight, gestation period, placental weight, and umbilical cord weight.

A high level of inflammatory diseases of the placenta is noted in both stillborn and liveborn babies; intrauterine infection, manifested by villusitis and deciduitis, increases the likelihood of stillbirth by 3.3 times at a gestation period of 22 to 28 weeks.

Correlation analysis revealed a moderate-strength relationship between the placentas, the frequency of implantation failure, and placental involution in stillborn babies in the period from 22 to 28 weeks of gestation: the presence of placental involution increases the risk of stillbirth by 17.3 times.

Thus, histological examination of the placenta is an important stage in the diagnosis of the causes of stillbirth at a gestation period of 22 to 32 weeks and can serve as the basis for the development of preventive measures for the prevention of extreme prematurity and stillbirth.

Table 2

Odds ratio between stillbirth and the factors studied

Indicators	Gestation period up to 28 weeks	Gestation period 28-32 weeks
Deciduit	3.95 (1.43-10.93)	0.75 (0.13-4.25)
Funiculitis	1.46 (0.5-4.19)	-
Placentitis	0.24 (0.09-0.67)	-
Chorioamnionitis	0.74 (0.30-1.81)	-
Villusit	2.52 (1.03-6.14)	6.0 (0.93-38.5)
Phlebitis vessels umbilical cord	0.30 (0.04-2.60)	-
Hypoplasia placenta	1.32 (0.49-3.58)	0.50 (0.05-4.83)
Involution placenta	17.26 (1.97-150.70)	-
Spicy violation placental blood circulation	1.174 (0.393-3.50)	-
Chronic decompensated placental insufficiency	1.25 (0.5-3.1)	-
Violation implantation	1.47 (0.13-6.33)	1.20 (0.11-12.53)

The authors declare no conflict of interest.

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FEATURES OF THE ORAL MICROBIOME COMPOSITION IN MEN WITH GASTROESOPHAGEAL REFLUX DISEASE WITH ESOPHAGITIS

This article presents a study conducted to investigate changes in the oral microbiome composition in patients with gastroesophageal reflux disease (GERD) with esophagitis and to identify potential microbiological predictors of complications. A total of 106 patients with a previously verified diagnosis participated. Quantitative real-time PCR was the primary method for assessing the oral microbiome composition. A significant decrease in all phyla of the studied bacteria was found in patients with GERD compared to the control group. The bacterial phyla studied can be used as a predictor of GERD development only in healthy individuals to determine the likelihood of inflammation in healthy mucous membranes, which requires further exploration and study of new biomarkers. The objective of the study was to determine the composition of the oral microbiome in patients with GERD of varying severity and to identify potential microbiological predictors of GERD complications. A total of 106 men aged 35.5±3.4 years were examined, 27 of whom were somatically healthy and 79 of whom were diagnosed with GERD with esophagitis (according to the Los Angeles classification: 26 people with GERD-A, 25 people with GERD-B, and 28 people with GERD-C), who were in remission at the time of examination. A comparison of the oral microbiome status was conducted in healthy men and men with GERD. In patients with GERD-A and GERD-B, reliable differences were found only in relation to bacteria. *Bacteroidetes* – a decrease in their level was noted, *Firmicutes* – an increase in their content in the oral cavity was recorded depending on the severity of GERD, and also phylum *Tenericutes* – an increase in bacterial counts was detected in severe stages of GERD. It is worth noting that patients with GERD-C showed a significant decrease in all phyla of the studied bacteria. The bacterial phyla we studied can be used as a predictor of GERD development only in healthy individuals, to determine the likelihood of GERD with esophagitis.

Keywords: gastroesophageal reflux disease, microbiome, predictor, *Bacteroidetes*, *Firmicutes*, *Tenericutes*

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Introduction. Gastroesophageal reflux disease (GERD) is a chronic polyetiologic disorder characterized by a primary impairment of the motor-evacuation function of the upper gastrointestinal tract (GIT) and the presence of pathological gastroesophageal reflux [2]. According to statistics, both in Russia and worldwide, GERD is one of the leading causes of outpatient medical care for both men and women of young, middle-aged, and elderly age [5]. According to the Russian Ministry of Health, the prevalence of this pathology in the population reaches 13.98% and continues to grow steadily [2]. According to the results of a multicenter study of the prevalence of GERD symptoms in the regions of the Russian Federation, this figure is 34.2%. According to foreign sources, the prevalence of GERD in various countries of the world ranges from 8% to 37% and also shows an upward trend [10]. Due to the increasing frequency of occurrence of the nosology, the presence of complicated forms (esophageal and gastric cancer), as well as extraintestinal manifestations of the disease, such as stomatitis, tonsillitis, chest pain, cough, tooth damage, lesions of the oral mucosa, bronchial asthma, in patients of all age categories, early diagnosis of the disease is becoming especially relevant.

It is known that the adult human body contains 10^{12}–10^{14} different microorganisms. Interaction between the microbiome and the individual occurs in absolutely all structures of the gastrointestinal tract. Special studies have confirmed that certain bacterial strains can cause chronic inflammation of the oral mucosa and the upper gastrointestinal tract (esophagus, stomach, and duodenum). Patients with GERD have a mixed flora, including the oral microbiome (gram-positive bacteria) and gastric microbiome (gram-negative anaerobes), which, as a result of reflux, tends to grow in the mucosa [1, 4]. A number of authors have demonstrated the role of the microbiome in esophageal motor function, including the development of reflux. This is associated with the activation of Toll-like receptors by interaction with lipopolysaccharides of the bacterial cell wall, which entails the activation of nuclear factor and the production of inflammatory cytokines [3, 6, 7].

The aim of our study was to determine the composition of the oral microbiome in patients with GERD and esophagitis of varying severity and to identify possible microbiological predictors of the development of GERD complications.

Materials and methods of research. The study involved 106 men (27 healthy subjects and 79 patients with GERD and esophagitis). All subjects were comparable in age (35.5±3.4 years) and anthropometric characteristics (p>0.05); all had a negative smoking history. All patients provided voluntary informed consent to participate in the study.

Patients with GERD and esophagitis were followed up at the Voronezh City Clinical Polyclinic No. 1, a state-funded healthcare institution in the Voronezh Region. The diagnosis of the underlying disease was verified based on the results of EGD and clinical manifestations (heartburn was observed in 87% of cases (n = 69), chest pain in 51% (n = 40),

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and extraesophageal manifestations in 51% (n = 40)). Patients with GERD with esophagitis were divided into 3 groups according to the Los Angeles classification [10]: GERD-A – one or more areas of mucosal damage in the form of erosion or ulceration less than 5 mm, not extending beyond the mucosal fold (n = 26), GERD-B – one or more areas of mucosal damage more than 5 mm, not extending beyond the mucosal fold (n = 25), GERD-C – damage to two or more mucosal folds, in total occupying less than 75% of the esophageal circumference (n=28). Belonging to the GERD-D group (damage to more than 75% of the mucosal circumference of the esophagus) was an exclusion criterion. Healthy subjects constituted the control group (n = 27). The studied biomaterial was saliva, samples of which were collected in sterile 5 ml tubes 2 hours after the last consumption of food and liquid by the subjects. At the time of biomaterial collection, the patients were not taking any medications and were in remission of the underlying disease. Saliva samples were frozen at -17ºC for up to 4 days and transported to the laboratory under cold chain conditions [8]. The quality of the obtained product was assessed by electrophoresis in 2% agarose gel. DNA extraction was performed using the PROBA-GS reagent kit (DNA-technology, Russia). After centrifugation, the supernatant containing the isolated DNA was transferred to the reaction mixture for PCR amplification. DNA concentration was determined using a Hitachi F-7000 spectrophotometer at a wavelength of 260 nm. The purity of the obtained preparations was judged by the A260/A280 ratio. Quantitative polymerase chain reaction was performed on a Bio-Rad CFX 96 instrument (Bio-rad, USA) using a mixture consisting of 16 µl of water, 5 µl of 5X qPCRmix-HS SYBR (Eurogen, Russia), 1 µl of forward primer, 1 µl of reverse primer, and 2 µl of DNA template. The primers used are presented in Table 1. Comparison of bacterial types was assessed by ΔCT between the control and experimental groups. The average CT value obtained for each pair of primers was converted to a percentage using the following formula:

$$x = \frac{(Eff.Univ)^{CT_{univ}}}{(Eff.Spec)^{CT_{spec}}} \times 100\%$$

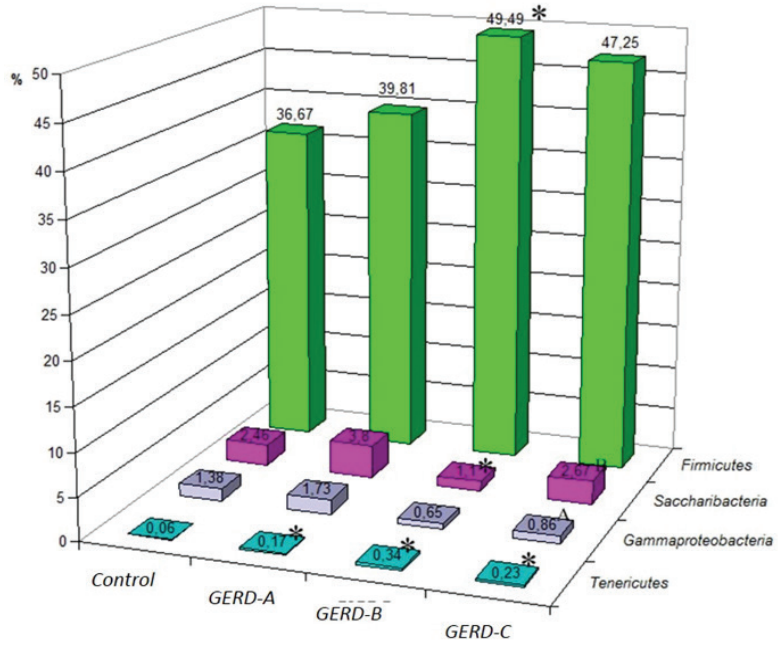
where *Eff.Univ* – estimated efficiency of universal primers (2 = 100% and 1 = 0%); *Eff.Spec* – efficiency of taxon-specific primers; CT_{univ} and CT_{spec} – values *CT*, registered by the amplifier; *x* – proportion of the number of bacteria of a certain type (%).

Statistical processing of the results was carried out using software packages STADIA 8.0 («InCo» (Russia)) and MedCalc 20.104 («MedCalc Software» (Belgium)). The average relative abundance of bacteria of a given phylum in the microbiome, the error of the mean, the standard deviation, the median, and the 95% confidence interval of the mean were calculated. A comparison of the proportions of each phylum in GERD patients and controls was performed using the test χ^2.

Table 1

Pairs of specific primers for microbiome analysis

Type of bacteria	Primer	Primer sequence (5'-3')	Amplicon length (bp)
Bacteroidetes	Bac960F	GTTTAATTCGATGATACGCGAG	122
	Bac1100R	TTAASCCGACACCTCACGG	122
Firmicutes	Firm934F	GGAGYATGTGGTTTAATTCGAAGCA	126
	Firm1060R	AGCTGACGACAACCATGCAC	126
Actinobacteria	Act664F	TGTAGCGGTGGAATGCGC	277
	Act941R	AATTAAGCCACATGCTCCGCT	277
Saccharibacteria	Sac1031F	AAGAGAACTGTGCCTTCGG	187
	Sac1218R	GCGTAAGGGAAATACTGACC	187
Deferribacteres	Defer1115F	CTATTTCCAGTTGCTAACGG	150
	Defer1265R	GAGHTGCTTCCCTCTGATTATG	150
Verrucomicrobia	Ver1165F	TCAKGTCAGTATGGCCCTTAT	97
	Ver1263R	CAGTTTTYAGGATTTCCTCCGCC	97
Tenericutes	Ten662F	ATGTGTAGCGGTAAAATGCGTAA	200
	Ten862R	CMTACTTGCGTACGTACTACT	200
Betaproteobacteria	Beta979F	AACGCGAAAAACCTTACCTACC	174
	Beta1130R	TGCCCTTTCGTAGCAACTAGTG	174
Epsilonproteobacteria	Epsilon940F	TAGGCTTGACATTGATAGAATC	189
	Epsilon1129R	CTTACGAAGGCAGTCTCCTTA	189
Delta and Gammaproteobacteria	Gamma877F	GCTAACGCATTAAGTRYCCCG	189
	Gamma1066R	GCCATGCRGCACCTGTCT	189
Universal	926F	AAACTCAAAKGAATTGACGG	136
	1062R	CTCACRRCACGAGCTGAC	136



Features of the composition of the intestinal microbiome in the study groups

Table 2

Content of some bacterial phyla in individuals with gastroesophageal reflux disease and in control

	Control	GERD-A	GERD-B	GERD-C
Bacteroidetes	50.58±5.39 s_x=25.84 Me=48.46 ДИ=11.04	44.96±6.30 s_x=28.17 Me=47.21 ДИ=13.03	42.76±4.43 s_x=21.23 Me=40.10 ДИ=9.07	43.45±5.52 s_x=25.30 Me=42.66 ДИ=11.38
Firmicutes	36.67±4.57 s_x=21.90 Me=34.43 ДИ=9.36	39.81±6.10 s_x=27.26 Me=37.30 ДИ=12.61	49.49±5.29* s_x=25.38 Me=55.59 ДИ=10.84	47.25±5.25 s_x=24.05 Me=51.94 ДИ=10.82
Actinobacteria	8.64±2.72 s_x=13.04 Me=3.17 ДИ=5.57	9.25±4.18 s_x=18.68 Me=1.28 ДИ=8.64	5.43±2.37 s_x=11.38 Me=1.27 ДИ=4.86	5.50±1.88 s_x=8.60 Me=2.14 ДИ=3.87
Saccharibacteria	2.46±1.34 s_x=6.45 Me=0.81 ДИ=2.76	3.80±1.58 s_x=7.05 Me=1.13 ДИ=3.26	1.10±0.27* s_x=1.31 Me=0.72 ДИ=0.56	2.67±0.74^B s_x=3.33 Me=1.14 ДИ=1.50
Gammaproteo-bacteria	1.38±0.86 s_x=4.13 Me=0.36 ДИ=1.77	1.73±0.82 s_x=3.68 Me=0.19 ДИ=1.70	0.65±0.30 s_x=1.43 Me=0.18 ДИ=0.61	0.86±0.396^A s_x=1.77 Me=0.28 ДИ=0.80
Tenericutes	0.06±0.02 s_x=0.09 Me=0.02 ДИ=0.04	0.17±0.09* s_x=0.39 Me=0.02 ДИ=0.18	0.34±0.32* s_x=1.54 Me=0.003 ДИ=0.66	0.23±0.14* s_x=0.63 Me=0.007 ДИ=0.28
Betaproteo-bacteria	0.23±0.16 s_x=0.80 Me=0.04 ДИ=0.32	0.28±0.19 s_x=0.84 Me=0.05 ДИ=0.39	0.24±0.16 s_x=0.78 Me=0.03 ДИ=0.34	0.12±0.07 s_x=0.31 Me=0.02 ДИ=0.14

Designations: * – differences from the control group are statistically significant (p<0,05);
A – differences from the GERD group-A statistically significant (p<0,05);
B – differences from the GERD group-B statistically significant (p<0,05).

Differences between comparison groups were considered significant when p<0,05.

Results and discussion. An analysis of the oral microbiome was conducted in healthy subjects and those with GERD (Fig. 1, Table 2). It was shown that the predominant bacterial phyla in the oral cavity of both healthy and GERD subjects were *Bacteroidetes* and *Firmicutes* (totaling approximately 90% of the microbiome). A trend toward a decrease in the relative abundance of *Bacteroidetes* bacteria compared to controls was observed in all groups of GERD patients; however, no statistically significant differences were found between the groups. *Bacteroidetes* are able to adapt to low pH conditions. Acid can irritate the mucous membrane and destroy the protective enamel layer, which also facilitates bacterial proliferation [8, 9].

The proportion of *Firmicutes* in patients with GERD-B (49.49%) increased compared to healthy subjects (36.67%). A trend toward an increased relative abundance of *Firmicutes* was observed in patients with GERD-C. Thus, in patients with GERD, there was a redistribution of the proportions of dominant phyla in favor of Firmicutes. This may be due to a change in the pH of the oral cavity toward increased acidity. The change in the abundance of *Firmicutes* is associated with increased acidity in the oral cavity, as these microorganisms prefer a neutral or slightly alkaline environment. With an increase in pH, the activity of antimicrobial components of saliva, peroxidases, and lysozyme decreases, which contributes to a decrease in protection against pathogenic bacteria. Microorganisms in the oral cavity colonize various areas (tooth surfaces, tongue, buccal mucosa, saliva). Saliva plays a crucial role in the colonization of the oral cavity by microorganisms. Not only does it provide a nutrient medium for microbial growth, but it also contains numerous components with antibacterial properties, including antimicrobial peptides, secretory immunoglobulins, lysozyme, and lactoferrin. Catalase, present in saliva, promotes the breakdown of hydrogen peroxide, acting as an antimicrobial protein compared to other well-studied antimicrobial components. These components significantly contribute to the control of microbial communities in the oral cavity and the maintenance of homeostasis, despite the presence of esophagitis, suggesting the development of a compensatory mechanism in the early stages of the disease. The formation of a protective film can facilitate the attachment of various microorganisms and alter the pH of saliva, which minimizes the colonization of pathogenic and opportunistic microorganisms [6, 8, 9, 10].

Microbiome changes were found in patients with GERD regarding the subdominant phyla *Actinobacteria, Saccharibacteria, Gammaproteobacteria, Tenericutes*, and *Betaproteobacteria*. In patients with GERD-B, the proportion of *Saccharibacteria* decreased to 1.10% (compared to 2.46% in controls). Bacteria of this phylum may be associated with inflammation and oral health. Current research suggests that decreased levels of *Saccharibacteria* are a consequence of GERD-induced dysbiosis [8].

In all patients with GERD, the relative abundance of *Tenericutes* significantly exceeded that in healthy individuals (Table 2). This type of bacteria constitutes the majority of oral microorganisms. They play a significant role in the development of periodontal disease—the extraesophageal manifestation of GERD. This may be associated with the release of multiple virulence factors that facilitate tissue penetration, tissue destruction, and disruption of the host immune response. An increase in this phylum is associated with aggressive gastric contents, which determines the severity of GERD [6,7].

For other phyla, no differences in their abundance were found in the microbiomes of healthy individuals and patients with GERD.

Conclusion. It's worth noting that a study of oral microbiome phyla in patients with GERD-C revealed a significant decrease in all phyla of the studied bacteria. This is due to widespread changes in the mucosal layer of the esophagus and oral cavity, which leads to the inability of these bacteria's compensatory mechanisms to function due to constant exposure to acidic contents due to reflux from the stomach. Therefore, the bacterial phyla we studied can be used as a predictor of GERD development only in healthy individuals, to determine the likelihood of inflammation occurring in healthy mucosa, which requires further exploration and study of new biomarkers.

The oral microbiome is directly linked to the development of upper gastrointestinal diseases associated with reflux lesions, which may be a promising direction in differentiating at-risk patients

before endoscopic screening at the outpatient stage.

The authors declare no conflict of interest.

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VARIABILITY OF PNPLA3 AND GCKR GENES, AND THEIR INFLUENCE ON BIOCHEMICAL PARAMETERS IN RESIDENTS OF THE REPUBLIC OF SAKHA (YAKUTIA)

The article presents a study of the frequencies of *PNPLA3* and *GCKR* gene variants in samples of Yakuts, Evenks, and Russians. A total of 728 people living in the Sakha Republic (Yakutia) participated (331 Yakuts, 147 Evenks, and 250 Russians). Single nucleotide polymorphisms were determined by polymerase chain reaction followed by restriction fragment length polymorphism analysis. The study revealed significant differences between the studied samples. For the rs738409 polymorphism of the *PNPLA3* gene, the G allele was 72-75% in Yakuts and Evenks versus 53% in Russians. For the rs2294918 polymorphism, the protective allele A is virtually absent in Yakuts (6.7%) and very rare in Evenks (17%), the Russian population has a significantly higher proportion of A (43%). For rs1260326 of the *GCKR* gene, the risk allele T was more common in Russians than in Yakuts and Evenks. For the associated SNP rs780094, Russians have a higher percentage of the risk allele A, approximately 48% versus 40% in Yakuts and 44% in Evenks. Linkage disequilibrium (LD) analysis between the pair of polymorphisms rs738409 and rs2294918 in the *PNPLA3* gene showed an extremely weak association between these SNPs. Polymorphisms rs780094 and rs1260326 *GCKR* demonstrated strong linkage in all three studied samples. In the Russian sample, an association was noted between the genotype of the rs738409 *PNPLA3* polymorphism and the concentration of triglycerides, and polymorphisms of the *GCKR* gene showed a significant effect on ALT activity. The obtained data are consistent with the hypothesis that some pathological alleles became established in northern populations due to previous adaptive advantages, but in modern conditions, they have transformed from beneficial to harmful.

Keywords: *PNPLA3, GCKR, NAFLD,* Yakuts, Evenks, Russians

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Introduction. The populations of the Republic of Sakha (Yakutia) represent a unique model for studying genetic and ecological interactions. Russians, Evenks, and Yakuts living in this region differ in their genetic background, history, and traditional diets formed under harsh climates and extreme environmental factors. Until the middle of the 17th century, there was no agriculture in Yakutia, and the nutrition of the indigenous peoples was based on products of animal and plant origin [1]. With the development of industrialization, the historically established way of life and nutrition of the population have changed, so the traditional protein-lipid diet has been replaced by a modern Western one with a predominance of carbohydrates. The main organ of food metabolism is the liver. Consumption of high-calorie foods with high fructose content leads to an increase in circulating triglycerides and very low-density lipoproteins (VLDL), increased ALT levels, which in turn leads to insulin resistance and accumulation of visceral and liver fat [5, 17].

Yakutia is one of the most disadvantaged regions in terms of liver diseases, while the indigenous population is more susceptible to chronic diffuse liver diseases than newcomers [3]. Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in developed and developing countries, its prevalence varies from 2.8% to 24.0% in different populations. It accounts for 60% of all chronic liver diseases [15]. Also, up to 15% of all liver cancer cases are detected in patients with NAFLD [2]. The main causes of NAFLD are sedentary lifestyle, poor nutrition, and genetic polymorphism of various genes 11]. Thus, the genetic variants involved in lipid and glucose metabolism, rs738409 (C/G) in gene 3 containing the domain of patatin-like phospholipase *(PNPLA3*), rs780094 (G/A) and rs1260326 (C/T) in the glucokinase regulatory protein (*GCKR*) gene, are consistently associated with the risk of NAFLD and liver complications of NAFLD.

The rs738409 polymorphism of the *PNPLA3* gene, which leads to the substitution of isoleucine for methionine at position 148 of the protein (I148M), is the most well-known genetic determinant of NAFLD [7]. Thus, the I148M variant disrupts the function of the enzyme adiponutrin (a product of the *PNPLA3* gene), which leads to the accumulation of lipids in hepatocytes and accelerates the progression of the disease. The association of this allele with NAFLD has been confirmed in various populations of the world, including the Chinese, Indians, and Malays [6] and the peoples of Central Asia [7]. In addition to rs738409, the rs2294918 polymorphism is described in the *PNPLA3* gene, which itself is not directly related to the disease, but modifies the effect of the I148M variant. This SNP is localized in the same gene and is associated with reduced expression of the PNPLA3 protein [18]. The carriage of the rs2294918 A allele leads to a decrease in the amount of the active enzyme, which to some extent weakens the negative effect of the rs738409 allele.:G affects the accumulation of fat in the liver [10].

The *GCKR* gene encoding the glucokinase regulator was first identified among the NAFLD-associated loci in 2011 [13]. Two related SNPs have been most studied: rs780094 and rs1260326 in the exon of the *GCKR* gene. The A alleles in rs780094 [4] and T alleles in rs1260326 are considered unfavorable. These variants are associated with a decrease in the function of the glucokinase regulator, which leads to increased glucokinase activity and enhanced lipogenesis in the liver [16]. A decrease in the function of the GCKR protein leads to a redistribution of metabolic fluxes: fatty acid synthesis in the liver increases, which promotes steatosis, although paradoxically the same alleles are associated with low blood glucose and elevated triglycerides in population studies [9].

The purpose of this study is to compare the frequencies of polymorphisms rs738409, rs2294918 of the *PNPLA3* gene and rs780094, rs1260326 of the *GCKR* gene in samples of Yakuts, Evenks and Russians.

Materials and methods. The study protocol was approved by the local Committee on Biomedical Ethics at the Yakut Scientific Center for Complex Medical Problems (YSC CMP). Informed written consent was obtained from all the volunteers. Clinical information about patients was collected in a special database, and DNA samples were stored in the collection of biomaterial of the YSC CMP using the USU "Genome of Yakutia" (reg. no. USU_507512). The study included 728 healthy volunteers, including 331 Yakuts (244 men average age 46.5±0.78, 87 women average age 51.8±1.18), 147 Evenks (54 men average age 49.9±2.68, 93 women average age 51.1±2.1) and 250 Russians (90 men average age 44.7±1.78, 160 the average age of women was 43.6±1.22). Ethnicity was taken into account up to the third generation, all subjects live in the Republic of Sakha (Yakutia). SNP genotyping was performed using classical polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) in the Laboratory of Hereditary Pathology of the Department of Molecular Genetics of the YSC CMP. The conditions for amplification of the gene region containing polymorphic variants, indicating the sequence of oligonucleotide primers, the restrictase used, and the lengths of the extraction fragments, are presented in Table 1.

The correspondence of the genotype distributions to the expected values at Hardy-Weinberg equilibrium and the comparison of the frequencies of allelic variants/genotypes were carried out using the $\chi 2$ (chi-squared) criterion with the Yates correction. SNP linkage disequilibrium analysis was studied by pairwise comparing r2 and D using Haploview software (version 4.2; Broad Institute, Cambridge, Massachusetts, USA) [14].

Results and discussions. A comparative analysis of the frequency distribution of the genotypes and alleles of the *PNPLA3* and *GCKR* gene polymorphisms revealed significant differences between the studied samples (Table 2).

According to the rs738409 polymorphism of the *PNPLA3* gene, Yakuts and Evenks have an extremely high proportion of the G allele (with impaired adiponutrin function): 72-75% against 53% for Russians. More than half of the Yakuts (57.9%) and Evenks (51.5%) had the GG genotype, while only 40.5% of Russians have GG. Statistically, the differences in *PNPLA3:* G frequencies between Yakuts and Russians are significant ($\chi 2 \approx 38.6$; $p<0.001$), while there is no significant difference between Yakuts and Evenks ($p=0.42$). This confirms that both northern peoples carry a sharply increased proportion of the *PNPLA3* 148M variant, whereas it is significantly less common among Europeans (Russians). At the second *PNPLA3* locus (rs2294918), the A allele, characterized by reduced protein expression, is practically absent in Yakuts (6.7%) and very rare in Evenks (17%); the Russian population has a significantly higher proportion of A (43%). Thus, the protective effect of the rs2294918 variant is practically absent in the Yakut and Evenk groups, while it is much more pronounced in Russians.

In contrast to the above, according to variant rs1260326 of the *GCKR* gene, on the contrary, the T allele (which weakens the function of glucokinase and increases the risk of steatosis) was more common in Russians than in Yakuts and Evenks. The difference between Yakuts and Russians for this allele was statistically significant ($p=0.02$). Similarly, according to the related SNP rs780094, Russians have a higher percentage of the A allele, about

Table 1

Primers and restriction enzymes used to detect *PNPLA3* and *GCKR* gene polymorphisms

Gene / SNP	Primers	Annealing Temperature (˚C)	Restriction Endonuclease	Restriction fragments
PNPLA3 rs2294918	F: CCTCTAAGCCAACTTCCTCC R: CCTCAAGTGACTCACAGACTC	66	Ama87 I	AA - 271 b.p. GG – 160, 111 b.p.
PNPLA3 rs738409	F: TGGGCCTGAAGTCCGAGGGT R: CCGACACCAGTGCCCTGCAG	66	BstF5 I	CC – 200, 133 b.p. GG – 333 b.p.
GCKR rs780094	F: CATGTTGGCTAGGCTTGTTGAG R: AGCTCACGCTGGAACTTCTG	62	Pci I	GG - 126, 176, 258 b.p. AA - 302, 258 b.p.
GCKR rs1260326	F: TGCAGACTATAGTGGAGCCG	63	MspI	TT - 231 b.p. CC - 81, 150 b.p.

48% versus 40% for Yakuts and 44% for Evenks.

The analysis of linkage disequilibrium (LD) between a pair of rs738409 and rs2294918 polymorphisms in the *PNPLA3* gene showed an extremely weak association of these SNPs in the representatives of the studied populations. Low LD was observed in the samples of Yakuts, Evenks, and even Russians: the values of D' were only 0.032, 0.131, and 0.045, respectively, with virtually zero coefficient of determination (r2 ≈ 0.0). For comparison, in global populations, according to data from 1000 Genomes [12], these SNPs in *PNPLA3* are in almost complete linkage. So, for Africans, D' ≈ 1 with r2 ≈ 0.015; for Americans, D' ≈ 0.98, r2 ≈ 0.242; in East Asians, D' ≈ 1, r2 ≈ 0.12; in Europeans, D' ≈ 1, r2 ≈ 0.172; in South Asian populations, D' ≈ 1, r2 ≈ 0.097. Thus, in the studied samples of populations of Yakuts, Evenks and Russians, two *PNPLA3* variants are inherited almost independently, whereas in large global populations There is a strong cohesion between them (Fig.).

The polymorphisms rs780094 and rs1260326 *GCKR* demonstrated strong coupling in all three samples studied, so for Yakuts and Evenks, D' was 1.0 with r2 ~ 0.8–0.99, and for Russians, D' = 0.898, r2 = 0.769. Thus, in the studied populations, the alleles of these two *GCKR* SNPs are transmitted almost as a single block. The combination of alleles of two *PNPLA3* variants (rs738409 and rs2294918) forms four possible haplotypes. The frequency distribution of these haplotypes demonstrates noticeable differences between Yakuts, Evenks, Russians, and the reference populations of the world (Table 3).

As can be seen from Table 3, the G–G haplotype is most common in the populations of Yakutia. Among Russians, there is a more uniform distribution across several haplotypes: in addition to G–G, hap-

Table 2

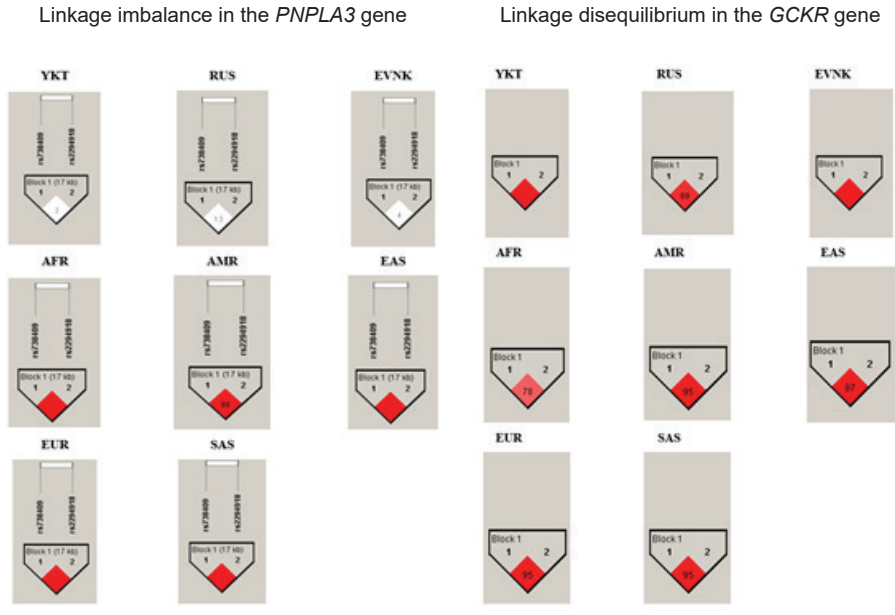
Comparison of the frequency distribution of genotypes and alleles of *PNPLA3* and *GCKR* gene polymorphisms in the studied populations

Population	Genotype frequency (%)			Allele frequency (%)		Chi-square	p
rs738409 PNPLA3	CC	CG	GG	C	G		
Yakuts	7.9	34.2	57.9	25.0	75.0	38.62	0.00
Russian	33.5	25.9	40.5	46.5	53.5		
Yakuts	7.9	34.2	57.9	25.0	75.0	0.66	0.42
Evenks	7.6	40.9	51.5	28.0	72.0		
Evenks	7.6	40.9	51.5	28.0	72.0	20.07	0.00
Russian	33.5	25.9	40.5	46.5	53.5		
PNPLA3 rs2294918	AA	AG	GG	A	G		
Yakuts	0.4	12.5	87.1	6.7	93.3	151.18	0.00
Russian	11.4	63.9	24.7	43.4	56.6		
Yakuts	0.4	12.5	87.1	6.7	93.3	18.67	0.00
Evenks	0.0	34.1	65.9	17.0	83.0		
Evenks	0.0	34.1	65.9	17.0	83.0	45.02	0.00
Russian	11.4	63.9	24.7	43.4	56.6		
GCKR rs780094	AA	AG	GG	A	G		
Yakuts	17.1	45.4	37.5	39.8	60.2	5.43	0.02
Russian	27.8	41.1	31.0	48.4	51.6		
Yakuts	17.1	45.4	37.5	39.8	60.2	1.04	0.31
Evenks	18.9	50.0	31.1	43.9	56.1		
Evenks	18.9	50.0	31.1	43.9	56.1	0.99	0.32
Russian	27.8	41.1	31.0	48.4	51.6		
GCKR rs1260326	TT	CT	CC	T	C		
Yakuts	17.1	45.4	37.5	39.8	60.2	5.43	0.02
Russian	25.3	46.2	28.5	48.4	51.6		
Yakuts	17.1	45.4	37.5	39.8	60.2	0.19	0.67
Evenks	11.4	53.0	35.6	37.9	62.1		
Evenks	11.4	53.0	35.6	37.9	62.1	6.07	0.01
Russian	25.3	46.2	28.5	48.4	51.6		

lotypes C–G (30.9%) and G–A (23.9%) have significant proportions. The G–A haplotype is practically absent in the main world populations, but, on the contrary, it is present in Yakuts and Evenks (5.2% and 12.2%, respectively). The European sample (EUR) has a remarkably high proportion of the C–A haplotype (37.1%), which is also quite common in South Asians (22.8%). The frequency of C–A in Russians is 17.1%, which is noticeably higher than in Yakuts (1.9%), but lower than in the European population. Thus, the Yakuts and Evenks are characterized by the predominance of the G–G haplotype and the presence of the G–A haplotype, which is unique to them, whereas the distribution of *PNPLA3* haplotypes in Russians is closer to the European type. For the *GCKR* gene, the combination of alleles of polymorphisms rs780094 and rs1260326 also forms four haplotypes. However, unlike *PNPLA3*, only two main haplotypes are observed in all populations, while the remaining two are extremely rare (Table 4).

According to Table 4, in each population considered, the main share (>90%) is accounted for by the G–C and A–T haplotypes, whereas combinations of G–T and A–C are rare minor haplotypes. These data confirm that the two substitutions under consideration in *GCKR* are closely related: in fact, only two main haplotype lines can be traced in all groups, whereas recombination variants (G–T, A–C) have evolved rarely and therefore persist with low frequency.

To assess the functional effect of genes, the average value of biochemical parameters in the studied samples of Russians and Evenks was stratified depending on the genotype according to a number of polymorphisms. The effect of the *PNPLA3* variant on the biochemical parameters manifested itself as expected. In the Russian sample, the rs738409 *PNPLA3* polymorphism genotype was associated with triglyceride concentration, so carriers of the unfavorable GG genotype had a lower TG level (on average 1.6±0.9 mmol/l), and carriers of the favorable CC genotype had a higher TG (2.5±1.6 mmol/l, p=0.01). This reverse effect is consistent with the known data on *PNPLA3* [6]. variant 148M promotes fat accumulation in the liver by reducing TG secretion into the blood, therefore, GG carriers often exhibit reduced levels of circulating triglycerides against the background of severe liver steatosis. In Evenks, *PNPLA3* genotypes also influenced the indicators, although not so significantly. For example, the average AST activity in Evenks with the GG gen-



Linkage disequilibrium in the *PNPLA3* and *GCKR* genes. Note. The color of the cell indicates the strength of the bond between the SNPs: red is a strong bond (D'= 1, LOD> 2), white is a weak bond (D' <1, LOD <2). Abbreviations: YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians.

Table 3

Frequency of PNPLA3 haplotypes (rs738409–rs2294918) in Yakutia and worldwide populations

haplotypes rs738409-rs2294918	Frequency of *PNPLA3* haplotypes							
	YKT (n=330)	RUS (n=178)	EVNK (n=138)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-G	0.701	0.281	0.599	0.118	0.482	0.350	0.226	0.246
C-G	0.228	0.309	0.235	0.778	0.306	0.468	0.404	0.526
G-A	0.052	0.239	0.122	0	0	0	0	0
C-A	0.019	0.171	0.044	0.104	0.210	0.182	0.371	0.228

Note: n is the number of people studied; YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians

Table 4

Frequency of *GCKR* haplotypes (rs780094–rs1260326) in populations of Yakutia and the world

haplotypes rs780094-rs1260326	Frequency of *GCKR* haplotypes							
	YKT (n=331)	RUS (n=250)	EVNK (n=147)	AFR (n=661)	AMR (n=347)	EAS (n=504)	EUR (n=503)	SAS (n=489)
G-C	0.580	0.489	0.568	0.851	0.628	0.512	0.579	0.792
A-T	0.417	0.449	0.378	0.076	0.350	0.469	0.400	0.191
G-T	0	0.025	0	0.018	0.012	0.012	0.010	0.009
A-C	0.003	0.037	0.054	0.055	0.010	0.007	0.010	0.007

Note: n is the number of people studied; YKT – Yakuts; RUS – Russians; EVNK - Evenks; AFR - Africans; AMR - Americans; EAS – East Asians; EUR - Europeans; SAS – South Asians

otype was higher (31.1 U/l) compared with CC (24.8 U/l), but this difference was not significantly significant (p=0.06). The *PNPLA3* genotype in Evenks did not significantly affect lipid levels (p>0.3 for TG, cholesterol), although the same trend was observed, GG carriers had a slightly lower average TG than CC carriers.

In the Russian sample, polymorphisms of the *GCKR* gene showed a significant effect on the activity of ALT, a key enzyme that reflects the degree of liver damage in NAFLD. Carriers of risky alleles had significantly higher ALT. For example, among Russians, the average ALT for carriers of the AA genotype (rs780094) was 19.2±11.6 U/L, while for the GG genotype it was only 13.5±5.3 U/l (p<0.001). A similar effect was confirmed for the associated rs1260326 variant: the TT genotype was associated with ALT of 18.3±11.6 U/l versus ~13.5 U/l for CC (p=0.02). In Evenks, the effect of *GCKR* on ALT and other indicators did not reach statistical significance. For example, according to rs780094, the ALT of Evenks was ~19-21 U/l for all genotypes (p=0.90). It can be assumed that with a smaller sample size of Evenks, the associations might not appear, although Evenks with the TT genotype according to rs1260326 had a slightly higher ALT than with CC, but did not achieve a significant difference.

Conclusion. Collectively, the genetic profile of Yakuts and Evenks for polymorphisms rs738409 and rs2294918 of the *PNPLA3* gene is characterized by an increased proportion of alleles associated with the risk of liver obesity, while Russians have significantly lower frequencies of these alleles. However, according to the polymorphisms rs780094 and rs1260326 of the *GCKR* gene, Russians have a higher proportion of alleles with reduced glucokinase function than the northern groups. When comparing the average biochemical parameters depending on the genotype, reliable values were found only in the sample of Russians, which may be due to the low variability of genotypes in Evenks. The results of the study demonstrate how genetic adaptation to extreme environmental conditions can affect the health of a population in new conditions. In Yakuts and Evenks, long-term evolution in conditions of cold and limited nutrition led to the consolidation of alleles optimizing the accumulation and use of energy, which, in an environment of excess calories, became factors of increased vulnerability to non-alcoholic fatty liver disease.

The authors declare that there is no conflict of interest.

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COMPREHENSIVE ASSESSMENT OF THE EFFECTIVENESS OF EARLY REHABILITATION AFTER HEART VALVE SURGERY IN THE STRUCTURE OF CARDIOVASCULAR SURGERY

The purpose of the study. To evaluate the impact of early cardiological rehabilitation on physical function and clinical outcomes in patients after mitral or aortic valve replacement. Materials and methods. The study included 20 patients (12 in the intervention group, 8 in the control group) who underwent elective heart valve surgery. The intervention group received early rehabilitation from day 2 after surgery, including physical activity, walking, and endurance exercises. The assessment was performed before surgery, at discharge, and 6 months later using the SPPB, SF-12, 6MWT, and HADS scales. The analysis was performed in IBM SPSS Statistics 21.0. Results. The patients in the intervention group demonstrated significant improvements in physical function (SPPB), endurance (6MWT), and PCS compared with the control group. SPPB proved to be a statistically significant predictor of readmission (p = 0.017) and mortality (p = 0.006) during 6 months of follow-up. Conclusions. Early cardiac rehabilitation is safe, effective and can be considered as a mandatory stage of treatment for patients after valve replacement. Further studies with an expanded sample are needed to confirm the long-term effectiveness of the program.

Keywords: cardiac rehabilitation, prosthetic heart valves, physical function, six-minute walking test, SPPB, prognosis, early mobilization.

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Introduction. Cardiological rehabilitation (CR) is a multi-level system of secondary prevention, covering physical training, educational modules, psychological support, lifestyle correction and rational drug therapy. It is aimed at restoring physical performance, stabilizing the emotional state and improving the overall quality of life in patients with cardiovascular diseases, including after heart surgery. CR becomes especially relevant for patients who have undergone surgery on the valvular heart apparatus, since it is in this cohort that high risks of postoperative complications and functional limitations are noted [7]. According to international studies, participation in rehabilitation programs can reduce overall mortality by 20-30% and the frequency of repeated hospitalizations by up to 30% [1, 4-6].

Given the high incidence of complications and the need to restore functional activity as soon as possible in this category of patients, the development and implementation of early rehabilitation protocols is of particular importance. In the framework of this study, early cardiac rehabilitation (RCR) refers to the activation of the patient, which begins in the early postoperative period - from the 2nd day after surgical intervention on the heart valves, provided stable hemodynamics. The RCR program includes a gradual increase in physical activity (breathing exercises, exercises for the limbs, walking around the ward and corridor, endurance training under the supervision of a physiotherapist). Unlike standard cardiac rehabilitation, which begins 2-4 weeks after surgery and is performed primarily on an outpatient basis, RCT is aimed at early recovery of physical function and prevention of physical inactivity, skeletal muscle atrophy, thromboembolic complications and psychological maladjustment. The novelty of the program lies in its structured phasing (mobilization - endurance training - individual load selection) and in the use of the SPPB and 6MWT functional scales as objective criteria for recovery dynamics already in the hospital period.

Despite the recognized clinical and economic effectiveness of CP, its implementation and implementation in practice, especially in the context of the treatment of acquired heart defects (CAD), including after valve replacement, still remain fragmentary [23]. Unlike patients after coronary bypass surgery, rehabilitation in patients who have undergone valve surgery has not been studied deeply enough, and protocols are poorly standardized [8,10]. In the Russian Federation, the implementation of the CR is complicated by the lack of specialized departments, poor hospital facilities and a shortage of trained personnel, especially at the outpatient stage, which reduces the coverage and quality of the program [3, 8-10]. In most cases, the management of patients after valvular surgery is limited to follow-up without active rehabilitation support in the early posthospital period, which reduces the potential for recovery and adaptation to physical activity [2].

An additional barrier to the wider implementation of CD is the lack of awareness and motivation on the part of both medical staff and patients themselves [12]. The traditional model of follow-up after heart valve surgery is reduced to occasional visits to the polyclinic with an emphasis on instrumental and laboratory parameters, while a holistic approach to rehabilitation is often absent [20]. In this context, the integration of digital and telemedicine solutions into the outpatient treatment process is becoming increasingly relevant [11]. Current data indicate the high effectiveness of remotely controlled programs: they allow for continuous rehabilitation, reduce the burden on the healthcare system, and increase patient compliance [12, 14, 16, 17].

For patients who have undergone heart valve surgery using artificial circulation (IC), a combined approach to

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rehabilitation based on continuity between inpatient and outpatient stages is of particular importance [24]. The use of telemedicine technologies at the third stage of the treatment ensures the maintenance of habits formed in a hospital setting, promotes better adaptation to physical activity, reduces anxiety and increases adherence to prescribed therapy [20]. However, in Russia, the experience of implementing such models is still limited to pilot projects, which requires a comprehensive assessment of their effectiveness, especially in the group of patients after surgical interventions on heart valves [8]. In this regard, further research is needed to optimize protocols, standardize remote solutions, and form a unified approach to early rehabilitation of this category of patients.

Thus, the aim of the study is to evaluate the clinical effectiveness of the early hospital stage of cardiac rehabilitation in patients after prosthetic heart valves, with an emphasis on the dynamics of physical function, quality of life and frequency of adverse outcomes in comparison with standard management without an active rehabilitation program.

Materials and methods. The present study was conducted as part of a prospective follow-up at the Clinical Hospital named after Peter the Great, St. Petersburg. The required sample size for comparing two independent groups was calculated using the MedCalc statistical package (version 20.1; MedCalc Software Ltd, Belgium), with the parameters: significance level α = 0.05, test power 80% and expected effect size 0.7. According to calculations, the minimum number of patients in each group should have been at least 18 a person taking into account possible retirement. As part of the pilot phase, 20 patients who underwent elective heart valve surgery between January 2022 and March 2024 were included in the study (Fig.1).

The clinical characteristics of the included patients are presented taking into account the genesis and volume of the valvular lesion. Among the 20 examined patients, patients with rheumatic (n = 11; 55%) and degenerative (n = 6; 30%) malformation predominated, less often with infectious endocarditis (n = 3; 15%). The majority of patients had isolated damage to one valve (mitral - 60%, aortic - 40%), while a two-valve lesion occurred in 3 (15%) of the examined patients.

Prior to surgery, all patients underwent a standard echocardiographic assessment with the determination of the main hemodynamic parameters: left ventricular ejection fraction (LVEF), terminal diastolic volume (CDV), terminal systolic volume (CSF), average pressure gradient on the valve and the degree of regurgitation. The average LVEF before surgery was 55 ± 6%, after surgical correction - 58 ± 5%, which indicates the preserved systolic function of the myocardium. At the time of the start of rehabilitation (2-3 days after surgery), the patients of both groups did not differ in age, gender, type of prosthetics (mechanical or biological valve), LV ejection fraction and frequency of concomitant diseases.

The early cardiological rehabilitation program was developed by the authors taking into account the adapted recommendations of the European Society of Cardiology [15] and the national clinical protocols of the Russian Ministry of Health [23]. The rehabilitation was carried out in stages and included three consecutive blocks:

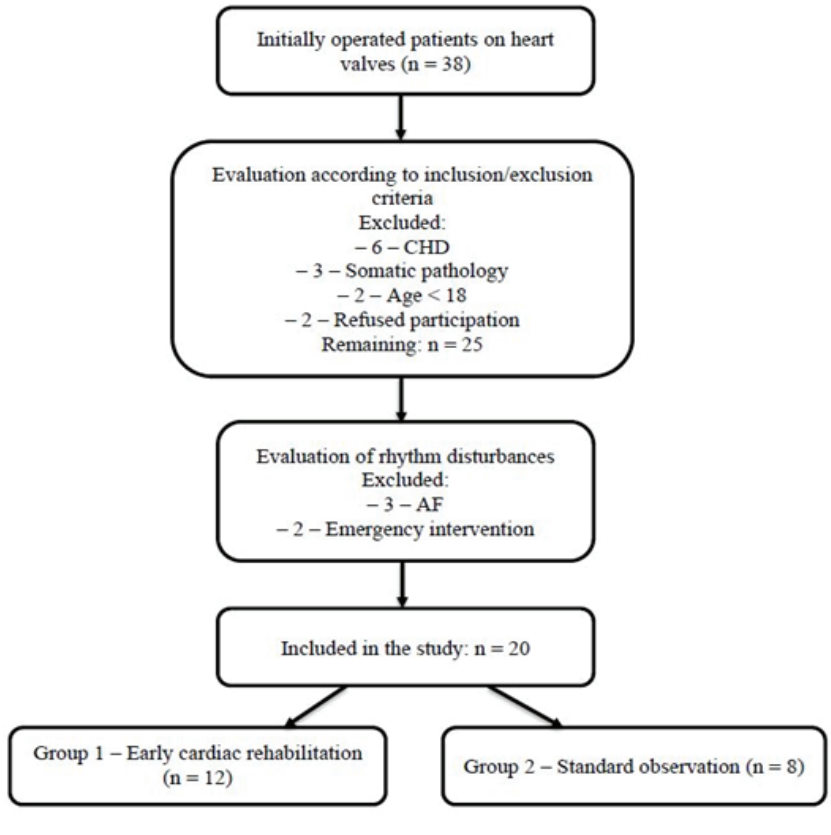
1. The stage of early mobilization is the beginning of the patient's activation on the 2-3 day after surgery; breathing exercises, passive and active limb movements, and gradual verticalization were performed under the supervision of a physiotherapist.

2. The exercise tolerance training stage was carried out on days 4-7 and included metered walks around the ward and corridor, exercises for coordination of movements and light isotonic loads with a gradual increase in walking distance to 400-500 m.

3. The stage of functional adaptation was carried out before discharge and was aimed at teaching the patient self-control of heart rate, blood pressure and saturation, the formation of individual recommendations for the outpatient stage and a gradual return to everyday activity.

All classes were conducted under constant monitoring of heart rate, blood pressure and blood oxygen saturation. A distinctive feature of the program was its early and phased structure, ensuring continuity between the hospital and outpatient stages of rehabilitation. Unlike standard schemes, which assume the onset of activation 2-4 weeks after surgery, the developed model allowed recovery to begin in the early postoperative period, which helps to prevent physical inactivity, thromboembolic complications and reduce anxiety in patients.

The study included 12 patients who underwent mitral or aortic valve replacement followed by an early stage of rehabilitation, and 8 patients who were under standard supervision without an active rehabilitation program. It should be noted that in the main group, an early hospital cardiorehabilitation program was conducted, implemented directly in the hos-



Flow chart of inclusion and exclusion of patients in the early cardiac rehabilitation program

pital and aimed at gradually activating the patient starting on the 2nd day after surgery. The term "remote" in the diagram (Fig. 1) it is used in a technical sense and implies the continuity of stages between hospital and subsequent outpatient follow-up, but not remote rehabilitation in a telemedicine format.

The selection was carried out by a cardiologist with experience in the field of postoperative management. Inclusion criteria: patients over the age of 18 who underwent elective mitral or aortic valve replacement, with preserved LV ejection fraction > 50%, stable hemodynamics and the ability to perform physical exercises under the supervision of specialists. Exclusion criteria: the presence of severe coronary heart disease, decompensated chronic heart failure, severe somatic and neurological diseases that interfere with physical activity, permanent or paroxysmal atrial fibrillation, emergency or repeated surgical interventions, refusal to participate in the study.

The control group included patients undergoing standard postoperative follow-up without a structured physical rehabilitation program. Unlike the main group, these patients did not receive daily sessions with a physical therapy instructor or a physiotherapist. Rehabilitation measures in this group were limited to the general recommendations of the attending cardiologist on the regime of physical activity, prevention of thromboembolic complications and control of hemodynamic parameters.

At the hospital stage, they received only basic consultations on the principles of gradual expansion of the motor regime and performing the simplest breathing exercises without individual selection of the load. The active development of the steps of motor activity (verticalization, metered walks, endurance exercises) was not carried out under the supervision of physical therapy specialists. At the outpatient stage, the patients of the control group were under the medical supervision of a cardiologist, without specialized physical rehabilitation. Thus, the main difference between the groups was the presence of a personalized multi-stage physical activation program in the main group and the limitation of standard advisory supervision in the control group.

The rehabilitation program began on the second day after surgery and included activation in the ward, endurance exercises and walking, gradually brought up to 500 m, under the supervision of physiotherapists. The control group received only basic medical supervision and recommendations for secondary prevention. Functional and psychological indicators were assessed in three stages: before surgery, at discharge, and after six months. Standardized tools were used for the assessment: SPPB (Short Physical Performance Battery) - a short battery of physical performance tests, SF-12 (Short Form-12 Health Survey) - a quality of life questionnaire including physical (PCS) and mental (MCS) components, 6MWT (Six-Minute Walk Test) - a six-minute walking test, and HADS (Hospital Anxiety and Depression Scale) - a scale of anxiety and depression. The main assessment tools were the SPPB, SF-12 (PCS and MCS) scales, the 6-minute walking test, and the HADS Anxiety/Depression scale. Statistical analysis was performed using IBM SPSS Statistics 21.0, adjusted for distorting factors, including age, gender, and type of surgery. The Shapiro–Wilk criterion was used to assess the normality of the data distribution. Quantitative indicators were compared between two independent groups using the Student's t-test (with a normal distribution) or the Mann-Whitney U–test (with an abnormal distribution). To analyze the dynamics within the groups, a variance analysis with repeated measurements (Repeated Measures ANOVA) was used. Categorical variables were compared using the χ2-test. The effect of functional indicators (SPPB, 6MWT, SF-12) on the risk of readmission and mortality was assessed using binary logistic regression. The results are presented as an average value ± standard deviation; the differences were considered statistically significant at $p < 0.05$.

All participants have given written informed consent to participate. The study protocol was approved by the Local Eth-

Table 1

Demographic and clinical characteristics of the study participants

Indicator	Intervention group (n = 12)	Control group (n = 8)	t (χ^2)	p
Gender, n (%)	Men – 8 (66.7%) / Women – 4 (33.3%)	Men – 5 (62.5%) / Women – 3 (37.5%)	0.13	0.72
Age, years (M ± SD)	58.6 ± 5.1	57.3 ± 4.7	0.42	0.68
BMI, kg/m2 (M ± SD)	24.1 ± 2.3	23.9 ± 2.6	0.36	0.72
Systolic blood pressure, mmHg (M ± SD)	142 ± 11	144 ± 12	0.78	0.44
Diastolic blood pressure, mmHg (M ± SD)	86 ± 8	85 ± 9	1.01	0.31
Total cholesterol, mmol/l (M ± SD)	4.5 ± 1.0	4.6 ± 1.1	0.72	0.47
Presence of symptoms before surgery, n (%)	10 (83.3)	7 (87.5)	0.11	0.74
Type of affected valve, n (%)				
– Aortic	6 (50.0)	5 (62.5)		
– Mitral	3 (25.0)	2 (25.0)		
– Double valve lesion	3 (25.0)	1 (12.5)		
Arterial hypertension, n (%)	8 (66.7)	6 (75.0)	0.09	0.76
Hypercholesterolemia, n (%)	5 (41.7)	4 (50.0)	0.18	0.67
LV ejection fraction after surgery, % (M ± SD)	51 ± 9	52 ± 10	0.84	0.41

Note: The data is presented as M ± SD (mean ± standard deviation) or n (%). There were no statistically significant differences between the groups in terms of the main demographic and clinical characteristics ($p > 0.05$).

Table 2

Dynamics of indicators of physical and mental state of patients in groups at different stages of observation

Indicator	Intervention Group (Basic)	Intervention Group (Extract)	Intervention group (6 months)	Control group (Basic)	Control group (Extract)	Control group (6 months)	F / p
SPPB	8.65 ± 1.40	9.88 ± 1.15	10.09 ± 1.42	8.52 ± 1.59	8.91 ± 1.22	8.73 ± 1.65	4.61 / 0.018
PCS	41.20 ± 5.11	50.10 ± 7.92	52.02 ± 7.64	40.75 ± 5.04	44.30 ± 6.88	45.11 ± 6.95	4.88 / 0.021
The ISS	46.90 ± 6.82	49.50 ± 6.31	51.10 ± 7.44	47.30 ± 6.94	48.10 ± 6.99	47.85 ± 7.90	1.11 / 0.317
6MW (m)	305.10 ± 52.88	355.00 ± 58.40	412.00 ± 61.21	306.55 ± 54.33	315.40 ± 57.20	365.10 ± 52.80	6.42 / <0.001
HADS-A	5.18 ± 1.10	5.00 ± 1.24	5.05 ± 1.61	4.89 ± 1.19	4.96 ± 1.08	5.00 ± 1.54	0.48 / 0.667
HADS-D	4.70 ± 1.42	4.80 ± 1.19	4.61 ± 1.12	4.85 ± 1.48	4.81 ± 1.05	4.55 ± 1.18	0.03 / 0.981

Note: The values are average ± standard deviation. SPPB is a battery of short physical characteristics; PCS is a summary of the physical component; HADS is a hospital scale of anxiety and depression, MCS is a summary of the mental component; 6MWT is a 6-minute walking test.

ics Committee of the Clinical Hospital. Peter the Great (Protocol No. 3 dated 15.01.2022) in accordance with the principles of the Helsinki Declaration.

Results. The study included 20 patients after heart valve surgery, of whom 12 were randomized to the early cardiac rehabilitation group, and 8 to the standard management control group. During the 6 months of follow-up, one patient dropped out of the control group for reasons unrelated to the intervention. Generalized demographic and clinical characteristics are presented in the table (Table 1).

The average age of the patients was 58.6 ± 5.1 years in the intervention group and 57.3 ± 4.7 years in the control group. Men dominated in both groups, accounting for 66.7% and 62.5%, respectively. All participants had diagnosed acquired heart valve defects, the most common of which were aortic valve stenosis (40%) and mitral regurgitation (30%). 91.7% of patients in the intervention group and 87.5% in the control group successfully completed the study. There were no statistically significant differences in the initial demographic and clinical parameters between the two groups, which indicates a correct random sample.

