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FACTORS IMPACTING THE EPIGENETIC AGE IN THE INDIGENOUS POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

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УДК 616.67, 612.68, 612.017.2

The epigenetic clock used to assess biological age by the level of DNA methylation is a promising method for studying the influence of unfavorable factors on the rate of aging and the development of age-related pathologies. The aim of the study was to analyze the relationship between lifestyle factors and epigenetic age in the indigenous population of Yakutia. The study involved 113 respondents living in the central region of Yakutia, aged 18 to 99 years. The average age of the subjects was 66.9 ± 23.6 years. We analyzed factors that can affect the acceleration of epigenetic age: BMI, abdominal obesity, waist/height and waist/hip ratio, diet, physical inactivity, health status, marital status, education, smoking, alcohol consumption, insomnia, health status. The relationship of these factors with age - related acceleration calculated using 4 biological clock models was assessed: PhenoAge, Horvath DNAm, Hannum DNAm, GrimAge. A tendency towards acceleration of epigenetic age was revealed in respondents with a high body mass index, low physical activity and an impaired diet (prone to overeating, consumption of highly refined carbohydrates and high-calorie foods).

Keywords: epigenetic age, Horvath DNAm, PhenoAge, Hannum DNAm, GrimAge, age acceleration, Yakutia, indigenous population, aging, body mass index, nutrition.

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Introduction. Investigations of aging processes is of great importance for maintaining health and increasing the life expectancy of the population. Identification of the causes and mechanisms of aging can help in developing methods to slow down or prevent the decline of physiological functions. To assess the rate of age-related processes, various models of biological age are used, which serve as an indicator of the level of health and adaptive reserve of a person [2]. Analysis of the methylation level of cytosine-phosphate-guanine sites (CpG) located throughout the genome is the basis for assessing epigenetic age, which has great potential for understanding the mechanisms of aging and clinical application [10]. Several models of epigenetic clocks have been developed to calculate epigenetic age, the most famous and studied of which are: Hannum DNAm, Horvath DNAm, DNAm PhenoAge, GrimAge. Hannum DNAm and Horvath DNAm was developed by identifying sets of CpGs in which DNA methylation changes with age [3, 4]. DNAm PhenoAge is based on a single measure of biological age, including age and 9 clinical biomarkers using a single CpG set [8]. Also, the biological age PhenoAge can be determined by the parameters of clinical blood test. The GrimAge is a composite marker combining 7 CpG sets, each of which evaluates the concentration of a specific plasma protein, a CpG set evaluating smoking history and self-assessment of age and gender [11]. The prognostic value and the possibility of using epigenetic clocks in determining predictors affecting the rate of aging and preventing age-related changes are currently being intensively studied. Most studies of epigenetic age and factors associated with it have been conducted in populations of European descent. While in other ethnic groups, epigenetic acceleration can be influenced by environmental factors, lifestyle characteristics, and genetics.

The indigenous population of Yakutia is characterized by a developed polar (northern) type of metabolism, adapted to the sharply continental subarctic climate [1, 9]. The first epigenetic studies of the Yakut population revealed differences in the methylation level in many areas of the genome compared to residents of central Russia [7]. At the same time, representatives of the Yakut population demonstrated a statistically significant acceleration of epigenetic age relative to central Russia for all major types of epigenetic clocks Horvath DNAm age, Hannum DNAm age, DNAm PhenoAge, GrimAge and their improved models [7]. The difference in epigenetic age between regions is most noticeable when using the Horvath DNAm clock (median acceleration of 5.36 years). Interestingly, for younger participants (under 40 years) and for older participants (after 80 years), only the Horvath DNAm age acceleration was

statistically significant between regions. In the present study, we extended these studies and considered some factors that may influence epigenetic age in the Yakut population. The aim of the present study was to analyze the relationship between lifestyle factors and epigenetic age in the indigenous people of Yakutia.

Materials and methods. The study was conducted among different age groups of the unorganized indigenous population over 18 years old of the central part (Tattinsky and Churapchinsky districts and the city of Yakutsk) of the Republic of Sakha (Yakutia). The study participants were 113 respondents - volunteers, representatives of the indigenous ethnic group of the Republic of Sakha (Yakutia) - Yakuts: 51 men (45.1%), 62 women (54.9%). The average age was 66.9±23.6 years. Each participant signed an informed consent and filled out a consent for personal data processing, taking into account the principle of confidentiality. The study was approved by the local biomedical ethics committee of the Medical Institute of NEFU (protocol No. 34 dated March 30, 2022). The exclusion criteria were non-indigenous nationality, acute and chronic diseases in the acute stage, pregnancy.

The respondents were examined according to a program that included: questionnaires (socio-demographic parameters, frequency method of assessing nutrition, questions regarding lifestyle (smoking, alcohol consumption, assessment of physical inactivity using a short international questionnaire to determine physical activity IPAQ)), anthropometric examination (weight, height, waist circumference (WC), hip circumference (OB)), double measurement of blood pressure (BP), triple measurement of pulse, fasting venous blood sampling. Body mass index (BMI), waist/hip ratio, height/hip ratio were calculated using the standard method. Obesity was assessed using the following criteria: body mass index (≥30 kg/m2); waist-to-hip ratio (WC/HG more than 0.9 in men and 0.85 in women); waist-to-height ratio (WC/HG ≥0.5); waist circumference for Asian populations (more than 80 cm in women and 90 cm in men) was used to assess abdominal obesity. The health status was assessed according to the health group criteria according to the Order of the Ministry of Health of the Russian Federation dated March 13, 2019 N 124n "On approval of the procedure for conducting preventive medical examination and medical examination of certain groups of the adult population".

Laboratory examination of venous blood was performed in the fasting state with determination of: white blood cells, mean corpuscular volume (MCV), red blood cell distribution width (RDW - CV) , lymphocytes, albumin, glucose, alkaline phosphatase, creatinine, C-reactive protein. Based on these 9 clinical biomarkers and chronological age, the biological age PhenoAge was calculated. DNA methylation analysis was performed using Illumina Infinium MmethylationEPIC BeadChip technology, which measures DNA methylation levels at 866,836 genomic sites with single nucleotide resolution [7]. After all pre-processing procedures, 739,168 CpG sites remained. Methylation data were estimated using the Horvath online calculator (https://dnamage.clockfoundation.org/) .

Statistical analysis of the data was performed in the IBM SPSS STATISTICS 22 package. When comparing groups depending on the type of data, the following were used: one-way ANOVA, Pearson's Chi-square contingency table. The critical value of the level of statistical significance of differences (p) was taken to be 5%. The K-means clustering method was also used. Age acceleration was calculated by subtracting chronological age from biological age. In order to analyze the influence of external factors on the acceleration or deceleration of biological age, we focused on the median. When detecting a deviation of biological age above the median, it was considered that there was a tendency toward age acceleration, if less than the median, there was a tendency toward age deceleration.

Results and discussion. Table 1 presents the clinical and demographic characteristics of the respondents and the difference between biological age, calculated using different models, and chronological age depending on the age groups.

In the older age groups there were more unmarried people, the majority of whom were widowers, and without higher education, there was also a predominance of people with chronic diseases (Table 1). Anthropometric parameters such as weight, BMI, waist circumference were statistically significantly lower in older people. Whereas, young people tended to be overweight and obese. In older age groups, statistically significant high blood pressure was observed.

The maximum age acceleration according to PhenoAge was observed in the group of participants aged 40-60 years, according to Horvath DNAm in the group under 40 years, which is consistent with the literature data [5]. In older age groups of 60-80 and over 80 years, the acceleration is insignificant for all biological clocks or a slowdown is observed relative to chronological age, which was also noted in other studies and is explained by a decrease in the rate of tissue regeneration [5, 16].

Considering the limited sample size and the weak acceleration of biological age by the epigenetic clock relative to the chronological age, the median was used to identify the influence of external factors on age acceleration. If the biological age was found to be higher than the median, it was assumed that there was a tendency toward age acceleration; if it was lower than the median, there was a tendency toward age deceleration. We analyzed the factors that could impact on epigenetic age acceleration: BMI, abdominal obesity, waist-to-height and waist-to-hip ratios, diet (n = 104), physical inactivity (n = 32), health status, marital status, education, smoking (n = 109), alcohol consumption (n = 107), and insomnia. Dietary habits were assessed using the frequency method, smoking at the time of the study, alcohol consumption more than once a week, and physical inactivity was assessed using the international IPAQ questionnaire only if the answers to the questionnaire were filled in correctly. BMI, nutrition and physical inactivity demonstrated the statistically significant association with the acceleration of epigenetic age (Table 2).

Most respondents with high BMI had an age acceleration rate above the median, suggesting that people with high BMI tended to have an epigenetic age acceleration. Statistical significance was observed for the biological clocks: Hannum DNAm, Horvath DNAm, GrimAge. For the nutrition analysis, respondents were divided into 2 clusters using the K-means method: Cluster 1 included subjects prone to overeating, eating fried foods, and highly refined carbohydrates; cluster 2 included people with a more conservative type of nutrition, including dairy and meat products more often. A large proportion of respondents from cluster 1 had an age acceleration rate above the median for the biological clock Hannum DNAm, Horvath DNAm, GrimAge. Thus, we can assume that the eating behaviors influenced to the age acceleration in the studied group. Also shown statistically significant association between physical inactivity and the epigenetic age acceleration according to the Hannum DNAm and GrimAge, but not PhenoAge and Horvath DNAm. No statistically significant association was found with other parameters such as: abdominal obesity, waist-to-height ratio, waist-to-hip ratio,

Table 1

Characteristics of respondents and epigenetic acceleration depending on age group

Indicators	Up to 40 years Me (CI 95%) n -20	40-60 years Me (CI 95%) n- 25	60-80 years old Me (CI 95%) n- 22	over 80 years old Me (CI 95%) n -51	p
Age. years	29.5 (27.1;32.4)	50 (47.9; 52.8)	69.5 (67.7;72.8)	91 (89.5;91.7)	<0.001
Sex: male female	 10 (50) 10 (50)	 12 (48) 13 (52)	 10 (45.5) 12 (54.5)	 19 (41.3) 27 (58.7)	0.908
Marital status: married single	 11 (55) 9 (45)	 20(80) 5 (20)	 13 (59.1) 9 (40.9)	 12 (26.1) 34 (73.9)	<0.001
Education: higher not higher	 14 (70) 6 (30)	 12 (48) 13 (52)	 6 (27.3) 16 (72.7)	 12 (26.1) 34 (73.9)	0.001
Health groups I II III a III b	 7 (35) 7 (35) 5 (25) 1 (5)	 2 (8) 3 (12) 19 (76) 1 (4)	 1 (4.5) 2 (9.1) 18 (81.8) 1 (4.5)	 42 (91.3) 2 (4.3)	<0.001
Smoking (n-109) Yes No	 6 (31.6) 13 (68.4)	 10 (43.5) 13 (56.5)	 7 (33.3) 14 (66.7)	 11 (23.9) 35 (76.1)	0.424
Drinking alcohol more than once a week (n -107) Yes No	 1 (5.6) 17 (94.4)	 2 (9.1) 20 (90.9)	 4 (19) 17 (81)	 3 (6.5) 43 (93.5)	0.381
Weight. kg	63.5 (58.8;72)	72 (67.5; 80.6)	63.5 (61.7; 71.2)	51.5 (48.4; 54.6)	<0.001
BMI	22.3 (21.2; 25)	26.7 (25.3; 29.5)	25.9 (25; 28.4)	21.7 (20.8;22.8)	<0.001
Waist circumference. cm	81.5 (75.7; 85.1)	94 (90.9;102.5)	89.5 (86; 95.2)	84.5 (81.8;87.7)	<0.001
SAD DAD	125.5 (117.9; 133.16) 85.2 (78.5; 91.8)	129.2 (122.5; 135.9) 85.6 (80.3 ; 91)	133.9 (126.7; 141.1) 80.6 (74.4; 86.8)	143 (136.6; 149.5) 78.7 (75.13; 82.3)	0.002 0.104
Age acceleration by PhenoAge	4.7 (0.6; 6.2)	**5.3 (-0.2;8.4)**	2.3 (-2.1; 6.0)	0.78 (-0.4; 4.4)	0.735
Epigenetic acceleration by Hannum DNAm	**-2.5 (-4.0;-1.1)**	-6.7 (-8.9; -5.7)	-13.4 (-14.3;-11.7)	-21.5 (-22.4 ;-19.9)	<0.001
Epigenetic acceleration by Horvath DNAm	**12.1 (8.8; 13.2)**	7.3 (5.2; 8.5)	2.4 (0.45;3.7)	-4.8 (-7.1;-4)	<0.001
Epigenetic acceleration by GrimAge	**-4.8 (-6.3;-3.0)**	-8.8 (-9.5;-6.9)	-13.5(-14.2; -11.4)	-18.8 (-17.8; -19.7)	<0.001

Note: statistical methods used: one-way analysis of variance, Pearson Chi-square contingency table, Health groups I – healthy; II – individuals with chronic diseases and risk factors; III a – individuals with chronic non-communicable diseases requiring follow-up observation and specialized care; III b – individuals with chronic non-communicable diseases requiring follow-up observation and high-tech care, The greatest acceleration of epigenetic age in age groups is highlighted in bold.

adaptive potential, health status, insomnia, smoking, alcohol consumption. This may be due to the main limitation of this study: the small sample size of the subjects.

Some of the most significant factors in accelerating epigenetic age, according to a systematic review, are BMI and physical activity [12]. Recent studies also note the influence of smoking and alcohol consumption [13]. However, at present, the relationship between BMI and methylation levels and its mechanisms are still poorly understood. Body mass index is the result of many factors, including gender, nutrition, hormonal signaling, psychosocial factors, smoking and medication use, obesity, and it is unclear which of them can mediate the relationship between BMI and epigenetic age. However, longitudinal study data show that obesity is a cause, not a consequence, of DNA methylation changes [15]. We have found a tendency to accelerate the aging process in individuals with a high body mass index according to models such as Hannum, Horvath, GrimAge. According to the other studies, the relationship between physical activity and the epigenetic clock was ambiguous [6]. Our data showed that individuals with hypodynamia had a tendency to accelerated aging according to Hannum and GrimAge. Another factor that undoubtedly plays a role in accelerating epigenetic age is the quality of nutrition. Thus, a large study involving postmenopausal women within the Women's Health Initiative reported that GrimAge and PhenoAge negatively correlated

Table 2

Epigenetic age acceleration according to PhenoAge , Hannum DNAm , Horvath DNAm , GrimAge depending on BMI, diet, physical inactivity

Indicators	Acceleration of epigenetic age							
	PhenoAge (Me=2.4)		Hannum DNAm (Me=-13.7)		Horvath DNAm (Me=1.5)		GrimAge (Me=-13.6)	
BMI	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)
<25 25-29,9 >30	46(70.8) 19(67.9) 13 (81.3)	19(29.2) 9 (32.1) 3 (18.8)	30(44.1) 18 (62.1) 11(73.3)	38(55.9) 11 (37.9) 5 (26.7)	39(57.4) 22(75.9) 14(87.5)	29 (42.6) 7 (24.1) 2 (12.5)	29(42.6) 18(62.1) 12 (75)	39(57.4) 11 (37.9) 4 (25)
r	0.623		0.036		0.033		0.031	
Nutrition (n =104)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)
1 cluster 2 cluster	36(73.5) 34(66.7)	13(26.5) 17(33.3)	43(82.7) 13(25)	9(17.3) 39(75)	49(94.2) 22(42.3)	3 (5.8) 30 (57.7)	41(78.8) 14(26.9)	11(21.2) 38 (73.1)
r	0.458		<0.001		<0.001		<0.001	
Hypodynamia (IPAQ) (n =32)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)	Higher N (%)	Below N (%)
Yes No	5 (41.7) 8 (57.1)	7 (58.3) 6 (42.9)	10(71.4) 4 (26.7)	4 (28.6) 11(73.3)	11(78.6) 9 (60)	3 (21.4) 6 (40)	9 (64.3) 3(20)	5 (35.7) 12 (80)
p	0.431		0.016		0.280		0.016	

Note: statistical methods used: Pearson Chi-square contingency table, linear-linear relationship.

with plasma carotenoid levels (indicators of fruit and vegetable consumption) [8, 11]. In a meta-analysis of studies Women's Health Initiative and Invecchiare nel Chianti (InCHIANTI) found a significant negative correlation of age acceleration with the consumption of poultry and fish [14]. In the present study, we observed a tendency towards accelerated aging in individuals prone to overeating and consumption of fried foods, and highly refined carbohydrates.

Conclusion. In this study, we analyzed the relationship between some clinical and lifestyle factors and epigenetic age acceleration in the Yakut population. Despite the small sample size, the effect of increased BMI, dietary pattern associated with overeating, consumption of fried foods, highly refined carbohydrates, and low physical inactivity on accelerated epigenetic aging was shown. These data confirm the role of nutrition, physical activity, and body weight maintenance in maintaining health and increasing life expectancy. The use of such a tool as an epigenetic clock with further expansion of the sample and inclusion of a larger set of clinical parameters will allow identifying new factors of accelerated aging.

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RELATIONSHIP BETWEEN THE LEVEL OF ANTIBODIES TO THE RA-33 ANTIGEN AND THE COURSE OF RHEUMATOID ARTHRITIS

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Objective: to study the relationship between the serum level of antibodies to the RA-33 antigen and the characteristics of the course of rheumatoid arthritis (RA).

Materials and methods. The study included 88 patients with a diagnosis of RA that met the ACR/EULAR criteria, 2010. All observed study participants were women (n=100%), aged from 22 to 81 years (M ± σ, 54.3 ± 12.1 years). Rheumatoid factor was detected in 64 people (72.7%). 59 (67%) study participants were positive for anti-CCP. The duration of RA was 0.5–30 years (M ± σ, 11.2 ± 8.6 years), the degree of activity according to DAS28: 0 degree of activity – 19 (21.6%) patients, 1 degree – 10 (11.6%), 2 degree – 52 (59.1%), 3 degree of activity – 7 (7.7%) patients. Among the observed patients, individuals with III radiological stage of the disease predominated. Statistical processing was performed using the Statistica 12.5 software package for Windows.

Results. The level of anti-RA-33 was assessed in a group of RA patients and healthy donors. The level anti-RA-33 was assessed in a group of RA patients and healthy donors. The level normal anti-RA-33 in healthy people, calculated as M±σ, was 10.3±10.2 U/ml (from 0.1 U/ml to 20.5 U/ml). The average level anti-RA-33 in RA patients, calculated as M±σ, was 12.7±31.6 U/ml (from 0 U/ml to 44.3 U/ml). The increase in the level anti-RA-33, compared with donors, is statistically significant (p=0.025) and was observed in 12.5% RA patients. Among 24 patients with RA seronegative by RF, an increase in the level anti-RA-33 was detected in 2 (8.3%) patients, and among 29 patients seronegative by ACCP - also in 2 (6.9%) patients. An increase in the level anti-RA-33 was mainly observed at the initial stages of the disease and with initial radiographic changes. In patients with an increased level anti-RA-33 (more than 20.5 U/ml), pronounced functional disorders were more often detected.

Findings. Thus, it can be concluded that antibodies to anti-RA33 can potentially provide additional diagnostic value in RA.

Keywords: rheumatoid arthritis, diagnostics of rheumatoid arthritis, antibodies to RA-33, heterogeneous nuclear ribonucleoprotein, HnRPA2B1.

Introduction. A relatively new laboratory marker for the diagnosis of rheumatoid arthritis (RA) is the determination of antibodies to RA-33 (anti-RA-33) [3, 4, 5].

RA-33 (heterogeneous nuclear ribonucleoprotein A2/B1, HnRPA2B1) is a 33 kDa protein that binds nucleic acids and performs multiple functions: DNA repair, telomere elongation, chromatin remodeling, mRNA processing, transport and translation. The pathogenetic role of antibodies to RA-33 is currently not entirely clear. It is suggested that anti-RA-33 and T cells directed against RA-33 may contribute to the development of inflammation and autoimmune conditions both by forming immune complexes and by secreting cytokines that can initiate and control the pathogenic process [8]. In RA, RA-33 is overexpressed in the synovial membrane of the joint. This leads to the development of an autoimmune response and an increase in the level of anti-RA-33 in the blood [9]. A number of studies note a fairly good diagnostic efficiency of antibodies to anti-RA33 as a serological marker of RA [2, 9].

According to the literature, autoantibodies against RA-33 occur in up to 15-30% of patients with RA and can be detected already at the earliest stages of the disease [11]. Anti-RA-33 are also found in SLE (in 20-30% of patients) and other systemic connective tissue diseases (up to 40%). The sensitivity of the test is estimated at 31% on average, and the specificity is 90%, while in the absence of clinical and laboratory signs of these diseases, the specificity of the test for RA increases to 96% [2]. Also, studies have noted that anti-RA33 are rarely found in other arthritis: osteoarthritis, reactive arthritis, ankylosing spondylitis or psoriatic arthritis, and therefore they can be used for the differential diagnosis of arthritis, especially in patients seronegative for RF or ACPA [6, 12].

Anti-RA-33 are less specific for RA than anti-CCP or RF and do not correlate with these antibodies [1]. However, the presence of anti-RA-33, especially in the absence of other autoantibodies, may indicate a good prognosis and is not associated with high disease activity and erosive changes in the joints. It should also be noted that anti-RA33 are detected at the earliest stage of the disease or even several years before the onset of the actual clinical disease [7]. It was found that the number of antibodies to RA-33 and ESR in the group of patients with subclinical synovitis were lower than in the group of patients with clinical manifestations of synovitis (p = 0.004) [10]. The usefulness of anti-RA-33 in the diagnosis of early arthritis when negative results of the study of ACPA and RF are obtained, as well as in differential diagnosis with other diseases of connective tissue is separately emphasized [1, 10]. However, at present, the frequency of detection of anti-RA33 in patients with RA, seronegative for RF and ACPA, as well as its relationship with other laboratory parameters reflecting the severity of the disease, have not been sufficiently studied.

Objective: to study the relationship between the serum level of antibodies to the

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RA-33 antigen and the characteristics of the course of rheumatoid arthritis.

Materials and methods. The study was conducted at the A.B. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd. The study included 88 female patients diagnosed with RA that met the ACR/EULAR, 2010 criteria: joint involvement, excluding distal interphalangeal, first metatarsophalangeal, first carpometacarpal; serological test (CCP and RF); acute phase markers of inflammation (ESR and CRP), and duration of disease symptoms. All observed study participants were women (n=100%), their age ranged from 22 to 81 years (M ± σ, 54.3 ± 12.1 years), with the majority of patients belonging to the older age group (over 50 years).

The patients' condition was assessed based on a survey (collection of anamnesis and subsequent identification of RA risk factors), anthropometric parameters (gender, age, height, weight), as well as the results of laboratory and instrumental studies.

The height of the subjects varied from 147 to 186 cm (M ± σ, 160.6 ± 6.6 cm), weight - 43-129 kg (M ± σ, 73.3 ± 15.4), body mass index 18.03 - 46.10 (M ± σ, 28.71 ± 6.26). The duration of RA was 0.5–30 years (M ± σ, 11.2 ± 8.6 years), the degree of activity according to DAS28: degree 0 activity – 19 (21.6%) patients, degree 1 – 10 (11.6%), degree 2 – 52 (59.1%), degree 3 activity – 7 (7.7%) patients.

Among the observed patients, individuals with stage III radiographic disease predominated.

The distribution of patients by functional insufficiency was as follows: 1 (1.1%) participant in the study belonged to FN 0, 22 (25%) to FN I, 58 (65.9%) to FN II, and 7 (8%) to FN III. Among the observed patients, 14 (15.9%) suffered from the articular-visceral form of RA with manifestations in the form of the following systemic disorders: fever, weakness and malaise, anemia, rheumatoid nodules, and cerebral vasculitis.

Rheumatoid factor was detected in 64 patients (72.7%), 59 (67%) study participants were positive for ACPA.

RA complications were as follows: lung lesions in 18 (20.5%), gastrointestinal tract lesions in 26 patients (29.5%). Osteoporosis according to densitometry data was detected in 37 patients (42%).

Statistical processing of the obtained results was carried out using the software package "STATISTICA 12.5". Statistical data processing included determining the normality of data distribution using histogram analysis and the Kolmogorov-Smirnov test. Indicators subject to normal distribution are presented as M±SD (95% confidence interval). Qualitative data were processed statistically using the Pearson goodness-of-fit test and Fisher's exact test; the results were considered statistically significant at $p < 0.05$.

The relationship between positivity for RA-33 and clinical manifestations of RA

Indicator	RA-33 (<20.5 U/ml) n = 77	RA-33 (>20.5 U/ml) n = 11	Reliability
Seropositivity RA			
Seronegative	10 (12.9)	1 (9.1)	p*= 0.592
Seropositivity	67 (87.0)	10 (90.9)	
Clinical stage			
Initial	2 (2.6)	1 (9.1)	χ^2= 2.05 p= 0.358
Detailed	6 (7.8)	0 (0)	
Late	69 (89.6)	10 (90.9)	
Disease activity			
0	18 (23.4)	1 (9.1)	χ^2= 4.38 p= 0.224
I	10 (13.0)	0 (0)	
II	44 (57.1)	8 (72.7)	
III	5 (6.5)	2 (18.2)	
X-ray stage			
Stage I	5 (6.5)	1 (9.1)	χ^2= 2.30 p= 0.509
Stage II	31 (40.3)	2 (18.2)	
Stage III	38 (49.4)	7 (63.6)	
Stage IV	3 (3.9)	1 (9.1)	
Functional class			
I	21 (27.6)	2 (18.2)	χ^2= 8.33 p= 0.039
II	49 (64.5)	8 (72.7)	
III	6 (7.9)	2 (18.2)	
Form of the disease			
articular	20 (26.0)	5 (45.5)	p*= 0.160
with extra-articular manifestations	57 (74.0)	6 (54.5)	
Extra-articular manifestations			
anemia	54 (70.1)	6 (54.5)	p*= 0.168
osteoporosis	30 (39.0)	7 (63.6)	p*= 0.113
lung damage	16 (20.8)	2 (18.2)	p*= 0.604
Concomitant diseases			
diabetes	7 (9.3)	1 (9.1)	p*= 0.727
arterial hypertension	52 (67.5)	6 (54.5)	p*= 0.302
gastrointestinal diseases	23 (29.9)	3 (27.3)	p*= 0.576

Note: $\chi 2$ – Pearson's goodness-of-fit test; p* – Fisher's exact test

Results. The level of anti-RA-33 was assessed in the group of RA patients and healthy donors. The level of normal anti-RA-33 in healthy individuals, calculated as M±σ, was 10.3±10.2 (from 0.1 U/ml to 20.5 U/ml). The average level of anti-RA-33 in RA patients, calculated as M±σ, was 12.7±31.6 U/ml (from 0 U/ml to 44.3 U/ml). An increase in the level of anti-RA-33, compared with donors, was observed in 12.5% of RA patients and is statistically significant (p=0.025).

Given the difficulties in diagnosing RA in seronegative forms of the disease, the frequency of detection of anti-RA-33 in RA patients seronegative for RA and anti-CCP was studied. 24 patients seronegative for RF were observed, of which 2 patients had anti-RA-33. Thus, the positivity for anti-RA-33 in patients seronegative for RF was 8.3%. RA seronegative for anti-CCP was observed in 29 patients, 2 of whom were seropositive for anti-RA-33, which amounted to 6.9%. The level of anti-RA-33 was also determined in patients with RA depending on the clinical picture of the disease. Statistically significant differences in the average level of anti-RA-33 were observed in pa-

tients with RA depending on the clinical stage of the disease (initial clinical stage 9.1+2.9 U/ml, advanced stage 0.3+0.3 U/ml, p=0.034) and depending on the severity of radiographic changes (stage I 2.6+3.2 U/ml, stage III radiographic 0.3+0.5 U/ml, p=0.043).

To determine the clinical and pathogenetic significance of determining the level of anti-RA-33 in patients with RA, patients were divided into 2 groups, in each of which the clinical and laboratory manifestations of RA were studied. The first group (n = 77) included patients with anti-RA-33 values corresponding to the normal limits (less than 20.5 U/ml), the second (n = 11) - with an elevated level of anti-RA-33 (more than 20.5 U/ml). The level of anti-RA-33 was studied depending on the clinical picture of the disease and the results of laboratory research methods. The results of the study are presented in Table.

From the data presented in Table 1, it can be concluded that the level of anti-RA-33 increases in patients with more severe functional impairment in RA.

Discussion of results and conclusions. It is known that early diagnostics of RA, which provides a window of therapeutic opportunities and improves the prognosis of the disease, occupies a special place in clinical practice. Therefore, laboratory markers that allow identifying patients at early stages, and especially potential patients in risk groups, are extremely relevant. Considering that, according to the literature, anti-RA-33 can appear in the blood of patients with RA at the earliest stages and even several years before the onset of the disease, studying the level of these antibodies seems promising. In our study, an increase in the level of anti-RA-33 was detected precisely at the initial stages of the disease and with initial radiographic changes. Moreover, in a certain percentage of cases, anti-RA-33 were detected in the absence of other RA markers (RF and ACPA, in 8.3% and 6.9% of cases, respectively). The results obtained indicate that the determination of anti-RA-33 can be used for early diagnostics of RA, including in individuals seronegative for RF and ACPA. At the same time, according to our data, seropositivity for anti-RA-33 was more common in RA patients with severe functional impairment. It can be assumed that the optimal diagnostic option for using anti-RA-33 determination is to examine patients with existing joint dysfunction that has not yet led to radiographic changes and who are seronegative for RF and ACPA. Further studies on a larger sample of patients are needed to confirm this assumption.

Thus, it can be concluded that antibodies to anti-RA33 can potentially provide additional diagnostic value in RA.

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DIFFERENT LEVELS OF MICRORNA EXPRESSION (MIR-30C-5P, MIR-221-3P AND MIR-375-3P) IN HEART FAILURE PATIENTS WITH PRESERVED AND REDUCED EJECTION FRACTION

MicroRNAs are key regulators of gene expression controlling components of signaling cascades involved in the pathogenesis of heart failure (HF). The expression profile of microRNAs may serve as a sensitive indicator of different types of HF.

The aim of the present study was to compare the gene expression of microRNAs miR-148b-3p, miR-30c-5p, miR-221-3p, miR-328-3p, miR-146a-5p, miR-375-3p, miR-22-3p, miR-15b-3p, miR-148a-3p, miR-590-5p in peripheral blood mononuclear cells (PBMC) and epicardial adipose tissue of coronary heart disease (CHD) patients with and without HF (Non-HF).

Among CHD patients with HF, the groups with mildly reduced/reduced and preserved ejection fraction (HFmr/rEF and HFpEF, respectively) were compared. Our study revealed a significant increase in the expression of miR-30c-5p, miR-221-3p and miR-375-3p microRNAs in PBMCs of patients with HFmr/rEF and HFpEF compared with the group of CHD patients without HF. Accordingly, the relative level of miR-30c-5p expression in PBMC of HFF/EFV patients was significantly higher by 1.99 times in comparison with patients without HF (P<0.0001). The expression of this microRNA in PBMC of HFpEF patients relative to patients without HF is significantly higher by 2.94-fold (P<0.0001). The expression level of miR-221-3p in PBMC of HFpEF patients was increased 4.04-fold relative to patients without HF (P<0.0001). A 2.63-fold increase in miR-221-3p expression was detected in PBMC of HFmr/rEF patients (P<0.0001). The expression of miR-375-3p in PBMCs of HFmr/rEF and HFpEF patients compared with Non-HF patients was significantly higher by 2.09- and 1.77-fold (P<0.0001). For all other investigated microRNAs, no significant expression changes were detected in PBMC. Similarly, we did not detect significant expression changes for any of the investigated microRNA genes in the epicardial adipose tissue of CHD patients.

Thus, the obtained data can be used to determine the role of the investigated microRNAs in the pathogenesis of HF in CHD patients. The results of the present study can be used for further studies of HF pathogenesis. Accordingly, they can be used for the development of modern clinical strategies to assess the risk of HF development in CHD patients.

Keywords. Heart failure, preserved ejection fraction, reduced ejection fraction, microRNA.

Introduction. HF is one of the most frequent causes of hospitalization and mortality worldwide [2]. This pathology increases disability and mortality of the population [1, 6]. HF is a clinical syndrome manifested by the presence of typical signs and symptoms caused by impaired cardiac structure and/or function, resulting in decreased cardiac output and/or increased cardiac filling pressure at rest or on exertion [1]. The European Society of Cardiology provides guidelines for defining HF based on physical examination, plasma natriuretic peptide levels, and echocardiographic examination, which allows the use of ejection fraction (EF) as a basis for dividing HF into three groups: HF with reduced EF - HFrEF (EF ≤40%), with mildly reduced EF - HFmrEF (40% <FV <50%) and preserved EF - HFpEF (EF ≥50%) [1, 8]. At the same time, modern data in the field of molecular biology and genetics of cardiovascular diseases dictate the necessity of their integration into research and clinical practice [7, 10].

Thus, the analysis of noncoding RNAs, among which the microRNA group is particularly prominent, may lead to a deeper understanding of the mechanisms of HF development with preserved and reduced ejection fraction. The aim of the study is to analyze microRNA gene expression in peripheral blood mononuclei and epicardial adipose tissue (EAT) samples from patients with HF with preserved and reduced ejection fraction.

Material and Methods. The present study was of a single-stage nature. 175 patients with CHD and atherosclerosis of coronary arteries who were indicated for coronary bypass surgery were included. Of these, 138 patients were diagnosed with HF. Due to the marked clinical similarity of patients with HFrEF with EF <40% and SNusPH with 40%>FV <50%, we combined them into one group of HFmr/rEF with EF less than 50%. Accordingly, patients were grouped into three cohorts: group 1 - patients without HF (n=37), group 2 - HFmr/rEF (n=44), group 3 - HFpEF (n=94).

HF with preserved and reduced EF was diagnosed according to the European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic HF 2021. Inclusion criteria in group 1 were: absence of HF symptoms, echocardiographic EF ≥50%, normal natriuretic peptide level. Inclusion criteria in group 2 were: symptomatic HF according to the New York Heart Association classification ≥II class, preserved left ventricular EF ≥50%, structural changes on echocardiography, increased natriuretic peptide level. Inclusion criteria for group 3 were as follows: symptomatic HF ≥II functional class according to the New York Heart

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Association classification, reduced left ventricular EF <50%, structural changes on echocardiography, and elevated natriuretic peptide level.

The study was approved by the local ethical committee of Bashkir State Medical University a (Protocol №11 from 15.11.2022). All patients underwent standard biochemical examination of blood serum with determination of lipid spectrum parameters, glucose, creatinine. The level of serum natriuretic peptide was investigated by immunoenzymatic method before surgical treatment. All patients were measured body mass index (BMI), waist and hip circumference, echocardiographic examination was performed. All patients with CHD received regular therapy with antiaggregants, beta-adrenoblockers, ACE inhibitors/sartans, and HMG-CoA reductase inhibitors according to the standards of CHD treatment. EAT samples were obtained (in the amount of 3-5 g) during coronary bypass surgery from fat depots localized predominantly around the right heart at the beginning of surgical treatment. The adipose tissue was excised using a scalpel.

Peripheral venous blood was collected by routine venipuncture. PBMC isolation with plasma sampling was performed according to the Boyum method [3]. Blood formed elements were separated by centrifugation at a Ficoll gradient of p = 1.077. RNA isolation was performed according to the protocol for total RNA isolation using the ExtractRNA reagent (Eurogen, Russia) with subsequent RNA quality control. Determination of microRNA and 'housekeeping' gene expression was carried out in two stages. The first stage included synthesis of complementary DNA using the MMLV RT kit (Eurogen, Russia). The second stage was performed according to the instructions for primer and probe sets for real-time PCR (DNA-Synthesis, Russia), using non-specific reagents from Eurogen (Russia). Amplification was performed on a StepOne Plus instrument (Applied Biosystems, USA).

The expression level of miRNA genes miR-22-3p, miR-15b-3p and miR-590-5p were normalized relative to the gene expression level of the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Due to higher stability, the reference gene for microRNA 148b-3p, 30c-5p, 221-3p, 328-3p, 146a-5p and 375-3p was used to further analyze the expression of microRNA genes 148b-3p, 30c-5p, 221-3p, 328-3p, 146a-5p and 375-3p. Further evaluation of the relative expression of the investigated microRNA genes was performed using the 2-ΔΔΔCT method (Livak, 2008) [11].

Subsequent statistical evaluation of the obtained results was performed using GraphPad Prism 8.0.1 program (244). SPSS Statistics 26 program was used for statistical processing of clinical data. Quantitative data were tested for normality of distribution using the Kolmogorov-Smirnov criterion. Student's criterion and ANOVA for independent samples were used to detect statistical differences of normally distributed data. If the data did not meet the conditions of normal distribution, Mann-Whitney criterion was used.

Results and Discussion. The sex distribution was similar in all three groups (p=0.14). The frequency of smoking was higher in groups 1 and 2 than in group 3 (p=0.026). The distribution of comorbidities such as diabetes mellitus, chronic obstructive pulmonary disease, and stroke did not differ between all formed groups. The rest of the laboratory parameters were comparable in all study groups. In group 2, echocardiography revealed a significant increase in left ventricular myocardial mass and left ventricular volume. All clinical data are presented in the table.

Results of clinical examination of the studied patients. including laboratory and echocardiographic parameters

Options	Group 1 (G1) Non-HF n=37	Group 2 (G2) HFmr/rEF n=44	Group 3 (G3) HFpEF n=94	G1/G2	G1/G3	G2/G3
				P		
Age. years	59.52±8.41	62.19±8.82	67.47±7.10	0.17	0.001	0.001
Male gender.%	30 (81)	35 (79.5)	63 (67)	0.14		
BMI. kg/m^2	28.20±4.51	32.94±13.41	29.08±4.37	0.25	0.55	0.11
Diabetes. %	10 (27)	17 (38.6)	23 (24.5)	0.16		
Atrial fibrillation. %	0 (0)	2 (4.54)	9 (9.6)	0.13		
Smoking. %	12 (32.4)	12 (27.3)	13 (13.8)	0.026		
COPD. %	10 (27)	18 (40.9)	35 (37.2)	0.38		
ONMC. %	4 (10.8)	7 (15.9)	11 (11.7)	0.68		
Laboratory parameters						
Natriuretic peptide. pg/mL	237.17±75.63	1273.19±607.53	1125.92±749.52	0.001	0.001	0.33
Creatinine. μmol/L	102.89±17.39	101.65±21.94	106.24±20.54	0.84	0.52	0.39
Glucose. mmol/L	7.30±3.04	7.18±2.74	6.23±2.14	0.12	0.096	0.89
Cholesterol. mmol/L	5.34±1.44	4.65±1.16	4.59±1.08	0.85	0.023	0.11
EchoCG parameters						
Ejection fraction. %	60.75±5.18	41.15±5.53	60.63±4.72	0.001	0.90	0.001
Left ventricular myocardial mass	221.40±48.97	268.55±64.43	210.89±48.31	0.001	0.28	0.001
Left ventricular myocardial mass index	116.74±31.46	151.31±27.46	110.79±26.47	0.005	0.52	0.001
End-systolic volume. ml	47.93±12.39	91.05±28.96	44.91±11.29	0.001	0.21	0.001
End-diastolic volume. ml	122.90±20.16	162.79±32.04	117.85±20.11	0.001	0.22	0.001

Note: Clinical parameters are given as mean and standard deviation. Without HF. no heart failure; HFpEF. heart failure with preserved ejection fraction; HFmr/rEF. heart failure with mildly reduced and reduced ejection fraction; BMI. body mass index; COPD. chronic obstructive pulmonary disease; ONMC. acute cerebral circulatory failure.

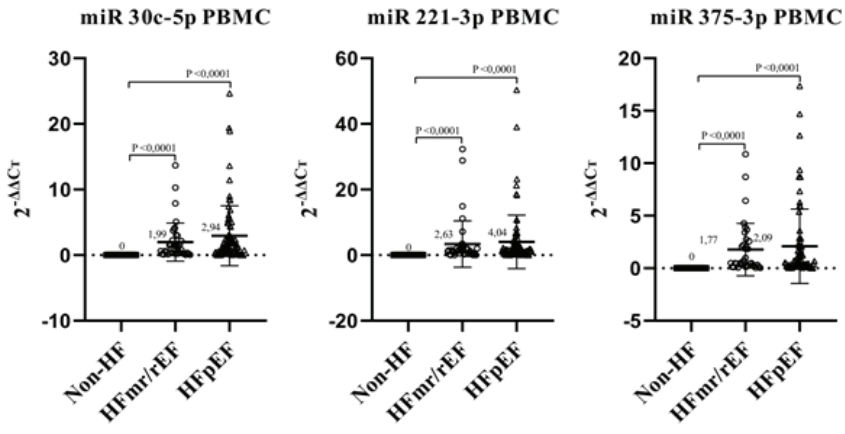
Our study revealed a significant increase in miR-30c-5p, miR-221-3p, and miR-375-3p microRNA expression in PBMC of patients in groups 3 and 2 compared with group 1 (Figure). Accordingly, the relative expression level of miR-30c-5p in PBMC of group 2 was significantly higher by 1.99-fold relative to group 1 (P<0.0001). The expression of this microRNA in PBMC of group 3 relative to group 1 was significantly higher by 2.94-fold (P<0.0001).

The change in miR-30c-5p expression has a high diagnostic potential in relation to HFpEF (group 3) [4]. This is probably due to the fact that increased miR-30c-5p expression negatively correlates with *SIRT1* expression and thus may enhance inflammatory response and apoptosis of myocardial cells [14]. Since no significant differences in miR-30c-5p expression were found between groups 2 and 3 in our study, we can assume that increased miR-30c-5p expression has diagnostic potential in patients with HFmr/rEF.

The expression level of miR-221-3p in PBMC of group 3 was increased 4.04-fold compared with group 1 (P<0.0001). PBMC of group 2 patients also showed a 2.63-fold increase in miR-221-3p expression (P<0.0001).

Increased expression of miR-221-3p was detected in cardiac tissue of patients with HF, which is attributed to its regulatory function against hypoxia-induced factor 1 (HIF-1) [12]. In addition, miR-221-3p suppresses *SIRT2* gene expression and thus promotes cardiomyocyte aging [16], and also contributes to cardiac fibrosis [9]. Accordingly, the results of our study may indicate a systemic effect of increasing miR-221-3p expression level. Given the absence of changes in miR-221-3p expression in EAT, the absence of a paracrine influence can be assumed. This necessitates further studies to clarify the specific mechanisms of development of this condition.

In our study, miR-375-3p microRNA expression in PBMC of group 3 and group 2 patients was increased 2.09- and 1.77-fold, respectively, compared with group 1 (P<0.0001). MiR-375-3p may enhance cardiac hypertrophy and thus contribute to the development of HF [13]. Accordingly, the significant increase in left ventricular volumes observed in our study in patients with HFmr/rEF and the significant increase in miR-375-3p expression in PBMC in patients with HFmr/rEF are most likely interrelated. Additional evidence is that inhibition of miR-375-3p enhances left ventricular function by reducing cardiomyocyte apoptosis and thus has a therapeutic effect against HF [15].