The results of the repeated analysis of variance revealed a statistically significant improvement in physical function (SPPB) over time, while the growth rate was more pronounced in the early rehabilitation group ($F = 8.11$; $p = 0.004$). There was also a significant difference between the average SPPB scores in the intervention and control groups ($F = 4.92$; $p = 0.017$), which indicates the advantage of rehabilitation intervention. A posteriori analysis showed that participants undergoing the cardiac rehabilitation program showed a more significant improvement in physical status both at discharge (average difference = 1.23 ± 1.74; $p = 0.009$; effect size = 0.41) and after 6 months (average difference = 1.44 ± 2.15; $p = 0.031$; effect size = 0.37) compared with the control group (Table 2).

The calculation of Cohen's d coefficient for comparing intergroup differences in SPPB showed values of 0.74 at discharge and 0.65 after 6 months, indicating a moderate but clinically significant effect of the intervention over both the short and long term.

The regression analysis assessed the impact of clinical, demographic, and functional characteristics on readmission and mortality in patients (n = 20) who underwent heart valve surgery. The logistic model included age, gender, type of surgery, as well as functional status indicators (SPPB, PCS, and 6MWT) measured after undergoing an early stage of cardiological rehabilitation (Table 3).

To assess the factors associated with death, a separate logistic model was constructed ($\chi2$ (6) = 11.84, $p = 0.041$, Nagelkerke R2 = 0.278). Of all the variables, the statistically significant predictor of mortality was the SPPB index (B = 0.891, $p = 0.006$, OR = 0.411; 95% CI: 0.205–0.788), which emphasizes the importance of physical function in predicting patient survival after cardiac surgery (Table 4).

Table 3

Results of logistic regression for predictors of readmission

The predictor	B	p	OR	95% ДИ
Age	0.054	0.245	1.056	0.958–1.165
Gender (male)	-0.227	0.551	0.797	0.377–1.684
Type of surgery	0.137	0.382	1.147	0.842–1.563
SPPB	-0.728	0.017	0.483	0.265–0.878
PCS	-0.091	0.118	0.913	0.812–1.026
6MWT	-0.005	0.067	0.995	0.989–1.001

Table 4

Results of logistic regression for mortality predictors

The predictor	B	p	OR	95% ДИ
Age	0.078	0.202	1.081	0.963–1.212
Gender (male)	-0.313	0.478	0.731	0.299–1.785
Type of surgery	0.106	0.428	1.112	0.843–1.578
SPPB	-0.891	0.006	0.411	0.205–0.788
PCS	-0.073	0.188	0.93	0.828–1.045
6MWT	-0.004	0.082	0.996	0.989–1.002

Discussion. Unlike traditional programs implemented at late stages, the early rehabilitation model we used assumed activation from the 2nd day after surgery, which made it possible to shorten recovery time and increase exercise tolerance. This protocol can be considered as a modified hospital version of postoperative rehabilitation based on the principle of early activation of patients after valvular interventions. The results obtained demonstrate the effectiveness of implementing the principle of early activation in patients after surgical correction of valvular heart defects. Upon discharge, and especially after 6 months of follow-up, patients undergoing the rehabilitation program showed significant improvements in physical function (SPPB), six-minute walking distance (6MWT), and physical quality of life (PCS) compared with the standard follow-up group. These results are consistent with the conclusions presented in Xue et al. [24], which also noted a significant advantage of early RCR in patients after heart valve surgery, especially in terms of restoring endurance and physical activity.

At the same time, the present study recorded a moderate but clinically significant difference on the SPPB scale between the groups (Cohen's d = 0.74 at discharge and 0.65 after 6 months), which is comparable to the effects described in the studies of Truong et al. [21] and Ennis et al. [14], which also used individualized mobilization programs in hospital settings. However, unlike most studies, including the study by Gach et al. [16], our work focused specifically on patients after valve replacement, rather than after interventions for coronary heart disease, which makes the results especially valuable for this subgroup.

An interesting difference in our work is the use of functional scales (SPPB and 6MWT) as primary outcomes, followed by modeling the effect of these variables on clinical events. Thus, according to the results of logistic regression, only the level of physical function (SPPB) turned out to be a statistically significant predictor of both re-hospitalization and mortality within 6 months ($p = 0.017$ and $p = 0.006$, respectively). This confirms the conclusions of Pelliccia et al [17] and Ambari et al. [12], which emphasize the role of assessing physical endurance as a criterion for risk stratification and an indicator of the effectiveness of rehabilitation measures.

The practical significance of the study is to confirm the benefits of early initiation of RCT in patients after prosthetic heart valves. Given the continuing shortage of outpatient rehabilitation centers in Russia and the shortage of specialized personnel [1, 8], the data from our study can be used as the basis for recommendations on mandatory hospital activation of patients on the second day after surgery. This is also consistent with the approaches reflected in ESC Guidelines [17], which emphasize the role of continuity between inpatient and outpatient stages of RCT.

However, it is necessary to take into account the limitations of the present study. Firstly, it is a small sample size (20 patients), which is due to the pilot nature of the work. Secondly, the follow-up was limited to 6 months, and it is impossible to judge long-term outcomes. Thirdly, despite random randomization, it is impossible to completely exclude the influence of external factors. Also, the rehabilitation program was implemented in one center, which limits the extrapolation of data to a wide population. In the future, it is advisable to conduct multicenter studies involving a larger number of patients and a long follow-up period to confirm the stability of the effects obtained.

Thus, this study confirms that the implementation of early cardiac rehabilitation in patients after surgical interventions on heart valves is associated with improved physical function, quality of life, and a reduced risk of adverse outcomes in the near future. The introduction of the hospital stage of RCT should be considered as an essential component of the comprehensive management of cardiac surgery patients.

Conclusion. As part of a pilot prospective observational study, the effectiveness of the early activation program for patients after mitral or aortic valve replacement was confirmed. Participation in the rehabilitation program from the second day after surgery contributed to a more pronounced improvement in physical function, the six-minute walking distance, and the physical component of quality of life by the time of discharge, as well as 6 months after the intervention. Analysis of logistic models showed that the level of physical activity (on the SPPB scale) was associated with a lower risk of re-hospitalization and death.

Despite the limited sample size, the results demonstrate the practical importance of introducing an early stage of rehabilitation directly in a hospital setting. The program can be recommended for inclusion in the standard of patient management after valve replacement as a way to increase the effectiveness of the recovery period. Large-scale randomized trials with a multicenter design and a long follow-up period are needed to verify the data obtained.

The authors declare that there is no conflict of interest.

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COMPARISON OF VARIANTS OF LEPR, *FADS1, FADS2* AND *FABP2* GENES IN THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

This study is devoted to studying the frequencies of gene variants (*LEPR, FADS1, FADS2, FABP2*) in Yakuts, Russians, and Evenks, as well as their relationship to body mass index (BMI). The study included 776 volunteers from the Republic of Sakha (Yakutia): There are 211 Russians, 140 Evenks and 425 Yakuts. The participants had no chronic diseases. Based on body mass index (BMI), participants were divided into three groups: normal BMI (18.5–24.9 kg/m2), pre-obese (25-29.9 kg/m2) and obese (≥30 kg/m2). The study of variants rs174537 of the enhancer genes *FADS1, FADS2*, rs1137101 of the *LEPR* gene and rs1799883 of the *FABP2* gene in populations of Russians (n=211), Evenks (n=140) and Yakuts (n=425) revealed significant population-specific differences.

Keywords: obesity, nutrition, Yakuts, Russians, Evenks, BMI, *LEPR, FADS1, FADS2, FABP2*

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Introduction. Obesity is one of the key public health problems of the 21st century, associated with an increased risk of cardiovascular diseases, type 2 diabetes, metabolic syndrome, and other chronic conditions [25]. Despite the fact that obesity is caused by the interaction of genetic, environmental, and behavioral factors, the role of genetic polymorphism in regulating metabolism and fat accumulation attracts special attention.

Numerous studies have attempted to understand the genetic basis of human adaptation to various environmental conditions and diets, and with the development of molecular genetic technologies, an understanding of the contribution of genetic variability to nutritional needs among various human subpopulations has emerged [20].

The nutritional history of the Yakut population provides an excellent opportunity to study the effect caused by the interaction between genes and food, which could exert selective pressure on certain SNPs associated with metabolism. Until the middle of the 17th century, agriculture was not practiced in Yakutia, respectively, the main food was animal and vegetable products. The beginning of grain farming in Yakutia dates back to 1652, when 6 exiled peasants took up farming [1], and potatoes were first imported in 1776 [3]. It has been established that under the influence of low temperatures in plants growing in Yakutia, the content of polyunsaturated fatty acids (PUFA) increases, among which 18:3n-3, 16:0 and 18:2n-6 dominate [18]. This, in turn, plays an important role in regulating the resistance of herbivores to prolonged low-temperature stress and the high content of 18:3n-3 in their meat, liver, and fat [10, 21].

Also, a distinctive feature of the Yakuts was the lack of a diet, they mostly ate once or twice a day, compensating for the large intake of it in the morning and evening hours. Animal and vegetable products were consumed in significant quantities in their natural raw form, which made it possible to preserve its nutritional properties [5].

According to physiological and biochemical studies, the entire indigenous population of Northeast Asia differs from the more southern Siberian peoples in a special "polar" type of metabolism, which was formed on the basis of a lipid-protein diet and is characterized by an increased role of lipids as an energy source [2].

In recent years, with changes in the eating habits of the population of Yakutia, the number of people with obesity and other metabolic diseases, such as type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), etc. has increased.

With the help of Human Genome Association Studies (GWAS), researchers from various parts of the world have cur-

rently identified a huge number of single nucleotide polymorphisms (SNPs) associated with obesity, some of which were not previously known to be associated with obesity. However, of all the identified SNPs for most ethnic groups, only a small percentage are significantly associated with obesity or body mass index (BMI).

The leptin receptor gene (*LEPR*), one of the widely studied candidate genes for increased BMI, is on the biological pathway to obesity (leptin-insulin pathway). Leptin is produced in adipose tissue in proportion to its mass, and is also produced in other organs. It is known that leptin has a multifaceted effect, including the regulation of several neuropeptides involved in appetite control and thermogenesis [8].

Polymorphisms in genes related to lipid metabolism, such as *FADS* (Fatty Acid Desaturase), play a key role in modulating polyunsaturated fatty acid (PUFA) levels, which affect energy balance and the risk of obesity [14].

The *FABP2* gene encodes Fatty Acid Binding Protein 2, which is involved in lipid absorption and transport in enterocytes. The rs1799883 polymorphism (G>A substitution), which causes the amino acid substitution Ala54Thr in this protein, is associated with changes in lipid and carbohydrate metabolism – carriers of the Thr allele have higher triglyceride levels and a tendency to insulin resistance [19]. The associations of Ala54Thr with obesity, type 2 diabetes mellitus, and metabolic syndrome have been repeatedly described in different populations [11, 13]

The purpose of this study is to compare the gene variants (*LEPR*, *FADS1*, *FADS2*, and *FABP2*) involved in lipid metabolism and their relationship to BMI in Yakuts, Russians, and Evenks.

Materials and research methods. The criteria for inclusion in the study sample were age 18 and over and written informed consent to the study. Criteria for non-inclusion:

• Presence of decompensated chronic pathology;

• Serious or uncontrollable physical or mental illnesses;

• Taking medications for the treatment of obesity in the postoperative period.

• The onset of pregnancy;

• The patient's refusal to continue participating in the study.

The study included 776 volunteers from the Republic of Sakha (Yakutia): There are 211 Russians, 140 Evenks and 425 Yakuts. The average age was 47.4±0.99 years for Russians, 50.7±1.65 years for Evenks, and 48.1±0.58 years for Yakuts. Bioassays and questionnaires of volunteers, including anthropometric indicators, were selected from various regions of the republic during field expeditions and business trips with doctors and laboratory technicians. DNA of the volunteers is included in the bioresource collection of the Yakut Scientific Center for Complex Medical Problems (YANC KMP) UNU "Genome of Yakutia" (reg. no.USU_507512). The desk work was carried out in the laboratory of Hereditary pathology of the Department of Molecular Genetics of the YANGTS KMP. The study was approved by the local biomedical ethics committee, and all participants provided written informed consent.

The sample was divided into three ethnic groups, followed by body mass index (BMI) categories, according to the criteria of the World Health Organization (WHO): normal BMI (18.5–24.9 kg/m2), pre-obesity (25-29.9 kg/m2) and obesity (≥30 kg/m2). SNP genotyping was performed using classical polymerase chain reaction (PCR) and restriction fragment length polymorphism (RDF). The conditions for amplification of the gene region containing polymorphic variants, indicating the sequence of oligonucleotide primers, the restrictase used, and the length of the extraction fragments, were described in early works [4, 16].

Statistical analysis: Statistical data processing was carried out using Micro-

Table 1

Percentage of BMI categories of ethnic groups

	Russians	Yakuts	Evenks
Normal	30.3	35.3	32.9
Pre-obesity	32.2	22.8	30.0
Obesity	37.4	41.9	37.1

Table 2

Frequencies of genotypes and alleles in Russians, Yakuts and the Evenks

Population	Frequency of genotypes (%)			Frequency of alleles (%)		Chi-square	p
rs174537 *FADS1, FADS2*	TT	GT	GG	**T**	G		
Russians	21.8	44.1	34.1	43.8	56.2	108.79	**0.00**
Evenki	70.7	25.7	3.6	83.6	16.4		
Russians	21.8	44.1	34.1	43.8	56.2	122.08	**0.00**
Yakuts	57.4	36.0	6.6	75.4	24.6		
Evenki	70.7	25.7	3.6	83.6	16.4	7.56	**0.01**
Yakuts	57.4	36.0	6.6	75.4	24.6		
rs1137101 *LEP*R	AA	AG	GG	A	**G**	**Chi-square**	**p**
Russians	21.3	49.8	28.9	46.2	53.8	44.98	**0.00**
Evenki	6.4	29.3	64.3	21.1	78.9		
Russians	21.3	49.8	28.9	46.2	53.8	109.24	**0.00**
Yakuts	4.0	28.5	67.5	18.2	81.8		
Evenki	6.4	29.3	64.3	21.1	78.9	0.93	0.34
Yakuts	4.0	28.5	67.5	18.2	81.8		
rs1799883 *FABP2*	CC	CT	TT	C	**T**	**Chi-square**	**p**
Russians	43.1	40.3	16.6	63.3	36.7	0.63	0.43
Evenki	39.3	41.4	19.3	60.0	40.0		
Russians	43.1	40.3	16.6	63.3	36.7	49.08	**0.00**
Yakuts	24.5	35.5	40.0	42.2	57.8		
Evenki	39.3	41.4	19.3	60.0	40.0	26.00	**0.00**
Yakuts	24.5	35.5	40.0	42.2	57.8		

Note: p – significance with the Yates correction for alleles.

Associations of genetic variants with BMI categories of Russians, Yakuts, and Evenks

Russians								Yakuts								Evenks							
Polymorphism/ sampling	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**	**Polymorphism/ sampling**	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**	**Polymorphism/ sampling**	**Frequence of genotypes (%)**			**Frequence of alleles (%)**		**OR**	**p**
rs174537 *FADS1*, *FADS2*	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**		**rs174537 *FADS1*, *FADS2***	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**		**rs174537 *FADS1*, *FADS2***	**TT**	**GT**	**GG**	**T**	**G**	**Regarding the T allele**	
Normal	15.6	34.4	50	32.8	67.2	1.988 (1.207-3.275)	**0.01**	Normal	61.3	34.0	4.7	78.3	21.7	1.359 (0.894-2.065)	0.18	Normal	73.9	19.6	6.5	83.7	16.3	1.027 (0.463-2.278)	0.89
Pre-obesity	23.5	51.5	25	49.3	50.7			Pre-obesity	53.6	38.1	8.2	72.7	27.3			Pre-obesity	69.0	28.6	2.4	83.3	16.7		
Obesity	25.3	45.6	29.1	48.1	51.9	1.898 (1.171-3.077)	**0.01**	Obesity	56.2	36.5	7.3	74.4	25.6	1.242 (0.863-1.786)	0.28	Obesity	69.2	28.8	1.9	83.7	16.3	1.003 (0.470-2.143)	0.85
Normal	15.6	34.4	50	32.8	67.2			Normal	61.3	34.0	4.7	78.3	21.7			Normal	73.9	19.6	6.5	83.7	16.3		
Pre-obesity	25.3	45.6	29.1	48.1	51.9	0.954 (0.603-1.510)	0.94	Pre-obesity	56.2	36.5	7.3	74.4	25.6	0.914 (0.615-1.357)	0.73	Pre-obesity	69.2	28.8	1.9	83.7	16.3	0.977 (0.450-2.119)	0.89
Obesity	23.5	51.5	25	49.3	50.7			Obesity	53.6	38.1	8.2	72.7	27.3			Obesity	69.0	28.6	2.4	83.3	16.7		
Normal	15.6	34.4	50	32.8	67.2	1.939 (1.256-2.993)	**0.00**	Normal	61.3	34.0	4.7	78.3	21.7	0.780 (0.558-1.089)	0.17	Normal	73.9	19.6	6.5	83.7	16.3	0.987 (0.503-1.936)	0.90
Pre-obesity + Obesity	24.5	48.3	27.2	48.6	51.4			Pre-obesity + Obesity	55.3	37.1	7.6	73.8	26.2			Pre-obesity + Obesity	69.1	28.7	2.1	83.5	16.5		
rs1137101 *LEP*R	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**		**rs1137101 *LEPR***	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**		**rs1137101 *LEPR***	**AA**	**AG**	**GG**	**A**	**G**	**Regarding the G allele**	
Normal	25.0	42.2	32.8	46.1	53.9	1.116 (0.687-1.814)	0.75	Normal	5.3	30.7	64.0	20.7	79.3	1.319 (0.823-2.112)	0.30	Normal	10.9	32.6	56.5	27.2	72.8	1.866 (0.895-3.891)	0.13
Pre-obesity	14.7	57.4	27.9	43.4	56.6			Pre-obesity	1.0	30.9	68.0	16.5	83.5			Pre-obesity	2.4	28.6	69.0	16.7	83.3		
Obesity	24.1	49.4	26.6	48.7	51.3	0.899 (0.564-1.435)	0.74	Obesity	4.5	25.3	70.2	17.1	82.9	1.260 (0.851-1.865)	0.29	Obesity	5.8	26.9	67.3	19.2	80.8	1.567 (0.802-3.062)	0.25
Normal	25.0	42.2	32.8	46.1	53.9			Normal	5.3	30.7	64.0	20.7	79.3			Normal	10.9	32.6	56.5	27.2	72.8		
Pre-obesity	14.7	57.4	27.9	43.4	56.6	0.806 (0.508-1.278)	0.42	Pre-obesity	4.5	25.3	70.2	17.1	82.9	0.955 (0.598-1.527)	0.94	Pre-obesity	5.8	26.9	67.3	19.2	80.8	0.840 (0.396-1.784)	0.13
Obesity	24.1	49.4	26.6	48.7	51.3			Obesity	1.0	30.9	68.0	16.5	83.5			Obesity	2.4	28.6	69.0	16.7	83.3		
Normal	25.0	42.2	32.8	46.1	53.9	0.993 (0.655-1.506)	0.941	Normal	5.3	30.7	64.0	20.7	79.3	1.280 (0.895-1.830)	0.21	Normal	10.9	32.6	56.5	27.2	72.8	1.690 (0.936-3.051)	0.11
Pre-obesity + Obesity	19.7	53.1	27.2	46.3	53.7			Pre-obesity + Obesity	4.3	27.7	68.1	18	82			Pre-obesity + Obesity	3.2	21.0	75.8	13.7	86.3		
rs1799883 *FABP2*	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**		**rs1799883 *FABP2***	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**		**rs1799883 *FABP2***	**CC**	**CT**	**TT**	**C**	**T**	**Regarding the T allele**	
Normal	37.5	50	12.5	62.5	37.5	1.316 (0.804-2.153)	0.31	Normal	26.7	28.7	44.7	41.0	59.0	1.079 (0.746-1.560)	0.76	Normal	37.0	43.5	19.6	58.7	41.3	1.125 (0.621-2.039)	0.95
Pre-obesity	36.8	38.2	25	55.9	44.1			Pre-obesity	17.5	43.3	39.2	39.2	60.8			Pre-obesity	38.1	38.1	23.8	57.1	42.9		
Obesity	53.2	34.2	12.7	70.3	29.7	0.706 (0.430-1.157)	0.21	Obesity	26.4	37.1	36.5	44.9	55.1	0.851 (0.624-1.161)	0.35	Obesity	42.3	42.3	15.4	63.5	36.5	0.818 (0.460-1.455)	0.59
Normal	37.5	50	12.5	62.5	37.5			Normal	26.7	28.7	44.7	41.0	59.0			Normal	37.0	43.5	19.6	58.7	41.3		
Pre-obesity	53.2	34.2	12.7	70.3	29.7	0.536 (0.332-0.867)	**0.02**	Pre-obesity	26.4	37.1	36.5	44.9	55.1	0.789 (0.553-1.126)	0.22	Pre-obesity	42.3	42.3	15.4	63.5	36.5	0.768 (0.426-1.382)	0.46
Obesity	36.8	38.2	25	55.9	44.1			Obesity	17.5	43.3	39.2	39.2	60.8			Obesity	38.1	38.1	23.8	57.1	42.9		
Normal	37.5	50	12.5	62.5	37.5	1.049 (0.682-1.611)	0.92	Normal	26.7	28.7	44.7	41.0	59.0	1.082 (0.813-1.439)	0.64	Normal	37.0	43.5	19.6	58.7	41.3	1.084 (0.652-1.801)	0.86
Pre-obesity + Obesity	45.6	36.1	18.4	63.6	36.4			Pre-obesity + Obesity	23.3	39.3	37.5	42.9	57.1			Pre-obesity + Obesity	40.4	40.4	19.1	60.6	39.4		

Note: OS is the odds ratio, p is the significance with the Yates correction for alleles.

soft Excel 2010 software. The comparison of allele and genotype frequencies between populations was performed using the χ2-Yates-corrected test. When analyzing the conjugation of the frequency of the unfavorable allele with obesity, a four-field conjugation table and the Yates-adjusted square criterion were used. To assess the significance of the odds ratio, the boundaries of the 95% confidence interval (95% CI) were calculated. The results were considered significant at p<0.05.

Results and discussion. In all ethnic groups, there is a predominance of obese people, the percentage of BMI categories among Russians and Evenks did not differ significantly from each other, unlike the Yakuts, where obese people are most common and least obese. (Table 1).

The distribution of genotypes for each SNP (rs174537, rs1137101, rs1799883) did not deviate from the Hardy-Weinberg equilibrium (p>0.05), except for the Yakut group in variant rs1799883 of the *FABP2* gene (chi2-31.41; p=0.00), which is probably due to the large predominance of carriers of the T allele.

Russian Russians (n=211), Evenks (n=140), and Yakuts (n=425) revealed statistically significant differences in the variants rs174537 of the enhancer genes *FADS1*, *FADS2*, rs1137101 of the *LEPR* gene and rs1799883 of the *FABP2* gene (Table 2) (Table 2). The frequencies of genotypes and alleles in Russians, Yakuts, and Evenks (n=140) revealed statistically significant differences (Table 2).

According to the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer, the highest frequency of the ancestral T allele was recorded in the Evenk population – 84%, followed by the Yakuts – 75%, while the Russian T allele is less common (44%). The Evenks have the TT genotype (71% of the sample), and the Yakuts have a similar high proportion of TT (57%), while the Russians have the GT and GG genotypes (only 22% have the TT genotype).

The *LEPR* (Gln223Arg) gene shows a similar pattern: the “unfavorable” Arg allele (G) dominates in Yakuts (82%) and Evenks (79%) compared with 54% in Russians. Russian Russians have only 29% of the GG genotype, while 21% of Russians have the protective AA (Gln/Gln) genotype, and homozygotes for Arg (GG) make up two–thirds of the sample of Yakuts (67.5%) and Evenks (64%). Russian Russians and Yakuts (p<0.001) and Evenks and Russians (p<0.001) differ significantly in the frequencies of the Arg allele, while Yakuts and Evenks do not differ (p=0.34).

FABP2 also significantly outweighs the unfavorable Thr54 allele in Yakuts (58% versus 40% in Evenks and 37% in Russians). The Thr/Thr genotype is found in 40% of Yakuts – more than twice as often as in Russians (17%) and Evenks (19%). Differences in the frequencies of the Thr allele between the Yakuts and both other groups are significant (p<0.001), whereas the Evenks and Russians have no significant difference in this variant (p=0.43).

Comparison of the frequencies of minor alleles (MAF) of genes of the studied ethnic groups with other populations of the world, according to the database "1000 Genomes Project Phase 3" [25, 26, 27] revealed the following:

– *FADS1*, *FADS2* (rs174537) MAF (T) in Russians 0.44 is similar to populations CLM 0.43 (Colombians in Medellin) and FIN 0.46 (Finns in Finland), Evenks 0.84 and Yakuts 0.75 are similar to populations CDX 0.78 (Chinese of the Dai population in Xishuangbanna) and KHV 0.82 (Kinh in Ho Chi Minh City);

– *LEPR* (rs1137101) MAF (G) in Russians is 0.54 similar to populations of ACB 0.56 (Afro-Caribbean origin in Barbados), PEL 0.50 (Peruvians in Lima), SAS 0.50 (South Asian populations), Evenks 0.79 and Yakuts 0.82 closer to populations of EAS 0.87 (East Asian populations);

– *FABP2* (rs1799883) MAF (T) in Russians 0.37 is similar to populations FIN 0.33 (Finns in Finland), BEB 0.33 (Bengalis in Bangladesh), GIH 0.39 (Gujarati Indians) and CHB 0.32 (Han Chinese in Beijing), Evenks 0.40 are similar to GIH 0.39 (Gujarati Indians), Yakuts 0.58 showed no similar frequencies with any of the populations.

The discrepancy and convergence of statistical indicators of genotype and allele frequencies between ethnic groups may reflect an adaptive strategy to food scarcity or extreme conditions, also with traditional nutrition.

The calculation of the odds ratio showed a reliable association of the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer with BMI only in the sample of Russians. Thus, in Russians, the T allele was associated with pre–obesity (OR=1.99, 95% CI: 1.21–3.27, p=0.01), obesity (OR=1.89, 95% CI: 1.17-3.08, p=0.01) and pre-obesity + obesity (OR=1.94, 95% CI: 1.26-2.99, p=0.00) compared to the norm, which is confirmed by multidimensional logistic regression taking into account the population. A significant association of rs1799883 polymorphism was also found in the Russian sample (OR=0.536, 95% CI: 0.332–0.867, p=0.02) (Table 3).

In the samples of Evenks and Yakuts, there was no significant association of BMI with any of the polymorphisms studied. Some researchers also do not find associations of the rs174537 polymorphism of the *FADS1* and *FADS2* gene enhancer with BMI Wang C et al. (2021) [23]. Studies of the rs1799883 associations of the *FABP2* gene by Raisa Sipiläinen et al. (1997), Han TK et al. (2019) and Albala C et al. (2004) also disagree [7, 13, 21]. A similar pattern is observed for the LEPR (Gln223Arg) gene, the results of other researchers differ from Boumaiza I et al. (2012), Becer E et al. (2013), Illangasekera, Y.A. et al. (2020), Thi Tuyet Le et al. (2025), Tkhakushinov R.A. et al. (2020) [6, 9, 10, 12, 22] The lack of statistically significant associations between different BMI categories with polymorphisms within each ethnic group may be due to heterogeneity and low variability. However, the results remain contradictory and require further study.

Conclusion. The study revealed statistically significant differences in the frequencies of alleles between ethnic groups of Russians, Yakuts and Evenks for all three polymorphisms (rs174537, rs1137101, rs1799883), however, the frequencies in the *LEPR* gene variant (rs174537) did not differ statistically between the Yakut and Evenk groups, similar is observed in the *FABP2* gene variant (rs1799883), where the group already Russians did not differ statistically from the group of Evenks. The high frequency of the ancestral T allele (*FADS1*, *FADS2* rs174537) in Evenks and Yakuts may indicate its role in adapting to a diet high in PUFA (meat and fish). The high prevalence of the "unfavorable" G allele (*LEPR* rs1137101) may reflect an adaptive strategy to food scarcity or extreme conditions. *FABP2* (rs1799883) is associated with the metabolism of fatty acids, which could be important for energy storage during periods of abundance of food.

The relationship between the studied polymorphisms and BMI categories in three groups was established only in the Russian group in the variant of the *FADS1* and *FADS2* genes (rs174537), the other two groups (Yakuts and Evenks) showed no associations. Further research is needed on a larger sample, taking into account biochemical parameters, as well as the use of additional other approaches.

The authors declare that there is no conflict of interest.

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CHANGES IN LIPID PEROXIDATION MARKERS AND ANTIOXIDANT STATUS IN LUNG ADENOCARCINOMA

In the present article, the dynamics of blood lipid peroxidation (LPO) markers and the antioxidant system (AOS) are investigated in patients with lung adenocarcinoma (LA) at different disease stages (I–IV). The study included 40 patients with histologically verified LA and 40 healthy donors. In blood serum, the concentrations of malondialdehyde (MDA), diene conjugates (DC), triene conjugates (TC), and Schiff bases (SB) were determined. In erythrocyte hemolysates, the activity of glutathione peroxidase (GPx), glutathione reductase (GR), glutathione S-transferase (GST), and the level of reduced glutathione (GSH) were measured.

In LA patients, a pronounced increase in LPO markers (MDA, DC, SB) and a decrease in GPx activity and GSH levels were revealed compared with the control group. A stage-dependent pattern was established: MDA levels were highest at stage I (a 3.4-fold increase), followed by a decline by stage IV. The concentration of DC (a primary LPO product) was elevated at the early stages, whereas secondary and terminal products (TC and SB) showed a progressive increase from stage I to stage IV (SB exceeding control values by 30.7-fold at stage IV). GPx activity was reduced at all stages, and GSH levels remained consistently decreased. GR activity exhibited a non-linear pattern.

The development of lung adenocarcinoma is accompanied by a profound imbalance in pro-/antioxidant homeostasis, manifested by enhanced LPO and depletion of antioxidant defenses. A specific stage-related dynamics of LPO markers is demonstrated: a marked rise in primary and secondary products at early stages, followed by a shift in the marker profile at advanced stages. The antioxidant system displays a phased response, with signs of partial compensation at stage III and decompensation at stage IV of the disease.

Keywords: lung adenocarcinoma; lipid peroxidation; oxidative stress; antioxidant system; malondialdehyde

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Introduction. Lung cancer remains one of the most pressing challenges in contemporary oncology, with persistently high incidence and mortality worldwide. Among histological variants, lung adenocarcinoma (LADC) is the predominant form of non-small cell lung cancer [6,10,15,33], underscoring the importance of elucidating the molecular mechanisms of its development.

Oxidative stress—arising from an imbalance between the generation of reactive oxygen species (ROS) and the activity of the antioxidant system (AOS)—is regarded as a key driver of carcinogenesis. Intensification of free-radical oxidation damages critical biomolecules, foremost the lipids of cellular membranes. Lipid peroxidation (LPO) initiated by ROS leads to membrane destabilization [18,19,28,35], impairment of barrier and receptor functions [16,21,26,35], and the formation of highly toxic secondary products [14,18,31,33] such as malondialdehyde (MDA) and conjugated dienes (CD). These compounds not only exacerbate cellular dysfunction but also possess mutagenic and carcinogenic potential, thereby promoting malignant transformation and tumor progression [4,27,31,32].

In response to enhanced LPO, a multilevel antioxidant defense is activated. However, during aggressive tumor growth, compensatory mechanisms may become insufficient, leading to aggravation of oxidative damage and disease progression [3,8,13,19].

Despite extensive research on the role of oxidative stress in cancer, the stage-dependent interplay between LPO markers and AOS status in lung adenocarcinoma remains insufficiently characterized. Establishing correlations between levels of LPO products, activities of antioxidant enzymes, and the extent of tumor spread is of both fundamental and applied significance. Such studies may deepen understanding of the molecular underpinnings of LADC progression, identify novel prognostic biochemical markers, and substantiate the rationale for antioxidant-oriented interventions within combined treatment strategies.

Study objective: To evaluate changes in the concentrations of primary and secondary LPO markers and in the activities of antioxidant system enzymes in blood from patients with lung adenocarcinoma across stages I–IV

Materials and Methods. The study was conducted in 2025 at the Laboratory of Precancerogenesis and Malignant Tumors, Department of Epidemiology of Chronic Non-Communicable Diseases, Yakut Science Center of Complex Medical Problems, in collaboration with the Yakut Republican Oncology Center (Yakutsk, Russian Federation).

We examined 40 patients with histologically confirmed lung adenocarcinoma and 40 apparently healthy volunteers matched to the patient group by age, sex, and ethnicity. Major exclusion criteria for controls were: presence of any oncologic disease, severe comorbid conditions, and use of medications with pronounced antioxidant properties.

The study complied with the Declaration of Helsinki and its subsequent amendments and was approved by the Local Ethics Committee of the Yakut Science Centre of Complex Medical Problems (Protocol No. 52, 24 March 2021). Baseline characteristics of participants are presented in Table 1.

Fasting venous blood served as the study material. Serum concentrations of lipid peroxidation (LPO) markers were determined by spectrophotometric methods: malondialdehyde (MDA) [2], conjugated dienes (CD) [22] and conjugated trienes (CT) [23], and Schiff bases (SB) [9]. In erythrocyte hemolysate, the activ-

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ities of glutathione peroxidase (GPx) [7], glutathione reductase (GR) [24], glutathione S-transferase (GST) [11], and the level of reduced glutathione (GSH) [20] were measured.

Statistical analysis was performed using SPSS version 23. Normality of the data distribution was assessed with the one-sample Kolmogorov–Smirnov test. Between-group differences were evaluated using Student's t-test (for normally distributed data) or the Mann–Whitney U test (for non-normal distributions). Differences were considered statistically significant at $p < 0.05$

Results. Comparison of LPO markers between patients with lung adenocarcinoma and the control group showed a statistically significant increase in most LPO indices (MDA, CD, SB), along with reduced GPx activity and lower GSH levels in the patient group (Table 2).

We identified a stage-dependent pattern for MDA levels (Table 3). At stage I, the MDA concentration was highest (2.61 ± 0.39 μmol/L), 3.4-fold above the control. At stages II and III, MDA remained elevated (3.0- and 2.8-fold above control, respectively), whereas at stage IV a statistically significant decrease was observed (1.5-fold above control). The sharp rise in MDA at early stages likely reflects active lipid peroxidation, whereas the subsequent decline may be attributable to depletion of oxidizable substrates, systemic intoxication, or activation of alternative pathways for the disposal of lipid peroxidation products.

The level of conjugated dienes (primary LPO products) was highest at stage I (1.5-fold above control). At subsequent stages, CD values stabilized at levels only slightly exceeding the control, indicating active initiation of free-radical processes at the early phase of carcinogenesis. Secondary LPO products—conjugated trienes and Schiff bases—increased progressively from stage I to stage IV, showing marked elevations at advanced stages (SB levels at stages III and IV were 20.9- and 30.7-fold above control, respectively). This pattern indicates the accumulation of deep, largely irreversible damage to lipids and proteins as the tumor progresses.

Against the background of intensified LPO, the antioxidant system exhibited phased changes—from compensation to exhaustion (Table 4).

Table 1

Characteristics of the examined patients with lung adenocarcinoma and the control group

Parameter	Patients (n = 40)	Controls (n = 40)
Sex, M/F (n)	34/6	34/6
Ethnicity, Sakha/ Russian (n)	34/6	34/6
Mean age (years)	66.4 ± 1.1	65.5 ± 1.4
Stage I (n)	3	-
Stage II (n)	6	-
Stage III (n)	15	-
Stage IV (n)	16	-

Table 2

Lipid peroxidation (LPO) markers and antioxidant system (AOS) parameters in patients with lung adenocarcinoma and in the control group

Parameter	Patients (n = 40)	Controls (n = 40)	p-value
MDA, μmol/L	1.79 ± 0.15	0.76 ± 0.14	< 0.001
CD, arbitrary units (a.u.)	1.04 ± 0.05	0.89 ± 0.05	0.012
CT, a.u.	0.41 ± 0.15	0.22 ± 0.02	0.603
SB, a.u.	0.33 ± 0.08	0.016 ± 0.001	< 0.0001
GPx, U/mL	9.44 ± 0.68	11.72 ± 0.27	0.003
GST, U/mL	1.56 ± 0.13	1.66 ± 0.10	0.194
GR, U/mL	4.75 ± 0.49	3.66 ± 0.20	0.646
GSH, μmol/L	2.38 ± 0.15	3.08 ± 0.13	< 0.001

Note: The p-value was calculated using the Mann-Whitney U test.

Table 3

Lipid peroxidation markers in patients according to disease stage

Parameter	Control (n = 40)	Stage I (n = 3)	Stage II (n = 6)	Stage III (n = 15)	Stage IV (n = 16)
MDA, μmol/L	0.76 ± 0.14	2.61 ± 0.39**	2.24 ± 0.40**	2.11 ±0.22***	1.17 ± 0.17*
CD, a.u.	0.89 ± 0.05	1.36 ± 0.00	0.91 ± 0.19	1.12 ± 0.06**	0.98 ± 0.06
CT, a.u.	0.22 ± 0.02	0.09 ± 0.00*	0.14 ± 0.03	0.24 ± 0.03	0.71 ± 0.36
SB, a.u.	0.016 ± 0.001	0.035 ± 0.000*	0.057 ± 0.012***	0.31 ± 0.07***	0.46 ± 0.16***

Note: p-values were calculated using the Mann-Whitney U test: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$.

Table 4

Antioxidant defense parameters in patients according to disease stage

Parameter	Control (n = 40)	Stage I (n = 3)	Stage II (n = 6)	Stage III (n = 15)	Stage IV (n = 16)
GPx, U/mL	11.72 ± 0.27	9.24 ± 4.56	7.93 ± 0.43***	8.67 ± 1.09*	10.76 ± 1.12
GST, U/mL	1.66 ± 0.10	1.45 ± 0.47	1.50 ± 0.26	1.51 ± 0.14	1.65 ± 0.28
GR, U/mL	3.66 ± 0.20	2.68 ± 0.00	4.05 ± 0.93	5.93 ± 0.92*	4.24 ± 0.70
GSH, μmol/L	3.08 ± 0.13	2.40 ± 0.17	2.28 ± 0.19*	2.30 ± 0.29**	2.50 ± 0.26

Note: p-values were calculated using the Mann-Whitney U test: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$.

Glutathione peroxidase (GPx) activity was reduced at all stages, with the greatest suppression at stages II and III (32.3% and 26.0% below control, respectively). Glutathione S-transferase (GST) activity remained relatively stable, showing no statistically significant differences from the control group. Glutathione reductase (GR) activity exhibited a non-linear pattern: a decrease at stage I, followed by an increase to a peak at stage III, and a subsequent decline at stage IV. The level of reduced glutathione (GSH) was consistently decreased across all disease stages.

Discussion. The present study revealed pronounced disturbances in lipid peroxidation (LPO) and antioxidant defense in patients with lung adenocarcinoma, supporting the central role of oxidative stress in the pathogenesis of this disease.

The increase in core LPO markers (MDA, conjugated dienes, Schiff bases) together with decreases in GSH level and GPx activity corroborates the concept that intense tumor growth is associated with induction of free-radical processes and depletion of antioxidant potential.

The stage-dependent behavior of MDA proved most informative. The peak concentration at stage I—3.4-fold above control—likely reflects a phase of active initiation of free-radical reactions. This interpretation is consistent with the findings of Zheng et al. (2024), who associated elevated MDA levels with early stages of cancer, underscoring its potential as a biomarker of tumor progression [35]. The subsequent decline at stage IV can plausibly be explained by depletion of peroxidation substrates, overall metabolic depression, and systemic intoxication in the terminal phase, in line with the observations of Jomova et al. (2023), who noted altered oxidative-stress profiles at advanced stages of cancer [14].

Analysis of stage-wise dynamics of LPO products clarifies the cascade of oxidative reactions. Elevated conjugated dienes at stage I indicate active initiation of free-radical oxidation at early carcinogenesis. This is consistent with findings by Lei et al. (2021), who emphasized the role of early oxidative damage, evidenced by accumulation of characteristic metabolites at initial stages of oncogenesis [18]. Stabilization of conjugated dienes at later stages, accompanied by substantial increases in conjugated trienes and Schiff bases, indicates efficient conversion of primary LPO products into secondary and terminal species. Progressive accumulation of Schiff bases clearly reflects the deepening of oxidative stress as the disease advances [2].

The antioxidant response to intensified LPO was phased. Persistent reductions in GSH and GPx activity at all stages appear to represent a fundamental defect characteristic of a deficit in the key peroxide-detoxifying system. This observation aligns with Barartabar et al. (2023), who reported that tumor growth is frequently accompanied by depletion of antioxidant reserves, thereby amplifying oxidative stress [4]. The nonlinear pattern of GR activity conforms to the classical transition from compensatory to decompensatory phases, culminating in exhaustion of antioxidant reserves at the terminal stage [17]. This is consistent with Chaudhary et al. (2023), who discussed how dysregulation of antioxidant-enzyme activity can aggravate oxidative injury and promote cancer progression [8].

In sum, these findings underscore a profound imbalance in pro-/antioxidant homeostasis associated with lung adenocarcinoma. The stage-specific dynamics of LPO markers—an early surge in primary and secondary products with a subsequent shift in the marker profile at later stages—provide valuable insight into the molecular mechanisms underpinning tumor progression. Moreover, the phased antioxidant response, with signs of compensation at stage III and decompensation at stage IV, points to the potential of therapeutic strategies aimed at mitigating oxidative stress, which could enhance the effectiveness of existing treatments and improve patient outcomes, as suggested by recent reviews on the role of antioxidants in cancer therapy [29].

Conclusions. The development of lung adenocarcinoma is accompanied by a profound imbalance in pro-antioxidant homeostasis, manifested by intensified lipid peroxidation (LPO) and depletion of antioxidant defenses.

A stage-specific pattern of LPO markers was identified: a sharp rise in primary and secondary products at early stages, followed by a shift in the marker profile at advanced stages.

The antioxidant system exhibits a phased response, with signs of compensation at stage III and decompensation at stage IV.

The authors declare that there is no conflict of interest.

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DIAGNOSTIC AND TREATMENT METHODS

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THE USE OF STEM CELLS IN OSTEOPLASTY OF JAW DEFECTS: A CELL - ENGINEERING APPROACH

The use of stem cells in osteoplasty of jaw defects is one of the most promising areas of modern cellular engineering regenerative medicine. Traditional osteoplasty methods have a number of limitations, from the risk of infections and pain to the limited amount of available graft. In this regard, stem cells open up new possibilities for creating biologically active structures capable of stimulating osteogenesis and restoring complex structures of the maxillofacial region. The review systematizes current data on the use of periodontal ligament (PDLSC), dental pulp (DPSC) and jawbone (JBMSC) stem cells in osteoplasty of jaw defects. Their morphological and molecular characteristics, osteogenic potential, interaction with the microenvironment of the defect, as well as integration with biomaterials and growth factors are considered. Special attention is paid to the results of preclinical and clinical studies confirming the safety and effectiveness of cellular therapies aimed at restoring the cement–periodontal ligament–bone complex and improving the osseointegration of implants. In addition, the work analyzes existing preclinical models of jawbone defects in small and large animals, providing an experimental basis for evaluating the effectiveness of cellular engineering structures and developing safe protocols for clinical use. The importance of DPSC and JBMSC exosomes as biologically active factors enhancing osteogenic differentiation and tissue regeneration is noted. The obtained data emphasize the high prospects of using stem cells from the oral cavity for bone tissue regeneration, the development of new biocompatible materials and individualized therapeutic strategies. The presented review can serve as a scientific basis for creating effective, safe and clinically justified approaches to the treatment of maxillofacial defects and improving the results of implantation therapy.

Keywords: stem cells, osteoplasty, jaw defects, tissue engineering, PDLSC, DPSC, JBMSC, bone regeneration

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Introduction. Jawbone defects remain one of the urgent problems of modern maxillofacial surgery, as they can occur due to congenital anomalies such as cleft lip and palate, injuries, tumors, or tooth extractions. [1, 2, 4, 5, 7]. According to the World Health Organization, about 15-20% of the population face problems with restoring the bone tissue of the jaw after injury or surgery, while in Russia more than 25 thousand cases of maxillofacial defects requiring osteoplasty are registered annually [6]. Delayed healing and non-healing of jaw defects can lead to functional disorders of chewing, aesthetic deformities and speech problems, which underlines the high clinical significance of the problem.

Traditional bone repair methods, including autogenic, allogeneic, and xenogenic grafts, distractive osteogenesis, and targeted bone regeneration, have limitations such as the risk of infection, mechanical complications, pain, prolonged rehabilitation, and limited volume of autografts [3, 6, 9, 17]. In this regard, cellular engineering approaches and tissue engineering open up new opportunities for bone structure regeneration by combining materials, biology and medicine. Stem cells, possessing multipotent differentiation and the ability to self-renew, are able to transform into osteoblasts upon transplantation into a defect, accelerating the restoration of the shape and function of the jaw. Choosing the optimal cell type and defect models requires a systematic approach, taking into account the features of the structure and physiology of the oral cavity [12, 24, 27, 47, 48].

Therefore, the relevance of the topic is due to the need to improve osteoplasty methods to accelerate bone tissue repair and reduce complications in the treatment of maxillofacial defects. The aim of this work is to analyze current data on the use of stem cells in osteoplasty of jaw defects, as well as to evaluate their osteogenic potential, interaction with the microenvironment, and integration with biomaterials to develop effective cellular engineering approaches to bone and periodontal tissue regeneration.

Materials and methods. The article is based on a systematic analysis of the literature on the use of stem cells in osteoplasty of the jaw and cellular engineering regeneration of bone tissue. The search was conducted in leading databases (eLIBRARY.ru, PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, ResearchGate) with keywords related to stem cells, bone defects, and cell models, with a focus on publications from 2010 to 2025. Clinical and preclinical studies, systematic reviews, and meta-analyses reflecting current understanding of stem cell types, their osteogenic potential, and cellular engineering structures were included. To systematize the data, content analysis and descriptive analytical methods were used to identify the relationship between cell types and recovery efficiency. Special attention was paid to the choice of the cell source, methods of cultivation and integration with biomaterials for the formation of bone regenerate. The approach to finding, evaluating, and structuring information is presented in Table 1, which ensures transparency and reproducibility of the study.

Results and discussion. This section discusses the results of using various types of stem cells (PDLSC, DPSC, JBMSC) for bone and periodontal tissue regeneration, including their interaction with the microenvironment and the possibilities of clinical application. In the future, the features of each cell population, preclinical models of maxillofacial defects, and prospects for the use of cellular and biomaterial therapies to restore the jawbone will be discussed in detail.

The use of stem cells for the reconstruction of jaw defects. There are several types of stem cells for jaw defect reconstruction: Ashour et al. [44] described PDLSC, Bi and colleagues [11] studied DPSC, and M.G. Semenov et al. [8] investigated JBMSC. In comparison with long bone stem cells, jaw cells demonstrate higher proliferation and osteogenic potential, which makes them effective for bone tissue repair [5, 7]. These cells actively interact with the microenvironment of the defect, including vascular and nervous components, which enhances regeneration [1, 2]. Therapy based on jaw stem cells provides accelerated restoration of anatomical shape and function, as well as differentiation into various bone and connective tissue lines [8, 9, 17]. Genetic models of mice are used to trace the lineage of stem cells in vivo and to study the role of nervous tissue, including Schwann cells, in the regulation of osteogenesis [1, 2]. The optimal combination of stem cells with biomaterials and growth factors significantly increases the speed and quality of osteoplasty, which makes the approach promising for clinical use [17].

Periodontal ligament stem cells (PDLSC) are multipotent postnatal cells localized in the periodontal ligament, capable of differentiating into osteoblasts, adipocytes, collagen-forming cells, and cement-like cells [12]. PDLSCS were first isolated and amplified in vitro by Seo and colleagues, and their molecular markers, including CD44, CD90, CD105, STRO-1, and SSEA4 in the absence of CD34 and CD45, were characterized in detail in studies by Kawasaki et al. [37] and Duan et al. [40]. Chopra et al. [29] demonstrated that PDLSCS have a high ability for osteogenic differentiation in vitro, forming calcium nodules and activating alkaline phosphatase, which confirms their potential for bone tissue regeneration. Moreover, Wang L. et al. [36, 43] showed that PDLSC transplantation onto biomaterial scaffolds promotes the restoration of the cement-periodontal ligament-bone complex in preclinical animal models, ensuring the formation of a functional periodontal structure. Clinical studies of L.Gan et al. [18] and Yu.I. Chergeshtova et al. [9] confirmed the safety and efficacy of autologous PDLSC cell membranes for the treatment of periodontitis, improving the depth of probing, bone height, and the level of clinical attachment of periodontitis.

Mesenchymal dental pulp stem cells (DPSC) are a rapidly proliferating population of cells isolated from the pulp of an adult tooth, capable of multipotent differentiation, including odontogenesis, adipogenesis, and myogenesis. A. Machavariani et al. [22] showed for the first time that the combination of DPSC with osteoplastic materials can promote targeted regeneration of jawbone defects, opening up prospects for clinical use in dental surgery. H. Sun et al. [41] demonstrated that exosomes secreted by DPSC enhance osteogenic differentiation and cell migration in graphene-porous titanium-aluminum frameworks, thereby improving the formation of new bone tissue. N.V. Popova et al. [4] contributed to understanding the characteristics of DPSCs by describing in detail their surface markers and the possibilities of integration with biomaterials for tissue engineering. Z. Jing and colleagues [21] demonstrated the effectiveness of 3D-printed skeletons for targeted bone regeneration using DPSC, and I. Mitra et al. [10] have shown that such structures increase the biocompatibility and osteogenic potential of cells. Finally, the research of S. Nikfarjam and colleagues [30] emphasized the importance of DPSC exosomes as modern biologically active factors capable of enhancing cell proliferation and differentiation, opening up new approaches for regenerative medicine.

Jawbone mesenchymal stem cells (JBMSC). JBMSCS originating from the jawbone have a high proliferative ability and are able to repair not only bone, but also cementoid and periodontal ligamen-

tous tissue, which makes them preferable for the regeneration of jaw defects compared to BMSCs [36]. Implantation of autologous JBMSCS into bone defects has shown efficacy in the treatment of maxillary defects and promotes osseointegration of implants by stimulating osteogenic differentiation [38]. Recent studies have identified osteogenic precursors of JBMSC with high Fat4 expression, which enhance the osteogenic potential of these cells. [12, 17, 27, 47, 48]. Additionally, the effect of DPSC exosomes increases the osteogenic differentiation of JBMSC, which further accelerates the regeneration of the jawbone [24].

Preclinical models of maxillofacial defects and their application. Animal experiments create a critically important bridge between basic research and clinical practice, allowing us to study the mechanisms of healing of jaw defects and test new therapeutic approaches [26]. Various types of jaw defects, including postextractional, traumatic, and congenital, may vary in location and degree of damage, which requires the use of specific preclinical models [16]. Both large animals (pigs, dogs, goats, rabbits) and small animals (rats, mice) are used to model jawbone defects, while the choice depends on the research objectives, accessibility, and complexity of surgical intervention [16, 25]. Large animals provide more anatomically approximate results, but their use is limited by the high cost and complexity of procedures, while small animals are more often used because of convenience and cost-effectiveness [25]. Collectively, the use of various preclinical models makes it possible to optimize bone regeneration strategies and pre-evaluate the effectiveness of implants and cell therapies, including stem cells and biomaterials [16, 25].

Further prospects for the use of stem cells (SC) in bone tissue regeneration. In recent decades, tissue engineering using oral SCS has shown significant progress in the regeneration of bone and periodontal tissue, including alveolar bone, dentin, pulp, and cement, with active contributions from S. Subramaniam et al. [25], Y. Wen et al. [16] and S.K. Boda et al. [31]. The development of preclinical models of jaw defects, including maxillary and mandibular models of drilling and tooth extraction, has made it possible to study the effectiveness of various SCS in vivo, as shown in the studies of E.S. Willett et al. [39]. However, unresolved issues remain, including the selection of the most suitable tissue for cell production, the safe use of allogeneic SCS, immunomodulation, and the

Clinical and preclinical studies using stem cells for jaw defect reconstruction

The authors' research	Year of research	A country	The type of stem cells	Main effects / benefits	Number of cases/ models	The control group
Popova N.V. et al. [7]	2024	Russia	DPSC / PDLSC	Characteristics of surface markers, possibilities of integration with biomaterials, application in orthodontics	15 patients	10 patients
Khlusov I.A. et al. [5]	2018	Russia	MSC	Modeling of the mesenchymal stem cell microenvironment, perspectives of tissue engineering	10 animals	5 animals
Chergeshtov Yu.I. et al. [9]	2014	Russia	BMSC / PDLSC	Dynamics of reparative regeneration of mandibular defects with implants and stem cells	12 animals	6 animals
Ashour et al. [44]	2020	Jordan	PDLSC	Increased osteogenic differentiation, restoration of periodontal structure	15 animals	5 animals
Bi et al. [11]	2023	China	DPSC	Accelerated bone formation, improved integration with biomaterials	20 animals	10 animals
Cai et al. [32]	2021	China	JBMSC	Restoration of bone and cement periodontal tissue, stimulates osteogenesis	12 animals	6 animals
Gan et al. [46]	2020	USA	PDLSC	Safety and effectiveness of autologous cell membranes, improvement of bone tissue height	10 patients	10 patients
Machavariani et al. [22]	2019	Georgia	DPSC	Targeted regeneration of jaw defects, increased osteogenic potential	8 animals	4 animals
Sun et al. [41]	2022	China	DPSC	Exosomes enhance osteogenic differentiation and cell migration	10 animals	5 animals
Jing et al. [21]	2020	China	DPSC	Effectiveness of 3D-printed skeletons for bone regeneration	6 animals	3 animals
Mitra et al. [10]	2021	USA	DPSC	Increasing biocompatibility and osteogenic potential in 3D printing	5 animals	5 animals
Willett et al. [39]	2017	USA	PDLSC / BMSC	A standardized rat model for assessing the effects of inflammation and transplantation on healing	24 animals	12 animals

development of optimal delivery systems. Despite this, fundamental and preclinical studies have provided convincing evidence of the potential of oral SC for bone tissue regeneration [39]. In the future, it is necessary to integrate these data to develop clinically safe, effective and economically viable methods of jawbone tissue engineering.

Conclusion. The analysis showed that the stem cells of the periodontal ligament, tooth pulp and jawbone have a high osteogenic potential and the ability to multipotent differentiation, which makes them effective for the regeneration of bone and periodontal tissue. The use of these cells in combination with biomaterials and growth factors accelerates the restoration of the anatomical shape and functional structure of jaw defects. Preclinical models have confirmed the safety and effectiveness of cell-based therapies, making it possible to optimize delivery methods and predict clinical outcome. The practical significance of the work lies in the possibility of applying these approaches to develop safe and effective strategies for jawbone tissue engineering, including the treatment of periodontitis, defects, and improved osseointegration of implants.

The authors declare that there is no conflict of interest.

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EFFECT OF COMBINED STERILIZATION ON THE STRUCTURAL AND FUNCTIONAL PROPERTIES OF BONE IMPLANTS: A STUDY OF RADIATION-INDUCED CHANGES IN COLLAGEN

This paper presents a comprehensive analysis of the effects of radiation and combined exposure on the structure and properties of bone tissue, with a particular emphasis on changes in the collagen matrix. This study aims to optimize a combined sterilization technology for biological implants and bone tissue, ensuring effective inactivation of pathogenic microflora while maintaining the structural integrity and biomechanical properties of the material. Particular attention is paid to the effect of ionizing radiation on the intermolecular interactions of collagen, its spatial organization, and degradation processes. A mathematical model has been developed describing changes in interfibrillar distances in collagen, enabling a quantitative relationship between the radiation dose and the level of protein matrix degradation. This work has practical implications for improving sterilization methods for biomaterials intended for transplantology and reconstructive surgery. The studies were conducted using Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), atomic force microscopy (AFM), and micromechanical analysis methods. For sterilization, an ozone-oxygen mixture obtained using a medical ozonizer with an adjustable concentration of active oxygen species was used. Radiation irradiation was carried out on a UELR-1-25-T-001 continuous-flow linear electron accelerator (Institute of Nuclear Physics, Lomonosov Moscow State University). It was found that combined sterilization allows reducing the radiation dose to 12 kGy, while maintaining the structural integrity of collagen and the mechanical properties of bone material. A model of collagen degradation under the influence of radiation is proposed, linking the dose load with a change in intermolecular distances; a quantitative correlation between the parameters Δr (according to the model) and structural changes in collagen was established; The possibility of reducing the radiation dose while maintaining the sterilizing effect through ozone pretreatment has been experimentally demonstrated. The proposed combined sterilization technology provides a pronounced synergistic effect, enabling a high level of sterility while preserving the biophysical properties of bone implants. This approach significantly reduces the radiation dose and thermal impact compared to traditional radiation sterilization methods, ensuring safer use for biomedical purposes.

Keywords: radiation sterilization, ozone, collagen, bone tissue, FTIR, atomic force microscopy, mathematical modeling

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Introduction. Modern trends in reconstructive surgery and tissue engineering place increased demands on the quality and biocompatibility of bone implants. One of the key conditions for their safe use is effective sterilization with minimal changes in the material structure. Radiation sterilization has proven itself as a highly effective method, ensuring reliable inactivation of pathogenic microorganisms without the use of toxic reagents. However, excessive radiation doses (more than 20–25 kGy) lead to the degradation of the organic bone matrix, particularly collagen, which significantly reduces the mechanical strength and biological activity of the material [2, 3, 7, 9].

Collagen is the main structural protein of connective tissue, providing strength, elasticity, and biocompatibility to bone [4, 11]. Its molecular organization is sensitive to physicochemical influences, especially ionizing radiation. Damage to the collagen matrix manifests itself as cleavage of peptide bonds, destabilization of the secondary structure, and an increase in intermolecular distances between fibrils, which leads to disruption of the bone tissue architecture. Understanding the mechanisms of radiation-induced collagen degradation is key to the development of gentle sterilization regimens. One promising area for optimizing radiation sterilization is the use of combined technologies that include preliminary exposure to ozone [8]. Ozone has pronounced bactericidal properties and promotes partial destruction of the cell membranes of microorganisms, increasing the effectiveness of subsequent radiation exposure. This approach allows for a reduction in the required radiation dose, thereby limiting radiation-induced damage to structural proteins. It has previously been shown that radiation causes dose-dependent changes in the spectra of collagen amide groups (Amide I, II, III) in the 1670–1500 cm^{-1} range, indicating disruption of the spatial organization of the protein matrix [8]. However, the quantitative patterns of changes in intermolecular distances and collagen fibril morphology parameters under the influence of radiation have been insufficiently studied. To address this issue, a mathematical model was developed in this study that relates the radiation dose to changes in the distances between dipoles in the collagen structure. Ozone treatment prior to radiation exposure not only enhances the sterilization effect but also stabilizes the structure of the protein matrix. This is due to an increase in oxygen content in bone tissue, which enhances the "oxygen effect" and reduces the radiation dose required to inactivate pathogens [8].

This study presents a comprehensive study of bone tissue collagen structures after various types of sterilization—se-

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lective (ozone and radiation) and combined. The primary objective is to assess the degree of radiation-induced collagen degradation and determine the optimal parameters for combined sterilization that ensure the preservation of bone tissue morphology and mechanical properties.

Materials and Methods. To study the structural changes in collagen in bone tissue exposed to ionizing radiation and ozone treatment, a combination of modern instrumental and computational methods was used. This allowed for a comprehensive characterization of the morphological, chemical, and mechanical changes in bone samples at the micro- and nanoscale levels. Compact fragments of bovine bone tissue (2 × 2 × 3 mm) were used as model samples. They were pre-cleaned, defatted, and dried at a temperature not exceeding 40 °C to preserve the collagen structure. Bone was considered as a two-phase system: a mineral component (calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$) and an organic matrix, represented mainly by type I collagen, responsible for elasticity and plasticity. All samples were stored in sealed bags at room temperature until analysis. IR spectra were recorded on a Varian 7000 FTIR spectrometer in the 4000–400 cm^{-1} range with a resolution of 2 cm^{-1}. FTIR provided quantitative data on the state of the organic and mineral phases of bone tissue. The spectra were analyzed using the main characteristic absorption bands. For quantitative analysis, deconvolution of the amide bands (I and II) was used, which allowed us to assess the degree of collagen fiber degradation and changes in their cross-links under radiation exposure. The morphology and nanostructure of the collagen fibril surface were studied using atomic force microscopy on a Solver NEXT system (NT-MDT, Russia). Three-dimensional images of 5×5 μm and 10×10 μm areas were recorded with a vertical resolution of up to 1 nm. Using specialized software (Nova and Image Analysis 3.4), the following were calculated: average fibril thickness (d_o), interfibrillar distance (r), orientation parameter (θ), root-mean-square roughness (R_a), and structural ordering coefficient (S). Particular attention was paid to the change in r, the average interfibril distance, reflecting the degree of radiation-induced destruction of the collagen network. Surface morphological analysis and elemental composition were performed on a JEOL JSM-7800F microscope (Japan) equipped with an energy-dispersive analysis system. SEM made it possible to evaluate: surface topography (cracks, defects, porosity), element distribution (C, O, Ca, etc.), etc. Microhardness was determined by the Vickers method using a DM8 device (Italy). For each sample, measurements were performed, followed by statistical averaging, and the results were compared between groups (control, ozone, radiation, and ozone + radiation). To quantitatively describe radiation-induced changes in collagen structure, a physical and mathematical model was developed based on the dipole representation of the collagen molecule. The model relates the absorbed radiation dose (D) to the change in intermolecular distance (Δr) between the dipole centers:

$$E_{abs} = D \cdot m$$

$$U = -\frac{A}{r^6},\ A = \frac{2}{3}\frac{p^4}{kT}$$

where: E_{abs} is the absorbed energy, m is the mass of the sample, A is the dipole interaction constant, p is the dipole moment of the collagen molecule, k is the Boltzmann constant, T is the temperature (K). From this follows the relationship:

$$r_2 = \sqrt[6]{\frac{A}{\frac{A}{r_1^6} - \frac{E_{погл} \cdot c}{2N}}}$$

where: r_1 and r_2 are the distances between the dipoles before and after irradiation; N is the number of collagen molecules; c is a parameter that takes into account the radiation quality factor and the dipole constant.

The difference $\Delta r = r_2 - r_1$ characterizes the degree of radiation-induced collagen destruction. The calculated Δr values were compared with experimental data, which allowed for quantitative confirmation of the correlation between the radiation dose and changes in collagen structure. Microbiological tests were conducted to confirm the sterilizing effect of the combined technology. The highest efficiency in inactivating fungal and bacterial spores was observed with combined treatment with ozone and radiation at a dose of 12–15 kGy. Experimental data were processed using OriginPro 2023, Statistica 13.3, and Matlab. Student's t-test was used to compare results at a significance level of $p < 0.05$.

Results and Discussion. Experimental data confirm that exposure of bone tissue to ionizing radiation causes a series of interrelated changes in the organic (collagen) and inorganic (mineral) phases. At doses up to 10–12 kGy, relative structural stability is maintained; however, above 15–20 kGy, signs of collagen network degradation are observed, accompanied by a decrease in the intensity of amide bands in the IR spectra and an increase in microporosity in AFM and SEM images. Radiation initiates the formation of reactive radicals, leading to the cleavage of peptide bonds and the destruction of the collagen triple helix. This is manifested by changes in fiber configuration, an increase in interfibrillar distances, and a localized decrease in surface microhardness. Ozone treatment prior to irradiation plays a significant role, reducing the number of radiation-active centers and partially offsetting the energetic effects of gamma quanta or electron beams.

Infrared spectroscopy: changes in collagen structure. Table 1 shows the characteristic spectra of bone tissue before and after irradiation with doses of 12 and 20 kGy: 1) the amide I band (1670–1650 cm^{-1}), corresponding to stretching of the C=O bond in the peptide group, gradually decreases with increasing dose, indicating the destruction of the secondary structure (α-helix and β-sheets); 2) the amide II band (1550 cm^{-1}), reflecting combined C–N and N–H vibrations, becomes less pronounced at doses above 15 kGy, indicating partial destruction of hydrogen bonds in the protein; 3) a decrease in the intensity of the amide III band (1240 cm^{-1}), associated with collagen cross-links, is observed. 4) A relative increase in the intensity of phosphate bands (560 and 604 cm^{-1}) is observed in the mineral phase, which is associated with a partial loss of the organic component and a relative increase in the proportion of apatite. These results confirm that the collagen component of bone tissue is the most radiosensitive component. A decrease in the intensity of amide group bands at doses ≥20 kGy indicates degradation of the protein matrix, which correlates with a decrease in microhardness and a change in the surface nanorelief.

Atomic force microscopy: collagen nanomorphology. AFM studies revealed dose-dependent changes in the nanostructure of the collagen network. Control samples exhibited clearly defined fibril ordering with a characteristic transverse striation pitch of ~67 nm, which corresponds to the normal D-periodicity of type I collagen. After irradiation with a dose of 12 kGy, the structure retains a regular pattern, with only minor height fluctuations observed (Fig. 1a, Fig. 2a). However, at 20–25 kGy (Fig. 1b, Fig. 2b), a loss of order, fibril rupture, and

Table 1

Changes in amide and mineral bands at different dose levels

Stripe (cm^{-1})	Structure	12 kGy	20 kGy	Interpretation
1673 (amide I)	C=O (peptide)	Minor decrease (~5%)	Significant weakening (~20%)	Rupture of collagen helices
1550 (amide II)	C–N, N–H	Minor fluctuations	Decrease in intensity	Hydrogen bond disruption
1240 (amide III)	C–N + N–H	It is saved	A decrease of 15–18%	Loss of cross-links
1030 (PO_4^{3-})	Mineral grid	Minor increase	Relative share growth	Relative exposure of apatite
870 (CO_3^{2-})	Substitution carbonate	No changes	Minor decrease	Loss of part of the carbonate group

aggregate formation are observed. The measured nanostructure parameters are presented in Table 2. An increase in interfibrillar distances (r) and a decrease in order (S) are direct markers of radiation-induced changes. These data are in good agreement with the predictions of the theoretical model, which describes an increase in Δr with increasing dose (Table 3). The results of mechanical tests demonstrate that at doses ≥20 kGy, collagen destruction occurs, leading to weakening of interfibrillar bonds and a decrease in elasticity.

Comparison of experimental data and the model. The results of atomic force microscopy and spectroscopy were compared with model calculations of changes in intermolecular distances (Δr) with increasing dose (Table 3). The theoretically calculated increase in Δr correlates with the increase in interfibril distances observed experimentally (correlation coefficient $R^2 = 0.94$). This high convergence indicates that the model correctly describes the physical mech-

Table 2

Measured nanostructure parameters

Parameter	Control	12 kGy	20 kGy	25 kGy
Average fibril thickness d_o , nm	95 ± 8	97 ± 10	112 ± 12	130 ± 14
Interfibrillar distance r , nm	41 ± 5	43 ± 6	62 ± 9	75 ± 11
Ordering coefficient S	0.92	0.89	0.71	0.64
R_a (roughness), nm	18 ± 3	19 ± 3	27 ± 4	34 ± 5

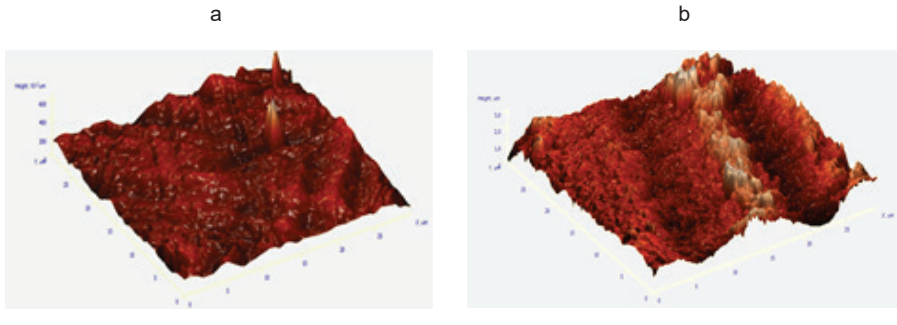

Fig. 1. Example of AFM images of collagen fibril structures after radiation exposure: a) 12 kGy, b) 20 kGy

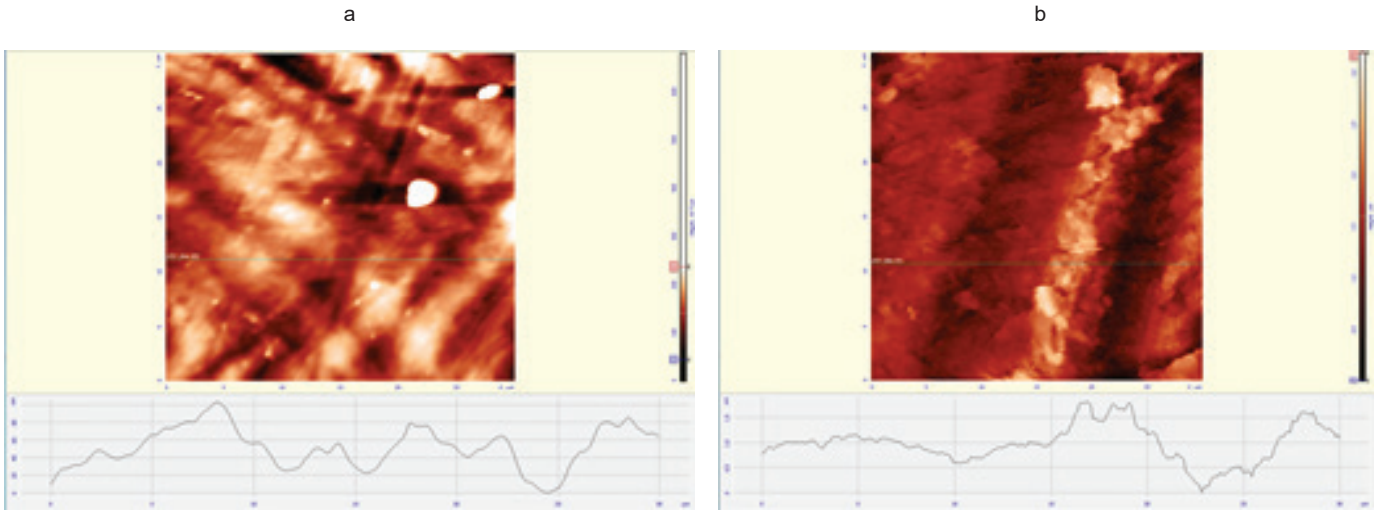

Fig. 2. Example of obtained images of the surface relief of samples (AFM) after exposure to radiation with a dose of: a) 12 kGy, b) 20 kGy

Table 3

Dependence of the change in intermolecular distance Δr on the values of the absorbed dose

Dose (kGy)	Δr (model), nm	Δr (AFM), nm	Deviation, %
5	4.6	5.0 ± 1.2	8.6
10	9.9	10.3 ± 1.5	4.0
12	12.3	12.8 ± 1.6	3.9
20	23.3	24.1 ± 2.2	3.4
25	31.2	30.8 ± 2.9	1.3

anism: radiation leads to an increase in the distances between collagen dipoles and a weakening of intermolecular interactions, resulting in a loss of order and a decrease in strength.

Experimental data and mathematical modeling mutually confirm that increasing the radiation dose leads to destruction of the protein matrix, manifested by an increase in intermolecular distances, cleavage of peptide bonds, and a change in the topology of the fibrillar structure. These effects are evident at doses of 15–20 kGy and become pronounced above 25 kGy, accompanied by a decrease in microhardness and a disruption of the elastic properties of the bone surface. IR spectroscopy revealed a decrease in the intensity of amide bands I–III, while AFM and SEM confirmed morphological changes such as fragmentation, thickening, and fibril aggregation. The developed model of collagen intermolecular interactions under radiation exposure agrees well with experimental data: an increase in the absorbed dose leads to an increase in the distance between dipoles (Δr), which can be considered a quantitative criterion for the degree of protein matrix degradation. The identified synergistic effect of ozone pretreatment is of particular significance. Ozone reduces the concentration of microbial cells and their radioresistance. This allows subsequent radiation exposure to be reduced to doses of 11–12 kGy, which ensures sample sterility without noticeable changes in the morphological and mechanical properties of the bone. This makes the combined technology a promising alternative to standard methods of bone implant sterilization, which use doses of 25 kGy or higher.

Conclusion. The obtained results open up the possibility of creating gentle technologies for radiation sterilization of bone and collagen-containing biomaterials, applicable not only in clinical practice (manufacture of bone implants), but also in paleontological research, where preservation of the structure of ancient bone remains is required without their thermal or chemical destruction [1, 5, 6]. The developed technology can be applied: in the production of bone implants and grafts in tissue banks; in sterilization of paleontological samples requiring preservation of micro- and nanostructure; in research laboratories to optimize the radiation-chemical stability of protein materials; for the development of new biocompatible composites based on collagen, etc. In addition, the mathematical model proposed in the work can be used to predict the degree of structural changes with various types of ionizing radiation (gamma, electron beam, X-ray). Prospects for further research: expansion of the range of dose loads, taking into account the relaxation time of collagen structures after irradiation; Using three-dimensional data correlation to construct spatial models of collagen network damage; and assessing the biocompatibility and osteoinductive properties of samples in cellular tests.

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A.J. Al-Mamoori, I.A. Redko, B.S. Dombaanai

ADVANTAGES OF THE SUBVASTUS APPROACH IN PRIMARY KNEE ARTHROPLASTY: A SYSTEMATIC LITERATURE REVIEW

This systematic review evaluates the effectiveness of the subvastus approach (SVA) in primary total knee arthroplasty compared to the medial parapatellar approach (MPA). The analysis includes 15 studies with a sample size exceeding 10,000 patients. The SVA demonstrated significant advantages in the early postoperative period: reduced pain syndrome, accelerated recovery of extension function, improved range of motion, and higher functional scores. A reduction in intraoperative blood loss was noted, although operative duration may increase. In the long-term period, differences between methods become negligible. The SVA demonstrates safety comparable to MPA without increasing complication risks. When combined with enhanced recovery protocols, this method facilitates early mobilization and reduces hospitalization duration.

Keywords: knee arthroplasty, subvastus approach, early rehabilitation, PRISMA.

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Introduction. Total knee arthroplasty (TKA) represents a highly effective treatment method for terminal stages of gonarthrosis, providing sustained relief of pain syndrome and restoration of joint function. Numerous studies demonstrate long-term improvement in patients' health-related quality of life following this intervention [13, 24, 35].

The medial parapatellar approach (MPA), first described by Langenbeck in 1879 [45], has remained the gold standard for performing TKA for decades. This approach provides excellent visualization of the surgical field and optimal conditions for implantation of prosthetic components [31, 40]. Despite its widespread use, the parapatellar approach involves incision of the quadriceps femoris tendon, which inevitably leads to trauma of the knee joint extensor mechanism. Consequences of such intervention may include excessive scarring, muscle weakness, and persistent anterior knee pain [15, 38].

As an alternative to the traditional approach, quadriceps-sparing surgical approaches have been developed, among which the subvastus approach (SVA) occupies a special position due to complete preservation of the anatomical integrity of the extensor mechanism. This technique allows minimization of soft tissue trauma while maintaining adequate exposure of the surgical field [8, 22].

Modern Enhanced Recovery After Surgery (ERAS) protocols have optimized perioperative management of patients after major joint arthroplasty, providing significant reduction in hospitalization length and decrease in postoperative complications [10, 29, 33]. The combination of SVA with ERAS principles demonstrates a synergistic effect, allowing achievement of faster restoration of joint range of motion after TKA, early straight leg raise, and reduction of intraoperative blood loss compared to the traditional parapatellar approach [4].

Analysis of data from the National Joint Registry of England and Wales, including 875,166 operations, revealed a 20% reduction in revision surgery risk when using quadriceps-sparing techniques, which emphasizes not only the clinical but also the economic feasibility of this approach [5]. In the context of the development of the minimally invasive surgery concept and the pursuit of optimization of early functional outcomes of TKA, there is sustained growth of interest in quadriceps-sparing techniques.

Study objective: To conduct a systematic review of current scientific literature in accordance with the PRISMA protocol for comprehensive evaluation of the advantages of the subvastus approach compared to alternative surgical approaches in performing total knee arthroplasty.

Materials and Methods. The systematic review was performed according to PRISMA guidelines [42]. Literature search was conducted from January 2018 to December 2024 in PubMed, Google Scholar, and eLibrary databases.

The search strategy included combinations of key terms: "subvastus approach", "total knee arthroplasty", "medial parapatellar", "surgical approach" and their variations in Russian and English. Additionally, manual search was performed in the reference lists of included studies.

Inclusion criteria: studies of adult patients (≥18 years) with terminal gonarthrosis undergoing TKA, where SVA was compared with other techniques. Randomized controlled trials (RCTs), systematic reviews, and meta-analyses were included. Revision surgeries, unicompartmental knee arthroplasty, and case reports with samples of fewer than 10 patients were excluded. Extracted data encompassed study characteristics, demographic parameters, clinical outcomes, and follow-up period. The search methodology is presented in Figure 1.

Results and Discussion. Characteristics of studies included in the review. Data from 15 publications were included, collectively encompassing 138 RCTs that compared SVA with alternative surgical approaches in TKA. The total sample of analyzed studies comprised 10,475 patients, which allows the obtained results

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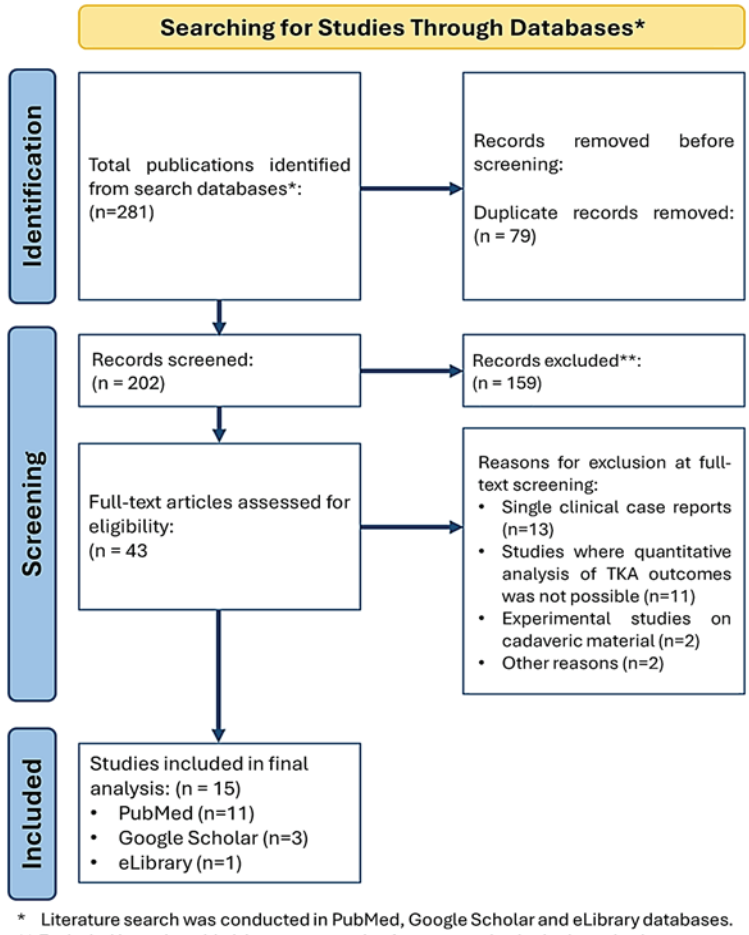
to be considered representative of the general population of patients requiring TKA. The vast majority of included studies were represented by randomized trials of high methodological quality, including several large meta-analyses, which provides a high level of evidence for the obtained data.

The primary object of comparison in most studies was the traditional MPA, which has been considered the gold standard in knee arthroplasty for decades. In a number of studies, comparative analysis was additionally conducted with other quadriceps-sparing techniques, including the midvastus approach (MVA) and mini-incision techniques.

Based on the conducted analysis, key clinical parameters were identified by which SVA demonstrated statistically significant advantages over alternative surgical techniques. These parameters include functional assessment scales for knee joint condition (KSS - Knee Society Score, WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index), range of motion in the operated joint, pain intensity on the visual analog scale (VAS), ability to perform active straight leg raise in the early postoperative period, operative time, length of hospitalization, volume of intraoperative blood loss, and frequency of postoperative complications.

Comprehensive evaluation of study results indicates the presence of substantial advantages of SVA, particularly pronounced in the early postoperative period. A brief characterization of studies included in the systematic review is presented in Table 1.



Block-Flowchart of the literature search conducted according to the PRISMA protocol

Functional outcomes according to KSS and WOMAC scales. SVA, characterized by preservation of the integrity of the quadriceps femoris tendon through dissection of the capsule under the edge of the vastus medialis muscle, demonstrates statistically significant advantages in the early postoperative period [2, 9, 11, 28, 37, 39, 46]. For example, in the study by Dileep et al. [9], on day 3 after surgery, the mean KSS score in the SVA group was 77.15 versus 67.15 in the MPA group ($p<0.00001$). In a prospective cohort study by Aladraii et al. [2], SVA showed statistically significantly better WOMAC assessment scores compared to MPA at 3 and 6 months after TKA ($p<0.05$). This advantage is explained by minimal trauma to the knee joint extensor mechanism with SVA, which promotes earlier restoration of quadriceps femoris function [26, 36]. Similar results are presented in the meta-analysis by Stubnya et al. [39], where SVA and mini-SVA approaches demonstrated the best indicators for both total and functional components of the KSS scale in the early postoperative period. However, long-term results show gradual leveling of differences between surgical approaches. By 3-6 months and beyond after TKA, no statistically significant differences in KSS and WOMAC scales between SVA and other approaches were detected [3, 7, 16, 19, 21]. This is confirmed by the study of Hosseini-Monfared et al. [19], where the use of SVA provided statistically significantly better WOMAC and KSS scores during the first year after surgery. However, in the long term, differences between groups become comparable, indicating the absence of influence of approach selection on the final functional outcome of TKA [6, 12].

Range of motion in the knee joint. Almost all RCTs note that patients who underwent TKA using SVA achieve significantly greater flexion range in the joint in the first days after surgery compared to traditional surgical approaches [4, 7, 9, 28, 39]. Thus, when using SVA within 6 months after surgery, an increase in flexion range of 11.1° was noted compared to MPA ($p<0.05$) [39]. In the study by Geng et al. [14], the difference was noticeable by day 3, and the mean flexion angle was 118.91° in the mini-SVA group versus 107.6° in the MPA group ($p<0.00001$). The advantage in range of motion persisted until day 30 of postoperative observation [14], after which differences became insignificant in the long-term period [9, 14, 21, 25, 46], indicating achievement of comparable functional results with long-term follow-up regardless of the chosen surgical approach.

The mechanism of early functional superiority of SVA is due to preservation of the anatomical integrity of the quadriceps femoris muscle and minimization of trauma to the knee joint extensor mechanism [8, 34]. The absence of the need to incise the quadriceps tendon in SVA promotes faster restoration of muscle strength and coordinated function of the extensor mechanism, which is directly reflected in the range of active movements in the early postoperative period [30, 43].

Pain syndrome in the early postoperative period. Analysis of studies

Brief comparative characteristics of studies included in the review

Author, year	Sample size	Mean age	Compared approaches	Follow-up duration (months)	Main analyzed parameters
Bouché et al., 2020 [7]	5042 (60 RCTs)	Н/Д	SVA, MVA, mini-PA, MPA, QSA	6	KSS scale, WOMAC scale, range of motion, VAS pain, operative time, complications
Stubnya et al., 2023 [39]	1774 (33 RCTs)	67,1±6,8	SVA, MPA, MVA	16,5	KSS scale, range of motion, VAS pain, straight leg raise, operative duration
Berstock et al., 2018 [4]	1694 (20 RCTs)	Н/Д	SVA, MPA	11, 58	KSS scale, range of motion, VAS pain, straight leg raise, operative duration, blood loss volume, com-plications
Wu et al., 2018 [46]	1172 (14 RCTs)	69,14	mini-SVA, MPA	36	KSS scale, range of motion, straight leg raise, op-erative duration, blood loss volume, length of hospitalization, complications
Madadi et al., 2021	50	64,8 ± 3,7	SVA, MPA	12	VAS pain, straight leg raise
Hosseini-Monfared et al., 2024 [19]	60	Н/Д	SVA, MPA	120	KSS scale, WOMAC scale, range of motion, VAS pain, straight leg raise, operative time, blood loss volume, length of hospitalization, complications
Güven et al., 2024 [16]	17	67,11±8,10	SVA, MPA	3	KSS scale, WOMAC scale, straight leg raise
Li et al., 2018 [28]	50	69,0±4,65	mini-SVA, MPA	12	KSS scale, range of motion, VAS pain, straight leg raise, operative time, blood loss volume, length of hospitalization, complications
Geng et al., 2022 [14]	58	65,0 ± 5,11	mini-SVA, MPA	1	Range of motion, VAS pain, straight leg raise, operative time, complications
Jhurani et al., 2021[21]	186	64,6±7,9	SVA, MPA	12	KSS scale, range of motion, VAS pain, straight leg raise, blood loss volume, length of hospitalization
Badawi et al., 2024 [3]	60	62,8±4,14	SVA, MPA	6	WOMAC scale, VAS pain, timing of straight leg raise, operative time, blood loss volume, compli-cations
Dileep et al., 2022 [9]	54	65,89±5,46	SVA, MPA	12	KSS scale, VAS pain, range of motion, timing of straight leg raise
Aladraii et al., 2024 [2]	98	63,9±7,5	SVA, MPA	12	WOMAC scale
Sood et al., 2024 [37]	100	62,52±6,75	SVA, MPA	12	KSS scale, WOMAC scale, VAS pain, length of hospitalization
Fahim et al., 2024 [11]	60	64,2±5,02	SVA, MPA	12	KSS scale, WOMAC scale, VAS pain, timing of straight leg raise, operative time, blood loss vol-ume, length of hospitalization, complications

included in the systematic review demonstrates substantial advantages of SVA regarding the severity of pain syndrome in the early postoperative period. This pattern is traced in most of the analyzed studies and is confirmed by meta-analysis results [3, 4, 7, 9, 14, 28, 37, 39]. In the meta-analysis by Stubnya et al. [39], it was established that the use of mini-subvastus technique is accompanied by a statistically significant reduction in pain intensity on the visual analog scale (VAS) during the first week after TKA. Similar results were obtained in a prospective randomized study by Geng et al. [14], where patients operated using mini-SVA demonstrated significantly lower pain scores both at rest and during active movements in the first days after TKA compared to the medial parapatellar approach (2.67 versus 3.38, $p<0.05$). An important feature revealed during analysis of literature data is the gradual leveling of differences in pain intensity between compared surgical approaches as the follow-up period increases. After 1-6 months following surgery, statistically significant differences in VAS scores between SVA and traditional parapatellar approach groups were absent in most studies [11, 14, 19, 21, 25, 28]. In studies by Madadi et al. [25] and Jhurani et al. [21], the severity of pain syndrome in SVA and MPA groups showed no statistically significant difference at 6 and 12 months after TKA.

The identified advantages of SVA regarding early postoperative pain syndrome can be explained by features of the surgical technique. Preservation of the integrity of the quadriceps femoris tendon and minimization of soft tissue

trauma with the subvastus approach contribute to reduction of nociceptive stimulation and inflammatory response in the early postoperative period. This creates favorable conditions for faster patient activation and early initiation of rehabilitation measures [17, 18, 30].

The absence of significant differences in the long-term period indicates that with adequate surgical technique and complete rehabilitation, long-term functional outcomes are determined primarily by the quality of prosthesis implantation and individual patient characteristics, rather than by the choice of surgical approach [1, 23, 47].

Restoration of quadriceps femoris function. One of the key advantages of SVA is faster restoration of knee joint extensor mechanism function. The most significant differences between subvastus and traditional approaches were observed in the early postoperative period [3, 4, 9, 11, 14, 19, 21, 28, 39, 46].

The straight leg raise (SLR) functional test served as the main objective criterion for assessing restoration of quadriceps strength in most analyzed RCTs. Wu et al. [46] in their study showed that in the mini-SVA group, patients could raise a straight leg after TKA on average 2.35 days earlier than in the MPA group (p=0.003). In the study by Hosseini-Monfared et al. [19], the median time to first successful performance of the straight leg raise test was 1.8 days in the SVA group versus 3.6 days in the parapatellar approach group (p<0.001). Similar results were shown by Geng et al. [14], where the mean time to restoration of the ability to raise a straight leg was 1.17 days in the SVA group versus 3.09 days in the MPA group (p<0.0001). This confirms the thesis of earlier quadriceps activation when its integrity is preserved. However, after 1-6 months following TKA, differences become insignificant [3, 4, 14, 28, 39, 46].

Operative time. Comparative evaluation of operative duration in SVA and MPA revealed heterogeneous results. Most studies noted a statistically significant increase in operative time with SVA [3, 4, 28, 39]. In particular, Li et al. [28] in their study showed a significant increase in operative time with mini-SVA (86.8 min.) compared to MPA (66.6 min.) (p<0.001). The authors emphasize that the clinical advantages of this approach—reduction of pain syndrome, acceleration of mobilization and verticalization of patients, as well as improvement of functional parameters of the knee joint—compensate for the slight prolongation of surgery [28]. At the same time, a number of studies demonstrate comparable duration of TKA with subvastus and traditional approaches [7, 11, 14, 19]. Fahim et al. [11] found no statistically significant differences in operative time between subvastus and parapatellar techniques (p=0.32).

Such variability in obtained results may be due to differences in the experience of orthopedic surgeons and passage through the learning curve, as SVA requires more delicate technique and careful visualization of anatomical structures [20, 30]. Moreover, data heterogeneity may be explained by differences in patient inclusion criteria, especially regarding body mass index and degree of knee joint deformity, which significantly affects the technical complexity of performing the approach [27]. Standardization of surgical technique and accumulation of experience in using SVA contribute to leveling of differences in operative time between compared techniques.

Blood loss. Intraoperative blood loss represents a significant parameter characterizing the degree of surgical intervention invasiveness and associated risks for the patient. Analysis of six comparative studies demonstrated the advantage of SVA in reducing blood loss volume compared to the medial parapatellar approach [3, 4, 21, 46].

Meta-analysis of 20 RCTs, including 1,694 patients, revealed a statistically significant reduction in blood loss when using SVA by 58 ml (95% CI: 10.5–106.4 ml; p = 0.02) compared to the parapatellar approach [4]. At the same time, in individual studies, no statistically significant differences in intraoperative blood loss volume between SVA and standard approaches were detected [7, 11, 19, 28].

The probable mechanism of blood loss reduction with SVA is minimization of musculotendinous structure trauma, which causes reduction of intraoperative tissue bleeding [32, 41, 44].

Length of hospitalization. Comparison of hospitalization length between SVA and MPA revealed no advantages of the subvastus approach [11, 19, 37, 46], and only two studies showed advantages of SVA [21, 28]. Thus, the prospective randomized study by Li et al. [28] showed a statistically significant reduction in hospitalization length in favor of SVA. The mean duration was 4.8±0.9 days (range 3-6 days) in the mini-SVA group versus 6.3±1.1 days (range 5-8 days) in the MPA group (p<0.001). This study shows the most pronounced advantage of SVA for this parameter.

The obtained results most likely reflect the multifactorial nature of hospitalization length, which depends not only on the surgical approach but also on multiple organizational, technical, and population factors. The study by Li et al. [28] stands out for its use of a strictly defined mini-subvastus technique in relatively young patients with unilateral TKA, which may explain the obtained differences.

Postoperative complications. Comparative analysis of postoperative complication rates when using SVA and traditional surgical techniques demonstrates comparable results in most studies. Numerous RCTs revealed no statistically significant differences in overall complication rates between these techniques [3, 4, 11, 14, 19, 28, 46].

The rate of infectious complications, including superficial and deep surgical site infections, remains comparably low in both patient groups. Analysis of randomized controlled trial data confirms the absence of significant differences in development of infectious complications between SVA and MPA [3, 11, 19].

Particular attention should be paid to the results of the study by Jhurani et al. [21], which identified a specific problem associated with SVA. This work documented a statistically significant increase in the frequency of proximal wound dehiscence and delayed soft tissue healing in the SVA group compared to the parapatellar group (p=0.03). The authors associate this complication with technical features of SVA, suggesting that limited incision length and reduced exposure of the surgical field may create excessive tension at wound edges in individual clinical cases.

It should be noted that the described wound healing problems were not confirmed in other studies. The overall rate of early postoperative complications, including hematoma formation, thrombotic complications, and infectious processes, remains comparable between different surgical approaches [19]. In studies by Badawi et al. [3] and Bouche et al. [7], a tendency toward reduction in the number of complications in the SVA group compared to control groups was noted, but these differences did not reach the level of statistical significance.

Thus, accumulated data indicate a comparable safety profile of SVA and traditional surgical techniques in TKA, while the question of potential risk of impaired wound healing requires further study in larger patient samples.

Conclusion. The systematic analysis conducted according to the PRISMA protocol demonstrates that the subvastus approach provides statistically significant improvement in functional outcomes on the KSS and WOMAC scales,

greater range of motion in the joint, early restoration of extension, and lower pain intensity in the early postoperative period. The advantages of this approach are not accompanied by an increase in intraoperative risks. After 3-6 months, differences between approaches level out, with the KSS and WOMAC functional scales showing comparable results. It should also be noted that the subvastus approach is particularly significant for the ERAS protocol, contributing to reduction of hospitalization period and economic costs. Limitations of the review include study heterogeneity and lack of long-term data.

Thus, the subvastus approach represents an effective alternative to the traditional approach, providing advantages in early recovery without deterioration of long-term outcomes.

The authors declare no conflict of interest.

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DIAGNOSTIC CHALLENGES OF A RARE KASABACH–MERRITT SYNDROME IN AN INFANT

The article is devoted to topical issues of the complexity of the diagnosis of a rare pathology – Kazabach–Merritt syndrome in infants. Against the background of progressive bilateral polysegmental pneumonia, the child retained thrombocytopenia and consumptive coagulopathy. Syndrome-by-syndrome treatment was performed in the intensive care units of the perinatal and pediatric centers of the republican hospital. The patient received a large amount of blood replacement therapy, and the pleural and abdominal cavities were repeatedly drained. In this clinical case, there were no external manifestations of the disease in the form of a tumor on the skin. Initially, the formation was not diagnosed on early CT scans. Kaposiform hemangioendothelioma complicated by Kasabach–Merritt syndrome was suspected by the exclusion method, which was confirmed at the Federal Center. Properly prescribed complex chemotherapy led to an improvement in the baby's condition. In clinical practice, there are often situations where the symptoms of the disease can be masked by other conditions, such as infectious processes or other hemorrhagic disorders. This highlights the importance of a multidisciplinary approach in the diagnosis and treatment of this disease.

Keywords: Kasabach–Merritt syndrome, kaposiform hemangioendothelioma, thrombocytopenia, consumptive coagulopathy, retroperitoneal formation, newborn, clinical case

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Introduction. Kaposiform hemangioendothelioma (KHE) is a rare congenital vascular tumor manifesting in infancy, histologically resembling Kaposi's sarcoma but not etiologically associated with herpesvirus type 8. According to the ISSVA classification, this tumor is classified as an intermediate malignancy with infiltrative growth and no metastatic potential. The most severe complication of KHE is the development of Kasabach–Merritt syndrome, which occurs in 80-90% of cases and manifests from birth in 50% of cases. The clinical signs of the syndrome are related to the size of the tumor. Kasabach–Merritt syndrome is a symptom complex characterized by the presence of a vascular tumor and associated consumptive coagulopathy and thrombocytopenia. Currently, due to the lack of randomized clinical trials, there is no standardized clinical protocol for the treatment of this disease.

The syndrome was first described by Kasabach and Merritt in 1940, and since then over 200 cases have been registered worldwide [5]. The incidence in the Russian Federation has not been reliably established [1, 2]. Among all vascular tumors, Kasabach–Merritt syndrome accounts for 1.0% in global pediatric practice [2, 5]. Mortality from this disease is quite high due to heart failure, infections, disseminated intravascular coagulation syndrome, and thrombocytopenia leading to massive bleeding, reaching 10-37.4% [1, 2, 5].

Treatment is primarily conservative, including propranolol, corticosteroids, vincristine, sirolimus [2, 3, 5, 8, 9]. Surgical treatment is often impossible due to coagulopathy, thrombocytopenia, and the infiltrative growth of the lesion [1].

Aim: To demonstrate the diagnostic challenges of a rare clinical case – Kasabach–Merritt syndrome in an infant during the first months of life.

Materials and Methods: We present the medical history of a patient who received inpatient treatment in the ICU of the Perinatal Center and later in the ICU of the Pediatric Center of the republican hospital.

Life History. A boy born in 2024. The child is from the 3rd pregnancy, which proceeded without complications. Pre-

natal screening results: I – 13 weeks pregnancy, marginal placenta previa; II – low-lying placenta, local myometrial tone; III – 26 weeks pregnancy, transverse lie of the fetus.

Childbearing: second, natural, at 39 weeks. Birth weight: 3540 g, height 56 cm. Condition at birth: satisfactory, Apgar score 8/9. Cried immediately. Put to the breast on the 1st day, sucked actively. Umbilical cord stump fell off on the 6th day. Vaccination: Hepatitis B, BCG-M – medical exemption due to thrombocytopenia in the complete blood count (CBC) at birth. Ultrasound screening of the abdomen, hip joints, neurosonography – no echopathology detected; Cardiac ultrasound – ventricular septal defect (VSD), patent foramen ovale.

Clinically, the child developed jaundice from day 2. At birth, CBC showed thrombocytopenia 113-109x10⁹/L, with a gradual decrease in platelet count (95x10⁹/L at discharge). Discharged home due to the mother's refusal of further inpatient observation and examination.

Medical history. The illness began on the 20th day of life. The child had decreased appetite, and the family visited the local central district hospital, where a pediatrician detected shortness of breath with intercostal retractions and general weakness. The child was urgently hospitalized in the ICU of the central district hospital; a pleural puncture was performed, yielding 97 ml of serosanguinous fluid. The child was transported by air ambulance to the republican hospital in the Department of Anesthesiology, Resuscitation and Intensive Care of Newborns at the age of 3 weeks. Upon admission, the condition was assessed as severe due to grade 3 respiratory failure and hemorrhagic syndrome. The patient was intubated and connected to a mechanical ventilator; hemostatic therapy was initiated, with transfusions of fresh frozen plasma (FFP), leukocyte- and platelet-depleted erythrocyte mass (LPDEM), and platelet concentrate. Contrast-enhanced computed tomography (CT) of the chest was performed, revealing bilateral polysegmental pneumonia and bilateral pleural effusion. Based on the mother's ELISA results, the child was diagnosed with congenital TORCH syndrome (mixed infection: mycoplasma, parvovirus, and chlamydia). Antibacterial therapy was prescribed: Cefepime/Sulbactam 50 mg/kg/day every 12 hours, Azithromycin 10 mg/kg/day once daily; antifungal therapy with Fluconazole; and for immunomodulation, Immunoglobulin G (Privigen) 1 g/kg/day intravenously, microstream, daily for 5 days. Biochemical analysis of pleural fluid showed increasing triglycerides up to 3.34 mmol/L; the patient was switched to total parenteral nutrition, and Octreotide was prescribed at a dose of 4 μg/kg/h microstream. With the ongoing treatment, the amount of pleural fluid decreased, and feeding with Alfare formula was started at 10 ml every 3 hours, gradually increasing the volume to 90 ml, without an increase in fluid output.

At the age of 1.5 months, the child was transferred to the Department of Anesthesiology and Resuscitation affiliated with the Surgical Department of the Pediatric Center, where he remained until further transfer to a Federal Center. At 2 months of age, contrast-enhanced CT of the chest and abdomen (Fig.1) and contrast-enhanced MRI of the abdomen (Fig.2) were performed. Findings included: a para-aortic mass at the level of the diaphragm, extending into the retroperitoneal space and into the pelvic cavity with involvement of the lumbar muscles; destruction of thoracic vertebrae Th9-Th12; fluid in the left abdominal cavity, possibly hemorrhagic; enlarged adrenal glands. The child was examined by a pediatric oncologist and a phthisiatrician. Tumor markers were within normal limits, ruling out a specific process. Kaposiform lymphangiomatosis or kaposiform hemangioendothelioma with Kasabach–Merritt syndrome of the lower mediastinum, retroperitoneal space, and pelvis was suspected. Following a remote consultation, emergency hospitalization to the N.N. Blokhin National Medical Research Center of Oncology was planned.

At 2 months of age, the child was transported to the airport for medical evacuation, accompanied by an intensivist. At the airport, the patient's condition was deemed non-transportable – there was an increase in signs of respiratory failure, cyanosis of the skin, and active hemorrhagic discharge of 80 ml from the pleural cavity. After fluid removal, the child's condition stabilized. The dressings were heavily soaked with hemorrhagic discharge. The patient was returned to the ICU of the Pediatric Center in extremely critical condition. Transfusion of leukocyte- and platelet-depleted erythrocyte mass, platelet concentrate, and fresh frozen plasma was performed, stabilizing the patient's condition.

A week later, the child developed symptoms of pseudomembranous enterocolitis, which improved with treatment: Metronidazole 7.5 mg/kg x 3 times/day IV + Vancomycin 40 mg/kg/day, divided into 4 doses per os. In coordination with the D. Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, the child was prescribed Sirolimus. This is a macrolide obtained from *Streptomyces hygroscopicus*, which blocks calcium-mediated and calcium-independent intracellular signaling upon activation of IL-2 receptors in T-cells, thereby suppressing their activation and causing an immunosuppressive effect, at a dosage of 0.1 mg every 48 hours enterally. The child's condition stabilized on this therapy.

According to laboratory data, the child had anemia, thrombocytopenia, leukopenia, impaired hemostasis of the hypocoagulation type, hypofibrinogenemia, and elevated D-dimer levels. Throughout the treatment, bacterial cultures from the oropharyngeal and nasal mucosa, blood, endotracheal tube, urine, stool, and drainage fluid from both pleural cavities and the abdominal cavity showed no growth.

Summarizing the treatment provided, the patient received 11 individually matched LPDEM transfusions, 42 FFP transfusions, and 26 platelet concentrate transfusions.

At the age of 2.5 months, the child was referred for hospitalization to the N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, where he was treated for 30 days. Upon admission to the medical center, the child's condition was severe, due to multiple organ failure (respiratory failure grade 2, heart failure 2A, gastrointestinal insufficiency), the course of an infectious process (intrauterine mixed infection, TORCH syndrome: parvovirus, chlamydia, community-acquired bilateral pneumonia), bone marrow suppression syndrome, DIC syndrome, and abdominal compartment syndrome due to a retroperitoneal space-occupying lesion.

At the Federal Scientific Medical Center, additional examinations were performed: tumor markers, myelogram, cytology of pleural and peritoneal fluid, consultations with specialists: geneticist, neonatologist, cardiologist. A review of the CT and MRI studies was conducted. PET CT of the whole body: at the time of the study, no data were obtained on the presence of 18F-FDG-positive tumor tissue in the retroperitoneal mass. A consultation was held jointly with the Federal Scientific Center. Considering the comprehensive examination data, the clinical diagnosis of "Kasabach–Merritt syndrome" against the background of a vascular formation of the posterior mediastinum was established. Given the child's severe condition (persistent respiratory failure, tachypnea, hypocoagulation,

Dynamics of Laboratory Parameters

Clinical blood analysis										
Indicator	15.11.2024	24.11.2024	04.12.2024	14.12.2024	25.12.2024	02.01.2025	05.01.2025	08.01.2025	10.02.2025	Ref. Interval
Erythrocytes (RBC)	3.23	4.57	3.93	5.1	3.99	3.72	3.87	3.52	3.02	(3.90 - 5.90) 10E12/ L
Leukocytes (WBC)	5.2	7.9	6.7	9.9	8.9	3.2	3.3	5.9	5.1	(9.00 - 30.40) 10E9/ L
Hemoglobin (HGB)	98.0	140.0	119	150	119	109	113	100	86	(168.00 - 208.00) g/L
Hematocrit (HCT)	29.3	41.4	34.5	44.9	34.8	32.1	33.4	29.9	25	(41.00 - 65.00) %
Platelets (PLT)	65.00	180	44	39	53	48	115	66	31	(150.00 - 400.00) 10E9/ L
Thrombocrit (PCT)	0.05	0.18	0.05	0.04	0.06	0.04	0.11	0.05	0.03	(0.15 - 0.40) %
Lymphocytes (LYMF) abs	2.2	3.0	3.2	5.4	3.5	1.4	1.6	2.1	1.9	(1.20 - 3.00) 10E9/ L
Monocytes (MON) abs	0.8			1.00			0.4	0.6		(0.09 - 0.60) 10E9/ L
Granulocytes (Gran) abs	2.2	3.8	2.6	3.5		1.3	1.3	3.2	2.6	(0.00 - 0.00) 10E9/ L
Band neutrophils	4	1	4	1	4	3	2		1	(1.0 - 6.0)%
Segmented neutrophils	26	56	36	19	53	41	39		46	(16.0 - 45.0)%
Eosinophils	13	7	10	17	0	1	2		1	(1.0 - 5.0)%
Lymphocytes	42	30	39	55	33	44	47		44	(45.0 - 70.0)%
Monocytes	15	6	11	8	10	11	10		8	(4.0 - 10.0)%
Normoblasts	1	-		1						(0.0 - 0.0)%
Reticulocytes			5							(2,0-12,0) %
Coagulogram										
Antithrombin-III	62.7	70.5	82.1							85.00 - 115.00%
Prothrombin time	17.80	14.8	16.8	17.1	17.4	15.7	16.2	15.4	14.8	9.00 - 12.60 sec
INR	1.57	1.3	1.48	17.1	1.3	1.35	1.39	1.32	1.27	0.81 - 1.13 units
APTT	50.30	29.8	42.3	42.00	41.7	No coagulation	No coagulation	32.9	36.3	23.40 - 35.00 sec
Fibrinogen	1.72	3.04	1.72	0.66	1.03					2.92 - 4.12 g/L
D-dimer	>10000	>5000	>5000							110.00 - 240.00 ng/ml
Prothrombin index	50.20	65.12	54.35	47.00	62.00	53.2	50.7	54.8	58.2	78.00 - 142.00 %

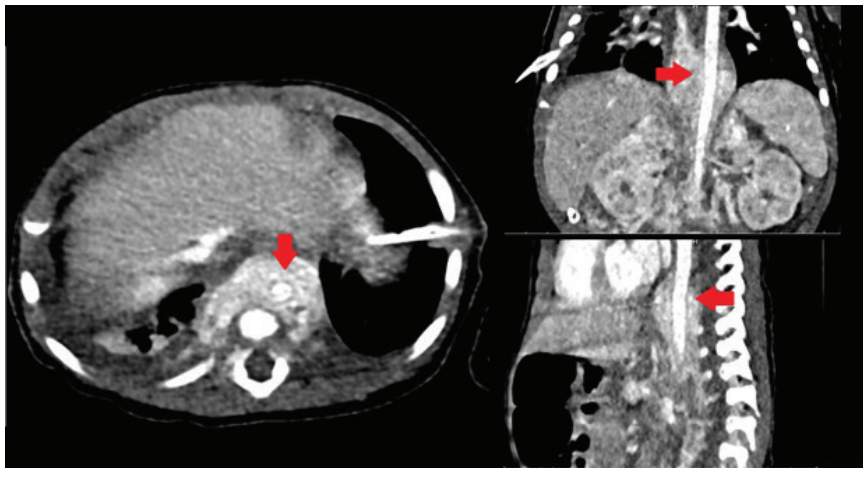

Fig.1. Contrast-enhanced CT of the chest and abdomen – revealed para-aortic mass

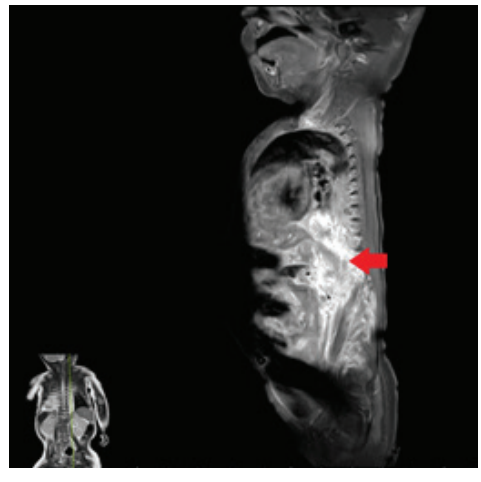

Fig.2. Contrast-enhanced MRI – retroperitoneal mass

thrombocytopenia) and the impossibility of surgical intervention (including biopsy of the mass), a decision was made to initiate special treatment without histological verification of the diagnosis for vital indications, in accordance with the consultation with the Federal Scientific Center. Metronomic therapy was prescribed – Cyclophosphamide, Vinblastine, Rapamycin for 3 courses. Metronomic therapy for 14 days: Cyclophosphamide 50 mg/m²/day, divided into two IV bolus injections over 14 days; Vinblastine 1 mg/m²/day 3 times a week. The course lasts 28 days, with chemotherapy administration from day 1 to day 14 of therapy; Rapamycin at a dose of 0.1 mg every 48 hours (during the 1st week with determination of the drug concentration in the blood, followed by possible dose adjustment). The child was discharged with recommendations for further treatment at the place of residence. The start of the 2nd course of therapy was scheduled for 02/11/2025. A follow-up examination after the 3rd course of metronomic therapy and contrast-enhanced MRI of the abdomen were recommended. The child was hospitalized in the oncology department of the Federal Scientific Center, where the 2nd course of therapy was administered: Rapamycin 0.2 mg/m²/day as 0.1 mg (0.1 ml) x 2 times a day, per os, daily; Vinblastine 1 mg/m² single dose – 0.28 mg IV strictly slowly, 3 times a week; Cyclophosphamide 50 mg/m²/day in 2 doses, single dose 7 mg, daily dose 14 mg, IV strictly slowly, 2 times a day.

The child was discharged with recommendations for further treatment at the place of residence; at the age of 4 months, he was hospitalized in the oncology department of the Pediatric Center of the republican hospital. The 3rd course of metronomic therapy was administered. Magnetic resonance imaging (MRI) of the abdomen and retroperitoneal space was performed, again revealing a pathological paravertebral, para-aortic mass of unclear etiology, with infiltration of the muscles on both sides, the right gluteus medius muscle, and right pleural effusion. Compared to previous studies, the mass was unchanged, and bone marrow edema of the Th9-L5 vertebral bodies was not detected. Clinically, the condition is stable, and the parents report no complaints regarding the child's well-being.

Conclusion. This clinical case demonstrates the difficulties in diagnosing and treating newborns with Kasabach–Merritt syndrome. The disease is characterized by an extremely severe course and high mortality. If a child presents with thrombocytopenia and hypocoagulation in coagulogram tests, it is imperative to perform CT/MRI of the retroperitoneal space, abdominal cavity, and chest organs with contrast to verify the diagnosis. Early treatment will help avoid severe hematological complications and reduce the likelihood of severe functional disorders.

The authors declare no conflict of interest.

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CONTINUOUS LONG-TERM RUNNING AS A MEANS OF PHYSICAL REHABILITATION FOR MILITARY PERSONNEL OF AIRBORNE TROOPS

This article presents the results of a study aimed at developing a training methodology based on steady, continuous long-distance running to restore the physical fitness and performance of wounded Airborne troops. This methodology aims to facilitate their rapid return to the combat zone and to scientifically substantiate its effectiveness. A three-week training program was developed, including warm-up, base, and warm-up microcycles aimed at gradually increasing the volume and intensity of running loads, developing overall endurance, speed, and sensory abilities. A distinctive feature of the program is the individualization of the training process based on monitoring heart rate variability. The effectiveness of the developed program was experimentally proven, as evidenced by statistically significant improvements in the morphofunctional indicators of physical performance and physical fitness of the experimental group.

Analysis of heart rate variability dynamics demonstrated the program's ability to ensure an optimal level of adaptive capacity and prevent the development of regulatory system overstrain. The results obtained can be used to improve the system of physical rehabilitation of military personnel and increase the combat readiness of Airborne Forces units.

Keywords: physical development, functional state, physical rehabilitation of military personnel, physical training, airborne troops, special military operation.

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Introduction. Physical fitness is a key element of military combat readiness, especially for elite Airborne Forces units operating in extreme conditions. Analysis of combat injuries shows that the extremities are the most vulnerable, accounting for 46% to 75% of all injuries. A significant proportion of these injuries (42.5–54.3%) are of a combined nature, and 9.5–14.4% result in limb avulsion or destruction. The main causes of such injuries are injuries from small arms, artillery munitions, and unmanned aerial vehicles (UAVs). [14,15].

The urgency of the problem of rehabilitation for airborne troops after injuries is driven by several factors. First, the high intensity of modern military conflicts and the use of various types of weapons result in a significant number of wounded, requiring effective rehabilitation methods to ensure their rapid return to duty. Second, the consequences of injuries can significantly reduce physical performance and the body's functional capabilities, limiting the combat effectiveness of military personnel.

Physical inactivity during the recovery period of military personnel after injuries is a significant risk factor for the development of obesity, which critically impedes the restoration of combat readiness and a prompt return to duty. Excess body weight reduces key physical performance indicators (endurance, mobility) and increases the risk of comorbidities, making the development of effective physical rehabilitation methods extremely urgent. In this context, steady, continuous long-distance running is considered a key tool, as it specifically promotes metabolic activation, improves cardiorespiratory function, and reduces weight, directly addressing the problem of obesity prevention and accelerating the readiness of military personnel for combat missions [1, 3, 6, 10].

An important aspect of using running exercises during the rehabilitation of military personnel after injuries is the individualization of the training process taking into account the body's functional capabilities and current health status. In this regard, the use of heart rate variability (HRV) analysis appears promising, allowing one to assess the body's adaptive reserves and select optimal physical exercise regimens [2].

The aim of the study is to develop a training method based on uniform continuous long-term running and to experimentally prove its effectiveness in restoring the physical fitness and performance of wounded military personnel and their rapid return to the combat zone.

Objectives:

1. To develop and scientifically validate a training program for the physical rehabilitation of military personnel, to ensure their rapid return to combat zones;
2. To experimentally demonstrate the effectiveness of the developed training program for the rehabilitation of military personnel returning from hospitals.

Study materials and methods. The study involved military personnel who had returned to their home base after receiving treatment for their wounds. The average age of the participants was 31.2±4.3 years, body length 173.8±6.4 cm, and body weight 89.1±6.1 kg.