Comparative analysis of miR-30c-5p, miR-221-3p and miR-375-3p expression in PBMC among different groups of CHD patients with and without HF. The graphs demonstrate a significant change in the relative expression level of miR-30c-5p, miR-221-3p and miR-375-3p in PBMC of patients with HF versus patients with CHD without HF

Thus, our results are in general agreement with the literature data. At the same time, in our study, miR-375-3p expression did not show statistically significant differences between the HFpEF and HFmr/rEF groups (P = 0.7565). Although existing literature sources indicate differences in miR-375-3p expression between patients with HFpEF and HFrEF [5], this discrepancy is likely due to the pooling of patients with HFmr/rEF and HFrEF into a single study group. It should be pointed out that for all other investigated microRNAs no significant expression changes in PBMC were detected. None of the investigated microRNAs showed significant expression changes in PBMC.

Conclusions. Our study revealed a significant increase of miR-30c-5p, miR-221-3p and miR-375-3p microRNA expression in PBMC in patients with CHD and heart failure (HF) with preserved and reduced/moderate ejection fraction (HFpEF and HFmr/rEF) compared with patients without HF. The expression of miR-30c-5p in PBMC was 1.99-fold higher in patients with HFmr/rEF compared with the group of patients without HS, whereas the expression level of this microRNA was 2.94-fold higher in the group of patients with HFpEF (P<0.0001). The expression of miR-221-3p in PBMC was increased 4.04-fold in patients with HFpEF, and 2.63-fold in patients with HFmr/rEF (P<0.0001). The expression of miR-375-3p was significantly higher 2.09-fold in the group of patients with HFmr/rEF and 1.77-fold in the group with HFpEF (P<0.0001). No significant changes in the expression of other investigated microRNAs in PBMC, as well as the expression of all investigated microRNAs in epicardial adipose tissue were observed.

The obtained data have value for understanding the role of the studied microRNAs in the pathogenesis of HF in patients with CHD. Our results can be used to conduct further studies on the mechanisms of HF development. A better understanding of the pathogenetic processes associated with microRNAs may be used to create new strategies for risk assessment of HF development in patients with CHD.

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SEARCH FOR FACTORS INCREASING THE RISK OF DEVELOPING ANXIETY AND DEPRESSIVE DISORDERS IN THE YAKUT POPULATION

The study is devoted to the study of factors increasing the risk of developing anxiety and depressive disorders in the Yakut population. Analysis of anxiety and depression indicators according to the HADS (Hospital Anxiety and Depression Scale) was conducted in a sample of 150 men and 183 women without neurological and mental diseases. It was found that HADS indicators are significantly higher in women compared to men, increased in groups of respondents over 25 years old, in groups of people with disabilities, in married people compared to single people. In a sample consisting of 33 men and 122 women, an analysis of the distribution frequencies of alleles (S and L) and genotypes (SS, SL, LL) of the 5-HTTLPR polymorphism of the SLC6A4 gene was carried out. The results showed a high degree of similarity with the populations of East Asia (Japanese, Chinese, Koreans) and significant discrepancies with Caucasian groups. A search for associations of the S and L allele frequencies was conducted in groups with different indicators of anxiety and depression according to the HADS. A statistically significant association of the L allele with subclinical anxiety without depression was revealed.

Keywords: 5-HTTLPR, depression, anxiety, serotonin transporter, psychogenetics.

Introduction. Anxiety and depressive disorders are among the most common diseases worldwide, having a negative impact on the quality of life and the level of public health [1]. Anxiety disorders are regulated in the International Classification of Diseases of the 10th revision (ICD-10) under the code F41, and depressive disorders are classified in several codes: F06.3, F31, F32, F33, F34 [10; 13]. Although anxiety disorder and depression are considered two different diseases, anxious depression (depression and concomitant anxiety) is a relatively common syndrome [8; 11]. Comorbid depression and anxiety disorder occur in 25% of general practice patients. About 85% of patients with depression experience significant anxiety, and 90% of patients with anxiety disorder suffer from depression, so the symptoms may seem vague and nonspecific [11]. These mental states with a complex pathogenic mechanism are associated in many studies with a disturbance in the level of serotonin, and its transporter, encoded by the *SLC6A4* gene, plays a key role in regulating the activity of the serotonergic system [1; 16; 20]. It is assumed that in the coming years, the study of genes that influence behavior will become key in psychiatry: the analysis of the links between genes and behavior at the mental level will radically change research related to the psychological state of the individual and, accordingly, the treatment of anxiety and depressive disorders [4; 13].

Extensive data from early studies of the functioning of the serotonergic system, especially polymorphisms of the serotonin transporter gene *(SLC6A4)*, indicate their association with various mental disorders [1; 16; 18]. Some studies in recent years indicate that the *SLC6A4* gene plays a role in the development of depression [14]. In particular, the functional polymorphism 5-HTTLPR (44-BP INS/DEL; rs774676466), which is an insertion/deletion of 44 base pairs in the promoter region of the *SLC6A4* gene, has two variants: a short allele S and a long allele L, of which S leads to lower gene transcription and is presumably associated with depressive and anxiety disorders [1]. The first studies indicated

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that carriers of the short version (S) of the 5-HTTLPR allele are at greater risk of developing depressive and anxiety disorders, especially in the presence of stressful events in life [16]. This connection is explained by the fact that decreased expression of the protein responsible for serotonin transport in neurons leads to disruption of the functioning of the serotonergic system of the brain, which, in turn, increases susceptibility to the negative effects of stress [17]. However, the results of a meta-analysis could not confirm this connection [24]. Evidence confirming the connection between the 5-HTTLPR polymorphism of the *SLC6A4* gene and affective disorders currently appears insufficient [22].

The aim of this work is to find factors that increase the risk of developing anxiety and depressive disorders and the contribution of the genetic polymorphism 5-HTTLPR of the *SLC6A4* gene to their development in the Yakut population.

Materials and methods. A total of 333 participants (150 men and 183 women) were tested for psychoemotional state using the Hospital Anxiety and Depression Scale (HADS). The study was conducted with the written consent of the participants. The questionnaire data included socio-demographic questions (health status, smoking, alcohol consumption, marital status and genetic diseases) and anthropometric data. The scale consists of 14 statements and includes two parts: anxiety (part I) and depression (part II). Each statement corresponds to 4 answer options. Each subject filled out the questionnaire individually and independently. The results were interpreted separately without the participation of the subjects.

The collection of material and filling out questionnaires was carried out during expedition trips to the regions of the Sakha Republic (Yakutia). All samples are included in the biomaterial collection of the Yakut Scientific Center for Complex Medical Problems using the Yakutia Genome Scientific Research Institute (registration number USU_507512). Genetic research and bioinformation data processing were carried out in the laboratory of hereditary pathology of the molecular genetics department of the Yakut Scientific Center for Complex Medical Problems (YSC CMP). A total of 155 people of Yakut nationality were tested, including 33 men and 122 women. The ethnicity of the participants was taken into account up to the third generation. The study included patients who signed informed consent for genetic research from January 2023 to December 2023.

Table 1

Conditions for conducting PCR analysis

Ген	Primer sequence	Length of amplicon bp	Annealing temperature
SLC6A4	F:5'-GGACCGCAAGGTGGGCGGGA-3'	SS – 376 b.p.; SL - 420 п.н., 376 b.p.; LL – 420 b.p.	62°C

For molecular genetic analysis, DNA extraction from whole blood was performed using a commercial DNA extraction kit "Newteryx" (Russia, Yakutsk) in accordance with the manufacturer's instructions. The DNA concentration in each sample was determined on an Implen Nano Photometer spectrophotometer (Germany). Analysis of the 5-HTTLPR (44-BP INS/DEL) polymorphism of the *SLC6A4* gene was performed by polymerase chain reaction (PCR).

Amplification of the gene region containing the polymorphic variant was carried out using primers manufactured by Lumiprob RUS LLC, Moscow. 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 and DNA – 1 µl. The amplification conditions are presented in Table 1.

Interpretation of genotyping results was performed based on different band templates for the genotypes SS – 376 bp; SL - 420 bp, 376 bp; LL – 420 bp (Figure).

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

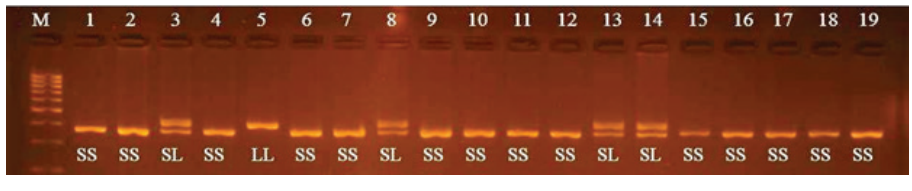
Results and discussion. When assessing the indicators of the Hospital Anxiety and Depression Scale (HADS), respondents were divided into groups by gender, age group, marital status and the presence of disability. When comparing the groups by gender, reliable differences were found between them both in the level of anxiety and depression ($p<0.001$). Thus, in the group of women, anxiety disorders are three times more common than in the group of men (OR=3.044; CI 95% 1.890-4.903), and depression is more than 2.5 times more common (OR=2.748; CI 95% 1.713-4.409) (Table 2).

To make further calculations, respondents were divided into age groups based on two types of periodization of human development *(Petrovsky A.V.; Erikson E.Kh.)*: early youth: 18-25 years; young age: 26-35 years; middle age: 36-50 years; old age: 51-65 years; old age: 66 years and older.

When comparing age groups, a statistically significant difference ($p<0.05$) was found between the groups of early youth and youth: after 25 years, both anxiety (OR=2.893; CI 95% 1.013-8.267) and depression (OR=3.1; CI 95% 1.01-9.516) increase. No significant differences in HADS scores were found between groups over 25 years of age (26-35, 36-50, 61-65, over 66 years).

A statistically significant relationship between anxiety and depression indicators and disability was also revealed ($p<0.001$). Respondents with disabilities were more anxious (OR=2.038; CI 95% 1.062-3.911) and more depressed (OR=3.082; CI 95% 1.661-5.718) compared to those without disabilities.

Analysis of marital status showed that in the group, married respondents were almost three times more likely to have anxiety ($p<0.001$) and depressive disor-



Electrophorogram of the amplification product of the SLC6A4 gene region in a 4% agarose gel: tracks № 1, 2, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 18, 19 – SS genotype; 3, 8, 13 and 14 – SL genotype; 5 is the LL genotype; M is the Step100 marker

ders (p<0.001) compared to single respondents (Table 2).

Table 3 shows the distribution of allele frequencies (S and L) and genotypes (SS, SL and LL) of the 5-HTTLPR polymorphism of the *SLC6A4* gene in the general sample of Yakuts in comparison with other populations. Comparison of the obtained allele frequencies and genotypes of Yakuts with other populations of the world showed the greatest similarity with East Asian populations (Japanese, Chinese and Korean) and significant differences with Caucasian populations [2]. Earlier, in the study of *Savostyanov A.N. et al. (2021)*, a significantly high frequency of the S allele of the 5-HTTLPR polymorphism was found in a sample of 79 indigenous people of Yakutia (63 Yakuts, 12 Evenks, 4 Yukaghirs) compared to Caucasians [10], which is consistent with our data.

As shown in the work of these authors, SS carriers exhibit an increased level of anxiety and a higher ability to regulate behavior in the conditions of the stop-signal paradigm (SSP) experiment. According to the researchers, carriers of the SS genotype adapt to high-risk climatic conditions more successfully than carriers of the LL and LS genotypes. The authors suggest that anxiety can act as an adaptive factor in extreme climatic conditions combined with an increased risk to life, and that in healthy people with the SS genotype, a decrease in the activity of 5-OHT neurons may be associated with increased activation control, rather than with a deterioration in inhibitory control [10].

Table 2

Hospital Anxiety and Depression Scale (HADS) scores

	Anxiety (HADS-A)				Depression (HADS-D)			
	n	Norm	Subclinical anxiety	Clinical anxiety	n	Norm	Subclinical depression	Clinical depression
By gender								
Men	150	76.7	14.7	8.7	152	75.7	13.2	11.2
Women	183	51.9	29.5	18.6	179	53.1	28.5	18.4
OR	**3.044 (1.890-4.903)**				**2.748 (1.713-4.409)**			
p	**<0.001**				**<0.001**			
By age periods								
up to 25 years	108	86.1	12.0	1.9	105	88.6	8.6	2.9
from 26 to 35	22	68.2	18.2	13.6	21	71.4	14.3	14.3
OR	**2.893 (1.013-8.267)**				**3.1 (1.01-9.516)**			
p	**0.04**				**0.03**			
from 26 to 35	22	68.2	18.2	13.6	21	71.4	14.3	14.3
from 36 to 50	42	54.8	23.8	21.4	39	59.0	20.5	20.5
OR	1.770 (0.599-5.231)				1.739 (0.555-5.447)			
p	0.442				0.501			
from 36 to 50	42	54.8	23.8	21.4	39	59.0	20.5	20.5
from 51 to 65	98	54.1	26.5	19.4	101	52.5	30.7	16.8
OR	1.028 (0.497-2.124)				1.488 (0.688-3.216)			
p	0.912				0.616			
from 51 to 65	98	54.1	26.5	19.4	101	52.5	30.7	16.8
Over 66	63	41.3	36.5	22.2	65	40.0	30.8	29.2
OR	1.676 (0.884-3.178)				1.656 (0.881-3.114)			
p	0.155				0.159			
On disability								
Disability	42	47.6	26.2	26.2	50	40.0	30.0	30.0
No disability	291	64.9	22.7	12.4	281	67.3	19.9	12.8
OR	**2.038 (1.062-3.911)**				**3.082 (1.661-5.718)**			
p	**0.046**				**<0.001**			
By marital status								
Married	132	55.3	27.3	17.4	134	54.5	26.9	18.7
Divorced	12	33.3	33.3	33.3	9	44.4	33.3	22.2
OR	2.475 (0.710-8.623)				1.496 (0.385-5.817)			
p	0.247				0.812			
Married	132	55.3	27.3	17.4	134	54.5	26.9	18.7
Widows/Widowers	33	39.4	30.3	30.3	30	43.3	33.3	23.3
OR	1.904 (0.874-4.144)				1.565 (0.704-3.477)			
p	0.150				0.367			
Married	132	55.3	27.3	17.4	134	54.5	26.9	18.7
Singles	140	77.9	15.7	6.4	142	76.8	14.1	9.2
OR	**0.352 (0.208-0.596)**				**0.362 (0.216-0.608)**			
p	**<0.001**				**<0.001**			

Table 3

Frequencies of genotypes and alleles of the 5-HTTLPR polymorphism of the *SLC6A4* gene in populations

Populations	n	LL	SL	SS	L	S	Link
Yakuts	158	5.7 (9)	32.3 (51)	62.0 (98)	21.8	78.2	This study
Japanese	101	3.7 (4)	31.4 (31)	65.7 (66)	19.3	80.7	[7]
Japanese (Tottori)	501	3.19 (16)	31.73 (159)	65.06 (326)	19.1	80.9	[5]
Chinese (Beijing)	558	6.09 (34)	36.02 (201)	57.88 (323)	24.1	75.9	[6]
Chinese (Shanghai)	587	6.30 (37)	41.39 (243)	52.29 (307)	27.0	73.0	[20]
Koreans	183	4.37 (8)	34.42 (63)	61.20 (112)	21.6	78.4	[25]
Taiwan	192	10.93 (21)	36.97 (71)	52.08 (100)	29.4	70.6	[22]
Thais	187	9.09 (17)	36.89 (69)	54.01 (101)	27.5	72.5	[16]
Russians (St. Petersburg)	908	38.10 (346)	46.69 (424)	15.19 (138)	61.5	38.5	[3]
Ukrainians	60	21.21 (14)	37.87 (25)	40.90 (27)	61.5	38.5	
Belarusians	39	46.15 (18)	41.02 (16)	12.82 (5)	66.7	33.3	
Chuvashes	372	24.46 (91)	51.61 (192)	23.92 (89)	50.3	49.7	
Kabardians	289	26.64 (77)	44.63 (129)	28.71 (83)	49.0	51.0	
Tatars	142	26.05 (37)	51.40 (73)	22.53 (32)	51.8	48.2	

In our work, when comparing the frequencies of the 5-HTTLPR polymorphism alleles of the *SLC6A4* gene between the groups with anxiety disorders and the norm (Table 4) and between the groups with depressive disorders and the norm (Table 5), no statistically significant differences were found. The S allele was predominant in all compared groups. The only exception was that in the "subclinical anxiety, depression within normal limits" group, carriers of the L allele were 2.5 times more common than in the group with normal HADS scores (Table 4). Our data do not correspond to the results of the works of *Savostyanov A.N. et al. (2021)* [10], which can be explained by differences in the methods for assessing personal anxiety (Spielberger Anxiety Scale instead of HADS).

Conclusion. Thus, it has been established that the factors increasing the risk of anxiety and depression in the Yakut

Table 4

Variability of the 5-HTTLPR polymorphism of the serotonin transporter gene SLC6A4 in groups of individuals with anxiety disorders

Scale	n	LL	SL	SS	L	S	OR (CI 95%)	p
Norm	69	4.3	27.5	68.1	18.1	81.9	0.565 (0.282-1.134)	0.152
Subclinical anxiety with subclinical and clinical depression	32	9.4	37.5	53.1	28.1	71.9		
Norm	69	4.3	27.5	68.1	18.1	81.9	0.811 (0.375-1.755)	0.741
Clinical anxiety with subclinical and clinical depression	28	3.6	35.7	60.7	21.4	78.6		
Subclinical anxiety with subclinical and clinical depression	32	9.4	37.5	53.1	28.1	71.9	1.435 (0.620-3.321)	0.526
Clinical anxiety with subclinical and clinical depression	28	3.6	35.7	60.7	21.4	78.6		
Norm	69	4.3	27.5	68.1	18.1	81.9	**0.391 (0.175-0.877)**	**0.036**
Subclinical anxiety, depression-norm	101	11.1	50.0	38.9	36.1	63.9		
Norm	69	4.3	27.5	68.1	18.1	81.9	0.885 (0.272-2.875)	0.916
Clinical anxiety, depression-norm	97	0	40	60	20	80		

Table 5

Variability of the 5-HTTLPR polymorphism of the serotonin transporter gene SLC6A4 in groups of individuals with depressive disorders

Scale	n	LL	SL	SS	L	S	ОШ (ДИ 95%)	p
Norm	69	4.3	27.5	68.1	18.1	81.9	1.011 (0.491-2.083)	0.878
Subclinical depression with subclinical and clinical anxiety	39	5.1	25.6	69.2	17.9	82.1		
Norm	69	4.3	27.5	68.1	18.1	81.9	0.562 (0.259-1.218)	0.207
Clinical depression with subclinical and clinical anxiety	23	8.7	39.1	52.2	28.3	71.7		
Subclinical depression with subclinical and clinical anxiety	39	5.1	25.6	69.2	17.9	82.1	0.555 (0.234-1.317)	0.263
Clinical depression with subclinical and clinical anxiety	23	8.7	39.1	52.2	28.3	71.7		
Norm	69	4.3	27.5	68.1	18.1	81.9	0.752 (0.329-1.721)	0.648
Subclinical depression, anxiety is normal	108	4.5	36.4	59.1	22.7	77.3		
Norm	69	4.3	27.5	68.1	18.1	81.9	0.664 (0.198-2.230)	0.742
Clinical depression, anxiety is normal	92	12.5	25	62.5	25	75		

population are female gender, age over 25 years, disability, and married/married status compared to single. An association of the L allele of the 5-HTTLPR polymorphism of the *SLC6A4* gene with subclinical anxiety without depression was revealed. In the future, to clarify the obtained results, genotyping of respondents with established mental disorders is required. These data emphasize the importance of an integrated approach to assessing factors affecting mental health.

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ASSESSMENT OF THE QUALITY OF LIFE OF ADOLESCENTS IN ALTAI KRAI

This article presents the results of the assessment of the quality of life of adolescents, aged fifteen to seventeen years, and the results of the assessment of the quality of life of adolescents by their parents, as revealed by the PedsQL-4.0 questionnaire for adolescents aged 13-18 years and their parents. The participants in this study were 126 adolescents, 63 girls and 63 boys, and 126 parents, respectively. The mean age of the adolescents questioned was 15.7+-0.72 years.

There were 6 blocks in this questionnaire - physical functioning, emotional functioning, social functioning, school life, psychosocial health and a summative score which is represented by the average of the responses for all four blocks.

The results obtained are presented as mean value with confidence interval (CI) -95%.

The Shapiro-Wilk test tested the hypothesis of normality of the distribution of empirical data. This test evaluates the sample data with the null hypothesis that the data set is normally distributed. A value of $p>0.05$ indicated that the data set is normally distributed, a value of $p<0.05$ indicated that the data set is subject to non-normal distribution of the trait.

The Mann-Whitney U-test was used to determine whether there was a significant difference between two independent non-normally distributed groups of data.

Differences were considered statistically significant at a significance level of $p < 0.05$.

In the final results of the self-assessed quality of life, the lowest scores were obtained on the “emotional functioning” and “life at school” scales, the highest on the “physical functioning” and “social functioning” scales, with significant low scores for girls on all scales except the “social functioning” scale, the trend of low scores was maintained when assessed by their parents.

When analyzing the indicators of quality of life assessment by parents of adolescents of different ages, a statistically significant difference was found only on the “emotional functioning” scale.

Keywords: quality of life, adolescents

Introduction. Quality of life is understood as a comprehensive concept that encompasses a general sense of well-being and has within it the idea of life satisfaction and happiness of the individual as a whole. [5,10].

A large amount of research is devoted to the study of the quality of life of people suffering from various diseases. In these studies, we are more interested in adolescents of different ages - from junior high school students to high school students. In the course of analyzing the obtained data, significant differences in the quality of life indicators among the studied groups are revealed. However, the interpretation of the results does not always take into account whether there is a potential influence of parents or official representatives on respondents' answers.

For example, a study on the quality of life of adolescents with auditory analyzer pathology revealed a decrease in the level of their well-being to the average value compared to healthy peers, who demonstrate high scores on all analyzed parameters. At the same time, the analysis of gender differences showed that boys feel significantly more alert and energetic than girls. [8]

Studies show that adolescents with various endocrine diseases have lower quality of life scores than their healthy peers.

In particular, adolescents with diabetes mellitus have significantly lower overall quality of life scores than their peers without chronic disease. At the same time, obese adolescents have even lower overall quality of life scores than diabetic patients, with physical and emotional functioning suffering most significantly. [1]

High school seniors with bronchial asthma are characterized by moderate to significant reductions in quality of life, primarily in the areas of social functioning, physical mobility, and economic status. [2]

Adolescents with motor and sensory impairments show lower physical health indicators related to physical and role functioning. At the same time, they show higher mental health indicators compared to their peers without any impairment. [3]

Adolescents with severe posture disorders tend to show reduced satisfaction with their physical well-being, functional abilities in daily life, and interpersonal interactions. which also indicates a reduced quality of life compared to adolescents without any medical conditions. [7]

Consequently, we can conclude that various diseases, both those mentioned above and those insufficiently studied in this aspect, have a rather negative impact on the quality of life of adolescents, leading to its decline.

Speaking about the quality of life of somatically healthy adolescents, such studies were previously conducted in Altai Krai. As a result, after analyzing the obtained data, it was found that the average score of adolescents of high school age was 71.3 points, insignificant differences between the assessments of adolescents and their parents were revealed, and it was concluded that these results can be used to assess the quality of life of adolescents. [4]

In the modern health care system, the priority is to improve the quality of life of our public. As noted by the President of the Russian Federation V.V. Putin, deci-

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sions in the development of the country and regions should be aimed at improving the welfare and standard of living of the citizens of our state [6].

According to the Decree of the President of the Russian Federation dated 31.12.2015 N 683 "On the National Security Strategy of the Russian Federation"- "Improving the quality of life of citizens is guaranteed by ensuring food security, greater accessibility of comfortable housing, high-quality and safe goods and services, modern education and health care, sports facilities, ... ensuring accessibility of social, engineering and transportation infrastructure for the disabled and other low-mobility groups of the population...". [9]

Since 2025, the national project "Long and Active Life" will be implemented, covering all areas of health care, from primary care to rehabilitation, including sports. This project is designed to improve the quality of life of Russians.

In this regard, it is necessary to develop a methodology for analyzing the criteria of quality of life, which will make it possible to comprehensively assess the physical, psychological and social aspects of adolescents' well-being.

Taking into account all the above-mentioned in the absence of clear criteria and the condition of conducting a survey to assess the quality of life, the main goal of this study was the following:

Objectives of the study: Our research objective is to assess the parameters of quality of life of adolescents living in Altai Krai, taking into account gender characteristics, and to identify the peculiarities of assessment of quality of life indicators by parents of adolescents.

Materials and Methods. The presented study is of a one-stage nature.

In 2023, on the basis of the Barnaul city secondary school, an assessment of the level of quality of life in adolescents was carried out through self-assessment of students and a questionnaire survey of their parents.

Adolescents participating in this study were divided into groups by age and gender, after which the data were analyzed, and the results are presented below. The sample of adolescents was formed based on inclusion and non-inclusion criteria.

Inclusion criteria: Belonging of adolescents to I-II health groups, students of 9-11 grades,

Providing consent for participation in the study and processing of personal data,

Full completion of the questionnaire by adolescents and their legal representatives;

Non-inclusion criteria: Presence of health pathology in the stage of exacerbation at the time of the study,

Refusal of the child's official representative to participate in the study and to process personal data,

Incomplete completion of questionnaire forms.

In the present study, an adaptation of PedsQL-4.0 for adolescents 13-18 years old and their parents was used to assess the quality of life. The analysis of the received answers made it possible to conduct an independent assessment of the level of students' quality of life.

The components of the questionnaire are physical functioning (PF), emotional functioning (EF), social functioning (SF), school life (SL), psychosocial health (PSH), which includes EF, SF, and SL blocks, and LSD - the total score, which is represented by the average of responses for all four blocks.

The obtained data were analyzed using STATISTICA 6.0 software.

Mean values are presented in the format of confidence interval (CI) with a confidence level of 95%.

The Shapiro-Wilk test was used to test the hypothesis of normality of distribution of empirical data. It evaluates the sample data with the null hypothesis that the data set is normally distributed. A value of $p>0.05$ indicated that the data set is normally distributed, a value of $p<0.05$ indicated that the data set is subject to non-normal distribution of the trait.

The Mann-Whitney U-test was used to determine if there was a significant difference between two independent non-normally distributed groups of data.

Differences were considered statistically significant at a significance level of $p < 0.05$.

Results and their discussion. This study involved 126 school adolescents living in Altai Krai - students in grades 9, 10 and 11 of general education school and 126 parents. The average age of pupils was 15.7+-0.72 years. Among girls - 63 people - 29 fifteen-year-olds, 27 sixteen-year-olds and 7 seventeen-year-old girls were questioned, the average age was 15.6 +_0.67 years. Among boys - 63 people - 32 fifteen-year-olds, 19 sixteen-year-olds and 12 seventeen-year-olds participated, average age 15.7 +_0.62 years.

Analysis of quality of life indicators of adolescents aged 15 to 17 years revealed a total quality of life index of 70.12 [72.68 - 67.56, 95% CI]. Analysis of the self-esteem of adolescents in this age group revealed the highest scores on the social functioning scale of 86.17 [89.11-83.06, 95% CI]. High scores were also noted on the "physical functioning" scale 75.96 [78.71 - 73.23, 95% CI]. The lowest values were recorded on the scales of "emotional functioning" 57.37 [61.1 - 53.64, 95% CI] and "school life" (63.17 [66.37-69.98, 95% CI]). Consequently, the scores on the "emotional functioning" and "life at school" scales were lower, accounting for the lower integrated psychosocial health score of 67.49 [70.2-64.78, 95% CI] compared to the mean score. (Table 1).

Statistically significant differences were found in the study of quality of life indicators for girls and boys. The mean total score for boys was 75.38 [79.77 to 72.69, 95% CI], which was higher than that for girls, 64.87 [68.21 to 61.67, 95% CI]. This difference was confirmed using the Mann-Whitney criterion ($p = 0.005$).

A similar trend was observed in the individual subgroups: the highest values were observed for the "social functioning" and "physical functioning" scales, while the lowest values were observed for the "emotional functioning" and "life at school" scales. In general, the quality of life indicators for girls were slightly lower. Statistically significant differences are observed for all scales, except for the "social functioning" scale (Table 2).

When comparing assessments of the quality of life received from adolescents and their parents, similarity in assessments of various spheres of functioning is revealed. Parents tend to score higher on all measures Both adolescents and parents score highly on "social functioning," although the parents' scores (89.78 points [87.38-92.18, 95% CI]) are slight-

Table 1

Quality of life indicators for adolescents in the 15-17 age group

Indicator	PF	EF	SF	SL	PSH	LSD
Adolescents aged 15-17	75.96 (78.71-73.23)	57.37 (61.1-53.64)	86.17 (89.11-83.06)	63.17 (69.98-66.37)	67.49 (70.2-64.78)	70.12 (72.68- 67.56)

ly higher than the adolescents' scores (86.09 points [83.06-89.11, 95% CI]). The worst performing group of adolescents was the “emotional functioning” score. Adolescents rated this scale at 57.37 points [53.64-61.1, 95% CI], while parents gave a score of 70.96 points [67.61-74.31, 95% CI], which borders on the older generation's score for “school life”, which is slightly lower at 70.21 points [67.08-73.35, 95% CI]

These differences are statistically significant, except for the differences on the “social functioning” scale (Table 3).

During the final stage of this study, the difference in opinion between parents of girls and boys was revealed. The parents of girls gave the highest score to the “social functioning” scale, while the parents of boys gave the maximum score to the “physical functioning” scale.

Parents of girls ranked “physical functioning” second in importance while parents of boys favored “social functioning”. The third place was shared by the indicators “life at school” for parents of girls and “emotional functioning” for parents of boys.

At the same time, both for parents of girls and parents of boys, the lowest indicators were recorded in the areas of “emotional functioning” and “life at school”.

It should be emphasized that statistically significant differences were observed only for the scales “physical functioning” (p=0.001) and “emotional functioning” (p=0.006). (Table 4).

Conclusion. Analysis of self-rated quality of life revealed the lowest scores in the domains of “emotional functioning” and “life at school”, and the highest scores in the domains of “physical functioning” and “social functioning”.

The research has shown that girls have significantly lower scores on all quality of life assessment scales, except for the “social functioning” scale. A similar trend was observed in parent-reported quality of life assessments.

When analyzing the assessments provided by parents of adolescents of different ages, a statistically significant difference was found only on the “emotional functioning” scale.

Analyzing the obtained results of our study, it should be noted that at the age of 15-16 years it is necessary to pay attention to emotional and school functioning with possible strengthening of the work of psychological and pedagogical services. Also in pediatrics for a reliable assessment of the quality of life questionnaire should be conducted by the researcher in direct work with the child, possibly in the presence of his official representative, taking into account the results obtained by us.

Quality of life indicators are labile at different ages, in contrast to parental assessment, in which the figures did not change significantly. In most cases, parents have the most unreliable information about their child's emotional functioning.

Statistical analysis revealed a reliable discrepancy in parents' assessments of adolescents's quality of life. This fact emphasizes the necessity of mandato-

Table 2

Comparative indicators of quality of life of boys and girls of the age group of 15-17 years old

Indicator / Gender	PF	EF	SF	SL	PSH	LSD
Boys	82.75 (87.07 – 80.23)	63.09 (69.63 – 58.18)	85.14 (89.86 – 82.27)	68.08 (73.46 – 64.22)	72.43 (77.1 – 69.43)	75.38 (79.77 – 72.69)
Girls	69.18 (72.76 – 65.6)	51.65 (56.01 – 47.36)	82.23 (86.94 – 77.51)	58.26 (62.37 – 54.23)	62.55 (66.16 – 59.0)	64.87 (68.21 – 61.67)
P*	0.001	0.001	0.252	0.001	0.001	0.005

Note: p* - Mann-Whitney criterion

Table 3

Comparative analysis of the subjective assessment of the quality of life in adolescents aged 15-17 and their parents' assessments

Indicator	PF	EF	SF	SL	PSH	LSD
Adolescents	75.97 (73.23 – 78.71)	57.37 (53.64 – 61.1)	86.09 (83.06 – 89.11)	63.17 (65.98 – 66.37)	70.12 (67.56 – 72.68)	67.49 (64.78 – 70.20)
Parents	85.19 (82.88- 87.9)	70.96 (67.61 – 74.31)	89.78 (87.38 – 92.18)	70.21 (67.08 – 73.35)	79.03 (76.60 – 81.47)	76.98 (74.55 – 79.42)
p*	0.001	0.009	0.073	0.001	0.016	0.009

Table 4

Comparative analysis of quality of life indicators in boys and girls aged 15-17 years, as assessed by parental audience

Indicator / Gender	PF	EF	SF	SL	PSH	LSD
Parents of girls	80.03 (76.43 - 83.63)	66.04 (61.46- 70.64)	89.62 (86.31 - 92.93)	67.75 (63.77- 72.12)	74.46 (71.31- 77.77)	75.86 (72.87 - 78.95)
Parents of boys	90.34 (88.97-93.67)	75.87 (72.08 - 81.35)	89.94 (87.41 - 94.40)	72.67 (68.67- 78.17)	79.49 (76.7- 83.9)	82.21 (80.08- 86.10)
p*	0.001	0.006	0.481	0.236	0.008	0.060

ry consideration and monitoring of this aspect when conducting scientific research devoted to the study of quality of life in schooladolescents of different age groups.

It is necessary to take into account the individual characteristics of each child, his/her age, maturity, gender and ability to realize and express his/her well-being. The quality of life of a child cannot be assessed by someone else.

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

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EVALUATION OF THE ACTIVITY OF THE GLUTATHIONE LINK OF THE ANTIOXIDANT SYSTEM IN PREGNANT WOMEN OF THE INDIGENOUS AND ARRIVED POPULATION OF THE AMUR REGION FROM AN ENVIRONMENTAL AND ETHNIC PERSPECTIVE

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In order to study the state of the glutathione link of the antioxidant system (AOS) in pregnant women of the alien and indigenous population living in urban and rural areas, using the example of the Amur region, 175 patients were examined during their initial visit in the first and second trimesters and in the absence of iron deficiency states. Depending on their ethnicity and place of residence, the pregnant women were conditionally divided into 3 groups: urban aliens (Caucasians) (n=67); rural aliens (Caucasians) (n=74); rural indigenous people of the Amur region (Nanai), belonging to the Mongoloid race (n=34). Comparative characteristics of the indicators of women in groups 1 and 2 (urban and rural aliens) indicated environmental features of glutathione antioxidant protection (AOP) during pregnancy. Analysis of data from groups 2 and 3 (rural newcomers and natives) revealed ethnic peculiarities of the studied detoxification zone.

Taking into account the participation of iron in the processes of free radical oxidation and antioxidant protection, the level of hemoglobin, serum ferritin in women was determined to exclude iron deficiency conditions, as well as the content of total glutathione, reduced (GSH) and oxidized (GSSG) forms in whole blood with the calculation of redox status (GSH/GSSG ratio) as a biomarker of AOS. Statistical data processing was performed using the programs "Microsoft Excel 2010", "Statsoft Statistica", version 6.1, 10.01. As a result of the studies, a reliable decrease in the content of total glutathione was found in urban patients of the newcomer population compared to rural newcomers due to a decrease in the reduced form both in the first and second trimesters with a multidirectional trend of the oxidized fraction in these groups, which showed the ecological orientation of the AOS functioning. Ethnic features in native women were revealed when comparing the parameters under study with newcomers living in similar rural areas, in the form of reliably low values of the reduced form of glutathione in the 2nd trimester of gestation, as well as a reliable decrease in the level of total and reduced glutathione in the 2nd trimester compared to the 1st. The optimal variant of the functional state of the glutathione link of the AOS was determined by the indicators of the oxidative stress level - the redox status in newcomer

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pregnant women of the village, based on its reliably high indicators in the 1st and 2nd trimesters compared to pregnant women of the native population of the village and especially with newcomers living in the city. The obtained data should be taken into account when carrying out therapeutic and preventive measures for complicated pregnancy, taking into account the ecological and ethnic features of oxidation-reduction processes.

Keywords: pregnant women, newcomers, indigenous people, city, village, glutathione, ferritin

Introduction. To maintain vital functions, balanced functioning of various organs and systems, the body at various stages of its existence requires a number of organic and inorganic components, macro- and micronutrients. One of the most important systems involved in key aspects of homeostasis is the polyphasic detoxification system, which ensures the integrity of cellular and subcellular membranes from the damaging effects of active oxygen species, includes the glutathione link of antioxidant protection (AOP), consisting of glutathione itself (GSH) and a number of glutathione-dependent enzymes in which glutathione functions as a cofactor [1]. GSH functions as the "main antioxidant" in all tissues, providing their multi-level protection. The fundamental significance of glutathione processes is the support of adequate oxidative-reductive signaling of cells, necessary for the physiological level of oxidative stress (OS), control over it and the state of the intracellular environment [13]. It plays a certain role in the detoxification of xenobiotics, gene expression, cell differentiation and proliferation, and immune response, which is especially important during pregnancy [5]. Glutathione exists in two forms, reduced (GSH) and oxidized (GSSG). The GSH/GSSG ratio determines the oxidation-reduction status of the cell and is used as a biomarker of OS. A deficiency of GSH and, accordingly, a violation of the ratio in the redox pair, exposes the cell to oxidative stress [5], damage that occurs in various conditions and diseases.

Iron ions, an essential element, actively participate in both reduction and oxidation reactions as a metal with variable valence [2]. Being a component of many proteins and enzyme systems, iron takes part in cellular metabolism (respiratory chain of mitochondria), in biological oxidation reactions, including the processes of detoxification of xenobiotics and endogenous decay products (cytochrome P450, peroxidase, catatalases, ceruloplasmin, etc.), in cell mitosis, synthesis of DNA, steroid and other hormones. The main biological role of this macronutrient in the body is to ensure oxygen transport to cells and its functioning [2, 3]. In order to prevent oxidative stress in the body, almost all metabolically active iron is in a protein-bound state [8].

As is known, even the physiological course of pregnancy is accompanied by the development of oxidative stress, as a result of excessive production of reactive oxygen species (ROS) [6, 9]. In a clinical and biochemical study by Olempieva E.V. [9] they indicate a compensatory-adaptive increase in the amount of reduced glutathione and the activity of glutathione-containing enzymes in response to an increase in ROS, which is explained by the leading protective role of this AOS system. According to the results of many researchers, in the absence of effective regulation of free radicals by the antioxidant system (AOS), a pregnant woman has a sharply increased level of oxidative stress markers, which in turn clinically characterizes the pathological course of pregnancy (early gestational losses, preeclampsia, premature birth) [6, 11, 12, 14, 15, 17].

Purpose of the study: to study the state of the glutathione link of the antioxidant system and the significance of its redox status as a biomarker of oxidation-reduction processes during pregnancy in women of the alien and indigenous population living in urban and rural areas of the Amur region, during initial treatment in the first and second trimesters and in the absence of iron deficiency conditions.

Materials and methods: To achieve this goal, 175 pregnant women of the alien and native population of the city of Khabarovsk and the Nanai districts of the Amur region were examined. The pregnant women we observed were divided into 3 clinical groups depending on their ethnicity (Caucasian and Mongoloid races) and place of residence: 1 - urban aliens (Caucasians) living in the city (n = 67); 2 - rural aliens (Caucasians) living in rural areas (n = 74); 3 - rural indigenous (Mongoloids) of the Amur region living in rural areas (n = 34). The ecological approach to assessing the glutathione link of the antioxidant system is based on a comparison of the 1st and 2nd groups (urban and rural alien women), the ethnic approach is based on the interpretation of the data obtained for the 2nd and 3rd groups (rural aliens and natives).

At the initial visit to the antenatal clinic, all pregnant women underwent examination in the volume corresponding to the current standards of medical care, with informed voluntary consent and approved by the ethics committee. Blood was collected in the morning, on an empty stomach, by puncture of the cubital vein.

Inclusion criteria for the study: primary visit; examination in the first and second trimesters up to 24 weeks of pregnancy; absence of iron deficiency (according to ferritin, as the most accurate indicator of iron levels), not less than 30 mg/dl [18]; no intake of iron-containing drugs; chronic extragenital pathology in the period of stable remission and compensation; absence of acute inflammatory diseases. Exclusion criteria for the study: primary visit after 24 weeks; repeated visit; pregnant women diagnosed with iron deficiency; receiving iron-containing drugs; presence of acute inflammatory diseases at the time of examination, chronic extragenital pathology in the acute stage, including type II diabetes mellitus, arterial hypertension, obesity of grades 2-3.

In women, the hemoglobin level was determined (complete clinical blood test - CBC) on an automatic hematology analyzer. Ferrodynamics was assessed based on the serum ferritin level by the enzyme immunoassay using a kit (cat. No. 416-6005 (ORG FE), ZAO BioKhimMak - ORGenTec Diagnostika GmbH) (ELISA). The total glutathione content, the concentration of the reduced (GSH) and oxidized (GSSG) forms in the blood were determined using the method of A.V. Voshchenko (1998), the total assessment of the functional state of the glutathione link of the antioxidant defense system, in particular, the level of oxidative stress, was reflected in the calculation of the redox status (GSH/GSSG ratio). Statistical processing of the obtained data was performed using the programs "Microsoft Excel 2010", "Statsoft Statistica", version 6.1, 10.01. The values of the series with normal data distribution are presented as – M±m – mean ± “standard error of the mean” (SD/sqrt (n) = SEM (Standard Error Means), where n is the sample size. The statistical hypothesis of equality of group means for the series of data with normal distribution was tested using Student’s t-test (two-sample t-test). Differences between groups were considered significant at $p \leq 0.05$, $p \leq 0.01$, $p \leq 0.001$.

Results and discussion. One of the most important factors directly influencing the reproductive potential of the

population, especially women, should be noted as environmental, in particular, the uniqueness of the region of residence. The formation of adaptive reactions to environmental factors is carried out at various levels of integration of the body, including easily reversible shifts in physiological reactions, and complex morpho-functional changes in various organs and systems [7].

In accordance with the purpose and criteria of this work, no significant difference in serum ferritin levels was found in the observed groups. Its content was determined in the range from 52.9 mg / dl in the group of native villagers to 67.4 mg / dl in urban newcomers. Also, no significant dynamics were found in the change in the level of this indicator between trimesters in the groups. This indicates the identity of the examined groups in ferrodynamics and confirms the absence of iron deficiency states in pregnant women, regardless of the trimester, zone of residence and ethnicity.

Under physiological conditions, the reduced form of glutathione (GSH) predominates in cells, which, by inactivating ROS, turns into the oxidized form (GSSG), and their ratio GSH/GSSG is an integrating test of free radical oxidation processes and AOS [1, 10].