The study consisted of three stages (Figure 1). The first stage (organizational) involved selecting candidates and assigning them to the control (CG) and experimental (EG) groups by randomization, assessing their initial functional status, performance, and physical fitness,

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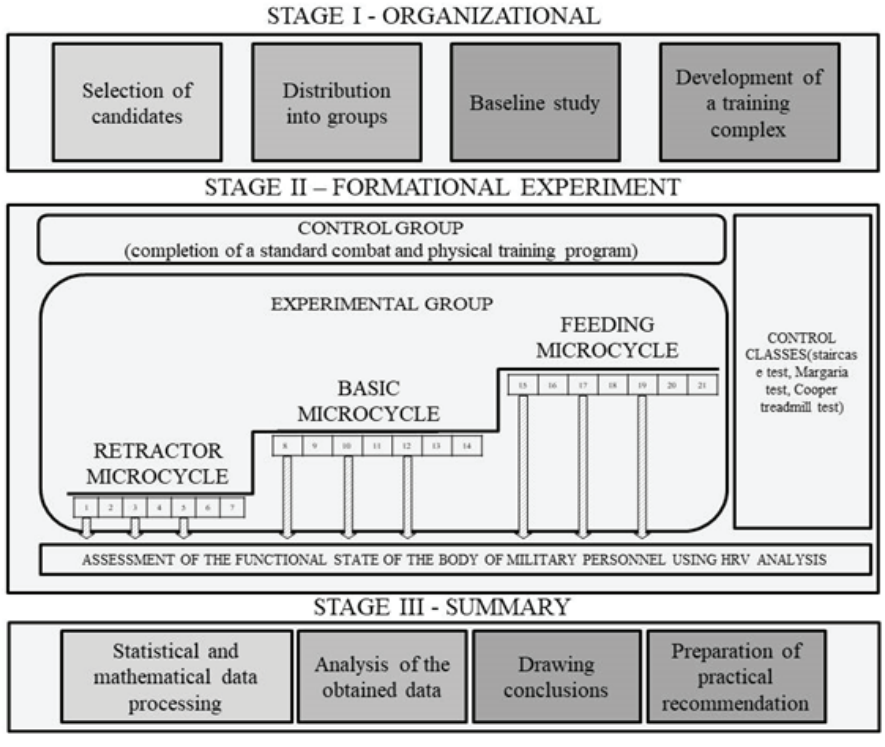
and developing a training program based on the data obtained. The second stage (formative experiment) consisted of conducting training sessions with military personnel according to the developed program and adjusting training plans based on heart rate variability indicators and conducting tests to assess functional status, physical performance, and physical fitness after completing the training programs. The third stage – summarizing the results – included mathematical and statistical processing of the obtained data, discussion of the study results, drawing conclusions, and developing practical recommendations.

Heart rate variability analysis was used to assess functional status. The analysis was conducted within an hour of arriving for duty in the morning. Before the examination, service members remained motionless in a dark room for 15 minutes. The results were recorded in an individual protocol. Cardiac rhythmograms were recorded for 300 cardiac cycles in clinostasis. Spectral HRV parameters were assessed, frequency power parameters were calculated in the high-frequency (HF, ms²), low-frequency (LF, ms²), and very-low-frequency (VLF, ms²) ranges, total spectral power (TP, ms²), temporal parameters (SDNN, ms² and rMSSD, ms²), and the stress index (SI, c.u.) and regulatory system activity indicators (PARS, score) were also assessed.

To assess the level of physical performance of military personnel, the "Staircase Test" test was used, and their physical fitness was determined using the Margaria test, the Cooper running test, and the «Complex agility exercise» test – Exercise No. 30 from the NFP-2023.[11] The choice of these tests was due to the need to ensure a moderate load and the possibility of prompt medical support.

We used various statistical methods to analyze the obtained results. The Kolmogorov-Smirnov test was used to check the normality of the distribution of quantitative variables. One-way analysis of variance was used to compare the results of multi-day measurements. Comparisons of quantitative variables within and between groups were performed using the Student's t-test for dependent and independent samples (M ± m). When comparing qualitative variables, we additionally used the Pearson chi-square test with significance adjustment (for between-group differences) and the McNemar test (for within-group changes) (Md [Q1;Q3]). Differences were considered statistically significant at $p < 0.05$. Mathematical and statistical data processing



Study design

was performed using STATISTICA 10 software.

Key provisions. Rehabilitation of military personnel in medical and health resort facilities (HRFs) is primarily focused on the following objectives: accelerating the resolution of edema and hematomas; preventing the development of contractures; restoring the functionality of the damaged organ; stimulating blood and lymph circulation; developing compensatory mechanisms for the loss of basic motor functions; improvement of the general condition of the patient [3, 6].

The existing approach to the rehabilitation of wounded military personnel, while successfully restoring them to a level of basic working capacity, is insufficient for the full return to duty of airborne assault units. Modern combat demands fundamentally different requirements: the ability not only to march long distances with heavy equipment under enemy fire, but also, crucially, to react instantly and maneuver with high agility to evade UAV attacks. Thus, there is an urgent need to rethink rehabilitation, shifting the emphasis from simple recovery to the targeted development of key physical qualities—endurance, speed, strength, and agility – to ensure not just a return to duty, but true combat readiness [3, 8, 13].

Researchers A. A. Musin and I. V. Polyakova (2024) argue in their work that, in order to rehabilitate and restore the professional readiness of military personnel, it is first and foremost necessary to use game-based physical training, justifying this by the popularity and spectacle of team sports, especially football, which, in addition to the physical development of almost all necessary qualities (speed, endurance, and agility), contribute to stress relief [10].

Unlike the game-based method, which is difficult to individualize and carries the risk of overexertion and injury, steady, continuous running is a more effective and accessible means of physical rehabilitation for wounded soldiers. This type of exercise is easily dosed and adapted to individual plans, allowing for targeted development of overall endurance, speed, and willpower, ensuring a safe and gradual restoration of physical fitness for a return to professional activity. [3, 7, 5, 12].

An integrated approach combining running training, proper nutrition, and flexibility exercises ensures comprehensive recovery for military personnel. Running effectively normalizes body weight, develops strength endurance, and, importantly, significantly improves psycho-emotional well-being by reducing stress. Incorporating flexibility exercises into the program directly accelerates physical recovery, reducing muscle tension and the risk of re-injury. Combining these elements allows for faster and more complete physical and psychological rehabilitation, facilitating the rapid re-

Average indicators of physical development, performance and physical fitness of military personnel in the experimental and control groups before and after the experiment

Indicators		Before			After			p	
		CG	EG	p	CG	EG	p	CG	EG
Body weight, kg		89.9±1.1	88.4±1.1	0.15	85.8±1.1	75.5±1.1	0.05	0.05	0.01
BMI, kg/m^2		29.4±0.4	29.7±0.6	0.3	28.1±0.4	25.4±0.5	0.05	0.1	0.05
Staircase test, bpm		139.8±1.8	140±1.7	0.8	125.6±1.7	114.5±1.9	0.05	0.05	0.01
Margaria test	Watts	401.6±9.4	390.5±9.2	0.25	424±9.8	557.8±15	0.05	0.25	0.001
	Watts/kg	4.5±0.1	4.4±0.1	0.5	4.9±0.1	7.4±0.2	0.05	0.25	0.05
Exercise №30, sec		13.7±0.4	14.3±0.3	0.05	13.4±0.3	13.1±0.3	0.1	0.1	0.05
Cooper test, m		2167.2±31.6	2164.3±29.2	0.25	2381.8±37.4	2665.2±38.9	0.05	0.05	0.05

turn of military personnel to full duty. [5, 6, 7, 9]

Based on the above-mentioned characteristics, our working group developed a training plan for the physical rehabilitation of military personnel in a military unit setting. This plan consists of a three-week mesocycle aimed at improving marching composure, developing general endurance, speed, and sensory abilities, as well as weight management through a gradual increase in running volume.

The first, induction microcycle (Figure 2) serves as a fundamental stage for the smooth and safe adaptation of military personnel to the demands of continuous long-distance running. Its program, designed for five training sessions, is built on the principle of gradual progression: initially, walking predominates, but with each session, the emphasis gradually shifts toward increasing the proportion of running. Each session begins with a preparatory exercise program aimed at activating muscles and preparing the body, and concludes with restorative exercises to relieve tension and accelerate recovery. A key control and safety tool is strict heart rate monitoring (conducted using personal fitness trackers and heart rate monitors (Garmin, Polar, Suunto)), the threshold of which is set at no higher than (130) 150 bpm, with planned rest breaks if this threshold is exceeded. This carefully considered approach allows for careful adaptation of the cardiovascular and respiratory systems, minimizing the risk of injury and building a solid foundation of physical fitness necessary for a successful transition to more intense exercise during the subsequent micro-cycle of rehabilitation.

The basic microcycle (Figure 2), which comprises the second week of rehabilitation, aims to gradually increase running volume to 175 minutes over five training sessions. Its key feature is the introduction of a post-run routine, alternating specific running exercises (4-6) to improve running technique and strength exercises (3-4) for the muscles of the arms, shoulder girdle, torso, and legs to reduce injury. The training process takes place in the first developmental mode at a heart rate of 130-150 bpm, ensuring optimal training effects with minimal risk of overtraining. This microcycle structure promotes the effective development of overall endurance and running fitness, creating conditions for the body's safe adaptation to increasing workloads.

The preparatory microcycle, implemented in the third week (Figure 2), aims to integrate speed training by introducing accelerations (30–50 m) into the structure of five training sessions. During the training, basic running in the first developmental mode (heart rate 130–150 bpm) is interrupted by a progressively increasing number of accelerations (from 6 to 10 per session), during which the intensity reaches the third developmental mode (heart rate from 170 bpm). This structure simulates the «jerky» nature of running typical of combat conditions and promotes the body's comprehensive adaptation to high-intensity loads. As a result, this final stage of the mesocycle ensures the development of not only general endurance but also the specific speed qualities, attention, and sensory abilities of the service member.

At the end of three weeks, the study was repeated with the servicemen of the EG and CG groups (Table 1).

The servicemen in the experimental group showed statistically significant and more pronounced positive changes compared to the control group. In particular, the experimental group showed a significant decrease in body weight (by 12.9 kg; $p<0.01$) and a significant improvement in physical performance according to the "Staircase test" (a decrease in heart rate by 25.5 bpm; $p<0.01$). A highly significant ($p<0.001$) increase in absolute and relative power according to the Margaria test and an improvement in agility indicators in exercise #30 ($p<0.05$) were also revealed, while in the control group similar dynamics were statistically less significant. In addition, the increase in overall endurance according to the Cooper test in the experimental group (500.9 m) was more than twice as high as the results in the control group (214.6 m).

An analysis of HRV dynamics confirmed the high adaptability of the experimental program. The servicemen in the control group, who initially had normal parameters, demonstrated an adequate response to the load: by the end of each week, a temporary, statistically significant ($p<0.05$) increase in regulatory systems was recorded (e.g., a 20.5% increase in SI), which was fully compensated for after two days of rest, which also allowed for individual adjustments to the program. A key result was the state after the control tests: unlike the control group, which demonstrated pronounced signs of overexertion (a 25.6% decrease in SDNN, a 30.7% decrease in rMSSD; $p<0.01$), the servicemen in the control group maintained HRV parameters within physiological norms. This demonstrates the effectiveness of the developed method in increasing the body's adaptive potential and preventing adaptation failure.

Conclusion. The study experimentally validated the high effectiveness of the developed three-week physical rehabilitation method for military personnel after injuries, based on steady-state running with individualized loads based on HRV parameters.

The developed program, including warm-up, base, and warm-up microcycles, provided statistically significant improvements in physical performance, overall endurance, power, and agility in the experimental group, while reducing body weight. HRV monitoring confirmed that the program maintains an optimal level of adaptation, preventing overstrain of regulatory systems, making it a reliable and effective tool for comprehensive

recovery and accelerated preparation of military personnel for return to combat zones.

The authors declare no conflict of interest.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

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METHOD OF ASSESSMENT AND RISK MANAGEMENT IN PREGNANT WOMEN WITH PREGESTATIONAL AND GESTATIONAL DIABETES BASED ON MEDICAL AND SOCIAL DETERMINANTS OF PUBLIC HEALTH

A method for evaluating the qualification of medical specialists (endocrinologists, obstetricians-gynaecologists, physicians-therapists) based on the analysis of risk factors arising in the management of pregnant women with carbohydrate metabolism disorders has been developed. As part of the pilot testing of the method in September-November 2024, quantitative sociological research, online survey (author's questionnaire) of 140 doctors of the above specialties from different subjects of the Russian Federation (Arkhangelsk, Vladimir, Volgograd, Kaliningrad, Kostroma, Lipetsk, Moscow, Nizhny Novgorod, Tula, Ryazan regions, Moscow, Altai and Stavropol Krai, Republics: Adygea, Ingushetia, Karelia, Komi, Mordovia), analysed survey data on the management of pregnant women with gestational diabetes mellitus and pregestational diabetes mellitus. The proposed approach can serve as a basis for a systematic approach to analysing the professional potential of doctors of different profiles and diseases. Innovative aspects of the method are protected by patents.

Keywords: medical determinant of public health; professional potential; medical risks; endocrinologists; obstetricians and gynecologists; internists.

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Introduction. In accordance with Decree No. 400 of the President of the Russian Federation dated 2 July 2021 'On the National Security Strategy of the Russian Federation,' the national interest of Russia is defined as 'saving the people of Russia, developing human potential, improving the quality of life and well-being of citizens.'

Public health serves as a medico-social resource of society. Risk factors have a detrimental impact on public health. This is evident in individuals experiencing limitations in their social functions, while a decline in reproductive capacity directly reduces demographic potential [7].

Contemporary research identifies five determinants of public health: genetic and physiological characteristics; socio-cultural conditions; natural and climatic factors; individual behavioural patterns; and the quality of medical care. The medical factor is particularly important, covering the organisation of care, its material and technical basis, and management systems [7].

Crucial aspects include human resources factors such as qualification levels, work engagement, job satisfaction, the risk of professional burnout and the degree of trust in the institution. These factors have a direct impact on the effectiveness of the healthcare system and consequently on public health [5].

In accordance with the Rules for the Development and Approval of Professional Standards (as approved by Decree No. 23 of the Government of the Russian Federation on 22 January 2013), the implementation of professional standards within Russian medicine was accompanied by research into the professional competence that can be regarded as a methodological foundation for the introduction of the term 'professional potential of healthcare workers'. The term is proposed not only as an assessment of competencies, but also as an indicator of medical personnel's readiness to develop a professional identity, enhance their expertise and improve their knowledge and skills. The authors propose a unified concept of the personnel potential of the healthcare sector, which aligns with the aims and objectives of our research. This concept is based on an expert assessment.

The personnel potential of the healthcare sector is defined as the capacity of a specifically professionally trained and organised labour force (healthcare workers) to achieve, to the fullest extent possible, the objectives of improving the quality of public health. It encompasses components including the labour force structure and its equitable distribution; the anticipated duration of professional activity within the healthcare sector; the continuous enhancement by medical per-

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[1] Decree No. 400 of the President of the Russian Federation dated 2 July 2021 'On the National Security Strategy of the Russian Federation.'

sonnel of their professional knowledge, skills, and abilities in the domains of medical prevention, treatment, and rehabilitation, as well as medical deontology and ethics; and a high externally-derived valuation of the professional competencies of the labour force.

The professional potential of healthcare workers can be regarded as a personal attribute that encompasses both professional knowledge, skills, abilities, and the capacity to implement them in professional healthcare practice, as well as integration into the professional medical community. Furthermore, it incorporates a receptiveness to professional growth and development aimed at improving population health, the prioritisation of work within one's life values; satisfaction with both the chosen medical profession and the current employment; an association of one's professional future with the medical profession; and discipline, coupled with a sense of responsibility for the work performed.

The development of a novel instrument for evaluation of the professional capabilities of healthcare workers is driven by the mounting imperative to ensure the adequate supply of qualified personnel to the healthcare system, a component that is of paramount importance in the context of public health.

The development of programmes for the prevention of reproductive health disorders and the early detection of diseases is a priority for both the Russian healthcare system and the National Strategy for Women 2023–2030. The primary objectives are to improve the demographic situation, enhance the quality of medical care, reduce pregnancy complications and improve perinatal outcomes [1, 2].

Carbohydrate metabolism disorders (CMD) during gestation are among the most common pathologies encountered in the clinical practice of endocrinologists and obstetrician-gynaecologists [7]. Several clinical conditions are included in this category. These are: gestational diabetes mellitus (GDM), which is hyperglycaemia first detected during pregnancy that does not meet the diagnostic criteria for overt diabetes; overt diabetes mellitus, which is a chronic elevation of blood glucose levels identified for the first time during pregnancy; and pre-gestational diabetes mellitus, which is a condition diagnosed prior to the onset of pregnancy.

Annually, between 50,000 and 150,000 newborns are born to women with disorders of glycaemic control, thereby highlighting the scale and relevance of this issue in the context of perinatal medicine. [3]. Diabetes mellitus has been demonstrated to exert a deleterious effect on the course of pregnancy, giving rise to vascular disorders and placental insufficiency. This, in turn, has a detrimental effect on foetal development and neonatal adaptation. [3, 6]. Pre-gestational diabetes has been demonstrated to be associated with elevated perinatal morbidity. The early infant mortality rate in this group is 3–4 times higher than the population average. The elevated incidence of perinatal mortality (exceeding 65%) has precipitated the establishment of specialised medical services catering to these patients [4].

The study analyses the level of training of medical specialists in the regions of the Russian Federation working with pregnant women with carbohydrate metabolism disorders (CMD). This analysis is based on a standardised questionnaire and digital data collection tools.

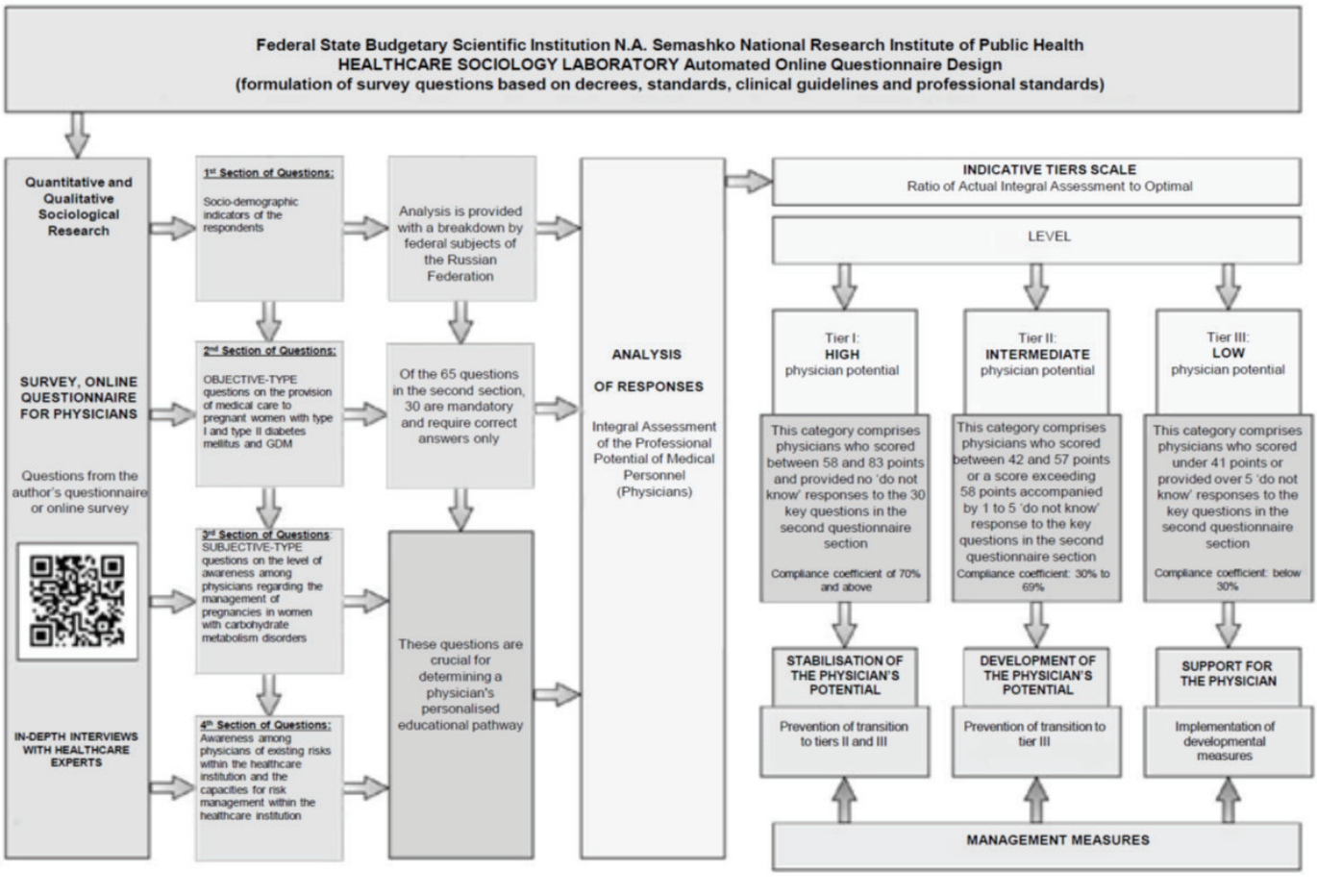

Fig. 1. A method for evaluating the qualification of medical specialists (endocrinologists, obstetricians therapists) based on the analysis of risk factors arising in the management of pregnant women with carbohydrate metabolism disorders. Industrial Design Patent No. 142286

Materials and Methods. A method for evaluating the qualification of medical specialists (endocrinologists, obstetricians-gynaecologists, physicians-therapists) based on the analysis of risk factors arising in the management of pregnant women with carbohydrate metabolism disorders has been developed. As part of the pilot testing of the method in September-November 2024, quantitative sociological research, online survey (author's questionnaire) of 140 doctors of the above specialties from different subjects of the Russian Federation (Arkhangelsk, Vladimir, Volgograd, Kaliningrad, Kostroma, Lipetsk, Moscow, Nizhny Novgorod, Tula, Ryazan regions, Moscow, Altai and Stavropol Krai, Republics: Adygea, Ingushetia, Karelia, Komi, Mordovia) was conducted, followed by an analysis of the survey data on the management of pregnant women with gestational and pregestational diabetes mellitus.

An analysis was conducted of the medical care provided to pregnant women with carbohydrate metabolism disorders, based on quantitative sociological study data. The analysis identified medical risk factors associated with the professional training of endocrinologists, obstetricians and therapists as a factor impacting public health.

A system based on a comparison with approved clinical guidelines and treatment protocols was employed to determine the level of qualification of physicians (endocrinologists, obstetricians and gynaecologists, and therapists) (see Fig. 1).

A pilot test of the method was conducted among endocrinologists, gynaecologists, and physicians, including residents. The gender distribution of respondents was 82.6% female and 17.3% male. The age structure showed a predominance of young specialists: 59.7% were under 30 years old and 33.8% were aged 30–45 years. In terms of work experience, 39.6% had no practical experience (residents), and 30.2% had up to 10 years of experience. The overwhelming majority (89.1%) did not hold an academic degree, and 87.0% did not have a professional category, indicating a significant predominance of young specialists without substantial practical experience or scientific qualifications in the sample.

A digital data collection workbench was employed for the study. The survey was administered by distributing links to the questionnaire electronically via corporate email and popular messaging platforms such as WhatsApp and Telegram. The data obtained during the sociological research was automatically aggregated in Excel on a cloud storage platform.

Table 1

Algorithm for Assessing Questionnaire Responses

Indicator	Scale	Question Numbers (Quantity)	Minimum Score	Maximum Score
Key 30 questions of the second section	Indicative tiers scale	2.1-2.30 (30)	0	83

Table 2

Stratification of Physicians' Professional Competence

Professional Potential Level	Total Score Range
High	The score between 58 and 83 points, with no 'do not know' responses to the key questions in the second section.
Intermediate	The score between 42 and 57 points or a score exceeding 58 points accompanied by at least one 'do not know' response to the key questions in the second section.
Low	The score under 41 or 5+ 'do not know' responses to the key questions in the second section.

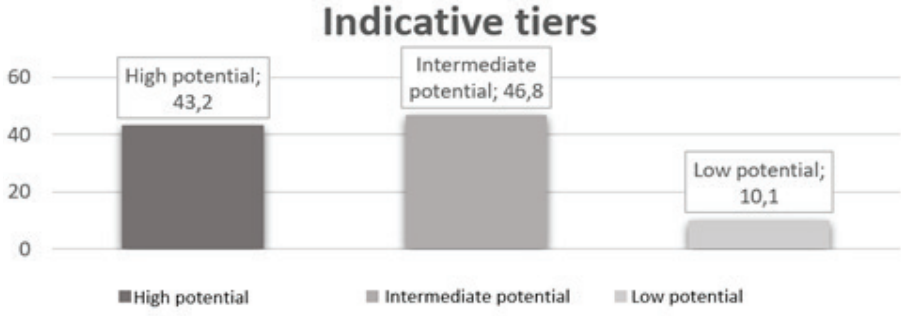

Fig. 2. Distribution of respondents by level of professional competence

Results. The electronic questionnaire comprised four mandatory sections: socio-demographic indicators, an objective assessment of physicians' knowledge (30 mandatory questions out of 65), a subjective evaluation of priorities for continuing medical education, and clinical risk management system assessment. The developed assessment system comprises a grading scale that categorises professional competence into three levels: high (a minimum of 70 points), medium (30-69 points), and low (less than 30 points). High level denotes that the individual has undergone comprehensive training, medium level indicates basic training, and low level signifies substantial knowledge deficiencies.

The methodology is based on a points-based scoring system capable of both manual and automated data processing. Key functional capabilities include diagnosing professional status, identifying factors influencing competencies, and developing targeted management decisions. It is proposed that a range of differentiated development strategies be implemented at each level, as follows: maintenance of qualifications at the high level, targeted professional development at the medium level, and intensive training with mentorship at the low level.

The technical implementation of the system is characterised by the electronic completion of tasks via automated physician workstations and online platforms. The overall structure of the questionnaire comprises 97 questions, 86 of which pertain to professional topics, and 11 to socio-demographic data. The proposed system facilitates a comprehensive evaluation of healthcare professionals' competencies and the development of effective professional development programmes.

For questions 2.1–2.16, 2.23, 2.27 and 2.28, 2 points are awarded for each correct answer, while incorrect answers and 'do not know' responses receive 0 points. For questions 2.17–2.22, 2.24–2.26, 2.29 and 2.30, 1 point is awarded for each correct answer, while incorrect answers and 'do not know' responses receive 0 points. (Table 1).

The survey, which was conducted using the developed instrument, provides a comprehensive analysis of the following: the level of professional preparedness among the physician cohort; the current state of clinical competencies; and the potential for professional growth.

Discussion. According to the survey results, respondents fell into one of three categories. High potential was noted in 43.2% of participants, intermediate potential in 46.8%, and low potential in 10.1%. (Figure 2).

The identification of key clinical risks is enabled by the presented algorithm for assessing the professional potential of medical specialists. Survey results demonstrate that 80.44% of respondents incorrectly allow the use of a glucometer to diagnose gestational diabetes mellitus (GDM). Only 60–70% of those surveyed correctly identified the objectives of glycaemic control. Even fewer—just 36.23%—accurately specified the target glucose values for standardised continuous monitoring metrics. Furthermore, 59.42% of respondents reported experiencing difficulties when selecting an insulin regimen approved for use during pregnancy.

When it came to pre-gravid preparation and the potential risks of pregnancy complications for the mother and foetus, 46.38% of respondents were able to list the contraindications to conception. When asked about the risk of the foetus developing diabetes mellitus given that the parents have type 1 diabetes, the correct answer was given by 44.2% of respondents for the father, 29.71% for the mother and 36.23% for both parents.

Conclusion. The study identified specific areas for improvement in the training of healthcare professionals managing pregnancies in women with carbohydrate metabolism disorders. The key issues identified include deviations from the standards for GDM diagnosis, occasionally improper selection of therapeutic approaches, and limited awareness of pre-conception counselling principles.

Promising future directions include the establishment of specialised centres with multidisciplinary teams, the updating of educational programmes with an emphasis on interdisciplinary collaboration, and the development of a system for pre-conception counselling. The implementation of these measures is expected to enhance access to healthcare and improve pregnancy outcomes, thereby aligning with the objectives of national initiatives focused on motherhood and childhood. The developed diagnostic tool has the potential to be applied in healthcare management practice.

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EFFECTIVENESS OF AN INTERDISCIPLINARY APPROACH TO EARLY DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

The implementation in the Republic of Sakha (Yakutia) of a set of measures aimed at eliminating parenteral viral hepatitis and improving the provision of medical care to the adult population with oncological diseases has had a significant impact on the effectiveness of hepatocellular carcinoma diagnosis. Patients with advanced fibrosis and cirrhosis of the liver require special attention, as it is in this group of patients that the highest proportion of fatalities is observed, as well as the greatest burden on the healthcare system budget.

The aim of the study was to evaluate the impact of an interdisciplinary approach on the etiological verification of the diagnosis and the effectiveness of HCC detection using the example of the Republic of Sakha (Yakutia).

Materials and methods. A retrospective analysis was conducted of data from 632 patients with HCC in the Republic of Sakha (Yakutia) who were examined and treated at the Yakutsk Republican Oncology Dispensary, and an analysis of the incidence rate based on official statistics before and after the introduction of the interdisciplinary approach.

Results and discussion. Due to improved screening, the proportion of patients with viral hepatitis markers increased 2.5 times and approached 70%. Clinical and laboratory diagnosis of liver cirrhosis improved, which is extremely important when choosing a treatment strategy for a patient. The rate of early diagnosis at stage I according to the TNM classification increased from 5.1% to 12.0% over 5 years. The increase in the proportion of patients with early-stage HCC opens up broad opportunities for the use of local tumor destruction methods and is expected to increase the overall survival of patients. It has been shown that an interdisciplinary approach reduces the time it takes to refer a patient from an infectious disease specialist to an oncologist and improves the quality of morphofunctional diagnosis of the liver.

Conclusion. The experience of the Republic of Sakha (Yakutia) shows that improving dispensary observation of risk groups and continuity in patient management within the framework of interdisciplinary cooperation between specialists is a promising direction that can ensure early diagnosis of HCC and improve treatment outcomes.

Keywords: hepatocellular carcinoma, early diagnostics, malignant neoplasms, organization of medical care.

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Introduction. Due to its widespread prevalence and alarming growth rate, hepatocellular carcinoma (HCC) has become a pressing health care issue. Among malignant neoplasms, HCC ranks fifth in the world in terms of prevalence and second in terms of mortality, second only to colorectal cancer [1]. Every year, more than 600,000 patients worldwide die from HCC [1].

As a rule, HCC develops against a background of fibrotic changes in the liver and directly depends on the duration, severity, and stage of the disease. In 80–90% of cases, HCC develops against a background of liver cirrhosis (LC) [8]. An exception is viral hepatitis B, in which the virus genome integrates into the hepatocyte genome and has oncogenic properties [18].

In most countries around the world, hepatitis B and C viruses play a leading role in the development of HCC. Due to vaccination of the population in all countries of the world, its significance as a risk factor for HCC has significantly decreased. Therefore, the emphasis in the structure of etiological significance has shifted towards hepatitis C. The pathogenesis of HCC in hepatitis C involves the development of liver cirrhosis as the first stage, against which the risks of HCC increase many times over. Thus, even after the elimination of the virus as a result of antiviral therapy, patients remain at risk of developing HCC, which is 2.1% per year for Child-Pugh class A cirrhosis and 7.8% per year for class B cirrhosis [11].

The absence of clinical symptoms in the early stages and, consequently, late diagnosis have led to high mortality rates and low treatment effectiveness for HCC. Thus, in 2023, the total number of newly diagnosed patients with HCC in Russia was 6,321 and the number of deaths from malignant liver tumors was 10,571. This fact indicates that the diagnosis was often made post-mortem. It is worth noting that 78.2% of the identified patients were in stages III-IV of the disease [4]. At the same time, in cases of early diagnosis and radical treatment, the 5-year survival rate of patients increases to 70% [15, 16].

In this regard, improving dispensary observation of risk groups and continuity

in the management of patients within the framework of interdisciplinary cooperation between specialists appears to be a promising direction capable of ensuring early diagnosis of HCC and improving treatment outcomes.

The aim of the study was to evaluate the impact of an interdisciplinary approach on the etiological verification of the diagnosis and the effectiveness of HCC detection using the example of the Republic of Sakha (Yakutia).

Materials and methods. A retrospective analysis was conducted of data from 632 patients with HCC in the Republic of Sakha (Yakutia) who were examined and treated at the Yakutsk Oncology Dispensary between 2019 and 2023. Men predominated among the patients observed. For comparative assessment, parameters such as gender, age, presence of viral hepatitis B, C and D, liver cirrhosis, and HCC stage according to the TNM scale were selected. The choice of the periods being compared (2019 and 2023) is due to the introduction of a number of regional regulatory documents in the Republic of Sakha (Yakutia) after 2019 aimed at improving the detection of viral hepatitis, HCC, patient routing, and interdisciplinary collaboration among specialists. To assess the long-term incidence and staging of patients with HCC, we used official statistics for the Republic of Sakha (Yakutia) [5], in which malignant neoplasms (MN) of the liver and intrahepatic bile ducts (IBD) are grouped under code C22.

Statistical processing was performed using the "Statistica" software package, version v.10. Student's t-test and chi-square ($\chi 2$) were used to analyze differences between groups. The indicators in the tables are presented as the frequency of occurrence of the indicator (%) or the mean value with standard error (M ± m). The mean value, standard deviation, and median were calculated. Statistical significance was assessed at $p \leq 0.05$.

Results and discussion. As in the rest of the world, the incidence of malignant liver tumors is growing annually in the Russian Federation. Thus, since 2007, an increase in this indicator has been observed in both men (Fig. 1) and women (Fig. 2). Moreover, this oncopathology occurs in men 2.2-2.7 times more often. In the Sakha Republic (Yakutia), incidence rates in both sexes significantly exceed the national average, which cannot but cause concern [3, 4]. Despite the heterogeneity of indicators in the Sakha Republic (Yakutia) from year to year and a clear predominance of men, among people diagnosed with the disease, a trend towards a decrease in incidence rates among women in this subject of the Russian Federation is observed (Fig. 2), which is confirmed by the regression equation y = 11.599 - 0.1673x.

HCC is a multifactorial disease, the risks of developing which are determined by a combination of congenital and modifiable risk factors [8]. It is clear that today, HCC should be viewed not so much as an independent disease, but as a sequential change in pathological conditions (hepatosis → hepatitis → liver fibrosis → cirrhosis → hepatocellular carcinoma) that fall within the competence of various internal medicine specialists. Given the leading role of viral agents, this sequence also determines the patient's path from one specialist to another: therapist/general practitioner → infectious disease specialist/gastroenterologist → oncologist. The lack of a well-thought-out referral system for these patients leads to late diagnosis and low five-year survival rates for patients with hepatocellular carcinoma associated with hepatitis B and C [6, 9].

In this regard, based on Order No. 116n of the Ministry of Health of the Russian Federation dated February 19, 2021 "On the Approval of the Procedure for the Provision of Medical Care to the Adult Population with Oncological Diseases" for 2020-2023, a number of regulatory documents were adopted in the Republic of Sakha (Yakutia) aimed at improving the dispensary observation of patients with viral hepatitis, the diagnosis and treatment of oncological diseases, namely:

- Order of the Ministry of Health of the Republic of Sakha (Yakutia) No. 01-07/1074 dated August 6, 2020, "On the Organization of Region-Specific Screening Studies of Persons in Groups at Increased Risk of Cancer";
- Order of the Ministry of Health of the Republic of Sakha (Yakutia) dated No-

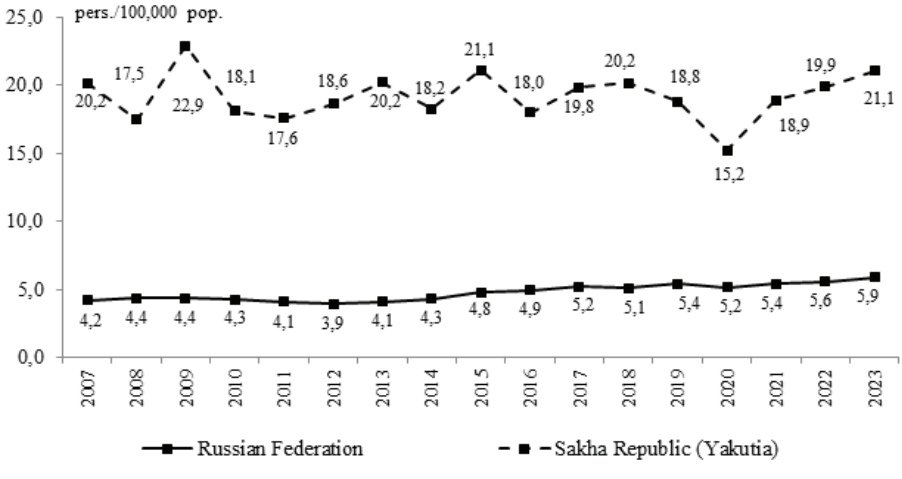

Fig. 1. Standardized incidence rate of liver cancer in men in the Russian Federation and Yakutia (2007-2023)

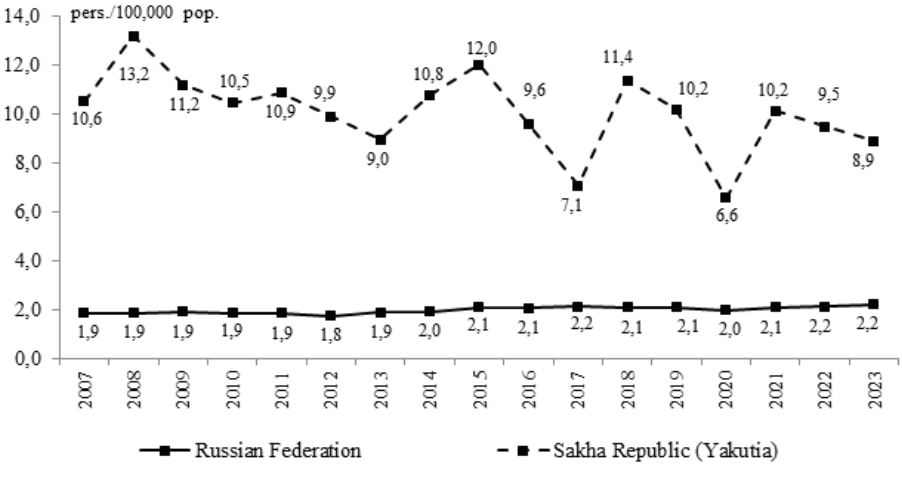

Fig. 2. Standardized incidence rate of liver cancer in women in the Russian Federation and Yakutia (2007-2023)

vember 2, 2020, No. 01-07/1607 "On the organization of dispensary observation of adults with oncological diseases in the Republic of Sakha (Yakutia)";

- Order of the Ministry of Health of the Republic of Sakha (Yakutia) dated October 6, 2021, No. 01-07/1368 "On the organization of medical care for patients with chronic viral hepatitis in the Republic of Sakha (Yakutia)";

- Order of the Ministry of Health of the Russian Federation No. 168n dated March 15, 2022, "On the Approval of the Procedure for Dispensary Observation of Adults";

- Order of the Ministry of Health of the Republic of Sakha (Yakutia) dated March 15, 2023, No. 01-07/509 "On the organization of specialized medical care for patients with chronic viral hepatitis in the Republic of Sakha (Yakutia)".

Later in the period under review, the following orders of the Ministry of Health of the Republic of Sakha (Yakutia) came into force: "On the implementation of measures aimed at improving the provision of medical care to the adult population with oncological diseases in the Republic of Sakha (Yakutia)" (dated July 24, 2024, No. 01-07/1179), "On improving medical care for adult patients with chronic viral hepatitis in the Republic of Sakha (Yakutia)" (dated February 6, 2025, No. 01-07/239-OD), as well as the order of the Government of the Republic of Sakha (Yakutia) "On the approval of the regional program "Fighting cancer in the Republic of Sakha (Yakutia) for 2025-2030" (dated June 30, 2025, No. 503-r).

All these regulatory acts should have a significant impact on improving patient routing and interdisciplinary interaction between related specialists. Patients with risk factors, primarily viral cirrhosis of the liver, are subject to a specific algorithm of observation and examination, which significantly reduces the time required for examination. Dispensary observation of patients with chronic viral hepatitis (CHV) and cirrhosis of the liver of viral etiology is carried out on an outpatient basis by an infectious disease doctor, or in his absence, by a district therapist, general practitioner (family doctor). The results of the patient's examination are sent in electronic format to the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Center for the Prevention and Control of AIDS and Infectious Diseases" to decide on the appointment of antiviral therapy and monitoring to achieve a sustained virological response. In chronic hepatitis C, this type of treatment should be prescribed for up to 1 year. However, patients with se-

Comparative characteristics of patients with HCC before and after the introduction of an interdisciplinary approach in the Republic of Sakha (Yakutia)

Indicator		Total (n = 280)	2019 (n = 138)	2023 (n = 142)	P
Male (M), n (%)		158 (56.4)	74 (53.6)	84 (59.2)	0.351
Female (F), n (%)		122 (43.6)	64 (46.4)	58 (40.8)	
F:M ratio		1:1.3	1:1.2	1:1.5	
Age of men (M+m), years		63.7±0.9	63.8±1.3	63.7±1.3	>0.05
Age of women (M+m), years		69.5±0.8	68.6±1.1	70.5±1.1	>0.05
Total with hepatitis, n (%)		132 (47.1)	35 (25.4)	97 (68.3)	**<0.001**
of which:	hepatitis C, n (%)	67 (50.7)	21 (60.0)	46 (47.4)	0.203
	Hepatitis B, n (%)	31 (23.5)	5 (14.3)	26 (26.8)	0.135
	Hepatitis B+D, n (%)	27 (20.5)	7 (20.0)	20 (20.6)	0.939
	Hepatitis B+C, n (%)	4 (3.0)	2 (5.7)	2 (2.1)	0.635
	Hepatitis B+D+C, n (%)	3 (2.3)	0	3 (3.1)	0.256
Cirrhosis of the liver, n (%)		112 (40.0)	15 (10.9)	97 (68.3)	**<0.001**
TNM stage I, n (%)		24 (8.5)	7 (5.1)	17 (12.0)	**0.04**
TNM stage II, n (%)		64 (22.9)	33 (23.9)	31 (21.8)	0.679
TNM stage III, n (%)		110 (39.3)	64 (46.4)	46 (32.4)	**0.017**
TNM stage IV, n (%)		82 (29.3)	34 (24.6)	48 (33.8)	0.093

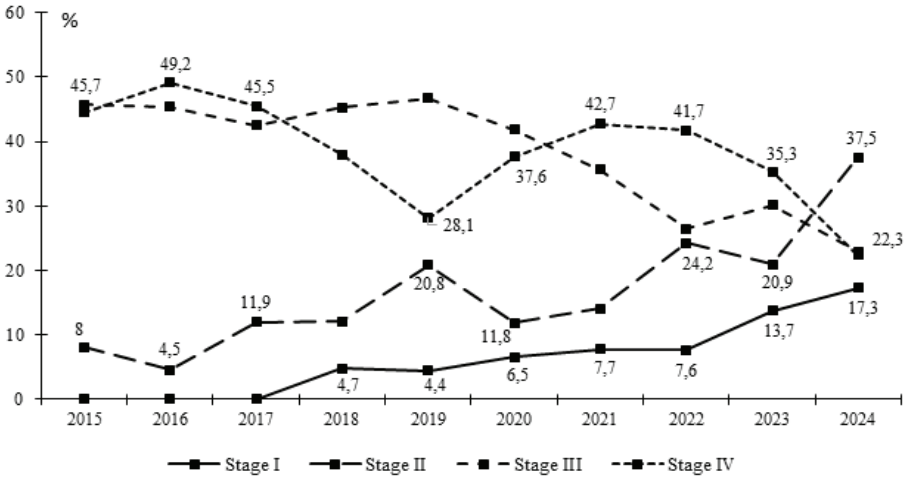

Fig. 3. Distribution of patients with HCC diagnosed in Yakutia by stage (2015-2023)

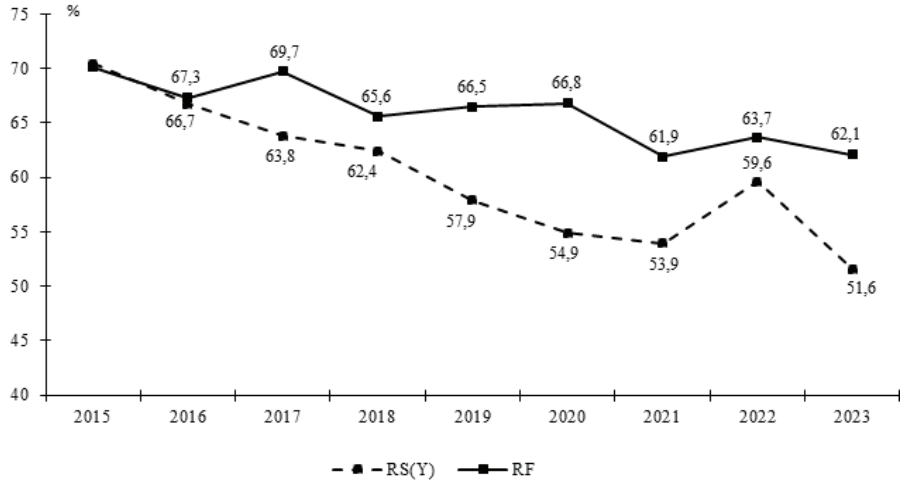

Fig. 4. One-year mortality of patients with HCC in the Russian Federation (RF) and Yakutia (Republic of Sakha (Yakutia)) (2015-2023)

vere fibrosis or cirrhosis of the liver, due to the high risk of developing HCC, are subject to lifelong monitoring by a gastroenterologist or therapist with mandatory examinations every 6 months, including ultrasound examination of the abdominal organs and determination of the level of a specific tumor marker.

It is important to note that in recent years, Yakutia has seen positive trends in increasing the coverage of antiviral therapy for people with hepatitis. In 2024, 1,198 people with chronic hepatitis C and 262 people with chronic hepatitis D received a full course of treatment, which exceeds the 2023 figures by 2.8 and 1.7 times, respectively.

For comprehensive centralized monitoring of patients at risk for HCC, a federal registry of patients with viral hepatitis was launched in Yakutia on September 1, 2024. Thanks to this data, specialists from medical organizations can track the availability of examinations and treatment for their patients and monitor the timeliness of antiviral therapy prescriptions.

As can be seen from Table 1, the implementation of measures aimed at improving the provision of medical care to the adult population with cancer in the Republic of Sakha (Yakutia), including the formation of interdisciplinary interactions, over a five-year period has led to a significant improvement in the etiological interpretation of the causes of liver damage and the quality of assessment of the functional and morphological state of the liver. Due to improved screening, the proportion of patients with markers of viral hepatitis increased 2.5 times and approached 70%, which corresponds to the literature data for the Euro-Asian region [2, 12, 13]. The inclusion of infectious disease specialists and gastroenterologists in the process of monitoring patients was accompanied by an improvement in the clinical and laboratory diagnosis of liver cirrhosis, which is extremely important when choosing a treatment strategy for a patient, as well as in the early differential diagnosis of focal liver lesions.

One of the key indicators of the effectiveness of dispensary observation of patients from risk groups is the early diagnosis of HCC. The proportion of patients diagnosed at stage I according to TNM at the Yakutsk Oncology Dispensary over 5 years increased 2.4 times (Table), and in the Republic of Sakha (Yakutia) as a whole, 3.9 times (Fig. 3). This indicates the effectiveness of primary health care in terms of cancer awareness and prevention, primarily on the part of infectious disease specialists, therapists, and gastroenterologists.

An important informative criterion for diagnostic effectiveness is one-year mortality, i.e. the proportion of patients who died from HCC within the first year after diagnosis among patients registered in the previous year (Fig. 4). This indicator depends on the regularity of dispensary observation, which is confirmed by the increase in the detection of persons with stage III-IV liver cancer in 2021-2022 in the republic, associated with quarantine restrictions on routine examinations of persons, including those from risk groups.

The five-year survival rate of patients with HCC diagnosed during the study period increased by 1.7 times and amounted to 18.3% and 31.9%, respectively, confirming the positive impact of the organizational and managerial measures taken.

In accordance with current regulations, each patient with a confirmed cancer diagnosis is subject to review by a multidisciplinary team to determine the treatment strategy. It should be noted that an interdisciplinary approach is important not only for the early diagnosis of HCC, but also after confirmation of the diagnosis, in the treatment of concomitant complex pathologie with different morpho-functional statuses of liver damage. A significant reduction in mortality ($p<0.01$) and an increase in 3-year survival to 92% in patients with HCV-associated HCC after achieving a sustained virological response [10, 14, 17,] was made possible solely through the coordinated interdisciplinary collaboration of oncologists and infectious disease specialists. Given the unfavorable situation in the region with regard to chronic viral hepatitis and its outcomes (cirrhosis of the liver and hepatocellular carcinoma), it is necessary to further expand access to antiviral therapy for people with chronic viral hepatitis B, C and D, early initiation of antiviral therapy regardless of the stage of fibrosis, rational use of compulsory health insurance funds and regional programs. It is precisely this approach that ensures the timely and safe administration of antiviral therapy and directly determines the improvement of the oncological prognosis.

Conclusion. The literature data and the republic's experience in implementing an interdisciplinary approach to the routing and clinical observation of patients with HCC allow us to recommend its widespread use. It is necessary to continuously improve the rules for routing patients with chronic viral hepatitis in order to decentralize the provision of medical care and expand access to treatment. The question remains open as to how the introduction of an interdisciplinary approach will affect the overall survival of patients with HCC. The answer to this question requires prospective observation of patients and careful analysis, and the authors of the article hope to continue the research in the foreseeable future.

The authors declare no conflict of interest.

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DETECTION OF ANTIBODIES TO THE HEPATITIS B VIRUS CORE ANTIGEN IN DONORS OF YAKUTIA AS A METHOD OF ENHANCING VIRAL SAFETY

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The article presents the results of the study on antibodies to the hepatitis B virus core antigen (anti-HBcore) among donors of the Republican Blood Transfusion Station during the period of 2021–2024. The purpose of this study is to determine the most effective method of identification and exclusion from blood donation of individuals with latent infection and past hepatitis B virus infection. In addition, the article reviews virus-safe blood components procurement, reduction of discarded blood and minimization the risk of post-transfusion complications during hematransfusions.

Throughout the study period, the overall detection rate of anti-HBcore was 26.3%, with no statistically significant gender-based difference (25.3% in men vs. 28.2% in women; p = 0.912). Donor age appeared to be one of the main factors influencing anti-HBcore prevalence. The findings indicate that routine anti-HBcore testing at every donation made by the age group of over 30-35 years old is recommended.

Keywords: donor, hepatitis B virus, hepatitis B core antibodies, hematransfusion safety.

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Introduction. An essential prerequisite of hemotransfusion therapy is the assurance of the infectious safety of blood and its components [7, 10, 13]. At present, in Russia, the cases of HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) transmission to recipients are not being registered [8,12]. This is largely due to continuous monitoring of all stages of the process, thorough and attentive donor selection, proper blood testing, and pathogen inactivation. According to official data, in 2020, out of 1,205,295 donors in Russia, more than 9,000 cases of infections were detected: HIV (9.4%), HBV (18.8%), HCV (37.8%), and syphilis (37.3%) [3, 4].

The prevalence of chronic HBV infection in the Republic of Sakha (Yakutia) remains consistently high and exceeds the average national level by 2.3 times. In 2024, 214 new cases of chronic HBV were reported in the republic, with an incidence rate of 21.45 per 100,000 popu-

lation (compared with 9.37 per 100,000 in the Russian Federation) [6]. This fact underlines the persistent risk of HBV infection among recipients of allogeneic transfusions, despite the widespread use of highly sensitive laboratory testing methods of donor blood.

Ensuring viral safety in hematransfusion practice requires comprehensive prevention of transfusion-transmitted infections (TTIs) [8, 9]. Since 2021, mandatory testing for anti-HBcore has been introduced in Russia in accordance with Order No. 1166n of the Ministry of Health of the Russian Federation, dated October 28, 2020, "On the approval of the procedure for donor medical examination and the list of medical contraindications (temporary and permanent) for blood and/or blood component donation, as well as deferral periods in the presence of temporary medical contraindications."

High sensitivity and specificity of diagnostic tests, together with the expansion of infectious marker screening, have significantly reduced the probability of transfusion-related HBV transmission [15]. Nevertheless, latent HBV infection (LHBV) in a donor, if blood or components are collected and subsequently transfused, may result in the development of clinical hepatitis in the recipient [14]. Standard donor screening can fail to detect HBV during the serological "window period," in cases of "wild-type" virus with suppressed replication, gene expression or in infection with mutant HBV strains, which are undetectable by reagents [11, 14].

The introduction of PCR testing for HBV DNA has shown that this marker is detectable only in a small proportion of HBsAg-negative donors worldwide. The detection of virus DNA depends on regional infection prevalence. Donors with LHBV and mutant HBV strains can only be identified through anti-HBcore testing, about 50% of whom also test positive for anti-HBs [5]. Therefore, blood screening for anti-HBcore is necessary to ensure transfusion safety. Following the implementation of this new approach, no proven cases of transfusion-related HBV transmission have been recorded [11].

Thus, continuous research and development of methods for detecting anti-HBcore in donors remains highly relevant [11, 2].

Objective of the study: To assess the prevalence of anti-HBcore antibodies among donors in the Republic of Sakha (Yakutia).

Materials and methods. The study material comprised blood donations made at the Blood Transfusion Station of the Republic of Sakha (Yakutia) in 2021–2024. In total, 59,456 donations were analysed, including 616 samples tested for anti-HBcore.The results interpretation included the analysis of the following: enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay, Architect HBsAg Qualitative II, Architect Anti-HBc II Reagent Kit, and polymerase chain reaction (PCR). Statistical analysis was conducted using IBM SPSS Statistics v26. Descriptive statistics and Pearson's χ^2 test were applied, with significance set at $p < 0.05$.

Results and discussion. During the study period of 2021 to 2024, 59,456 donations were collected and presented by gender on Table 1. This gender analysis demonstrates that male donations are significant and represent 68,5% of the total amount of donations between 2021 and 2024.

Yakutia is distinguished by a predominance of male donors (68.5%), compared with the donors of other regions with the following male representation: Khabarovsk krai - 53.91%, Sakhalin Region - 55.93% and the Republic of Dagestan - 56.2.0% [5].

There were 616 blood donor samples collected with uncertain results from recurring immunological tests for hepatitis B virus markers, and this accounted for 1.04% out of those 59,456 of total donations. All of them were included into the study to reveal the antibodies to hepatitis B core antigen. Male donations represented 64,3%, whilst female ones - 35.7%, which differed significantly from the overall gender distribution of all donations (Table 2).

The analysis of the frequency of the antibodies to the hepatitis B virus core antigen (anti-HBcore) in donor samples revealed the following: in 2022 there was a remarkable difference between male donations (14.8%) and female donations (26.0%), and 17.6% and 22.2% respectively in 2023 However, during the entire study period the overall detection rate of anti-HBcore was 26.3% (considering anti-HBcore positive was detected in 162 out of 616 blood samples), with no statistically significant gender-based difference (25.3% in men vs. 28.2% in women; $p = 0.912$) (Table 3). These numbers not only exceed the average across regions in the Far East Federal district, but also in the entire Russia [1, 5].

Table 1

Donation distribution by gender (absolute number in %)

Donor gender	Year				
	2021	2022	2023	2024	Total
Male	9 737 (67)	10 073 (68.6)	10 288 (69.4)	10 659 (69.2)	40 757 (68.5)
Female	4 800 (33)	4 620 (31.4)	4 535 (30.6)	4 744 (30.8)	18 699 (31.5)
Total	14 537	14 693	14 823	15 403	59 456

Table 2

Number of anti-HBcore tests by gender (absolute number in %)

Donor gender	Year				Total
	2021	2022	2023	2024	
Male	27 (64.3)	81(61.8)	102 (61.8)	186 (66.9)	396 (64.3)
Female	15 (35.7)	50 (38.2)	63 (38.2)	92 (33.1)	220 (35.7)
Total	42	131	165	278	616

Table 3

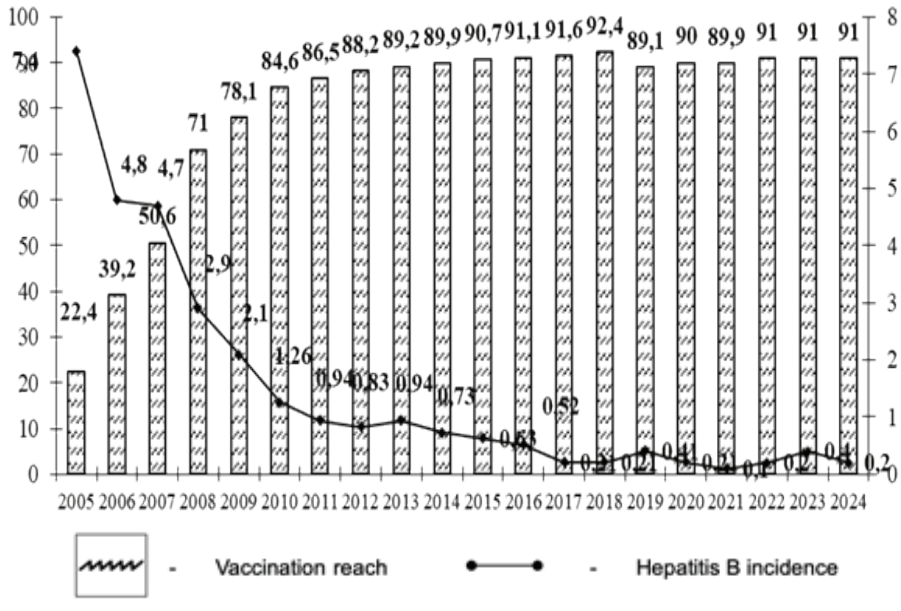
Frequency of anti-HBcore detection by gender (absolute number in %)

Gender	2021	2022	2023	2024	General	p-value
Male	25 (92.6)	12 (14.8)	18 (17.6)	45 (24.2)	100 (25.3)	0.912*
Female	14 (93.3)	13 (26.0)	14 (22.2)	21 (22.8)	62 (28.2)	
Total	39 (92.9)	25 (19.1)	32 (19.4)	66 (23.7)	162 (26.3)	

NB: *- χ^2 Pearson's criteria

Screening tests conducted as part of a research project, approved by the Ethics Committee of the National Medical Research Center for Hematology of the Ministry of Health of Russia (2019), revealed anti-HBcore in 21.6% of donors in the Republic of Sakha (Yakutia) [1].

Further analysis examined the distribution of the anti-HBcore positive donors based age groups (Table 4). In the group aged younger than 20 years, the anti-HBcore was not detected. The lowest prevalence was observed in the 21-30 age group, representing 3.8% and likely due to the mass immunisation program initiated in the Republic of Sakha (Yakutia) in 2005 (Figure). In the group age of 31-40 years the prevalence of anti-HBcore was 20.3% The highest proportion of positive anti-HBcore cases was observed among donors aged 41–50 years and over 50 years (58.8% and 41.0% respectively), with the latter two groups being the highest. Similar results were found in other studies conducted in the Russian Federation, where the highest frequency of anti-HBcore detection was registered in the age group of 50 years and older (23.39%), the lowest was in the age group of 21-30 years old (3.37%), whilst 31-40 years old was at 11.49%, and 41-50 years old at 22.48% [4, 1]. Thus, the donor age was found to be one of the main factors influencing the frequency of anti-HBcore detection.



Dynamics of the hepatitis B incidence and vaccination reach of the population in the Republic of Sakha (Yakutia), 2005 - 2024

Simultaneously, along with determining the antibodies to Hepatitis B Virus Core Antigen (anti-HBcore), the structure of discarded donor blood was studied. Those donations were rejected due to hepatitis B and represented 45.3% - 90.1% of all cases where the blood was discarded and associated with transfusion-transmittable infections (TTI). The discarded donor blood components due to anti-HB core ranged between 23.3% - 42.7%. The absolute volume of discarded donor blood increased from 39.5 liters in 2021 to 54.6 liters in 2024 (Table 5).

Table 4

Frequency of anti-HBcore detection based on donor age (number, %)

Age group	Anti-HBcore (n)		
	Male, %, (n, anti-HBcore positive / tested)	Female, %, (n, anti-HBcore positive / tested)	Total, % out of tested, (n)
<=20	0 (0/12)	-	0 (0/12)
21-30	5 (7/141)	0 (0/42)	3.8 (7/183)
31-40	21.2 (28/132)	18.6 (13/70)	20.3 (41/202)
41-50	64.2 (43/67)	53.6 (37/69)	58.8 (80/136)
>50	47.8 (22/46)	32.4 (12/37)	41.0 (34/83)
Total % (anti-HBcore positive / tested)	25.3 (100/398)	28.2 (62/218)	26.3 (162/616)

Table 5

Discarded blood due to transfusion - transmissible infections (TTIs)

Year	Total discarded due to TTIs (HBV, HCV, HIV, Syphilis), liters	Discarded due to hepatitis B (liters, % of total discarded)	Discarded due to anti-HBcore (liters, % of total discarded)
2021	39.5	35.6 / 90.1	12.2 / 30.9
2022	34.2	15.5 / 45.3	8.0 / 23.3
2023	34.5	19.5 / 56.5	11.6 / 33.6
2024	54.6	28.5 / 52.1	23.3 / 42.7

The results of the study of the anti-HBcore and also the detection of the Hepatitis B virus in 90.1% discarded donor blood is the evidence of high morbidity of chronic Hepatitis B virus among the population. The most obvious reasons for the rise of the discarded donor blood from 39 liters to 54 liters in 2024 are: 1) an increase in the amount of donations and blood cells and 2) predominancy of donors aged 35 years and above.

Based on the above, it is confirmed that in the Sakha Republic (Yakutia) there is a detrimental situation regarding hepatitis B virus among individuals over 30 years old.

Conclusion. As the findings indicate, we can conclude that in order to support and enhance viral safe transfusion it is advisable to prioritise blood collection from younger donors (under 35 years), who are protected by the mass HBV immunization program. This measure would significantly reduce the volume of discarded blood due to HBV.

To prevent HBV transmission during hematransfusions and minimize the risk of post-transfusion complications, routine anti-HBcore testing at every donation made by the age group of over 30-35 years old is recommended.

In future, it is suggested to expand the research on the detection of the anti-HBcore among donors of diverse ethnic backgrounds and examine the possible association with erythrocyte antigen group affiliation. These studies will have important scientific and practical implications for ensuring virologically safe and immunologically compatible transfusions.

The authors declare no conflict of interest.

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ANALYSIS OF OCCUPATIONAL INJURIES IN THE MINING INDUSTRY OF RUSSIA AND THE REPUBLIC OF BASHKORTOSTAN

The mining industry is one of the key industries for the economy of Russia and the Republic of Bashkortostan. However, despite its significant contribution to economic development, this sector is characterized by a high level of industrial injuries. In this article, we will consider the main causes of injuries, statistical data, and measures to reduce them.

According to statistics, the main causes of injuries in the mining industry are: violation of safety rules, faulty equipment, low level of production control, insufficient training of workers, poor working conditions, lack of personal and collective protective equipment, and the human factor.

Industrial injuries in the mining industry of Russia and the Republic of Bashkortostan remain a serious problem that requires attention from both employers and government agencies. Taking effective measures to improve working conditions, train workers, and monitor compliance with occupational safety standards can significantly reduce the number of accidents at work and improve overall safety in the industry.

Keywords: mining industry, injuries, fatalities, statistics, industrial control

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Introduction. The mining industry is a key component of the Russian economy, encompassing the extraction of coal, precious metals, rare earth elements, and natural stones. In Russia, as in other countries with developed mining industries, this sector has a significant impact on technological progress, living standards, and generally accepted standards. Without mining, many industries, including construction, electronics, and many others, would be impossible.

The mining industry encompasses all stages of deposit development—from prospecting and exploration to extraction and processing. Despite the innovative technologies and equipment used, mining enterprises pose a high risk of harm to worker health, due to the specific nature of their production.

Over the past 10 years, the proportion of workers working in hazardous and harmful conditions at copper-zinc ore mining enterprises has ranged from 40% to 71.9%. These are extremely alarming statistics, especially considering that in underground ore mining units, this figure reached 100% [1-3, 6]. A high rate of occupational injuries, including group accidents and fatalities, is a direct consequence of harmful and hazardous working conditions. Therefore, the analysis of occupational injuries at mining enterprises is of paramount importance [7].

Given the development trends of the industry, as well as its specific characteristics at the national and industry levels, it is necessary to implement scientific and methodological foundations for risk management. One of the key aspects and relevant areas for further research is an objective assessment of working conditions and safety systems at production facilities.

Research Materials and Methods. This study analyzed statistical annual reports from Rostekhnadzor and the Federal State Statistics Service for 2013-2023 on accidents and injuries in the mining industry. Statistical data processing was performed in Microsoft Excel. Descriptive statistics were used to analyze the data obtained.

Results and Discussion. Hazardous production facilities in the mining industry include underground mines (shafts), quarries, processing plants, crushing and screening plants, sintering plants, and subsoil use facilities for purposes unrelated to mineral extraction.

According to official data from the Federal State Statistics Service, 30 to 35% of workers in the Russian mining industry perform heavy work and work in hazardous and harmful conditions, under conditions of elevated levels of the following factors: chemicals, aerosols (primarily fibrogenic), noise, vibration, insufficient lighting, microclimate, and the severity and intensity of the work process.

The proportion of workers in the Republic of Bashkortostan mining industry engaged in hazardous working conditions during the period under review was 44.5–43.0%, ranking first among all types of economic activity [4].

In recent decades, the number of accidents at Russian mining sites has declined, despite an increase in rock extraction volumes by 169 million m³. This is possibly due to a reduction in the number of workers in this industry by 197,780,000.

Over the past 10 years, accident rates have more than halved across the constituent entities of the Russian Federation. In 2014, the number of accidents peaked at 58, and in 2023, it dropped to 28 (Figure 1). A total of 499 accidents occurred during the period under review. In the Republic of Bashkortostan, there were no accidents at

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enterprises in this industry during the period under review.

The number of fatal occupational injuries from 2013 to 2023 decreased from 7 to 3 (in the Republic of Bashkortostan, from 5 to 2 cases, respectively) (Figure 2).

Having examined the distribution of incidents and fatalities in the Russian mining industry from 2013 to 2023 (Table 1), it can be concluded that in a number of situations, fatal injuries were not related to natural disasters. Based on this, it can be argued that the human factor plays a significant role in the occurrence of life-threatening crises.

In practice, the most common traumatic factors are falls from heights, injuries caused by moving machinery, and incidents related to rock falls (Table 1). These circumstances often lead to serious consequences not only for the health of workers but also for overall production efficiency.

The distribution of accidents by traumatic factors in the mining industry is an important aspect of industrial safety and occupational health analysis. In the complex technological environment typical of this industry, accidents can occur for various reasons.

As can be seen from the data presented (Table 2), insufficient control over production processes was the primary cause of the greatest number of injuries due to inadequate control over production processes was the primary cause of the largest number of injuries. These injuries resulted from untimely inspections of mining equipment, improper organization of work areas, the absence of protective structures at mine workings, poor coordination among personnel, and the failure to start vehicles during maintenance work. Violations of work procedures, such as deviations from design solutions, technical standards, and work permits, are also a primary cause of accidents. Failure to comply with work regulations and discipline, including arriving at work intoxicated, also has a significant impact. Insufficient knowledge of safety rules and regulations, in particular, allowing individuals without the necessary training and instruction to enter hazardous areas, has caused between 2% and 7% of worker deaths over the years.

According to the Department for Technological and Environmental Supervision of the Federal Service for Environmental, Technological and Nuclear Supervision in the Republic of Bashkortostan, industrial injuries at mining enterprises in Bashkortostan are due to severe equipment deterioration—70-80%. To improve safety at these enterprises, it is essential to ensure

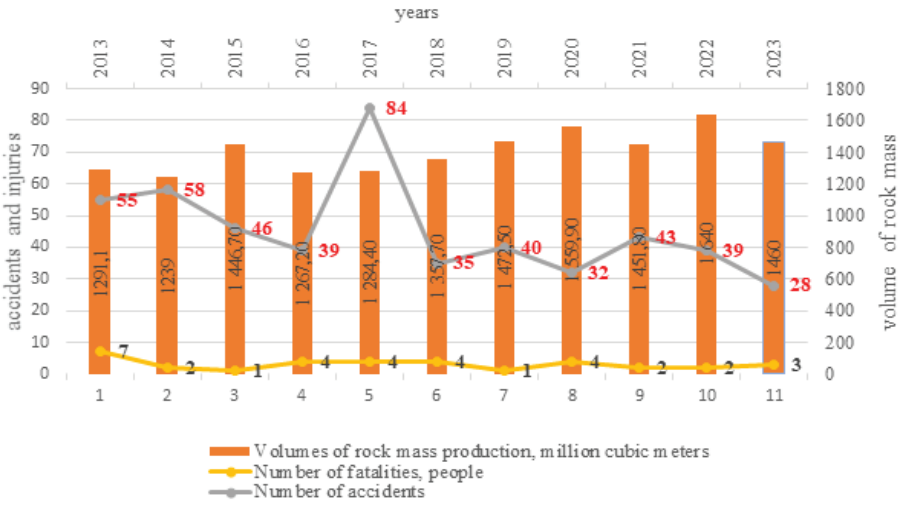

Fig. 1. Dynamics of indicators of rock mass extraction, accidents and fatalities at mining and non-metallic industry enterprises, underground construction sites [4]

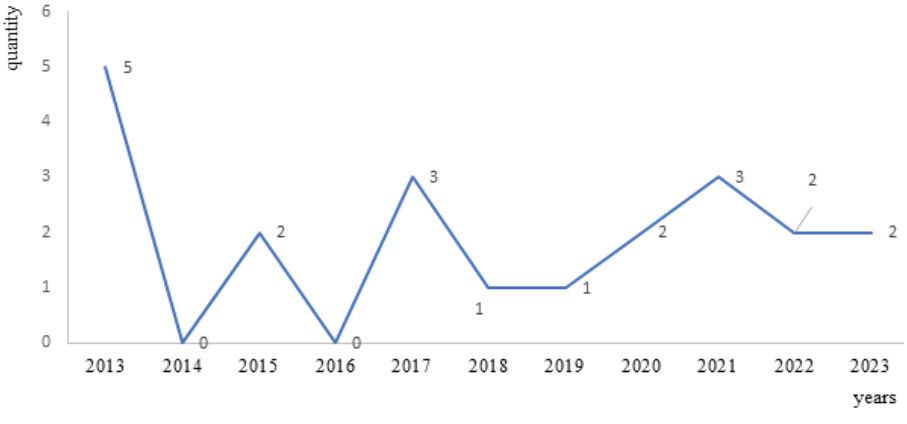

Fig. 2. Fatal industrial injuries in the mining industry in the Republic of Bashkortostan

a sufficient supply of serviceable equipment, and equipment that has reached its standard service life must undergo timely inspections. Furthermore, given the specific nature of their operations, mining enterprises in the region are particularly in need of qualified specialists, whose competence is crucial for resolving issues related to industrial safety and subsoil protection.

According to statistics, the majority of fatalities occurred as a result of the operation of load-haul-dump machines (LHDs) in underground mining opera-

Table 1

Distribution of accidents by injury factors in the mining industry for 2013–2023 in the Russian Federation, number [4]

Traumatic factor	years										
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Destruction of machinery and equip-ment	-	-	-	-	-	-	-	-	-	2	1
Motor transport	5	-	-	2	-	-	-	-	-	1	-
Accidents involving cranes and lifting equipment	-	-	-	-	-	-	1	-	-	1	1
Collapses	1	1	1	1	-	-	-	1	-	-	-
Destruction of technical equipment	-	-	-	1	2	3	-	-	-	-	-
Destruction of structures	-	-	-	-	-	-	-	1	-	-	1
Fires, conflagrations, uncontrolled explosions	-	-	-	-	1	1	-	-	-	-	1
Flooding	-	1	-	-	-	-	-	1	-	-	-

Table 2

Distribution of causes of accidents and incidents in the mining industry for 2013–2023 in the Russian Federation, % [4]

Causes of the accident	years										
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Low level of production control	19	24	16	32	32	53	45	41	48	39	65
Violations of work procedures	8	11	40	32	22	11	20	38	22	28	20
Severe violations of work regula-tions and labor discipline	24	9	13	7	15	21	15	9	10	10	5
Poor organization of work pro-cedures	42	52	27	27	29	11	18	6	13	18	5
Low level of knowledge of safe-ty standards and regulations	7	4	4	2	2	4	2	6	7	2	5

tions and conveyors at crushing and processing plants. The primary cause of fatal accidents involving LHDs and conveyors was poor production control—10 of the 17 incidents investigated (59%). In the case of LHDs, this was due to a lack of safety oversight by technical supervision, poor workplace conditions, poor visibility and lighting, the use of faulty equipment, and the presence of people in hazardous areas. Regarding conveyors, the main problems were the lack of collective safety equipment (rotating and moving parts were not guarded), the absence of shut-off devices to stop the conveyor in the event of belt slippage, the performance of production operations in the conveyor operating area, and the start-up of equipment without warning signals.

Conclusion. Injuries in the mining industry are caused by a variety of factors, including mechanical, chemical, and physical impacts. To reduce the risk of injury, it is necessary to implement modern safety technologies and strictly adhere to occupational health and safety standards at all stages of production.

Industrial control in the mining industry plays a key role in ensuring occupational safety and environmental protection. It is a system of measures aimed at monitoring and managing technological processes, which helps minimize risks and increase production efficiency. Fundamental aspects of control include continuous measurement of parameters, analysis of the obtained data, and the implementation of modern technologies.

A key element of industrial control is the development and implementation of standards regulating production processes, which clearly define employee responsibilities and ensure compliance with safety regulations. Furthermore, regular audits and inspections help identify deviations from established procedures and prevent emergencies.

The introduction of new technologies, such as process automation, sensors, and monitoring systems, significantly improves the accuracy of control and the speed of response to unforeseen situations. Thus, effective industrial control is not only a safety tool, but also a key factor in increasing the competitiveness of mining companies in the global market.

The authors declare no conflict of interest.

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EVALUATION OF THE APPLICABILITY OF NONPARAMETRIC REGRESSION MATHEMATICAL MODELS FOR ASSESSING CAUSE-AND-EFFECT RELATIONSHIPS BETWEEN DRINKING WATER QUALITY AND POPULATION MORBIDITY

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Introduction. The health of the population depends on the chemical composition of water used for domestic and drinking purposes. The chemical composition of consumed drinking water can have a negative impact on various human organ systems. There are sanitary and hygienic standards for maximum permissible concentrations (MPC) of chemicals in drinking water, which can be used to determine its safety. To study the degree of influence of the chemical composition of drinking water on public health, it is necessary to identify causal relationships between water quality and specific disease nosologies in the population. There is also a need to find the optimal statistical and mathematical model and to compare different models.

Objective. To assess the applicability of regression models for establishing a relationship between drinking water quality (water samples non-compliant in chemical indicators) and population morbidity.

Materials. Open data from social-hygienic monitoring over an 11-year period (2013–2023) for the Republic of Bashkortostan.

Methods. Correlation analysis (Spearman's) and three regression models robust to small samples and outliers: robust regression, polynomial regression, and Theil-Sen regression.

Results. Statistically significant relationships were identified between poor-quality water in terms of chemical indicators and the following diseases: angina pectoris, diseases of the circulatory system, and diseases of the musculoskeletal system. For many other diseases (congenital anomalies, respiratory diseases, diabetes mellitus, neoplasms, etc.), no significant relationship with water quality was found within this model.

Discussion. The results partially agree with literature data (e.g., the influence of hard water on the cardiovascular system, strontium on the musculoskeletal system). The main limitation is the small sample size (only 11 data points - by year), which reduces the study's power. The model is generalized and does not account for specific chemicals and their concentrations (e.g., hardness, nitrates, iron) that are prevalent in the region. Morbidity is also influenced by other factors (lifestyle, environmental conditions, socio-economic factors) not accounted for in the model.

Conclusion. Potential causal relationships were found between poor-quality drinking water and the incidence of angina pectoris, other diseases of the circulatory system, and possibly diseases of the musculoskeletal system in the Republic of Bashkortostan. Further research with larger datasets, analysis of specific pollutants, and consideration of additional risk factors is needed to confirm these links. Enhanced monitoring of both the chemical composition of water and population morbidity is necessary for implementing targeted measures to improve the situation.

Keywords: drinking water, mathematical model, regression, causal relationship, morbidity, public health monitoring (SGM).

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Introduction. Providing the population with high-quality drinking water is a significant challenge. Although access to quality drinking water is increasing, a portion of the population still receives water of unsatisfactory quality from centralized water supply systems. According to Rospotrebnadzor, cases of morbidity associated with the consumption of poor-quality drinking water have been registered in the Russian Federation. The chemical composition of drinking water can affect the gastrointestinal tract, genitourinary and musculoskeletal systems, among others [27].

Within the framework of the global sustainable development goals set for 2030, one of the key tasks is to ensure universal and equitable access to safe and affordable drinking water for all inhabitants of the planet. In Russia, the regulation of drinking water quality is particularly important, as it directly affects the health and quality of life of the population. In this context, state initiatives and measures to control and improve water supply quality become a priority, aimed at creating conditions for sustainable development and the well-being of citizens [14, 18].

The chemical composition of drinking water is one of the factors affecting public health, both in terms of general morbidity and specific disease nosologies. The most common diseases associated with the consumption of poor-quality drinking water are considered to be diseases of the genitourinary, digestive, musculoskeletal, and cardiovascular systems. Exceeding hygienic standards for certain chemicals can negatively affect the health of both adult and child populations [1, 5, 6, 9, 10, 12, 16, 23, 26].

The list of controlled chemical substances in drinking water includes about 70 chemicals, but it is also necessary to consider that water should be physiologically complete for human health. The list of sanitary-chemical indicators of drinking water that significantly affect public health includes chemicals of both natural and artificial origin [3, 17, 25].

Establishing cause-and-effect relationships between the health status of the population and the influence of environmental factors is the basis of social-hygienic monitoring (SGM). This system ensures continuous observation and assessment of environmental factors, as well as forecasting potential adverse consequences. Based on the data obtained, decisions are made aimed at reducing risks to public health [28].

Research Objective. To assess the applicability of regression models for evaluating causal relationships between drinking water quality and population morbidity.

Materials and Methods. Data from open sources were used as materials. Morbidity rates per 1000 population of the Republic of Bashkortostan were taken from statistical collections, and information on drinking water quality was obtained from the annual state reports of the UPRNRB.

Morbidity categories per 1000 population included: neoplasms, diseases of the endocrine system (including diabetes mellitus), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (including anemias), diseases of the nervous system, diseases of the circulatory system (including diseases characterized by elevated blood pressure, ischemic heart disease, including angina pectoris and myocardial infarction), diseases of the respiratory and digestive organs (including gastric and duodenal ulcers), diseases of the skin and subcutaneous tissue, as well as diseases of the musculoskeletal system and connective tissue.

The analyzed factors influencing population morbidity were selected as the proportions of drinking water samples from non-centralized and centralized (distribution network) water supply systems that did not comply with sanitary-chemical standards (Figure 1).

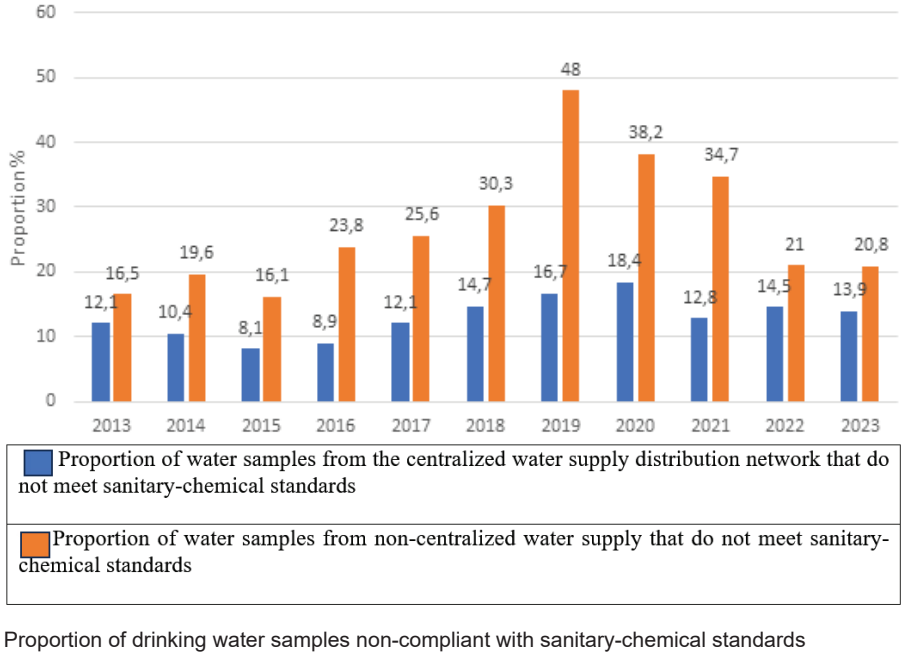
The sample covered an 11-year period from 2013-2023. The average proportion of non-compliant samples for hardness was 26.7%; the average proportion of non-centralized water supply samples non-compliant for sanitary-chemical indicators was 26.8%; the average proportion of non-centralized water supply samples for the rural population non-compliant for sanitary-chemical indicators was 26.8%; the average proportion of samples from centralized water supply systems non-compliant for sanitary-chemical indicators was 12.9%.

Average morbidity rates over the 11-year period according to state statistics (per 1000 population) were: neoplasms – 42.6; Diseases of the endocrine system, nutritional and metabolic disorders – 67.5; Diabetes mellitus – 29.9; Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism – 24.4; Anemias – 23.2; Diseases of the nervous system – 128; Diseases of the eye and adnexa – 110.25; Diseases of the ear and mastoid process – 45.86; Diseases of the circulatory system – 286.6; Elevated blood pressure – 128.9%; Ischemic heart disease – 62.4%; Acute myocardial infarction – 1.22%; Angina pectoris – 18.31%; Diseases of the respiratory organs; Diseases of the digestive organs – 166.38%; Gastric and duodenal ulcers – 7.05%; Diseases of the genitourinary system; Diseases of the skin and subcutaneous tissue – 69.8%; Diseases of the musculoskeletal system – 146.7%; Congenital anomalies – 6.53%. The statistical collections provided general morbidity rates per 1000 population without specifying ICD codes.

Spearman's correlation and three regression models were used as statistical methods: robust regression, polynomial regression, and Theil-Sen Regression. The choice of these methods is justified by the fact that non-parametric methods are robust to non-normal distribution, outliers, and small sample sizes.

Spearman's correlation calculation and correlation matrix construction were performed in the JASP statistical program, and regression model construction was done in Python using libraries such as pandas, numpy, scipy.stats, sklearn, etc.

Results. The results of the correlation analysis (Table 1) indicate a significant relationship between the proportion of non-compliant drinking water samples and population morbidity. The most pronounced relationships are with diseases



Proportion of drinking water samples non-compliant with sanitary-chemical standards

Table 1

Spearman's correlation between the proportion of non-compliant drinking water samples by sanitary-chemical indicators and morbidity per 1000 population

Proportion of non-compliant water samples (according to UPRNRB data)	Morbidity category per 1000 population (according to Bashstat data)	Spearman's Correlation Result
Proportion of non-standard samples by hardness, %	Congenital anomalies (malformations), deformations and chromosomal disorders	r=0.59 p-value =0.029
Proportion of water samples from non-centralized water supply non-compliant by sanitary-chemical indicators, %	Diseases of the respiratory organs	r=0.55 p-value =0.044
	Angina pectoris	r=0.53 p-value =0.047
Proportion of water samples from the centralized water supply distribution network non-compliant by sanitary-chemical indicators, %	Diseases of the musculoskeletal system	r=0.71 p-value =0.007
	Diseases of the respiratory organs	r=0.65 p-value =0.016
	Angina pectoris	r=0.76 p-value =0.003
	Diseases characterized by elevated blood pressure	r=0.64 p-value =0.017
	Diseases of the circulatory system	r=0.67 p-value =0.011
	Diseases of the endocrine system, nutritional and metabolic disorders	r=0.60 p-value =0.026
	Diabetes mellitus	r=0.59 p-value =0.028

Table 2

Regression Models for Establishing Causal Relationships between Drinking Water Quality and Population Morbidity

Variables		Regression/Significance			
Dependent Variable	Independent Variable	Robust Regression	Polynomial Regression	Theil-Sen Regression	Significance
Congenital Anomalies	Hard Water Samples	0.0112	[0.0, 0.2872, -0.0038]	0.0208	Not significant (all three models)
Angina Pectoris Incidence	Non-Centralized Supply Samples	0.1914	[0.0, 0.5021, -0.0062]	0.2252	Significant (Robust and Theil-Sen)
Respiratory Diseases	Non-Centralized Supply Samples	1.7916	[0.0, 19.7936, -0.2916]	3.3431	Not significant (all three models)
Angina Pectoris Incidence	Non-Centralized Supply Samples	0.6475	[0.0, 2.2391, -0.0560]	0.6149	Significant (Robust and Theil-Sen)
Circulatory System Diseases	Distribution Network Samples	5.1629	[0.0, 37.3473, -1.1780]	5.2005	Significant (Robust and Theil-Sen)
Elevated Blood Pressure	Distribution Network Samples	2.9351	[0.0, 19.0614, -0.5915]	3.3820	Not significant (all three models)
Musculoskeletal System Diseases	Distribution Network Samples	1.1405	[0, 14.3667, -0.4946]	1.0695	Significant (Robust Regression only)
Respiratory Diseases	Distribution Network Samples	10.4147	[0, 54.9851, -1.6850]	8.9512	Not significant (all three models)
Diabetes Mellitus	Distribution Network Samples	0.5689	[0, 1.9577, -0.0518]	0.8297	Not significant (all three models)
Endocrine, Nutritional and Metabolic Diseases	Distribution Network Samples	0.8676	[0; 8.4592; -0.2790]	0.9350	Not significant (all three models)
Elevated Blood Pressure	Distribution Network Samples	2.9351	[0, 19.0614, -0.5915]	3.3820	Not significant (all three models)
Angina Pectoris Incidence	Distribution Network Samples	0.6475	[0, 2.2391, -0.0560]	0.6150	Significant (Robust Regression only)
Circulatory System Diseases	Distribution Network	5.1629	[0, 37.3473, -1.1780]	5.2005	Significant (Robust Regression only)

of the cardiovascular system, respiratory system, and musculoskeletal system.

For further analysis of the causal relationship, pairs of variables with positive satisfactory Spearman correlation coefficients from Table 1 were selected, and regression analysis was conducted. Three types of regression models were chosen (Table 2): robust, polynomial, and Theil-Sen Regression. These methods are robust to outliers, small sample sizes, and non-normal distribution.

Based on the statistical data processing [19, 20], conclusions can be drawn and it can be suggested that:

- A significant relationship is observed (according to robust regression and Theil-Sen Regression) in the case of drinking water samples from non-centralized water supply and angina pectoris. This indicates a possible influence of water quality from non-centralized sources on the incidence of angina pectoris.
- A significant relationship was found (according to robust regression and Theil-Sen Regression) in the case of samples from the distribution network and angina pectoris. This may indicate the influence of water quality from the distribution network on the risk of developing angina pectoris.
- A significant relationship was identified (according to robust regression and Theil-Sen Regression) in the case of samples from the distribution network and diseases of the circulatory system. This suggests that water quality in the distribution network may influence the incidence of circulatory system diseases.
- A significant relationship was found (only according to robust regression) between samples from the distribution network and diseases of the musculoskeletal system. This may indicate a weak link between water quality and musculoskeletal diseases, but additional data are needed for confirmation.

For congenital anomalies, diseases of the respiratory organs, elevated blood pressure, diabetes mellitus, diseases of the endocrine system, and other diseases, no significant relationship with water samples was found. This may mean that water quality is not a primary risk factor for these diseases in this study.

Discussion. The mathematical model is generalized; the chemical composition of drinking water is diverse, and it is necessary to account for the maximum permissible concentrations (MPCs) of chemicals and the degree of their influence on human organ systems. The model also presents a general indicator of oncological morbidity without localization. For example, according to literature sources, long-term consumption of drinking water with high nitrate content is known to cause malignant neoplasms in the genitourinary system [21]. Our calculations did not find a link between drinking water and malignant neoplasms from the generalized data, but a causal relationship was found between drinking water and diseases of the cardiovascular and musculoskeletal systems.

The research results are supported by literature data. Foreign literature sources contain information on the influence of hard water (calcium and magnesium) on the incidence of cardiovascular diseases [29, 30, 31, 33]. It is known that the water in the Republic of Bashkortostan is quite hard, but our model did not detect a statistically significant link from the generalized data. To establish a connection, it is necessary to study several districts with exceeding hardness indicators and the dynamics of cardiovascular diseases. Literature data also confirm the relationship between the consumption of poor-quality drinking water and diseases of the musculoskeletal system. It is known that strontium in drinking water negatively affects the development of the musculoskeletal system, particularly in children [4, 24, 32]. In addition to musculoskeletal morbidity, literary sources present studies on the influence of the mineral composition of drinking water on the dental morbidity of the child population [22].

The problem of assessing the hygienic safety of water is exacerbated by the insufficient reliability of the maximum permissible concentrations (MPCs) of some chemicals. For example, the MPCs for lead, perchlorates, molybdenum, arsenic, and acrylonitrile do not always provide sufficient protection. In particular, the MPC for arsenic is not sufficiently reliable for women's reproductive health. Furthermore, the MPCs for molybdenum, antimony, perchlorates, nitrates, fluoride, cyanides, dimethylamine, and phthalates do not provide adequate protection for children. These shortcomings highlight the need to revise and refine existing standards to ensure a more reliable assessment of the hygienic safety of water [8, 15].

According to Rospotrebnadzor data for 2023 (Figure 1), 98.435% of the population is supplied with drinking water from centralized systems; an increase in drinking water samples non-compliant for sanitary-chemical indicators is noted. Drinking water does not meet standards for indicators such as "Turbidity," "Total Hardness," "Total Mineralization," "Iron," "Manganese," "Nitrates," "Sulfates," "Lithium," "Strontium" [20].

Conclusion. The study is a mathematical model; the smaller the sample size, the lower the study's power. The sample size significantly affects the accuracy of calculations. In our case, the sample consisted of an 11-year period.

Statistically significant causal relationships are observed between drinking water samples from non-centralized and centralized water supplies, non-compliant for sanitary-chemical indicators, and some diseases of the cardiovascular system, as well as the musculoskeletal system. This may indicate a potential influence of water contaminants on the cardiovascular and musculoskeletal systems. For other diseases, no significant link was found, which may indicate the absence of water quality influence on these diseases within the scope of this study.

To confirm the causal relationship, additional research is needed, including analysis of specific chemicals in drinking water and their impact on public health, as well as accounting for other factors (e.g., socio-economic conditions, lifestyle, etc.).

To reduce diseases associated with the consumption of poor-quality drinking water, monitoring of morbidity and the chemical composition of drinking water is necessary.

To manage the risks associated with exposure to poor-quality drinking water on public health, it is necessary to enhance the chemical monitoring system, improve the regulatory framework and water treatment technologies, and implement zoning for areas with high environmental risks within industrial and economic zones.

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TOPICAL ISSUE

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SELECTED ASPECTS OF HERPES VIRUS INFECTIONS IN THE IRKUTSK REGION

This study examined the incidence of the main herpesvirus infections (HVI) in the Irkutsk Region for 2014-2024 with the results of monitoring for herpes zoster since 2019. In the structure of HVI, the largest share is occupied by chickenpox (88.8%) and the smallest - cytomegalovirus infection with a share of less than one percent (0.4%). The dynamics of HVI incidence rates is unstable, with some upward trend in recent years. Children predominate among those affected, excluding shingles. Risk groups among the child population for the studied HVIs have been identified, which indicates the importance of preventive measures and monitoring of morbidity, primarily for these population groups. According to the forecast, an increase in the incidence of chickenpox and cytomegalovirus infection is expected, therefore, the importance of educational work to inform parents about the risks and symptoms of HVI, the role of vaccination in the fight against chickenpox increases. Effective management and prevention of these infections can significantly reduce infectious diseases and improve the overall health of the region's population.

Keywords: epidemiology, morbidity, herpesvirus infections, prognosis.

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Introduction. Herpesvirus infections (HVI) are becoming increasingly important in the structure of infectious pathology. The ongoing spread of the human immunodeficiency virus and SARS-CoV-2 contribute to the reactivation of herpesviruses and an increase in the number of registered forms of HVI [4, 5, 9].

HVI is a widespread group of infections. It is believed that by the age of 18-20, more than 90% of people are infected with one or more of the 8 known types of human herpes viruses. This article discusses four key infections caused by viruses of the *Herpesviridae* family: chickenpox, shingles, cytomegalovirus infection, and infectious mononucleosis [7].

Among the HVIs, one of the most frequently registered is chickenpox. This nosology is characterized by a high level of morbidity, uncontrollability of the epidemic process and often the development of severe complications [1, 11].

A chronic recurrent form of chickenpox is herpes zoster (HZ), which, in turn, is characterized by widespread distribution and prevalence among elderly patients; in children and adolescents it is rare and is associated with metabolic and tumor disorders. The disease manifests itself in various clinical stages with variable manifestations, some of which increase the risk of complications [7].

Unlike the previous diseases, cytomegalovirus infections are latent and opportunistic. In most cases, the infection is asymptomatic or the symptoms are mild. However, in vulnerable groups (immunocompromised patients and newborns), the virus can replicate to high levels and cause serious disease of target organs [3, 10].

As for infections caused by the Epstein-Barr virus (EBV), in childhood they are usually mild or asymptomatic; in adolescents and adults, primary EBV infections are usually characterized by infectious mononucleosis (IM) [6, 12].

The aim of the study is to study the trends in the epidemic process of key herpesvirus infections in the Irkutsk region for 2014-2023.

Materials and methods of the study. A retrospective epidemiological analysis of the incidence of the main herpesvirus infections was carried out according to the reporting forms of the Office of Rospotrebnadzor No. 2: chickenpox, cytomegalovirus infection, infectious mononucleosis for 2014-2024 and herpes zoster for a 6-year period, since the registration of cases of this

Table 1

Incidence of the total population of HVI in the Irkutsk region for 2014-2024 and forecast for 2025 (per 100 thousand, 95% CI)

HVI	average long-term indicator	average annual growth/ decrease rate (%)	forecast indicator for 2025
chicken pox	598,3 [588,5÷608,0]	-1,5	762,5 [629,4÷895,6]
herpes zoster*	33,9 [31,6÷36,3]	+19,4	42,8 [36,9÷48,7]
infectious mononucleosis	18,8 [17,0÷20,5]	+5,2	16,8 [11,9÷21,7]
cytomegalovirus infection	2,3 [1,7÷2,9]	+0,7	5,0 [3,4÷6,6]
Σ HVI *	597,3 [587,5÷607,1]	+3,9	-

* 2019-2024, the forecast is approximate due to the short dynamic series

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nosology began in 2019. The structure of HVI was calculated based on the sum of four nosological forms for 2019-2024; the forecast for 2025 was calculated based on statistical analysis of dynamic series of indicators (regression equation, standard regression error and forecast interval $P \pm m_R$) using a polynomial trend of the second and higher orders. The material was processed using mathematical and statistical methods using Windows applications (Microsoft Excel).

Results and discussion. The incidence of HVI in the total population of the Irkutsk region for the period under study is characterized by very unstable dynamics with different values of average annual growth rates (Table 1) and a tendency to increase in recent years (Fig. 1).

Forecast calculations indicate a continuing increase in the incidence of cytomegalovirus infection and chickenpox in the total population of the Irkutsk region (Fig. 1), although the latter has an average annual decline rate of 1.5%.

The largest number of registered cases of HVI are varicella pox (VP), which accounts for 88.8% of the total number of cases. Children predominate in the structure of cases - 94.3%. The epidemiological manifestations of VP in the region were previously presented [2]: an increase in incidence in 2021-2022 with a risk group of children under 6 years of age, and an increase in the volume of vaccination, against which the epidemiological effectiveness of this measure is not observed. The situation remains unfavorable in 2024 (Fig. 2); the highest incidence of morbidity is recorded among children aged 3-6 years.

Herpes zoster accounted for 7.0% of the total number of herpes zoster cases. A clearly expressed upward trend was also observed in the dynamics of herpes zoster incidence: over the 6-year observation period, the incidence rate increased more than 2-fold. The average long-term incidence rate (ALI) of the total population was 33.9 per 100 thousand [31.6 ÷ 36.3]. The ALI of adult incidence was statistically significantly 2.3 times higher than that of children under 17: 39.2 [36.4 ÷ 42.1] and 17.2 [13.8 ÷ 20.6] per 100 thousand, respectively. The incidence rates varied among adults within the range of 22.1–57.2 per 100 thousand, and among children 13.6–25.6 per 100 thousand. Adults predominated in the structure of cases – 87.8%. However, cases of herpes zoster were also observed in children, with the highest proportion in the 7-14 age group – 63.0%. Age-specific incidence rates

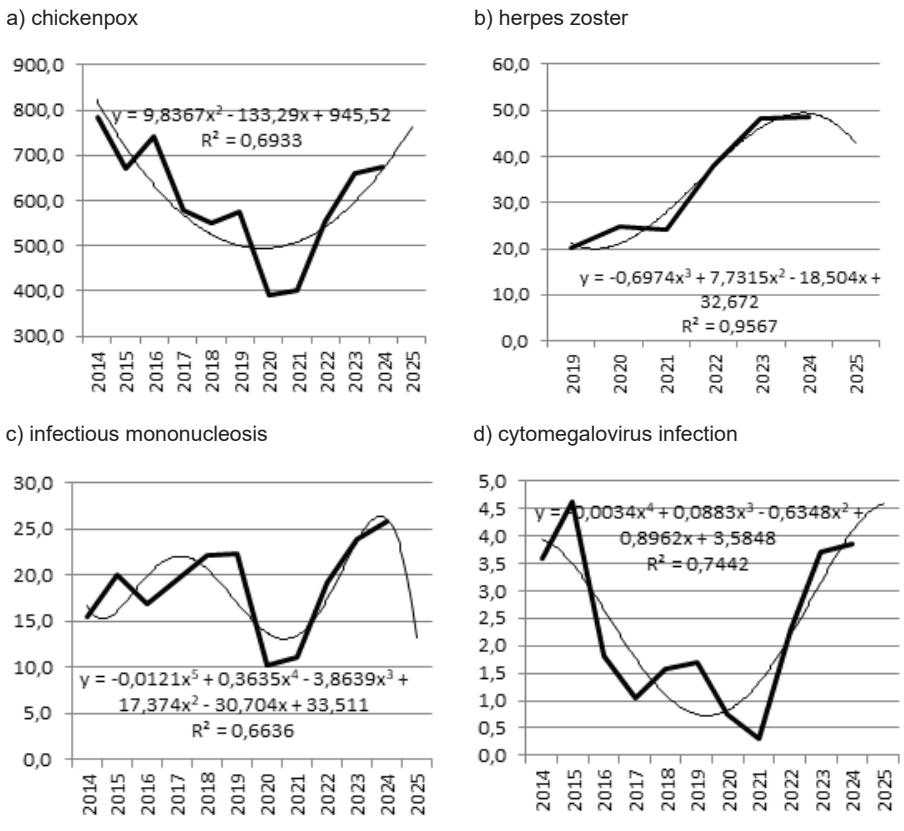

Fig. 1. Incidence of the total population of the Irkutsk region with HVI with a forecast for 2025 (per 100 thousand)

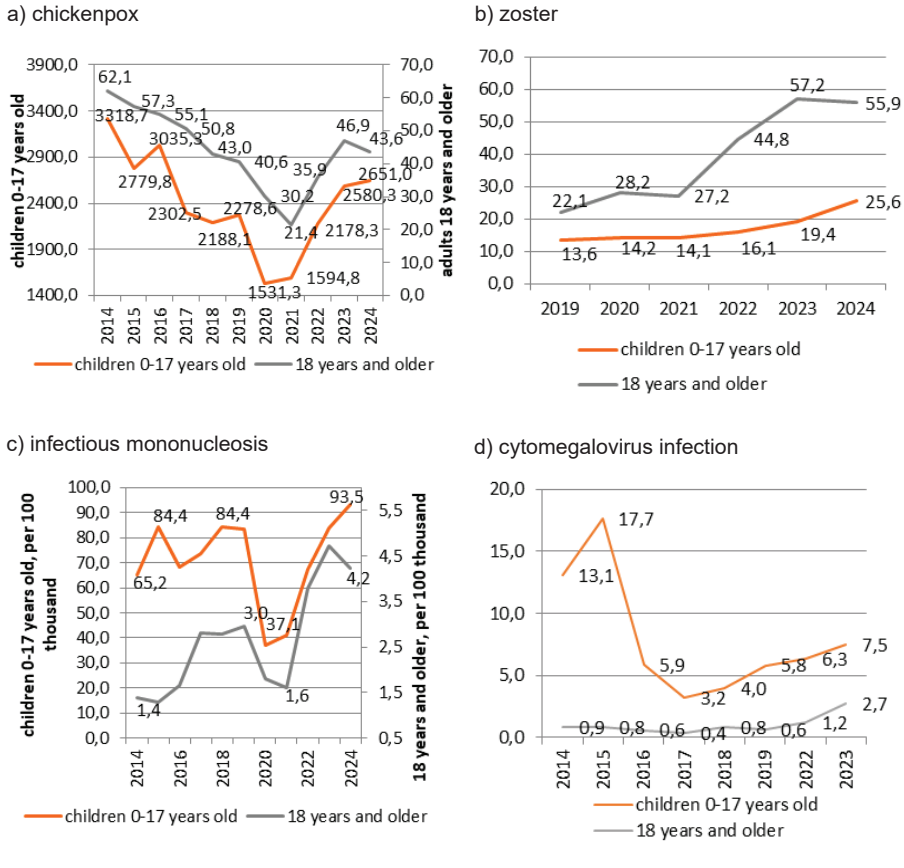

Fig. 2. Dynamics of incidence rates of HVI among children and adults in the Irkutsk region for 2014-2024 (per 100 thousand)

Table 2

Average long-term indicators and average annual growth rates of HVI among children of different age groups in the Irkutsk region for 2014-2024 (per 100 thousand, 95% CI; %)

HVI	long-term average, 95% CI / average annual growth/decrease rate, %				
	up to 1 year	1-2 years	3-6 years	7-14 years	15-17 years
chicken pox	1181.9 [1061.0÷1302.9] / -0.5	2829.3 [2701.7÷2956.9] / +2.4	5840.8 [5716.8÷5964.8] / -1.9	1176.7 [1134.5÷1218.8] / -0.2	490.7 [442.0÷539.3] / -1.9
herpes zoster*	36.3 [15.0÷57.6] / +14.4	165.9 [134.6÷197.2] / +2.6	114.7 [96.8÷132.6] / +3.5	38.1 [30.5÷45.8] / +8.2	35.5 [22.4÷48.6] / +12.2
infectious mononucleosis	43.7 [20.3÷67.1] / +8.2	19.0 [8.4÷29.6] / -4.3	5.1 [1.3÷8.9] / -6.4	1.2 [0.0÷2.6] / -21.9	0.6 [0.0÷2.4] / -
cytomegalovirus infection	2.6 [0.0÷8.7] / -	5.9 [0.0÷12.2] / +51.6	10.3 [4.8÷15.7] / +13.7	22.8 [17.1÷28.5] / +9.0	22.3 [12.2÷32.5] / +15.7

* 2019-2024

among children were unevenly distributed: risk groups are children aged 7-14 and 15-17: 22.8 [17.1÷28.5] and 22.3 [12.2÷32.5] per 100 thousand, respectively – Table 2.

Infectious mononucleosis (IM) accounts for 3.8% of the total number of HVIs. The incidence of IM during the observation period was without a clearly defined trend; the rates varied from a minimum in 2020 - 10.3 [9.0 ÷ 11.6] to a maximum in 2024 of 25.8 per 100 thousand [23.7 ÷ 27.8]; the average incidence rate of the total population is 18.8 per 100 thousand [17.0 ÷ 20.5]. Adults and children are involved in the epidemic process of IM in a ratio of 1: 8.4. The group of children aged 3-6 years prevailed in the structure of cases (39.0% of the total number of children or 34.8% of the total number of cases). The incidence rates of infectious mononucleosis (per 100 thousand) were: in children - 71.2 [64.2 ÷ 78.1]; in adults - 2.6 [1.9 ÷ 3.4]. The period of epidemiological unfavorability for this infection was 2024, when the highest level of MI incidence was observed.

Cytomegalovirus infection (CMV) accounts for only 0.4% of the total number of HCV infections. The average long-term incidence rate of CMV in the Irkutsk region was 2.3 [1.7 ÷ 2.9] per 100 thousand people. The incidence rate varied significantly by year, the minimum incidence rates were recorded from 2020 to 2021. Children prevailed in the structure, among whom children under 2 years of age predominated. The average incidence rate of children was 6.8 [4.6 ÷ 9.0], adults - 1.0 [0.6 ÷ 1.5] per 100 thousand people.

An analysis of the incidence rates of HVI infection in individual age groups of children showed (Table 2) that the risk group for CMV infection are children under 1 year of age, and for infectious mononucleosis, children aged 1–2 years. A short-term forecast was calculated for these age groups, according to which, most likely, in 2025 for children aged 1 to 2 years, the incidence rate of infectious mononucleosis is expected to be almost the same as in 2024: 207.5±43.1 per 100 thousand, i.e. in the range from 164.4 to 250.7; and for cytomegalovirus infection, the incidence rate of children under 1 year will continue to increase - up to 95.8±27.6; i.e. the indicator will be in the range from 68.2 to 123.5 per 100 thousand (Fig. 3).

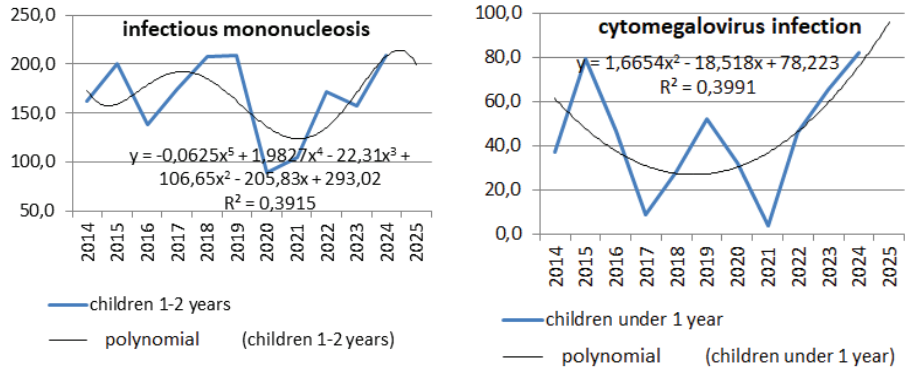

Fig. 3. Forecast of incidence rates of infectious mononucleosis and cytomegalovirus infection ir risk groups of children in the Irkutsk region for 2025 (per 100 thousand)

No clear cyclical pattern was observed in the long-term dynamics of incidence in the HVI group during the analyzed observation period. The sharp decline in rates in 2020-2021 was associated with the implementation of anti-epidemic measures against the novel coronavirus infection COVID-19 [8]. For certain HVIs (shingles, infectious mononucleosis), the incidence rate in 2023-2024 significantly exceeded the previous period in the compared groups – by 1.5-2 times, respectively.

The intra-annual dynamics of incidence for the studied infections in the region did not differ significantly from published data [7]. For example, chickenpox was characterized by a pronounced winter-spring seasonality. Cases of shingles and infectious mononucleosis were evenly distributed throughout the calendar period, with the highest number of registered cases in the fall-winter period. Isolated cases of CMV were recorded throughout the year without a pronounced seasonal increase.

Conclusion. According to the results of the analysis, the incidence of HVI in the total population of the Irkutsk region from 2014 to 2024 demonstrates unstable dynamics with an upward trend in recent years, which raises serious concerns in the field of public health. Children predominate in the structure of cases of all studied HVIs, excluding herpes zoster, which is more often registered in adults. Chickenpox remains the most common infection, accounting for a significant proportion of cases (89%), especially among children (94%). Each age group of children is a risk group with the highest average long-term rates for one of the HVIs: children under 1 year old – for CMV; 1-2 years – for infectious mononucleosis; 3-6

years – for chickenpox, 7-14 and 15-17 years – for herpes zoster. Projections for 2025 indicate a further increase in the incidence of chickenpox and cytomegalovirus infection (including in the risk group of children under 1 year of age), which emphasizes the need for active preventive measures and monitoring to protect vulnerable population groups.

Full-scale epidemiological surveillance of HVIs (including recording the absolute number of cases and incidence rates, identifying risk factors and groups, and implementing anti-epidemic and preventive measures) is only implemented for officially registered HVIs. For HVIs not subject to official registration and reporting, anti-epidemic measures are limited. Despite the availability of vaccines against chickenpox and shingles, these infections are considered "uncontrollable" by immunoprophylaxis.

Given the high prevalence of varicella-zoster virus infections and the limitations of specific preventive measures, it is important to focus efforts on early detection, isolation, and laboratory testing of all patients with symptoms of herpes infections. At the regional level, there is an objective need to change the chickenpox vaccination strategy from selective to routine, with a gradual expansion of the cohorts eligible for vaccination.

Effective management and prevention of these infections can significantly reduce the incidence and improve the overall health of the region's population.

The authors declare no conflict of interest.

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SOCIAL DETERMINANTS OF BREAST CANCER RISK AND LATE DIAGNOSIS: A MEDICO-SOCIOLOGICAL STUDY OF KHABAROVSK KRAI

This study analyzes the social determinants of breast cancer (BC) among the female population of the Khabarovsk Krai. The relevance of the problem is determined by the complex influence of not only biomedical but also socioeconomic factors. An analysis of the studied cohort revealed a characteristic clinical and demographic profile, which includes a predominance of patients from older age groups and a burdened somatic history. The key conclusion of the work is that the effectiveness of measures to combat BC is significantly limited by structural, predominantly organizational, deficiencies within the healthcare system. Manifestations such as low accessibility and untimeliness of medical care, expressed in delays in diagnosis and treatment, as well as insufficient follow-up care, exacerbate the existing social inequality in healthcare provision in the region.

Keywords: breast cancer, epidemiological indicators, psychosocial factors, healthcare accessibility, Khabarovsk Krai (Russia).

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Introduction. Breast cancer remains a critical medico-social problem, leading in terms of oncological morbidity and persisting as the primary cause of cancer-related mortality among the female population worldwide [3]. The distribution of the breast cancer burden is characterized by significant heterogeneity, both between countries and within them. Contemporary research indicates that this disparity is determined predominantly not by the biological characteristics of the tumor, but rather by socioeconomic factors and structural barriers within the healthcare system [1]. Although the role of modifiable lifestyle factors [12] and genetic predisposition [6] in the pathogenesis of breast cancer is acknowledged, it is the social determinants of health—income level, education, and geographic accessibility of medical care—that serve as critical predictors of adverse disease outcomes.

Within the framework of Russian scientific discourse, the problem of breast cancer has traditionally been considered through the prism of an organizational-clinical approach. This is reflected in studies devoted to the reorganization of healthcare services [7, 9], the improvement of diagnostic algorithms [11, 10], and the assessment of patients' quality of life [2, 8]. However, a systemic analysis of the impact of structural barriers and social inequality factors on the regional specifics of breast cancer epidemiological indicators remains an understudied area.

In this regard, reducing the burden of breast cancer requires the implementation of a comprehensive approach that, along with health promotion and the assessment of genetic risks, must be fundamentally oriented towards minimizing socio-economic disparities in access to all components of the healthcare system—from prevention and early detection to high-tech treatment and palliative care. The necessity for a comprehensive study of the social determinants of health defines the relevance of this research.

Materials and Methods. The research methodology was structured according to a sequence of stages, implying the comprehensive use of data collection and analysis methods. The initial stage involved an analysis of secondary data, which included examining official statistics from the P.A. Hertsen Moscow Oncology Research Institute (for the Russian Federation, the Far Eastern Federal District, and Khabarovsk Krai) [4, 5], alongside federal statistical reporting forms No. 7 and No. 12. The obtained statistical trends formed the basis for conducting a targeted sociological survey aimed at their in-depth understanding through the acquisition of relevant empirical data.

The main group consisted of women with a verified diagnosis of breast cancer (n=100) who received treatment at the Khabarovsk Krai Regional Clinical Oncology Center of the Ministry of Health. The control group (n=100) comprised women without oncological pathology, who were employees of medical organizations in the same region. Respondents were selected using a simple random sampling method. Data collection was carried out from November 2024 to May 2025 using two specialized questionnaires, the validity of which was confirmed by high Cronbach's alpha coefficient values (0.76–0.81). Statistical processing was performed using the SPSS.10 statistical data analysis package, employing descriptive statistics methods and the non-parametric Mann-Whitney U test for comparing independent groups; the statistical significance of differences was determined at $p<0.05$. The study was approved by the ethics committee, and all participants provided informed consent.

Discussion of Results. The dynamics of key statistical indicators for breast cancer (BC) in Russia from 2013 to 2023 are characterized by contradictory yet overall positive trends. Despite a steady increase in primary incidence (by 21.6% over the decade), likely associated with improved diagnostics, a substantial decrease in mortality—by almost 25%—has been observed. The anomalous decline in incidence during 2020-2023 is presumably an artifact caused by disruptions in the system of prophylactic medical check-ups during the COVID-19 pandemic.

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The cumulative lifetime risk of developing BC increased from 5.34% to 6.45%, reflecting both a real growth in the threat and improved detection rates. Progress in early diagnosis is confirmed by a significant increase in the proportion of BC cases detected at stages I-II (from 66.7% to 75.2%) and a concomitant decrease in the proportion of advanced cases. However, the persistently high proportion of diagnoses established at late stages (24.9% in 2023) indicates unresolved systemic problems in the organization of healthcare and the timeliness of patients seeking medical attention.

The epidemiological situation regarding breast cancer in the Far Eastern Federal District (FEFD) is characterized by systemic under-detection. This is masked by a formally low incidence rate (475.7 per 100,000 population) but manifested by a high mortality rate (12.19 per 100,000 population), suggesting frequent diagnosis at late stages. The situation is particularly critical in the Khabarovsk Krai, where high primary incidence (65.61 per 100,000 population) and high mortality (14.11 per 100,000 population) point to systemic challenges in the organization of healthcare. Despite a five-year survival rate close to the national average (66.2%), a low accumulation index for registered patients (10.2) and high case fatality rate (2.6%) confirm problems in follow-up care and patient routing. This dictates the necessity of prioritizing improvements in active case finding and the accessibility of BC diagnostics in the region.

Despite demonstrating higher treatment outcomes than the national and Far Eastern Federal District averages (five-year survival rate - 66.5%, cancer prevalence index - 11.4), the 20.2% increase in primary morbidity recorded between 2018 and 2023 in the Khabarovsk Territory represents an ambiguous epidemiological indicator that masks significant inter-territorial disparities. Sharp fluctuations in indicators across municipalities, including the multi-year absence of registered cases in some districts and a sporadic surge in others, point to systemic issues: unreliable statistics, chronic instability of cancer registration, patient migration, and an acute shortage of medical personnel in peripheral areas.

A conducted sociological study and subsequent analysis revealed key characteristics of the sample of female cancer patients compared to the control group. Patients diagnosed with breast cancer (Group I) were significantly older than women without oncopathology (Group II), as evidenced by the median age values: 51.5 years (interquartile range 25th–75th percentile 46.3–67.0 years) versus 45.0 years (37.0–50.7 years), respectively ($p < 0.05$). Analysis of the geographical distribution of participants showed a similar pattern in both the main and control groups: the majority (59.0±4.9% and 60.0±4.8%, respectively) resided in major regional cities (Khabarovsk, Komsomolsk-on-Amur), while the remainder (41.0±4.9% and 40.0±4.8%) represented urban settlements of municipal districts, such as Vanino, Chegdomyn, and Nikolaevsk-on-Amur, among others.

Despite a comparable proportion of individuals with higher education in the groups (66.0±4.7% and 63.0±4.8%, respectively), their employment status differed radically. In the control group, it was one hundred percent, whereas among patients with breast cancer, only 36.8±4.8% were employed; the rest were distributed among the statuses of temporary unemployment (24.2±4.2%), disability (24.0±4.2%), and being students (15.0±3.5%). However, the questionnaire data indicate a potential inaccuracy in self-reported employment status in the latter group.

Medical indicators also demonstrated a substantial difference: the prevalence of chronic diseases in Group I reached 50.0±5.0%, significantly exceeding the rate in the control group (11.0±3.1%). Furthermore, in 60.0±4.8% of patients in the main group, the duration of chronic pathology exceeded five years. The distribution by stages of breast cancer at the time of diagnosis in Group I was as follows: Stage I — 21.0±4.0%, Stage II — 31.0±4.6%, Stage III — 38.0±4.8%, Stage IV — 10.0±3.0%.