Table presents the data of the study of the glutathione link of antiradical protection, obtained during the examination of pregnant women of the immigrant and indigenous population of the Amur region during their initial visit to the antenatal clinic.

Indicators of the glutathione link of the AOS at the initial visit to pregnant women of the indigenous and newcomers population of the Amur region

	Trimester	City/ newcomers	Village/ newcomers	Village/ native
		M±m	M±m	M±m
Total glutathione, mg %	1	17.1±1.13	21.3±1.09**	22.0±1.28
	2	14.8±1.47	20.3±1.40**	15.9±1.08
P		0.1460	0.5829	0.0021
Reduced glutathione (GSH), mg %	1	10.6±0.909	15.8±1.00***	15.1±1.25
	2	8.48±1.24	13.3±1.22**	8.62±1.14º
P		0.1468	0.1223	0.0012
Oxidized glutathione (GSSG), mg %	1	6.51±0.616	5.83±0.579	6.97±1.14
	2	6.37±0.683	7.40±0.765	7.32±0.978
P		0.8828	0.1000	0.8331
Redox status (reduced glutathione/ oxidized glutathione) (GSH/GSSG)	1	2.48±0.354	4.38±0.632**	3.66±0.805
	2	1.63±0.258	2.75±0.427	1.83±0.433
P		0.129937	0.050	0.095101

Note: Group reliability: * - $p \leq 0.05$ ** - $p \leq 0.01$ *** - $p \leq 0.001$ – between newcomers to the city and village; o - $p \leq 0.05$ oo - $p \leq 0.01$ – between natives and newcomers to the village; P - between the first and second trimesters

In the course of comparative analysis of the glutathione link of the AOS in groups of migrant population living in different ecological conditions (urban and rural areas), significant features in the indicators of total and reduced glutathione were revealed. Urban women have significantly lower indicators of both total glutathione (17.1 mg%) compared to the group of migrants from the village (21.3 mg%), ($p \leq 0.01$); and reduced - 10.6 mg% versus 15.8 mg%, respectively, ($p \leq 0.001$).

Taking into account the fact that during pregnancy there is an increase in oxidation-reduction processes to oxidative stress, adaptive activation of the glutathione link of the AOS occurs. Due to its chemical structure, glutathione directly interacts with active radicals, acts as a cofactor for various enzymes, participates in the detoxification of lipid peroxidation products, and also takes part in phases 2 and 3 of the detoxification system of xenobiotics and/or their metabolites [1, 10]. From this, we can make certain assumptions that in the conditions of the city, an industrial center with a developed transport structure, technogenic pollution, more frequent use of imported food products leads to tension of the glutathione link of the antioxidant defense system, forming background conditions before pregnancy. Consequently, even in the early stages of gestation, there is a decrease in the indicators of total and reduced glutathione with a subsequent further drop, which is confirmed by a significant reliable difference in the redox status (GSH / GSSG): 2.48 in women in the city versus 4.38 in rural newcomers ($p = 0.00885$). A similar trend in the compared groups is maintained in the second trimester of pregnancy: total glutathione among pregnant women in the city was 14.8 mg%, in the rural immigrants - 20.3 mg% ($p \leq 0.01$), reduced glutathione - 8.48 mg% and 13.3 mg%, respectively ($p \leq 0.01$). The low content of total glutathione in the group of pregnant women of the urban immigrant population is possibly due to the depletion of the reserves of components of the glutathione link of the antiradical defense system.

We also identified ethnic features of the components of the glutathione system when comparing women living in identical rural areas of the Amur region, but belonging to different nationalities and races. The level of restored glutathione in the second trimester is significantly lower in the group of native pregnant women of the village - Nanayek (Mongoloid race) - 8.62 mg% compared to higher rates among rural newcomers (Caucasian race) - 13.3 mg% ($p \leq 0.05$). Despite minor or more pronounced trends in the decrease in total and reduced glutathione in newcomers to urban and rural areas in the second trimester of gestation compared to the first, only native residents showed a reliable decrease in total - from 22.0 mg% to 15.9 mg% ($p = 0.0021$) and reduced - from 15.1 mg% to 8.62 mg% ($p = 0.001189$) glutathione without any dynamics in the content of the oxidized form.

When assessing the efficiency of the glutathione link of the detoxification system, it is important to take into account not only the concentration of total, reduced (GSH) and oxidized (GSSG) glutathione separately, but also the ratio between them (GSH / GSSG) - the redox status, which determines intracellular signaling and regulates the activity of transcription factors [5].

The integral indicator of the glutathione link of the AOS, as a biomarker of oxidation-reduction processes and oxidative stress, represented by the redox status, was the highest both in the first ($p \leq 0.01$) and second trimesters, but less significant, in the migrant pregnant women of the village. This can be explained by the lower impact of technogenic pollution in rural areas, the use of food and water of local origin. Despite the fact that the redox status indicators of the indigenous female population are slightly lower than those of rural migrants, they are higher than the data obtained in urban migrant pregnant women. This allows us to assume a greater reserve of compensatory capabilities of the glutathione link of the AOS in the indigenous population, due to the formed genetic characteristics that require further study and confirmation.

Conclusion. The conducted studies in pregnant women using the example of the immigrant and indigenous population of the Amur region living in different ecological conditions (city and village), in the absence of iron deficiency conditions, revealed some ecological and ethnic features of the glutathione link of the antioxidant defense system.

1. Ecological peculiarities in the glutathione link of the AOS consisted of a reliable decrease in the content of total glutathione in urban pregnant women of the migrant population in comparison with migrant rural population due to a decrease in the reduced form both in the first and second trimesters with a multidirectional trend of the oxidized fraction (in the 1st trimester - a decrease, in the 2nd - an increase in pregnant women of the village) in these groups.

2. An ethnic feature was the identification of changes in the glutathione link of the AOS depending on the trimester of gestation and place of residence. Indigenous women showed a reliable decrease in total and reduced glutathione in the second trimester in comparison with the first. When comparing the indicators in indigenous and migrant pregnant women living in a similar rural area, in the 2nd trimester, reliably low values of the reduced form of glutathione were noted in Nanai.

3. The integrated assessment of the indicator of the biomarker of oxidation-reduction processes on the example of pregnant women of the alien and native population is presented by the ratio of reduced and oxidized glutathione, shows the ecological-ethnic orientation. The optimal variant of the functional state of the glutathione link of the AOS is determined in alien (Caucasian) pregnant women living in rural areas, based on reliably high indicators of the redox status in the first, less significant in the second trimester in comparison with native residents of the village and especially and aliens of the city.

4. The obtained data should be taken into account when carrying out therapeutic and preventive measures for complicated pregnancy in women, taking into account the ecological-ethnic characteristics of oxidation-reduction processes.

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FREQUENCY OF OCCURRENCE OF MODIFIABLE RISK FACTORS FOR OSTEOPOROSIS IN YOUNG PEOPLE

The prevalence of modifiable risk factors for osteoporosis has been studied in young people. The study included 396 (75.1%) women and 131 (24.9%) men, for a total of 527 people. A questionnaire was developed that included questions on physical activity, nutrition, lifestyle, and the presence of bad habits. The following frequency of occurrence of risk factors was established: 233 (44.2%) people had one risk factors 166 (31.5%) - two, 92 (17.5%) - three, 36 (6.8%) people had four. The majority of respondents (425 (80.6%) people) had insufficient dietary calcium intake (56.2% of the age norm). The results of the study demonstrate a high prevalence of modifiable risk factors in young people, which undoubtedly indicates the need for preventive measures to prevent the development of osteoporosis and its complications in the future.

Keywords: osteoporosis, young age, risk factors, vitamin D, calcium, physical activity.

Introduction. For a long time, osteoporosis (OP) was considered a disease of "old age" associated with bone loss. In recent years, it has been proven that the critical period of bone development occurs during childhood and adolescence and reaches a peak between the ages of twenty and thirty years [3, 12]. The greatest increase in bone mineral density occurs during adolescence, accounting for about 60% of bone growth over a lifetime [13]. Epidemiological studies have found that a 10% increase in maximum bone mass at a young age reduces the risk of fractures later in life by 50%. It has been shown that low bone mass may be associated with bone loss caused by various conditions or processes that occur during adolescence and young adulthood [14, 18].

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Timely identification of risk factors (FR) is a key aspect in the prevention of OP. Modifiable risk factors, such as low body mass index, insufficient calcium intake and vitamin D deficiency, a sedentary lifestyle and the presence of bad habits, are of particular interest, since they play a leading role in the formation of bone mass in childhood and adolescence [4, 15, 18], and in unlike non-modifiable risk factors, lifestyle changes can be made to improve bone health and reduce the risk of future fractures.

Currently, most of the works devoted to the study of OP and assessment of the risk factors of OP are focused exclusively on the pediatric population and people in the older age group, which served as the impetus for the implementation of this scientific project.

Purpose of the study. To assess the incidence of modified FR osteoporosis in young people.

Materials and methods. The study included 396 (75.1%) women and 131 (24.9%) men, for a total of 527 people. The average age of the participants was 20.4 [19.0; 21.0] years. This work was carried out in strict accordance with the ethical standards laid down in the Declaration of Helsinki, as well as in compliance with the principles of Good Clinical Practice. Approval was obtained from the appropriate local ethical committee Federal State Budgetary Educational Institution of Higher Education Kemerovo State Medical University of the Ministry of Health of Russia (meeting No. 315 of November 8, 2023).

A questionnaire was developed that included questions on physical activity, nutrition, lifestyle, and the presence of bad habits. Daily calcium (Ca) intake was estimated using the formula: Ca intake from dairy products (calculated in milligrams) plus 350 mg, which is considered equivalent to the average amount of Ca a person obtains per day from other foods. Low physical activity (in the absence of other physical activities) was defined as walking less than 30 minutes per day. According to the latest data from the World Health Organization for 2023, there is no safe dose of alcohol. According to generally accepted standards, a standard dose of alcohol corresponds to 10 grams of pure ethanol (100 ml of wine, 200 ml of beer or 25 ml of strong (40%) alcohol). Drinking alcohol daily in a dose of more than 26 ml in terms of pure ethanol qualifies as FR OP. This study assessed the number of days in a week or month on which alcohol was consumed at a dose of more than 26 ml/day in both women and men.

Statistical data analysis was performed using Statistica software, version 6.1.478.0 from the developer StatSoft, Inc., for the Windows operating system. The results are presented as a median and interquartile range (Me [Q1; Q3]) when describing quantitative characteristics, and as an absolute number or relative values in percentage (%) for qualitative characteristics. To identify differences between groups in terms of qualitative characteristics, two-sided Fisher's exact test or Pearson's $\chi 2$ test was used; in cases of multiple comparisons, when calculating statistical significance, the adjusted p-value. The threshold value for statistical significance of the null hypothesis was 0.05.

Results. When assessing the frequency of occurrence of risk factors for OP in young people, it was found that 233

(44,2%) people had one risk factor, 166 (31,5%) had two, 92 (17,5%) respondents had three, 36 (6,8%) %) people - four. Thus, on average, 1,7 risk factors were identified per respondent. (Figure 1).

In this study, the majority of respondents (425 (80,6%) people) were found to have insufficient dietary calcium intake. Other risk factors for OP were distributed as follows: low physical activity - 234 (44,4%), alcohol consumption - 316 (59,9%), smoking - 143 (27,1%), low body weight - 48 (9,1%) Human. Only 68 (12,9%) respondents knew their vitamin D level, which undoubtedly cannot reflect real data on the status of vitamin D deficiency or insufficiency in the study group.

It was found that the average daily amount of calcium from all food products was 674.21 ± 106.3 mg, which corresponds to 56.2% of the age norm. Only 102 (19.3%) people consumed the recommended daily calcium intake, 147 (27.9%) people consumed half the daily intake, and 278 (52,8%) respondents consumed less than half the daily intake. It was shown that 146 (27.7%) girls and 132 (25,0%) boys consumed less than 500 mg of calcium per day with food. Of dairy products, respondents most often consumed soft and hard cheeses (24.6 and 19.2% of respondents) (Figure 2).

Only 68 (12.9%) respondents knew their vitamin D level, of which 49 (9.3%) women and 19 (3.6%) men ($\chi 2$ =3.34, p = 0.068), which undoubtedly cannot display actual data on vitamin D deficiency or insufficiency status in the study population. To indirectly assess vitamin D status, given the low awareness among respondents, the questionnaire included questions regarding the type, duration and frequency of exposure to sunlight. It was revealed that in the summer, 249 (47.3%) respondents were outdoors for 5 or more hours daily, 203 (38.5%) - from 3 to 4 hours, and only 75 (14.2%) young people less than 3 hours a day. The majority of respondents – 483 (91.6%) people spent the summer months outside the city. There were no statistically significant differences between the groups ($\chi 2$=0.76, p=0.684). In addition, 186 (35.3%) respondents took additional vitamin D as dietary supplements. When comparing by gender, it was noted that women took vitamin D significantly more often than men: 132 and 54 people, respectively ($\chi 2$ = 4.16, p = 0.041).

Low body weight was significantly more common among females: 42 (7.9%) women and 6 (1.2%) men ($\chi 2$=10.64, p=0.0011).

It was shown that slightly less than half of the respondents did not have physical activity on a regular basis (237 (44.9%) people): low physical activity was detected in 124 (23.5%) girls and 113 (21.4%) boys ($\chi 2$=0 .73, p=0.468). It was found that more men than women performed physical activity of 5 hours or more per week: 62 and 4 people, respectively ($\chi 2$=17.21, p=0.0002).

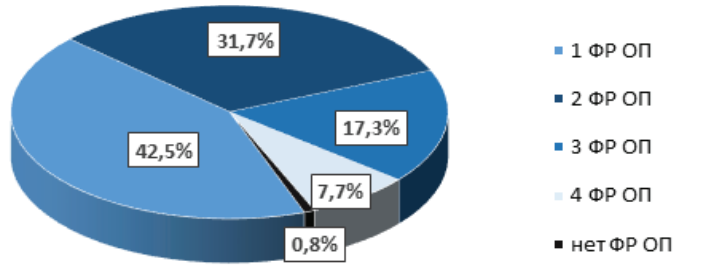

Fig. 1. Frequency of occurrence of risk factors for AP in young people

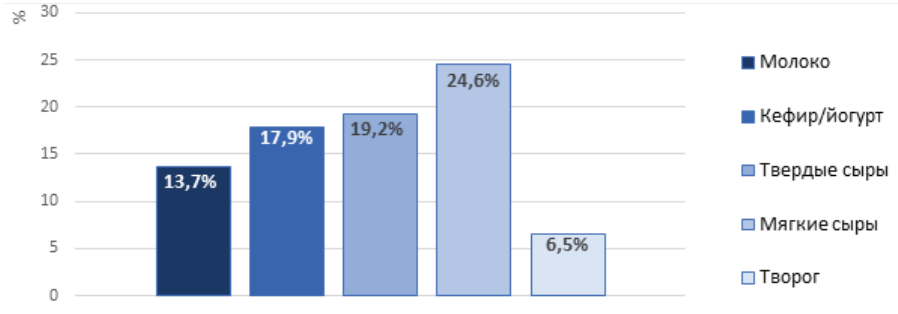

Fig. 2. Frequency of consumption of dairy products by young people, according to survey data

When assessing bad habits, it was recorded that 72 (13.7%) surveyed girls and 83 (15.7%) boys drank alcohol in a dose of more than 26 ml/day (in terms of pure ethanol) more often than once a month ($\chi 2$= 1.43, p=0.231). Weekly alcohol intake was noted by 8 (1.5%) and 12 (2.3%) girls and boys, respectively. Current smoking was confirmed by 98 (18.6%) girls and 89 (16.9%) boys ($\chi 2$=0.03, p=0.862).

Discussion. The results of the work showed that insufficient calcium intake from food is a widespread risk factor and was recorded in more than 80% of respondents. Similar data were obtained as part of scientific work carried out on the territory of the Russian Federation in recent years. According to a study carried out by the Federal State Budgetary Institution of Science “Federal Research Center for Nutrition and Biotechnology”, it is shown that the average level of calcium consumption by persons over 18 years of age ranges from 510–560 mg per day. It was noted that the maximum values were recorded in men in the age group from 45 to 55 years, while the lowest values were found in women aged 18 to 30 years. In general, calcium intake was lower in women than in men in all age groups [1].

Lifestyle features with temporary limitation of sun exposure and the use of active protection from its radiation are one of the key reasons for the high prevalence of vitamin D deficiency [7, 10]. Thus, in the work carried out by Suplotova L.A. It has been established that low levels of vitamin D are registered in more than 70% of the total population of the Russian Federation [2]. It was shown that regularly spending time in nature in the summer, at least three hours a day, allowed 85% of participants to achieve adequate levels of vitamin D due to natural insolation. However, it should be noted that the area of residence of the survey participants highly indicates the lack of sufficient insolation in the autumn-winter period. It was revealed that only 68 (12.9%) respondents knew their vitamin D level, which undoubtedly cannot reflect real data on the status of vitamin D deficiency or insufficiency in the studied group.

Most of the studies have proven the positive effect of regular physical activity at a young age on bone tissue and, as a result, reducing the likelihood of fractures in old age to 36%-39% [17, 11]. This study found that slightly less than half of the respondents (44.9%) do not regularly engage in sports, which is consistent with the results of previous studies [5].

An analysis of the dynamics of alcohol abuse among the population of the Russian Federation indicates positive changes taking place in our society. Thus, al-

cohol consumption in the Russian Federation over the past 15 years has decreased by 43% according to 2019 data [9]. However, the data obtained in our study on alcohol consumption over 26 ml/day (in terms of pure ethanol) more than once a month among 13.7% of girls and 15.7% of boys is alarming. Smoking increases the risk of osteoporotic fractures of various locations by 1.3 times, and hip fractures by 1.8 times due to disturbances in the process of bone formation due to bone resorption. Smokers (more than 20 pack years) have a 12% reduction in bone density compared to non-smokers [6, 16]. According to the results of the study, smoking was detected in 109 (20.7%) girls and 89 (16.9%) boys, which is consistent with Rosstat data for 2019 on the number of smokers at a young age [8].

Conclusion. The results of the study indicate a high prevalence of modifiable risk factors in young people, which undoubtedly indicates the need for preventive measures to prevent the development of AP and its complications in the future.

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DIAGNOSTIC AND TREATMENT METHODS

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BIOCHEMICAL METHOD TO DETERMINE BURN WOUND READINESS FOR AUTODERMOPLASTY

The choice of tactics for surgical treatment of burn injury mainly depends on the course of the injury process, the presence of inflammatory changes in the wound, the addition of pathogenic microbial flora, the state of the body's immune system and the presence of concomitant pathology. Determining the optimal and early terms for autodermoplasty is of particular importance in severely burned patients with a large deficit of donor resources. Therefore, the issues of determining the readiness of the burn injury surface for skin graft transplants remain relevant at present, and the search for solutions to this problem continues. The purpose of the study is to study injury discharge from the surface of burn injuries with the determination of biochemical indicators of total protein and fibrinogen and the level of bacterial contamination to develop a method for determining the readiness of burn injuries for autodermoplasty. Materials and methods. To achieve the stated objective, 70 samples of biochemical analyses of total protein and fibrinogen of injury discharge, as well as bacterial cultures with determination of the level of bacterial contamination of injuries, taken from 19 patients with deep burns of III (IIIb-IV) degree were studied. Autodermoplasty was planned for all patients during treatment. Injury discharge sampling was collected for studying the concentrations of biochemical markers and determining bacterial contamination the day before plastic surgery. Results and discussion. The analysis of the data revealed statistically significant high levels of total protein and a decrease in fibrinogen levels in wound discharge with a degree of contamination of burn injuries ≤ 103 CFU/g, than with higher levels of bacterial contamination of the injury. Based on the results obtained, a method was developed for determining the readiness of the burn injury surface for autodermoplasty. Conclusion. Determining the degree of readiness of burn injuries for plastic surgery, according to the proposed method, allows you to quickly obtain and analyze data on the state of the injury process and simultaneously determine the tactics of surgical treatment in burn patients.

Keywords: burn injury, autodermoplasty, fibrinogen, total protein

Introduction. As far as it is known, the main method of treating deep burn injuries is surgical interventions in the amount of necrectomy with one-stage or delayed autodermoplasty [4, 9]. However, when preparing the injury surface to accept a skin graft, as well as after unsuccessful plastic surgeries, combustiologists face a number of problems in the form of the addition of polyresistant hospital flora, inflammatory changes and microcirculation disorders of recipient wounds, lysis and rejection of transplants, a shortage of donor resources in severely burned patients, cicatricial deformations in delayed results [5, 6, 8, 11]. Therefore, the issues of the degree of readiness of burn injuries for autodermoplasty and the choice of adequate timing of plastic surgeries remain relevant at present.

One of the indicators of the readiness of the wound to accept a skin graft is the degree of bacterial contamination from the injury surface. The following acceptable criteria have been established: 10^5 colony-forming units per gram (CFU/g); with these indicators, the transplant can survive. Some authors consider the degree of bacterial contamination of 10^4 CFU in combination with signs of systemic and local inflammatory changes to be a criterion for invasive forms of wound infections. However, according to K.V. Lipatov, the optimal indicator for autodermografting is 10^3 CFU in 1 ml of discharge [3, 5, 7, 10].

In addition to the microflora, inflammatory changes should be taken into account when preparing a wound for plastic surgery. Based on the characteristic features of the course of the wound process and the pathophysiology of burn injuries, changes in the level of fibrinogen (Fb) and total protein (TP) in the wound discharge are of particular interest. An increase in the concentration of soluble fibrinogen, as an acute phase protein, prevents the attraction of leukocytes and can contribute to the cessation of inflammation processes, and also characterizes local lysis of fibrin deposits [12]. Total protein and albumin can be considered as "negative" acute phase proteins. In the early stages of the wound process, as a result of a cascade of lipid peroxidation reactions, there is a decrease in protein synthesis, a change in the conformation of protein molecules, and an increase in proteolysis processes [1, 2].

The aim of the study is to study wound discharge from the surface of burn injuries with the determination of biochemical indicators of total protein and fibrinogen and the level of bacterial contamination in order to develop a method for determining the readiness of burn injuries for autodermoplasty.

Materials and methods. The study included 70 samples of biochemical analyses of total protein and fibrinogen of wound discharge, as well as bacterial cultures to determine the level of bacterial contamination of wounds taken from 19 patients with deep III (IIIb-IV) degree burns. All patients were planned to undergo autodermoplasty during treatment. The area of skin surface damage varied from 1% to 90%. The average age of all patients ranged from 21 to 85 years. The study was conducted during 2023 at the burn department of the traumatology and orthopedics center of the Astrakhan Region State Healthcare Institution, Aleksandro-Mariinsky Regional Clinical Hospital in the city of Astrakhan.

Wound discharge sampling was taken for studying the concentrations of biochemical markers and determining bacterial contamination one day before the plastic surgery. No specific preparation of patients was required for collecting samples and their subsequent study. Wound discharge was collected during necrectomy or by scraping the discharge into Eppendorf tubes. Fibrinogen and total protein concentrations were assessed in g/l using commercial test systems "NPO Renam" (Russia) and "Erba Rus" (Russia).

The accumulation and systemati-

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zation of the data obtained during the study were carried out in Microsoft Office Excel 2016; the SPSS Statistic version 27 program was used for statistical analysis. When processing statistical data, non-normally distributed variables were identified, in connection with which non-parametric statistics methods were used using the Mann-Whitney criterion. The values of quantitative data were described using the median and the upper and lower quartiles (25 and 75 respectively). Differences were considered statistically significant at p-values less than 0.05.

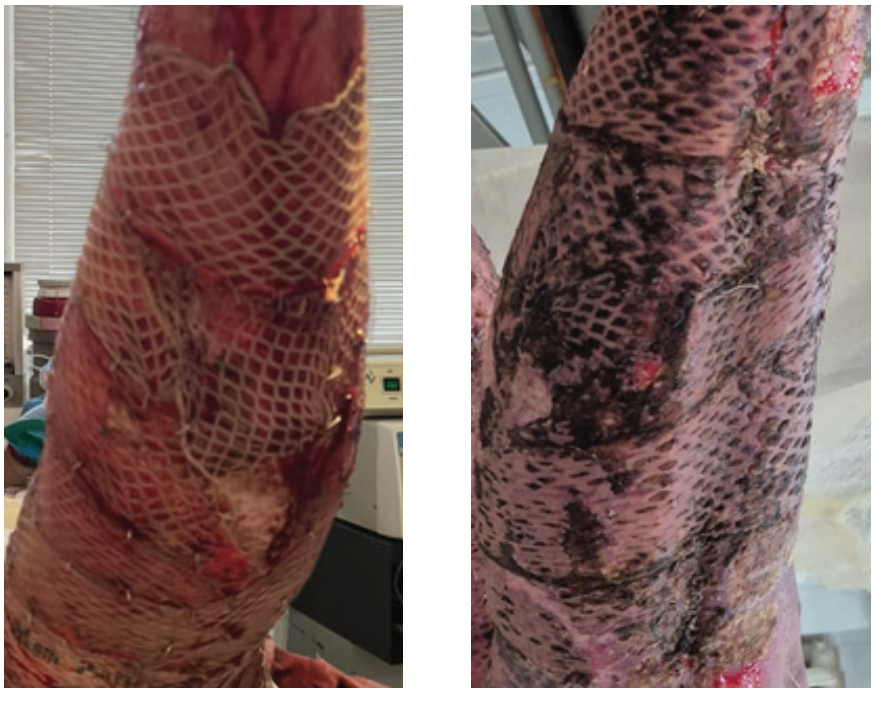
Results and discussion. Retrospective analysis showed the presence of a relationship between the level of the studied biochemical indicators of Fb, and TP of wound discharge with the level of bacterial contamination of the burn wound surface. The study revealed (see the table) a statistically significant increase in the level of total protein of wound discharge (73,2 [61,4-86,1] g/l) at a concentration of microorganisms ≤ 10^3 CFU/g compared to the group with a higher level of contamination -> 10^3 CFU/g (total protein level 40 [26,6-64,9] g/l). At the level of bacterial contamination of the wound ≤ 10^3 CFU/g, there was a decrease in fibrinogen indicators, while with an increase in bacterial contamination of the wound, there was a decrease in fibrinogen indicators.

The results of our study of TP and Fb obtained allow us to determine the timing of surgical intervention in a timely manner, without waiting for the results of bacterial contamination of injuries. In accordance with this, a method was developed for determining the readiness of the burn wound surface for autodermoplasty using the ratio coefficient (K), calculated by the formula K = Fb / TP. Favorable conditions for autodermoplasty were diagnosed at a coefficient less than or equal to 0,4. All patients with such indicators underwent autodermoplasty. In the case of autodermoplasty, complete engraftment of the skin graft on the recipient wound was noted (Figure).

Comparison of biochemical markers of wound discharge from the surface of burn injuries depending on the level of their bacterial contamination

Biochemical indicators	Level of bacterial contamination, CFU/g Me [IQR]	
	≤ 10^3 (n=49)	> 10^3 (n=21)
Total protein, g/l	73.2 [61.4-86.1]*	40 [26.6-64.9]*
Fibrinogen, g/l	21.6 [16.6-38.1] *	35.2 [20.7-38.5] *

* Различия показателей статистически значимы (p<0,05)



Results of free autodermoplasty performed in accordance with the proposed method: A) free autodermoplasty with K ≤ 0,4; B) complete survival of autograft, the wound was epithelialized.

A priority certificate was received for the invention "Method for determining the readiness of burn wounds for autodermoplasty" No. 2024106868 dated 15 March, 2024.

Conclusion. In our study the dependence of the concentration of total protein in wound discharge on the level of bacterial contamination of the burn wound surface was established. The change in fibrinogen levels shows a tendency towards its decrease by the time of plastic surgery. All patients with deep burns of grade III (IIIb-IV) underwent autodermoplasty with coefficient values of K ≤ 0,4. The result of plastic surgery was complete engraftment of the skin graft with subsequent active epithelialization of wounds. The proposed method, which does not depend on the degree of bacterial contamination of wounds, allows one-time decision-making on the volume of surgical treatment to be performed, without waiting for the results of bacterial cultures, which, in turn, increases the effectiveness of the operation and reduces the number of complications associated with lysis and rejection of the flap, can reduce the percentage of cosmetic defects and mortality.

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EVALUATION OF THE ANTITUMOR EFFICACY OF DOXORUBICIN IN COMBINATION WITH A HIF-1A INHIBITOR IN A VIVO MODEL OF HEPATOCELLULAR CARCINOMA

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Hepatocellular carcinoma (HCC) is a prevalent form of primary liver cancer, ranking among the most common and lethal forms of oncological diseases. Transarterial chemoembolization (TACE) is one of the standard treatments for unresectable HCC, in which one of the key points is the embolization of tumor arteries, resulting in hypoxia that activates the HIF-1α signaling pathway. According to numerous literary data, bortezomib (BTZ) is capable of blocking the biological effects of HIF-1α. Based on the analyzed data, it can be assumed that the combination of bortezomib and TACE may lead to a synergistic effect, increasing the effectiveness of therapy and improving the prognosis for patients with unresectable HCC.

In our work, we attempted to improve the antitumor efficacy of doxorubicin by combining it with an HIF-1α inhibitor in a model of hepatocellular carcinoma. During this study, it was established that the most effective suppression of tumor growth occurred in group 3, in animals with reduced blood flow and the administration of doxorubicin. The mean volume of tumor nodules was 395.33±95.70 mm3 ($p<0.05$), which was 2.1 times smaller than the mean volume in the control group, which was 830.56±144.86 mm3. In Group 2, in animals with reduced blood flow and the use of a combination of doxorubicin and bortezomib, the mean tumor node volume was 761.48 ± 117.95 mm³, which did not differ statistically from the volume of tumor nodes in the control group. Our findings indicate that a reduction in hepatic vascular blood flow in conjunction with doxorubicin exerts a pronounced inhibitory impact on the proliferation of intrahepatic tumor nodes. However, the introduction of bortezomib to this regimen does not result in the inhibition of tumor growth. Nevertheless, our results provide a rationale for a more comprehensive investigation of the mechanisms underlying the antitumor response or the reasons for its absence, as well as alternative candidates for HCC therapy.

Keywords: liver cancer, hepatocellular carcinoma, bortezomib, HIF-1α, TACE, HepG2.

Introduction. Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide [1]. Despite the emergence of promising treatment strategies, prognosis for patients with HCC is extremely heterogeneous and due to the complexity of diagnosis at an early stage of the disease.

Over the past decades, research has shed light on the epidemiology, risk factors, and genetic profiles of HCC, contributing to the development of prevention, surveillance, early diagnosis, and treat-

ment strategies [1-2]. Treatment options for hepatocellular carcinoma (HCC) depend on the stage of the disease, the general condition of the patient, and comorbidities.

Surgical intervention, including resection of the tumor or liver transplantation, is the main method in the early stages of cancer, when complete removal of the tumor is possible. Other treatment options include local therapy, such as radiofrequency ablation or trans-arterial approaches, and systemic therapy with sorafenib, regorafenib, and nivolumab [3]. For patients with inoperable HCC, the main treatment methods are t-ransarterial approaches and systemic chemotherapy [3].

One of the standard treatments for unresectable HCC is transarterial chemoembolization (TACE), which is based on two complementary mechanisms: cytotoxic chemotherapy and embolization of the arteries feeding the tumor. The restriction of tumor growth in this procedure is achieved both due to the action of the cytostatic drug doxorubicin and due to hypoxia, which occurs as a result of blocking the blood supply to the tumor [3-4]. Cancer cells, in turn, respond differently to reduced oxygenation. On the one hand, hypoxia causes growth arrest, death of cancer cells, and a decrease in their mobility, due to which the antitumor effect of arterial embolization is realized. On the other hand, it is known that a number of publications describe hypoxia as a factor associated with a clinically aggressive phenotype, increased invasive ability, perifocal spread of tumor cells, regional and remote spread, and resistance to various treatment methods [4].

Thus, it is assumed that hypoxia can contribute to the selection of a population of tumor cells that can adapt to hypoxia by activating the HIF-1α signaling pathway. In this regard, inhibition of HIF-1α signaling pathway can be considered a potentially effective way to overcome the negative effects of hypoxia [5-6-6].

According to literary sources, Bortezomib (BTZ), the first FDA-approved proteasome inhibitor, is also known to block the biological effects of the HIF-1α signaling pathway [7]. Some preclinical studies suggest that the therapeutic advantage of BTZ in the treatment of solidx tumorseй may be associated with inhibition of HIF-1α [7].

BTZ also implements its antitumor effect through the mechanism of inhibition of the proteasome, a cell complex responsible for protein degradation, which leads to the accumulation of pro-apoptotic factors and inhibition of the cell cycle, which ultimately contributes to the death of cancer cells [8].

In in an in vitro study, Baiz D. et al. The effects of bortezomib on cell lines such as HepG2 and JHH6 were studied. The authors concluded that, depending on the given dosage, it significantly reduces the number of living tumor cells [9].

In vitro studies have shown that BTZ, alone or in combination with other drugs, has a strong cytotoxic effect against a wide range of cancers, including breast, lung, prostate, and liver cancers [10].

In this regard, the aim of the study was to study the possibility of improving the anti-tumor efficacy of doxorubicin by combining it with a HIF-1α inhibitor in a model of hepatocellular carcinoma.

Materials and methods. *Animals and their content.* During the experiment, 15 female BalbBalb/c Nude mice aged 12-14 weeks were used, the average weight of which was 27-30 – 30g. The animals were obtained from the vivarium of the Testing Laboratory Center of the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation. Mice were kept in individual ventilated cages, and food and water were provided without restrictions. All manipulations performed in the course of the study were carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrates Used for Experiments or Other Scientific Purposes (ETSN 123, Strasbourg, 18 March 1986). The study protocol was approved by the local bioethical Committee of the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation.

Technique for creating an orthotopic FCC model. All surgical interventions were performed using intramuscular injection anesthesia Xila at a dose of 20 mg / kg, Zoletil-100 at a dose of 50 mg/kg. To create an orthotopic model of HCC, approximately four female Balb / c Nude mice were injected with a 5 million cell culture of HepG2 cells in 200 µl of DMEM culture medium without serum and antibiotics subcutaneously in the right side. When the tumorы nodes reached a diameter of 1.5 cm, the animals were euthanized, the neoplasm was removed and divided into small fragments measuring 2x2x2 mm for further implantation.

When the required depth of anesthesia was reached, the skin and abdominal wall were excised along the white line of the abdomen, the duodenum and stomach were displaced caudally exposing the left lobe of the liver. Tumor fragments obtained from a subcutaneous HCC model were transplanted to recipient animals in a pre-created liver pocket. At the end of the manipulation, the organs were returned to the peritoneum according to their anatomical location. The surgical wound was sutured with a continuous surgical suture.

Evaluation of the tumor node. Linear dimensions of tumor nodes were measured during diagnostic laparotomy using calipers on 14the 14th day after surgery to create an orthotopic model of HCC.

Study design

Group	Number of animals (nude mice), gender	Implantation of cells/ hcc fragment	Manipulation	Therapy	Method of administration, dosages and timing of drug
Administration 1	5♀	Fragment implantation	without exposure	saline solution	intraperitoneal saline solution, 200 µl, 3 times a week
2	5♀	Fragment implantation	blood flow reduction	BTZ + doxorubicin	intraperitoneal, 5 mg / kg + 5 mg / kg, 3 times a week
3	5♀	Fragment implantation	blood flow reduction	doxorubicin	intraperitoneally 5 mg / kg, 3 times a week

The volume of the tumor node was determined by the formula:

$$V=LW^2/2,$$

where L, W are linear dimensions of the tumor.

Distribution by groups. The size of the tumor node on 14the 14th day after intrahepatic implantation of the tumor fragment was used as a criterion for the distribution of animals into groups. The animals were divided into groups so that the spread of the average values of the volume of tumor nodes between groups was minimal. The animals were divided into groups according to the data shown in Table.

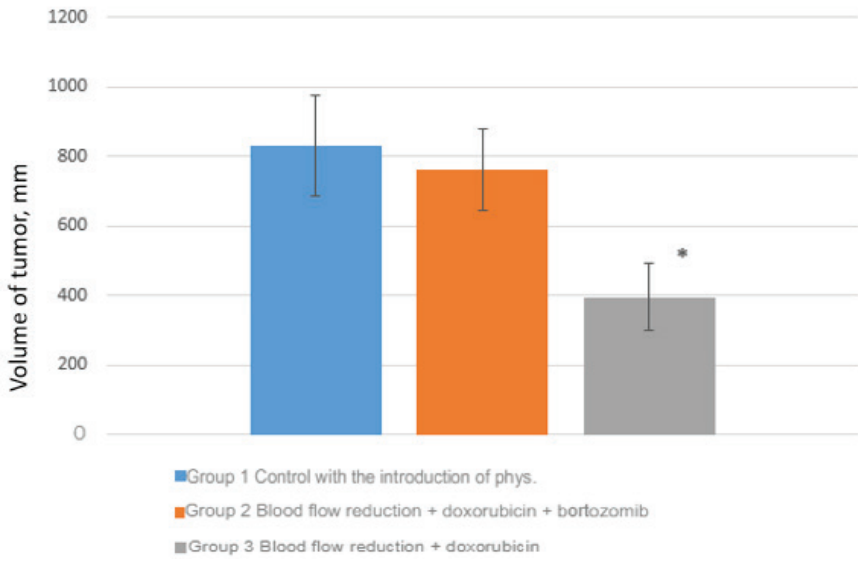
Technique of reducing blood supply to the liver by occluding the portal triad. Reduction of liver blood flow by occlusion of the portal triad was performed using a proven technique to create a hypoxic effect [11]. Reduction of liver blood flow in laboratory mice in this study was performed to simulate the biological effects of the transarterial embolization procedure performed in patients with HCC.

Statistical analysis. The obtained data were analyzed using the STATISTICA 10.0 software package. The data are presented as an average value ± standard error of the mean, comparison was performed using the Student's criterion, and differences were considered statistically significant at $p<0.05$.

Euthanasia. Euthanasia was performed on2-1 days from the start of administration of the studied drugs, using decapitation, after which measurements of isolated tumor nodes were performed.

Research results and discussion. Given the limited effectiveness of modern chemical therapy for inoperable HCC, it seems relevant to consider the possibility of improving the results of treatment by applying a therapeutic scheme using BTZ. Our study aimed to evaluate the antitumor efficacy of doxorubicin alone and in combination with bortezomib, a HIF-1α inhibitor, in a model of hepatocellular carcinoma.

In the course of this study, it was found that the most effective suppression of tumor node growth occurred in group 3, in animals with reduced blood flow and the use of doxorubicin, the average value of tumor node volumes was 395.33±95.70 мм^{mm3} ($p<0.05$), which was 2.1 timesa less than the average volume of the control group, equal to 830.56±144.86 mm^3. In group 2, in animals with reduced blood flow and the use of a combination of doxorubicin and bortezomib, the average value of tumor node volumes was



The size of tumor nodes on the 21st day after the start of drug administration.
*- statistically significant differences in relation to the control group ($p<0.05$).

761.48±117.95 мм^{mm3}, which did not statistically differ from the volume of tumor nodes in the control group (Figure).

According to the literature, the use of a combination of bortezomib and doxorubicin gives hope for achieving a pronounced antitumor effect: in an experiment on cell lines, the synergistic effect of these drugs was demonstrated in each tested sequence [12]. Bortezomib has also been shown бортезомибто restore sensitivity to doxorubicin in cell lines that previously developed resistance to its cytotoxic effects [12].

Despite the fact that there is evidence of addictive activity of bortezomib in relation to other chemotherapy drugs, in our study, we did not observe an improvement in antitumor efficacy when using a combination of bortezomib and doxorubicin. Our results correspond to the data of Y.J. Lee et al. (2022), which also demonstrated the limited effectiveness of the combination of bortezomib with doxorubicin in the treatment of ovarian cancer, only 2 out of 23patients showed a partial response [13]. Further, NGS analysis of tumor samples found that two patients who responded to therapy had somatic mutations in the BRCA2, ATM, and CDK12 genes, which may have been the reason for sensitivity to this therapy, however, the authors emphasize that this explanation is only a hypothesis and нfurther research is needed to study prognostic biomarkers of the therapeutic activity response to bortezomib-doxorubicin combination therapy.

Also Ciombor K.K. et al. used this combination for HCC in their experiment, where the limited effectiveness of this approach was also demonstrated, which is probably due to the small sample size [14]. The authors also suggest evaluating the levels of cytokines and chemokines (IL-6, IL-8, MGSA/Gro-α, MIP-1α,VEGF, etc.) as biomarkers of the therapeutic response to the combination of bortezomib with doxorubicin and indicate the need for further research in this direction.

Conclusion. Our results showed that reduction of blood flow in the liver vessels and in combination with doxorubicin has a significant inhibitory effect on the growth of intrahepatic tumor nodes, while the addition of bortezomib to this scheme does not lead to inhibition of tumor growth. Nevertheless, our results provide an incentive for a more detailed study of the mechanisms of the antitumor response or the reasons for its absence, as well as alternative candidates for HCC therapy.

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HEALTHY LIFESTYLE. PREVENTION

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SEARCH FOR ENVIRONMENTAL FACTORS AFFECTING TEMPERAMENT TRAITS IN YAKUTS

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For the first time, study of the influence of environmental factors (place of birth - city/village, season of birth, birth order, number of children in the family, smoking addiction, level of stressful situations experienced) on temperament traits in Yakuts (n=237) was carried out. To assess temperament traits - extraversion/ introversion and neuroticism - the Russian version of the questionnaire by G. Eysenck was used. It was found that the peculiarity of the studied sample is a high level of neuroticism: in men - 46%, in women - 72%. When analyzing the associations of temperament traits with various environmental factors, it was found that neuroticism rates in young people correlate with the number of traumatic events experienced in their childhood. In addition to the stress factor, temperament traits may be influenced by the season of birth: in women born in the spring and summer, on average, higher rates of extraversion are observed, and those born in autumn and winter have increased rates of neuroticism.

Keywords: temperament traits, neuroticism, extraversion/introversion, stressful situations, Yakuts (Sakha)

Introduction. According to modern concepts, temperament represents a person's innate tendency to experience a certain set of emotions, as well as the characteristic level of their intensity and reactivity in response to various stimuli of the environment [46]. Temperament is correlated with two indicators of personality traits according to the Eysenck questionnaire - extraversion and neuroticism [44]. Extraversion is characterized by a willingness to interact with the environment with energy, cheerfulness, sociability, and confidence, whereas introversion refers to a tendency to be more reserved and solitary [16]. Neuroticism is defined as the tendency to experience frequent and intense negative emotional reactions, including anxiety, fear, irritability, anger, sadness, etc. [16]. This exaggerated emotionality is often accompanied by the belief that the world is a threatening place and that the person is unable to cope with or control negative events. High levels of neuroticism are considered a risk factor for the development of anxiety disorders and depression [20; 24; 46]. One prospective study found that young adults with higher scores on negative emotionality and high stress reactivity actually reported more negative life events over time [20].