At the same time, parameters such as a history of at least one pregnancy (100% in both groups) and childbirth (70.0±4.0% vs. 75.0±4.3%) showed no significant difference ($p > 0.05$). The observed trend towards a lower prevalence of breastfeeding in the breast cancer group (60.0±4.8% vs. 66.0±4.7%), in the absence of statistical significance, indicates the need for further analysis of this protective factor. The unexpectedly low frequency of hormonal contraceptive use in the breast cancer group (61.0±4.8% vs. 100%) requires additional verification regarding its reliability. Thus, the obtained results underscore the multicomponent nature of breast cancer risk, with the dominant role of endocrine and genetic components.

The study results revealed statistically significant differences in a number of behavioral factors between women diagnosed with breast cancer and the control group of healthy women.

Systemic discrepancies were observed in the perception of working conditions, where breast cancer patients demonstrated a more critical assessment ($U=850$, $p<0.001$): only 25.0±4.3% characterized them as favorable compared to 48.0±4.9% in the control group. Furthermore, the vast majority of patients (87.5±3.3%) considered work a factor that worsened their health, whereas only 11.3±3.1% of healthy women shared this view ($p < 0.001$).

A significant difference was recorded in the subjective assessment of income level ($U = 500$, $p < 0.001$). While 81.0±3.9% of respondents in the control group reported a high income, only 31.0±4.6% in the breast cancer group gave a similar assessment, and 40.0±4.8% reported a low income. Paradoxically, despite the serious diagnosis, breast cancer patients subjectively assessed their stress levels as lower ($U = 3352$, $p < 0.001$): 41.0±4.9% reported a low level versus 41.0±4.9% of healthy women reporting a high level. However, the structure of stressors differed radically: for women with breast cancer, the main source was work (51.0±4.9%), while for healthy women it was financial issues (76.0±4.2%). This was accompanied by a significantly higher level of constant health anxiety among breast cancer patients (59.0±4.9% vs. 34.0±4.7%; $U = 3352$, $p < 0.001$).

The results of the statistical analysis demonstrated a significant deterioration in sleep quality in the group of patients with breast cancer (BC) compared to the control group ($U = 2940$, $p < 0.001$). Specifically, 20.0 ± 4.0% of respondents in the study group rated their sleep as low-quality, with none of the participants selecting the highest rating on the five-point scale. However, it should be noted that, as additional analysis showed, the identified differences may be partially attributable to age disparities between the compared groups.

Regarding eating behavior, the opposite pattern was observed: the diet in the BC patient group was more balanced, and the attitude towards it was more positive ($Me = 3.5$, $Mo = 4$), whereas in the control group, the ratings were statistically significantly lower and unanimously negative ($Me = 1$, $Mo = 1$; $U = 1850$, $p<0.001$).

Concerning behavioral factors, no significant differences were found in the frequency of alcohol consumption or smoking intensity among smokers

(p>0.05). However, a significantly lower reported prevalence of coffee consumption was recorded among BC patients (39.0 ± 4.8% vs. 83.5 ± 3.7%; U = 20506, p < 0.001), with no differences in the amount consumed among consumers, which may indicate a socially desirable response bias. At the same time, BC patients demonstrated significantly higher adherence to regular physical activity (80.0 ± 4.0% vs. 28.0 ± 4.4%; U = 2400, p < 0.001).

The most alarming differences were identified in the realm of healthcare accessibility. Women with BC were significantly less engaged in the system of dispensary observation prior to diagnosis (U = 4656, p < 0.001). They also faced more substantial systemic barriers: 90.0±3.0% reported various obstacles in obtaining care, and the hospitalization process lasted more than a month for 61.0 ± 4.8%, with 20.0 ± 4.0% waiting from four to five months. No statistically significant differences were found between the groups regarding the difficulty of scheduling an initial appointment with a general practitioner (U = 4643, p = 0.3). However, scheduling specialized diagnostic procedures for BC patients was associated with greater difficulties (U = 4260, p<0.05).

Thus, the experience of an oncological disease shapes a distinct system of evaluations, shifting the focus of perceived distress from financial difficulties and general stress onto systemic problems: the perceived threat from working conditions and, most critically, the catastrophic inaccessibility of timely and high-quality medical care, which exacerbates the course of the disease and creates an atmosphere of constant struggle.

Conclusion

1. Despite a nationwide positive trend of decreasing breast cancer mortality and improved early-stage diagnosis, the situation in the Far Eastern Federal District, and in particular, the Khabarovsk Territory, remains challenging. The identified discrepancies between the relatively low officially registered incidence, high mortality, and problems with follow-up care indicate systemic under-detection and late diagnosis in the region. This negates nationwide achievements and necessitates the development of differentiated approaches to organizing medical care, taking into account geographical and logistical specificities. The validity of this conclusion is based on the consistency of official statistics and epidemiological patterns.

2. The conducted study revealed a complex interplay of similarities and differences in the medico-social characteristics between women with breast cancer and the control group in the Khabarovsk Territory. While statistically significant differences (p < 0.05) were found for age (mean age in the breast cancer group was 6.5 years higher), level of comorbidity (50.0±5.0% vs. 11.0±3.1%), and socioeconomic status (a significantly higher percentage of unemployed individuals was recorded in the breast cancer group), the groups were comparable in terms of education level and geographical distribution. In both groups, the proportion of residents living in large regional cities was approximately 60.0±4.8%, indicating homogeneity of the samples for this parameter.

3. The analysis revealed the complex nature of behavioral and reproductive risk factors for breast cancer. Statistically significant differences (p < 0.05) confirm the key role of endocrine background, manifested in a significantly more frequent history of hormonal disorders, irregular menstruation, and use of hormone replacement therapy (HRT), as well as a family history of the disease. At the same time, factors such as smoking and alcohol consumption did not demonstrate a significant difference between the groups; however, the high proportion of evasive answers among breast cancer patients may indicate an underestimation of their actual contribution. The subjective perception of lifestyle appears to be important: women with breast cancer were significantly more likely to rate their working conditions as negative and their income level as low. This, along with identified dietary peculiarities and increased adherence to physical activity *after* diagnosis, paints a multifaceted picture of behavioral patterns associated with the disease.

The obtained data, which are statistically significant (p < 0.05), indicate low accessibility and timeliness of medical care for female oncology patients. The current situation is characterized by significant obstacles in organizing follow-up care (only 7.0±2.5% of patients visited a doctor annually), widespread difficulties in scheduling diagnostic procedures (encountered by 90.0±3.0% of respondents), and critically long waiting times for hospitalization. For the majority of patients (61.0±4.8%), inpatient treatment began a month or more after it was prescribed. These facts point to a profound gap between the needs of patients and the actual capabilities of the healthcare system.

The authors declare no conflict of interest.

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SCIENTIFIC REVIEWS

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VEGFA GENE POLYMORPHISMS AND THE RISK OF MALIGNANCIES OF THE FEMALE REPRODUCTIVE SYSTEM: A META-ANALYSIS

Malignant neoplasms of the reproductive system are the leading cause of cancer mortality among women. Vascular endothelial growth factor (VEGF) is one of the most important factors in the malignancy process, but association of its gene polymorphisms with the risk of developing reproductive organ cancers remain contradictory. Polymorphisms in the *VEGFA* gene promoter region (rs2010963, rs699947) are functionally significant and associated with increased protein expression, which enhances angiogenesis. The rs3025039, located in the 3'-UTR, influences post-transcriptional regulation of the gene. **The aim of the study** was to compare the association of rs2010963, rs699947 and rs3025039 polymorphisms of the *VEGFA* gene with the risk of developing malignant neoplasms of the female reproductive system using a meta-analysis method. **Materials and Methods**. A systematic literature search of domestic and international databases identified 15 case-control studies. Statistical analysis was performed using a random-effects model. **Results.** A significant increase in the risk of female reproductive system cancers was associated with the minor alleles of *VEGFA* polymorphisms rs2010963 (OR = 1.24; 95% CI: 1.09–1.41; p = 0.0008) and rs699947 (OR = 1.16; 95% CI: 1.04–1.28; p = 0.0058). No such association was identified for rs3025039. The analysis indicated substantial heterogeneity among the included studies. **Conclusion.** The results of the meta-analysis confirm the role of *VEGFA* gene polymorphisms in modulating the risk of female reproductive system cancer and indicate the need to consider ethnic and nosological characteristics in further research.

Keywords: VEGFA, rs2010963, rs699947, rs3025039, polymorphism, meta-analysis, gynecologic malignancies.

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One gene whose protein product may potentially be involved in malignant growth is *VEGFA* (Vascular endothelial growth factor A) [16]. This gene is located on chromosome 6p21.1 and is over 16 kb in size; its coding region consists of 8 exons and 7 introns [26]. The VEGF family consists of five homologous members: VEGF-A (commonly known as VEGF), VEGF-B, VEGF-C, VEGF-D, and placental growth factor [12]. Vascular endothelial growth factor A (VEGFA), encoded by the *VEGFA* gene, plays a critical role in angiogenesis. Angiogenesis is a key process for tumor growth and metastasis. Therefore, the *VEGFA* gene and its products are of considerable interest in the context of oncology [7, 8]. Single-nucleotide polymorphisms of this gene may serve as potential markers of oncogenesis. The rs2010963 (c.-634C>G) polymorphism, located in the promoter region of the *VEGFA* gene, is functionally significant and may affect protein expression levels [9]. There is literature data on increased plasma VEGFA levels with this single-nucleotide substitution [13]. Experimental data indicate that genetic variability in the regulatory regions of the *VEGFA* gene can influence cancer risk and the progression of tumors that rely on angiogenesis. The c.-634C>G allele (rs2010963) can affect translation by potentially enhancing the efficiency of translation initiation, leading to increased VEGFA production [9]. The variable locus rs3025039 C>T of the *VEGFA* gene is located in the 3'-UTR region and can affect post-transcription processes and gene expression [27]. It has been reliably studied that rs3025039/*VEGFA* affects the secreted levels of VEGFA protein and in most studies has been identified as having a clear association with the risk of developing cancer [18]. The rs699947 is localized in

the promoter region of the *VEGF* gene and is associated with the substitution of cytosine for adenine at position 2578 of cDNA. The presence of the A allele of rs699947 was found to be significantly associated with increased *VEGF* expression [11]. A number of studies have demonstrated the contribution of these polymorphisms to the development of malignant neoplasms of the female reproductive system [2,3,4,10,14, 17, 19, 21, 23, 24, 29]. However, the results of these studies remain contradictory. A meta-analysis summarizing the results of these studies is necessary to obtain a single statistically valid assessment.

The aim of the study was to compare the association of rs2010963, rs699947 and rs3025039 polymorphisms of the *VEGFA* gene with the risk of developing malignant neoplasms of the female reproductive system using a meta-analysis method.

Materials and Methods. Literature Search and Selection. For each polymorphism (rs2010963, rs699947, rs3025039), an independent systematic search was conducted in PubMed, Web of Science, Google Scholar, CyberLeninka, and Elibrary. Search queries included combinations of keywords related to the *VEGFA* gene and its polymorphisms (including alternative designations: *VEGF* -634G>C, *VEGF* -2578C>A, *VEGF* 936C>T) and gynecologic malignancies (ovarian cancer, endometrial cancer, cervical cancer). The search was limited to human studies with no language or publication date restrictions. Inclusion criteria: case-control studies containing data on genotype distribution in patients with gynecologic

Table 1

Main characteristics of the studies included in the meta-analysis

First author	Year	Nosology	Country	Population	Case (n)	Control (n)	Minor allele frequency	
							(cases)	(control)
rs2010963/*VEGFA*								
А.В. Рогалев [7]	2023	Cervical cancer	Russian Federation	Eastern European	120	112	41.25	30.8
A. Madrid-Paredes [23]	2020	Breast cancer	Spain	Mediterranean	80	123	32.50	33.33
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	45.75	37.36
Д.Р. Долгова [1]	2019	Ovarian cancer	Russian Federation	Eastern European	87	70	37.93	22.86
R. James [17]	2014	Breast cancer	India	South Asian	200	200	33.50	35.25
J. Rahoui [24]	2014	Breast cancer	Morocco	North African	70	70	39.29	27.14
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	41.84	40.70
rs699947/*VEGFA*								
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	23.94	25.46
A. Madrid-Paredes [23]	2020	Breast cancer	Spain	Mediterranean	80	123	41.88	51.63
Al Balawi I.A. [10]	2018	Breast cancer	Saudi Arabia	Arabian	100	100	40.50	27.50
M. Rezaei [25]	2016	Breast cancer	Iran	Near Eastern	250	215	42.00	33.02
J. Rahoui [24]	2014	Breast cancer	Morocco	North African	70	70	34.29	44.29
S. Zidi [29]	2014	Cervical cancer	Tunisia	North African	86	124	40.70	31.05
В.И.Коненков [4]	2012	Breast cancer	Russian Federation	Eastern European	389	287	52.44	45.64
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	24.37	25.83
Y. Li [21]	2010	Ovarian cancer	China	East Asian	303	303	25.91	22.44
rs3025039/*VEGFA*								
Андреева Е.А. [3]	2025	Ovarian cancer	Russian Federation	Eastern European	205	259	15.85	16.41
Bricia M Gutiérrez-Zepeda [14]	2024	Breast cancer	Mexico	Latin American	231	201	31.17	21.89
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	16.22	19.45
M. Rezaei [25]	2016	Breast cancer	Iran	Near Eastern	250	215	15.00	13.95
R. Kapahi [19]	2014	Breast cancer	India	South Asian	192	192	9.90	5.73
В.И. Коненков [4]	2012	Breast cancer	Russian Federation	Eastern European	389	241	16.58	15.56
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	18.18	20.33
Y. Li [21]	2010	Ovarian cancer	China	East Asian	303	303	16.17	18.15

malignancies and in the control group. Exclusion criteria were duplicate data, lack of full text or required genotype frequency data, and non-compliance with Hardy-Weinberg equilibrium ($p<0.05$). The final analysis included 7 studies for the rs2010963 polymorphism, 9 studies for rs699947, and 8 studies for rs3025039. The main characteristics of the studies included in this meta-analysis are presented in Table 1.

Statistical Analysis of Study Results. An independent meta-analysis was conducted for each polymorphism using a random-effects model. Associations were assessed by calculating the pooled odds ratio (OR) with a 95% confidence interval (CI) within an additive model. Heterogeneity among studies was assessed using the I^2 statistic. Statistical analysis was performed in MC Office Excel.

Results and Discussion. The meta-analysis included data from 15 studies, comprising 2,771 cases of gynecological cancer and 2,698 controls. The results of the meta-analysis are presented in Table 2.

The meta-analysis revealed a statistically significant association with the risk of gynecological cancer for two polymorphic loci, rs2010963 and rs699947, of the *VEGFA* gene. The presence of the minor allele C of the rs2010963 polymorphism was associated with a 24% increased risk (OR = 1.24; 95% CI: 1.09–1.41; p = 0.0008). For the rs699947 polymorphism, the pooled OR was 1.16 (95% CI: 1.04–1.28; p = 0.0058), corresponding to a 16% increased risk. For the rs3025039 polymorphism, no statistically significant association was found (OR = 1.05; 95% CI: 0.92–1.18; p = 0.4487). Since the rs2010963 and rs699947 polymorphic loci are located in the promoter region, their effect on *VEGFA* expression and, consequently, on the intensity of angiogenesis seems to be the most likely mechanism for increasing the risk. The rs3025039, located in the 3'-UTR, may have a less significant regulatory effect. The available literature data are limited to meta-analyses focused on individual nosological forms [15,28]. The present study offers a comprehensive assessment of the associations of *VEGFA* polymorphisms for a heterogeneous group of malignant neoplasms of the reproductive system as a whole, which is a poorly studied area. Moderate to high heterogeneity (I^2 = 59.1% - 70.5%) was observed for all analyses, indicating variability in effect size between studies. The observed level of heterogeneity may be associated with ethnic differences in the populations and the diversity of disease entities in the pooled sample.

Table 2

Results of the meta-analysis of associations of *VEGFA* gene polymorphisms with the risk of gynecological malignancies

Polymorphism	Number of studies (case/control)	Pooled OR (95% CI)	P-value	I^2, %
rs2010963	7 (1015/1063)	1.24 (1.09–1.41)	0.0008	59.8
rs699947	9 (1736/1710)	1.16 (1.04–1.28)	0.0058	70.5
rs3025039	8 (2028/1899)	1.05 (0.92–1.18)	0.4487	59.1

Conclusion. The rs2010963 and rs699947 polymorphisms of the *VEGFA* gene are significant risk factors for female reproductive system cancers and can be considered candidate markers for the development of genetic predisposition profiles. The identified heterogeneity necessitates validation of the obtained data in large, homogeneous cohorts, separating the samples by disease entity and ethnicity.

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The authors declare no conflict of interest.

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APPROACHES TO THE TREATMENT OF AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIAS

This article is devoted to prospects for treating neurodegenerative diseases caused by dynamic mutations, based on published studies searching for therapeutic approaches to spinocerebellar ataxias. Although these diseases are incurable, research results show that some medications and physiotherapy can alleviate symptoms of cerebellar ataxia. Thanks to progress in the study of spinocerebellar ataxias in recent years, there is considerable hope that gene-therapy methods can be developed that will slow disease progression or even halt it.

Keywords: spinocerebellar ataxia, dynamic mutations, treatment, gene therapy, physiotherapy

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Introduction. Autosomal dominant spinocerebellar ataxias (ADSCA) represent a large heterogeneous group of hereditary ataxias, currently including about 40 types that differ by geno-phenotypic manifestations [18, 55]. ADSCAs are numbered chronologically as the genes responsible for the disease are discovered; for example, SCA47 was recently described by Gennarino V. et al., 2018 [5,30]. The most studied are SCA1, SCA2, SCA3, SCA6, SCA7, SCA17. Certain ADSCA forms are known to be concentrated in particular world populations: SCA1 in the Yakut population [3,31,63]; SCA2 in the Indian population [56]; SCA3 in Portuguese, Brazilian and Chinese populations [27].

Characteristic clinical signs of ADSCA are slowly or rapidly progressive dysarthria, oculomotor disorders and gait ataxia, and impaired coordination. The cerebellum, brainstem and spinal cord undergo neurodegeneration [1].

A common feature of all ADSCA subtypes is the presence of an unstable (dynamic) mutation caused by expansion of CAG repeats in the coding region of a gene, leading to formation of a polyglutamine (polyQ) tract in the encoded protein [43,55]. There is a relationship between age at onset and severity of neurological symptoms and the size of the polyQ-repeats expansion [45]. The expanded polyglutamine tract causes synthesis of a misfolded, aggregation-prone protein which, at advanced stages of aggregation, disrupts regulation of gene expression at the transcriptional level and leads to disturbance of neuronal homeostasis [26].

Table 1. Various ADSCA diseases with polyglutamine mutations.

The Republic of Sakha (Yakutia) is a region with the highest accumulation

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of autosomal-dominant ataxia type 1 (SCA1). Epidemiological, population, molecular-genetic and bioethical studies of this socially significant neurodegenerative disease have been conducted earlier [3,31,63].

Currently there is no treatment for hereditary neurodegenerative diseases with polyglutamine mutations, but it is necessary to discuss directions for improving patient condition.

At present there are three main therapeutic approaches to ADSCA:

- symptomatic treatment using known pharmaceutical agents [18,38];
- gene methods or gene-edited products to reduce toxic consequences of polyglutamine mutations [22,27,43];
- neurorehabilitation [14].

Most studies related to SCA pathogenesis are carried out using populations of transgenic mice that overexpress mutant and normal transgenes (the latter as controls) [6]. In addition, studies are performed directly in Purkinje cells of mice with gene knock-outs using genetic vectors carrying large segments of the human gene with expanded polyglutamine sequences and regulatory elements [6,32,43].

Studies on the Use of Certain Pharmacological Agents in ADSCA Therapy. The main cellular disturbances in the cerebellum (Bergmann glia, Purkinje cells) targeted by therapeutic strategies are:

- disrupted expression and function of ion channels and receptors [32];
- excitotoxicity, where excessive accumulation of glutamate in the extracellular space (synaptic cleft) causes toxicity to neurons [2,33];
- decreased levels of potassium-calcium channels in Purkinje cells [19].

Studies of 3,5-dimethyladamantane-1-amine (memantine) for possible neuroprotective effects and synaptic plasticity with long-term use in SCA1 model mice (Belozor et al., 2024) showed that memantine increases expression of amino-acid transporter proteins, thereby reducing reverse glutamate uptake and enhancing signaling within Purkinje cells. It is claimed that memantine reduces anatomical signs of neurodegeneration in SCA1 model mice and partially ameliorates the ataxic phenotype; at the same time it also affects cerebellar plasticity and impairs motor learning. The authors suggest that clinical use of memantine in SCA1 may be complicated by its suppression of cortical plasticity [2,38,46].

Kalla R. & Strupp M., 2019, in recent studies showed the promise of obtaining a neuroprotective effect in SCA1 treatment with 4-aminopyridine. In SCA1 mouse models motor activity was disrupted due to decreased electrical activity (firing rate) in Purkinje cells, their dysfunction and atrophy. Nonselective blockade of voltage-dependent potassium channels with 4-aminopyridine increased Purkinje cell excitability, partially protected against cell atrophy and improved motor behavior of the animals [8,36].

Over the last ten years there has been intensive research and clinical trials of the amino acid derivative acetyl-DL-leucine in symptomatic therapy of different SCA types. Acetyl-DL-leucine regulates the membrane potential of Purkinje cells by interacting with membrane phospholipids. In a series of clinical trials across different research groups, modified acetyl-DL-leucine improved ataxia and dysarthria in patients with SCA1, SCA2, SCA3, SCA6 [54,64,65].

Another therapeutic strategy is studying mechanisms of autophagy in the cell, by which excess or damaged proteins and organelle structures are degraded by enzymes and removed from the cell; this may become a new approach to ADSCA therapy. It has been shown that enhancing autophagy in cells of mouse models reduced neurodegeneration and eased the course of SCA3 [10,41]. For example, in SCA3 excessive polyglutamine repeat length causes misfolding of ataxin-3 and formation of aggregates that disrupt cellular processes, cause cellular toxicity and degeneration [42,60]. This protein is toxic; one of the main pathways for degradation of misfolded proteins is autophagy [42]. Burnett et al. suggest that the ubiquitin–proteasome pathway, where ataxin-3 is involved, plays a key role in the development of neurodegenerative diseases characterized by misfolding and aggregation of proteins [13]. The deubiquitinating active ataxin-3 is widely expressed in the brain. The polyQ domain of ataxin-3 binds the Beclin-1 (BECN1) protein, which initiates autophagy [42,44].

Cellular repair systems and mitochondrial energy production become active under caloric restriction. Food shortage engages protective systems of the organism and activates autophagy. The beneficial effects of fasting observed in mice remain to be confirmed in patients with neurodegenerative diseases [59,60]. The well-known protein sirtuin 1 (SIRT1) induces autophagy and suppresses neuroinflammation. In a study by Zhu L. et al., 2025, the dietary supplement resveratrol was shown, via activation of SIRT1, to influence core mechanisms of neurodegeneration. As a result of SIRT1 activation by resveratrol, oxidative stress, mitochondrial dysfunction and protein aggregation decrease, while neuronal survival and function and neuroinflammation improve [35].

The widely consumed and well-known compound 1,3,7-trimethylpurine-2,6-dione (caffeine) has recently been studied as an effective protective agent in some neurodegenerative disorders. Caffeine is a nonselective antagonist of adenosine receptors (A2A). These receptors participate in synaptic viability, neuroinflammation and neuronal apoptosis. Inactivation of A2A receptors reduces neurodegeneration, making caffeine a potential therapeutic candidate for neurodegenerative diseases [11,47].

Potential Gene-Therapy Methods for Neurodegenerative Diseases. Gene-therapy strategies are developing along several directions:

- regulation of gene expression using RNA interference with small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs) and microRNAs (miRNAs) to target and degrade mRNA molecules. Gene silencing occurs via a multiprotein ribonucleoprotein complex [29,53];
- application of targeted therapies based on antisense oligonucleotides (ASOs) [58];
- gene editing using CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats / associated nuclease 9) [22].

Table 2 presents results of gene-therapy methods for some types of SCAs; as a rule these are at the stage of studies in genetically modified model organisms and have not reached clinical trials. Wide use of various regulatory microRNAs is due to their universality and ability to induce or inhibit gene expression (transcription, translation, processing, etc.) [4,7,25,37,50]. The goal of gene therapy in SCA is to inhibit or remove the expanded gene region that encodes the toxic protein. Animal-model studies have shown encouraging results: reduced levels of toxic proteins, decreased degeneration of cerebellar cells, alleviation of motor deficit and overall improvement in neuropathological measures [4,7,25,37,50].

The CRISPR-Cas9 system was discovered and obtained from Streptococcus pyogenes as an adaptive bacterial immune system for protection against viruses; in this system CRISPR and guide RNAs work together with Cas proteins [9]. It turned out that this system is very convenient not only for various genomic modifications in research, but also for

Table 1

Various ADSCA diseases with polyglutamine mutations [30]

name	gene	locus	protein	repeats	number of repeats of normal alleles	number of repeats of intermediate alleles	number of repeats
SCA1	*ATXN1*	6p22.3	Ataxin-1	$(CAG)_n (CAT)_n (CAG)_n$	of pathological alleles	36-38	39-91
SCA2	*ATXN2*	12q24.12	Ataxin-2	$[CAG_n CAA (CAG)_n]_n$	14-31	32	33-500
SCA3	*ATXN3*	14q32.12	Ataxin-3	CAG2 CAA AAG CAA $(CAG)_n$	11-44	45-59	60-87
SCA6	*CACNA1A*	19p13.13	CACNA1A	(CAG)n	4-18	19	20-33
SCA7	*ATXN7*	3p14.1	Ataxin-7	(CAG)n	4-19	28-33	34-460
SCA17	*TBP*	6q27	TBP	[(CAG)n (CAA)n (CAG)n]	25-40	-	41-66

Note. (CAG)n – cytosine-adenine-guanine repeats; CAT – cytosine-adenine-thymine stop codon; CAA – cytosine-adenine-adenine-stop codons; AAG – adenine-adenine-guanine-stop codon.

gene therapy via selective targeting of the eukaryotic cell genome [39]. Delivery of CRISPR-Cas9 components into target cells occurs as a ribonucleoprotein consisting of the Cas9 protein and an sgRNA — single-guide RNA [9,21,39].

A case of deleting the coding poly-Q region using CRISPR/Cas9 gene-editing was described by Ouyang S. et al., 2018. For the first time the authors provided preliminary data for CRISPR/Cas9 editing in SCA3 in the ATXN3 gene and showed the possibility of using a pair of single-guide RNAs to delete the expanded polyglutamine region of the gene [22].

In the study by He et al., 2021, in induced pluripotent stem cells (iPSCs) derived from a patient with SCA3, using paired single-guide RNAs and a homology-directed repair strategy, they successfully repaired 74 CAG expansions in exon 10 of ATXN3, leading to specific and effective suppression of mutant ataxin-3 protein expression [23]. Using CRISPR/Cas9 with homology-directed repair, Song et al., 2022 developed effective approaches for one-step genetic correction of patient-derived SCA3 iPSCs. They later advanced their research by developing disease models in disease-relevant neurons differentiated to cerebellar phenotypes [24]. The study by Pappadà et al., 2022 allowed development and validation of a therapeutic approach using CRISPR/Cas9 for fibroblasts obtained from patients with SCA1. This sgRNA/Cas9 method effectively reduced production of both normal and mutant ATXN1 protein [52].

Neurorehabilitation as an Adjunctive Therapy for SCA. Researchers conducting clinical studies in neurodegenerative diseases suggest that cerebellar changes are associated with significant cognitive and affective deficits in ADSCA patients due to degeneration of the cerebellum and its connections [17,61,62].

Antal, 2022 described in detail non-invasive brain stimulation methods for studying brain function in healthy people and the possibility of improving cognitive processes using these methods [40]. Methods such as transcranial magnetic stimulation (TMS) and transcranial direct-current stimulation (tDCS) are used to accelerate neuropsychological or psychiatric rehabilitation by modulating neuroplasticity. In TMS protocols, a coil placed over the scalp delivers a brief high-amplitude current generating a magnetic pulse that induces a brief electric current on the brain surface beneath the coil. At sufficient intensity a single

Table 2

Examples of gene therapy for some SCAs [30]

disease	method	model system	effect
SCA1	Created microRNA containing siRNA	mice SCA1 K1	Improvement of neuropathology parameters and reduction of ATXN 1 protein levels by 58-72% [50].
SCA2	AON: decreased levels of ataxin-2 protein	mice ATXN2 , BAC-Q72 SCA2	A 75% reduction in ATXN2 protein levels in mouse brain Purkinje cells and significant improvement in motor phenotype [7].
SCA3	shRNA: allele-specific downregulation	rats SCA3	Reduction of neuropathological abnormalities [4]
SCA6	miRNA-3191-5p	mice SCA6 K1	Alleviation of motor deficits and Purkinje cell degeneration [37]
SCA7	miRNA-124	Cells N2A and mice SCA7	80% reduction in ATXN7 protein levels [25]
SCA3	CRISPR/Cas9	Neurons derived from patient-specific immunopluropatent stem cells	Successful removal of the polyQ coding region [22]

Note. AON – antisense oligonucleotide; iPSCs – immunopluropatent stem cells; mi RNA – short RNA; si RNA – short interfering RNA; sh RNA – short hairpin RNA

TMS pulse elicits highly synchronized action potentials in the target area (Fig. 1). Ten or more minutes can lead to modulatory effects that extend the period of stimulation for many minutes or hours, with more pronounced behavioral effects often observed immediately after the end of stimulation [51].

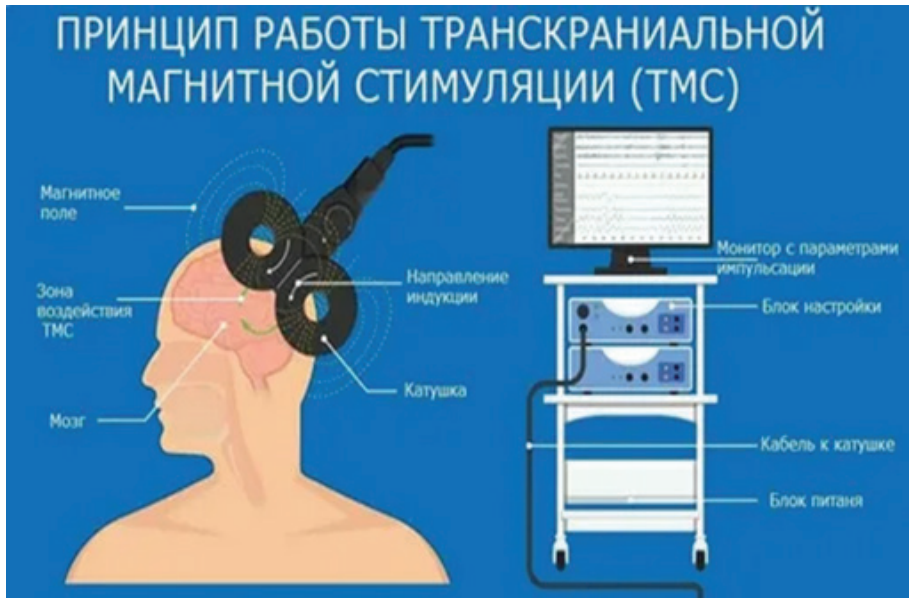
Some data indicate TMS effectiveness in treating core symptoms and cognitive functions in various neurological and neuropsychiatric disorders, as well as in improving behavioral and socio-affective deficits [16,30].

Farzan F. et al., 2013 provide evidence for cerebellar stimulation as a treatment strategy for degenerative cerebellar ataxia. Observed improvements in physical function, gait kinematics and coordinated muscle contraction, as well as cerebellar–cortical interactions, were fairly convincing. However, the authors noted that the study lacked control participants and control conditions, and they emphasized the need for further controlled studies to examine the effects of TMS in SCA patients [15].

The aim of the study by Maas et al., 2022 was to determine whether a two-week regimen of daily cerebellar tDCS sessions reduces ataxia and severity of nonmotor symptoms and whether it changes cerebello–M1 connectivity in individuals with spinocerebellar ataxia type 3 (SCA3). Change in the Scale for the Assessment and Rating of Ataxia (SARA) after two weeks was the primary endpoint. After the final stimulation session both groups showed significant short-term improvements in several motor, cognitive functions and patient-reported outcomes, but no treatment effect in favor of active tDCS was found. Some patients in the intervention group showed sustained reduction in SARA scores for six or even twelve months, indicating individual variability in treatment response [16].

The main adjunctive neurorehabilitation method for patients with cerebellar ataxia is therapeutic physical exercise (physiotherapy), so mechanisms by which aerobic training and balance exercises improve cerebellar ataxia symptoms have been studied more closely.

In Burciu, 2013, postural and clinical assessments as well as structural magnetic resonance imaging were performed before and after training. The main results were: first, training improved balance measures in patients with cerebellar damage. Second, unlike the control group, patients showed a significant increase in gray-matter volume in the dorsal premotor cortex after training. Third,



Transcranial magnetic stimulation

associated with training there was an increase in cerebellar gray-matter volume that was more pronounced in the control group than in patients [12].

Recent studies provide evidence that intensive motor training can be effective in degenerative ataxia: coordination training — via physiotherapy or game-based exercises — benefits ataxia patients; improvements result from remediation of ataxia-specific deficits rather than nonspecific changes; maintenance of training effects depends on continued training; even patients with progressive neurodegeneration benefit from these treatments. This research asserted that intensive aerobic training is safe for people with cerebellar ataxia, with high participant engagement and adherence. Home aerobic training for people with cerebellar ataxia may be more effective against ataxia than balance training, because aerobic exercise may induce neuroplastic changes in the degenerating cerebellum [28,34,49,57].

Conclusion. There is currently intensive growth of ADSCA gene-therapy related research. Animal studies have shown promising results: reduced levels of toxic proteins, decreased degeneration of cerebellar cells, alleviation of motor deficits and overall improvement in neuropathology.

On the one hand, these diseases are incurable, but on the other hand studies show that known pharmaceuticals, dietary supplements, noninvasive transcranial neuromodulation and physiotherapy are alternative treatment options and can alleviate ataxia symptoms.

Thanks to progress in SCA research in recent years, there is strong hope that therapies can be developed that will slow disease progression or even halt it.

Авторы заявляют об отсутствии конфликта интересов.

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CLINICAL AND MORPHOLOGICAL FEATURES OF DESMOID TYPE FIBROMATOSIS

In order to study the clinical and morphological features of fibromatosis of the desmoid type, a literature review was conducted. It was found that fibromatosis of the desmoid type is a locally ag-gressive myofibroblastic tumor that occurs in muscular-aponeurotic structures. The clinical picture is affected by the localization of the tumor and its invasive growth into the surrounding tissues.

The complexity of diagnosis is due to the rarity and morphological similarity to soft tissue sar-comas. Immunohistochemical research is used to exclude malignancy. It was found that the features of fibromatosis of the desmoid type are characterized by pronounced diffuse nuclear expression of beta-catenin, reactions to DOG1, CD117, S-100 and SMA are negative.

Keywords: fibromatosis, desmoid tumor, immunohistochemistry, morphological features

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Introduction. Desmoid tumors (synonyms: desmoid fibromatosis, aggressive fibromatosis, desmoid fibroma) are rare connective tissue neoplasms [6, 24] with an intermediate degree of malignancy [5], arising in deep soft tissues [10] and characterized by locally aggressive growth [5, 6]. They can reach 5-20 cm in diameter [16] and lead to compression or invasion of adjacent structures [2, 6]. The growth pattern of this tumor is variable: it can gradually increase, remain stable, or in some cases spontaneously regress [10].

Desmoid tumors (DT) have a low incidence: from 2-4 [10, 29] to 5-6 cases per year per million people [11, 27], which is approximately 0.03% of all tumors [9, 10, 16, 29] and less than 3% of soft tissue tumors [15, 17]. It should be noted that from 3.5% to 32% of cases are associated with familial adenomatous polyposis (FAP) [5, 10, 11, 27].

These tumors do not metastasize. About 20% arise in the abdominal cavity (the mesentery of the small intestine is most often affected) [13, 28], 16% on the abdominal wall (more often in women during or after pregnancy) [13] and 64% are extraperitoneal localizations (extremities, pelvic girdle, chest, head and neck) [13, 27]. DT can also affect the urinary system [18], mammary [12] and pancreas [28].

DT of the abdominal cavity usually present in two forms: large, dense formations that are palpable or sheet-like white plaques found in the mesentery [16]. DT is 2-3 times more common in women than in men [8, 27]. Most patients are diagnosed between the ages of 15 and 60 years [20], with the peak incidence occurring between the ages of 30 and 40 years [5, 20, 27]. Thus, the population of patients with DT includes a significant number of women of reproductive age (70%) [5, 23, 30, 31]. In turn, low incidence is observed in children, with its peak occurring between the ages of 5 and 8 years [2].

The low prevalence of this pathology limits awareness of it [8]. In turn, diagnosis is complex due to morphological heterogeneity and variability of clinical manifestations [8, 18].

Treatment of DT is a challenge for healthcare due to their diverse clinical presentation and unpredictable disease course [6] with cycles of tumor progression, stabilization [26], and spontaneous regression [17] observed in 20-30% of patients within 2-3 years [31]. All this affects the quality of life, as well as daily activities in some patients [6].

The aim of our study is to analyze publications devoted to the study of clinical and morphological features of desmoid fibromatosis.

Materials and methods. In this review, we examined the literature on desmoid fibromatosis. We searched PubMed, Web of Science, and Google Scholar for the period 2020–2025. Search terms included fibromatosis, desmoid tumor, immunohistochemistry and morphological features.

A microscopic method conducted at the Belgorod Pathological Anatomy Bureau was also used during our own research. The material was fixed in 10% neutral buffered formalin for 24 hours, then it underwent histological processing in a Thermo Scientific Excelsior AS closed-loop histoprocessor (sequential dehydration, degreasing, and tissue impregnation with paraffin). Sections of 4 μm thickness were cut from the prepared paraffin blocks using a Thermo Scientific HM340e semiautomated rotary microtome. The sections were stained with hematoxylin and eosin, and antibodies manufactured by Cell Marque (USA) were used for immunohistochemical examination: beta-catenin (clone E247), CD117 (clone YR145), DOG1 (clone SP31), S-100 (clone 4C4.9), SMA (clone 1A4).

Results and discussion. Desmoid fibromatosis (DF) is a locally aggressive

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myofibroblastic tumor [18] that arises in musculoaponeurotic structures [21, 22]. The World Health Organization (WHO) defines desmoid as a clonal fibroblastic proliferation that arises in deep soft tissues, characterized by infiltrative growth and a tendency to local recurrence without the ability to metastasize [11, 22, 23].

The term "desmoid tumor" was introduced in 1838 by Mueller and comes from the Greek term desmos, indicating its consistency and resemblance to tendons [4, 11]. However, the first description of this disease was made in 1832 by MacFarlane [11].

The etiology of DF is not fully understood [11, 23] and genetic, endocrine and physical factors play a decisive role in the development and growth of the tumor [9]. Depending on the etiology, DF can be divided into two groups: sporadic and familial [16, 30].

Sporadic DF occurs in 85-90% of cases, predominantly in extraperitoneal locations [11, 21] and is associated with various factors. Thus, most patients have a history of surgery or trauma [10], including breast [14], pregnancy [9], cesarean section, hormonal fluctuations [10, 14], and use of oral contraceptives [11, 21]. However, the exact role of hormonal influences has not been fully studied [19, 23].

In contrast, the familial form of DF is an autosomal dominant inherited form associated with familial adenomatous polyposis (FAP) [16]. These tumors are located predominantly in the abdominal wall or abdominal cavity, mesentery, and visceral organs [6, 11, 21, 29].

The pathogenesis of DF also remains unclear, but studies have shown that activation of the Wnt/β-catenin signaling pathway is crucial in the development of DF [9, 10, 33]. The Wnt protein plays an important role in the proliferation of mesenchymal cells. Mutations in this signaling pathway lead to the absence of the Wnt protein and disruption of the regulation of fibroblast proliferation, resulting in mesenchymal stem cells remaining undifferentiated (in a proliferative state) [16]. β-catenin is a molecule with multiple functions that are regulated by the adenomatous polyposis coli (*APC*) gene and the Wnt signaling pathway [11, 20, 30].

Most sporadic tumors are associated with a somatic [31] mutation in exon 3 of the β-catenin 1 gene (*CTNNB1*) [6, 9, 20-22, 29], most commonly at mutation sites *T41A* (50-55%), *S45F* (25-35%) and *S45P* (9-10%) [10, 11, 31].

The *CTNNB1* mutation interferes with the phosphorylation of β-catenin protein, blocking its proteasomal degradation in the cytoplasm. This leads to the accumulation of β-catenin, which translocates to the nucleus [4, 10, 31], activates transcription factors [9, 20] and forms a complex with T-cell factor/lymphoid enhancer factor (TCF/LEF), increasing the expression of target genes [10, 20], which promotes cell proliferation, differentiation, migration, and apoptosis [9].

In DF associated with FAP, a mutation in the *APC* gene is usually observed [10]. Most mutations are located on chromosome 5q21 [16], which interferes with the phosphorylation of β-catenin, leads to an increase in the amount of cytoplasmic β-catenin and increased cell proliferation [10], which ultimately leads to tumor development [9, 11, 18, 21].

The second pathway involved in the development of desmoid tumors is the Notch pathway, which is activated in response to dysregulation of the Wnt pathway [8, 14]. Overactivation of the Notch pathway in desmoid tumors can be regulated by γ-secretase inhibitors, as they block Notch signaling through selective inhibition of γ-secretase-mediated cleavage of Notch receptors [8, 9, 17].

Although DF do not metastasize, they can exhibit a wide range of clinical manifestations, including spontaneous regression, indolent progression, or potentially life-threatening organ damage [8, 32].

Clinically, the tumor appears as a dense, well-defined or poorly defined mass [4]. It should be noted that the clinical picture of DF is influenced by the location of the tumor [18] and its invasive growth into surrounding tissues. This can affect vital structures or disrupt body

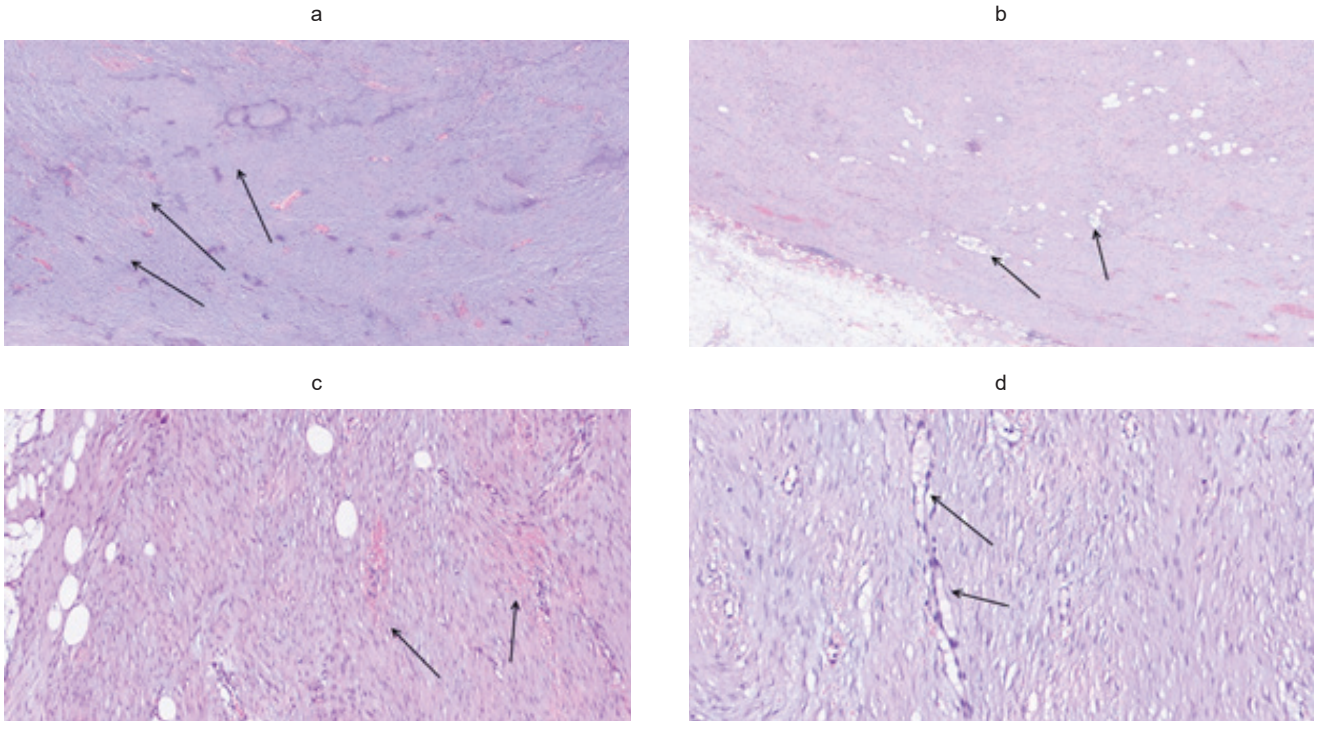

Fig. 1. Patient, born in 1955. Desmoid fibromatosis in the stomach wall. a – the tumor is represented by multidirectional bundles of spindle-shaped cells; b – infiltrative tumor growth in the fatty tissue of the omentum; c – extravascular accumulations of erythrocytes (extravasates); d – elongated capillary blood vessels (magnification a, b x50, c x100, d x200, staining: hematoxylin and eosin).

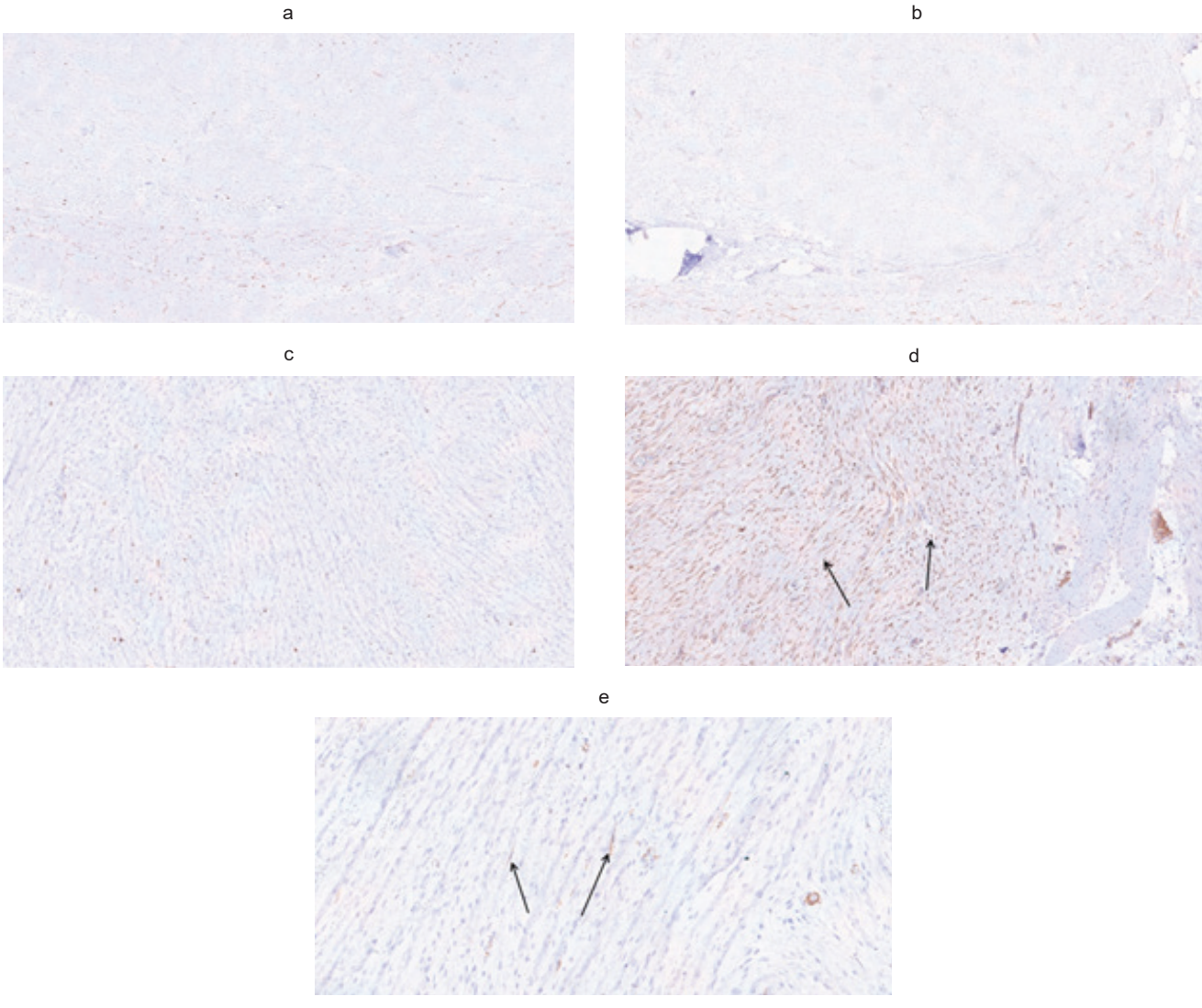

Fig. 2. Patient, born in 1955. Desmoid fibromatosis in the stomach wall. a - tumor cells lack CD117 expression (stain: antibody to CD117); b - tumor cells lack DOG1 expression (stain: antibody to DOG1); c - tumor cells lack S-100 expression (stain: antibody to S-100); d - tumor cells show diffuse nuclear expression of beta-catenin (marked with arrows, stain: antibody to beta-catenin); e - tumor myofibroblasts show weak cytoplasmic expression of smooth muscle actin (marked with arrows, stain: antibody to SMA) (magnification a, b x50, c, d x100, e x200).

functions [26], compress blood vessels and nerves [20, 31], cause paresthesia, severe pain or polyneuropathy [4, 11, 14, 25], and also destroy bones and affect muscles [31].

Thus, tumors located in the abdominal cavity grow asymptomatically until they reach a large size. They cause intestinal obstruction, ischemia and, in rare cases, perforation, bleeding [11, 24, 31], abscess [23], fistula [9], as well as flatulence, constipation [3, 9, 25], weight loss, cachexia and malaise [9, 31], ureteral obstruction and hydronephrosis [3, 15, 16]. In case of invasion of the bladder, clinical manifestations of DF are a sensation of volume with frequent urination or hematuria [18].

Extraperitoneal DF are most often localized in the head and neck region, where they affect the airways or large vessels, which can manifest as dysphonia and shortness of breath. In patients, tumors in the extremities manifest as palpable masses [23]. Limited joint mobility [5, 8, 15, 31], muscle contractures [23], problems with arm or hand movement, lameness, or other movement disorders may also be observed [17].

In addition, specific symptoms of DF may negatively impact (everyday life): study, work, psychosocial functioning [8, 15, 25], cognitive and emotional spheres [31]. Fatigue, insomnia, anxiety and depression may be observed [5]. In rare cases, a fatal outcome is possible [26], which is due to the local aggressiveness of the tumor, especially with intraperitoneal location [16].

FAP is associated with adenomatous polyps of the colon (tubular, villous, tubulovillous), adenomatous polyps of the stomach and small intestine, and a risk of developing periampullary carcinomas. In addition, osteomas and various types of skin lesions (fibromas, neurofibromas, pigmented skin lesions) are observed in 50% of cases, occurring in almost two-thirds of patients [16].

Tumors associated with FAP usually progress more aggressively and present 10 years earlier as larger multifocal tumors than in the sporadic variant [11].

Accurate differential diagnosis is a serious challenge due to its rarity and numerous histological and clinical similarities with other soft tissue sarcomas. According to some authors, the misdiagnosis rate during initial examination can reach 30-40% [5, 24].

Macroscopically, DF appear as dense, uneven, elastic [16] formations of gray or white color, elongated in the direction

of muscle fibers and resembling fibrous scar tissue [11, 16, 31]. A cross-section reveals a shiny white surface with a rough trabecular structure [16].

The histological hallmark of DF is a heterogeneous, poorly defined [11] and uniform proliferation of elongated spindle-shaped cells with rare mitotic figures [29] that resemble myofibroblasts embedded in a collagen-rich stroma and unencapsulated vasculature. Atypia, necrosis or mitoses are typically absent. The nuclei may contain euchromatin or heterochromatin [11, 18, 24, 31]. In turn, the proliferation of cells without clear boundaries with uneven collagen deposition may mimic the proliferative phase of wound healing [14, 19]. These tumors are unencapsulated and infiltrate surrounding tissues, often merging with adjacent normal structures [2] and demonstrating intratumoral heterogeneity [14].

Our study is consistent with the authors' opinion, since DF consists of multidirectional bundles of spindle-shaped cells, elongated capillary-type blood vessels, and extravascular accumulations of erythrocytes (fig. 1 a-d).

Immunohistochemical testing for specific cellular markers of various origins is an effective method for differentiating DF from other tumors. DF has characteristic immunohistochemical features, primarily nuclear staining of β-catenin, to be considered positive [14, 19, 28], and can also be positive for vimentin and smooth muscle actin, indicating their fibroblast origin. Their mitotic activity is usually low and they do not have marked nuclear atypia or necrosis, which distinguishes them from malignant sarcomas [2, 18], cyclooxygenase-2 (COX-2) and often β-estrogen receptors [31], androgens [11, 16] and negative expression of CD34, CD117, S-100 and SMA, which excludes gastrointestinal stromal tumor, schwannoma, leiomyoma and leiomyosarcoma, respectively [16, 19, 23, 28].

The results of our immunohistochemical study are consistent with the results of other authors; thus, diffuse nuclear expression of beta-catenin is detected in tumor cells; reactions to DOG1, CD117, S-100 and SMA are negative (Fig. 2 a-e).

Due to the unpredictable course of DF, it resolves on its own in 20-28% of cases, remains stable in 32-60% of cases, and progresses in 20-40% of cases [6]. Due to possible spontaneous tumor regression, dynamic observation of asymptomatic patients is recommended [20]. Until the 2010 [7], the main method of treating this pathology was surgery [1]. It should be noted that resection of locally aggressive tumors without clear borders [13] and invasive growth patterns [28] leads to local recurrences in more than 40% of cases [7], and also negatively affects local soft tissue structures, including muscles, nerves, or blood vessels, which can lead to more serious complications [13]. Risk factors for recurrence include patient age under 30-37 years, tumor size greater than 5 cm in diameter, and a history of trauma in the area of the primary tumor [13].

In recent decades, active surveillance in combination with pain relief [18, 31, 33] has been recommended as an alternative to surgical treatment [9]. The term active surveillance was introduced in the 1990. Initially, active surveillance was offered only to patients with recurrent tumors, but after 2005, it was also offered to patients with primary tumors [1]. This approach to the management of patients with this pathology is justified, since spontaneous tumor regression is possible [1, 33] without treatment [31].

Conclusion. The analysis revealed that desmoid fibromatosis is a locally aggressive myofibroblastic tumor arising in musculoaponeurotic structures. The clinical presentation is influenced by the tumor's location and its invasive growth into surrounding tissue.

The diagnosis is challenging due to its rarity and morphological similarity to soft tissue sarcomas. Immunohistochemistry is used to exclude malignancy. Desmoid fibromatosis is characterized by pronounced diffuse nuclear expression of beta-catenin, and negative reactions to DOG1, CD117, S-100, and SMA, which we confirmed in our study.

The authors declare no conflict of interest.

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THE NEUROPROTECTIVE POTENTIAL OF BILINGUALISM IN THE PREVENTION OF COGNITIVE IMPAIRMENT

This literature review analyses current scientific research that focuses on the impact of bilingualism and multilingualism on human cognitive functions. The focus is on the impact of two or more language experiences on executive functions such as inhibitory control, cognitive flexibility and working memory. The article examines the concept of «bilingual advantage» and the factors that modulate its manifestation, as well as the role of bilingualism in the formation of cognitive reserve.

Keywords: bilingualism, multilingualism, cognitive functions, neuroplasticity, cognitive reserve, neuropsychology.

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The phenomenon of bilingualism has stimulated scientific interest in studying how the experience of managing multiple language systems affects cognitive processes and brain structure.

In the context of globalization and growing cross-cultural communication, the phenomenon of bilingualism and multilingualism is attracting increasing attention from researchers in psychology, neuropsychology and neurology.

A central focus in research on the cognitive effects of bilingualism is the study of its influence on executive functions – a set of higher-order cognitive processes responsible for planning, attention control, ignoring distractions, and multitasking.

The key components of executive functions are inhibitory control, cognitive flexibility, and working memory. The "bilingual advantage" hypothesis suggests that the constant need for bilinguals to control and manage two simultaneously activated language systems, by inhibiting the irrelevant language, acts as continuous training for executive functions [32].

Numerous studies confirm the existence of this advantage. For example, the work of A.N. Veraksa and co-authors (2020) demonstrated that bilingual children exhibit higher performance in tasks requiring attentional switching and the suppression of impulsive responses compared to their monolingual peers [18].

The constant practice of switching between languages seems to develop a general ability for cognitive flexibility, that is the ability to switch between different tasks or mental settings.

Studies using non-verbal tests, such as the Stroop task or the task-switching paradigm, often show that bilinguals perform better on them, with faster reaction times and fewer errors [16]. All of the above is related to the fact that the mechanism used to inhibit one language and activate another is domain-general and extends its influence to other cognitive tasks requiring control.

However, simply being bilingual or multilingual is not enough to protect against cognitive decline. It is important to note that only certain types of so-called "active" bilingualism have the greatest impact on brain health, namely those where individuals are sufficiently exposed to their languages, use them regularly, and are actively engaged in situations that require switching between languages [14].

Bilinguals constantly face an additional cognitive load: unlike monolinguals, they have to control their languages. Research shows that all languages of bilinguals/multilinguals are constantly activated, regardless of contextual necessity or conscious intention. Lan-

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guages need to be managed to switch the choice to the one that matches the given communicative context [15], thereby avoiding unwanted interference from a contextually irrelevant language. For bilinguals, the necessity of switching between languages in the real world is dynamic, complex, and not always predictable. One might use language X or switch between languages X and Y (because the interlocutor's context allows and requires it) when someone exclusively associated with language Y enters the room or calls. However unexpected this may be, an instantaneous switch to (another) monolingual mode is required. It is argued that this constant suppression of contextually irrelevant language through substantial and continuous engagement of executive control processes "trains" the relevant cognitive skills and brain networks, making them more efficient. Indeed, this "training" has been shown to alter general processes and the underlying neural architecture directly and fundamentally [10].

However, it is worth noting that the hypothesis of the "bilingual advantage" is not universally accepted and has been subjected to active criticism in recent years. A number of studies have failed to replicate previously obtained results or have shown that the advantage only manifests under strictly defined conditions and depends on a multitude of factors, such as the age of second language acquisition, proficiency level, and sociolinguistic context [17].

Reas E.'s research revealed the "dose effect": each additional decade of active second language use reduces the risk of cognitive impairment by 20%, and proficiency in 3+ languages quadruples the likelihood of maintaining cognitive health in old age [26]. The key is not formal knowledge, but regular communicative use of languages throughout life [14].

Unlike formal education or professional complexity, bilingual experience creates a daily cognitive load comparable to continuous training. Ellen Bialystok emphasizes that it is precisely the constant switching between languages that trains the prefrontal areas, compensating for changes in the hippocampus. This explains why bilingualism affects not memory itself, but the compensatory capabilities of the frontal lobes [23].

Some authors argue that the observed differences may be attributable not to bilingualism itself, but to other confounding variables, such as socioeconomic status or cultural specificities. Thus, the contemporary discussion is shifting from the question "Does an advantage exist?" to the question "Under what conditions does it arise and through what mechanisms is it mediated?".

Advances in neuroimaging have enabled a shift from observation to the study of the neural underpinnings of bilingualism's influence. Research indicates that the experience of multilingualism leads to significant structural and functional changes in the brain, demonstrating its high neuroplasticity [2; 3].

Most studies demonstrate changes in the brains of bilinguals that topographically coincide with areas closely associated with language processing and control, memory, and executive functions [13]. MRI studies show increased efficiency of neural engagement during task performance in bilinguals, even in the absence of measurable behavioral differences [14]. More recently, neuroimaging work has demonstrated how greater bilingualism is associated with individual neuroanatomical variations and more efficient neural engagement during behavioral tasks [28].

Bilinguals exhibit increased gray matter density in regions associated with language control and executive functions, specifically the inferior parietal lobule and the dorsolateral prefrontal cortex [5; 6]. These brain areas play a crucial role in attention, task switching, and interference suppression.

Functional MRI studies suggest that bilinguals often exhibit more efficient neural network activation during cognitive tasks, implying that their brains may utilize fewer resources compared to monolinguals to achieve the same outcome [13].

The idea that bilingualism creates "cognitive noise" has long given way to the concept of structured neurocognitive training. The essence of the phenomenon lies not in the parallel storage of two linguistic systems, but in the formation of a dynamic system for suppressing interference, where the prefrontal cortex acts as an arbiter of competing signals [31]. MRI studies demonstrate that even during silent speech production, bilinguals maintain a background level of activation in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) – areas responsible for conflict resolution and the selection of relevant stimuli [20; 21]. This explains the phenomenon of neural economy: when performing non-verbal executive control tasks, bilinguals show reduced activation of control networks compared to monolinguals, indicating a more efficient allocation of resources [15].

Neurophysiological differences are also evident in information processing strategies. While monolinguals engage the right middle frontal gyrus to compensate for age-related changes, bilinguals activate the left inferior parietal lobule (IPL) [30]. The left IPL is involved in phonological and semantic processing and plays a key role in second language acquisition and vocabulary knowledge [24]. This alternative activation pattern allows for the maintenance of cognitive performance even in the presence of early degenerative processes.

Enhanced neural efficiency is a result of constant training of cognitive control networks [25]. Furthermore, studies using diffusion tensor imaging (DTI) have revealed higher white matter integrity in the corpus callosum and other tracts connecting different brain regions in bilinguals. The foregoing, thus, indicates a more sophisticated and rapid transfer of information between and within hemispheres, which is a prerequisite for the effective management of two language systems [10; 11; 12].

Diffusion Tensor Imaging (DTI) in the study by Reyhaneh Bakhtiari, Carol Bolik, and Jacqueline Cammin [7] revealed structural differences underlying functional advantages. Individuals with extensive bilingual experience exhibit:

- Increased fractional anisotropy in the inferior fronto-occipital fasciculus and superior longitudinal fasciculus, indicating enhanced myelination and axonal tract organization.
- Increased functional connectivity between nodes of the Default Mode Network (DMN) and the executive control network, with the strength of the correlation directly depending on the frequency of foreign language use.

These changes create a neuroanatomical substrate for cognitive reserve. The epidemiological study by Alladi and colleagues (2013), which included 648 patients with dementia in India, showed that the clinical manifestation of Alzheimer's disease began 4.5 years later in bilinguals than in monolinguals, regardless of education level and socioeconomic status [1]. Paradoxically, however, bilinguals with dementia showed a greater degree of atrophy in medial temporal structures compared to monolingual patients with the same symptom severity.

Neuroanatomical and neurofunctional changes underlie the observed advantages in bilinguals and serve as a clear example of how life experience can shape the structure and functioning of the human brain throughout life.

One of the most significant and practically important areas of research is the

role of bilingualism in the formation of cognitive reserve. Cognitive reserve is the brain's ability to withstand pathological changes (e.g., age-related or neurodegenerative diseases) and maintain normal cognitive functioning [8].

The concept is that life experiences, including education, professional activities, and multilingualism, create a "reserve capacity" in the brain that allows for compensation of emerging impairments [22].

A series of large epidemiological studies has shown that older adults who are bilingual or multilingual experience the onset of dementia symptoms, particularly Alzheimer's disease, on average 4–5 years later than monolinguals [19].

It is important to note that bilingualism does not prevent the disease itself – pathological changes in the brain (e.g., amyloid plaque accumulation) occur just as they do in monolinguals. Nevertheless, thanks to the developed cognitive reserve, the bilingual brain is capable of compensating for these changes for longer, maintaining functionality at an adequate level [9; 27].

The mechanism of this protective effect is linked to the same brain changes discussed above: more developed executive functions and increased efficiency of neural networks [28].

When some neural pathways are damaged as a result of illness, the bilingual brain is better able to find alternative routes to solve cognitive tasks, utilizing more flexible and efficient networks trained by years of language management experience [1; 29].

This effect is seen even when a second language is learned as an adult, suggesting potential for language learning as a preventative measure for cognitive health in old age.

Analysis of contemporary scientific literature shows that the experience of bilingualism and multilingualism has a profound and multifaceted impact on cognitive functions and the neural organization of the brain. The constant need to manage multiple language systems leads to significant changes, manifesting both at the behavioral level in the form of improvements in certain aspects of cognitive control, and at the neurobiological level in the form of structural and functional reorganization of the brain.

Therefore, bilingualism can be considered a contributing factor to cognitive plasticity and the development of a lifelong neurocognitive reserve.

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SOME CLINICAL ASPECTS OF ANTIRESORPTIVE TREATMENT IN PATIENTS WITH BONE METASTASES

Complications associated with bone metastasis and bone involvement in multiple myeloma include pain, disability, loss of self-care abilities, and a decline in quality of life, often requiring the use of narcotic analgesics. The use of bone-modifying agents (BMAs) helps to delay or avoid the development of bone complications.

All practical recommendations are consistent with each other and follow a single strategy for administering antiresorptive therapy (ART) to patients with bone metastases. Despite this, there are several practical issues that are of particular interest to clinicians: 1) the choice of drugs for ART in patients with various types of tumors and bone metastases; 2) schemes and regimens for the safe use of BMAs, and the prevention of adverse events during long-term treatment. The review article discusses some aspects of the use of ART to preserve bone microarchitecture and reduce the risk of fractures in patients with bone metastases. The authors conclude that there is currently no alternative to ART for the prevention of bone complications and the management of pain.

Keywords: antiresorptive therapy, bone-modifying agents, bone metastases.

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Introduction. Modern antiresorptive therapy (ART) is aimed at reducing bone loss, preserving bone microarchitecture, and decreasing fracture risk. The key to preventing bone loss is the suppression of osteoclast function — multinucleated giant cells responsible for bone tissue resorption. Osteoclasts initiate physiological bone remodeling during growth, tooth eruption, and fracture healing [30]. However, they can also cause bone loss in pathological conditions such as bone metastases [23].

Bisphosphonates, synthetic analogues of pyrophosphates that naturally occur in the bone matrix, are among the most widely used agents for suppressing osteoclast activity [9, 25, 26, 31]. In bisphosphonates, an oxygen atom is replaced by a carbon atom, which makes the molecule more stable. The mechanism of action of bisphosphonates (alendronic, zoledronic, risedronic, and ibandronic acids) is not fully understood. It is believed that during bone resorption, the osteoclast — while removing bone tissue — takes up the bisphosphonate, most likely along with calcium and the bone matrix [32].Consequently, the alteration of signaling proteins crucial for osteoclast activity is halted, potentially inducing apoptosis in the bone-resorbing cell [11].

Within this class of compounds, zoledronic acid (ZA), a nitrogen-containing bisphosphonate, demonstrates the highest activity [29]. ZA has a high affinity for bone because it binds to hydroxyapatite in bone tissue through Ca^{2+} chelation [10, 28]. After being taken up by bone-resorbing osteoclasts, ZA can induce osteoclast apoptosis by inhibiting the mevalonate pathway mediated by farnesyl pyrophosphate synthase (FPPS), as well as through the activation of reactive oxygen species (the ROS-induced pathway) [33]. In addition, ZA can suppress the differentiation of macrophages into osteoclasts. It also reduces the expression of the receptor activator of nuclear factor-kB ligand (RANKL), thereby diminishing the interaction between RANKL and RANK. The results are in a reduced number of osteoclasts and a subsequent decrease in bone resorption and tumor-related bone destruction. ZA can also influence non-canonical Wnt signaling by lowering the levels of the signaling proteins Wnt5a and CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II). It markedly decreases intracellular Ca^{2+}, suppresses the expression of calmodulin and CaMKII, and ultimately inhibits osteoclast differentiation. ZA exerts multifaceted antitumor effects by inhibiting proliferation, survival, migration, invasion, and angiogenesis of cancer cells, inducing apoptosis, counteracting chemoresistance, stimulating immunity, and synergizing with other anticancer therapies.

Denosumab [19] is another agent that suppresses bone resorption. It is a fully human recombinant monoclonal IgG2 antibody against RANKL, a cytokine that plays a key role in osteoclast activation [27]. By blocking RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby reducing the intensity of bone resorption. Thus, denosumab exhibits antiresorptive activity. Recent studies have shown that denosumab may also modulate the antitumor immune response by enhancing the activity of cytotoxic T-lymphocytes [16]. Comparative studies have demonstrated that denosumab is more effective than bisphosphonates in slowing the development of skeletal-related complications [13, 18]. Denosumab reduces osteoclast formation without impairing the function of mature cells. As a biologic agent, denosumab does not accumulate in bone tissue and does not exert delayed effects, with its impact fully reversible upon treatment discontinuation [8].

The prevention of skeletal complications is especially important in patients with bone metastases from malignant tumors. Such complications are often associated with pain, functional disability, loss of independence in daily activities, and a decline in quality of life, frequently requiring the use of opioid analgesics. Studies indicate that 65–75% of patients with bone metastases experience pain, impaired mobility, and reduced physical function [21].

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Early initiation of bone-modifying agents (BMAs) can delay or even prevent the onset of skeletal complications. Evidence suggests that BMA therapy reduces the incidence of such complications by 41–54% [12], thereby improving five-year survival in cancer patients and lowering the additional healthcare costs associated with managing these events. Consequently, antiresorptive agents have become an essential component of supportive care for oncology patients with bone metastases or bone involvement in multiple myeloma.

In Russian Federation, physicians can follow the practical guidelines of the Russian Society of Clinical Oncology (RUSSCO) for supportive therapy in "Bone Tissue Pathology" [6], which are updated annually in accordance with new scientific evidence and international approaches to patient management. In other countries, practical guidelines are developed by organizations such as NCCN, ESMO, ASCO, and others. All these guidelines are largely consistent with one another and follow a unified strategy for prescribing ART to patients with bone metastases. Nevertheless, several practical issues remain of particular interest to clinicians. Key among these are: 1) the selection of agents for ART in patients with different tumor types and bone metastases; and 2) the regimens and schedules for the safe use of BMAs, including the prevention of adverse events during long-term treatment.

The use of BMAs for specific disease entities is outlined in the clinical guidelines of the Russian Ministry of Health for the management of patients with breast cancer [3], prostate cancer [4], and lung cancer [2]. In addition, a guideline entitled "Metastatic Bone Disease in Malignant Tumors" has been developed and is available on the websites of the Russian Society of Clinical Oncology and the Association of Oncologists of Russia [22]. BMAs are an effective component of supportive therapy and should be administered alongside primary cancer treatment. Their effectiveness in preventing skeletal complications has been consistently demonstrated in numerous clinical studies [1, 5, 7, 21].

Antiresorptive therapy for tumors with bone metastases. This section focuses on selected aspects of ART use in solid tumors with a high incidence of bone metastases. There are certain discrepancies in the approaches to ART in prostate cancer (PC). According to the general description of the drug denosumab 120 mg, its administration is recommended for patients with solid tumors in the presence of bone metastases. In other words, the presence of metastases, regardless of their characteristics, may be an indication for prescribing BMAs. However, according to all clinical guidelines, ART is prescribed only upon the development of castration resistance. Data from randomized clinical trials indicate that adding zoledronate to first-line long-term hormonal therapy (STAMPEDE trial) in patients with endocrine-sensitive prostate cancer (ESPC) did not show any signs of improved survival. Moreover, in the CALGB 90202 study, comparing zoledronate and placebo in ESPC with bone involvement as the primary endpoint, early treatment with zoledronate did not lead to a significant reduction in the incidence of skeletal events. Similar studies have not been conducted to assess the efficacy of denosumab 120 mg. Nevertheless, a beneficial effect of bone-modifying agents in reducing pain in these patients cannot be excluded. In randomized clinical trials comparing denosumab and zoledronate in men with bone metastases from castration-resistant prostate cancer, denosumab delayed the time to the first skeletal-related event and reduced the overall incidence of skeletal complications by 18% compared to zoledronate [17].

In contrast to prostate cancer, there is no controversy over administering BMAs to all patients with bone metastases from breast cancer. Randomized clinical trials have shown that in these patients, denosumab was statistically superior to zoledronate in delaying both the first and subsequent skeletal-related events, as well as in slowing the progression of bone pain [15].

ART is recommended for patients with breast cancer and castration-resistant prostate cancer who have bone metastases, regardless of the presence of clinical symptoms. For other solid tumors, therapy with bone-modifying agents is advised when the expected survival is ≥3 months or if the symptoms are clinically significant [12].

Over the past decades, the use of BMAs for the treatment of patients with metastatic malignancies has increased. The patients with oligometastatic disease may survive more than 10 years after diagnosis. As life expectancy has increased, it has become important to assess the cumulative risks of long-term use of bone-modifying agents, the incidence of adverse events, and the frequency of drug administration [12].

Regimens and protocols for the safe use of bone-modifying agents. The choice of ART administration schedule is of critical importance. Randomized clinical trials in patients with breast cancer, castration-resistant prostate cancer, or multiple myeloma demonstrated comparable efficacy in preventing skeletal complications when zoledronate was administered every 12 weeks versus every 4 weeks. However, a greater number of patients receiving zoledronate every 12 weeks required surgical intervention on bones [20]. Considering that the follow-up period was relatively short and the results suggested a potential increase in serious skeletal events with less frequent dosing, a 4-weekly administration schedule is considered appropriate during the first 3–6 months of treatment [12]. Based on pharmacokinetics, treatment interruptions with denosumab are not recommended [14]. Denosumab 120 mg should be administered once every 28 days for an extended period, until otherwise indicated. Unlike bisphosphonates, denosumab does not integrate into the bone matrix. This drug can be regarded as "heavy artillery," providing faster and more effective suppression of bone resorption compared with zoledronic acid, thereby helping to prevent disabling complications. Maximum benefit from denosumab is observed in patients with active malignancy, multiple metastases localized in the axial skeleton, and at risk of pathological fractures. If denosumab is discontinued for more than 6 months, a single dose of zoledronic acid is recommended to suppress rebound osteolysis [6].

In most cases, therapy with osteomodifying agents (OMAs) is initiated upon detection of bone metastases and continued throughout the course of cancer treatment. Therefore, the safety profile of OMAs and the incidence of adverse events are of particular importance. Among these, osteonecrosis of the jaw (ONJ) and atypical fractures are the most clinically significant. ONJ occurs more frequently with intravenous administration of OMAs and is influenced by both dose and dosing frequency. Monthly administration of bisphosphonates or denosumab is associated with a higher risk of ONJ compared to oral bisphosphonates or administration of zoledronate or denosumab 60 mg every six months for bone loss prevention. The risk may be somewhat higher in patients with multiple metastases compared to those with solid tumors and can be further increased when OMAs are combined with antiangiogenic agents or corticosteroids [6]. With monthly treatment, the incidence of ONJ for both zoledronate and denosumab is approximately 1% per year [12]; however,

some studies suggest that this rate for denosumab may be substantially underestimated [24].

Another serious adverse effect associated with the use of BMAs is atypical femoral fractures in the subtrochanteric region and femoral shaft in patients. Radiographic studies of fractures indicate a link between femoral fractures and the use of bisphosphonates, which tend to accumulate in areas where stress fractures develop, while suppression of intracortical remodeling at fracture sites may impair healing processes. The absolute risk of fractures in patients receiving bisphosphonates or denosumab is low, ranging from 3.2 to 50 cases per 100,000 person-years. The risk is higher with long-term use of BMAs (on average 7 years) and may decrease after discontinuation of therapy [12].

It should be noted that most clinical questions regarding the use of antiresorptive drugs are addressed in the supportive care guidelines available on the RUSSCO website [6]. Bone-modifying agents are compatible with all existing anticancer drugs and radiation therapy methods, and their administration is not a contraindication for surgical treatment.

Conclusion. Antiresorptive agents are an essential component of supportive therapy for oncology patients with bone metastases and bone involvement in multiple myeloma. To date, there is no alternative to ART for preventing skeletal complications and managing pain in these patients. This is supported by numerous clinical studies.

The authors declare no conflict of interest.

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ТОЧКА ЗРЕНИЯ

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ASSOCIATION OF OBESITY WITH C-REACTIVE PROTEIN LEVELS AND NON-ALCOHOLIC FATTY LIVER DISEASE IN FEMALE RESIDENTS OF SOUTHERN YAKUTIA

A study working women in Southern Yakutia to analyze obesity rates and their association with serum C-reactive protein levels and the prevalence of non-alcoholic fatty liver disease revealed that only 25% of the participants had normal body weight. Obesity, as measured by their body mass index, was found in half of the women, abdominal obesity, as measured by waist circumference, was found in four out of five women, and abdominal obesity. Extreme obesity (class III) is typical for women nearing menopause. Body mass index, waist circumference, and hip circumference are closely correlated with serum C-reactive protein levels, the frequency of elevated C-reactive protein levels, and the incidence of non-alcoholic fatty liver disease. The frequencies of elevated C-reactive protein levels and non-alcoholic fatty liver disease show signs of a complete functional relationship. One-third of the study participants with normal body weight are likely at risk for developing non-alcoholic fatty liver disease and related diseases. The analysis revealed an urgent need for targeted care, including medical assistance, involving clinical specialists in nutrition and physical fitness. The lack of timely and effective healthcare response will exacerbate the progression of obesity and related diseases among working women in Southern Yakutia.

Keywords: body mass index, inflammation, women's health.

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Introduction. Nowadays Obesity has become a global crisis. The World Health Organization defines obesity as a chronic, complex disease characterized by excess fat deposition, which negatively impacts health. Obesity can lead to an increased risk of type 2 diabetes and cardiovascular disease, affect bone health and reproductive function, and can also increase the risk of certain cancers. Obesity was once considered a problem in high-income countries, but today, some of the highest rates of overweight and obesity are found in middle-income countries [9]. Obesity is most often assessed using the body mass index (BMI) [1]. Other body parameters, particularly waist circumference, also provide additional information to BMI for predicting morbidity and mortality risk [6].

Closely associated with obesity is non-alcoholic fatty liver disease (NAFLD), which is characterized by excess accumulation of fat in the liver and is one of the most common liver diseases worldwide with a global prevalence of approximately 30%. The rising prevalence of obesity is projected to further increase the prevalence of NAFLD, which is the basis of chronic liver diseases, including cirrhosis and hepatocellular carcinoma. NAFLD has multiple clinical phenotypes and is heterogeneous due to the complexity of its pathogenesis and clinical onset conditions. The gold standard for confirming fatty tissue changes is a biopsy, but it has limitations related to its inherent non-safety concerns due to the invasive nature of the procedure. Non-invasive methods, such as computed tomography, ultrasound, and magnetic resonance imaging, are also used to detect fatty changes in the liver. Therefore, data on the incidence and prevalence of NAFLD vary depending on the diagnostic method used. Since NAFLD is characterized by chronic inflammation, inflammatory markers have been studied in patients with NAFLD. It has been established that C-reactive protein (CRP) levels are associated with liver inflammation, and their determination (high-sensitivity CRP) can predict NAFLD progression [2].

In 2022 the Yakut Scientific Center of Complex Medical Problems conducted an expeditionary survey of working-age individuals in Southern Yakutia to analyze their health. Among the results a link was identified between NAFLD and arterial hypertension [8].

The aim of this study was to analyze the relationship between obesity rates and serum CRP levels and the prevalence of NAFLD among women working in enterprises in Southern Yakutia.

Materials and methods. The study contains sample data from an expeditionary survey of working-age individuals in Southern Yakutia [8]. Indicators were selected from women of Russian nationality who underwent anthropometric measurements (height, weight, waist circumference (WC), and hip circumference (HC)), abdominal ultrasound, and serum CRP levels determined using an enzyme-linked immunosorbent assay. Based on these criteria, the total number of study participants was 69, ranging in age from 22 to 66 years.

The following were calculated: BMI in kg/m^2 using the generally accepted formula [1], waist-to-weight ratio (WTR) using the formula WTR=WC (cm)/weight (kg), and waist-to-hip ratio (WHR) using the formula WHR=WC (cm)/HC (cm).

In accordance with the classification of obesity in BMI values for the Caucasian population as outlined in the Russian National Recommendations [1], five comparison groups were formed. Group I - 17 women with normal body weight

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(NormW) with a BMI of 18.5-24.9 kg/m2, group II - 19 women with overweight (OvW) with a BMI of 25.0-29.9 kg/m2, group III - 18 women with Class I obesity (Ob1) with a BMI of 30,0-34,9 kg/m2, group IV - 9 women with Class II obesity (Ob2) with a BMI of 35,0-39,9 kg/m2 and group V - 6 women with Class III obesity (Ob3) with a BMI> 40,0 kg/m2.

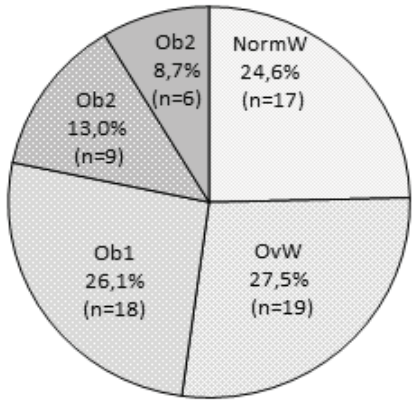
The Shapiro-Wilk test was used to test the normality of variable distribution. A one-way analysis of variance was used to identify differences between indicators in five or two samples with normally distributed data. If the distribution was not normal, the Kruskal-Wallis test was used to determine differences between data in five samples, and the Mann-Whitney test was used between two samples. The mean (M) and standard deviation (SD) were calculated. Quantitative and qualitative data were also described as relative variables (%). Spearman's correlation coefficient (*rho*) was used to identify pairwise relationships. Differences and *rho* were considered statistically significant at $p < 0,05$.

The study was conducted in accordance with the ethical principles of the Helsinki Declaration of the World Medical Association (2008) and approved by the Protocol of the Bioethics Committee of the Yakut Scientific Center of Complex Medical Problems.

Results and discussion. The distribution of the participants in this study by body weight type depending on their calculated BMI, presented in Figure 1, showed obesity to varying Classes had half of them, approximately a quarter were overweight, and only the remaining quarter had normal body weight. Signs of abdominal obesity - WC values above 80 cm and/or WHR values above 0,85 [9] were detected in 79% of cases (54 of 69 people) and in 48% of cases (33 of 69 people), respectively. The combination of BMI above 25 kg/m2 and WC above 80 cm was detected in 49% of cases (47 of 69 people). The prevalence of obesity among the participants of this study significantly exceeds the results of the ESSE-RF epidemiological study, which showed the presence of obesity in a third of cases among all Russian women [1].

A between-group analysis was performed to determine the differences in age, anthropometry, and serum CRP levels according to body mass type, the results of which are shown in Table 1. The study participants' anthropometric parameters, including weight, WC, HC, WTR, and WHR, differed statistically significantly between the groups. Their mean values across the comparison groups increased with increasing BMI, so it was expected that they would have a complete functional relationship with the group' mean BMI values (*rho*=1, *p*=0,000).

The height and age indicators of the study participants did not show statistically significant group differences, although for differences between mean age values, the obtained p-level (0,167) still suggests a greater than 80% probability of their presence. Moreover, the average age of women with stage III obesity was statistically significantly higher than that of women with normal body weight (*p*=0,014 for paired one-way analysis of variance). To confirm the presence of statistically significant differences in age depending on body mass type, whereby older age corresponds to a higher BMI, a larger number of study participants is needed. However, an increasing BMI with age in some ethnic groups has been confirmed [10]. Similar to other recent scientific studies [4], this study revealed statistically significant differences in serum CRP levels varies by body mass type. Herewith, mean values in the comparison groups as well as anthropometric parameters (except height) are increasing with increasing BMI. Accordingly, the mean values of serum CRP and BMI showed a close functional relationship (*rho*=1, *p*=0,000), calculated for the study participants' groups.



Distribution of the number of study participants by their body weight type (abbreviations here and below are presented in the text of the article).

Elevated serum CRP levels (>5 IU/ml) were detected in 65% of the study participants (45 of 69 people) and found in all groups: in women with normal body weight - in 36% of cases (6 of 17 people), with overweight - in 53% of cases (10 of 19 people), with Class I obesity - in 73%

Table 1

Age. anthropometry. and serum CRP levels in female patients by body mass type

Body mass type		BMI	Age (years)	Height (cm.)	Weight (kg.)	WC (cm.)	WWR	HC	WHR	CRP (mg/l)
Normal body mass (n=17)	M	22.56	40.70	162.94	59.88	73.41	9.48	93.52	0.78	4.97
	SD	0.85	11.13	7.38	5.08	8.02	0.88	3.29	0.07	5.13
	P^1	0.107	0.439	0.776	0.197	0.268	0.101	0.699	0.074	0.002^
Overweight body mass (n=19)	M	27.57	44.11	162.95	73.31	85.47	9.99	104	0.82	7.03
	SD	1.58	12.28	6.99	7.41	6.78	0.68	3.94	0.06	6.68
	P^1	0.144	0.787	0.579	0. 871	0. 530	0. 854	0.632	0.365	0.003^
Class 1 Obesity (n=18)	M	31.81	42.89	163.28	85.00	94.83	10.29	109.83	0.86	9.07
	SD	1.53	10.44	5.10	8.04	9.41	0.75	7.12	0.06	5.41
	P^1	0.175	0.691	0.797	0. 368	0. 447	0. 648	0.005^	0.995	0.331
Class 2 Obesity (n=9)	M	36.98	42.33	163.00	98.33	109.78	11.08	118.88	0.92	12.22
	SD	1.40	10.25	8.00	8.89	8.01	0.70	6.31	0.08	5.57
	P^1	0.605	0.072	0.538	0. 904	0. 740	0. 213	1	0.230	0.126
Class 3 Obesity (n=6)	M	41.26	53.83	160.17	106.00	116.00	11.28	127	0.91	15.22
	SD	0.77	10.80	8.21	9.96	7.10	0.55	3.28	0.04	3.35
	P^1	0.555	0.218	0.919	0. 744	0. 854	0. 978	0.890	0.955	0.093
P^2		0.000*	0.167	0.902	0.000*	0.000*	0.000*	N/A	0.000*	N/A
p^3		N/A	N/A	N/A	N/A	N/A	N/A	0.000*	N/A	0.000*

Note: M - the mean value, SD - the standard deviation; p1 - the significance level of the Shapiro-Wilk test, ^ - the distribution is not normal; p2 - the significance level of the multiple one-way analysis of variance; p3 - significance level of the Kruskal-Wallis test, * - the differences in the indicators have reached the required significance level; N/A - not applicable.

of cases (13 of 18 people), with Class II obesity - in 67% of cases (6 of 9 people) and with Class III obesity - in 100% (all 6 people). These data had a statistically significant strong positive relationship with the average BMI value calculated for the groups of study participants (*rho*=0,9, *p*=0,037).

NAFLD, detected using an abdominal ultrasound, was observed in 26% of women (18 of 69 people) and also occurred in all groups: in women with normal body weight in 6% of cases (1 of 17 people), with overweight - in 16% (3 of 19 people), with Class I obesity - in 39% (7 of 18 people), with Class II obesity - in 23% (2 of 9 people) and with Class III obesity - in 84% (5 of 6 people). The prevalence of NAFLD, as well as the above-mentioned prevalence of elevated serum CRP levels, showed a statistically significant strong positive association with the mean BMI value calculated across the study all participants (*rho*=0,9, *p*=0,037).

The conducted correlation analysis revealed a complete functional relationship between the frequency of elevated levels of serum CRP and the occurrence of NAFLD (*rho*=1, *p*=0,000).

A paired correlation analysis among all study participants (69 individuals), regardless of body weight, revealed statistically significant positive relationships between serum CRP levels and BMI, weight, WC, HC, WTR, and WHR. The results of which are shown in Table 2. Although the *rho* values for these relationships did not reach the values required for medical research (*rho* should be at least 0,7), but moderate positive correlation was found between serum CRP levels and WC and between CRP and HC.

It is known that the values of the WC and related indices can reflect the amount of abdominal fat [6]. Abdominal fat acts as an endocrine organ, secreting inflammatory cytokines such as IL-6 and TNF-α. The constant release of IL-6 signals the liver to secrete CRP and leads to low-grade systemic inflammation throughout the body, which maintains elevated levels of serum CRP [5]. Systemic inflammation contributes to the development of NAFLD and is present in the chain of its pathogenesis, in which also includes lipid metabolism disorder, apoptosis, fibrogenesis in the liver, etc. [2].

We were interested in the relatively high prevalence of elevated serum CRP in normal-weight study participants—almost a third of them (36% of cases, as noted above). Of course, elevated serum CRP levels are associated not only with abdominal obesity and NAFLD, but are also present in many infectious and immune-inflammatory diseases. However, research has shown that elevated serum CRP levels can predict the development of NAFLD in non-obese individuals [3]. Therefore, to identify differences between their anthropometric parameters depending on the level of serum CRP, the parameters of the study participants with normal body weight were divided into two subgroups: with normal (11 people) and with elevated levels (6 people) of serum CRP (Table 3). Although the analysis revealed no statistically significant differences, the mean values of anthropometric parameters—BMI, weight, WC, HC, WTR, and WHR —were still lower in the subgroup with normal serum CRP levels than in the subgroup with elevated levels. For differences between the mean BMI and weight values in the subgroups, the obtained p-value (0,120 and 0,183, respectively) suggests a greater than 80% probability of their presence. Of course, to confirm the hypothesis of statistically significant differences in BMI and other anthropometric parameters depending on serum CRP levels in women with normal body weight, a larger number of study participants is needed.

Thus, it was found that only 25% of the participants in this study had a normal body weight. Obesity, as measured by BMI, was found in half of the women, abdominal obesity, as measured by WC, was found in four out of five women, and abdominal obesity, as measured by WHR, was found in half of the study participants. Extreme obesity (Stage III) is typical for women nearing menopause.

I this study along with the increase in BMI, WC, HC and their indices, there is a parallel increase in such indicators as the mean of serum CRP, the frequency of its elevated values and the prevalence of NAFLD. The frequencies of elevated serum CRP levels and the prevalence of NAFLD show signs of a complete functional relationship. One-third of the women with normal body weight are likely at risk of developing NAFLD and related diseases [7].

Conclusion. The results demonstrate that women in Southern Yakutia are not immune to the global obesity crisis, which poses a health threat. Although obesity and NAFLD are known to be lifestyle-related, primarily to diet and physical activity, the significantly increased prevalence of obesity and NAFLD in the examined women and the high potential risks of developing them in women with normal body weight highlight the urgent need for targeted care, including medical interventions, involving clinical specialists in nutrition and

Table 2

Spearman's rank correlation coefficients (*rho*) between CRP values and age and anthropometric parameter in all female patients

	Patients (n=69)	
	rho	*p*
Age	0.082	0.504
Height	-0.017	0.888
Weight	0.474*	0.000
WC	0.503*	0.000
HC	0.527*	0.000
WWR	0.441*	0.000
WHR	0.367*	0.002
BMI	0.496*	0.000

Note: * - differences in indicators have reached the required level of significance

Table 3

Age and anthropometric parameters in normal-weight female patients depending on CRP levels

		BMI	Age (years)	Height (cm.)	Weight (kg.)	WC (cm.)	HC	WWR	WHR
Normal CRP levels (n=11)	M	22.10	40.91	162.82	58.54	71.90	92.90	9.38	0.77
	SD	1.77	8.61	5.84	5.04	8.65	3.78	0.81	0.07
	P^1	0.547	0.629	0.234	0.558	0.374	0.887	0.223	0.248
Elevated CRP levels (n=6)	M	23.39	40.33	163.16	62.33	76.16	94.66	9.66	0.80
	SD	0.92	13.41	8.56	5.88	7.93	1.96	0.96	0.08
	P^1	0.517	0.563	0.981	0.741	0.314	0.659	0.728	0.549
P^2		0.120	0.915	0.922	0.183	0.335	0.309	0.541	0.459

Note: M - the mean value, SD - the standard deviation; p1 - the significance of the Shapiro-Wilk test; p2 - the significance of the one-way analysis of variance.

physical fitness. The lack of timely and effective healthcare responses will exacerbate the progression of obesity and related diseases among working women in Southern Yakutia.

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CLINICAL CASE

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CARTAGENE SYNDROME: PROBLEMS OF DIFFERENTIAL DIAGNOSIS

Introduction. Kartagener syndrome is a classic variant of primary ciliary dyskinesia, characterized by abnormal structure or function of cilia, leading to impaired mucociliary clearance, and manifested by chronic respiratory infections and incomplete or complete abnormal arrangement of internal organs. The rarity of this disease, the lack of a "gold standard" for diagnosis, the unavailability of high-tech diagnostic tests and low alertness of physicians, complicate the diagnosis, which leads to a late start of treatment and a decrease in the quality of life of such patients.

Description of a clinical case. The patient, 12 years old, was urgently admitted to the hospital with symptoms of iron deficiency anemia. During the physical examination, changes in the fingers of the hands of the "drumstick" type and nail plates of the "watch glass" type were recorded. From the anamnesis it was established that from the first days of life the child was diagnosed with dextrocardia, incomplete rotation of the intestine and annular pancreas. Since 1.5 years old the child has been regularly observed in medical institutions with repeated inflammatory diseases of the upper and lower respiratory tract, periodically undergoes treatment for diseases of the urinary system. Since 8 years old chronic bronchitis was diagnosed. During the examination a decrease in spirometry indicators, dextrocardia, chronic bronchitis changes in the lungs were revealed. The number of points on the PICADAR scale is 13. The set of clinical, laboratory and instrumental data, assessment on the PICADAR scale, allowed to establish the diagnosis of primary ciliary dyskinesia: Kartagener syndrome.

Conclusion. The presented clinical case clearly demonstrates the problems of differential diagnosis of Kartagener syndrome. Increasing the alertness and awareness of doctors about this disease can help in rapid diagnosis, timely treatment and improving the quality of life of such patients.

Keywords: Kartagener syndrome, primary ciliary dyskinesia, differential diagnosis, late diagnosis.

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Introduction. Ciliopathies are a group of rare hereditary diseases caused by mutations in proteins that determine the structure and functions of cilia. Due to the widespread prevalence of the ciliary epithelium in the body, cyliopathies are affected by various tissues and organs, including a number of states, including the Cartagener syndrome (KS) occupies a significant place.

Cartagener syndrome is a classic version of primary ciliary discinesia (PCD), characterized by pathology of the structure or function of the cilia leading to a violation of mucociliary clearance, and manifested by chronic infections of the respiratory tract and incomplete or complete abnormal arrangement of internal organs [11]. Currently, more than 50 genetic variants of the UK, characterized by clinical heterogeneity [3]. So, according to Kondratyeva E.I. Sub. (Moscow, 2024), patients with SK in 90% of cases are born of full-term, in 47% of cases are hospitalized in intensive care units in the neonatal period, suffer from recurrent bronchitis, pneumonia, sinusitis and otitis media in 86.6% -76% -51.6% of cases, respectively. In 28.3% of such patients, heart defects are recorded, in 5% - nasal polyposis, in 8.3% - kidney pathology [5].

Despite the presence of clinical recommendations, the diagnosis of the KS remains difficult due to the fact that the clinical picture is not specific only for the PCD, there is no “gold standard” diagnostics and all diagnostic recommendations include a combination of various anamnestic, functional, structural and molecular genetic methods [4]. Currently, the characteristic clinical- (quantitative assessment of the significance of clinical features is the PICADAR scale (from the English. Primary Ciliary Dyskinesa Rule) and instrumental data in conjunction with the results of special studies: measuring the nasal oxide (NO) in exhausted nasal air, high-speed digital. Video microscopy (to evaluate the mobility of ciliary viable cells), transmission electron microscopy (assessment of the state of ultrastructure of the axonema), immunofluorescent staining of various structural proteins and genetic testing [10]. Due to the inaccessibility for wide use of high -tech diagnostic tests in non -specialized hospitals, and the PCD are often diagnosed by the PDC is often diagnosed by late life dates or are not diagnosed at all, which leads to the late start of treatment or its absence.

The complexity of the diagnosis of PCD demonstrates the presented clinical case.

Clinical case. A child from fifth uncomplicated pregnancy, from young healthy parents who were not related. With a prenatal screening of 20 weeks, was revealed. A full-term baby with a

weight of 3600 g and a height of 53 cm was born from the second birth. Evaluation on the Apgar scale 7/7 points. Due to the manifestations of increasing respiratory disorders, she was transferred from the delivery room to the neonatal intensive care unit.

On the fourth day of life, the symptoms of intestinal obstruction developed, due to the incomplete turn of the intestines and the ring-shaped pancreas. During the examination, it was confirmed that the child has a right -handed heart, lumbar dystopia of the left kidney.

Throughout the first year of life, the condition of the child was stable. From the age of 1.5, she often (6-7 times a year) suffered from respiratory diseases, manifested in the form of laryngotracheobronchitis, bronchiolitis, and broncho-obstructive syndrome. During the convalescence period, a productive cough persisted for a long time. At the age of 5, an X-ray computed tomography examination revealed hypoplasia of the right lung. Upon repeated CT examination, at the age of 8 years, the changes characteristic of chronic bronchitis were determined: thickening of the bronchial walls, the presence of a parietal substrate (sputum). At the age of 9 years, a urolithiasis clinic appeared, and therefore, a lithotripsy was performed in the "NMIC of the health of children" (Moscow).

Preventive vaccinations were carried out according to the individual schedule. Allergic history without any special features. Neonatal screening was carried out, pathology was not detected.

At the age of 12, the child is admitted to the hospital of the regional children's clinical hospital named after N.V. Dmitrieva with signs f iron deficiency anemia.

During the physical examination, a change in the fingers of the hands according to the type of "drumsticks", a change in the nail plates according to the type of "watch glasses" was recorded (Fig. 1). Acrocyanosis of the fingers was observed, which increased in the standing position. The child's physique is asthenic. When calculating the body mass index, moderate malnutrition was detected (z-score -2.27). A number of dysembriogenesis stigmas have been identified: high palate, knee joint recurvation, and low nipple location. During auscultation of the lungs, uneven harsh breathing was detected, mainly dry diffuse wheezing is heard, more on inspiration. SaO2 96-99%. During auscultation of the heart, a short systolic murmur is heard to the right of the sternum in the fourth intercostal space. Physiological functions without special features.

Fig. 1. Changes in the fingers of the hands according to the "drumstick" type, changes in the nail plates according to the "watch glass" type

The child underwent a comprehensive examination. A general blood test revealed a decrease in the level to 66 g / l, MCV (from English Mean Corpuscular Volume) was 68.4 fl, single reticulocytes in the smear. In blood biochemistry, there is a decrease in serum iron levels to 6.0 mmol/L, serum ferritin to 2.5 mg/L, and other indicators (bilirubin, alkaline phosphatase, ALT, AST, creatinine, urea, protein, electrolytes, and CRP) are within reference values. Plasma coagulation levels are within the age range. When assessing the acid-base state of the blood, no changes were detected. Oxaluria is detected in urine: daily excretion was 209.8 mmol/day (the norm is up to 134.8 mmol/day). The study of humoral immunity (immunoglobulins A, E, M, G) is within the normal range. Screening for celiac disease is negative. The level of fecal calprotectin is <50 mcg/g. Coprology showed no signs of pathology, and no hidden blood was found in the stool.

Fibroesophagogastroduodenoscopy revealed fibrinous reflux esophagitis, cardia insufficiency, duodeno-gastric reflux, and a condition after gastroenteroanastomosis. A comprehensive ultrasound examination revealed: rotation and lumbar dystopia of the left kidney, concretions in the calyx-pelvic system of both kidneys up to 6 mm in size; uterine hypoplasia. Changes in the thyroid gland and abdominal organs have not been established. On an EchoCG, a congenital heart anomaly: a right-angled right-angled heart, pulmonary artery pressure less then 30 mmHg.

Computed tomography (CT) of the chest organs shows signs of congenital malformations: dextrocardia, hypoplasia of the right lung (due to the middle and lower lobes); transposition of the right upper lobe bronchus into the area of the middle lobe and lower lobe bronchus; signs of chronic bronchitic changes in the acute stage (thickening of the walls of the distal bronchi on the right; parietal substrate (sputum) in the lumen of large bronchi and trachea; multiple centrilobular nodules and Y–shaped structures with the formation of a "tree in the kidneys" pattern, lobular seals) (Fig.2 and 3). According to spirometry data, there was a marked decrease in forced vital capacity and forced exhalation volume after a salbutamol test without dynamics. An MRI scan of the brain revealed no pathology.

The child is rated on the PICADAR scale, the number of points is 13 ("diagnosis is valid") [2].

The combination of clinical, laboratory and instrumental data, assessed on the PICADAR scale, made it possible to establish the diagnosis of primary ciliary dyskinesia: Kartagenera syndrome.

Discussion. The presented clinical case demonstrates the complexity of the

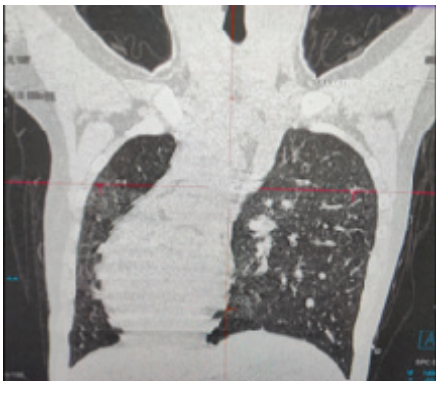

Fig. 2. Computed tomography of the chest. Dextrocardia (right-sided, right-formed heart)

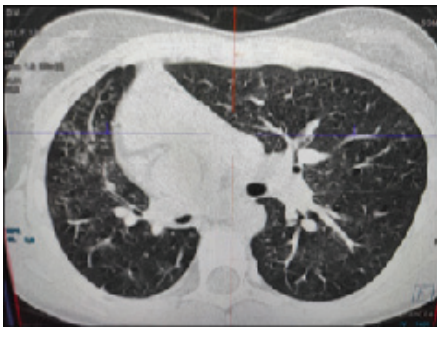

Fig. 3. Computed tomography of the chest. Thickening of the walls of the distal bronchi on the right; parietal substrate in the lumen of large bronchi and trachea; multiple centrilobular nodules and Y-shaped structures with the formation of a "tree-in-bud" pattern

diagnosis of PCD. The average age of verification of this disease is an important indicator of the effectiveness of the healthcare system in detecting a rare pathology in children [1,6]. Thus, according to A.A. Novak (Moscow, 2024), the average age of verification of the disease in the Russian Federation is 5.8 years, in the Australian cohort of patients, the diagnosis is established at the age of 6.4 years, in China-8.2 years, and in South Korea-11.8 years [3,13,7,8].

Due to the relatively low frequency of the KS, the variety of phenotypes, the lack of screening, low awareness and alertness of doctors, the diagnosis of PCD is often postponed for years, which significantly reduces the quality of life of such patients [12]. According to the clinical recommendations of the Russian Federation, as well as the diagnostic recommendations of the European respiratory and American thoracic societies, patients with constant productive coughing, the anomalies of the location of the internal organs and congenital heart defects are subject to an additional comprehensive examination using high -tech diagnostic tests for the verification of PCD [10,9].

In the case presented from the first days of life, the child was diagnosed with dectrocardia, incomplete intestinal rotation and ring-shaped pancreas. From the age of 1.5, the child is regularly observed in medical institutions with repeated inflammatory diseases of the upper and lower respiratory tract, and periodically undergoes for diseases of the urinary system. From the age of 8, chronic bronchitis was diagnosed. This child, despite the frequency of outpatient visits and inpatient hospitalizations, was not comprehensively examined, and did not take into account the dispensary accounting for chronic bronchitis.

Conclusion. The presented clinical case clearly demonstrates the problems of the differential diagnosis of the KS. An increase in the awareness of doctors about this disease can help in quick diagnosis, timely treatment and improve the quality of life of such patients.

The authors declare no conflict of interest.

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A FAMILY CLINICAL CASE OF COMBINATION OF TWO MENDELIAL DISEASES: SPINOCEREBELLAR ATAXIA TYPE 1 AND HYPOPHOSPHATEMIC RICKETIS

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The combination of two genetic syndromes in a single patient is a rare occurrence. This article describes a clinical case of a rare combination of two Mendelian diseases: spinocerebellar ataxia type 1 and hypophosphatemic rickets in a single Yakut family. Given the low incidence of both diseases, this finding is of scientific and practical interest. The paper discusses a clinical observation of family members examined in 2012 and 2025. This clinical example is also relevant for practicing physicians. It is necessary to develop algorithms for monitoring complications of spinocerebellar ataxia and phosphate diabetes and to identify pathogenetic therapy.

Keywords: spinocerebellar ataxia type 1, hypophosphatemic rickets, bone deformity, phosphate diabetes, family case.

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Introduction. Spinocerebellar ataxia type 1 (SCA1) is a heterogeneous neurodegenerative disorder with an autosomal dominant inheritance pattern, characterized by progressive cerebellar ataxia, dysarthria, and gradual deterioration of bulbar function [5]. In the early stages of the disease, patients may experience gait disturbances, slurred speech, balance problems, brisk deep tendon reflexes, hypermetric saccades, nystagmus, and mild dysphagia. Later symptoms include slowing of saccade velocity, development of upward gaze palsy, dysmetria, dysdiadochokinesia, and hypotonia. In late stages, muscle atrophy, decreased deep tendon reflexes, loss of proprioception, cognitive impairment (e.g., frontal dysfunction, verbal memory impairment), chorea, dystonia, and bulbar dysfunction are observed [3, 7]. The disease typically presents between the ages of 30 and 40 years, although cases have been reported in childhood and the elderly. Patients whose disease onset is after 60 years may have a purely cerebellar phenotype. The interval from disease onset to death ranges from 10 to 30 years; patients with juvenile onset have more rapid progression and a more severe course of the disease. Axonal sensory neuropathy, detected by electrophysiological testing, is common; brain imaging typically shows cerebellar and brainstem atrophy [3, 8].

Hypophosphatemic rickets (phosphate diabetes) is a hereditary tubulopathy with a defect in phosphate reabsorption in the proximal tubules and high resistance to normal doses of vitamin D, resulting in hyperphosphaturia, hypophosphatemia, and clinical features of rickets [6]. The relevance of studying phosphate diabetes is associated with many unresolved issues in patients suffering from this pathology. Issues of diagnosis, drug therapy, dispensary observation, and rehabilitation of patients with complications remain open [2]. Late diagnosis of hypophosphatemic rickets is associated with a great similarity of the clinical features with other genetically determined metabolic disorders and diseases of mineral-bone metabolism [1]. A small number of publications with clinical examples of phosphate diabetes in recent years also leads to late detection of this pathology in clinical practice [4].

Materials and methods. Family V., a member of the Yakut ethnic group living in a rural area, was studied. An increase in the number of trinucleotide (CAG) repeats up to 42 in one of the alleles of the 6p21.3 locus in the ataxin-1 (*ATXN1*) gene and a deletion of exon 15 of the PHEX gene were detected.

Research methods:

1. Molecular genetic testing to determine mutations in the ataxin-1 *(ATXN1*) and PHEX genes;
2. Montreal Cognitive Assessment (MoCA);
3. Hospital Anxiety and Depression Scale (HADS);
4. Morse Falls Risk Scale;
5. Hendrick Fall Risk Model II;
6. Scale for the Assessment and Rating of Ataxia (SARA);
7. Magnetic resonance imaging;
8. Spirometry;
9. Radiography;
10. Biochemical research methods.

Clinical observation. Patient V., 43, was admitted to the neurology department of the Center for Neurodegenerative Diseases (CND) of the Yakut Scientific Center for Complex Medical Problems (YSC CMP) in 2025. Complaints upon admission included unsteadiness and instability when walking, deterioration of handwriting, slurred speech, occasional choking on solid and liquid food, stiffness and weakness in the legs (which suddenly become "wobbly"), general weakness, increased fatigue, and occasional loose stools.

Medical History and Past Medical History: Patient V. was born the third of four children. The author identified the patient in 2012 as part of a mobile team in the Lensky District, in the village of Tolon. Examination revealed short stature (127 cm), varus deformity of the femoral shafts (more on the left), and shortened lower limbs. Since she began walking independently as a child, she developed leg deformities, which required repeated surgical treatment from 1987 to 2004. She was diagnosed with chondrodysplasia and has been disabled since childhood.

The patient has two sons, both of whom have short stature, rickets-like skeletal changes, knee and ankle deformities, and varus deformities of the lower extremities.

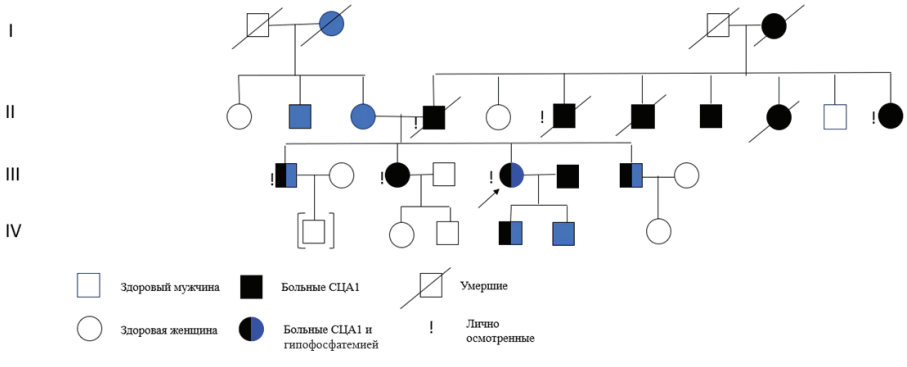

Fig 1. Pedigree of proband V

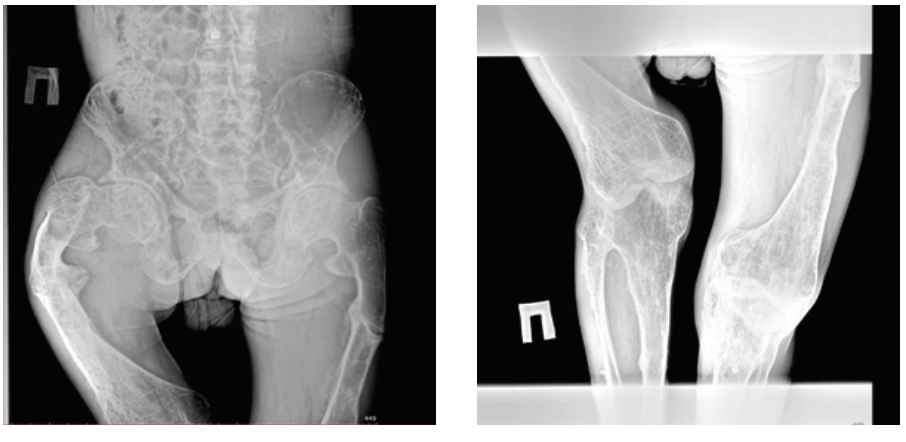

Fig. 2. X-ray of proband V's sibling

The diagnosis of phosphate diabetes was confirmed in both sons using molecular genetic testing. A heterozygous mutation—a deletion of exon 15 of the PHEX gene—was also detected in the mother and her siblings.

In 2015, following a referral from the Medical Genetic Center of the Republican Hospital No. 1 - National Center of Medicine, she was hospitalized for the first time at the FSBI "NMRC of Endocrinology" of the Ministry of Health of Russia, where she was diagnosed with E83.3 X-linked dominant hypophosphatemic rickets. Deletion of exon 15 of the PHEX gene. Bow-shaped deformity of the lower extremities (post-surgical correction). Osteoarthritis of the left and right knee joints. Somatic short stature. Secondary hyperparathyroidism. Decreased BMD. Vitamin D deficiency.

The diagnosis of phosphate diabetes was confirmed in both sons by molecular genetic testing. A heterozygous mutation—a deletion of exon 15 of the PHEX gene—was also detected in the mother and her siblings.

In 2012, patient V. underwent DNA testing at the molecular genetics laboratory of the Medical Genetics Center of Republican Hospital No. 1, which revealed an increase in the number of trinucleotide (CAG) repeats to 42 in one allele of the 6p21.3 locus in the ataxin-1 (*ATXN1*) gene. She had no symptoms of SCA type 1 at the time of testing.

Family history of hypophosphatemic rickets and spinocerebellar ataxia type 1. Figure 1 shows the pedigree of patient V. for both conditions. She has a strong maternal family history of phosphate diabetes. The proband was born the third of four children. All four suffer from this hereditary disorder. A genealogical study of the proband revealed that three of the four siblings suffer from these two hereditary disorders: the proband and two brothers (Fig. 3). The older sister was diagnosed with only type 1 spinocerebellar ataxia; no heterozygous mutation (deletion of exon 15 of the PHEX gene) was detected. The remaining three children were found to have two concurrent mutations in the genes that cause hypophosphatemic rickets and type 1 spinocerebellar ataxia.

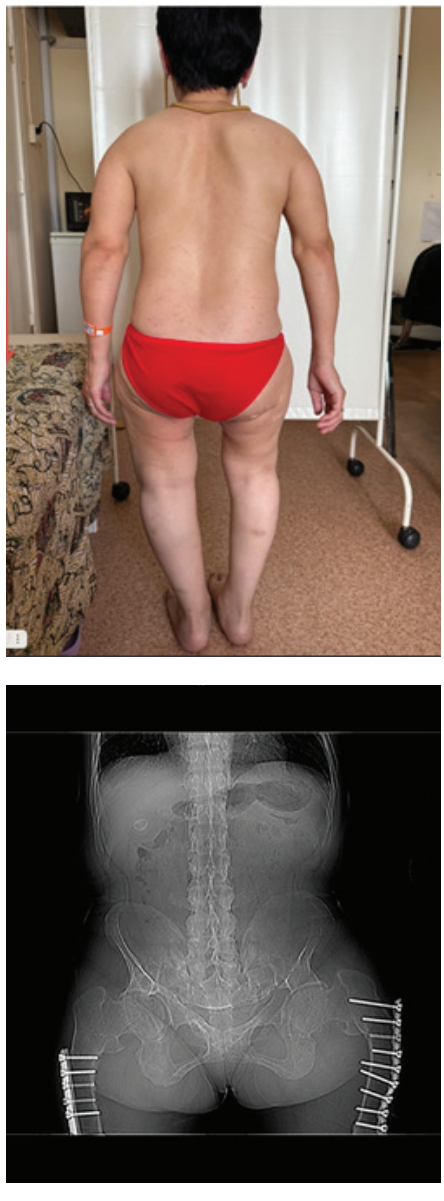

Fig. 3. Patient B. Typical changes in the skeleton and lower extremities in hypophosphatemic rickets

A family history of spinocerebellar ataxia type 1 was identified on the paternal side. The father, at age 42, developed unsteadiness when walking and speech impairment. He was bedridden for the last five years due to unsteadiness and died at age 67 from aspiration pneumonia. According to his daughter, molecular genetic testing was performed on the father, which revealed a mutation in the ATXN1 gene with a repeat count of 32/48. The father's mother had the disease and died at age 55. She had the disease for 15 years, walking with assistance due to unsteadiness. The father was the eldest child. Of the father's eight siblings, two currently have spinocerebellar ataxia type 1, and four have died from spinocerebellar ataxia type 1.