Historically, extraversion/introversion and neuroticism were considered as stable, genetically determined traits. The idea that children are born with a certain temperament, manifested from a very early age in habitual patterns of behavior and emotional reactivity, arose in ancient times [46]. Temperament is believed to be moderately stable throughout a person's life and is determined genetically, however it can be assumed that environmental factors may influence its formation to some extent in early life. In particular, some studies have shown differences in temperament types depending on the place of birth. Several empirical studies highlight the increased vulnerability of people from rural areas [18; 43; 47], while others came to the opposite conclusion - there is evidence that adults in urban environments are more neurotic and are at higher risk of developing mental disorders, the most common of which is depression [17; 21; 45]. In addition to place of birth, season of birth was also considered as a possible factor influencing personality traits [15; 26; 40]. Although this factor includes many environmental variables, a large number of association studies indicate possible links between season of birth, personality traits and the incidence of various neurological and psychiatric disorders, including schizo-

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phrenia, bipolar disorder [13; 31] and suicidal tendencies [37; 41].

Environmental factors that can potentially influence the formation of personality traits include birth order and the number of children in the family. Many studies have found differences in personality traits between an only child and children with siblings [30; 34]. It is assumed that in families with several children, the birth of a second child is an event that can cause psychological stress for the firstborn, but this point of view remains controversial [49]. The birth of a second child can create problems for very young firstborns, but it can also contribute to their rapid development and growth [38; 49].

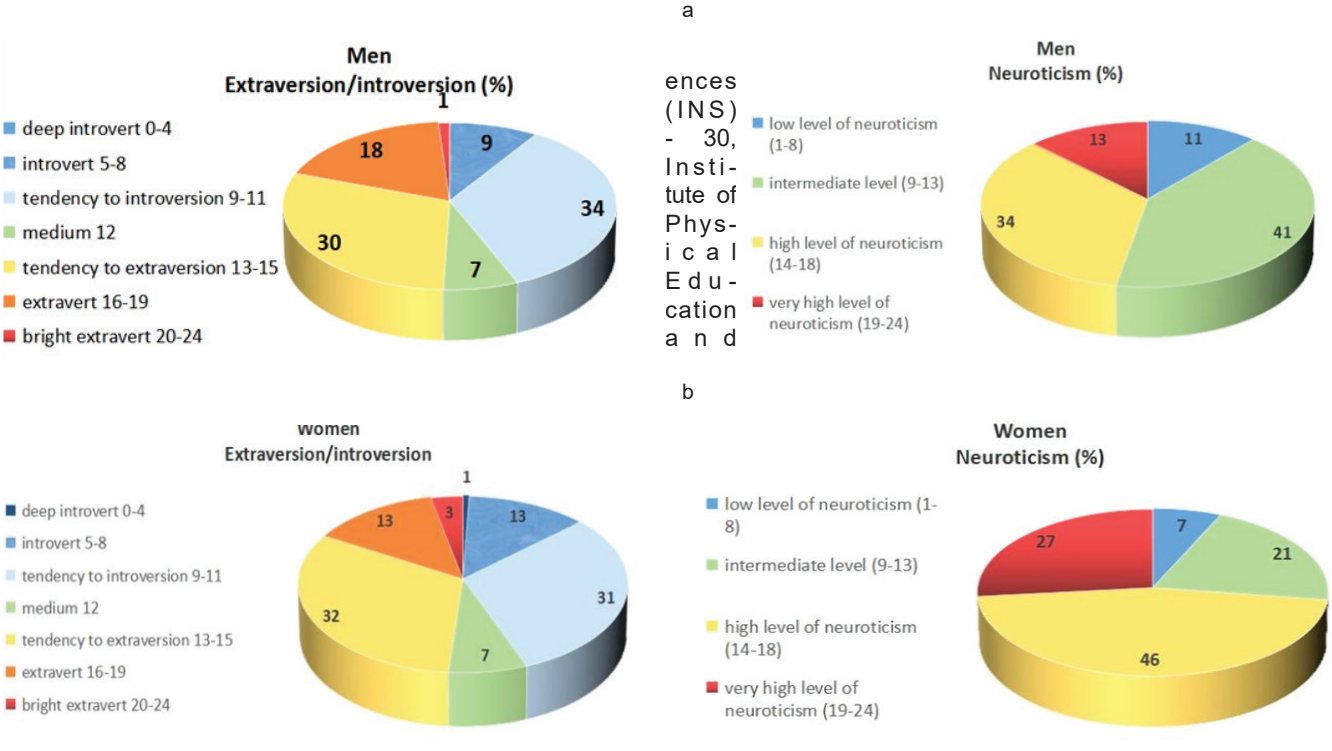
There are also quite a few studies indicating a link between smoking status and personality traits [2; 29; 32; 36]. It has been found that extraversion and neuroticism are higher in smokers, however, given that most of this data is obtained as a result of observational studies, it is difficult to establish whether these relationships are causal.

Finally, one of the factors potentially influencing the level of neuroticism may be stress. Studies of the prevalence of traumatic events conducted on a pooled sample of 68,894 adults from 24 countries showed that 70% of people experienced one or more traumatic events in their lives, and 4% of the population suffers from post-traumatic stress disorder (PTSD) [48]. The lifetime prevalence of PTSD varies from 0.3% in China to 6.1% in New Zealand [23]. Thus, the literature data indicate possible links between temperament traits and individual socio-demographic factors, but the results of these studies are quite contradictory and were conducted mainly in European populations. The aim of our study was to search for environmental factors influencing the rates of extraversion/introversion and neuroticism in young people of Yakut nationality.

Materials and methods. To determine personality traits, 328 young people, students and employees of M.K. Ammosov North-Eastern Federal University (NEFU) and Arctic State Agrotechnological University (ASAU) aged 18 to 29 years were tested. The Russian-language version of the Eysenck Personality Inventory (EPI) was used. The EPI contains 57 questions, 24 of which are aimed at identifying extraversion/introversion, another 24 - at assessing emotional stability/instability or neuroticism, the remaining 9 constitute a control group of questions designed to assess the sincerity of the subject and the reliability of the results. In 34 men out of 121 and 57 women out of 207 respondents, elevated rates of insincerity in their answers (>4) were found. The sample included only those respondents whose results showed sincerity when completing the test: 87 men and 150 women. Distribution by faculties of NEFU: Medical Institute (MI) - 159, Institute of Natural Sciences (INS) - 30, Institute of Physical Education and Sports (IPES)- 29, ASAU - 19 people. The average age of men in the studied sample was 20.3±2.7 years, women - 20.2±2.7 years. The questionnaire data included the status of the place of birth (urban/rural), season of birth, birth order and number of children in the family, the presence of smoking addiction and the level of stressful situations in life, i.e. factors that presumably influence the indicators of extraversion/introversion and neuroticism.

To assess the level of stressful situations, the "Stressful Events Rating Scale" [22] was used, adapted into Russian by Schutzenberger [11], including 16 potentially traumatic events: death of a parent, divorce of parents, use of psychoactive substances by close friends, accidents, suicide attempts, low family income, poor living conditions, disasters, sexual or physical abuse, serious health problems or other impacts associated with the impact on the nervous system. When collecting data, potentially traumatic events experienced before the age of 16 were taken into account.

Statistical analysis was performed using STATISTICA software (StatSoft, Inc., USA, 2014) version 12.0. The calculated parameters are presented in the format: M ± SE, where M - mean, SE - standard error.To check the normality of the distribution, the Kolmogorov-Smirnov criterion was used. In independent samples with a normal distribution of more than 50 peo-



Extraversion/introversion and neuroticism (%), a - in men (n=87), b - in women (n=150)

Table 1

Level of neuroticism in Yakuts (Sakha) according to previously published data

Age	University	n	Level of neuroticism %			Reference	Year of publication
			Low	Middle	High		
Men							
20.3±2.7	NEFU (MI. INS. IPES). ASAU	87	11	41	47	This study	2024
-	NEFU (MI)	51	32	33	35	[10]	2019
18-21	NEFU	50	50	26	24	[9]	2012
19.08±0.2	NEFU (MI)	-	38	27	35	[3. 4]	2008.2011
Women							
20.2±2.7	NEFU (MI. INS. IPES). ASAU	150	7	21	72	This study	2024
-	NEFU (MI)	98	21	43	36	[10]	2019
-	NEFU	-	28	33	39	[4]	2011
Total							
19.56±0.2	NEFU (PI)	51	25	12.5	62.5	[8]	2021

Table 2

Level of neuroticism depending on various environmental factors

Фактор		Total			Women			Men		
		n	M±m	p	n	M±m	p	n	M±m	p
Place of birth	urban	83	14.52±0.49	0.98	52	15.52±0.58	0.67	31	12.84±0.81	0.69
	rural	153	14.54±0.33		97	15.22±0.41		56	13.36±0.55	
Season of birth	[1]winter	127	14.91±0.38	[1-2] **0.03** [1-3] 0.40 [1-4] 0.94 [2-3] 0.17 [2-4] *0.09* [3-4] 0.55	82	15.77±0.46	[1-2] **0.04** [1-3] 0.28 [1-4] 0.68 [2-3] 0.22 [2-4] **0.05** [3-4] 0.22	45	13.36±0.63	[1-2] 0.55 [1-3] 0.49 [1-4] 0.87 [2-3] 0.68 [2-4] 0.47 [3-4] 0.96
	[2]spring	23	12.83±0.88		14	13.29±1.18		9	12.11±1.33	
	[3]summer	61	14.36±0.49		42	14.93±0.60		19	13.11±0.81	
	[4]autumn	26	14.81±0.92		12	16.50±0.92		14	13.36±1.44	
Birth order	[1] firstborn	114	14.35±0.43	[1-4] 0.52 [1-5] 0.70 [2-4] 0.77 [2-5] 0.98 [3-4] 0.47 [3-5] 0.64 [4-5] 0.82	76	15.36±0.47	[1-4] 0.52 [1-5] 0.51 [2-4] 0.58 [2-5] 0.70 [3-4] 0.55 [3-5] 0.52 [4-5] 0.26	38	12.32±0.77	[1-4] 0.45 [1-5] 0.13 [2-4] 0.89 [2-5] 0.48 [3-4] 0.39 [3-5] 0.12 [4-5] 0.39
	[2] only child	28	14.57±0.89		20	15.20±1.04		8	12.88±1.61	
	[3] eldest child	86	14.28±0.49		56	15.41±0.52		30	12.17±0.89	
	[4]second child	66	14.79±0.50		39	15.87±0.65		27	13.22±0.67	
	[5] third child and beyond	56	14.63±0.52		35	14.80±0.69		21	14.38±0.82	
Number of children in the family	1	31	13.65±0.87	[1-2] 0.46 [1-3] 0.12 [1-4] 0.34 [2-3] 0.20 [2-4] 0.63 [3-4] 0.48	21	14.38±1.03	[1-2] 0.48 [1-3] 0.12 [1-4] 0.56 [2-3] 0.13 [2-4] 0.86 [3-4] 0.31	10	12.10±1.56	[1-2] 0.93 [1-3] 0.47 [1-4] 0.51 [2-3] 0.47 [2-4] 0.46 [3-4] 0.96
	2	75	14.27±0.48		49	15.10±0.59		26	12.69±0.73	
	3	72	15.14±0.49		42	16.33±0.52		30	13.47±0.84	
	≥4	58	14.62±0.55		38	15.16±0.70		20	13.60±0.88	
Smoking	smokers	41	14.54±0.59	0.97	20	15.40±0.77	0.82	21	13.71±0.86	0.50
	non-smokers	196	14.56±0.31		130	15.35±0.37		66	13.00±0.53	
Level of stress situations	0-2	127	13.56±0.39	**0.00008**	70	14.40±0.54	**0.006**	57	12.53±0.54	0.06
	3-12	109	15.72±0.36		79	16.23±0.39		30	14.40±0.78	
	0	47	14.09±0.62	**0.0002**	24	14.92±0.91	**0.05**	23	13.22±0.81	0.09
	1-2	80	13.25±0.50		46	14.13±0.67		34	12.06±0.72	
	3-12	109	15.72±0.36		79	16.23±0.39		30	14.40±0.78	
Total		237	14.56		149	15.36		87	13.17	

Note: values in bold indicate p<0.05.

ple, the reliability of differences in mean values was assessed using Student's t-test. For nonparametric distribution and comparison of small samples of less than 50 people, the Mann-Whitney-Wilcoxon U test and the Wald-Wolfowitz test were used. When comparing several groups, the Kruskal-Wallis test was used for small samples (n<50), and ANOVA was applied for samples with a size >50. The analysis of the relationship between neuroticism and the number of stressful events was carried out using Spearman's linear correlation algorithms. Values of p≤0.05 were considered statistically significant.

All examinations were conducted in compliance with the principle of informed consent. Within the framework of the study, each participant was informed of the purposes of the study and gave written consent for the use of personal information obtained from the results of psychological testing and questionnaires. Before the start of the study, approval was obtained from the local committee on biomedical ethics of the YSC CMP (protocol No. 41 dated November 12, 2015).

Results and discussion. Figure shows the distribution of extraversion/introversion and neuroticism scores in the studied groups of men (n=87) and women (n=150). Among men, the largest proportion falls on individuals with a "tendency to introversion" (34%) and "tendency to extraversion" (30%), pronounced "extraverts" make up 18%, "introverts" - 9%, the smallest proportion falls on "bright extraverts" (1%), "deep introverts" were not found (0%) (Figure A). In terms of neuroticism, the majority of men in the studied sample have average scores (41%), individuals with a "high" and "very high" level of neuroticism make up 46%, and those with a "low" level - only 11%. Among women, there is also a predominance of individuals with a “tendency to introversion” (31%) and a “tendency to extraversion” (32%), pronounced “extraverts” and “introverts” make up 13% each, “bright extraverts” - 3%, “deep introverts” - 1% (Figure B). Unlike men, most women were found to have a “high” and “very high” level of neuroticism (72%), only 7% and 21% of the 150 participants had, respectively, a “low” and “intermediate” level of neuroticism.

Gender differences in the level of neuroticism were established in early studies: women, as a rule, score higher than men [27; 28]. These differences are manifested regardless of race and ethnicity and are universal [50]. Significantly higher values on the neuroticism scale in women compared to men were also noted in the studies conducted by Russian researchers on students of universities in Bashkortostan, Udmurtia [5; 7], and Kemerovo [6].

In general, the frequency ratio in the general sample of students of various educational profiles that we studied (MI - 67%, INS - 13%, IPES - 12%, ASAU - 8%) is shifted towards emotionally anxious psychotypes. High rates of neuroticism were observed in all groups of young people from different institutes accordingly it cannot be explained by the peculiarities of the choice of educational profile and are obviously determined by other factors. Table 1 shows the level of neuroticism in the general sample in comparison with data published from 2008 to 2021. A high level of neuroticism was found only in the work published in 2021 among students of the Pedagogical Institute (PI) of NEFU (62.5%), in earlier publications, neuroticism rates range from 24% to 35% of men, from 36% to 39% in women. Thus, it can be assumed that high values of the level of neuroticism in the younger generation of Sakha are determined mainly by the influence of environmental factors.

In order to determine the causes underlying the differences identified, a search for associations of temperament indicators with various environmental factors was conducted. Table 2 presents the average values of neuroticism in the overall sample not divided by gender, as well as in groups of men and women depending on place of birth (city/village),

Table 3

Level of extraversion/introversion depending on various environmental factors

Factor		Total			Women			Men		
		n	M±m	p	n	M±m	p	n	M±m	p
Place of birth	urban	83	12.93±0.40	0.84	52	12.89±0.51	0.96	31	13.00±0.66	0.33
	rural	153	12.07±0.27		97	11.99±0.36		56	12.20±0.42	
Season of birth	[1]winter	127	12.29±0.31	[1-2] 0.20 [1-3] 0.38 [1-4] 0.15 [2-3] 0.35 [2-4] **0.04** [3-4] 0.08	82	12.02±0.39	[1-2] 0.17 [1-3] 0.08 [1-4] 0.10 [2-3] 0.76 [2-4] **0.03** [3-4] **0.02**	45	12.78±0.52	[1-2] 0.71 [1-3] 0.31 [1-4] 0.62 [2-3] 0.31 [2-4] 0.38 [3-4] 0.77
	[2]spring	23	13.30±0.74		14	13.50±0.94		9	13.00±1.25	
	[3]summer	61	12.78±0.45		42	13.21±0.57		19	11.79±0.70	
	[4]autumn	26	11.23±0.65		12	10.17±0.97		14	12.14±0.84	
Birth order	[1] firstborn	114	12.77±0.35	[1-4] 0.20 [1-5] 0.17 [2-4] 0.18 [2-5] 0.21 [3-4] 0.32 [3-5] 0.27 [4-5] 0.87	76	12.63±0.45	[1-4] 0.74 [1-5] 0.16 [2-4] 0.57 [2-5] 0.26 [3-4] 0.86 [3-5] 0.34 [4-5] 0.34	38	13.08±0.57	[1-4] *0.07* [1-5] 0.47 [2-4] 0.16 [2-5] 0.51 [3-4] 0.11 [3-5] 0.53 [4-5] 0.53
	[2] only child	28	13.25±0.82		20	13.25±1.08		8	13.38±1.16	
	[3] eldest child	86	12.62±0.38		56	12.41±0.47		30	13.00±0.66	
	[4]second child	66	12.06±0.40		39	12.38±0.58		27	11.59±0.50	
	[5] third child and beyond	56	11.96±0.43		35	11.57±0.49		21	12.38±0.80	
Number of children in the family	1	31	13.19±0.74	[1-2] 0.33 [1-3] 0.33 [1-4] 0.19 [2-3] 0.70 [2-4] 0.54 [3-4] 0.79	21	12.81±0.97	[1-2] 0.64 [1-3] 0.79 [1-4] 0.46 [2-3] 0.46 [2-4] 0.65 [3-4] 0.28	10	14.00±1.07	[1-2] 0.36 [1-3] *0.06* [1-4] 0.24 [2-3] 0.28 [2-4] 0.77 [3-4] 0.51
	2	75	12.44±0.41		49	12.27±0.52		26	12.77±0.67	
	3	72	12.22±0.40		42	12.64±0.54		30	11.63±0.57	
	≥4	58	12.07±0.43		38	11.87±0.52		20	12.45±0.75	
Smoking	smokers	41	12.90±0.48	0.34	20	12.85±0.70	0.53	21	12.95±0.68	0.46
	non-smokers	196	12.29±0.26		130	12.27±0.32		66	12.33±0.42	
Level of stress situations	0-2	127	12.11±0.29	0.63	70	12.01±0.40	0.31	57	12.23±0.41	0.35
	3-12	109	12.72±0.36		79	12.62±0.43		30	12.97±0.68	
	0	47	11.91±0.47	0.37	24	11.79±0.68	0.51	23	12.04±0.68	0.55
	1-2	80	12.25±0.36		46	12.13±0.51		34	12.35±0.52	
	3-12	109	12.72±0.36		79	12.62±0.43		30	12.97±0.68	
Total		237	12.40		150			87		

season of birth (winter, spring, summer, autumn), birth order, number of children in the family, smoking addiction, and level of stressful situations in life. It was found that of the above factors, the level of stress experienced has the greatest effect on the neuroticism indicators of young people (Table 2). Women with a high level of stressful situations in life (≥3) have a higher level of neuroticism, in contrast to those who have previously experienced fewer stressful situations (0-2) (p=0.006). In the group of men, the influence of stress is noted at the trend level (p=0.06). In the overall group, this relationship becomes even more significant (p=0.00008). It is interesting to note that when dividing the overall sample into 3 groups based on the number of stressful events, the level of neuroticism in the group with a small number of stressful situations (1-2) is reduced compared to the groups with no stress (0) and high levels of experienced stress (3-12) (p=0.0002) (Table 2). This trend is observed in both women (p=0.05) and men (p=0.09).

The influence of stress on some personality traits was also noted by us earlier when using the TCI questionnaire by R. Cloninger [1]. Correlation analysis confirmed that the neuroticism indicators have a weak relationship with the level of stress experienced both in men (r=0.27, p<0.05) and in women (r=0.22, p<0.05). In the general group, this correlation becomes higher (r=0.32, p<0.05). In general, our results indicate that traumatic events experienced in childhood significantly increase (n ≥3) the level of neuroticism in young people, and to a greater extent in women than in men. It is noteworthy that almost half of the young people in the studied sample (46%) experienced a fairly high level of stress (from 3 to 12 traumatic events). In 7 of 150 women (4.7%) and 2 of 87 men (2.3%), a suicide attempt was noted in the questionnaire data. Associations between stressful events, neuroticism levels, and depressive symptoms have been previously reported in studies of adolescents and students [19; 20; 24]. Most studies have found higher rates of depression among female participants compared to males [12; 25; 35].

When examining the possible influence of other factors on neuroticism levels, a weak association with season of birth was found: in the group of women born in autumn and winter, average neuroticism rates were higher than in those born in spring (p=0.05 and p=0.04), while in men these differences did not reach the level of significance (Table 2). Season of birth was also associated with the level of extraversion/introversion: women born in spring and summer showed significantly higher extraversion rates compared to those born in autumn (p=0.03 and p=0.02, respectively), while this association was not found in the group of men (Table 3). Similar associations of personality traits with season of birth have been previously found in the Swedish population using the TCI questionnaire [42]. Although we cannot draw definitive conclusions regarding the stability of the associations found due to the small size of the compared groups, our results are somewhat consistent with large cohort studies of adults (n=2130) in Sweden [42]. Based on our data, it can be assumed that Sakha girls born in autumn and winter are at greater risk of developing emotional instability when experiencing traumatic events in childhood.

The influence of the season of birth on psychological characteristics of a person may be due to complex and still relatively unknown mechanisms. According to one hypothesis, the season of birth may influence personality traits through biochemical mechanisms associated with dopamine and its derivatives [39]. It has been established that the duration of daylight affects not only the production of melatonin, but also the level of dopamine and its metabolites, which, in turn, can affect some personality traits [42]. It is known that dopamine and melatonin are in balance and mutually suppress their activity: at night, when the level of melatonin increases, the level of dopamine decreases, while during the day the opposite dynamics are observed. The maternal melatonin rhythm during pregnancy varies depending on the season and affects the melatonin rhythm of the child [14], accordingly, the duration of daylight during the neonatal period also affects the level of dopamine metabolites by influencing the monoaminergic system of the newborn's brain. In particular, Natale et al.(2002) found that those born in winter are more likely to be early risers than those born in summer/spring and suggested that dopamine levels are higher in those born in winter than in those born in summer (total sample size: 3709 students from Sweden and Italy) [33]. The influence of season of birth on personality traits was also found in a study conducted in the USA: men born in winter demonstrated higher scores on the sensation seeking scale than men born in other seasons of the year (n=195) [39].

Conclusion. This study represents the first assessment of the influence of environmental factors on temperamental traits in young people of Yakut nationality. Our results allow us to state that of the environmental factors analyzed that may influence the level of neuroticism, the level of stress experienced in the childhood (under 16) is significant. In addition to traumatic events, season of birth may also influence temperamental traits.

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ORGANIZATION OF HEALTH, MEDICAL SCIENCE AND EDUCATION

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AVAILABILITY OF MEDICAL PERSONNEL AND MEASURES FOR THEIR RETENTION IN PUBLIC HEALTH CARE INSTITUTIONS

The geographical uneven distribution of medical personnel characteristic of the Russian Federation affects the sustainability of the country's healthcare system and, consequently, the availability and quality of medical care.

The aim of the study is to analyse the provision of medical personnel in federal districts, constituent entities of the Russian Federation and measures to attract and retain them for 2018-2023 in the constituent entities of the Russian Federation on the example of the North-Western Federal District.

On the basis of statistical data from Russian research Institute of Health and the State Statistics Service (Rosstat), an analysis of the staffing of medical organisations of the public health system in the Russian Federation as a whole, federal districts, constituent entities of the Russian Federation in the North-West Federal District was carried out, with the calculation of indicators and their growth/decline rates for the period of implementation of the federal project 'Providing medical organisations of the health system with qualified personnel' (2018-2023).

The indicator of provision with doctors in the Russian Federation as a whole and in most federal districts showed a positive trend, while the opposite trend was recorded in the provision with middle medical personnel, possibly due to defects in planning the need for training of middle medical personnel at the regional level. The North-Western Federal District has the highest rate of doctors (44.3 doctors per 10,000 population), but there are marked interregional differences in the rates of doctors and paramedical staff (with medical education), which indicates that the work to attract and retain medical personnel is not sufficiently effective.

Despite significant differences between the constituent entities of the Russian Federation that make up the North-West Federal District, the measures to attract and retain medical personnel are similar in almost all constituent entities of the Russian Federation. To improve the effectiveness of regional personnel policy it is necessary to clearly differentiate the measures taken at the level of a medical organisation in a particular municipality, normative and legal regulation of the powers of local governments to create favourable conditions for attracting medical workers, economic incentives for medical workers, increasing the targeting and filling of social support measures in rural health care, in hard-to-reach, remote areas with a low density of us.

Keywords: medical personnel; personnel deficit, personnel imbalance, personnel attraction; social support measures.

Introduction. The main goal of improving the health sector of each country is to create a sustainable system, the functioning of which will contribute to ensuring high quality and accessibility of health care for every resident regardless of their place of residence, social or material status. The World Health Organisation attaches particular importance to the role of the health workforce in building the resilience of countries to adequately respond to emergencies and believes that even the most advanced technologies cannot have a positive impact on public health if there is a shortage of health workers [3,17].

It is proved that the level of accessibility and quality of medical care to the population, the efficiency of the health care system as a whole determine human resources [7]. However, today the personnel crisis in healthcare has become an international level problem that concerns most countries of the world [8,17]. According to foreign experts (2019), in 20 years, the projected shortage of human resources in the health care system worldwide will reach 18 million people. Five years ago, there was a shortage of at least two million doctors worldwide and the problem is particularly acute for people living in rural areas [9,17].

The Russian healthcare system is characterised by uneven geographical distribution of medical personnel, which is confirmed by significant differences in the indicator of medical personnel supply in the constituent entities of the Russian Federation. According to O.L. Zadvornaya (2018) [3], A.V. Meltser et al. (2019) [13], Son M.M. et al. (2021) [11], the indicator of provision of the population with medical personnel varies significantly in the constituent entities of the Russian Federation, municipalities and depends on the territorial location of medical organisations, which affects the accessibility of medical care [9].

The problem of medical personnel supply in regions with a low level of socio-economic development, in territories with low population density, rural areas located in high latitudes, arctic and subarctic zones remains extremely urgent [5-7, 10, 12-15].

The aim of the study: to analyse the availability of medical personnel and measures taken by state and municipal authorities to attract and retain medical personnel in the constituent entities of the Russian Federation on the example of the North-Western Federal District.

In accordance with the goal, the following tasks were defined: to analyse the availability of doctors and nurses in the Russian Federation (hereinafter - RF), federal districts, constituent entities of the Russian Federation, including the North-Western Federal District (hereinafter - NWFD) for the period 2018-2023; to analyse the measures of the state and municipal level to attract and retain medical workers; to develop proposals to strengthen the role of local governments to create favourable conditions to attract and retain medical workers.

Materials and methods of research. The study was carried out using statistical data of Russian research Institute of Health in terms of continuous statistical observation and analysis of staffing of medical organisations of the state health care system subordinate to the Ministry of Health of the Russian Federation in the Russian Federation as a whole (hereinafter - the Ministry of Health of Russia),

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in federal districts, in the subjects of the Russian Federation. Relative indicators of the provision of the population with doctors and paramedical staff with medical education (per 10 thousand population) working in municipal and state medical organisations subordinate to the Ministry of Health of the Russian Federation, growth/decline rates of indicators for the period of implementation of the federal project 'Provision of medical organisations of the healthcare system with qualified personnel' (2018-2023) were calculated. Statistical processing of data was carried out using Microsoft Excel 2019 software package, Statistica 15.0 application programmes.

The authors analysed the data of the authors' publications devoted to the measures of social support of medical workers, their effectiveness and efficiency in attracting and retaining medical personnel. Research methods: statistical, analytical, comparative analysis, content analysis.

Results and discussion. In the Russian Federation as a whole, with multidirectional dynamics of the indicator of provision with doctors of the state health care system subordinate to the Ministry of Health of Russia for the period 2018-2023, there is a positive trend of its growth, but the values of indicators by federal districts differ significantly (Table 1).

The maximum level of physician supply, with positive dynamics over the period of the federal project implementation, remains in the Northwestern Federal District, with the Far Eastern Federal District (FEFD) in second place in terms of the indicator level. The Southern Federal District (SFD) has the lowest indicator (more than a quarter below the level of the indicator in the Northwestern Federal District) with negative dynamics, while the Urals Federal District (UFD) has a slightly higher indicator with a positive trend of indicator growth. The provision is at the level of the average Russian indicator in the Siberian Federal District (SibFD) and the Central Federal District (CFD).

Despite the measures taken within the framework of the federal project, the number of nurses (with medical education) is declining annually both in the Russian Federation as a whole and in all federal districts (Table 2).

In the CFD and SFD, the indicator of provision of medical organisations of the state health care system with secondary medical personnel with medical education is lower than the average Russian level, which apparently indicates defects in planning the need for training of secondary medical personnel at the regional level, since the planning of the need and financing of educational organisations of secondary vocational education is carried out at the expense of regional budgets.

The North-West Federal District includes 11 constituent entities of the Russian Federation with different geographical, national and social features. According to Rosstat data, the population in the constituent entities of the Russian Federation that make up the North-West Federal District varies considerably - from 5.5 million in the megalopolis city of St. Petersburg to 42 thousand in the smallest constituent entity of the Russian Federation in terms of population - the Nenets Autonomous District. Population density also varies significantly within the North-West Federal District: from 0.24 in the Nenets Autonomous District to 3,890 people per square kilometre in St. Petersburg. High population density (more than 100 people/sq. km) is observed in St. Petersburg, medium (50-100 people/sq. km) - in the Leningrad, Kaliningrad, Novgorod and Pskov Regions, and low (less than 50 people/sq. km) - in the Republics of Karelia, Komi, Nenets Autonomous District, Arkhangelsk, Vologda and Murmansk Regions. The level of urbanisation in the NWFD is quite high and ranges from 66.16% in the Leningrad Oblast to 94.33% in the Murmansk Oblast.

The North-West Federal District as a whole has a high rate of physician supply (44.3 physicians per 10,000 population), but in individual constituent entities of the Russian Federation within its territory, physician supply rates vary from 27.4 per 10,000 population in the Pskov Oblast with negative trends; 29.8 in the Leningrad and Vologda Oblasts with negative trends to 42.3 in the Republic of Karelia; 49.1 in the Nenets Autonomous Okrug by 2023 and 60.3 in St. Petersburg with positive growth trends (Table 3).

This situation indicates the presence of imbalance of medical personnel in the constituent entities of the Russian Federation in the district, which may also be the reason for the decrease in the availability of medical care in some of its territories.

The indicator of provision with average medical personnel in the district as a whole in dynamics repeats the trend in the Russian Federation as a whole with the rate of decline by more than 6% over the observation period. Nevertheless, the Komi Republic and the Murmansk Oblast show positive dynamics of the indicator with its value above the average. Low indicators are noted in the Leningrad Oblast - the indicator decreased from 59.9 in 2018 and 51.9 per 10 thousand population in 2023 and in the Kaliningrad Oblast - the indicator decreased from 62.9 per 10 thousand population in 2018 to 58.9 in 2023 (Table 4).

Stating the problems of staffing of medical organisations of the public health care system in one of the most 'prosperous' federal districts of the Russian Federation in terms of staffing indicators, we have analysed measures to attract and retain medical personnel.

It should be emphasised that since 2012, after the adoption in 2011 of the federal law No. 323-FZ 'On the Fundamentals of Health Protection of Citizens in the Russian Federation' as a result of the transfer of powers to provide primary health care from the municipal level to the regional level, the managerial impact

Table 1

Dynamics of the indicator of supply of doctors in medical organizations of the state healthcare system subordinate to the healthcare authorities of the constituent entities of the Russian Federation and the Ministry of Health of Russia in the federal districts (per 10,000 population) for 2018-2023 (per 10,000 population)

Subjects	2018	2019	2020	2021	2022	2023	Rate (%) of growth 2020/2018	Rate (%) of growth 2023/2018
RF	37.4	37.6	38.1	37.5	37.0	37.5	1.9	0.27
CFD	37.4	37.9	38.9	37.7	36.8	37.6	4.0	0.53
NWFD	43.0	43.8	44.3	44.3	44.0	44.8	3.0	4.19
SFD	34.5	34.2	34.3	33.4	32.7	33.1	-0.6	-4.06
NCFB	34.9	35.2	35.7	34.9	35.0	35.3	2.3	1.15
PFD	36.2	36.3	36.8	36.4	36.1	36.6	1.7	1.10
UFD	34.3	34.4	34.8	34.5	34.3	34.7	1.5	1.17
SibFD	37.9	37.7	38.0	37.9	37.1	37.4	0.3	-1.32
FEFD	40.0	40.2	40.3	40.4	39.9	39.8	0.7	-0.50

on the factors of satisfaction with medical care at the level of municipal education has been lost [1,11].

Measures to attract and retain medical personnel in almost all regions of the NWFD turned out to be similar, despite the significant differences between the constituent entities of the Russian Federation [13]. Thus, on the one hand, there is the megacity of St. Petersburg with a high population density, industrially developed, urbanised regions, such as the Kaliningrad and Leningrad Oblasts, and on the other hand, there are regions belonging fully or partially to the Arctic zone, with extremely low population density, underdeveloped transport infrastructure, and the presence of remote hard-to-reach areas - the Republics of Karelia, Komi, NAO, Murmansk and Arkhangelsk Oblasts.

Attraction and retention of personnel, social support of medical workers is mainly provided in the following areas: support for students on target directions in the framework of targeted training, cash payments, housing, payment for housing and utilities and other measures. Support for students is mainly limited to additional payments to the scholarship, in rare cases - to the establishment of personal scholarships. Cash payments include lump-sum payments under the 'Zemsky Doctor' / 'Zemsky Feldsher' programmes, lump-sum payments upon employment ('lift'), monthly payments, as well as payments to doctors in the most in-demand specialties.

Measures such as the provision of service housing from the State housing fund, the provision of service housing from the municipal housing fund, the provision of dormitory accommodation, compensation for the down payment on a mortgage loan, compensation for the rent of residential premises, social payments for the construction (acquisition) of housing in rural areas, preferential (mortgage) loans (credits) for the construction (acquisition) of housing, social payments for the construction (acquisition) of housing, and social payments for the construction or purchase of housing are used to solve the housing problems of recruited medical specialists.

A number of regions provide for the privatisation of office accommodation in accordance with an agreement. All medical workers living in rural areas are compensated for the cost of housing and utilities. In a number of constituent entities of the North-West Federal District, compensation is provided for expenses incurred when moving from other regions, places in preschool educational establishments are provided for the children of medical workers, and privileges are granted for visits to physical culture and health-improvement establishments and for children attending paid clubs and sections of municipal subordination. The Murmansk Oblast is implementing the Doctor project for resettlement of compatriots.

It is noteworthy that almost all of the above measures are financed from regional budgets, while the participation of local governments remains minimal. At the same time, Article 17 of Federal Law No. 323-FZ 'On the Basics of Health Protection of Citizens', paragraph 2, item 1, Article 6, Article 14 of Federal Law No. 131-FZ of 06.10.2003 'On General Principles of Organisation of Local Self-Government' stipulate the powers of local governments to create favourable conditions for attracting medical and pharmaceutical workers. But at the federal level these powers are not specified and not detailed, which creates conditions for their non-implementation [1,11].

Comparison of measures to attract and retain personnel, additional measures of social support for medical workers and personnel provision of regions in the Northwestern Federal District shows

Table 2

Dynamics of the indicator of availability of middle medical personnel with medical education in medical organisations of the state healthcare system subordinate to the healthcare management bodies of the constituent entities of the Russian Federation and the Ministry of Health of Russia in the federal districts (per 10,000 population) for 2018-2023 (per 10,000 population)

Subjects	2018	2019	2020	2021	2022	2023	Rate of Growth		
							2020/ 2018	2023/ 2021	2023 /2018
RF	83.4	82.8	81.9	80.1	77.2	76.6	-1.8	-4.4	-8.2
CFD	76.7	76.1	75.5	73.8	69.4	68.6	-1.6	-7.0	-10.6
NWFD	83.3	83.2	82.2	80.6	79.0	78.1	-1.3	-3.1	-6.2
SFD	76.9	76.0	74.5	72.3	68.0	67.4	-3.1	-6.8	-12.4
NCFB	80.7	80.3	81.1	81.0	78.3	78.3	0.5	-3.3	-3.0
PFD	88.1	87.4	86.3	84.1	82.3	81.6	-2.0	-3.0	-7.4
UFD	90.0	89.3	89.0	87.0	84.9	84.1	-1.1	-3.3	-6.6
SibFD	89.6	88.7	87.2	84.8	83.3	82.9	-2.7	-2.2	-7.5
FEFD	85.5	85.2	84.6	83.0	82.6	81.7	-1.1	-1.6	-4.4

Table 3

Dynamics of the indicator of availability of doctors in medical organisations of the state healthcare system subordinate to the healthcare authorities of the RF subjects and the Ministry of Health of Russia in the RF subjects in the North-West Federal District (per 10 thousand population) for 2018-2023 (per 10 thousand population)

Subjects of the Russian Federation in the North-West Federal District	2018	2019	2020	2021	2022	2023	Rate of growth 2023/2018, %
Karelia Republic	42.3	42.2	43.2	42.6	47.4	48.0	**13.5**
Komi Republic	41.2	40.8	40.2	38.7	42.1	41.4	0.5
Arkhangelsk Oblast	40.7	40.3	39.6	38.7	43.1	44.0	**8.1**
Nenets Autonomous Okrug	42.2	46.2	45.7	44.6	48.1	49.1	**16.4**
Vologda Oblast	29.8	30.0	30.2	29.1	29.4	29.4	-1.3
Kaliningrad Oblast	30.1	30.9	30.8	31.7	31.2	31.9	**6.0**
Leningrad Oblast	29.8	30.0	29.9	30.5	28.5	29.3	-1.7
Murmansk Oblast	34.6	34.3	34.4	34.0	36.2	38.1	**10.1**
Novgorod Oblast	32.7	32.1	31.3	29.8	30.7	30.3	-7.3
Pskov Oblast	27.4	26.0	26.2	26.0	26.9	25.8	-5.8
Saint Petersburg	57.9	59.9	61.9	61.7	59.0	60.3	**4.1**

Table 4

Dynamics of the indicator of availability of middle medical personnel with medical education in medical organisations of the state healthcare system subordinate to the healthcare authorities of the RF subjects and the Ministry of Health of Russia in the RF subjects in the North-West Federal District (per 10 thousand population) for 2018-2023 (per 10 thousand population)

Subjects of the Russian Federation in the North-West Federal District	2018	2019	2020	2021	2022	2023	Rate of Growth 2023/2018
Karelia Republic	95.3	95.7	93.6	99.7	95.0	94.7	-0.6
Komi Republic	121.7	123.2	120.5	128.4	125.8	123.7	1.6
Arkhangelsk Oblast	99.9	100.5	97.8	102.1	98.7	97.6	-2.3
Nenets Autonomous Okrug	115.4	132.6	121.7	125.3	117.2	108.0	-6.4
Vologda Oblast	94.1	94.9	93.0	91.7	90.3	89.3	-5.1
Kaliningrad Oblast	62.9	63.8	63.7	61.1	59.0	58.9	-6.4
Leningrad Oblast	59.9	63.0	62.7	54.6	53.3	51.9	-13.4
Murmansk Oblast	86.2	88.3	87.3	92.1	88.9	88.7	2.9
Novgorod Oblast	82.9	82.9	82.7	74.5	71.4	69.5	-16.2
Pskov Oblast	83.7	86.9	85.0	81.8	80.1	78.7	-6.0
Saint Petersburg	81.5	86.8	87.3	78.7	77.8	77.4	-5.0

the insufficient effectiveness of the measures taken: personnel provision at the level of constituent entities of the Russian Federation varies significantly, local and regional peculiarities, the level of infrastructure development, attractiveness for employment and targeting of benefits provided are not taken into account, which is noted by researchers in other regions of the Russian Federation [2,6].

One of the ways to solve the staffing issue of medical organisations in rural areas, remote territories and regions with low population density is the rotational method. The introduction of this method requires the adoption of a number of regulatory legal documents at all levels, the definition of types, conditions, forms and volumes of medical care that can be provided on a rotational basis. Due to the fact that there are significant differences between business trips and rotations, including the requirements for medical workers, as well as the methods and mechanisms of payment for their labour, the rotational method requires the drafting of a separate contract, in which it is necessary to clearly indicate the living conditions of medical staff and the amount of salary. We believe that it is advisable to use this method in combination with staff retention in rural and remote areas. Medical personnel working in medical organisations in rural areas can be sent for a certain period of time to work in medical organisations at the regional level, from where the specialist was sent on a rotational basis, in order to improve their professional level.

Social support measures should be clearly differentiated by regions, municipalities, medical organisations, primarily by strengthening the role of local governments in creating favourable conditions for medical workers: development of rural infrastructure, ensuring transport accessibility, providing access to the Internet [6,8].

The development of differentiated measures to attract and retain medical personnel at the level of medical organisation requires normative legal regulation of the powers of local governments to create favourable conditions for attracting medical workers, the development of measures of economic incentives for medical workers, increasing the targeting and filling of social support measures in rural health care, in hard-to-reach, remote areas with low population density, taking into account regional conditions [7,14]. Medical workers in rural areas and in regions with low population density should have undeniable advantages in wages and social guarantees. Such guarantees may include preferential taxation or exemption from income tax after certain years of work experience in rural areas or in regions with low population density; certain advantages in calculating preferential medical experience for medical workers in rural settlements, taking into account 'rural' experience when certifying for a qualification category, conducting specialised professional selection of candidates in addition to competitive selection among school graduates for admission to a medical university for training on a target basis.

Conclusion. Thus, the provision of doctors in the Russian Federation and federal districts for the period 2018-2023 has a mainly positive trend, with the maximum level of provision of doctors with positive dynamics for the entire period 2018-2023 remaining in the Northwestern Federal District, but pronounced interregional differences have been identified. The indicator of provision with secondary medical personnel (with medical education) tends to decrease both in the Russian Federation as a whole and in all federal districts, including the NWFD, which indicates defects in planning the need for secondary medical personnel at the regional level, insufficient funding of regional educational organisations of secondary vocational education, insufficient measures to attract and retain middle-level medical specialists.

Despite significant differences in climatic and geographical conditions, demographic characteristics (population size and density, level of urbanisation), social support measures in all constituent entities of the Russian Federation are not diverse and are quite similar [6]. The most common measures to attract and retain medical workers at the state level are support for those studying in targeted areas within the framework of targeted training, lump-sum compensatory cash payments, housing, partial or full compensation for the purchase or construction of housing, payment for housing and utilities services and other measures [4,14].

In connection with the established low interest of local governments in retaining specialists in medical institutions located in the territory of a particular municipality, it is necessary to establish normative legal regulation of the powers of local governments to create favourable conditions for attracting medical workers and provide targeted benefits in the territory of a particular municipality.

There is a need for a broad expert discussion of both general trends in personnel policy, including in rural health care and remote areas with unfavourable climatic conditions, and regional experience in the introduction of new organisational, economic and management tools for attracting doctors and nursing staff and their economic incentives to optimally address the staffing issue.

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DETERMINING TRENDS IN THE EPIDEMIOLOGICAL PROCESS AND QUALITY OF MEDICAL CARE FOR BREAST CANCER

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The analysis of primary breast cancer incidence among women in the Irkutsk region for 2011–2023 and mortality from it was conducted based on general indicators and by age groups for women under 50 and over 50 years old to clarify the epidemiological situation and trends of ongoing processes. The primary breast cancer incidence continues to grow in the region: «rough» indicators – by 1.4 and standardized indicators – by 1.2 times. The increase in breast cancer incidence is also demonstrated in two large age groups with a greater increase in women under 50 – 1.8 versus 1.3 times in women over 50. The mortality rate of women from breast cancer in these age groups has a multidirectional trend: up to 50 years of age, an increase of 9% was registered; over 50 years of age – an insignificant decrease of 8.3%. In contrast to the all-Russian trend towards a decrease in mortality in 2011–2023, in the Irkutsk region the overall mortality rate from breast cancer did not change in relative terms and decreased insignificantly by 17.0% in standardized terms. In contrast to the all-Russian trend towards a decrease in mortality in 2011–2023, in the Irkutsk region the overall mortality rate from breast cancer did not change according to «rough» indicators and decreased insignificantly by 17.0% according to standardized ones. In women in the region, cancer is most often diagnosed in the upper quadrants, the central part of the breast, as well as cancer that extends beyond one or more localizations C50.0–C50.6 according to ICD-10. All indicators of the quality of oncological care for women with breast cancer improved in the Irkutsk region during the study period. Moreover, in 2023, two quality indicators were higher than the all-Russian values: 48.6% of patients with breast cancer were actively identified (44.0% in the Russian Federation) and in almost 100% of cases, diagnoses were confirmed morphologically (99.8% versus 99.2% in the Russian Federation). Achieving the all-Russian level for all indicators of the quality of oncological care will make it possible to reverse the situation with regard to mortality and achieve optimal results in improving the quality of life of women with breast cancer.

Key words: breast cancer, trends, primary morbidity, mortality, neglect, one-year mortality, quality of medical care.

Introduction. Breast cancer (BC) is the second most common cancer in the world after lung cancer (2.3 million cases or 11.6%) and the fourth cause of death from malignant neoplasms (670 thousand; 6.9%) [1, 13]. In countries with a low sustainable development index, due to poor health care, low access to basic oncological services and quality treatment, BC is more often diagnosed at late stages, thereby increasing the burden and costs at all levels of health care [1, 13, 14]. Therefore, there are significant differences in the results of cancer diagnosis and treatment between and within countries. It is predicted that by 2050 the number of new cancer cases worldwide will increase by 77% compared to 2022 and will reach 35 million [1]. If the current dynamics of the epidemiological process are maintained, the incidence of breast cancer will continue to increase in Russia and its regions [2, 7, 10]. On the one hand, timely diagnostics using modern medical equipment [5] is accompanied by the detection of new cases and an increase in incidence [7], on the other hand, due to this, as well as the improvement of treatment methods, the survival rates of patients [6], the duration and quality of their life are improving [15].

Purpose of the study: analysis of trends in the epidemiological process and quality of medical care for breast cancer in the Irkutsk region.

Materials and methods of research. Analysis of «rough» and standardized indicators (world standard) was carried out according to statistical collections of the Ministry of Health of the Russian Federation [3, 4, 8, 9]. The quality of oncological care was assessed using information from the database of the population cancer registry (DB PRR) of the Irkutsk region and form No. 30. The calculation of primary breast cancer incidence rates for women of two age groups (under 50 and over 50) was carried out using forms No. 7; similar mortality rates according to tables C51; 95% confidence interval; growth/decline rates. The methods of comparative analysis and ranking of indicators in descending order were used using standard Windows programs (version 10.0).

Results and discussion. In the Irkutsk region, a statistically significant increase in the primary incidence of breast cancer was registered for 2011–2023: the «rough» indicators – by 1.4 times from 78.1 [73.3 ÷ 82.9] to 108.7 per 100 thousand [103.0 ÷ 114.4]; standardized indicators – by 1.2 times from 50.7 [47.4 ÷ 53.9] to 61.2 per 100 thousand [57.7 ÷ 64.6]. Breast cancer mortality in the region does not have a significant downward trend, since despite fluctuations in values during the analyzed period, the «rough» indicator remained at the same level – 28.3 per 100 thousand (Fig. 1). According to standardized indicators, in the Irkutsk region and in Russia, in 2011-2023, the primary incidence of breast cancer in women increased by 1.2 and 1.3 times, respectively. According to standardized mortality rates from breast cancer, the region registered a decrease of 17.0% from 17.0 [15.2 ÷ 18.9] to 14.1 per 100 thousand [12.5 ÷ 15.7], in Russia - a statistically significant decrease of 24.8% from 16.5 [16.2 ÷ 16.7] to 12.4 per 100 thousand [12.2 ÷ 12.5]. In 2023, among the constituent entities of the Russian Federation, according to standardized indicators of primary incidence of breast cancer in women, the region ranked 30th;

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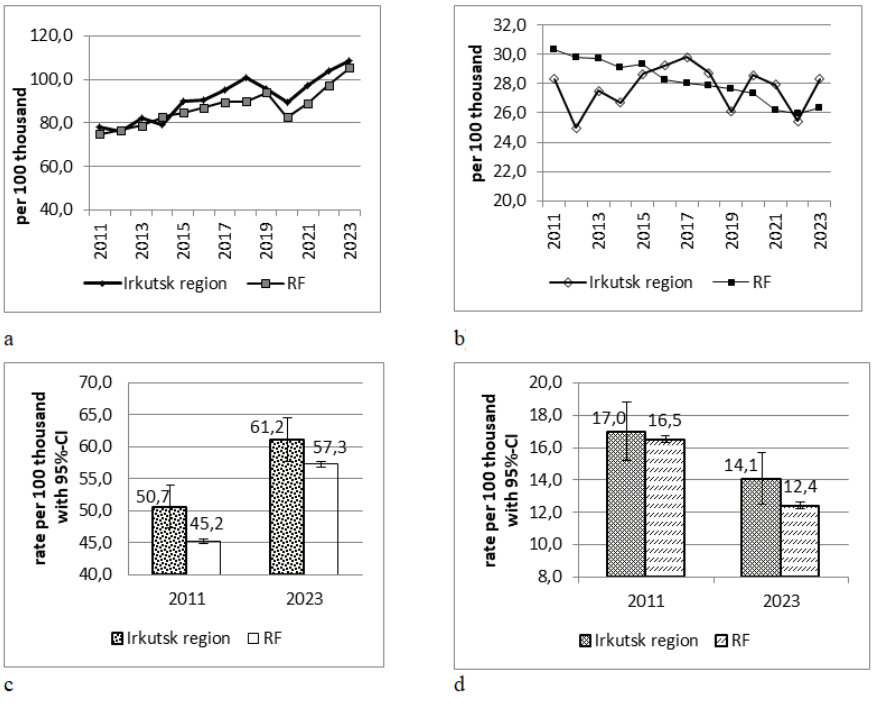

Fig. 1. Dynamics of <<rough>> indicators of primary incidence of breast cancer in women (a), mortality from it (b) in the Irkutsk region and the Russian Federation for 2011-2023; standardized rates of morbidity (c) and mortality (d) in 2011 and 2023 (per 100 thousand with 95% CI)

in mortality, it shared 13th-14th place with Kamchatka Krai [3, 4].

The region has seen an increase in the primary incidence of breast cancer in women of two age groups: under 50 years of age - by 1.8 times from 34.9 [28.9 ÷ 40.9] to 63.3 per 100 thousand [55.8 ÷ 70.8], over 50 years of age - by 1.3 times from 180.9 [168.5 ÷ 193.3] to 231.8 per 100 thousand [218.1 ÷ 245.4] - Fig. 2. In 2023, among all types of malignant neoplasms, breast cancer occupied the first place in the mortality structure of women in the Irkutsk region, starting from the age group of 30-34 years. The exceptions are two age groups: women aged 40–44, where cervical cancer was prevalent, and aged 80–84, where breast cancer shared 1st–2nd place with colon cancer. The mortality rate from breast cancer in women under 50 increased by 9.0% from 10.0 per 100,000 in 2011 [7.1 ÷ 12.9] to 10.9 per 100,000 in 2023 [7.8 ÷ 14.1]; in women over 50, the mortality rate decreased by 8.3% - from 71.2 [63.4 ÷ 78.9] to 65.3 per 100,000 [58.1 ÷ 72.6], respectively. The mortality rates from breast cancer in women under 50 and over 50 in some years statistically significantly differed by 5-10 times, while there were no significant changes in the mortality rate from breast cancer in all women (Fig. 2).

In women of the Irkutsk region, cancer is most often localized in the upper outer (C50.4), upper inner (C50.2) quadrants and the central part (C50.1) of the mammary gland, accounting for 64–76% of the total number of registered cases, including postmortem cases, in different years (Fig. 3). In addition, breast cancer is common, extending beyond one or more localizations C50.0–C50.6 according to ICD-10, although the proportion of such malignant neoplasms with code C50.8 statistically significantly decreased from 23.5% [20.9 ÷ 26.1] in 2013 to 12.7% [11.0 ÷ 14.4] in 2023.

Outcomes of breast cancer largely depend on women's timely visits to a doctor, accessibility of medical care, i.e. organization of oncology services (Table 1) and other factors. During the study period, the accessibility of oncology care for breast cancer improved in the Irkutsk Region: the number of mammography departments (offices) and machines increased by 1.4 times. However, at present, almost half of the operating machines have been in operation for over 10 years.

Analysis of qualitative indicators characterizing the organizational aspects of providing medical care to women with

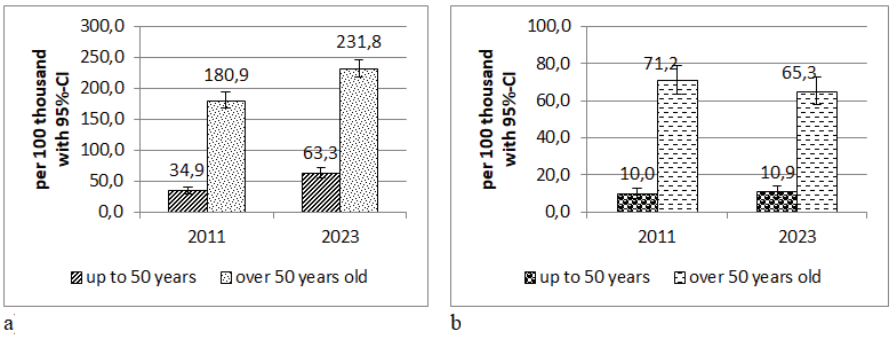

Fig. 2. Levels of primary incidence of breast cancer in women under 50 years of age and over 50 years of age (a) and mortality from it (b) in the Irkutsk region in 2011 and 2023. («rough>>> indicators, per 100 thousand)

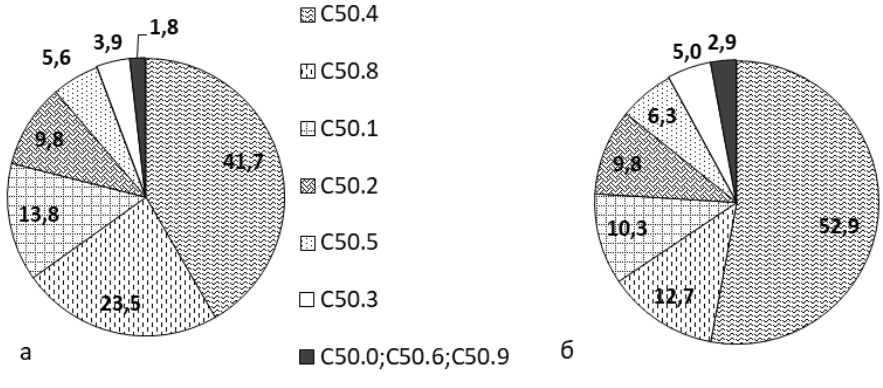

Fig. 3. Dynamics of the localization structure of breast cancer in women of the Irkutsk region: a) 2011; b) 2023 (percentages)

breast cancer allows not only to assess the dynamics of these indicators, but also to identify shortcomings in the oncology service, on which the future fate of these women and their quality of life largely depend [6, 12].

The following figures show the improvement in medical care for women in terms of breast cancer diagnostics: in the region, the number of ultrasound examinations increased by 1.7 times in 2011–2023, and the number of preventive X-ray examinations increased by 2.5 times. Moreover, the share of the latter, performed on digital devices and computer radiography systems, increased by 5 times (from 12.0% in 2011 to 59.4% in 2023). Over the period under study, the proportion of women diagnosed with breast cancer at early stages (I and II) increased by 10.2% in Russia, while in the Irkutsk Region the growth was more significant – by 15.1% (Table 2).

The quality of diagnostics can be judged by the neglect rate, assessing the proportion of patients with detected cancer at stage IV for non-visual localization or in total with stages III–IV for non-visual localizations [6–9]. The proportion of women with advanced breast cancer at stages III–IV for 2011–2023 in the region statistically significantly decreased from 40.2% [37.3 ÷ 43.2] to 26.6% [24.3 ÷ 28.9]; in the Russian Federation – from 33.9% [33.5 ÷ 34.3] to 24.4% [24.1 ÷ 24.7] – Fig. 3. However, the neglect rate in the Irkutsk region did not have a clearly defined annual downward trend: minimum values were recorded in 2015–2019, which were lower than the all-Russian indicators, then there was an increase in the indicator in 2020 and a gradual return to the pre-pandemic level. In Russia, the neglect rate for breast cancer decreased annually with an average annual decline rate of 2.7%.

During the study period, all indicators of medical care for women with breast cancer improved in the Irkutsk region, with a statistically significant difference in 6 of the 9 analyzed indicators (Table 2). According to the 2023 figures, two indicators of the quality of medical care are better than in the Russian Federation: the proportion of patients identified actively and with a morphologically confirmed diagnosis, which allows for the correct and timely selection of a treatment method [7] and the achievement of positive results [12]. In the region, in 2023, compared to 2011, the level of one-year mortality from breast cancer among women in all age groups over 35 years old decreased (Fig. 5). The ratio of one-year mortality in the reporting year to the neglect rate of the

Table 1

Оснащённость оборудованием и диагностические исследования по РМЖ в Иркутской области в 2011 и 2023 гг. (единицы)

list of equipment and research	2011	2023
mammography departments/rooms	39	55
mobile	1	2
flummammas	-	3
operating mammography machines	60	84
of which with a service life of over 10 years	10	44
number of preventive X-ray examinations	68963	175493
on film machines	60688	71302
on digital devices and computer radiography systems	8275	104191
on mobile units	60634	3430
on devices with homosynthesis function	-	320
number of x-ray diagnostic studies:	-	64734
on film	-	82343
digital	-	153841
Ultrasound	39736	67095
MRI	240	15

Table 2

Indicators of the quality of medical care for women with breast cancer in the Irkutsk region and the Russian Federation in 2011 and 2023 (% and units)

indicators	Irkutsk region		RF	
	2011	2023	2011	2023
proportion of women identified at early stages (I and II). %	58.4	73.5*	65.0	75.2*
proportion of women identified at later stages (III–IV stages). %	40.2	26.6*	33.9	24.4*
proportion of patients actively identified. %	28.1	48.6*	27.1	44.0*
share of morphologically confirmed diagnoses. %	98.6	99.8*	96.6	99.2*
one-year mortality rate. %	11.7	5.1*	8.7	4.4*
lethality. %	4.6	2.6	4.2	2.3*
contingent accumulation index. units	8.8	10.5	9.5	10.7*
ratio of the one-year mortality rate of the reporting year to the neglect indicator of the previous year. units	0.75	0.53	0.87	0.56*
percentage of those registered for 5 years or more. %	56.6	63.7*	57.6	64.0*

* changes are statistically significant

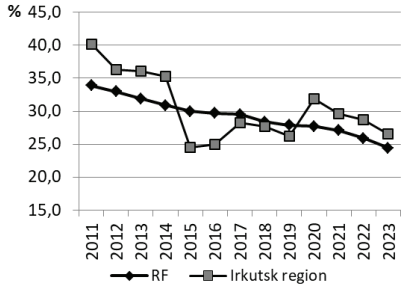

Fig. 4. Dynamics of advanced breast cancer in stages III-IV in the Irkutsk region and the Russian Federation for 2011-2023 (%)

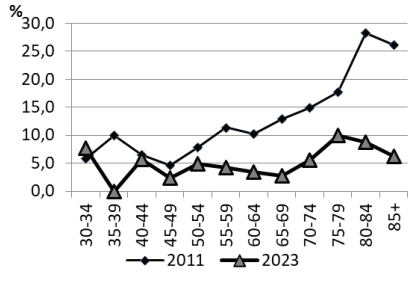

Fig. 5. Dynamics of one-year mortality of women in the Irkutsk region from breast cancer by individual age groups in 2011 and 2023 (%)

previous year allows us to determine the frequency of clinical errors in assessing the tumor process. Experts consider a value exceeding one unacceptable. According to the results of the analysis, the actual values of this indicator for breast cancer and its decrease in 2023 to 0.56 in the Russian Federation and to 0.53 in the Irkutsk Region indicate an improvement in the quality of diagnostics.

Conclusion. The current epidemiological situation for breast cancer in the Irkutsk region is characterized by: a significant increase in «rough» and standardized indicators of primary morbidity, unchanged mortality rates and an insignificant decrease in standardized indicators for breast cancer. In Russia as a whole, there is a tendency to decrease relative indicators of mortality among women from breast cancer, but not in the Irkutsk Region, although some changes have already been noted - although not significant, but a decrease in mortality from breast cancer in women over 50 by 8.3%, which indicates positive success in the treatment of patients. In the Irkutsk region, malignant neoplasms in women are most often diagnosed in the upper quadrants and central part of the mammary gland, as well as cancer that extends beyond one or more localizations C50.0–C50.6 according to ICD-10.

All indicators of the quality of oncological care for women with breast cancer have improved: the indicators of neglect and one-year mortality have significantly decreased, the indicators of early and active detection of breast cancer, patient survival, etc. have increased [6–9, 11]. Currently, according to two indicators of oncological care for women with breast cancer, the region is assessed as better off than the average for the Russian Federation (active detection 48.6%; morphologically confirmed diagnoses in 99.8% of cases). But there are reserves for improving breast cancer diagnostics in the Irkutsk region, since the level of other indicators of cancer care for women with breast cancer, as well as their dynamics, have not yet reached the all-Russian level.

As a result of improving the quality of medical care for breast cancer, after the indicators return to the pre-pandemic level and reach the average Russian level, a turning point in the dynamics and a decrease in the mortality rate from breast cancer should be expected. Monitoring the indicators of the quality of medical care in individual municipalities to identify problems in the territories will help to move the process towards improving the situation and eliminating inequality in receiving oncological care [1, 12, 13].

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UVEITIS ASSOCIATED WITH JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN OF THE REPUBLIC OF SAKHA (YAKUTIA): EPIDEMIOLOGIC DATA AND A SERIES OF CLINICAL OBSERVATIONS

The article presents a comprehensive cohort retrospective study of patients diagnosed with JIA who underwent examination and treatment in the cardiorheumatology department of the Pediatric Center of the Republican Hospital No. 1 – the National Center of Medicine named after M.E. Nikolaev in 2016-2023. Patients who have developed uveitis have been selected for a detailed analysis. The prevalence of uveitis in the RS(I) was 8.6 per 100,000 children, of which 11.8 among Sakha children and 5.6 among Russians. Uveitis among children with JIA is more common in boys of Sakha nationality, and is more common in older children without correlation with types of JIA. Low efficacy of initial methotrexate therapy has been demonstrated. All cases of de novo uveitis have been recorded only in children of Sakha nationality, most of whom are boys.

Keywords: uveitis, juvenile idiopathic arthritis, children, Russians, Sakha, Yakutia.

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Introduction. Juvenile idiopathic arthritis (JIA) is one of the most common chronic rheumatic diseases from the group of inflammatory arthropathies of unknown etiology, occurring in persons younger than 16 years of age, with a disease duration of at least 6 weeks [28].

Uveitis is one of the most frequent extra-articular manifestations of JIA [16]. Uveitis is a pathological condition characterized by inflammation of various parts of the ocular vasculature and/or adjacent structures [1,24,32,36]. Clinically, it can be manifested by ocular redness, lacrimation, photosensitivity, pain syndrome, and decreased visual acuity [31], which is characteristic in patients with enthesitis-associated JIA [24]. However, uveitis is more often asymptomatic or asymptomatic in patients with JIA [24], thus requiring careful screening [4]. In addition, inflammation of the uveal tract may also develop during the course of the disease, presenting a clinically significant problem [31].

Uveitis can lead to complications and vision-threatening consequences up to total blindness, as well as disability, in case of late onset or lack of effective therapy [17] and is characterized by significant socioeconomic losses, both due to direct medical costs and through the impact on quality of life [33]. In addition, children with uveitis have a more severe course of arthritis, which may require more aggressive immunosuppressive therapy [25]. Early diagnosis and timely interdisciplinary collaboration are crucial for the long-term prognosis of the disease [4,34,37].

The main goal of therapy of a patient with JIA with ocular involvement is to achieve first drug and then drug-free remission [8]. In JIA-associated uveitis, a stepwise therapy regimen is used [4,37,8,14].

Currently, many countries have developed clinical guidelines for the therapy of JIA-associated uveitis [4,2,9].

First-line therapy of uveitis includes topical glucocorticoids, mydriatics, and nonsteroidal anti-inflammatory drugs (NSAIDs) [4,31]. If the inflammatory process cannot be controlled, the prescription of non-biologic disease-modifying antirheumatic drugs (nbDMARDs), including methotrexate, mycophenolate mofetil, leflunomide and others, is switched to. The indication for the prescription of nbDMARDs is the inability to establish control of inflammatory activity within three months when administered more than 3 drops per day [14,29]. When the disease course is resistant or aggressive, combination therapy is used, which includes the use of non-biologic and biologic DMARDs (bDMARDs). In addition, bDMARDs are used in case of nbDMARDs intolerance [35]. The most

commonly used bDMARD is TNF-a inhibitor adalimumab[35]. Also, in severe uveitis, in case of cataract, glaucoma, some patients may require surgery, which can improve visual outcomes in this group of patients [21].

The aim and the objectives of the study: on the basis of the analysis of the republican register of children with JIA, to study the clinical and demographic data of patients suffering from JIA with uveitis; to evaluate the variants of the course of uveitis (activity of the process, debut of uveitis in relation to the debut of the joint syndrome); to identify the variants of the course of JIA, in which uveitis is significantly more frequent; to evaluate the effectiveness of therapy.

Material and methods. The continuous cohort retrospective study included data from the medical records of all patients (n=225) diagnosed with JIA who underwent examination and treatment in the cardio-rheumatologic department of the Pediatric Center of the Republican Hospital No.1 - the National Center of Medicine named after M.E. Nikolaev in 2016-2023.

Ethical Review: The study was approved by the local biomedical ethics committee of Federal State Budgetary Scientific Institution "Yakutsk Scientific Center of Complex Medical Problems" for compliance with the provisions of the Declaration of Helsinki Number 54 of 20.12.2021, Resolution No. 1. All patients 15 years and older, as well as legal representatives of patients of any age signed informed consent in the medical history, authorizing the use of data in anonymous form. All patients' personal data were appropriately concealed.

The Inclusion Criteria:

1) Diagnosis of juvenile idiopathic arthritis

2) Age less than 18 years of age

The Eligibility Criteria:

- The diagnosis of JIA was established according to ILAR criteria [16].

Study parameters:

The following data were extracted from the medical records:

1) *Demographic characteristics:* gender, date of birth, year of disease, region of residence, ethnicity of patients, family history, provoking factor.

2) *Clinical characteristics:* subtype of JIA, age of JIA debut, number of active joints at debut, presence of uveitis (biomicroscopy performed by an ophthalmologist), time to development of uveitis, presence of complications of uveitis

3) *Laboratory characteristics:* clinical blood test data, erythrocyte sedimentation rate (ESR) at debut, C-reactive protein (CRP) at debut, presence of HLA-B27 antigen, antinuclear factor (ANF) positivity.

4) *Therapy:* the use and timing of non-biologic disease-modifying antirheumatic drugs (nbDMARDs), and biologic disease-modifying antirheumatic drugs (bDMARDs) were evaluated.

5) *Outcomes:* achievement of remission of uveitis according to SUN criteria [4].

Patients with uveitis (n=23) and without (n=202) were compared.

Methods of statistical analysis. Statistical analysis of data was performed using Statistica 10 program. Categorical data were represented by absolute values. Comparisons of independent categorical variables were analyzed using 2x2 contiguity tables and Fisher's exact criterion. Quantitative variables were tested for normality using the Kolmogorov-Smirnov criterion and were represented by mean, median, quartiles (25%; 75%). The Mann-Whitney criterion was used to compare two independent quantitative variables due to the absence of normal distribution. A value of $p < 0.05$ was considered reliable.

Results of the study. *Frequency of uveitis in the population of patients with juvenile idiopathic arthritis in the Republic of Sakha (Yakutia)*

In total, 225 children with JIA are in the republican register on 01.01.2024: 107 girls (47.6%) and 118 boys (52.4%). The median age at the debut of JIA was 9 (5; 12) years. By ethnicity, Sakha children prevailed - 168 (74.7), Russians 49 (21.8%), other ethnicities accounted for 8 children (3.5%). By ethnicity, uveitis was diagnosed in 18 Sakha children (78.2%) and 4 (17.4%) Russian children. The prevalence of uveitis in the Republic of Sakha (Yakutia) was 8.6 per 100,000 children, including 11.8 among Sakha children and 5.6 among Russian children. Uveitis was more common in urban residents - 15/23 (65.2%) and less common in rural residents - 8/23 (34.8%), but the differences were not significant (p=0.283).

Demographic characteristics of patients with uveitis. The median age of arthritis debut was 8.0 (4.0; 12.0) years, and the median age of uveitis development was 10.0 (6.0; 13.0) years. Uveitis was diagnosed in 23 (10.2%) children, in 5/23 (21.7%) of them uveitis was manifest, symptomatic (red eye syndrome). Uveitis was diagnosed in 18/168 (10.7%) Sakha and 4/49 (8.2%) Russian children (p=0.603) and 1/8 (12.5%) of a child from an ethnic group other than Sakha and Russian. Anterior uveitis was recorded in 15 children (65.2%), panuveitis in 2 children (8.7%), and information on the type of uveitis was missing in 6 (26.1%) children. Manifest uveitis occurred predominantly (p=0.098) in patients with ERA - 4/5 (80%) and in one (20%) case in OA variant, chronic asymptomatic uveitis occurred in patients with OA (=9/18, 50%), ERA (n=5/18, 27.8%) and polyarthritis (n=4/18, 22.2%). Manifest uveitis was more common in boys (80%) than girls (44.4%) and was highly associated with HLA B27 antigen (80%, p=0.034). According to anatomical classification, all cases of manifest uveitis were anterior uveitis. All cases of manifest uveitis were reported in Sakha patients, and no cases were among Russian patients.

Among patients with JIA and uveitis, there were 11 (47.8%) girls and 12 (52.2%) boys, the median age of debut of JIA associated with uveitis was 9 years (5; 12 years). The median age of arthritis in boys was 9.0 (6.0; 12.0) years compared to girls 8.0 (3.0; 13.0; p=0.371) years, the median age of uveitis in boys was 11.5 (7.5; 15.0) years compared to girls 10.0 (4.0; 13.0; p=0.216) years. The age of JIA debut was similar (p=0.678) in children who developed 8.0 (5.0; 12.0) years and those who did not develop uveitis, 9.0 (5.0; 12.0) years. Three patients (13%) had uveitis diagnosed in association with arthritis, three patients (13%) developed uveitis before the development of arthritis, and 17 patients (74%) developed uveitis after the debut of the joint syndrome. Uveitis de novo was detected in 4/23 children (17.4%). Uveitis was bilateral in 56.5% of patients (13 patients). Among children with uveitis, oligoarthritis was most common 10/23 (43.5%), ERA 9/23 (39.4%) and less common polyarthritis 4/23 (17.4%). ANF was found in 7/23 (30.4%) children with uveitis and 28/41 (68.3%) children without uveitis (p=0.459). HLA B27 antigen was found with equal frequency (p=0.748) in the group of children with uveitis 9/23 (39.1%) and without, 79/198 (39.9%); however, children positized for HLA B27 antigen had an older age of arthritis debut 12.0 (9.0;13.0) vs. 6.0 (3.0;9.0) years (p=0.023) and uveitis 12.0 (11.0;17.0) vs. 8.5 (5.0;12.0) years (p=0.027). Panuveitis occurred in one child with polyarticular and one child with oligoarticular variants of JIA, whereas anterior uveitis occurred with approximately olinaconic frequency in patients with oligoarticular (53.3%) and enthesitis-associated (40.0%) variants of JIA and rarely (6.7%) with polyarticular variants.

The frequency of uveitis did not significantly depend on the category of JIA. Uveitis occurred in 9/99 (9.1%) children

with ERA, 4/33 (12.1%) children with polyarticular variant and 10/76 (13.2%) children with oligoarticular variant of JIA (p=0.713). The highest age of arthritis 12.0 (9.0; 13.0) years and uveitis 12.0 (11.0; 17.0) years was in patients with ERA, the lower age of arthritis 9.5 (4.8; 12.5) years and uveitis 11.5 (9.0; 14.5) in children with polyarticular variant and the least age of arthritis 4.5 (3.0; 8.0, p=0.043) years and uveitis 6.0 (4.0; 10.0, p=0.021) years was in children with oligoarticular variant of JIA (Figure a, b).

No cases of uveitis were recorded among children with psoriasis and psoriatic arthritis. Uveitis was most common among patients with ERA 9/99 (39.1%), oligoarthritis -10/76 (43.4%). No correlation of involvement of specific joints with the risk of developing uveitis was found. Among laboratory tests, patients who developed JIA at debut had a higher (p=0.034) hemoglobin level of 123 (113; 140) g/L compared to children without uveitis - 116 (106; 126) g/L. No differences in other markers of inflammation in the debut of JIA were found.

Complicated course of uveitis was detected in 7/23 (30.4%) children, including 2 (100%) children with panuveitis and 4/15 (26.7%) children with anterior uveitis (p=0.042). The most frequent complicated course of uveitis was in children with the oligoarticular variant of JIA (71.4%), with no association with HLA B27 antigen carriage (14.3% of positive cases). Complicated uveitis was less common in Sakha children (22.2%) than in Russian children (60.0%). Cataract developed in 6/23 (26.1%) children; it was the most frequent variant of the complicated course of uveitis, 6/7 (85.7%). Surgical treatment was performed in 5/23 (21.7%) children with uveitis: cataract extraction with implantation of artificial lens - intraocular lens (n=2). Retinal detachment occurred in one girl and corneal dystrophy was diagnosed in one child.

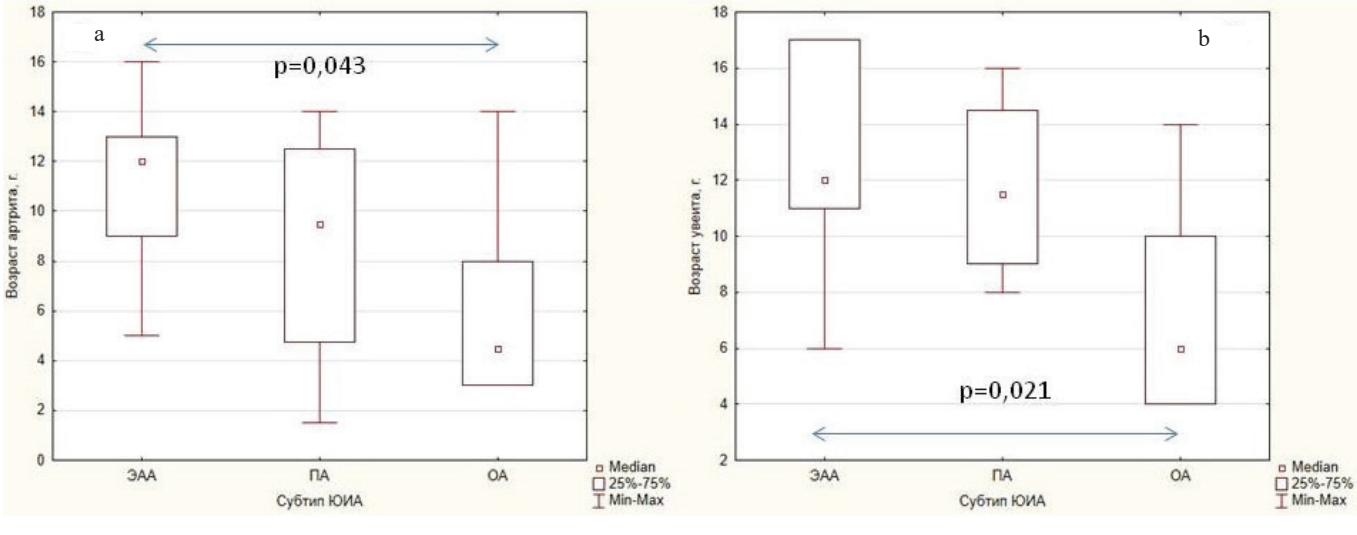
Analysis of therapy and outcomes of patients with JIA and uveitis. Initially, 22 children (95.6%) received methotrexate. Cyclosporine was added to methotrexate therapy in 6 children (26%) - in three children (13%) due to high activity of joint syndrome, in one child (4.3%) methotrexate was changed to cyclosporine due to intolerance, in two patients (8.7%) cyclosporine was added to therapy due to diagnosed uveitis. One child is now on combination therapy with methotrexate and cyclosporine, and the second child is receiving cyclosporine with tofacitinib. One child (4.3%) is receiving cyclosporine monotherapy.

At the present time, 5/22 children (22.7%) receive methotrexate monotherapy; the episodes of uveitis in these children were one-time and were treated with topical Glucocorticosteroids . Cure of uveitis against the background of therapy with topical GCS and methotrexate in five children was noted at 3-4 weeks of treatment. No recurrences of uveitis were detected.

A total of 16 children (69.5%) with JIA-associated uveitis received bDMARDs therapy. Conversion to genetically engineered therapy in the majority was due to the severity of arthritis and recurrent course of uveitis. In 6 (37.5%) children, conversion to genetically engineered biological products (“GEBPs”) was due to the severity of arthritis and recurrent uveitis, including three de novo uveitis: etanercept was prescribed due to the severity of arthritis, then adalimumab therapy was initiated due to recurrent/severe uveitis. Recurrent and severe uveitis was the reason for transfer to GEBPs in 8 (50.0%) children - all receiving adalimumab. Transfer to GEBPs due to the severity of arthritis was due to two children (12.5%) - one child receiving adalimumab, the other child receiving etanercept, a single episode of uveitis, and de novo uveitis. Methotrexate intolerance and severity of arthritis was the reason for transfer to GEBPs in two children (9.1%) - one girl (ANF-positive, HLA B27-negative) receives adalimumab, the second child receives tofacitinib in combination with cyclosporine. Tofacitinib is the third drug (after adalimumab, abatacept, due to exacerbation of joint syndrome on each of the drugs). Remission of uveitis was achieved on adalimumab after 4 weeks, arthritis of the first degree of activity remains on tofacitinib therapy.

Adalimumab was received by 14 (87.5%) patients, out of the total number of children treated with biological DMARDs: 9 children (56.2%) are on combined therapy with methotrexate and adalimumab, adalimumab was added for combined indications - due to the severity of the course of arthritis and recurrent uveitis. Monotherapy with adalimumab was given to 4 children (25%), in whom methotrexate was discontinued due to remission. Remission of active uveitis on adalimumab therapy was achieved in 12 out of 14 patients receiving adalimumab (86%) in 2 (2; 8) weeks from the beginning of treatment.

One girl is receiving mofetil mycophenolate in combination with adalimumab. Mofetil mycophenolate was prescribed by ophthalmologists due to the severity of uveitis; the joint syndrome appeared later. After the onset of the joint syndrome, the uveitis recurred and adalimumab was added to the therapy. The child is HLA



Age of debut of arthritis (a) and uveitis (b) in the study group

B27 positive and ANF negative. At present, the uveitis is sluggish, and remission has been achieved for arthritis.

One patient receives combined therapy - methotrexate with etanercept, uveitis was de novo, there was one episode of uveitis, it was quickly resolved against the background of GCS and combined therapy, which was a reason not to cancel etanercept therapy. Among the patients with JIA-associated uveitis receiving biological DMARDs concomitant therapy with non-biological DMARDs 12/16 patients (75%), 10 patients (83,3%) received methotrexate at a dose of 15 mg/m2 per week, one patient (8,3%) received cyclosporine A at a dose of 3 mg/kg/day, one patient (8,3%) received mycophenolate mofetil 600 mg/m2 x 2 times per day.

Remission of uveitis was achieved in 13/16 (81.3%) children on the background of bDMARDs therapy. Three children (18.7%) were observed with subacute and sluggish uveitis. Remission of arthritis was achieved in 9 patients (56.3%), and 7 patients (43.8%) had low-grade arthritis. The age of debut of arthritis, uveitis, and the time between arthritis and uveitis did not influence the likelihood of achieving remission for uveitis.

Uveitis remission was more frequent in uncomplicated uveitis (93.8% vs. 71.4%), was associated with joint syndrome remission (70% vs. 33.3%), and was more frequently recorded among patients with enthesitis-associated (45.0%) oligoarticular (40.0%) and less frequently among patients with polyarticular (15.0%) variants of JIA. Remission of uveitis was

The characteristics of the patients with uveitis associated with juvenile idiopathic arthritis

No., p/p	Age of debut, years	Age of uveitis, g.	Gender	Nationality	ANF	HLA B 27	JIA type, ILAR [2]	Manifest uveitis	Type of uveitis	Sequence of therapy	Withdrawal of methotrexate	Current therapy	Complications	Remission arthritis	Remission uveitis	Uveitis de novo
1	7	11	M	S	ND	+	EAA	A	ND	MTT>GKS+MTT>MTT	-	MTT	-	+	+	-
2	3	4	F	R	ND	-	OA	C	PAN	MTT>CsA>GCS+CsA>CsA	+(AE)	CsA	AF, OS	+	+	-
3	3	5	F	U	ND	-	OA	C	ND	MTT>MTT+CsA+GCS>MTT+CsA	-	MTT+CsA	-	+	+	-
4	12	13	M	S	+	+	EAA	A	A	MTT>GCS+MTT+ADA> MTT+ADA	-	MTT+ADA	-	+	+	-
5	8	10	F	R	-	-	OA	C	A	MTT>GKS+MTT>MTT	-	MTT	-	+	+	-
6	9	12	M	S	+	+	EAA	C	A	MTT>MTT+GCS+ADA> MTT+ADA>ADA	+(REM)	ADA	-	-	+	-
7	8	8	F	S	+	-	PA	C	A	MTT>MTT+CsA>GCS+MTT+CsA>CsA>ADA	+(AE)	ADA	-	-	+	-
8	4	4	F	R	ND	-	OA	C	A	MTT>GKS+MTT>MTT	-	MTT	AF,KAT	+	+	-
9	16	17	M	S	-	+	EAA	A	A	MTT>GKS+MTT>MTT	-	MTT	-	-	+	-
10	5	6	M	R	-	+	EAA	C	ND	MTT>MTT+GKS>MTT+ADA	-	MTT+ADA	CAT,AF	+	+	-
11	5	6	M	S	+	-	OA	C	A	MTT>GKS+ADA>ABA>TssA+TOC>TssA+TOF	+(AE)	TsSA+TOF	DR	-	+	-
12	11	13	F	S	ND	-	PA	C	ND	MTT>MTT+CsA>GCS+MTT+CsA>MTT+ADA	-	MTT+ADA	-	+	+	-
13	9	9	M	S	-	-	OA	C	A	GKS+MTT> MTT+ADA	-	MTT+ADA	ArtF, KAT, DR	+	+	-
14	10	10	M	S	+	+	EAA	A	A	MTT>MTT+GKS>MTT+ADA	-	MTT+ADA	-	-	+	-
15	14	16	F	S	+	-	PA	C	PAN	MTT>MTT+GKS>MTT+ADA	-	MTT+ADA	CAT	-	-	-
16	16	17	M	S	-	+	EAA	C	A	MTT>MTT+GKS>MTT+ADA	-	MTT+ADA	-	+	+	-
17	14	14	F	S	-	-	OA	C	A	GKS>GKS+MMF>MMF+ADA	-	MMF+ADA	KAT, RSH, ArtF	+	-	-
18	4	4	F	S	+	-	OA	A	A	MTT>MTT+GKS>MTT+ADA	-	MTT+ADA	-	-	-	-
19	13	12	F	S	-	+	EAA	C	A	GKS>MTT	-	MTT	-	+	+	-
20	1,5	10	F	S	ND	-	PA	C	ND	MTT>MTT+CsA>ETA> GKS+ADA>ADA	+(AE)	ADA	-	+	+	+
21	7	12	M	S	-	-	OA	C	A	MTT>MTT+ETA>GCS+MTT+ADA>MTT+ADA	-	MTT+ADA	-	+	+	+
22	12	17	M	S	-	+	EAA	C	ND	MTT>MTT+ETA> GCS+ MTT+ETA>MTT+ETA	-	MTT+ETA	-	-	+	+
23	3	6	M	S	-	-	OA	C	A	MTT>MTT+ETA> GCS+MTT+ADA> MTT+ADA>ADA	+(REM)	ADA	-	+	+	+

Abbreviations: ADA - adalimumab, ANF - antinuclear factor, ArtF - artifacia, AF - aphakia, GCS - glucocorticosteroids, DR - corneal dystrophy, G - female, CAT - cataract, M - male, MMF - mofetil mycophenolate, MTT - methotrexate, ND - no data, NE - ineffectiveness, NA - adverse events, A - acute (manifest) uveitis, OA - oligoarthritis, RD - retinal detachment, A - anterior uveitis, PA - polyarthritis, PAN - panuveitis, REM - remission, R - Russian/a, RSH - retinoschisis, S - Sakha, TOF - tofacitinib, U - uzbek, C - chronic uveitis, CsA - cyclosporine A, EAA - enthesitis-associated arthritis.

recorded in all male patients and 72.7% of girls (p=0.052), and in all HLA B27 antigen carriers (100% vs. 78.6%) was not related to the type of uveitis manifestation: the remission rate in acute manifest uveitis was 80% and in chronic uveitis 88.9%. Among the types of uveitis, remission was more often recorded among patients with anterior uveitis (86.7%) and less often among patients with panuveitis (50.0%).