During examination and assessment of the neurological status, the following was revealed: short stature - 120 cm, with varus deformity of the lower limbs, shortening of the right lower limb by 1.5-2.0 cm, weight 40 kg (Fig. 2). Consciousness is clear, orientation in space and time, in one's own personality is not impaired. CN: sense of smell is not impaired, pupils D = S, photoreaction is brisk, no limitation of the visual fields was revealed by the control-comparative method, double vision does not bother. Eye movements are full. Convergence is insufficient. Trigeminal points are painless upon pal-

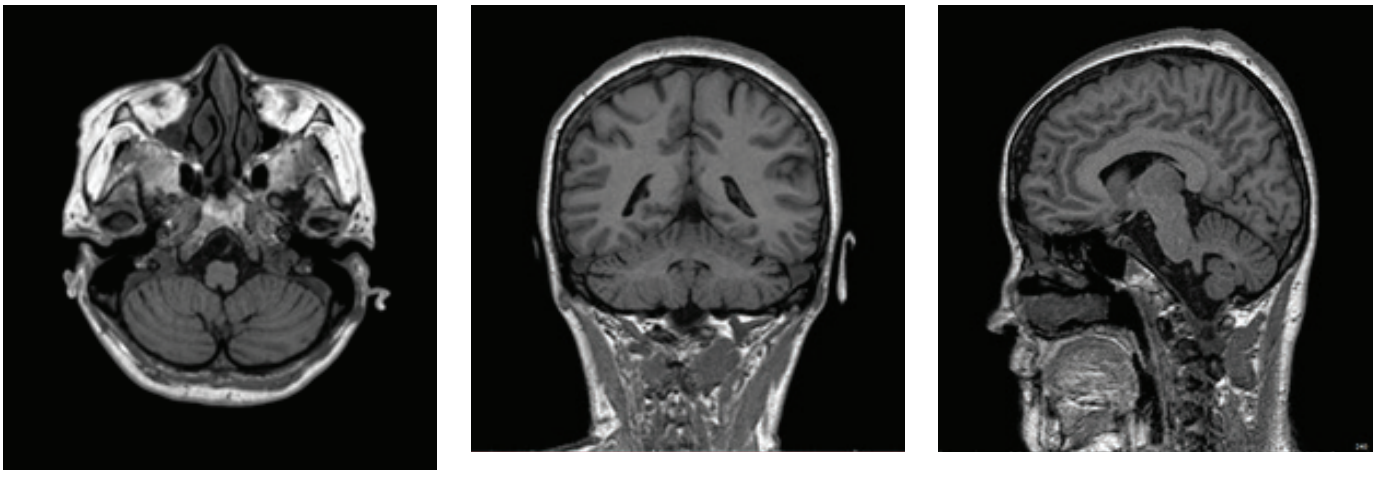

Fig. 4. MRI picture of isolated cerebellar atrophy

pation, sensitivity on the face is normal. Asymmetry of the nasolabial folds is mild - smoothed on the left. Tongue slight deviation to the right, uvula is mobile, to the right. Speech is slightly altered according to the type of cerebellar dysarthria. Mild dysphagia for liquid and solid food. Pharyngeal reflex is slightly reduced. The patient can distinguish whispered speech from left to right at a distance of 6 meters. The sternocleidomastoid and trapezius muscles are intact. Motor function: wide-legged gait with the aid of two canes, similar to cerebellar ataxia.

Muscle tone: D=S, increased in the arms. Contractures in the extremities are present at the hip joints on both sides, with movement limited at the knees when lying horizontal. Muscle strength in the extremities is equal proximally to 5.0 points, equal distally to 5.0 points, equal proximally to 4.0 points, equal distally to 4.0 points. Tendon reflexes in the upper and lower extremities: D=S, high, with widened reflexogenic zones. Abnormal foot signs (-) on both sides. In the Romberg position, there is moderate unsteadiness, which increases with eye closure. The patient performs the finger-to-nose test with ataxia on both sides; heel-to-knee tests are impossible due to deformities in the lower extremities. There is no impairment of deep sensory sensation in the fingers or toes. No impairment of superficial sensory sensation was objectively detected. Pelvic functions are normal.

Results:

Montreal Cognitive Assessment (MoCA) - 30 points (normal).

Hospital Anxiety and Depression Scale (HADS): Anxiety - 4 (normal), Depression - 5 (normal).

Morse Falls Risk Scale - 80 points, indicating a high risk of falls.

Hendrick Fall Risk Model II - 5 points, also indicating a high risk of falls.

Scale for the Assessment and Rating of Ataxia (SARA) - 16 points (maximum 40 points).

Magnetic resonance imaging (MRI) of the brain: signs of mild cerebellar and brainstem atrophy (Fig. 4).

Needle electroneuromyography: needle EMG revealed... Left, Vastus lateralis, Femoralis, L2, L3, L4 – no spontaneous activity detected; interference EMG – horizontally extended turn-amplitude cloud, increased average MUAP frequency to 600/s; MUAP examination revealed EMG stage IIIa (intermediate type). Clinically, no evidence of primary muscular or primary neuronal disorders was detected.

Spirometry, conclusion: moderate decrease in vital capacity. Moderate restrictive VFL impairment.

Blood tests showed thrombocytopenia: 11 *10 10 9/L upon admission, rising to 74 *10 10 9/L by discharge; parathyroid hormone – 27.2 pg/ml. Thyroid hormones: TSH - 0.20, free T4 - 8.41, free T3 - 3.12, antibodies to TPO - 34.6 IU/ml.

Discussion. In this case report, we describe a previously unreported case of two concurrent hereditary diseases transmitted in an autosomal dominant manner from both parents. The mother suffered from hypophosphatemic rickets, and the father from spinocerebellar ataxia type 1. As a result, the couple had children with both conditions. All affected siblings developed symptoms of hypophosphatemic rickets in childhood, and all were recognized as disabled from childhood. Symptoms of spinocerebellar ataxia type 1 began at the age of 39-40 years.

Molecular genetic analysis revealed a heterozygous mutation—a deletion of exon 15 of the PHEX gene—and a pathological expansion of 40 CAG repeats in the ATXN1 gene in both patient V. and her siblings.

The patient developed SCA type 1 symptoms at age 40 in 2021: unsteadiness when walking and slurred speech. Due to unsteadiness and limited mobility in her legs, she cannot walk down stairs independently and only walks short distances. She has noted a worsening of her condition over the past year and uses a wheelchair for longer distances.

The onset of SCA type 1 in her older brother and older sister also occurred at age 40. Both brothers were diagnosed with a mutation in the ATXN1 gene with a pathological expansion of 40 CAG repeats.

The older sister was diagnosed with an expansion of 29/42 CAG repeats in the ATXN1 gene, but was not diagnosed with a heterozygous mutation (deletion of exon 15 of the PHEX gene) and has no signs of chondrodysplasia. At the same time, she is also registered with a rheumatologist with the following diagnosis: Rheumatoid arthritis, seropositive, anti-CCP?, late stage, low DAS28CRP-2.72 activity, erosive arthritis, radiographic stage III, functional class 1. Partial ankylosis of both wrist joints. Secondary gonarthritis II-III.

Thus, based on the family history, molecular genetic testing for type 1 SCA and hypophosphatemic rickets, neurological status, and clinical examination data, the final clinical diagnosis was:

Primary: G11.2 - Late-onset cerebellar ataxia: Spinocerebellar ataxia type 1, autosomal dominant inheritance pattern (mutation in the ATXN1 gene, increased CAG repeats 29/42), with cerebellopyramidal and mild bulbar syndrome, moderately progressive course.

Concomitant: E83.3 - Disorders of phosphorus and phosphatase metabolism: X-linked dominant hypophosphatemic rickets. Deletion of exon 15 of the PHEX gene. Bow-shaped deformity of the lower extremities (condition after multiple surgical corrections). Osteoarthritis of the left and right knee joints. Somatic short stature. Secondary hyperparathyroidism. Decreased BMD. Vitamin D deficiency.

Varus deformity of the lower extremities (post-severe surgical corrections). Osteoarthritis of the left and right knee joints. Biconcave deformity of the bodies of the Th5 (grade 1), Th6 (grade 2), Th7 (grade 2), Th8 (grade 2), Th9 (grade 2), Th1O (grade 1), L1 (grade 1), L2 (grade 1), L3 (grade 2), L4 (grade 2), and L5 (grade 3) vertebrae.

BPPV syndrome. Left-sided nodular goiter, euthyroidism. D69.5 - Secondary thrombocytopenia: mixed genesis, due to severe secondary immunodeficiency; H52.2 - Astigmatism: Simple myopic astigmatism OU.

Conclusion. The authors present a family case of a previously undescribed combination of two genetic syndromes. The combination of two hereditary pathologies in this clinical description presents a very challenging diagnostic challenge for neurologists due to the rare nature of the two hereditary disorders and the fact that the symptoms of hypophosphatemic rickets may overlap with those of ataxia, which can complicate timely diagnosis. This family case should alert the medical community and health authorities not only of the Lensky District but also of the entire Republic of Sakha (Yakutia) and should direct the efforts of the medical organization toward public education regarding hereditary diseases, taking into account the bioethical issues that inevitably arise when discussing this area of medicine.

The authors declare no conflict of interest.

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PAGET'S DISEASE OF BONE AS A RARE CAUSE OF HEADACHE

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Headache is one of the most common complaints encountered in clinical practice. Although primary headaches (such as migraine and tension-type headache) are most prevalent, timely identification of secondary headaches is essential, as they require distinct diagnostic and therapeutic approaches. This paper presents a clinical case of Paget's disease of bone with isolated skull involvement, manifested solely by chronic headache. Based on elevated serum alkaline phosphatase levels, further examination was performed in a 47-year-old patient initially diagnosed with tension-type headache. Magnetic resonance imaging (MRI), computed tomography (CT), and bone scintigraphy confirmed the diagnosis of Paget's disease of bone, after which pathogenetic therapy was initiated.

Keywords: headache, secondary cephalgia, Paget's disease of bone, alkaline phosphatase.

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Introduction. Headache is one of the most common reasons for seeking medical care [1, 8]. According to the Global Burden of Disease (GBD, 2022) study, the overall prevalence of headache was 52.0% (95% CI: 48.9–55.4), migraine – 14.0% (95% CI: 12.9–15.2), and tension-type headache – 26.0% (95% CI: 22.7–29.5). Chronic headaches lasting 15 or more days per month were reported in 4.6% (95% CI: 3.9–5.5) of cases [16]. Headache significantly reduces quality of life and often leads to temporary or permanent disability [14].

In most cases, primary headaches—migraine, tension-type headache, and cluster headache—are observed. However, secondary headaches are not uncommon; these are symptoms of other, often more serious disorders, requiring specific diagnostic approaches [8].

Paget's disease of bone (PDB, also known as deforming osteitis) is a chronic, slowly progressive skeletal disorder characterized by focal abnormalities in bone remodeling [2]. Excessive osteoclastic resorption, coupled with disorganized osteoblastic bone formation, results in structurally weakened, deformed, thickened, and hypervascularized bone [3]. PDB typically affects older individuals, particularly men, and occurs in approximately 1–5% of people over 50 years old [5]. There is marked geographic variation, with the disease being more common in populations of European descent and relatively rare in Asians [11]. Although its exact cause remains unclear, PDB is thought to develop in genetically predisposed individuals, as a positive family history is reported in 5–40% of cases [9]. Environmental factors, including viral infections (especially paramyxoviruses) and vitamin D deficiency, have been proposed as contributing factors [3].

Clinically, the disease manifests with bone pain (73.8%), bone deformities (18.1%), hearing loss (7.9%), and pathological fractures (5.7%). However, in up to 22% of patients, PDB may remain asymptomatic [15]. Neurological complications include hearing loss (76%), neck pain (2–5%), cranial nerve palsies (0.2–41%), and peripheral nerve involvement (2–5%) [13]. Although headache is frequently reported in PDB, it is a nonspecific symptom [4]. Typically, headaches are localized in the posterior head and are aggravated by increased intracranial pressure, such as during coughing or defecation. Possible mechanisms include skull hypervascularization, basilar impression, hydrocephalus, compression of trigeminal nerve roots, thickening of facial bones, and intracranial hemorrhage [7].

Thus, although rare, Paget's disease of bone should be considered in the differential diagnosis of chronic headache. We present a clinical observation of a patient in whom headache was the only manifestation of Paget's disease of bone.

Case Description. A 47-year-old man was admitted in August 2025 to the neurology department with persistent dull and aching headaches localized in the temporal and infraorbital regions (VAS score 7), unaccompanied by nausea or vomiting.

History of present illness. The patient had been experiencing headaches since

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2023, initially on the right side only, later involving both sides and the infraorbital area. The onset was associated with a remote head injury (without loss of consciousness). The headache was nearly continuous. Self-administration of nimesulide (2 tablets three times daily) provided moderate relief. There were no clear triggers or factors affecting the frequency or intensity. The patient denied nausea, vomiting, photophobia, phonophobia, and aura. He had not been under neurological supervision prior to this hospitalization.

Comorbidities: hypertension; chronic sinusitis with frequent exacerbations.

Medications: nimesulide 2 tablets three times daily.

Family history of headache: unremarkable.

Neurological examination: within normal limits.

Upon admission, based on the duration and nature of the headache, chronic tension-type headache complicated by medication-overuse headache due to prolonged use of simple analgesics (nimesulide) was suspected.

Laboratory findings: Routine blood and urine tests, coagulation profile, parathyroid hormone, serum protein electrophoresis, and tumor markers were within normal limits. Biochemical testing revealed elevated alkaline phosphatase of 183.0 U/L (reference range: 40–150 U/L). Given this abnormality, further evaluation was undertaken.

Ultrasound of the abdominal organs and prostate showed no pathology

Brain MRI (FLAIR sequence) demonstrated foci of pathological bone remodeling in both parietal bones, accompanied by reactive changes in the adjacent dura mater and soft tissues (Fig. 1). Brain CT confirmed areas of pathological bone remodeling in the same regions (Fig. 2).

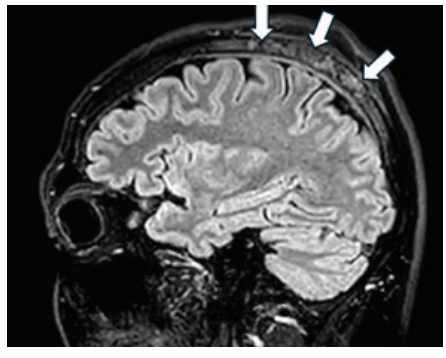

Fig. 1. Brain MRI (FLAIR sequence), sagittal slice – foci of bone remodeling in the parietal bones

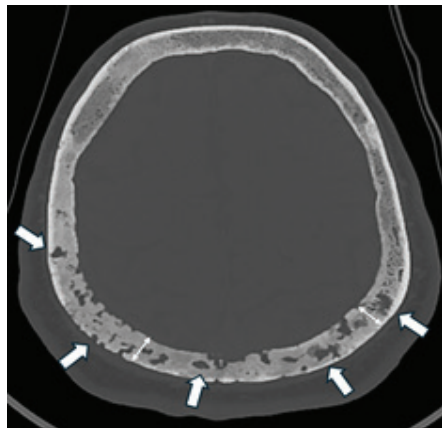

Fig. 2. Brain CT, axial slice – bone remodeling in both parietal bones.

Whole-body bone scintigraphy performed three hours after radiopharmaceutical administration revealed physiological tracer uptake in the facial skeleton, sternum, scapular angles, spine, iliac wings, and shoulder and hip joints. A focus of increased radiotracer accumulation was identified in the parietal bones, more pronounced on the right (Fig. 3).

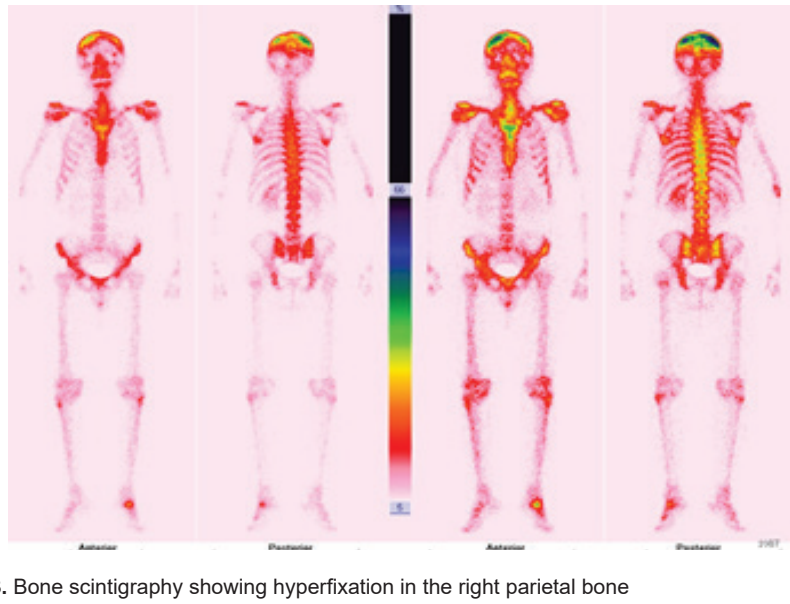

Fig. 3. Bone scintigraphy showing hyperfixation in the right parietal bone

Sternal bone marrow aspiration, performed to exclude multiple myeloma, revealed no abnormalities.

A multidisciplinary consultation involving a neurologist and a rheumatologist concluded with a diagnosis of Paget's disease of bone with isolated skull involvement. Treatment with zoledronic acid 5 mg/100 mL intravenously once yearly was prescribed. The patient was referred for long-term rheumatologic follow-up.

Discussion. Paget's disease of bone is the second most common metabolic bone disorder, with a prevalence ranging from 1.5% to 8.8% [10, 17]. Neurological symptoms are reported in approximately 76% of patients [6]. Headache is a rare manifestation, described in only about 1.6% of cases; seizures are also uncommon [4, 7]. Radiographic methods, including CT, MRI, and bone scintigraphy, play a crucial role in diagnosis. Differential diagnosis may be required to distinguish PDB from metastatic lesions, lymphoma, or multiple myeloma [12].

The present case illustrates a rare but clinically important manifestation of PDB—chronic headache as the only symptom. Given the high prevalence of tension-type headaches, such cases can easily be misinterpreted as primary headache disorders. In this case, the elevated alkaline phosphatase level prompted further investigation, leading to the correct diagnosis through MRI, CT, and bone scintigraphy, and subsequent initiation of pathogenetic therapy.

Conclusion. Headache remains one of the most common reasons for medical consultation. Although the vast majority of cases (up to 90–95%) are due to primary headache disorders such as tension-type headache or migraine, clinicians must maintain vigilance for secondary causes. Secondary headaches may indicate serious underlying pathology and typically require specific diagnostic and therapeutic approaches. The presented case emphasizes the importance of comprehensive evaluation and consideration of Paget's disease of bone as a potential cause of chronic headache, particularly in middle-aged and older patients with elevated alkaline phosphatase levels.

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A CASE REPORT OF FREDERICK'S SYNDROME: COMPLETE TRIFASCICULAR BLOCK WITH ATRIAL FIBRILLATION

This article presents a clinical case of a patient with newly diagnosed Frederick's syndrome, in this case persistent atrial fibrillation and complete trifascicular block, including proximal complete AV block, anterior hemiblock, and complete right bundle branch block. The possible mechanism of development of this condition and the treatment provided at Regional Clinical Hospital No. 1 in Tyumen, Russian Federation, are discussed.

Keywords: Frederick's syndrome; electrocardiogram; atrial fibrillation; trifascicular block; complete heart block; anterior hemiblock; complete right bundle branch block

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Introduction. As is often the case in medicine, Frederic's syndrome (FS) is an eponym. In 1904, the Belgian physiologist L.L. Frederick, during an experiment, established that in animals with atrial fibrillation (AF), the intersection of the His bundle causes regular contractions of the ventricles, despite the persistent arrhythmia in the atria [7]. In humans, FS is characterized by a combination of complete atrioventricular (AV) block and AF or atrial flutter, which leads to a complete cessation of impulse conduction from the atria to the ventricles. Under these conditions, the ventricles are excited by the pacemaker from the AV node or ventricular conduction system, while chaotic contractions of individual muscle fibers occur in the atria. On an electrocardiogram (ECG), this manifests itself as both an f-wave and regular ventricular contractions. FS occurs in 0.6–1.5% of patients with AF [1,4]. Data on the epidemiology of FS are outdated and require updating. FS is mentioned in isolated English-language publications, which suggests the use of this eponym by physicians in the post-Soviet space rather than the extreme rarity of this pathology. The clinical presentation of FS may include episodes of loss of consciousness (Morgagni–Adams–Stokes attacks), dizziness and weakness, as well as bradycardia.

Objective: to describe a clinical case of a patient with FS, with a trifascicular block against the background of AF.

Materials and Methods: A retrospective analysis of the medical records of an inpatient in the arrhythmology department of the Tyumen Regional Clinical Hospital No. 1 was conducted. Data from clinical observation, laboratory tests, instrumental diagnostics, and the surgical protocol were used.

Case Report. A 74-year-old man presented to our emergency department with complaints of severe general weakness, dizziness, hypotension for 3 months, and syncope for 1 year. The last brief, unattended loss of consciousness, without bladder or bowel movement, occurred 2 months ago. There was no previous histo-

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ry of similar complaints. He discontinued his cardiotonic medications (losartan, indapamide, bisoprolol) 3 months ago due to low blood pressure as self-monitored. His cardiac history revealed hypertension and persistent AF for 5 years, for which he regularly takes apixaban. He did not report taking any other medications.

Patient history. No family history. He denies any bad habits. His allergy and epidemiological history are unremarkable. He has a sigmoid colon tumor. He underwent surgery in 2011, which resulted in a temporary stoma. No other treatments were performed. He was removed from the oncologist's list in 2022. Does not report any other chronic diseases.

Objective data. Examined in a horizontal position. The body constitution is abnormal - congenital deformities of the limbs, fusion and rotation of the toes on the left foot, as well as on the right and left hands. Consciousness is clear. Mucous membranes are clean, moist. The skin is clean, somewhat pale. The lymph nodes are intact. Moderate pastosity of the lower third of the shins and feet. The number of breaths per minute is 18 per min. SpO2 98%. On auscultation, breathing is vesicular, conducted in all parts, no wheezing. The shape of the chest is normosthenic. Heart rate is 32 beats per minute. Pulse is rhythmic. Blood pressure on the right arm is 150/80 mmHg, on the left arm 150/70 mmHg. Heart sounds are clear, rhythmic. Heart murmurs are not auscultated. Pulsation in the peripheral arteries is determined. The abdomen is not distended and is soft. The liver is at the costal margin. Urination and defecation are unremarkable.

Laboratory diagnostics. Troponin I is 18 ng/L (reference range up to 22 ng/L), sodium uretic peptide is 1492 pg/mL (reference range up to 440 pg/mL), glomerular filtration rate (MDRD) is 95.03 mL/min, and there is mild normocytic anemia (Red blood cells (RBC) 4.32 10*12/L; Hemoglobin (HGB) is 118 g/L; Mean corpuscular volume (MCV) is 86.2 fl). Other laboratory tests showed no significant abnormalities.

The patient was admitted to the intensive care unit due to severe bradycardia and complete heart block leading to syncope.

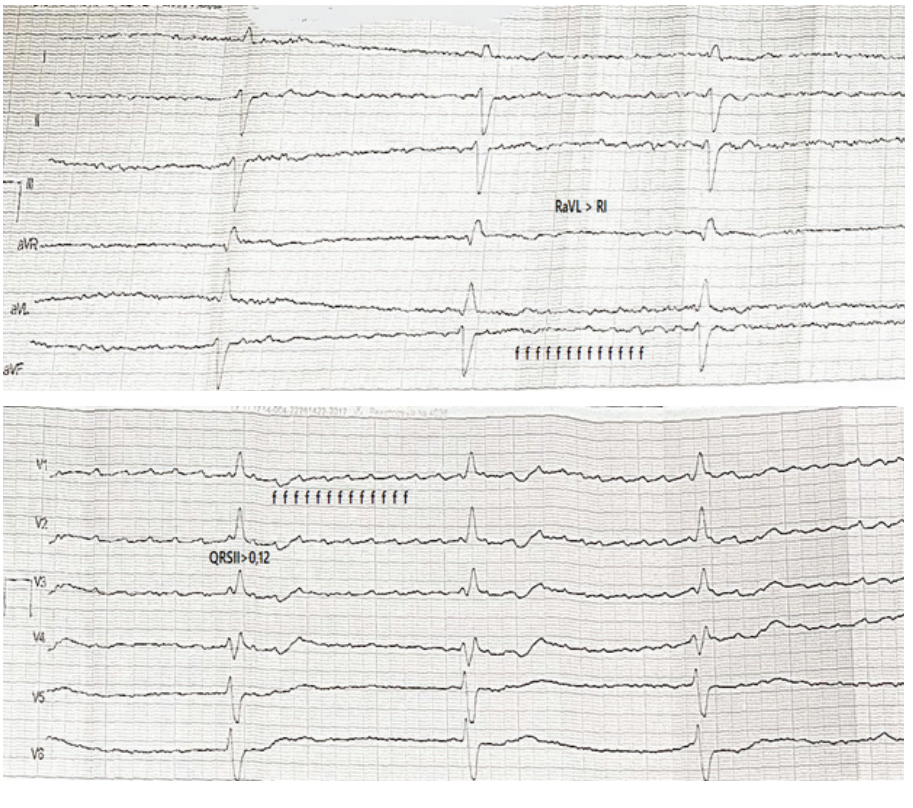
Instrumental diagnostics. Figure shows the patient's ECG. Echocardiography (table 1) reveals moderate right heart dilation, signs of pulmonary hypertension, marked left atrial dilation, and moderate concentric left ventricular (LV) myocardial hypertrophy. Grade 1 aortic and mitral valve regurgitation was present. Against the background of diffuse myocardial hypokinesis, areas of local contractility impairment were not reliably identified. Global contractility of the LV myocardium is reduced, ejection fraction is 32%.

Coronary angiography (CAG) was performed - no significant obstructive lesion of the coronary arteries was detected. According to ultrasound dopplerography of the brachiocephalic arteries, hemodynamically insignificant atherosclerosis is present. Triglycerides are 1.11 mmol/L, high-density lipoproteins are 1.22 mmol/L, cholesterol is 4.16 mmol/L, and low-density lipoproteins are 2.8 mmol/L.

Surgery was then performed. An Ingevity 7842 59 cm endocardial electrode was inserted into the right ventricle via the subclavian vein and positioned in the middle third of the interventricular septum. The electrode was connected to the Essentio SR pacemaker in VVI mode. Pacemaker monitoring data are presented in table 2. During subsequent hospital observation, syncope was absent, episodes of hypotension were not recorded, and a neurologist examined the patient. Neurogenic causes of syncope were excluded. For technical reasons, stress tests for coronary artery disease were not performed.

The final clinical diagnosis was coronary artery disease. Cardiac rhythm and conduction disturbance: third-degree atrioventricular block secondary to atrial fibrillation (Frederick's syndrome). CHA2DS2-VASc 3 points. HAS-BLED 2 points. Implantation of the Essentio SR (VVI) pacemaker with an endocardial electrode on August 12, 2025. Stage 1 CHF (RKO 2023), CHF IIA (according to Vasilenko-Strazhesko), low EF-32%, FC 2. Stage III hypertension. Target blood pressure level not achieved. Risk 4 (very high). The patient was discharged in a satisfactory condition. Upon discharge, the following medications were recommended for regular use: Dapagliflozin 10 mg, 1 tablet once a day. Bisoprolol 2.5 mg, 1 tablet in the morning. Apixaban 5 mg, 1 tablet 2 times a day. Valsartan 80 mg, 1 tablet in the morning. Amlodipine 10 mg, 1 tablet in the evening. Spironolactone 25 mg, 1 tablet in the morning. Atorvastatin 20 mg, 1 tablet in the evening. An appointment with a cardiologist qualified to program pacemakers is scheduled in two months.

Discussion. The main period of studying the cardiac conduction system, mostly in animal models, occurred in the 20th century, but today, various conduction pathologies continue to be investigated by the medical community. Of interest is the newly identified Bayes syndrome, characterized by the association of severe interatrial block and atrial arrhythmias, in particular AF, with an increased risk of dementia, stroke, and mortality [6]. Also recently, a rare case of combined cardiac conduction disor-



ECG of the patient upon admission (recording speed 50 mm/s, amplitude 10 mm/mV)

der was described, in which alternating bundle branch block was accompanied by second-degree AV block [10]. FS, like the above-described Bayes syndrome and alternating block, are an uncommon cardiac conduction disorder in the daily clinical work of a cardiologist, but this fact does not reduce its severity and significance. In routine practice, when reading an ECG, it is necessary to increase physician alertness to changes in the characteristics of the pacemaker and slowing of impulse conduction through various parts of the myocardium.

The causes of FS are pronounced sclerotic, degenerative, or inflammatory changes in the myocardium due to severe organic heart diseases, such as coronary artery disease (CAD), acute myocardial infarction, myocarditis, cardiomyopathy, or other structural disorders. Factors that provoke manifestation may be excessive physical activity, taking medications that have negative chronotropic, dromotropic and bathmotropic effects, as well as electrolyte imbalance and stress [3]. There is also evidence that CAD and hypertension are the main cause of the combination of right bundle branch block and left anterior fascicular block [9].

The presence of significant cardiac rhythm and conduction disturbances and the patient's advanced age may suggest infiltrative myocardial diseases, particularly amyloidosis. The echocardiographic picture (absence of both asymmetrical pronounced hypertrophy and dilation of the heart, absence of signs of restriction, absence of significant damage to the aortic valve, absence of myocardial heterogeneity), as well as the absence of clinical signs of a systemic pathological process, namely, damage to the gastrointestinal tract, nervous system, eyes and kidneys in addition to the heart, speak against this diagnosis in this patient. However, there is evidence that trifascicular block may be a primary manifestation of cardiac amyloidosis [11].

In the present case, we observe prominent AF f-waves and regular, infrequent ventricular contractions, as well as signs of anterior hemiblock and complete right bundle branch block. AF f-waves are not always visualized on the ECG, which creates difficulties in differential diagnosis. The deformation of the QRS complexes on the ECG in this patient is moderate and is associated with a block along the left and right branches of the His bundle, with the pacemaker located in the AV junction, indicating a proximal type of block, often not accompanied by a disturbance in the biomechanics of cardiac contraction [2, 5, 8]. Distal AV block is characterized by widened, deformed ventricular-type QRS complexes.

Table 1

Echocardiography data

Parameters	Value
Left Atrium EDV ICV	46 mm 89 ml 50 ml/m^2
Right atrium	41x59 mm
Right ventricle	36 mm
Anterior wall of the right ventricle	6 mm
Aorta	not dilated, walls are compacted, in the ascending section - 39 mm
Aortic valve leaflets Systolic leaflet opening Leaflet divergence Vmax Pgmax Regurgitation	compacted unlimited 18 mm 1.6 m/s 11 mmHg 1st degree
Left ventricle: EDV EDV ESR ESV Simpson ejection fraction Local contractility Myocardial mass: LVM LVMI TCR	 51 mm 124 ml 43 mm 83 ml 32% диффузный гипокинез 241 g 137 0,47
Mitral valve: Customers Diastolic valve opening peak E: Vmax Regurgitation	 not thickened, compacted unlimited 0.7 m/s 1st degree
Interventricular Septum diastolic Posterior Wall of the Left Ventricle diastolic	12 mm 12 mm
Tricuspid valve: Customers Diastolic valve opening Vmax Regurgitation Pgmax	 not thickened unlimited 0.55 m/s Physiological 1.2 mmHg
Pulmonary valve: Cutlets Systolic leaflet opening Vmax Pgmax Regurgitation	 thin unlimited 1.4 m/s 8 mmHg 1st degree
Collapse of the IVC during inspiration IVC Signs of pulmonary hypertension: pulmonary artery diameter PAS	less than 50% 20 mm 28 mm 47 mmHg

As mentioned above, such cardiac rhythm and conduction disturbances in patients may be associated with CAD. Initially, a large volume of atherosclerotic coronary lesions, possibly multivessel plaque localization, can be suspected. Also, given the high incidence of AV block in inferior myocardial infarction, the physician should assess for patterns of vascular accident in the leads of the corresponding location. In our case, there were no electrocardiographic signs of myocardial infarction, and the intact coronary arteries according to invasive coronary angiography and a negative troponin test in the patient rule out acute forms of coronary artery disease as a cause of FS.

The development of complete AV block in the context of AF is associated with significant cardiac remodeling, the development of various complications, and a worsening prognosis, which is often underestimated by doctors. The ab-

Table 2

Pacemaker examination

Parameters	Meaning
Model of pacemaker	Essentio SR
On the monitor	rhythm from pacemaker in VVI mode 60 bpm
Stimulation mode	VVI
Base rate	60 bpm
Amplitude RV	3.5 V
Duration RV	0.4 ms
Threshold RV	0.4 V
Sensitivity RV	2.5 mV
Voltage of wave RV (R)	14.9 mV
Impedance RV	678 Ohm
Expected service life	more than 8 years
Statistics	AsVs: 4 %; AsVp: 96 %

sence of atrial systole in AF, as well as the presence of AV dyssynchrony with a marked decrease in heart rate, lead to a decrease in the atrial and ventricular contribution to LV filling during diastole. As a result, the degree of mitral regurgitation and pulmonary artery wedge pressure increases, the load on the right ventricle increases, which over time causes its dysfunction and expansion, as well as dilation of the fibrous rings of the AV valves. Similar echocardiographic characteristics are observed in our patient, who likely has arrhythmogenic cardiomyopathy.

The first step in treating patients with bradycardia is discontinuing medications that lower the heart rate, primarily beta-blockers and digoxin. A detailed patient history is helpful in this regard. The next step, if bradycardia persists and the accompanying symptoms described above appear, is pacemaker implantation. The literature describes the practice of implanting a permanent pacemaker with bundle-His pacing in FS, which ensures the most physiological conduction of the impulse through the cardiac conduction system [5]. Our clinic does not yet use this technique. To date, there is no scientific data on the comparison of different pacemaker modes for FS and their effectiveness.

Conclusion

This clinical case contributes to expanding knowledge about FS. Due to the difficult diagnosis and treatment of this combined arrhythmia, especially in elderly patients, increased attention is required to the possible development of FS. Early detection of cardiac symptoms allows for timely administration of drug therapy and/or referral of the patient for pacemaker implantation, which will contribute to an improved prognosis and reduced mortality among patients with such a common arrhythmia as AF.

The authors declare no conflicts of interest.

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A RARE CLINICAL CASE OF TUBEROUS SCLEROSIS WITH CARDIAC RHABDOMYOMA IN A NEWBORN

This article presents a rare case of tuberous sclerosis with cardiac rhabdomyoma in a newborn. Rhabdomyoma is a benign tumor in the heart cavity, arising from embryonic muscle cells, and is frequently associated with tuberous sclerosis (TS), serving as its diagnostic marker. The disease was not detected prenatally. Postnatally, the infant was found to have a heart murmur; within days depigmented patches appeared all over the body, predominantly on the back, groin area, and legs. The diagnosis was established based on echocardiography. To determine further management tactics, a telemedicine consultation was conducted with the Federal Center for Cardiovascular Surgery in Khabarovsk, and the diagnosis was confirmed. Urgent planned surgical intervention was indicated.

Keywords: cardiac rhabdomyoma, tuberous sclerosis, cardiac tumors, newborn.

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Introduction. The most common benign cardiac tumor in children is rhabdomyoma. In 50% of cases, the tumor has an intracavitary localization, in 30% - it affects the myocardium, and it is extremely rare for it to be found on the heart valves [3]. The clinical presentation of rhabdomyoma is variable and depends on the localization, size of the tumor, involvement of the cardiac conduction system, and may manifest as an asymptomatic condition and a result of an incidental finding, or may lead to a fatal outcome in the perinatal period [4]. Rhabdomyoma is frequently (in 50-86% of cases) associated with tuberous sclerosis (TS), and is its diagnostic marker [4]. Tuberous sclerosis (Pringle–Bourneville disease, epiloyia) is an autosomal dominant disorder phenotypically manifesting as benign hamartomas in various organs and systems. Its prevalence is established as ranging from 1:6,000 to 1:10,000 in different populations [5, 6]. The cause of tuberous sclerosis (TS) is mutations in chromosomes 9 and 16 —specifically, in region 34 of the long arm of chromosome 9 (TS type 1—TSC1), and in region 13 of the short arm of chromosome 16 (TS type 2—TSC2) [1, 5, 7, 8].

This article presents a clinical example of a child with cardiac rhabdomyoma in the setting of tuberous sclerosis.

Objective: To describe a rare clinical case of a child with cardiac rhabdomyoma in tuberous sclerosis.

Materials and Methods: A retrospective analysis of the medical records of a patient hospitalized in the Department of Pathology of Newborns and Premature Infants No. 2 (DPNPI No. 2), Republican Hospital No. 1 – National Medical Center named after M.E. Nikolaev (RH No. 1 – NMC), was performed.

Clinical Case. A newborn girl was admitted to State Autonomous Institution RS(Y) "RH No. 1–NMC named after M.E. Nikolaev ", Department of Pathology of Newborns and Premature Infants No. 2 (DPNPI No. 2) on the 6th day of life. According to the mother's obstetric history, she had been under observation at an antenatal clinic since 7–8 weeks of pregnancy. The child was born from the fourth pregnancy. The first half of pregnancy was complicated by threatened miscarriage, marginal placenta previa, and retrochorial hematoma, for which she received inpatient treatment at her place of residence. In the second half of pregnancy, she developed grade 1 anemia, which was treated on an outpatient basis.

Prenatal screening results: First screening (12 weeks): marginal chorionic previa, retrochorial hematoma; Second screening (22 weeks and 4 days): no pathological findings; Third screening: not performed.

The third delivery occurred at 40 weeks of gestation, with vertex presentation. Birth weight was 3896 g, length 57 cm, head circumference 37 cm, chest circumference 37 cm. Apgar score was 8/9 points. The newborn's condition at birth was assessed as relatively satisfactory. A pronounced blowing murmur was detected at all auscultation points of the heart. No resuscitation was required.

At the central district hospital (CDH), a complete blood count and blood bio-

chemistry showed no abnormalities; blood gas analysis was not performed. Abdominal ultrasound and chest X-ray revealed no pathology. Echocardiography (ECHO-KG) was not performed due to the lack of equipment.

Upon admission to DPNPI No. 2: the skin was pink with peeling, and there were single round depigmented patches, up to 1.0 mm in diameter, on the posterior trunk and buttocks (Fig. 1).

The heart sounds were rhythmic but muffled, with a systolic murmur of moderate intensity at all auscultation points. In the subsequent days, the spots spread over the entire body, predominantly on the back, inguinal area, and legs; there were numerous solitary whitish lesions resembling areas of depigmentation, without hyperemia.

The results of the complete blood count, blood biochemistry, blood gas analysis, ELISA, PCR for intrauterine infections, infectious screening, coagulation profile, and urinalysis were unremarkable. Instrumental studies – Including neurosonography (NSG), abdominal ultrasound (US), hip joint ultrasound, EEG, abdominal CT, and brain MRI – revealed no pathology.

During the clinical-instrumental examination, the following findings were identified:

- Chest X-ray: Congenital heart defect. Pulmonary hypertension. Hypervolemia in the pulmonary circulation. Grade 3 thymomegaly.

- ECG: Intraventricular conduction disturbance. Increased potentials of the right ventricle (RV). Disturbed repolarization processes.

- Echocardiography (EchoCG): Additional masses detected in the left ventricular (LV) cavities; the right ventricle shows obstruction of the inflow tract of the left ventricle and of the inflow tract of the right ventricle (presumably rhabdomyomas). Patent foramen ovale (0.34 cm). Grade 1 regurgitation at the tricuspid valve. Right ventricular dilation. Ejection fraction 74.2% (Fig. 2).

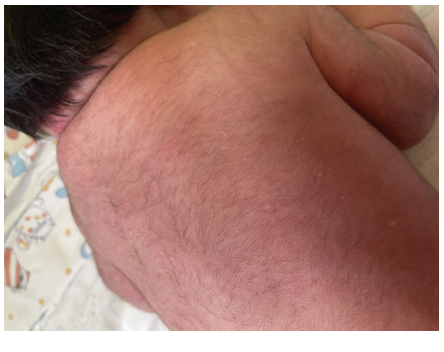

Fig. 1. Areas of skin depigmentation

- Holter ECG: Baseline ventricular repolarization disorders. ECG signs of right ventricular enlargement.

- Cardiac CT with contrast: Additional structures in the outflow tracts of the left and right ventricles. Small areas of ground-glass opacity in the dorsal segments of the lungs, most likely zones of hypoventilation. Grade 3 thymomegaly. Nodule in the right lobe of the thyroid gland.

- Lab studies: Elevated cardiac markers: CK-MB 29.05 U/L, high-sensitivity troponin 35.200 ng/L, and tumor marker AFP 24,590.60 IU/mL.

The child was examined by a cardiologist, dermatovenerologist, geneticist, ophthalmologist, and neurologist. The patient had two major criteria for tuberous sclerosis: skin depigmentation and cardiac rhabdomyoma.

To determine further treatment tactics, a consultation with a federal center was conducted. Following a telemedicine board decision with the Federal Center for Cardiovascular Surgery in Khabarovsk, the patient was indicated for surgical removal of the cardiac tumor-like masses.

On the 8th day of life, considering the increased risk of fatal outcome due to obstruction, the board decided to transfer the child for observation in the ICU. During observation in the ICU, the baby required no respiratory support and was subsequently transferred to the specialized department (DPNPI No. 2) for further preoperative preparation.

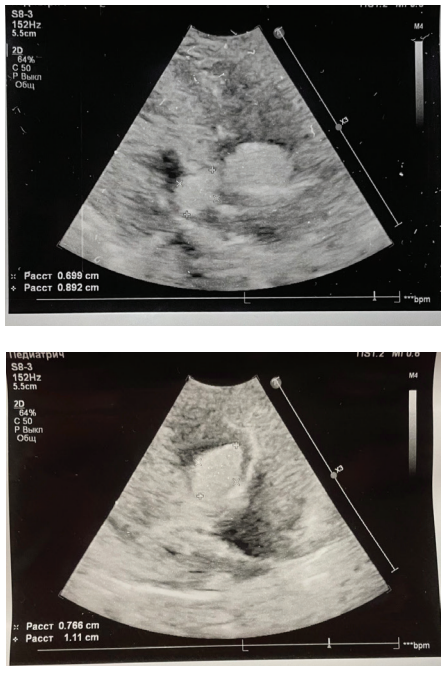

Fig. 2. Masses in the cavities of the left and right ventricles of the heart

During hospitalization, the child was exclusively breastfed and received conservative treatment.

On the 13th day of life, in stable condition, the child was transferred to the Federal Center for Cardiovascular Surgery in Khabarovsk for further surgical treatment with the following diagnosis: Multiple congenital malformations. Benign cardiac neoplasm. Rhabdomyomas (in the left ventricle cavity, 0.7 × 0.9 cm; right ventricle, 0.7 × 0.8 × 1.1 cm and 0.4 × 0.4 cm) with obstruction of the LV outflow tract and right ventricular inlet. Patent foramen ovale, 0.34 cm. Heart failure 0. Tuberous sclerosis. Thyroid gland nodule (right lobe). Unspecified anetoderma.

Conclusion: This case demonstrates the potential for early diagnosis and timely surgical correction of cardiac rhabdomyoma in early childhood. Early diagnosis and surgical intervention improve prognosis. Cardiac rhabdomyoma in newborns requires a multidisciplinary approach (involving cardiologists, cardiac surgeons, and geneticists). The management strategy depends on the tumor size, the presence of symptoms, and its association with tuberous sclerosis.

In recent years, only isolated cases of prenatal diagnosis of cardiac rhabdomyoma have been reported in the literature. For instance, during fetal ultrasound at 21 weeks of gestation, volumetric masses were detected in the region of the right and left ventricles. Histopathological examination revealed the presence of "spider cells." Molecular genetic testing identified a pathogenic variant in the TSC2 gene [2].

Thus, early diagnosis of cardiac rhabdomyoma is possible in the perinatal period using the tools of prenatal ultrasound and molecular genetic studies.

The authors declare no conflicts of interest.

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VENOUS THROMBOSIS OF THE LOWER EXTREMITY IN A 13-YEAR-OLD PATIENT

A clinical case of the venous thrombosis of the lower extremity in a 13-year-old patient is represented in the article, the thrombosis occurred in the course of post-COVID syndrome (enzyme-linked immunosorbent assay for SARS-CoV2 by 18.09.2024 detected 50000 BAU/mL. Onset of the disease acute fever up to 38C, abdominal pain. Diagnostic laparoscopy performed in the central district hospital. Diagnosis: right ovarian apoplexy, cystic ovaries, adhesions, anemiya (hemoglobin - 75 g/l, dizziness, weakness). Prior to that, she was examined in Yakutsk, autoimmune thyroiditis was diagnosed. On the 6th day after laparoscopy, fever up to 39,2C, pain in the popliteal pits and lower legs appeared. Transferred to the childrens department of the central district hospital, from there sent to the admission and diagnostic department of the pediatric center RH1. Electroneuromyography revealed signs of progressive muscle damage. Transferred to the cardiorheumatology department for further examination and treatment. Laboratory data showed an increase in all inflammatory markers (CRP, D-dimer, ferritin). Ultrasound imaging revealed occlusive thrombosis of the sural veins of both lower extremities. Received low molecular weight heparin, antucosgulants, aspirin, diclofenac as treatment. The adequate therapy resulted in positive dynamics.

Keywords: thrombosis, thromboembolism, coronavirus, children, vessels, veins

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Introduction. Thrombosis is the formation of the blood clots in the blood vessels both in the arteries and the veins. Venous thromboembolism is most common and results in fatalities in the adult population. However, it is uncommon and rare among children and adolescents. Its estimated prevalence varies from 0.5 to 1.9 per 10,000 children population. Those children diagnosed with blood clotting disorders are at the highest risk [2,8].

Deep vein thrombosis can be complicated with thromboembolism and post-thrombotic syndrome. Most of the thromboses are associated with central veinous catheterization. The other factors are traumas, surgical interventions, post-traumatic disorders, hereditary and acquired thrombophilic conditions, such as the presence of the factor V Leiden mutation, protein C and protein S deficiencies, disorders of the intestines, kidney, circulatory system, infections, rheumatic diseases, antiphospholipid syndrome and many others. The other causes of thrombosis are the inherited abnormalities (inferior vena cava agenesis, atresia, occlusion or uncomplete substitution) [3,6].

As a rule, the onset of deep vein thrombosis in children is asymptomatic, though there can be swollen upper and lower extremities, elevation of body temperature, weakness, erythema, positive Homan's sign (pain response in the dorsiflexion of the foot). The diagnosis of venous thrombosis is confirmed by Duplex ultrasonography with color Doppler imaging; contrast venography, computed tomography, angiography and MRI are less common [2,4,8,9].

Despite all the mentioned causes post-COVID and multisystemic inflammatory system should be added, as they manifest by vasculopathy and hemostasis. The pathogenesis of SARS-coV-2 affects the vascular endothelium, disturbs hemostasis that result in risk of clot formation [10]. The patients after COVID-19 show high indices of D-dimmer and fibrinogen which increase clot formation [3,9].

The clinical case. The female patient K., aged 13, was admitted to the department of cardio-rheumatology of the Pediatric Center of the Republican hospital #1, M.E. Nikolaev National health center. She complained of weakness, pains in the lower extremities when walking, nausea and dizziness.

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Case history: She lost consciousness a month before the admission to the Pediatric center, the patient was admitted to the neurological department of the Central regional hospital. On examination no neurological abnormalities were revealed. Thyroid profile changes as well as changes in the thyroid gland were noticed. On the 13-th day after the onset of the disease she was discharged from the hospital with the diagnosis of autoimmune thyroiditis. At home she felt pains in the abdomen, the body temperature increased up to 38C. The diagnostic laparoscopy was carried out. She was diagnosed with apoplexy of the right ovarium, cystic changes in the ovarium, peritoneal adhesion, anemia (hemoglobin – 75g/L). To increase the level of the hemoglobin the erythrocyte mass was transfused on the 16th day. On the 2nd day after blood transfusion the body temperature increased up to 38-39C, the fever lasted for a week. On the 20-th day she experienced pains on the calves and lower legs.

The results of the tests showed: LDH – 896Un/L (N-250 Un/L), CRP-30.0 mg/L (N-5mg/L); coagulogram: time – 12.5 sec. (N: 6+-1.6), Protromb.index -97% (N:89+-4.2), PT – 1.02 (RI:0.8-1.14), PLT – 200-280 (RI: 160-380), ferritin – 192 mcg/L (7-140).

Past medical history: chicken-pox, acute respiratory diseases.

Family history: Her mother is 40, she suffers from chronic bronchitis, pyelonephritis, hypertension, bronchial asthma in close relatives. Her father is 39, with no medical conditions.

On admission, the patient's condition was moderately severe. There was marked weakness. Appetite and sleep were not disturbed. Clinically, swollen lower extremities, which were more marked at the lower legs, were noticed, the vascular pattern was expressed on the skin of the lower legs. The other organs and the systems had no abnormalities.

Local status: the patient limps, the patient cannot crouch. She has difficulties with tiptoeing and walking on heels. The muscles of the thigh and lower legs are painful on palpation.

Complete blood count on admission: increase erythrocyte sedimentation rate – 50mm/h, (N-4-15mm/h), neutrocytosis – 72% (N-40-65%), granulocytosis – 63,3x10E9/l (N-4.5-13,0x10E9/l), hemoglobin – 92g/l (N-115-150g/l). During the treatment, all blood counts returned to normal, hemoglobin increased to 114g/l.

Blood chemistry is presented in Table 1.

The coagulogram on the 33rd day of the disease showed that: free protein S was 55.00% (normal rages are 50.00-134.00), antithrombin III was 110.00% (normal ranges are 96.00-126.00), protein C – 126.00% (normal ranges are 68.00-125.00);

The coagulogram on the 61st day of the disease showed that: prothrombin index was 100.00% (normal ranges: 70.00-140.00), Prothrombin time was 12.30 sec. (normal ranges: 13.50-17.00), INR was 1.00 (normal range: 0.81-1.13), fibrinogen was 3.71 g/L (normal range: 2.12-4.33), aPTT/PTT was 30.60 sec. (normal range: 30.80-41.40);

The coagulogram on the 89th day of the disease showed that: prothrombin index was 100.00% (normal range: 70.00-140.00), Prothrombin time was 12.80 sec (normal range: 13.50-17.00), INR was 1.00 (normal range: 0.81-1.13), fibrinogen was 4.49 g/L (normal range: 2.12-4.33), aPTT/PTT was 30.70 sec (normal range: 30.80-41.40).

Enzyme-linked immunosorbent assay for SARS-CoV2 by 18.09.2024 detected IgG>5000.0 BAU/mL.

The main values of thromboelastography are represented in the table 2.

The result of the lower extremities ultrasound scan is represented in the table 3.

Table 1

Biochemical blood test dynamics

The day of the disease	AST (Un/L) Normal value is up to 40	ALT (Un/L) Normal value is up to 37	Albumin (g/L) Normal level: 38-54	D-dimer (mcg/mL) Normal range: 0.16-0.39	Ferritin (mcg/L) Normal range: 7-140	LDH (Un/L) Normal range: 250-295	C-RP (mcg/L) Normal range is up to 5mcg/L
The 33-rd day	17.70	9.70	32.80	3.48	192	896.0	30.0
The 42-th day	16.10	9.90	-	1079.82	-	158.40	
The 52-nd day	38.70	64.20	42.80	799.93	46.10	-	
The 55-th day	43.90	58.40	38.10	-	39.50	136.50	
The 61-st day	21.30	25.30	38.90	349.57	24.80	117.30	
The 70-th day	39.50	41.30	43.40	1.42	-	165.30	
The 79-th day	16.20	15.60	43.50	0.27	29.10	125.30	1.25
The 89-th day	16.50	15.60	43.30	-	-	132.70	2.09

On the 32-nd day of the onset she was referred to the diagnostic department of the Pediatric center of the Republican hospital #1, the National health center. Later she was admitted to the department of cardio-rheumatology for further examination and treatment.

Anamnesis: The patient is a second child born after the second pregnancy; the pregnancy had no abnormalities during its course. It was a spontaneous vaginal delivery at due time. Her birth weight was 3750 g, height 52 cm.

Table 2

Thromboelastography (TEG) data on the 42nd day of the disease

The procedure code	TEG parameter	Measurement	Result	Normal value
1002237	Clot formation	min	2.30	Up to 6 min
1002377	Reaction time	min	8.00	Up to 12 min
1002302	Maximum amplitude	mm	56.70	50 mm
1002252	Maximum clot strength	mm	58.10	40-65

Table 3

The results of the ultrasound scan of the veins of the lower extremities

The day of the disease	The 33rd	The 52nd	The 67th	The 90th
Medical assessment report	Occlusive deep vein thrombosis of the both lower extremities	Non-occlusive deep vein throm-bosis of the lower extremities with-out expressed floating parts. There is moder-ate infiltration in subcutaneous adipose tissue of the both lower legs. Inguinal lymphadenitis of the both sides.	Ultrasound signs of the partial re-canalization of the right femoral vein, deep veins of the lower leg. Oc-clusing thrombosis of the right femo-ral vein, deep veins of the both lower legs.	Ultrasound signs of the partial canaliza-tion of the popliteal veins of the both sides. Non-occlusive throm-bosis of the external iliac vein, common femoral, great sa-phenous vein on the both sides.

Electromiography was carried out on the 33rd day. The medical finding: the motor point needling of the m.Tibialis anterior s. revealed the signs of progressive initial muscular disturbance: the potentials of the motor units showed expressed reduced time, amplitude (by 34.9%), all entirely polyphase, disperse, denervation / reinnervation process (DRP) is at the stage 2.

Secondary examinations on the 30th day of the disease revealed: 1) the syndrome of the median, ulnar, fibular and tibial nerves disorders was not detected on the both sides;

2) Motor point needling of m.Tibialis anterior s. revealed signs of initial muscular disturbance: the potentials of the motor units are reduced by 12.4%, polyphase, denervation / reinnervation process (DRP) was at stage 2 in comparison with the previous investigation (19.09.2024) positive dynamics is noticed: the amplitude of the potentials of the motor units (PMU) was normal, time of PMU increased, the polyphase index reduced.

Echocardiography of the 39th day of the disease revealed regurgitation of the tricuspid valve stage 1, unstable in the aortic valve – 1st stage. Mitral valve disease with minimum regurgitation. The heart cavities are not enlarged. Ejection fraction was 66%.

The ultrasound scan of the organs of the abdominal cavity and the kidneys was carried out on the 2nd day of the hospitalization. Findings: deformation of the gallbladder. Additional blood vessel was noticed in the right kidney.

Examination of the specialists.

An ophthalmologist revealed mixed astigmatism. Myopia of the 1st degree, complicated myopic astigmatism of the left eye. Retinal angiopathy of the both eyes.

A hematologist diagnosed thrombosis of the lower extremities. Secondary antiphospholipid syndrome.

A vascular surgeon indicated no surgical treatment according to the objective medical examination and findings of the instrumental investigations. Conservative treatment and follow up control examination are recommended.

A rheumatologist of the Federal center corrected the course of treatment, the patient was recommended to take etanercept 50 mg 1 per week, rivaroxaban 2.5 mg 2 times a day for 10 days, low-molecular heparin, aspirin, diclofenac and omeprazole.

Taking into account hyperinflammatory phenotype such as increased markers of inflammation (CRP, D-dimmer, LDH, ferritin) in the serum of the patient's blood etanercept was prescribed.

The condition was moderately severe on discharge. The patient does not complain of anything. She does not limp and she can crouch. She can tiptoe and go on her heels.

The patient is recommended a follow-up care in her local polyclinic and to apply for disability, walk moderately and wear compression stockings; physical trainings at school are contraindicated.

The hematologist and the vascular surgeon should be consulted again in a month. The patient should continue taking rivaroxaban in the recommended dose.

Discussion. We have presented the clinical case of a rare childhood disease, thrombosis of the veins of the lower extremities at the age of 13. The childhood thrombosis is always a great clinical issue due to the severity of its course and outcome. One of the main causes of the venous thrombosis in childhood is the central venous catheterization and a genetic predisposition [3,9]. The researchers revealed that the risk of thrombosis increases and results from the deficiencies in antithrombine III, protein C and protein S due to gene mutation, thrombophilia is one of the candidates [11]. According to the scientific data it is relatively rare complication of post-COVID syndrome. Moreover, multisystem inflammatory syndrome (MIS) can develop after COVID infection in children and adolescents. According to the latest investigations of the recent years, the criteria of multisystem inflammatory syndrome (MIS-C) diagnosis were updated by the Council of state and territorial epidemiologists (CSTE) and the Center for disease control (CDC) of the USA this could allow to identify the disease from the other similar conditions. Thus, MIS-C is diagnosed in all patients under 21 years with COVID infection in the anamnesis which occurred within 60 days before or during the hospitalization, accompanied with high fever of 38C or above and lasting for any time. The only laboratory finding was an increased level CRP from 3.0 mg/dL and more. To diagnose MIS-C there should be at least two signs of the organ or system involved: affection of the heart, skin and mucous membranes, gastro-intestinal tract, hematologic changes in the laboratory findings and shock [1,5]. The risk of thrombosis increases in that case. Disfunction of the platelets is most commonly associated with COVID-infection.

According to the researchers, who studied the link of COVID-19 and development of thrombosis in such COVID-patients, the infection results in thrombotic complications as there is accumulation of the proinflammatory factors. Pathogenesis of the thrombotic complication is associated with a complex of pathophysiological mechanisms which develop afterwards. Thus, viral respiratory infections including COVID-infections, are associated with platelet activation and hypercoagulation. The platelets display the receptors on the surface, which recognize the viruses and release lots of pro-inflammatory mediators, which are responsible for interaction of platelets with leukocytes and endothelial cells initiating coagulation and activation of different interleukins [11]. In that case an increased inflammatory and coagulant activity takes place, which results in thrombosis [7,11].

Conclusion. This clinical case shows that there are long-lasting post-COVID effects, which was asymptomatic when it was complicated by thrombosis. The

main feature of the disease manifestation is its comorbidity course in the child. The description of this case underlines the importance of early diagnosis and adequate therapy administration to treat such patients.

The authors declare no conflicts of interest.

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