Uveitis de novo. Four children (17.4%) developed de novo uveitis against the background of etanercept therapy. Children with de novo uveitis had a younger age of arthritis - 5.0 (2.3; 9.5) years compared to the other children 9.0 (5.0; 13.0) years (p=0.180) and a comparable age of uveitis debut 11.0 (8.0; 14.5) years compared to the other children 10.0 (6.0; 13.0) years (p=0.654). All cases of this uveitis developed in children receiving etanercept therapy. Uveitis de novo was only in Saha children and accounted for 2.4% of the total number of Sakha children with JIA (p=0.297). When patients with de novo uveitis were categorized by JIA subtypes, one patient had EAA, one had polyarticular variant, and two had oligoarticular variant JIA. In all cases, the de novo uveitis was chronic uncomplicated nonmanifest nonmanifest anterior uveitis. All patients were seronegative for ANF, no correlation with HLA B27 antigen carriage was found (p=0.601). Remission was achieved in all cases of de novo uveitis.

The first patient had JIA debut at the age of 1.5 years, uveitis developed 8.5 years after JIA debut at the age of 10 years, the child was on baseline therapy with methotrexate, which was discontinued due to intolerance. Cyclosporine was prescribed, and etanercept was prescribed in the sixth year of the disease due to joint syndrome activity. After 2 years of etanercept therapy uveitis developed, adalimumab in combination with methotrexate was prescribed. The child is negative for HLA B27 antigen. The girl is currently in remission.

The second child developed the debut of JIA at the age of 7 years. The boy received methotrexate therapy for three years, but etanercept was prescribed due to arthritis activity. After 2 years of therapy with etanercept and methotrexate, uveitis developed in the 5th year of the disease at the age of 12 years and adalimumab was prescribed. The child was negative for ANF and HLA B27. The patient is currently in remission.

The third child (boy) developed JIA at age 12, methotrexate therapy was initiated, etanercept was prescribed after 1 month of illness due to high arthritis activity. The child received combined therapy with methotrexate and etanercept for six years. Uveitis developed in the 5th year of the disease at the age of 17 years and was quickly resolved with topical corticosteroids. The boy continues to receive etanercept in combination with methotrexate. The child is negative for ANF and positive for HLA B27 antigen. The patient is currently in remission for uveitis, and arthritis remains low grade.

The fourth child developed JIA at the age of 3 years and was treated with methotrexate for two years, then etanercept was prescribed due to arthritis activity, but after 2 years of etanercept therapy, uveitis developed at the age of 6 years, which required the prescription of adalimumab. The child was negative for ANF and HLA B27 antigen. The patient is currently in remission. Detailed patient characteristics are presented in Table.

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MONITORING OF THE PREVALENCE AND ANTIMICROBIAL RESISTANCE OF KLEBSIELLA PNEUMONIAE STRAINS IN A MULTIDISCIPLINARY HOSPITAL

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The study evaluated the prevalence and resistance of Klebsiella pneumoniae strains to antibacterial drugs in a multidisciplinary hospital in Yakutsk. This study included 4580 Klebsiella pneumoniae strains isolated from patients of the Republican Hospital No. 2 - Emergency Medical Care Center in the period from 2016 to 2022. The analysis showed that the majority of Klebsiella pneumoniae strains detected in intensive care and surgical departments. The dynamics show an increase in the prevalence of Klebsiella pneumoniae strains and an increase in resistance to carbapenems, against the background of a high proportion of isolates producing extended-spectrum β-lactamases.

Keywords: Klebsiella Pneumoniae, antibiotic resistance, carbapenems, carbapenemase, AMRcloud, monitoring.

Introduction. In recent years, the intensive growth of resistant Klebsiella pneumoniae strains, especially nosocomial isolates, to all clinically significant antibiotics has become a serious problem, which has determined their dominant role among opportunistic pathogens [10].

Klebsiella pneumoniae strains with multiple drug resistance, producing extended-spectrum beta-lactamases or carbapenemases, pose a serious clinical threat. The presence of carbapenemases in bacterial strains is an important marker of extreme antibiotic resistance [1, 5, 6, 12].

In this regard, the relevance of studying the prevalence and resistance of Klebsiella pneumoniae strains to antibacterial drugs in a multidisciplinary hospital is beyond doubt.

The aim of the study. To study the prevalence and resistance to antibacterial drugs of Klebsiella pneumoniae strains in the conditions of a multidisciplinary hospital of the Republican Hospital №2 – Emergency Medical Center.

Materials and methods. The study included 4580 strains of Klebsiella pneumoniae isolated from patients (urine, bronchoalveolar lavage (BAL), pleural fluid, wound discharge, peritoneal fluid) of the Republican Hospital №2 – Emergency Medical Center in the period from 2016 to 2022.

Since 2011, the laboratory has been a participant in multicenter studies of the Research Institute of Antimicrobial Chemotherapy (RIAC) of the Federal State Budgetary Educational Institution of Higher Education "Smolensk State Medical University" of the Ministry of Health of the Russian Federation, the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC), and the Alliance of Clinical Chemotherapists and Microbiologists.

Species identification was carried out

until 2020 on automatic PHOENIX analyzers (BD, USA), and in 2021–2022 on a VITEK-2 Compact analyzer (bioMerieux, France). Determination of sensitivity to antibacterial drugs was performed using an automated method on PHOENIX (BD, USA), VITEK-2 Compact (bioMerieux, France) analyzers, and also by the disk diffusion method on Mueller-Hinton agar using disks with antibiotics (BioRad, USA). Susceptibility testing was carried out in accordance with the Clinical Guidelines for Testing the Susceptibility of Microorganisms to Antibacterial Drugs (EUCAST), with annual update. Beta-lactamases were detected by the method of "double disks" with clavulanate - extended spectrum beta-lactamases (ESBL). To detect the production of carbapenemases, the immunochromatographic express test NG-Test CARBA 5 (France) was used.

Statistical processing and data analysis were carried out using the AMRcloud resource (https://amrcloud.net/).

Results and discussion. During the analyzed period, a microbiological study of 40,251 samples (urine, bronchoalveolar lavage, pleural fluid, wound discharge, peritoneal fluid) was carried out in the laboratory of clinical microbiology (bacteriology) of the Republican Hospital №2 – Emergency Medical Center. The proportion of samples without growth was 54.8% (24848 samples), samples with growth 45.2% (15403). A total of 45305 strains of microorganisms were isolated and identified. Among them, the proportion of isolated strains of Klebsiella pneumoniae was 10.1% (4580 strains).

In dynamics from 2016 to 2022, the share of isolated Klebsiella pneumoniae strains increased from 10.2% to 15.9%. It should be noted that during the COVID-19 pandemic, this indicator reached 18.6% in 2020 and 21.4% in 2021 (Figure 1).

The frequency of occurrence of Klebsiella pneumoniae strains depended on the profile of the department. Thus, the highest rates were noted in resuscitation departments (anaesthesiology department of intensive care - 25.9%, resuscitation department, intensive care for patients with acute cerebrovascular accidents (ACVA) - 15.3%). In surgical departments, the frequency of detection was: surgical department No. 2 – 9.2%, surgical department No. 1 – 8.3%, coloproctology department – 4.4%, burn department – 4%. In the therapeutic departments, the majority of strains were detected in the neurological department for patients with acute cerebrovascular accident (13.3%) and the emergency department (5.6%). In other departments,

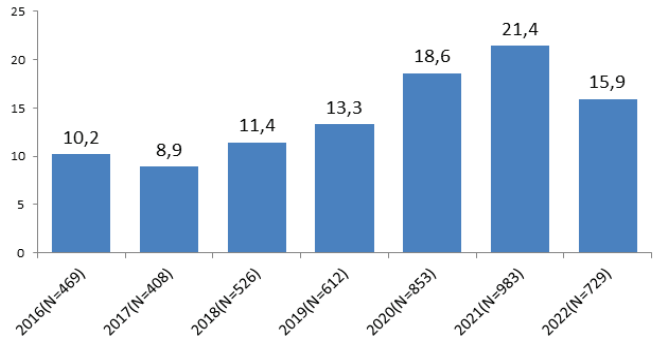

Fig. 1. Prevalence of Klebsiella pneumoniae in a multidisciplinary hospital in Yakutsk, 2016-2022 (%)

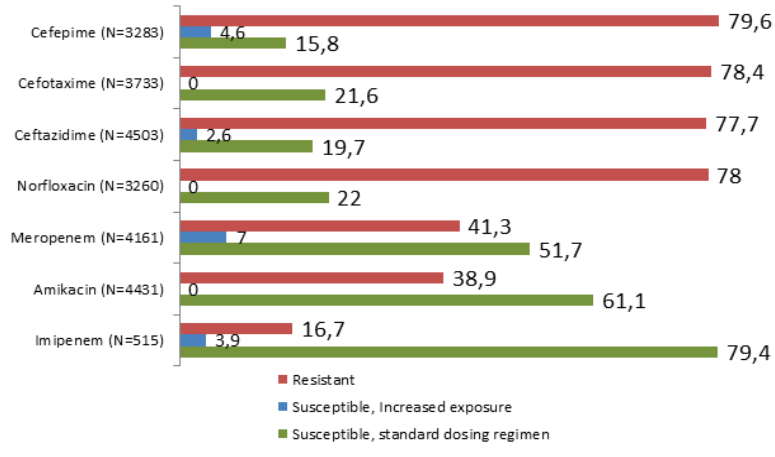

Fig. 2. Antibiotic susceptibility of the isolates of Klebsiella pneumoniae (%)

the frequency of detection of Klebsiella pneumoniae strains ranged from 0.09% to 2.9%.

In 26.8% (N=1229) of cases, Klebsiella pneumoniae was isolated from urine, in 23.6% (N=1085) from bronchoalveolar lavage, in 23% (N=1054) from sputum, and in 16.9% (N=775) from wound discharge.

Figure 2 presents summarized data on the sensitivity of all studied Klebsiella pneumoniae isolates to some antibiotics. The total number of tested strains was 4580. The highest level of susceptibility of the tested isolates was observed to imipenem (79.4% CI: 73.9-81.1), amikacin (61.1% CI: 59.6-62.5) and meropenem (51.7% CI: 50.1-53.1). A high frequency of resistance to III-IV generation cephalosporins was revealed: to cefotaxime (78.4% CI: 77.1-79.71), ceftazidime (77.7% CI: 76.5-78.9), cefepime (79. 6% CI:78.2-80.9).

The proportion of ESBL producers in all Klebsiella pneumoniae strains isolated in 2016–2022 was 48.6% (2230 strains out of 4580). The dynamics show a consistently high proportion of ESBL producers (55% in 2016, 54.1% in 2017, 57.2% in 2018, 65.8 in 2019, 49.5% in 2020, 26.2% in 2021, 57% in 2022), which have a broad resistance profile (Figure 3).

Data on the dynamics of resistance of Klebsiella pneumoniae strains to meropenem for the period from 2016 to 2022 are presented in Figure 4. There is a rapid increase in meropenem-resistant strains from 20% (N = 54) CI: 15.7-25.3 in 2016 to 46.6% (N = 335) CI: 43.0-50.3 in 2022. During the COVID-19 pandemic, there was a sharp increase in the proportion of meropenem-resistant strains: in 2020 - 56.9% (N = 483) CI: 53.6-60.3 and in 2021 - 52.4% (N = 513) CI: 49.3-55.6.

According to multicenter studies, carbapenemase production is detected in 349 (26.5%) Klebsiella pneumonia isolates. The researchers also noted that the proportion of nosocomial isolates of enterobacteria producing carbapenemases increased from 7.8% in 2012–2013 to 14.4% in 2015–2016 (p=0.0001). Carbapenemases of molecular class D of the OXA-48 group were detected in 11.4%, molecular class D of the NDM-1 group in 2.7%, and in 0.3% of Klebsiella pneumoniae in combination with OXA-48 and NDM-1 [3, 4].

In the laboratory of clinical microbiology (bacteriology) of the Republican Hospital №2 – Emergency Medical Center until 2021, the production of carbapenemases was not detected. In 2022, the production of carbapenemases was stud-

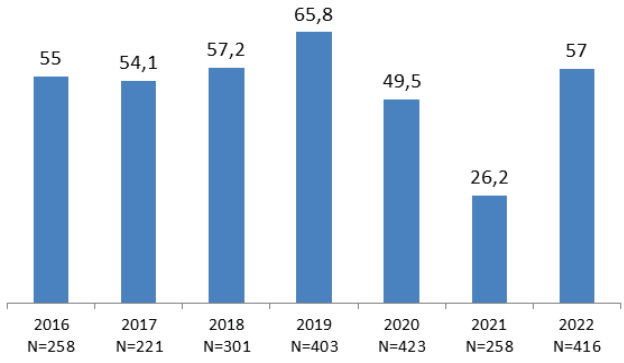

Fig. 3. Prevalence of isolates of Klebsiella pneumoniae producing extended-spectrum β-lactamases (%)

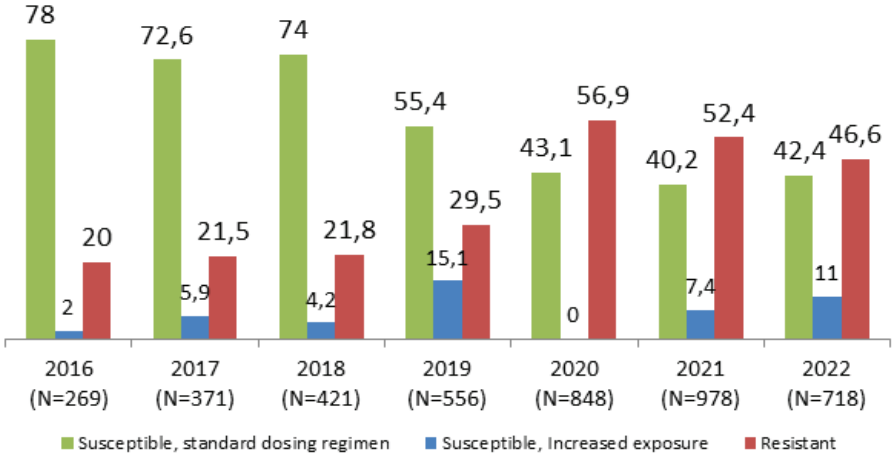

Fig. 4. Dynamics of resistance of the isolates of Klebsiella pneumoniae to meropenem (%)

ied in 20 strains of Klebsiella pneumoniae that showed phenotypic resistance to meropenem. The results of the study showed that the most common were serine carbapenemases OXA-48 (16(80%)). In 20% (N=4) of cases, the simultaneous presence of OXA-48 and NDM genes was detected.

Thus, according to the monitoring results for the period 2016–2022, in the multidisciplinary hospital Republican Hospital №2 – Emergency Medical Center in Yakutsk the prevalence of Klebsiella pneumoniae strains has increased. The majority of strains were detected in intensive care and surgical departments. The proportion of isolates producing ESBL remains consistently high, and an increase in carbapenem-resistant strains of Klebsiella pneumoniae is observed. Using meropenem as an example, the rapid increase in the number of resistant strains of Klebsiella pneumoniae in the period 2016-2022 is shown. Similar trends in the growth of the prevalence of Klebsiella pneumoniae and the resistance of these microorganisms to antibacterial agents are observed in other territories of the Russian Federation, as well as in the world as a whole [2, 4, 7, 8, 9, 11]. This justifies the need to create and develop a well-designed infection control strategy, what has a great importance in effectively combating the spread of resistance.

Conclusion. In a multidisciplinary hospital, given the diversity of resistance mechanisms of Klebsiella pneumoniae strains, it is of great importance to conduct continuous microbiological monitoring, expand methods for identifying and detecting resistance determinants, which will improve the effectiveness of antibacterial therapy.

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COMPARATIVE ASSESSMENT OF IMMUNE PROFILE IN CHILDREN UNDER BENZO(A)PYRENE AND COLD FACTOR INFLUENCE IN A CASE-CONTROL STUDY WITH MODELING AND VERIFICATION OF RESULTS IN AN *IN VIVO* EXPERIMENT

The comparative assessment of immune profile indicators in children under = benzo(a)pyrene and cold factor influence in a case-control study with the modeling and verification of obtained results in an in vivo experiment was performed. In the course of a case-control study in children under airborne benzo(a)pyrene exposure the signs of phagocytic leukocyte activity inhibition and specific haptenic hypersensitivity formation (IgG to benzo(a)pyrene) associated with blood contamination with benzo(a)pyrene were established. Revealed changes in the immune profile and xenobial biomedia composition in children under airborne benzo(a)pyrene exposure at a dose of 0.00761 mcg/(kg*day) in the subarctic urbanized area, it is comparable to its level in children living under the conditions of external environmental benzo(a)pyrene exposure at a dose of 0.08689 mcg/(kg*day) in an urbanized area in a temperate climate zone ($p>0.05$). The results of the experimental study of the immunotropic effects of oral benzo(a)pyrene exposure at an average daily dose of 0.175 mcg/kg*day and cold factor influence (15.1±2.6 °C) in vivo also show the signs of phagocytosis inhibition in mice (OR=7.33 - 16.20, $p<0.05$). At the same time, the minimum values of phagocytosis percentage, phagocytic number and phagocytic index are observed with the combined benzo(a)pyrene and cold factor effect which confirms the hypothesis of immunotoxic benzo(a)pyrene exposure effect modification by a cold factor

Keywords: benzo(a)pyrene; cold stress; children; immune profile; phagocytosis; in vivo experiment

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Introduction. Polycyclic aromatic hydrocarbons (PAHs), such as benzo(a) pyrene, are highly toxic environmental pollutants. Benzo(a)pyrene belongs to substances of the first hazard class possessing carcinogenic and immunosuppressive properties, capable of influencing both adaptive and innate immunity [1]. Phagocytosis is the one of key innate cellular immunity elements. According to the scientific literature, phagocytosis inhibition under benzo(a)pyrene influence may be the result of direct cytotoxic PAH effect [15], or an indirect benzo(a) pyrene-dependent oxidative stress manifestation [11].

Subarctic climatic conditions characterized by extremely low air temperatures create an additional unfavorable background for the impact of various man-made chemical factors, including benz(a) pyrene, on public health, exacerbating their maladaptation and immunotoxic effects even with a low-dose exposure [3].

Therefore, the study of the phagocytosis features under external environmental benzo(a)pyrene exposure in the Far North is particularly relevant in the terms of identifying sensitive immune chronic intoxication markers under the exogenous chemical factor influence in special climatic conditions. In turn, experimental haptenic exposure modeling using the example of benzo(a)pyrene under cold stress *in vivo* can become an effective tool for verifying the results of children population studies in urbanized territories with the justification of the mechanism of immunotropic benzo(a)pyrene effects by the criterion of phagocytic leukocyte activity [2, 9].

The aim of the work is to evaluate the parameters of the phagocytic leukocyte activity in children under combined benzo(a)pyrene and cold factor exposure in the case-control study with verification of the results in an *in vivo* experiment.

Materials and methods. In the course of the case-control study the comparative analysis of the phagocytic leukocyte activity, specific sensitization and xenobial biomedia composition features was performed in 1254 preschool children (3-6 years old) living in various climatic zones

of Eastern Siberia. During the study four groups of children living in different climatic conditions were formed: Group A — 525 children living in an urbanized area in the subarctic climatic zone (69°C); group B — 182 children living in a conditionally clean area in the subarctic climatic zone (69°C); group C — 374 children living in an urbanized area in a temperate climatic zone with a sharply continental climate (56°C); group D — 171 children living in a conditionally clean area in the temperate climate zone (51°C).

To determine the benzo(a)pyrene concentration in atmospheric air and in children blood the HPLC method was used in accordance with the methodological guidelines of MUC 4.1.3040-12 and MUC 4.1.1273-03.

The experimental study of phagocytosis features under combined benzo(a)pyrene and cold factor exposure *in vivo* was carried out on 48 heterosexual nonlinear laboratory mice which were also divided into 4 groups: 3 observation groups and a control group. Observation group 1 included 12 mice (6 males and 6 females) exposed orally to benzo(a)pyrene under standard vivarium conditions with an average air temperature of 23.6±3.1°C. The observation group included 12 mice (6 males and 6 females) kept under cold stress at an air temperature of 15.1±2.6 °C. Observation group 3 included 10 mice (6 males and 4 females) exposed to benzo(a)pyrene under cold stress. The control group consisted of 14 mice (6 males and 8 females), which were kept in standard vivarium conditions. Subchronic oral benzo(a)pyrene exposure in mice at an average daily dose of 0.175 mcg/kg*-day in observation groups 1 and 3 was modeled by intragastric administration through 0.5 ml probe of benzo(a)pyrene suspension (GSO 7515-98) based on isotonic sodium chloride solution at a concentration of 7 mcg/l once a day for 21 days [1, 10]. At the end of the exposure blood was taken from the hyoid vein in all mice. The study was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association and the European Convention for the Protection of Vertebrates Used for Scientific Purposes (ETS No. 123).

For the comparative assessment of phagocytic leukocyte activity in the examined children and in an *in vivo* experiment tests based on the formalinized sheep erythrocytes absorption *in vitro* were used [8]. The level of specific benzo(a)pyrene sensitization was determined by the IgG criterion to benzo(a)pyrene using an allergosorbent test with an enzyme label. ANOVA analysis was used using the Statistica 10.0 application software package for statistical data processing of the comparative phagocytosis indicators analysis. The results of the study are presented in the form of arithmetic mean (X) and standard error (SE). The data distribution character was assessed using the Kolmogorov-Smirnov criterion. The parametric Tukey-Kramer criterion and the nonparametric Dunn criterion were used to assess the level of differences in multiple comparison reliability. The relationship of changes in laboratory parameters with exposure to benz(a)pyrene and cold stress conditions was assessed by calculating the odds ratio (OR) and its 95% confidence intervals (95%CI). The differences between the samples were con-

Table 1

Average daily doses of airborne benzo(a)pyrene exposure of the child population of territories in the subarctic and temperate climatic zones of Eastern Siberia, mcg/(kg*day)

Group A (n=525)	Group B (n=182)	Group C (n=374)	Group D (n=173)
0.00761	0.00012	0.08689	0.00866

Note. Table 1-3: Groups of children living in: A - urban area in subarctic climate zone (69° C); B - relatively clean area in subarctic climate zone (69° C); C - Temperate zone urbanized territory with a very continental climate (56° C); D - Temperate zone area with a very continental climate (51° C).

Table 2

Benzo(a)pyrene concentration in the blood of children living in the subarctic and temperate climatic zones of Eastern Siberia, mg/dm^3

Reverence level [4]	Group A (n=525)	Group B (n=182)	Group C (n=374)	Group D (n=173)
0	0.00225± 0.00026	0.00114± 0.00032	0.00227± 0.00032	0.00110± 0.00027

Table 3

Features of phagocytic leukocyte activity and the formation of specific haptenic sensitization in preschool children under airborne benzo(a)pyrene exposure in the subarctic and temperate climatic zones of Eastern Siberia

	Group A (n=525)	Group B (n=182)	Group C (n=374)	Group D (n=173)
The percentage of phagocytosis, %				
X±SE	50.074±0.458	63.052±0.845	46.650±0.590	59.654±0.779
p	0.001		0.001	
OR (95%CI)	2.49 (1.73 – 3.59)		3.08 (2.13– 4.45)	
Phagocytic number, c.u.				
X±SE	0.983±0.016	1.351±0.031	0.895±0.015	1.222±0.029
p	0.001		0.001	
OR (95%CI)	2.36 (1.65 – 3.39)		2.95 (2.05 – 4.27)	
Phagocytic index, c.u.				
X±SE	1.925±0.016	2.113±0.028	1.897±0.012	2.025±0.024
p	0.001		0.001	
OR (95%CI)	2.23 (1.59 – 3.15)		2.04 (1.43 – 2.92)	
IgG to benzo(a)pyrene, c.u.				
X±SE	0.208±0.008	0.080±0.002	0.212±0.011	0.074±0.005
p	0.001		0.001	
OR (95%CI)	4.08 (2.86 – 5.82)		5.65 (3.81 – 8.36)	

sidered statistically significant at p<0.05. The work was approved by the LEC of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (minutes of meeting No. 2 dated January 17, 2022).

Results and discussion. As a result of environmental quality assessment in the territories where the surveyed children live it was found that benzo(a) pyrene concentration in atmospheric air at observation points in an urbanized area in the subarctic climatic zone (territory A) is 0.64 MPCC; in a conditionally clean subarctic area (territory B) – 0.012 MPCC; in an urbanized area territories in the temperate climatic zone (territory C) – 7.33 MPCC; in the relatively clean territory of moderate latitude (territory D) – 0.71 MPCC [5, 6, 7]. The average daily benzo(a)pyrene dose affecting the children body living in a city in subarctic climatic zone (group A) is significantly higher than in children living in the relatively clean area of middle latitude (group B) (p= 0.001). The average daily dose of benzo(a)pyrene affecting the urban child population in the temperate climate zone (group C) also exceeds not only the same indicator for children from the relatively clean territory of the middle latitude (group B), but also for children from the city in the Subarctic (group A) (p=0.001) (Table. 1).

The level of blood contamination with benzo(a)pyrene in children in group A exceeds the same indicator in children in group B and the reference level (p<0.05). The content of benzo(a)pyrene in the blood of children from group C is also higher than in children from group D (p=0.006). Nevertheless, the concentration of benzo(a)pyrene in the blood of children living under the conditions of aerogenic exposure to this substance at an average daily dose of 0.00761 mcg/(kg* day) in the urbanized territory of subarctic climatic zone (group A) is comparable to its content in the blood of children in a temperate climate zone with external environmental exposure to benzo(a) pyrene at a dose of 0.08689 mcg/ (kg*-day) (p=0.98) (Table 2).

The results of comparative immune status analysis in children living under airborne benzo(a)pyrene exposure in subarctic and temperate climatic zones of Eastern Siberia indicate a decrease in the phagocytic activity of leukocytes which, in turn, may be associated with the formation of specific hypersensitivity to this carcinogen (Table 3). In particular, 83.8% (n=440) of children from group A and 63.9% (n=239) of children from group C showed a decrease in the percentage of phagocytosis compared with groups B and D, respectively (p<0.05). 77.3% (n=406) of children from group A and 79.7% (n=298) of children from group C showed a decrease in phagocytic number compared with similar indicators in groups B and D (p<0.05). In addition, 70.3% (369) of children from group A and 65.5% (n=245) of children from group C had a decrease in the phagocytic index compared with groups B and D (p<0.05). It is worth noting that the indicators of phagocytic activity of leukocytes in children under the conditions of aerogenic exposure to benzo(a)pyrene at an average daily dose of 0.00761 mcg/(kg*day) in the urbanized territory of the subarctic climatic zone (group A) were comparable with those of children living under the conditions of external environmental exposure to benzo(a)pyrene at a dose of 0.08689 mcg/(kg*day) in the temperate climate zone (group C). This indicates that the physical and haptenic factors that form immunosuppressive effects can enhance each other.

Inhibition of phagocytic protection in children who live in areas with high levels of air pollution with benzo(a)pyrene is associated with the specific hypersensitivity emergence to this polycyclic aromatic hydrocarbon (PAH). Studies have shown that 74.5% (n=391) children living in Subarctic cities (group A) and 92.8% (n=347) children from temperate cities (group C) have significantly higher levels of specific IgG to benzo(a)pyrene than in children from control groups (groups B and D) (p<0.05). The concentration of immunoglobulin G (IgG) to benzo(a)pyrene in the blood serum of children living in the urbanized territory of the Subarctic climatic zone, where the average daily dose of benzo(a)pyrene is 0.00761 mcg/(kg*day) (group A), is comparable to the level of this indicator in children living in the temperate climatic zone belts, where the benz(a)pyrene dose is 0.08689 mcg /(kg*day) (group C). This indicates that the threshold for the formation of haptenic sensitization in low temperature conditions may decrease.

Oral benzo(a)pyrene exposure in mice at a dose of 0.175 mcg/kg*day in an *in vivo* experiment showed a decrease in the percentage of phagocytosis by 26.4%, phagocytic number by 30.5%, phagocytic index by 8.8% relative to the control group (p<0.05). When exposed to the cold factor (15.1±2.6 C), mice showed a decrease in the percentage of phagocytosis by 39.3%, phagocytic number by 39.1%, phagocytic index by 5% relative to the values of these indicators in the control group (p<0.05). With the combined effect of benzo(a)pyrene at an average daily dose of 0.175 mcg/kg*day and the cold factor (15.1±2.6°C), a maximum decrease in the percentage of phagocytosis was found by 52.7%, phagocytic number by 54.4%, phagocytic index by 9.4% relative to the control

Table 4

Features of phagocytic leukocyte activity in mice under the influence of benzo(a)pyrene and cold factor in an *in vivo* experiment

	Control group (n=14)	Benzo(a)pyrene [0,175 mcg/kg*day] (n=12)	Cold factor [15,1±2,6°C] (n=12)	Benzo(a)pyrene [0,175 mcg/kg*day] + Cold factor [15,1±2,6°C] (n=10)
Percentage of phagocytosis, %				
X±SE	30.21±2.01	22.55±2.82	18.33±1.29	14.30±0.83
p	–	0.039	0.001	0.001
OR (95%CI)	–	8.10 (1.23 – 53.20)	9.00 (1.39 – 58.45)	16.20 (1.57 – 167.75)
Phagocytic number, c.u.				
X±SE	0.46±0.04	0.32±0.04	0.28±0.02	0.21±0.01
p	–	0.009	0.001	0.001
OR (95%CI)	–	6.67 (1.14 – 38.83)	7.50 (1.31 – 43.03)	10.00 (1.44 – 69.26)
Phagocytic index, c.u.				
X±SE	1.60±0.04	1.46±0.03	1.52±0.04	1.45±0.03
p	–	0.043	0.386	0.031
OR (95%CI)	–	7.33 (1.27 – 42.30)	9.00 (1.39 – 58.45)	12.50 (1.85 – 84.45)

group ($p<0.05$), this demonstrates the manifestation of a synergistic effect of a combination of physical (cold factor) and chemical (benzo(a)pyrene) effects.

Phagocytosis is the most important link in innate cellular immunity, providing non-specific immune protection [17]. Inhibition of the phagocytic leukocyte activity under benzo(a)pyrene influence is associated with oxidative stress and reactive oxygen species cytotoxicity [12, 13]. Thus, cigarette smoke including benzo(a) pyrene provokes oxidative macrophage damage, induces cell apoptosis and contributes to a decrease in the phagocytic ability of macrophages associated with the oxidation of mannose-binding lectin, cell membranes lipoproteins damage, as well as the formation of less differentiated macrophage population due to their early maturation and aging [14].

Conclusion. During a comparative analysis of the immune status of children exposed to aerogenic benzo(a)pyrene effects (groups A and C), the case-control study revealed signs of phagocytosis inhibition and specific haptenic hypersensitivity formation associated with blood contamination with benzo(a)pyrene. The results of the study showed that changes in the immune status in children living in airborne benzo(a)pyrene exposure at an average daily dose of 0.00761 mcg/(kg*-day) in the Subarctic climatic zone (group A) are comparable to changes in children living in a temperate climate zone (group C) when exposed to the dose is 0.08689 mcg/(kg*day). This indicates that the combined effects of physical and chemical factors (haptens) enhance immunosuppression, as well as a lower threshold of sensitization to benzo(a) pyrene at low temperatures. An experimental study of the immunotropic effects of oral benzo(a)pyrene exposure at an average daily dose of 0.175 mcg/kg*day and cold factor influence (15.1±2.6°C) *in vivo* also revealed the signs of phagocytic leukocyte activity decrease in mice (OR=7.33 – 16.20, $p<0.05$). At the same time, the minimum values of percentage of phagocytosis, phagocytic number and phagocytic index are observed with the combined benzo(a)pyrene and cold factor effect which verifies the hypothesis of immunotoxic benzo(a)pyrene effect modification by cold factor exposure in subarctic climatic conditions. Thus, identified in the case-control study in a children population sample and verified on an experimental model of phagocytosis inhibition under conditions of combined exposure to benzo(a)pyrene and cold factor confirm the hypothesis of immunosuppression formation by a more than additive mechanism (synergistic effect), when both subarctic climatic conditions and the cold factor model *in vivo* benz(a) pyrene were aggravated the immunotoxic benzo(a)pyrene effects.

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IMPACT OF OCCUPATIONAL AND NON-OCCUPATIONAL RISK FACTORS ON THE DEVELOPMENT OF DENTAL PATHOLOGY AMONG CHEMICAL INDUSTRY

Objective: to examine how occupational and non-occupational factors contribute to the development of dental diseases among chemical industry workers, especially those exposed to hazardous materials. Given the potential effects of chemical exposure on oral health and the need for strict oral health standards for workers in high-risk environments, this research seeks to provide an in-depth analysis of these impacts.

Materials and Methods: This research was conducted at an ethylene oxide production facility during a periodic medical examination of 188 plant operators and 148 automation center employees as a comparison group. Dental health assessments followed the WHO-recommended protocol, including the OHI-S index, and a questionnaire capturing demographic and lifestyle factors.

Results: Statistical analyses revealed that, while caries rates exceeded 90% in both groups, significant differences were observed in periodontal disease severity ($\chi 2=9,8$; $p=0,002$). Chemical exposure to ethylene oxide, was associated with increased dental hypersensitivity ($\chi 2=5,46$; $p=0,02$) and greater clinical attachment loss ($U=1113,0$, $p=0,026$). Notably, severe chronic periodontitis was 2.4 times more prevalent among chemical industry workers compared to automation employees. The logistic regression highlighted workplace chemical exposure (OR=2,04 [95% CI: 1,09–3,77] p=0,023) and infrequent brushing as key risk factors (OR=1,80 [95% CI: 1,05–2,90] p=0,035).

Conclusion: These findings underscore the significant impact of chemical exposure on dental health, with airborne chemicals identified as primary occupational hazards. Protective equipment usage appears effective in minimizing some risks, but dental hypersensitivity and severe periodontitis remain prevalent. The study confirms similar associations between chemical exposure and dental health issues observed in other research but found no link between periodontal health and obesity or education level. Current preventive measures are insufficient in reducing high rates of dental pathology among chemical industry workers. This study highlights the need for a comprehensive, targeted prevention program at both individual and corporate levels to improve oral health outcomes.

Keywords: oral diseases, chemical industry, periodontitis, risk factors, smoking.

Introduction. According to the World Health Organization (WHO), dental caries and periodontal disease remain among the most prevalent health issues globally. In Russia, periodontitis rates vary by region, affecting 70–90% of the population, with severe forms found in approximately 15% of the adult population [1].

Previous studies have shown that various non-modifiable risk factors have a detrimental impact on oral health. Recently, attention has shifted to modifiable factors such as obesity, low education levels, and occupational exposure to harmful chemicals and aerosols [2, 3,17].

Oral health is crucial for overall health, with confirmed links between periodontitis and several systemic diseases, including diabetes, coronary heart disease, chronic obstructive pulmonary disease, and rheumatoid arthritis [4, 7, 10, 13]. Additionally, the oral cavity, as a primary interface between the external environment and the body, acts as an entry point for hazardous chemicals. These substances can accumulate in hard dental tissues, oral mucosa, and periodontal structures [9, 14].

Workers handling equipment involving chemical reactions under high temperatures and pressure, often using flammable substances, are required to use respiratory protective equipment (RPE). Due to the potential impact of certain oral health issues on RPE use, stringent oral health standards are imposed on these workers. According to the Russian Ministry of Health Order No. 29N of January 28, 2021, workers in hazardous industries must undergo an annual health examination, including a dental assessment.

The significance of this study lies in the high prevalence of oral diseases among workers in hazardous industries and the need to enhance oral health to maintain productivity.

Objective of the Study: To examine how occupational and non-occupational risk factors contribute to the development of dental diseases among workers in hazardous conditions.

Materials and Methods: The study was conducted at the PJSC “Nizhnekamskneftekhim” enterprise during a periodic medical examination organized by specialists from the Ufa Research Institute of Occupational Health and Human Ecology. As part of the research, a clinical examination was carried out on 188 ethylene oxide production operators (Group I) and 148 employees from the automation center, who formed the comparison group. Occupational monitoring materials were studied, and based on these, a workplace conditions assessment was performed in accordance with Guidelines R 2.2.2006-05.

Dental examinations were conducted following the standard WHO-recom-

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mended protocol, which included gathering complaints, medical and life history, and conducting external and intraoral examinations with a focus on periodontal health. Oral hygiene was assessed using the OHI-S index, as proposed by Green J.R. et al. (1964). The clinical examination also included a questionnaire assessing employees' oral hygiene knowledge and skills, education level, and harmful habits.

Data analysis was performed using IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, USA). Normality within groups was assessed using the Kolmogorov-Smirnov test, and the appropriate statistical methods were chosen based on the results. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion. The structure and key characteristics of the studied groups of enterprise employees are presented in Table 1.

The results of statistical analysis revealed no significant differences between the groups in terms of age characteristics, work experience (ANOVA, $p > 0.05$), obesity prevalence (BMI > 30 kg/m²), or smoking (χ^2 test, $p > 0.05$). However, the proportion of individuals with higher education differed significantly between the groups: 24.5% in Group I and 70.3% in the comparison group ($\chi^2 = 67.63$; $p = 0.001$).

The analysis of occupational monitoring data established that the leading harmful occupational factor was chemical exposure (table 2).

Laboratory tests showed that the composition of air pollutants in the work area depended on the type of raw materials used and the substances circulating in the technological processes and pipeline systems. The most toxic of these pollutants was ethylene oxide, classified as a second-level hazard. During hazardous gas-handling tasks, the permissible exposure limit (PEL) was exceeded by up to 5.7 times.

According to the dental examination results, the average OHI-S index for both groups indicated a poor level of oral hygiene. The index was slightly higher among operators exposed to ethylene oxide than among automation center employees (3.10±1.05 vs. 2.88±0.91), although this difference was not statistically significant ($p > 0.05$, Mann-Whitney test). The examination also revealed significant differences between the groups in the average number of remaining teeth. The average number for chemical production operators was 21.06±3.41 teeth, significantly lower than in the automation center group, where the av-

Table 1

Main characteristics of the studied groups

Indicator	Group I, (n=188)	Comparison group (n=148)	*p*-value
Male gender, (%)	100	100	-
Age, (years)	40.5±13.2	38.6±11.1	0.67
Work experience, (years)	16.7±11.8	16.1±10.8	0.89
Proportion of individuals with higher education, (%)	24.5±6.2	70.3±7.4	**0.001***
Smoking, (%)	46.3±7.1	50.7±8.1	0.49
BMI> 30 (kg/m²), (%)	17.0±5.4	23.6±6.9	0.17

* Statistically significant differences compared to the comparison group (χ^2 test, $p < 0.05$).

Table 2

Working conditions of chemical production workers

Groups surveyed	Harmful production factor				
	Noise	Chemical factor	Labor intensity	Labor strain	Final class
Group I (n=188)	3.1	3.3	2	2	3.3
Comparison group (n=148)	2	2	2	2	2

Table 3

Frequency of certain dental diseases in workers from various industries, %

Disease nosology	Group I (n = 188)	Comparison group (n = 148)	*p*
Non-carious dental diseases			
Wedge-shaped defect	9.0±4.0	10.8±5.0	0.72
Pathological tooth abrasion	8.4±3.9	7.4±4.2	0.87
Tooth hypersensitivity	34.6±6.8*	22.3±6.7	**0.02**
Oral mucosal diseases			
Leukoplakia	4.8±3.1	2.0±2.3	0.30
Aphthous stomatitis	4.3±2.9	5.4±3.6	0.81
Desquamative glossitis	1.1±1.5	2.0±2.3	0.48

* - Statistically significant differences from the comparison group (χ^2 test, $p < 0.05$).

Table 4

Results of logistic regression on risk factors affecting the development of destructive processes in periodontal tissues

Indicator	Group I (n=188) OR (95% CI)	Comparison group (n=148) OR (95% CI)
Secondary education vs. higher education	1.36 (0.81–1.90)	1.25 (0.58–2.04)
Smokers vs. non-smokers	2.94 (1.58-5.49)*	2.51 (1.10-5.85)*
BMI > 30 vs. BMI ≤ 30	1.19 (0.60–2.44)	1.30 (0.85–1.89)
Brushing teeth < 2 times a day vs. ≥ 2 times a day	1.80 (1.05-2.90)*	1.59 (0.94–2.70)*
Chemical factor (Group I vs. comparison groups)	2.04 (1.09–3.77) *	

Note: * - statistically significant differences

erage was 23.54±2.38 teeth (U=884.0; p=0.002).

The prevalence of dental caries exceeded 90% in both groups, with no statistically significant differences observed (χ^2, p > 0.05). However, dental hypersensitivity was diagnosed 1.4 times more frequently among Group I workers (χ^2=5.46; p=0.02) (Table 3).

Among inflammatory periodontal diseases, chronic periodontitis was the most common, diagnosed in 84.0% of Group I workers and 78.4% of comparison group employees (χ^2, p > 0.05). Severe chronic periodontitis was observed in 23.9% of cases among Group I workers, more than twice the rate in the comparison group (10.1%) (χ^2=9.8; p=0.002). The level of clinical attachment loss (CAL) was measured to assess the degree of periodontal tissue destruction. In the ethylene oxide production group, the average CAL was 5.56±2.51 mm, significantly higher than in the automation center employees, where the CAL was 4.45±1.90 mm (U=1113.0, p=0.026).

Table 4 presents the results of logistic regression analysis examining the relationship between clinical attachment loss and independent factors such as education level, smoking, body mass index, frequency of tooth brushing, and exposure to chemical factors at the workplace.

The analysis indicated that workplace exposure to chemical substances (OR=2.04 [95% CI: 1.09–3.77], p=0.023), smoking in Group I (OR=2.94 [95% CI: 1.58–5.49], p=0.002, and in the comparison group OR=2.51 [95% CI: 1.10–5.85], p=0.029), as well as infrequent tooth brushing (less than twice a day) among ethylene oxide production workers (OR=1.80 [95% CI: 1.05–2.90], p=0.035) were significant risk factors for clinical attachment loss.

The hygienic investigation showed that the primary negative occupational factor affecting workers' health was harmful airborne chemicals in the work area. Despite the implementation of modern technological processes in the chemical industry, the risk of adverse health effects from these substances remains. The highest concentrations of toxic substances were recorded during hazardous gas-handling tasks, where levels exceeded the permissible exposure limits (PEL) substantially.

Despite working with sensitizing and potentially carcinogenic chemicals, the frequency of oral mucosal diseases among ethylene oxide workers was comparable to that of the automation center employees. This outcome may be attributed to the effective use of personal respiratory protection equipment (RPE) by chemical industry workers.

The incidence of severe chronic periodontitis was significantly higher among chemical industry workers compared to the comparison group. It is likely that pathological changes in periodontal tissues are indirectly linked to the toxic effects of ethylene oxide on immune system components, as immune response dysfunction can trigger inflammatory processes in periodontal tissues [5, 15]. Severe chronic periodontitis, characterized by considerable loss of tooth-supporting tissues, is currently the leading cause of tooth loss. Additionally, literature data indicate that patients with this condition often have associated dental hypersensitivity, a finding corroborated by our results [12].

The high risk of destructive periodontal processes was associated with harmful habits, poor oral hygiene, and chemical exposure at work. Similar associations have been noted in previous studies [3, 6, 8, 11].

One distinguishing feature of our results, differing from similar studies, is the lack of a relationship between obesity, education level, and periodontal health. On one hand, our findings may be partially explained by the centralized nutrition program at the chemical enterprise; on the other hand, our study compared the clinical periodontal status of workers with higher and secondary-special education, while other studies typically analyzed groups with high and low education levels [16].

Limitations of the study. Our study has certain limitations that could impact the interpretation of the results. Specifically, we did not investigate some predictors, such as microbiological, genetic, and immunological factors, which may influence the development of dental pathology. Additionally, we did not measure ethylene oxide metabolites in workers' biological samples, which could have allowed for a more precise assessment of chemical exposure levels on the body.

Conclusions. The high levels of tooth loss, severe chronic periodontitis, and dental caries indicate the insufficiency of current preventive measures within the organized cohort of chemical industry workers and highlight the significant role of occupational risk factors in the development of dental pathology. The findings underscore the need to establish a comprehensive oral disease prevention program for chemical industry workers, based on clinical and hygienic research results, and designed for implementation at both individual and corporate levels.

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TOPICAL ISSUE

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COMPARATIVE ANALYSIS OF RISK FACTORS FOR MORTALITY IN PATIENTS OF DIFFERENT AGE GROUPS WITH SEVERE COVID-19-ASSOCIATED PNEUMONIA

The study examines the risk factors for mortality in patients across various age groups through a retrospective analysis of 591 medical records of patients with severe COVID-19-associated pneumonia treated in the intensive care unit (ICU). Univariate and multivariate analyses were conducted to identify risk factors for mortality in two distinct groups: patients under the age of 60 (group 1) and those aged 60 years and older (group 2), and comparative analysis between these two groups was performed. Mortality in group 1 was observed to be 46.9%, whereas in group 2 it was 73.3%. Patients in group 2 exhibited a comparatively lower weight and body mass index (BMI), a higher number of concomitant diseases, and more severe assessments according to the APACHE II and SOFA scales. The clinical presentation on day 1 did not differ between the groups based on the following criteria: hypercoagulation (93.1% in group 1 and 93.3% in group 2, p=0.950), septic shock (11.9% in group 1 and 18.1% in group 2, p=0.080), acute kidney injury (AKI) (12.5% in group 1 and 16.7% in group 2, p=0.206), and multiple organ failure syndrome (MODS) (55% in group 1 and 52.2% in group 2, p=0.236). In group 1, a higher prevalence of acute liver failure was observed (25% vs. 5.1%, p<0.001), whereas group 2 exhibited a greater incidence of acute cerebral failure (ACF) (13.8% vs. 34.8%, p=0.001). Group 1 also demonstrated significantly elevated leukocytosis (p<0.001) and alanine aminotransferase (ALT) levels (p<0.001). Conversely, group 2 showed lower levels of lymphopenia (p<0.001), hypoalbuminemia (p<0.001), and platelet count (p<0.001), in addition to higher levels of blood urea nitrogen (p<0.001), creatinine (p<0.001), and brain natriuretic hormone (NTproBNP) (p=0.003). In patients under 60 years old with severe COVID-19-associated pneumonia, the independent risk factor for death was the development of MODS on the first day of admission in the ICU. For patients over 60 years old, independent risk factors for death were age, the presence of chronic kidney disease (CKD), the severity of hypoxia as determined by the PaO2/FiO2 ratio upon admission to the ICU, the development of MODS, septic shock, and acute cerebral disorder.

Keywords: coronavirus disease 2019, COVID-19, predictors, age, risk factors

Introduction. Age constitutes a non-modifiable risk factor for mortality associated with the novel coronavirus infection COVID-19. Large international studies examining treatment outcomes across various countries demonstrate a marked increase in mortality rates with advancing age [1-3]. In the Russian Federation in 2021, a significant 85% of individuals with COVID-19 who died were aged over 60 years [4]. This fact can be attributed to multiple factors, including the escalation of comorbidities, age-related alterations in immune system functionality, frailty syndrome, diminished reserve capacity of organs, and some social dimension (e.g., residing in nursing homes). Among younger and middle-aged patients, risk factors for mortality encompass the presence of comorbidities, obesity and the severity of hypoxia [5,6]. The limited number of studies addressing risk factors for mortality in patients with COVID-19-associated pneumonia under the age of 60 underscores the relevance of this investigation.

The aim of the research. To perform a comparative analysis of risk factors for mortality in patients younger and older than 60 years of age with severe COVID-19-associated pneumonia.

Materials and methods. *Estimation of sample size and statistical power of the study.* The sample was collected by random method, the sample size was calculated in G.Power 3.1 (Statistical power analysis program), with a mortality rate of 60%, study selection was two independent groups, general population (total number of patients for 2020-2022) – 1500 patients, α error was 0.05, the minimum number of 141 patients in the one sample was obtained. The power of the study was assessed on the AI Therapy Statistics website, the introduced study characteristic was the method of comparison of two independent groups, α error was 0.05, sample size 1 (160 patients) and 2 (431 patients), obtained a power of 1.0.

Study protocol. The analysis included 591 patients who had been treated in the ICU of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital" from March 2020 to December 2021. The data were extracted from "Database of main indicators of patients with severe COVID-19-associated pneumonia", certificate №2023622084 from 23.06.2023. All patients were divided by age – group

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1 with patients under 60 years old, group 2 included patients from 60 years old and older. The study was approved by the local biomedical ethics committee of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov (№4, 07.10.2020). There were no missing data.

Inclusion criteria: adult ICU patients 18 years of age or older, with a diagnosis of U07.1 “COVID-19, virus identified” or U07.2 “presumed COVID-19, virus not identified”; presence of severe COVID-19-associated pneumonia in patients (chest CT scan showing >50% pulmonary parenchyma involvement according to the adapted empirical visual scale – CT-3 and CT-4); patients' consent to participate in the study. Non-inclusion criteria: patients who died after admission to the ICU within 12 hours; patients without COVID-19; pregnant women, as well as early postpartum period of less than 2 months; patients without pneumonia, as well as mild to moderately course (not severe) (as assessed by CT-0, CT-1 and CT-2); presence of cancer pathology in stage 4 and/or specific cancer therapy (chemotherapy, radiotherapy, surgery) less than 3 months prior to COVID-19. Exclusion criteria: patients whose therapy did not comply with the current recommendations for the treatment of patients with COVID-19; patients with acute surgical pathology, acute cerebrovascular accident, acute coronary syndrome (ACS) who were transferred to specialized medical hospitals; patients with COVID-19 vaccine prophylaxis; refusal to participate in the study.

Statistical analysis was performed in SPSS version 26. The distribution of quantitative data was checked by assessing skewness and kurtosis, then the non-parametric comparative analysis was selected using the Mann-Whitney U test, the median (Me) and interquartile range (IQR) were determined. Nominal data were analyzed using Pearson's χ^2 test, determination of odds ratio (OR) with 95% confidence interval (CI). Multivariate analysis was performed using Cox regression and hazard ratio (HR) determination. Survival analysis was performed by constructing Kaplan-Meier curves. ROC analysis was performed for quantitative data and area under the curve (AUC), cut-off threshold and ROC were calculated.

Results and discussion. Group 1 included 160 patients with a mortality rate of 46.9%, and group 2 included 431 patients with a mortality rate of 73.3%. The duration of treatment in the ICU was 5 [3-11] days in group 1 and 7 [3-11] days in group 2 (p=0.01), and the total duration of hospitalization was 8 [5-15] and 12 [7-17] days, respectively (p<0.001). The median onset of death according to the Kaplan Meier method for group 1 was 11.0±0.7 (95% CI: 9.7-12.3) days, and for group 2 was 9.0±0.3 (95% CI 8.3-9.5) days (see Figure 1).

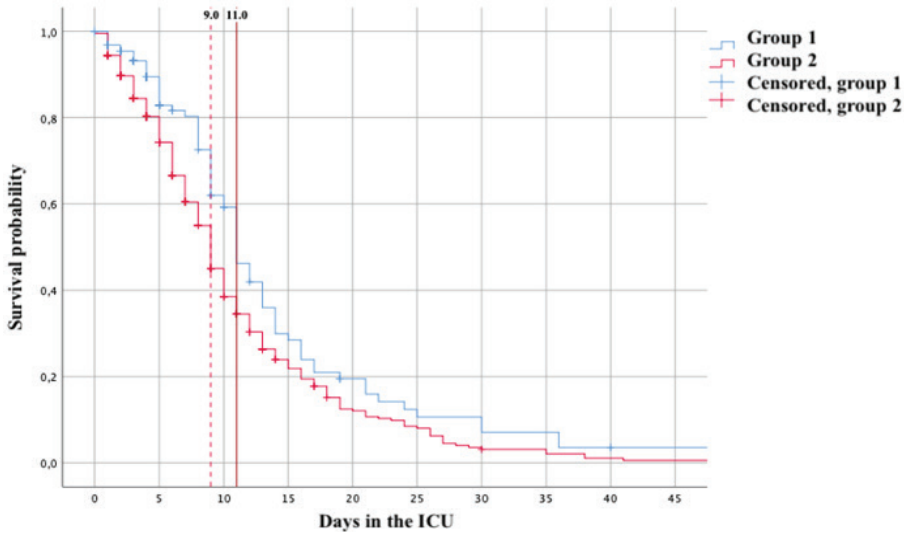

Fig. 1. Kaplan-Meier curve. The red solid line is the median time (days) of death for group 1. The red dashed line is the median time of death (days) for group 2

In the univariate analysis age was a risk factor influencing mortality. In group 1, deceased patients were older, 55 [51-57] years, than survivors, 52 [45-56] years (p=0.002). The AUC ROC for age was 0.643 (95% CI: 0.557-0.729), cut-off threshold 52.5 years, OR 2.4 (95% CI: 1.2-4.4, p<0.001, Cramer's V test 0.209). In group 2, the age of non-survivors and survivors was 72 [66-80] and 68 [63-71] years, respectively (p<0.001), AUC ROC was 0.661 (95% CI: 0.606-0.716) and OR of mortality for patients older than 68.5 years (cut-off threshold) were 2.4 (95% CI: 1.6-3.7, p<0.001, Cramer's V test 0.193).

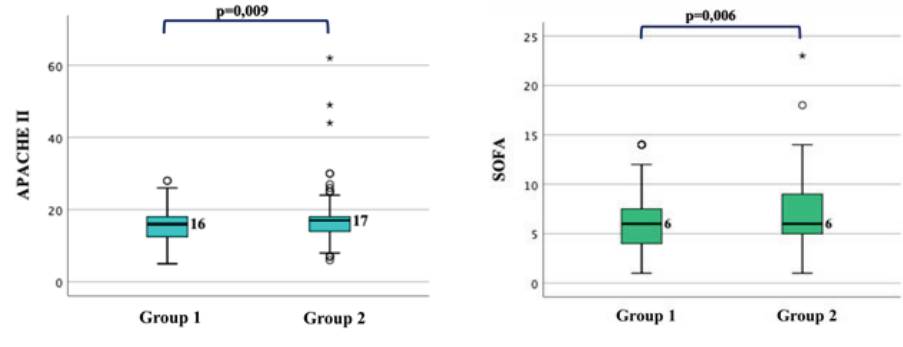

Fig. 2. APACHE II and SOFA severity scores on admission to the ICU

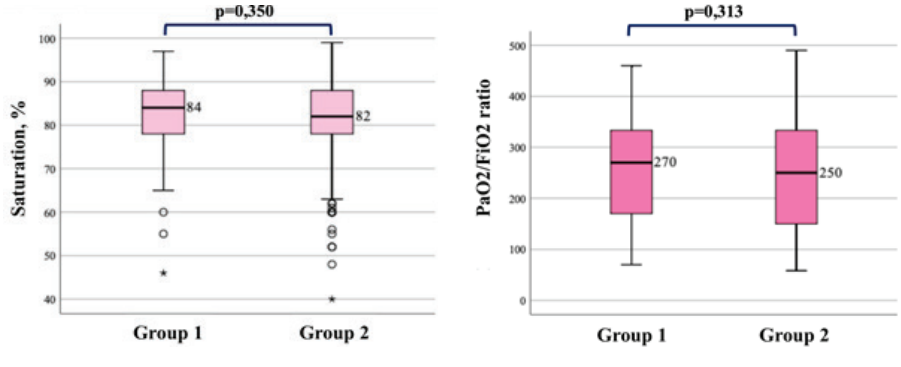

Рис. 3. PaO_2/FiO_2 ratio and SpO_2 on the admission to the ICU

Table 1

Impact of comorbidities and clinical picture in first 24-hours in the ICU on mortality (univariate analysis)

Variables	Group 1 (n=160)			Group 2 (n=431)			p-value for comparison between group 1and 2
	Patients proportion %	Impact on mortality (univariate analysis)		Patients proportion %	Impact on mortality (univariate analysis)		
		p-value	ОШ 95%ДИ		p-value	ОШ 95% ДИ	
Chronic cardiovascular diseases	127 (79.4)	p=0.52	-	426 (98.8)	p=0.090	-	<0.001*
Type 2 diabetes	56 (35)	p=0.561	-	169 (39.2)	p=0.383	-	0.349
Chronic respiratory diseases	53 (33.1)	p=0.288	-	193 (44.8)	p=0.063	-	0.011*
Chronic kidney disease	61 (38.1)	p=0.151	-	221 (51.3)	p=0.032*	1.5 (1.1-2.4)	0.004*
Chronic brain diseases	35 (21.9)	p=0.168	-	158 (36.7)	p=0.980	-	0.001*
CT-4	88 (55.0)	p=0.067	-	254 (58.9)	p<0.001*	2.6 (1.7-4.0)	0.185
Septic shock	19 (11.9)	p<0.001*	28.5 (8.7-52.5)	78 (18.1)	p=0.001*	3.3 (1.6-6.8)	0.080
Hypercoagulation	149 (93.1)	p=0.682	-	402 (93.3)	p=0.748	-	0.950
Acute liver failure	40 (25.0)	p=0.022*	2.3 (1.1-4.9)	22 (5.1)	p=0.090	-	<0.001*
Acute cerebral disorder	22 (13.8)	p=0.002*	4.7 (1.6-13.4)	150 (34.8)	p=0.003*	2.1 (1.3-3.4)	0.001*
Acute kidney injury	20 (12.5)	p=0.027*	3.0 (1.1-8.3)	72 (16.7)	p=0.008*	2.5 (1.3-5.1)	0.206
Multiple organ dysfunction syndrome	88 (55.0)	p<0.001*	4.5 (2.3-8.8)	225 (52.2)	p<0.001*	2.5 (1.6-3.9)	0.236

Note: Pearson's chi-squared test was used, *- statistically significant.

In both groups, median BMI was higher than normal range, but did not affect mortality in univariate analysis (p>0.05). Group 1 patients had more weight (p<0.001): median weight for group 1 was 87.5 kg [37.5-103.5], median BMI 31.6 [27.8-37.2], for group 2 was 78.0 kg [67.0-88.5], 28.8 [25.7-32.5], respectively.

The severity of the disease was assessed using APACHE II and SOFA scales on admission and demonstrated higher scores in group 2 patients (p=0.009 and p=0.006, respectively) (see Figure 2). The severity of hypoxia on admission, as measured by PaO_2/FiO_2 ratio and SpO_2, did not differ between groups 1 and 2 (p=0.350 and p=0.313) (see Figure 3), and associated with mortality only in group 2: PaO_2/FiO_2 ratio was lower in those who died (p<0.001) 250 [131-333] versus 290 [184-333] in survivors, AUC ROC was 0.618 (95% CI: 0.560-0.677), cut-off threshold was 283, below which the odds ratio of mortality increases 2.1-fold (95% CI: 1.4-3.2, p=0.001, Cramer's V test 0.162). SpO_2 in group 2 pa-

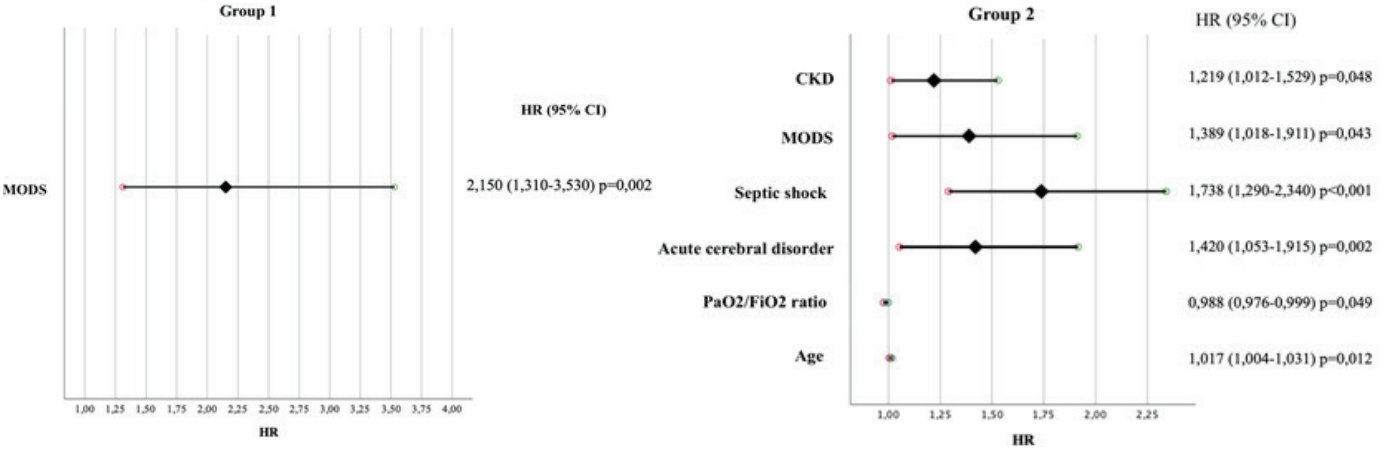

Fig. 4. Multivariate analyses by Cox regression for group 1 and 2

Table 2

Laboratory findings on admission to the ICU

Laboratory variable [Reference Values]	Group 1		Group 2		p-value, comparison groups 1 and 2
	Me [IQR]	AUC ROC	Me [IQR]	AUC ROC	
Leukocyte count [<12×10⁹/L]	11.84 [7.36-16.03]	-	9.83 [6.86-13.54]	-	0.020*
Lymphocyte [0,8-4,0×10⁹/L]	0.96 [0.61-1.40]	0.623	0.79 [0.51-1.10]	0.610	<0.001*
Neutrophil [2,0-7,0×10⁹/L]	9.36 [5.85-13.87]	-	8.19 [5.75-11.44]	-	0.260
Platelet count [100-300×10⁹/L]	252 [186.5-322]	-	227 [172-289]	0.619	<0.001*
Fibrinogen [2,4-4,3 g/L]	4.8 [3.8-5.9]	0.660	4.9 [3.8-5.8]	0.634	0.896
D-Dimer [0-250 mg/ml]	500 [304.4-1011.0]	-	530.4 [293.4-975.3]	0.604	0.637
IL-6 [<10 pg/L]	138.0 [26.9-2678.0]	-	246.5 [44.8-3194.0]	0.581	0.073
CRP [0,0-5,0 mg/L]	40.6 [7.0-131.0]	-	34.9 [3.6-115.2]	-	0.409
BUN [0,1-8,3 mmol/L]	6.95 [5.55-9.55]	0.719	8.60 [6.5-12.1]	0.617	<0.001*
Creatinin [44,0-80,0 µmol/L]	73.8 [63.1-90.0]	0.658	86.0 [70.6-109.0]	0.523	<0.001*
AST [<32,0 U/L]	36.5 [26.9-59.7]	-	35.4 [25.9-58.5]	0.606	0.186
ALT [<31 U/L]	42.0 [27.8-74.1]	-	34.6 [21.4-57.0]	0.562	<0.001*
Albumin [38,0-54,0 g/L]	35.0 [31.9-38.0]	0.640	32.0 [29.0-35.7]	0.573	<0.001*
LDH [135,0-214,0 U/L]	531.0 [390.0-779.0]	0.754	487.5 [399.0-651.7]	0.704	0.568
Ferritin [10,0-120,0 mcg/L]	857.2 [444.5-1483.0]	0.686	858.0 [458.0-1466.8]	0.607	0.498
CPK [0-145,0 U/L]	74.5 [42.1-162.6]	0.652	76.4 [40.8-154.9]	0.568	0.640
NTproBP [0-125 pg/mL)]	190 [90-489]	-	310 [129-690]	0.598	0.003*

Note: The Mann-Whitney U-test was used, *- statistically significant.

tients was also lower in non-survivors 82 [76-86] versus 85 [80-90] in survivors (p=0.002), AUC ROC was 0.596 (95% CI: 0.536-0.656), cut-off threshold was 84.5, OR 2.0 (95% CI: 1.3-3.2, p=0.001, Cramer's V test 0.152).

A univariate analysis of the association between mortality and comorbidities or the clinical presentation at 1 day in the ICU, as well as a comparative analysis of groups 1 and 2 are presented in Table 1. Expectedly, there were more comorbidities in group 2 patients. The clinical presentation on day 1 in the two groups is similar except for acute liver failure (more in group 1) and acute cerebral disorder (more in group 2).

Further, multivariate analysis using Cox regression was performed to study the complex influence of variables and the times-to-event outcome, which included risk factors for mortality according to the results of univariate analysis: age, comorbidities and clinical components on the first day of admission. As a result, the one independent risk factor of an unfavorable outcome in patients with severe COVID-19-associated pneumonia under 60 years old was found – the development of MODS on the first day in the ICU. For group 2 patients independent risk factors for mortality were identified – presence of CKD, development of MODS, septic shock, acute cerebral disorder, PaO_2/FiO_2 ratio and age (Figure 4).

Comparison of laboratory values at admission between groups, as well as the area under the curve for parameters statistically significantly associated with mortality in each group, are presented in Table 2.

In group 1, elevation of LDH, blood urea nitrogen, ferritin, fibrinogen and creatinine demonstrated the highest prognostic efficacy. In group 2, this referred to the increase of LDH, blood urea nitrogen, fibrinogen, thrombocytopenia and lymphocytopenia. As a result of comparison of Me±IQR values of laboratory parameters between groups, in group 2, the parameters reflected more severe organ and system damage. Severe lymphocytopenia indicates the severity of host immune response dysregulation [7]. Hypoalbuminemia in COVID-19, especially in older patients, is associated with impaired nutritional status and/or gastrointestinal lesions [8]. Decreased platelet quantity and quality, COVID-19-associated thrombocytopathy, is caused by direct viral damage to megakaryocytes and platelets and increased consumption due to immunothrombosis [9]. NTproBP as a marker of left ventricular functional potential, an indicator of the severity of chronic heart failure, is naturally higher in the group of patients over 60 years old, and in COVID-19 its increase is an unfavourable marker [10.11]. Note that transaminases were slightly higher in group 1 patients, but only in group 2 patients their increase was associated with mortality. Liver failure in COVID-19, whether caused by direct viral damage or secondary, as an indicator of the severity of MODS, as well as the development of toxic (drug-induced) hepatitis was characterized by transaminasemia, worsening hypoalbuminemia, secondary coagulopathy, and thrombocytopenia [12]. In the pathogenesis of acute kidney injury (AKI) in COVID-19, the main place is attributed to impaired renal perfusion – decreased renal blood flow of various etiologies: hypotension, hypoxia, ventilator-associated damage, neurohormonal changes, etc. The presence of CKD and the development of ARF were strong predictors of mortality in COVID-19 [13].

Conclusions. A risk factor for mortality in patients younger than 60 years of age with severe COVID-19-associated pneumonia was the development of MODS on the first day of admission (HR 0.150 95% CI: 1.310-3.530, p=0.002). For patients older than 60 years, inde-

pendent risk factors for mortality were age (HR 1.017 95%CI: 1.004-1.031, p=0.012), presence of CKD (HR 1.219 95%CI: 1.012-1.529, p=0.048), severity of hypoxia as measured by PaO_2/FiO_2 ratio at ICU admission (HR 0.988 95%CI: 0.976-0.999, p=0.049), development of MODS (HR 1.389 95%CI: 1.018-1.911, p=0.043), septic shock (HR 1.738 95%CI: 1.290-2.340, p<0.001) and acute cerebral disorder (HR 1.420 95%CI:1.053-1.915, p=0.002). Patients older than 60 years had more comorbidities and laboratory tests indicated more severe dysregulation of host response, hypoxia and MODS, had higher APACHE II and SOFA scores, and higher mortality (for group 1 – 46.9%, for group 2 – 73.3%).

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FEATURES OF PLACENTAL DAMAGE IN PATIENTS WITH PERINATAL LOSSES DURING PREMERATE BIRTH AND ACUTE COVID-19

A morphological study of the placenta in patients with perinatal losses in preterm labor and acute COVID-19 of varying severity, manifested in the II and III trimesters of gestation, was performed. It was found that the features of placental damage in patients with perinatal losses are statistically significant predominance of thrombosis, inflammatory changes and manifestations of placentitis SARS-CoV-2 in comparison with placentas of patients without perinatal losses.

Keywords: pregnancy, novel coronavirus infection, COVID-19, preterm labor, perinatal mortality, placental damage

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Introduction. Morphologic changes in the placentas of pregnant women with COVID-19 continue to be studied. Most studies indicate the detection of decidual vasculopathy, massive perivorhinal fibrin deposition, thrombosis of the intervillous space and infarcts of the villi, the presence of fetal vascular abnormalities, chorangiosis, villitis of unclear genesis [1, 4, 5, 8, 9, 14]. An increase in the number of syncytial nodules in placenta villi of pregnant women with mild to moderately severe COVID-19 symptoms has been found [2]. In cases of stillbirth in pregnant women with COVID-19, trophoblast necrosis, a significant increase in perivillous fibrin deposition combined with chronic histiocytic intervillusitis (HI) have been noted in the placenta [6]. In the placentas of pregnant women with antenatal

Morphological features of placenta in patients in study groups. abs. (%)

Parameter	1st group (n=22)	2nd group (n=29)	p
Decidual arteriopathy	1 (4.5)	5 (17.2)	0.218
Sharply defined syncytiocapillary nodules. buds and membranes	7 (31.8)	12 (41.4)	0.484
Massive fibrinoid deposition	15 (68.2)	8 (27.6)	0.004*
Villus agglutination	12 (54.5)	9 (31.0)	0.091
Thrombosis of the intervillous space	14 (63.6)	6 (20.7)	0.002*
Villous infarctions	13 (59.1)	3 (10.3)	<0.001*
Hemorrhages into the intervillous space	19 (86.4)	17 (58.6)	0.031*
Villus maturation disorder	10 (45.5)	13 (44.8)	0.964
Clusters of hyalinized avascular villi	12 (54.5)	3 (10.3)	0.001*
Chorangiosis	0 (0.0)	6 (20.7)	0.031*
Chorangiomatosis multifocal	1 (4.5)	9 (31.0)	0.030*
Thrombosis of villous vessels	13 (59.1)	3 (10.3)	<0.001*
Villous swelling	8 (36.4)	9 (31.0)	0.689
Purulent inflammation	9 (40.9)	4 (13.8)	0.028*
Productive inflammation of fruit membranes	20 (90.9)	16 (55.2)	0.006*
Productive willusite	17 (77.3)	12 (41.4)	0.010*
Trophoblast necrosis	11 (50.0)	1 (3.4)	<0.001*
Histiocytic intervillusitis	11 (50.0)	0 (0.0)	<0.001*

Note: * - the differences are statistically significant

fetal death (AFD), pronounced manifestations of maternal vascular malperfusion (thrombosis of the intervillous space, massive fibrin deposition, infarcts and agglutination of villi, inflammatory changes) are registered [3].

It is relevant to study the features of placental damage in patients with perinatal losses (PL) in preterm labor (PTL) during acute COVID-19.

The objective of the study: **to** evaluate the features of placental damage in patients with perinatal losses in preterm labor during acute COVID-19.

Materials and Methods. Based on data from a prospective cohort study of 1368 pregnant women with confirmed COVID-19 admitted from April 2020 to December 2021 for medical care at the COVID hospital in Chelyabinsk, a case-control study was conducted to analyze the features of placental damage in adverse perinatal outcomes (PI) (stillbirth, early neonatal death of the newborn) in women with PR during acute COVID-19.

Pregnant women with PL in PTL during acute COVID-19 constituted the 1st study group (n=22). The 2nd study group (control group) included patients without PL in PTL during acute COVID-19 (n=29).

The following criteria were developed for inclusion in group 1 of the study: confirmed case of COVID-19 (U07. 1) in a pregnant woman, acute COVID-19, PTL at 22/0 to 36/6 weeks of gestation, perinatal fetal/newborn death (for group 1) and no perinatal fetal/newborn death (for group 2), reproductive age of the woman, availability and accessibility of medical records to collect information for analysis, written informed consent of the patients for participation in the study and publication of its results in the open press. The criteria for non-inclusion in the study were as follows: on the part of the pregnant woman - multiple pregnancies, somatic diseases in decompensation, HIV infection, malignant and psychiatric diseases; on the part of the fetus - congenital malformations.

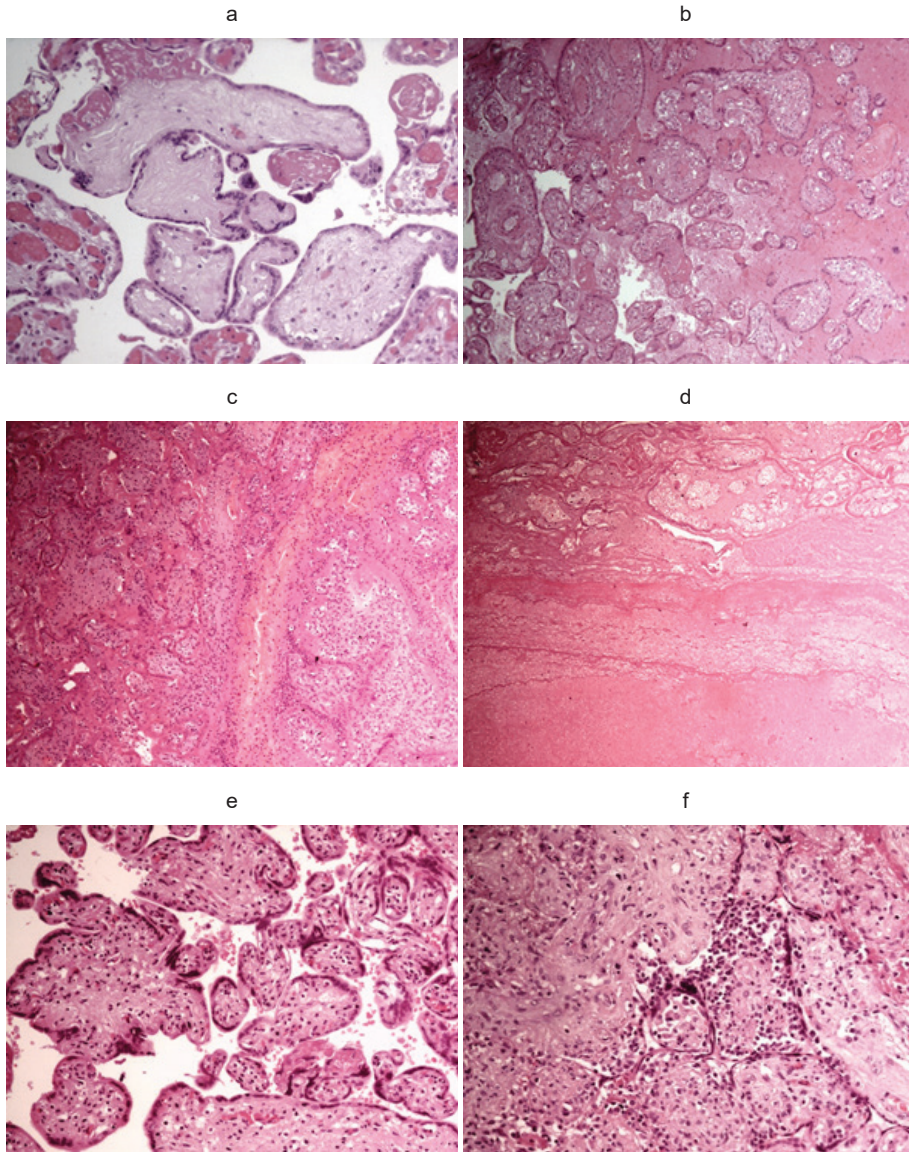
The afterbirths were subjected to careful macroscopic examination. Then, 1 fragment each was dissected from the paracentral zone of the placental disk from the choroidal and basal plate sides; a 0.7 cm wide strip was cut from the extraplacental membranes, which was then twisted into a roll. The obtained samples of the afterbirth were fixed in 10% neutral buffered formalin, dehydrated in alcohols of ascending concentration, embedded in paraffin, sections of 5 μm thickness were prepared, stained with hematoxylin-eosin and picrofxin according to Van Gieson. Placental abnormalities were assessed based on the classification of placental injuries proposed by the Amsterdam Placenta Workshop Group (2014), including placental vascular abnormalities, inflammatory-immune abnormalities, and other placental injuries [10].

The study was approved by the ethical committee of the Federal State Budgetary Educational Institution of Higher Professional Education "South Ural State Medical University" of the Ministry of Health of Russia (protocol No.8 of 20.09.2021).

Statistical processing of data was performed with the help of IBM SPSS Statistics-19 statistical software package using standard methods of nonparametric statistics depending on the type of data (the Mann-Whitney test, the x^2 test, the Fisher's exact test). Statistical hypotheses were tested at the critical significance level of $p \leq 0.05$.

Results and Discussion. The age of the pregnant women was not statistically significantly different, being 33.5 (28;36.2) and 30 (27.5;35.5) years in groups 1 and 2, respectively (p=0.355).

PTL at 22^0-24^6 weeks were observed in groups 1 and 2 in 7/22 (31.8%) and 0/29 (0.0%), respectively, in 25^0-27^6 weeks in 8/22 (36.4%) and 9/29 (31, 0%), in 28^0-31^6 weeks - in 2/22 (9.1%) and 8/29 (27.6%), in 32^0-33^6 weeks - in 0/22 (0.0%) and 6/29 (20.7%), in 34^0-36^6 weeks - in 5/22 (22.7%) and 6/29 (20.7%)



Features of placental damage in patients with perinatal losses during premature birth during acute COVID-19; a – accumulations of hyalinized avascular villi; b – hemorrhages in the intervillous space; c – thrombosis of the intervillous space; d – true placental infarction; e – productive intervillusite; f – histiocytic intervillusitis. Hematoxylin and eosin staining; magnification: x 100 – b, c; x 200 – a, d-f

cases (p=0.002). Thus in the group with PL, extremely early PTL were predominant.

PL in study group 1 included cases of stillbirth (19/22 - 86.4%) and early neonatal death (3/22 - 13.6%) (p=0.001). The pattern of stillbirth was statistically significantly dominated by AFD: 16/19 (84.2%) cases of AFD and 3/19 (15.8%) observations of intrapartum fetal death were recorded (p=0.004). All cases of early neonatal losses among live births against the background of acute COVID-19 in group 1 were registered in patients with severe course of infection.

Data on morphologic changes of postpartum in patients with PL on the background of acute COVID-19 in comparison with pregnant women without PL are presented in the Table.

As can be seen from the table, in the placentas of group 1 women statistically significantly more often compared with group 2 placentas, hyalinized avascular villi were registered (Fig., a), which indicates the presence of fetal stromal vascular lesions, which are signs of fetal blood supply disorders. The absence of chorangiosis signs in the placentas of group 1 patients and insignificant manifestations of chorangiomatosis in combination with the severity of fibrinoid deposition and agglutination of villi with statistically significant differences in comparison with the same parameters of group 2 women are noteworthy.

The revealed morphological features may indicate that against the background of acute COVID-19 in the placentas of patients with PP, compensatory changes are not formed in time to counteract the increasing hypoxia, which may lead to adverse perinatal outcomes (PO). According to N. Jaiswal et al. [5], chorangiosis was recorded in 13/27 (48.1%) placentas from asymptomatic and mild COVID-19 (confirmed infection) pregnant women with favorable PO. In a study by E.D. Shanes et al. [7], chorangiosis was observed in 4/15 (26.7%) placentas from third trimester pregnant women with manifest or history of COVID-19, in 30% with no clinical symptoms. The authors observed favorable PO in all cases analyzed. However, 1 case of fetal loss at 16 weeks' gestation showed villous edema and retroplacental hematoma, with no evidence of chorangiosis or acute or chronic inflammation [7].

In group 1 patients, we observed pronounced thrombosis processes in the placenta: hemorrhages in the intervillous space (Fig., b), thrombosis of the intervillous space (Fig., c), and villous infarcts (Fig., d) were statistically significantly more frequent compared to the placentas of group 2 patients. Productive villusitis (Fig., e) and productive inflammation of fetal membranes as a consequence of hematogenous infection were statistically significantly predominant in group 1. Purulent inflammation was also statistically significantly more frequent in the placentas of group 1 women.

G.B. Malgina et al. [3], C. Dubucs et al. [13] demonstrate the presence of thrombosis of the intervarsinal space, massive fibrin deposition, and inflammatory changes in the placentas in cases of AFD.

Signs of SARS-CoV-2 placentitis (HI, trophoblast necrosis, massive fibrinoid deposition) were statistically significantly more frequently registered in the placentas of group 1 patients (Fig., e). It should be noted that similar morphological changes in the placentas, as well as intervillous hemorrhages and subchorionic hematomas in cases of stillbirth against the background of COVID-19 manifestation are noted by other researchers [6, 9, 13]. Thus, in the study by D. Schwartz et al. [6], signs of HI and necrosis of syncytiotrophoblast were detected in the placentas of both stillborn (5 cases) and liveborn (5 cases) children in the presence of a positive result of syncytiotrophoblast testing for SARS-CoV-2 by immunohistochemical analysis and/or RNA in situ hybridization. In cases of stillbirth, all placentas were characterized by a marked increase in perivillous fibrin deposition, up to massive, in addition to HI and necrosis of syncytiotrophoblast, which resulted in placental/maternal malperfusion and contributed to fetal death. According to D. Schwartz et al. [9], of 68 cases of perinatal losses from pregnant women with confirmed COVID-19, all placentas showed increased fibrin deposition (in 63 it was massive) and necrosis of syncytiotrophoblast, in 66 - HI. Overall, the destructive state of the placenta due to SARS-CoV-2 placentitis included about 77.7% of the tissue lesions. Among other morphologic features, the authors noted the presence of multiple intervillous thrombi (25/68, 37%) and chronic villitis (22/68, 32%).

Some researchers [12] believe that morphologic changes in the placenta, called placentitis SARS-CoV-2, can be considered as a result of episodes of viremia, which may have both infectious and immunopathologic basis. Diffuse destruction of the placenta with more than 75% of its tissue volume affected by SARS-CoV-2 placentitis leads to rapidly progressive placental dysfunction against a background of severe maternal and fetal malperfusion, resulting in fetal distress, ASP or neonatal death.

In the study by S. Stenton et al. [11], revealed signs of massive perivillous fibrin deposition, HI and varying degrees of necrosis of extravillous trophoblast in the placentas of women with stillbirth in the second and third trimesters from COVID-19-positive mothers with both the presence and absence of clinical symptoms of infection.

Conclusion. Thus, the detected placental lesions during acute COVID-19 in patients with PTL and PL characterize multicomponent placental damage, including both vascular and inflammatory changes, accompanied by impaired metabolic processes between mother and fetus, which leads to unfavorable PO. In the placentas of patients with PTL and PL there is a statistically significant predominance of thrombosis processes, inflammatory changes and manifestations of SARS-CoV-2 placentitis in comparison with the placentas of patients without PL.

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ANALYSIS OF THE INCIDENCE OF HIV INFECTION IN THE ALTAI REGION IN 2022

Introduction: In the Altai Territory, there are the same trends in the change in the HIV epidemic as in Russia as a whole. Changing the "portrait" of a typical patient with HIV infection, as well as increasing coverage of patients with specific therapy, dictates the need to study the characteristics of HIV infection in the Altai Territory.

Purpose: analysis of the epidemiology of HIV infection in the Altai Territory in 2022, taking into account the genetic characteristics of circulating variants in the territory.

Materials and methods: An analysis of the main epidemiological indicators for HIV infection in 2022 was carried out. A collection of plasma samples from patients without therapy experience (n = 187) collected in 2022 in the Altai Territory was collected and analyzed. The genetic variant of HIV-1 was determined, an analysis of primary drug resistance was carried out in the Altai Territory in 2022.

Results: The article presents an analysis of epidemiological data indicating the continuation of changes in the structure of HIV-infected people in the Altai Territory, as in the Russian Federation as a whole (an increase in the proportion of the female population, the proportion of people over 30 years old, the dominance of the sexual transmission of infection). A high frequency of infection with the recombinant form of CRF63_02A6 was detected. At the same time, the Altai Territory is not distinguished by a high genetic diversity of HIV-1. A high frequency of drug resistance (including a high level) to first-generation NNRTIs has been established.

Conclusion: The HIV epidemic in the Altai Territory reflects the main trends in HIV infection in the Russian Federation, including the situation with primary drug resistance. Meanwhile, the characteristics of the genetic diversity of HIV-1 in this territory require further study.

Keywords: HIV infection, sequencing, genetic diversity, drug resistance.

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Introduction. According to the Federal Center for the Prevention and Control of AIDS at the end of 2022, the number of HIV-infected people living in the Russian Federation (RF) reached 1,168,076 people, and the average incidence rate in the country was 43.29 per 100 thousand population. Altai Territory (AT) is one of 34 constituent entities of the Russian Federation, the incidence rate in which exceeds the average level in the country. In this subject, it is 65.5 per 100 thousand population, which indicates the active spread of HIV infection in the Altai Territory in recent years.

In Russia, over time, not only the number of HIV-positive people changed, but also the "portrait" of a typical patient with HIV infection. If in the early 2000s the main vulnerable group were young people 15-30 years old, then by 2022 the age of the average patient increased to 30-60 years, i.e. people at the most economically active age have become susceptible to infection. At the same time, the route of infection through injection drug consumption (IDC), which has been dominant since the late 90s. of the last century, in the mid-tenths of this century began to yield to the heterosexual route of infection. As a result, by 2022, heterosexual contacts have become the main method of transmission in the country. At the same time, almost 55% of HIV-infected people in 2022 were women, while in previous years men predominated among HIV-infected patients: in 2010 and 2014 (69.4% and 63.1%, respectively) [1-3, 14, 15].

On the territory of the AT, a similar change in the portrait of a typical patient with HIV infection was noted. If in 2006 only 17.8% of patients belonged to the age group of 30 years and older, then by 2014 this figure was already 47.1%. The proportion of HIV-infected women rose from 27.3% in 2006 to almost 35% by 2014 [13]. Although in 2014-2017 the main route of transmission in the AT remained IDC (about 60%), there was a tendency towards a decrease in the proportion of this route of infection relative to sexual [5, 13].

The genetic diversity of HIV-1 in the AT historically has features. In particular, back in 2017, it was shown that the recombinant form of HIV-1 CRF63_02A6 (formerly called CRF63_02A1) dominates in the AT [5, 13], and only about a third of cases are associated with the genetic variant of HIV-1 subsubtype A6, which has historically dominated in Russia from the late 90s to the present [6, 9, 10, 11, 21]. This feature of the epidemiology of HIV infection is characteristic of the entire Siberian Federal District, where the recombinant form of CRF63_02A6 was first identified [16] and where it is currently the dominant genetic form of HIV-1 [18].

The coverage of people with HIV infection with antiretroviral therapy in Russia is growing every year. So, at the end

of 2022, more than 835 thousand people received antiretroviral therapy in the country [3].

The effectiveness of therapy is associated with the degree of prevalence in the country of HIV-1 options resistant to antiretroviral therapy. Moreover, the identification of "primary" drug resistance (DR) in a virus circulating among patients without therapy experience (ART-naive) has the greatest prognostic value. In this case, not only the fact of the presence of DR is considered, but also the degree of stability, estimated by the Stanford University algorithm [8, 12, 20]. According to WHO recommendations, if the prevalence of DR in any class of drugs used in the country reaches 10%, all patients starting therapy should be tested for DR HIV-1 [5]. The results of a study of DR in the world showed that the level of primary DR to classic drugs of the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), primarily nevirapine (NVP) and efavirenz (EFV), exceeds 10%. For this reason, WHO does not recommend the use of first-generation NNRTIs in therapy regimens [11, 20]. Similarly, the 2023 MoH guidelines suggest nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and HIV-1 integrase inhibitors (AIs) as preferred therapies. Of the NNRTI, only the 2nd generation NNRTI elsulfavirin (ESV) is recommended [4]. This approach to the formation of therapy regimens has a basis: a study in 2023 showed that the prevalence of DR among patients without therapy experience in Russia reached 12.7% by 2022 due, first of all, to resistance to NNRTI (10%) [8, 20].

Finally, in addition to LN itself, the prevalence of LN mutations from the list of so-called surveillance mutations (SDRM) is assessed, whose presence in HIV-1 variants indicates a high risk of therapy failure [19].

Thus, surveillance of transmissible resistance (in patients with a recent diagnosis of HIV infection and without therapy experience) is the most important issue of HIV epidemiology in every region of the country [7, 8, 17].

The purpose of this study was to analyze the epidemiology of HIV infection in the Altai Territory in 2022, taking into account the genetic characteristics of circulating variants in the territory.

Materials and methods. Analysis of epidemiological data. To assess the specifics of the epidemiology of HIV infection in the AT in 2022, the following documents were analyzed:

1. Form No. 2 "Information on infectious and parasitic diseases in the Altai Territory for 2013-2022";

2. Report "On the state of sanitary and epidemiological well-being of the population in the Altai Territory in 2022" FBUZ "Center for Hygiene and Epidemiology in the Altai Territory";

3. Statistics of the official website of the Altai Regional Center for the Prevention and Control of AIDS and Infectious Diseases (https://altaids22.ru/).

Descriptive and evaluative epidemiological research methods were used in the work. The analysis used calculation of absolute and relative values, calculation of confidence intervals (CI) by Wilson method with 95% confidence interval. Statistical analysis was performed using Microsoft Excel.

Analysis of HIV-1 variants in biological samples. During 2022, a collection of blood plasma samples from patients collected in the AT was collected and analyzed. Inclusion criteria:

1. Age 18 years or more;

2. Accommodation in the settlement of the AT;

3. Making a diagnosis of HIV infection in 2022;

4. Lack of experience in HIV therapy (ART-naive);

5. The level of viral load (VL, HIV-1 RNA concentration) in blood plasma is more than 500 copies/mL (sensitivity limit for possible further genetic analysis).

Exclusion criteria:

1. Age at enrollment is less than 18 years.

2. Permanent actual residence outside the AT;

3. Diagnosis of HIV infection earlier than 2022;

4. ART experience;

5. Undetectable VL or VL below 500 copies/mL.

Collection of blood plasma, collection of concomitant epidemiological and clinical information (age, sex, route of infection, information on residence, date of diagnosis, determination of the stage of HIV infection), determination of VL and the level of CD4-lymphocytes was carried out on the basis of the Altai Regional Center for the Prevention and Control of AIDS and Infectious Diseases. Extraction of HIV-1 RNA from blood plasma, sequencing and analysis of the HIV-1 genome (a fragment of the pol gene encoding protease, reverse transcriptase and HIV -1 integrase) and DR assessment were carried out on the basis of the Central Scientific Research Institute of Epidemiology of Rospotrebnadzor.

To determine the level of VL, a set of reagents RealBest RNA HIV quantitative (Vector Best, Novosibirsk, RF) was used, to obtain nucleotide sequences (sequences) of the HIV-1 genome, the Amplisens HIV-pol-NGS- test system was used (Central Scientific Research Institute of Epidemiology of Rospotrebnadzor, Moscow, RF) and MiSeq sequencing systems (Illumina, USA). Analysis of the viral genome (determination of the genetic variant of HIV-1 and detection of DR mutations) was carried out using the Mega v.6.0 program and online services HIVBlast, and HIVdb program/

Results. Features of the epidemiology of HIV infection in the Altai Territory in 2022:

In 2022, 1495 new cases of HIV infection were detected in the AT. At the same time, the main age group among these patients was people over 30 years old - 86.9% (Figure 1). The ratio of men to women was 61.8% and 38.2%, respectively.

In 2022, the dominant vulnerable group was individuals infected through sexual contact 82.1%, while IDUs accounted for only 17% of infections. Finally, 0.9% of infections were associated with perinatal mother-to-child transmission of HIV infection.

Social groups with the first diagnosis of HIV infection in 2022 in the Altai Territory were more represented by the non-working population - 70.8%. Employees and workers in industry and agriculture accounted for 27.3% (Figure 2).

Analysis of genetic variants of HIV-1 circulating in the Altai Territory in 2022. The nucleotide sequences of the HIV-1 genome in blood plasma samples obtained from 187 HIV-infected persons diagnosed with HIV infection in

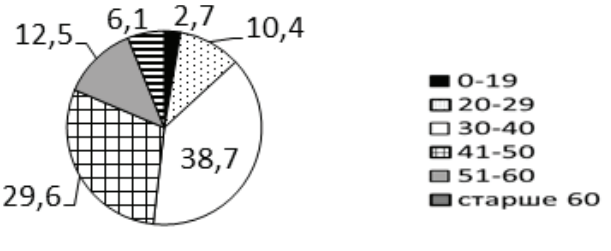

Fig. 1. Age structure of the incidence of HIV infection in 2022 in the Altai Territory (in%)

2022 were analyzed. The average age of patients on the day of sampling was 42 years (from 18 to 72 years). The ratio of men and women was 100 to 87, i.e. 53.5% to 46.5%, respectively. 161 patients (86.1%) were infected through sexual intercourse, the remaining 26 patients (13.9%) were IDUs. Thus, the age and sex composition, as well as belonging to a vulnerable group of examined patients, are close to the average for HIV infection in the Altai Territory in 2022.

The mean VL was 5.95 Log copies/ml (DI95 5.73-6.10) and the CD4 cell concentration was 333 cells/μl (DI95 301-364). The majority of patients (140/187, 74.9%) were at stage 3 HIV infection, 35 patients (18.7%) were at stage 4, and only 12 (6.4%) were at stage 2.

The dominant genetic variant of HIV-1 in the examined sample collection was CRF63_02A6 (127/187, 67.9%). Subsubtype A6 included 59 samples (31.6%) and 1 sample (0.5%) included subtype B virus of the IDU-B genetic variant (Figure 3).

Analysis of primary drug resistance in the Altai Territory in 2022:

For 187 samples, nucleotide sequences of the pol HIV-1 gene region encoding protease (PR) and virus reverse transcriptase (RT) were obtained (positions 2253-3869, relative to reference strain HXB-2, GenBank number K03455). Nucleotide sequences of the pol gene fragment encoding integrase (IN) HIV-1 were also obtained for 181 samples (positions 4230-5096). For another 6, nucleotide sequences of IN were obtained insufficient for reliable analysis of quality or extent. The results of the primary DR analysis for different drug classes are presented in Figure 4.

Fig. 2. The social structure of the incidence of HIV infection in 2022 in the Altai Territory (%)

Resistance to efavirenz (EFV) and nevirapine (NVP) and rilpivirine (RPV) was the most frequently reported. To the last two, was high-level drug resistance. The incidence of resistance to other drugs did not exceed 4%, and DR itself in the overwhelming number of cases was low. Finally, the low incidence of DR for II drugs (0.55% for each drug) was associated with one sample containing V151L replacement.

The frequency of SDRM mutations in the studied sample collection was analyzed(Figure 5).

No SDRM mutations to II drugs were detected. Of the most frequently detected, there was a K103N mutation detected in 7 (3.7%) samples and K103S in 3 (1.6%) samples. Substitutions in this position cause high-level resistance to EFV and NVP. Also, 4 samples contained M41L replacement associated with low-level resistance to zidovudine (AZT). The remaining SDRM mutations did not exceed 1%.

Discussion. The analysis of epidemiological data indicates a continuation of the trends outlined in past years. Despite the fact that the majority of HIV-infected people are men, the proportion of wom-

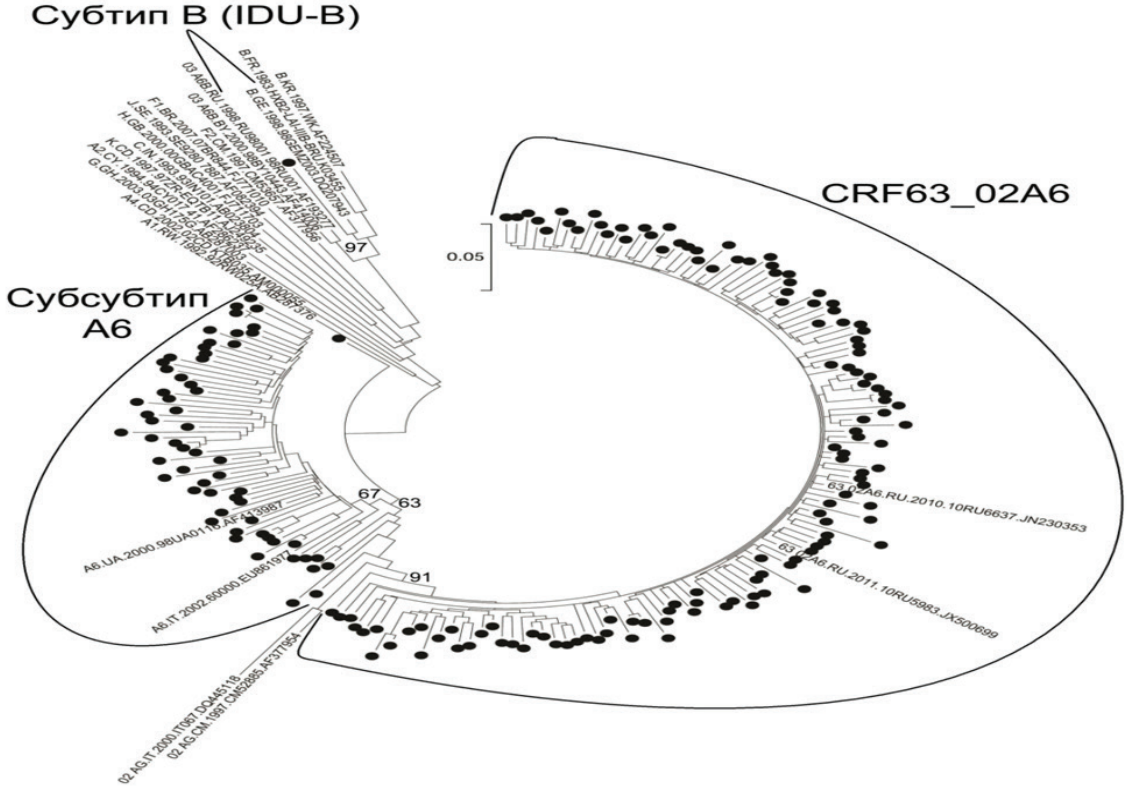

Fig. 3. The result of phylogenetic analysis of 187 nucleotide sequences (PR-RT) of the HIV-1 performed using the maximum likelihood method using the GTR + G + I model of nucleotide substitutions in 500 independent constructions

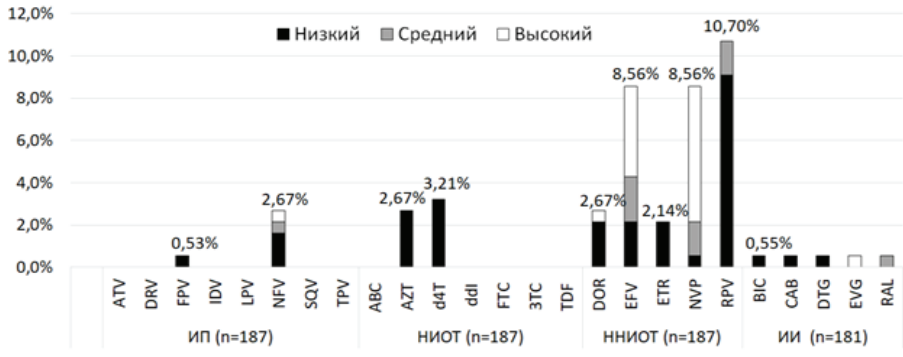

Fig. 4. The structure of primary drug resistance in the Altai Territory in 2022

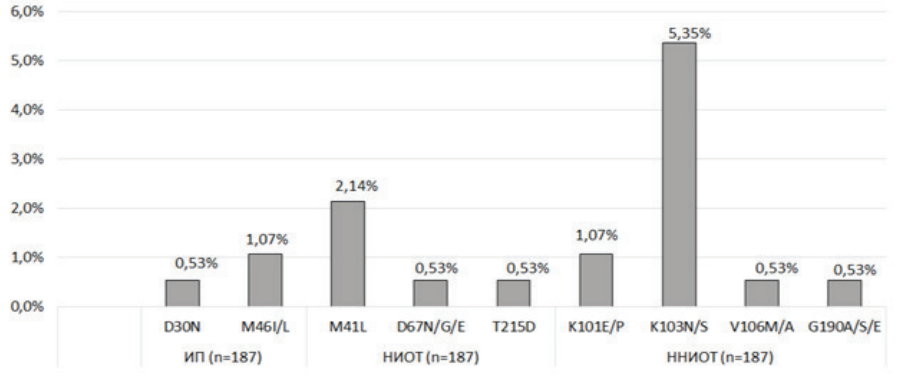

Fig. 5. Frequency of drug resistance mutations from the SDRM list in the AT in 2022

en is steadily growing: from 27.3% and 35% in 2006 and 2014, respectively [14, 15], to more than 38% in 2022. By 2022, the main age group was people over 30 years old (almost 87%), which is more than 1.8 times higher than the same indicator in 2014 [15]. In the AT, a typical trend for Russia in recent years has also been noted towards an increase in the proportion of the sexual route of infection in relation to IDU, which dominated at the end of the last century. However, the fact that more than 70% of HIV-infected people in AT in 2022 were unemployed indirectly speaks to the marginalization of HIV infection in the region. At the same time, the low incidence of HIV infection among students in schools and universities (1.9%) and people under 20 years old (2.7%) indicates the effectiveness of HIV prevention in AT.

The high frequency of infection with the recombinant form of CRF63_02A6 we have identified is typical of Siberia. However, if in 2017 CRF63_02A6 and subsbutype A6 accounted for 45% and 37% of HIV infections, respectively [14], then in 2022 this ratio was 68.1% and 31.4%, respectively. This indicates the further spread of the recombinant form of CRF63_02A6 in AA. At the same time, AT is not characterized by a high genetic diversity of HIV-1. If in 2017 only 3/82 (1.2%) of the sample belonged to subtype B and G [14], then in our collection only one sample (0.5%) belonged to the virus of the genetic variant IDU-B, first identified in Nikolaev (Ukraine) in the early 2000s. and actively circulating in Russia in the past [5, 16, 18].

The high incidence of DR (including a high level) to first-generation NNRTIs identified by us is similar to that identified for Russia as a whole [8, 13,14]. Therefore, the exclusion of these drugs from the basic ART regimens is quite justified for patients in the AT. Meanwhile, the low incidence of DR in other classes of drugs, especially II, indicates the potential high effectiveness of their use.

Conclusion. The HIV epidemic in the Altai Territory generally reflects the main trends in HIV infection in the Russian Federation, including the situation with primary drug resistance. Meanwhile, the features of the genetic diversity of HIV-1 in this territory require further study.

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RATIO OF IMMUNOCOMPETENT CELLS AND NLR INDEX IN MEN OF EXTREME PROFESSIONS (HYDROGRAPHERS) IN THE ARCTIC REGION OF THE RUSSIAN FEDERATION

Rotational shift work in the Arctic region's northern seas has a substantial influence on the physiological condition of the human body and has a high risk of reducing reserve capacities, particularly the immune system. Assessing immune homeostasis by identifying immune balance, specifically the levels of expression of lymphoproliferation and lymphoapoptosis markers that determine the body's susceptibility to diseases, is important for maintaining public health in the Arctic region's extreme climatic and professional environments. The aim of this study is to assess the ratio of lymphocyte phenotypes CD10, CD71, CD95 and the NLR index in men working on rotating shifts in the Arctic. Materials and Methods. The study comprised 65 healthy adults aged 43,2±2,7 years: 45 males working rotating shifts of less than 3 months, 3 to 6 months, and more than 6 months, and 20 male residents (control). The neutrophil-to-lymphocyte ratio (NLR), lymphocytes with the CD10 marker to CD95, and lymphocytes with the CD71 marker to CD95 were estimated. Results. The median neutrophil to lymphocyte ratio (NLR) among rotating shift hydrographers is within the ideal normal range (1-2), regardless of shift duration, as in contrast to permanent residents, whose median NLR is stress-increased (2-3). In rotating shift workers, the CD10/CD95 ratio is balanced between 0.85 and 1.15, with evidence of a relative rise in CD10 expression levels with shift durations of more than 6 months. In 65% of Arctic inhabitants, CD10 expression levels are quite low. The CD71/CD95 ratio is balanced between 0.85 and 1.1, regardless of shift duration or permanent residence in the Arctic region. Conclusions. In the investigated hydrographers, fluctuations in the median NLR and the CD10/95 ratio are associated with the duration of the shift; the median CD71/95 ratio is least susceptible to fluctuations in both rotating shift workers and the control group; the CD71/95 ratio is stable, determines the immune balance of the surveyed, and can be used to assess the immune system's adaptability to Arctic conditions.

Keywords: Arctic, Immune balance, Lymphoproliferation, Lymphopoptosis, Rotational shiftwork, Hydrographers

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Introduction: Professional activity in the Arctic region is associated with significant health risks related not only to the cold climate, poor sanitation, deteriorating water quality, and exposure to pollutants in the environment, but also to professional activities (rotational shift work), which affects both shift workers and the local population [11]. Harsh climatic conditions, including hypoxia and stress, as well as extreme professional working conditions in the Arctic region lead to many health problems, including cardiovascular [1, 5] and bronchopulmonary diseases (regional) [3, 4]. Extreme professional working conditions (rotational shift work), along with the harsh environment in the northern seas, lead to reducing the reserve capacity of immune homeostasis [2, 6].

The neutrophil to lymphocyte ratio (NLR) is an easily available biomarker that demonstrates the balance between the two elements of the immune response, allowing for the assessment of adaptive immunity as well as the diagnosis of acute and chronic inflammation. However, even in the absence of defined cutoff levels, fluctuations in NLR over time might be valuable indicators of immune system failure. There is a substantial and independent link between its levels and an increased risk of mortality from any physiological reason [8, 13, 14]. Neutrophil to lymphocyte ratio (NLR) serves as a valuable biomarker for predicting disease susceptibility by indicating systemic inflammation and potential defects in immune responses [17].

Maintaining a balance between lymphoproliferative and lymphoapoptotic mechanisms is important for preventing autoimmune manifestations and ensuring adequate homeostasis of the immune system. Any disruption of this balance can lead to autoimmune lymphoproliferative syndrome [9], chronic inflammation, and increased vulnerability to infectious diseases. The CD10 receptor is found in a variety of hematopoietic tissues, including human lymphoid progenitors, and plays a critical role in proliferative processes. CD10 expression is required for the production of TGF-β1, deficiency of which is recognized to impede cell proliferation and trigger apoptosis through upregulation of cell cycle inhibitors, including CD95 [12, 15, 18]. Expression of the marker (CD95) leads to proteolytic cleavage of NF-κB, a key transcription factor that promotes cell survival. This cleavage makes T cells more susceptible to apoptotic processes. In turn, NF-κB can modulate the expression of a marker (CD71), which plays an important role in cell proliferation and activation [10, 16].

The aim of the work is to assess the ratio of lymphocyte phenotypes CD10, CD71, CD95 and the NLR index in men working on rotating shifts in the Arctic.

Materials and methods: The study involved 65 practically healthy individuals with an average age of 43,2±2,7 years, of whom 45 were men working on a rotational basis in the northern seas (Barents Sea, White Sea) of the Arkhangelsk region of the hydrographic service of the Northern Fleet of the Russian Federation (ARHS NF RF). The investigated persons were divided into 3 groups depending on the duration of the shift: 14 people with a rotating shift duration of more than 6 months, aged 44,7±2,9 years (95% confidence interval (38,3-51,1)); 11 people with an average rotating shift duration of 3 to 6 months, aged 41,2±2,9 years (95% confidence interval (34,5-48,7)); 20 people with a short rotating shift duration of less than 3 months, aged 43,4±2,4 years (95% confidence interval (38,3-48,5)) [7]. The control group consisted of 20 male permanent inhabitants of the Arctic area of Arkhangelsk, aged 43,1±1,8 years (95% confidence interval (38,4-46,9)). They did not work on a rotating basis. All individuals participated in the study voluntarily; at the time of venous blood sampling, they had no acute or chronic diseases, as determined by the local clinic physician for the control group and the Military Medical Commission of the ARHS SF of the Russian Federation for rotational workers. The ratio of neutrophils to lymphocytes (NLR) using absolute neutrophil and lymphocyte counts. According to (Zahorec, 2021) [19], normal NLR values are in the range of (0.7-3.0), with optimal values in the range of (1.0-2.0), and stress ranges, which serve as an early warning of the possibility of developing a pathological condition or maladaptation, are (0.7-1.0) and (2.0-3.0), the ratio of the process of lymphoproliferation associated with the receptor (CD10) to the process of lymphoapoptosis associated with the receptor (CD95), and the ratio of the process of activation and lymphoproliferation associated with the receptor (CD71) to the process of lymphoapoptosis associated with the receptor (CD95) were determined in peripheral blood. NLR was determined by counting the number of leukocytes in a Goryaev chamber, the percentage of neutrophils and lymphocytes in a stained blood smear according to Romanovsky-Giemsa, then calculating the absolute numbers of neutrophils and lymphocytes. Lymphocyte phenotypes (CD10, CD71, CD95) were determined by indirect immunoperoxidase reaction using monoclonal antibodies on lymphocyte preparations of the "dried drop" type using a peroxidase conjugate and staining with a chromogen solution for analysis in immersion microscopy of labeled cells in the field(s) of vision in a total amount of 500 cells using the laboratory counter C-5. The work was carried out in the Laboratory of Physiology of Immunocompetent Cells, Institute of Physiology of Natural Adaptations of N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences, Arkhangelsk, Russia within the framework of State Assignment No. 122011700267-5. To conduct the study, a conclusion was obtained from the Ethics Committee of the Federal State Budgetary Scientific Institution Federal Research Center of N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences (Protocol No. 4 dated 10.02.2022).

Statistical processing of the results was performed using Microsoft Excel 2016 and SPSS 24.0 for Windows. The median (Me) with a percentile interval of 25–75 (Q1; Q3) was used to indicate the content of the studied indicators, as well as the 95% confidence interval (CI) (lower limit (L) – upper limit (H)) to determine the expected limits of the physiological norm, and the Mann-Whitney criterion was used for comparative analysis between the groups. Differences in the compared indicators were considered reliable at a significance level of $p < 0.05$.

Results and discussion: The median neutrophil to lymphocyte ratio (NLR) in rotating shift workers with shift durations of less than 3 months, 3 to 6 months, and more than 6 months was 1.32 (1.00; 1.77), 1.54 (0.60; 2.96), and 1.19 (0.71; 1.64), respectively (Table), which is within the optimal normal range (1-2) [19]. The values for shift durations of less than 3 months and more than 6 months are significantly lower than in the control group 2.07 (1.69; 2.72) ($p < 0.05$), which is at the stress-increased level (2-3) due to a relatively low lymphocyte count in 50.0% of the investigated males

The frequency of recording high (stress) NLR levels increased from 15.0% for shift durations of less than 3 months to 45.5% for shift durations of 3 to 6 months due to heterogeneous changes in the number of neutrophils and lymphocytes (either a relatively increased number of neutrophils or a relatively decreased number of lymphocytes), which led to an expansion of the 95% confidence interval (1.08–2.54).

Median (Me (Q1; Q3)) and 95% confidence interval (95% CI (L - H)) of immune parameters in hydrographers depending on the duration of the shift

Parameter	Statistical parameter	Rotating shift duration			Control[4] n=20	Significance of the Mann-Whitney criterion
		More than 6 months[1] n=14	From 3 to 6 months[2] n=11	Less than 3 months[3] n=20		
NLR	Me (Q1; Q3)	1.19 (0.71; 1.64)	1.54 (0.60; 2.96)	1.32 (1.00; 1.77)	2.07 (1.69; 2.72)	[1] и [4]. p=0.001 [2] и [4]. p=0.302 [3] и [4]. p=0.003
	95% CI (L - H)	(0.90 – 1.63)	(1.08 – 2.54)	(1.13 – 2.01)	(1.79 – 3.10)	
CD10/CD95	Me (Q1; Q3)	1.00 (0.93; 1.31)	0.94 (0.83; 1.06)	1.02 (0.82; 1.20)	0.58 (0.43; 2.02)	[1] и [4]. p=0.107 [2] и [4]. p=0.173 [3] и [4]. p=0.224
	95% CI (L - H)	(0.90 – 1.42)	(0.85 – 1.07)	(0.85 – 1.14)	(0.61 – 1.77)	
CD71/CD95	Me (Q1; Q3)	0.96 (0.87; 1.07)	0.89 (0.77; 1.00)	1.00 (0.72; 1.18)	1.00 (0.88; 1.18)	[1] и [4]. p=0.551 [2] и [4]. p=0.083 [3] и [4]. p=0.279
	95% CI (L - H)	(0.86 – 1.11)	(0.81 – 0.99)	(0.84 – 1.07)	(0.95 – 1.13)	

The frequency of recording high (stress) NLR levels decreases to 14.3% with a shift duration of more than 6 months due to a relative decrease in the number of neutrophils. It should be assumed that the rotating shift work system in the Arctic region affects the human body through a wide fluctuation in the levels of neutrophils and lymphocytes, thereby maintaining the state of the immune balance, the peak of which is achieved with a shift duration of 3 to 6 months with subsequent recovery with a shift duration of more than 6 months. It was revealed that in rotating shift workers aged 43.5±2.9 years, the neutrophil to lymphocyte ratio (NLR) remains within optimal normal limits, unlike permanent residents of the Arctic region, presumably shift workers have a more labile adaptive immunity, which helps to quickly rebuild and, possibly, shortens the immune response of a healthy person in extreme conditions, which requires additional research.

The median ratio of the lymphoproliferative process associated with (CD10) to lymphocytes apoptosis process associated with (CD95) is 1.02 (0.82; 1.20), 0.94 (0.83; 1.06) and 1.00 (0.93; 1.31) in hydrographers with a shift duration of less than 3 months, from 3 to 6 months, and more than 6 months, respectively, which indicates a practically balanced status regardless of the shift duration, which is obviously higher than that of the control group 0.58 (0.43; 2.02), while the lack of statistical significance is due to the wide range of distribution of these indicators.

Based on the concept of immune balance and the 95% confidence interval of the obtained data, it is reasonable to believe that the optimal CD10/CD95 ratio in practically healthy men ranges from 0.85 to 1.15. It is crucial to highlight that these limitations are broken in the group of permanent inhabitants of the Arctic area, which we believe is related to a relatively low level of CD10 expression in 65% and a significant rise in CD10 expression in 35% of the control group. Along with this, it is worth noting that in hydrographers with a shift duration of more than 6 months, the 95% confidence interval expands (0.90–1.42) due to a relative increase in the level of CD10 expression, which indicates the onset of the development of an adaptive immune response in conditions of rotational long-term shifts in the Arctic region.

The median of the ratio of the process of lymphoproliferation and activation associated with (CD71) to the process of lymphoapoptosis associated with (CD95) is 1.00 (0.72; 1.18), 0.89 (0.77; 1.00), and 0.96 (0.87; 1.07) in hydrographers with a shift duration of less than 3 months, from 3 to 6 months, and more than 6 months, respectively, which does not differ from the median in the control group 1.00 (0.88; 1.18). Thus, it can be assumed that the CD71/CD95 ratio, regardless of the duration of the shift or residence in the Arctic region with the expected normal range from 0.85 to 1.1, according to the 95% confidence interval, is an indicator of stable adaptation.

Therefore, within the cohort of investigated persons, variations in the median neutrophil to lymphocyte ratio (NLR) and the CD10/95 ratio exhibit a correlation with the duration of the rotational shift work; the median CD71/95 ratio demonstrates the least vulnerability to variations in both the shift worker population and the control group; furthermore, the CD71/95 ratio remains stable, serves to define the immune balance of the participants, and may function as an indicator of the adaptability of the immune response to extreme Arctic conditions.

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COMPARATIVE ANALYSIS OF CERVICAL CANCER STATISTICS AND ITS ASSOCIATION WITH HOUSEHOLD INCOME OF THE POPULATION IN THE ARCTIC ZONE OF RUSSIA IN 2016-2022

Taking into account the values of the cervical cancer (CC) statistics in the period 2016-2022 selected for the study - age-standardized incidence and mortality per 100 thousand population, deaths in the first year from the date of diagnosis and the relative quantity of patients registered alive with clinics for 5 years or more, the situation with CC in the State Entities of the Arctic zone of Russia (SE AZRF), with the exception of the Yamalo-Nenets Autonomous Okrug, tends to continue to deteriorate, especially compared to the all-Russian. The growth of the standard of living in Russia and SE AZRF, estimated by the values of per capita money income and its ratio to the subsistence minimum, did not show an association with CC incidence and, unlike Russia as a whole, in SE AZRF is not associated with a significant decrease in CC mortality. The indicators of the standard of living in the six out of nine SE AZRF are positively correlated with the relative quantity of patients registered alive with clinics for 5 years or more. But in three SE AZRF, no association was found between CC indicators and the standard of living. Thus, at the current time, the population living in the TU AZRF continues to be in dire need of increasing the effectiveness of the healthcare system to fight against CC.

Keywords: health disparities, human papillomavirus, ethnic groups, indigenous population, North

Introduction. Cervical cancer (CC) is a largely preventable disease, but, at the same time, it is one of the main causes of women's death in the structure of malignant neoplasms (MN). The highest rates of CC incidence and mortality are observed in low- and middle-income countries [1]. According to the World Bank classification, which is updated annually on July 1, based on the values of gross national income per capita for the previous calendar year, the Russian Federation is currently included in the list of high-income countries [2]. However, the Russian rates of CC incidence and mortality, standardized by age, calculated by the International Agency for Research on Cancer (IARC), are more than 2 times higher than similar indicators in a group of high-income countries. The latest IARC data, calculated for 2022, show CC incidence and mortality rates in Russia to be 17,6 and 6,4 cases per 100 thousand population, respectively; while in the group of high-income countries these same rates are 6,5 and 2,4 cases per 100 thousand population, respectively [3]. Previous studies have shown, that in the state upper-level territorial entities (SE, subjects) of the Russian Federation (RF), whose settlements are fully or partially classified as a part of the Arctic zone (AZRF), the situation for CC incidence and mortality in 2016-2020 was worse than in Russia as a whole [4].

New statistical indicators of cervical cancer in Russia and its regions have now been published for 2021 and 2022. Therefore, the aim of this study was a comparative analysis covering a longer period of time - 2016-2022. In addition to evaluating CC incidence and mortality, two of some main indicators of the quality for medical care for patients with CC were analyzed such as percent rate of deaths from CC in the first year from the date of diagnosis and relative quantity of CC patients registered alive with clinics for 5 years or more [5]. Also the association between these indicators and indicators of the living standard of population has studied. Monitoring disease information is necessary to evaluate decisions implemented in the public healthcare system, to adjust plans for improving their efficiency and to develop new strategies [6].

An increasing sample size is important to achieve greater statistical power and significance, which are more likely to contribute solving the stated objectives [7].

Materials and research methods. Statistical indicators of CC were used as objects of the study, such as incidence and mortality, standardized in accordance with the world population distribution by age and calculated per 100 thousand people (ASIR and ASMR, respectively), percent rate of deaths from CC in the first year from the date of diagnosis (1yDR) and relative quantity of patients registered alive with clinics for 5 years or more (RA5yM). The indicators of the RF and its subjects, which settlements fully or partially belong to the AZRF, were studied: Arkhangelskaya (AO) and Murmanskaya (MO) Oblasts, the Karelia (RKa), the Komi (RKo) and the Sakha (Yakutia) (RS(Ya)) Republics, Krasnoyarski Krai (KK), Nenetski (NAO), Yamalo-Nenetski (YaNAO) and Chukotski (ChAO) Autonomous Okrugs.

An average per capita money annual income of population (PCI) and its ratio to the annual subsistence minimum (PCI/SM) were selected from the indicators of living standard of population.

The source of CC indicators were the books of the Moscow Research Institute of Oncology named after P.A. Herzen - a branch of the Federal State Budgetary Institution "National Medical Research Center of Radiology" of the Ministry of Health of Russia, published in the Internet portal for medical and pharmaceutical workers [8], containing the data of state medical statistics form No. 7. The indicators of living standard of population were extracted from the Internet portal of the Federal State Statistics Service [9].

The time interval for studying the data was 7 years - from 2016 to 2022. The choice of the beginning the period is due to a separation malignant neoplasms' indicators between the NAO and the AO, which occurred only in 2016. Before this time, the indicators of these SEs were combined.

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Table 1

Annual values of CC indicators in RF and SEs AZRF in the period 2016-2022

Subject	Index	2016	2017	2018	2019	2020	2021	2022
1	2	3	4	5	6	7	8	9
RF	ASIR M (95% CI)	15.45 (15.21-15.69)	15.76 (15.51-16.01)	15.80 (15.56-16.04)	15.38 (15.14-15.62)	13.67 (13.43-13.91)	13.6 (13.36-13.84)	13.8 (13.56-14.04)
	ASMR M (95% CI)	5.26 (5.12-5.40)	5.18 (5.04-5.32)	5.07 (4.93-5.21)	5.01 (4.87-5.15)	4.84 (4.70-4.98)	4.57 (4.45-4.69)	4.67 (4.55-4.79)
	1yDR,%	14.6	14.3	13.8	13.5	12.6	11.9	11.9
	RA5yM,%	65.3	65.4	65.9	66.5	66.4	67.5	69.1
NAO	ASIR M (95% CI)	8.01 (0-19.48)	29.37 (8.42-50.32)	31.38 (12.54-50.22)	32.50 (12.14-52.86)	25.15 (1.20-49.10)	20.76 (1.04-40.48)	10.98 (0-23.6)
	ASMR M (95% CI)	0.00 (0.00-0.00)	18.98 (1.40-36.56)	6.53 (0-15.64)	9.53 (0-20.41)	5.39 (0-12.88)	0.00 (0.00-0.00)	6.6 (0-15.75)
	1yDR,%	12.5	0.0	14.3	9.1	0.0	0.0	0.0
	RA5yM,%	68.2	66.7	54.7	52.5	55.4	53.5	55.7
AO	ASIR M (95% CI)	18.32 (15.13-21.51)	17.78 (14.70-20.86)	23.69 (20.06-27.32)	28.85 (24.60-33.10)	15.16 (12.30-18.02)	17.09 (14.03-20.15)	18.58 (15.09-22.07)
	ASMR M (95% CI)	7.22 (5.30-9.14)	4.05 (2.70-5.40)	3.81 (2.44-5.18)	5.08 (3.43-6.73)	4.94 (3.43-6.45)	5.81 (4.07-7.55)	4.62 (3.05-6.19)
	1yDR,%	11.4	15.2	17.7	9.8	8.2	15.2	11.5
	RA5yM,%	68.2	69.3	67.0	66.6	67.0	66.8	67.1
MO	ASIR M (95% CI)	16.26 (12.93-19.59)	17.73 (13.77-21.69)	20.76 (16.96-24.56)	17.00 (13.45-20.55)	13.57 (10.43-16.71)	12.75 (9.71-15.79)	13.66 (10.19-17.13)
	ASMR M (95% CI)	6.83 (4.65-9.01)	7.09 (4.82-9.36)	5.21 (3.43-6.99)	7.35 (5.04-9.66)	3.84 (2.13-5.55)	5.11 (3.21-7.01)	5.08 (3.16-7.00)
	1yDR,%	11.7	18.1	20.5	12.6	10.2	9.6	13.4
	RA5yM,%	62.3	60.3	59.1	61.9	64.2	65.8	69.1
RKa	ASIR M (95% CI)	22.58 (17.64-27.52)	19.94 (15.47-24.21)	20.06 (15.69-24.43)	14.64 (11.13-18.15)	13.26 (9.59-16.93)	13.04 (9.63-16.45)	16.34 (12.13-20.55)
	ASMR M (95% CI)	5.06 (2.98-7.14)	5.60 (3.48-7.72)	5.56 (3.38-7.74)	4.90 (3.02-6.78)	5.60 (3.48-7.72)	6.09 (3.91-8.27)	5.92 (3.65-8.19)
	1yDR,%	9.4	13.5	11.8	11.6	11.8	16.1	14.8
	RA5yM,%	69.5	70.8	72.1	75.6	78.5	81.0	82.7
RKo	ASIR M (95% CI)	17.13 (13.76-20.50)	23.50 (19.50-27.50)	16.77 (13.26-20.28)	17.75 (14.30-21.20)	12.10 (9.20-15.00)	16.53 (13.22-19.84)	17.37 (13.55-21.19)
	ASMR M (95% CI)	6.84 (4.80-8.88)	4.89 (3.15-6.63)	5.59 (3.79-7.39)	6.01 (4.05-7.97)	5.35 (3.57-7.13)	6.76 (4.66-8.86)	6.44 (4.38-8.50)
	1yDR,%	9.4	13.6	8.6	14.4	11.6	15.1	11.3
	RA5yM,%	69.9	68.9	71.0	72.8	74.8	77.7	80
YaNAO	ASIR M (95% CI)	20.39 (15.31-25.47)	15.96 (10.88-21.04)	12.53 (17.87-25.27)	12.69 (8.95-16.43)	12.21 (8.37-16.05)	15.25 (11.23-19.27)	17.06 (12.55-21.57)
	ASMR M (95% CI)	5.64 (2.92-8.36)	4.13 (1.88-6.38)	4.43 (1.39-7.47)	4.03 (1.25-6.81)	5.22 (2.77-7.67)	2.76 (1.05-4.47)	4.35 (2.10-6.60)
	1yDR,%	8.8	9.7	6.3	11.6	10.6	7.0	5.9
	RA5yM,%	66.6	68.6	68.1	69.8	70.5	68.6	70.7

End of table. 1

1	2	3	4	5	6	7	8	9
KK	ASIR M (95% CI)	18.90 (16.96-20.84)	21.06 (19.04-23.08)	21.49 (19.47-23.51)	21.03 (18.99-23.07)	19.71 (17.75-21.67)	18.09 (16.19-19.99)	18.91 (17.01-20.81)
	ASMR M (95% CI)	6.61 (5.51-7.71)	6.80 (5.68-7.92)	6.40 (5.32-7.48)	6.21 (5.15-7.27)	6.06 (4.98-7.14)	6.15 (5.11-7.19)	6.22 (5.18-7.26)
	1yDR,%	14.7	13.9	13.7	13.5	12.6	12.4	12.3
	RA5yM,%	63.4	63.1	65.4	66.0	66.2	66.4	66.2
ChAO	ASIR M (95% CI)	21.30 (6.36-36.24)	13.11 (1.51-24.71)	9.01 (0-19.20)	11.28 (0.23-22.33)	11.76 (0-25.89)	8.06 (0-19.29)	24.93 (0-53.19)
	ASMR M (95% CI)	19.07 (3.66-34.48)	3.11 (0-9.21)	4.78 (0-11.46)	5.51 (0-13.15)	6.07 (0-14.48)	12.25 (0-26.77)	6.8 (0-16.54)
	1yDR,%	37.5	25.0	60.0	0.0	0.0	100.0	50
	RA5yM,%	50.0	60.0	69.8	73.3	67.4	78.9	74.4
RS(Ya)	ASIR M (95% CI)	22.85 (19.05-26.65)	20.20 (16.63-23.77)	21.57 (17.87-25.27)	18.38 (14.95-21.81)	16.43 (13.22-19.64)	19.56 (16.15-22.97)	18.57 (15.24-21.90)
	ASMR M (95% CI)	6.84 (4.74-8.94)	6.11 (4.13-8.09)	4.61 (2.96-6.26)	5.49 (3.67-7.31)	4.15 (2.58-5.72)	3.54 (2.13-4.95)	6.22 (4.36-8.08)
	1yDR,%	6.8	13.6	10.4	7.6	9.6	5.8	6.3
	RA5yM,%	54.7	53.7	53.8	57.0	57.0	57.2	59.4

Note. The abbreviations are explained in the text of the article. CI - confidence interval, M-average meaning.

Cancer localization is C53, according to the International Classification of Diseases (ICD, International Classification of Diseases, version 2010).

To detect differences in variables that have a normal distribution, the T-test was used. For rest of, the Friedman two-factor rank analysis for multiple samples and the Wilcoxon signed-rank test for paired samples were used. To establish an association between the values of two normally distributed variables, the Pearson coefficient (r) was chosen, and for the rest the Spearman coefficient (rho) was chosen.

Differences and associations were considered significant at $p<0.05$.

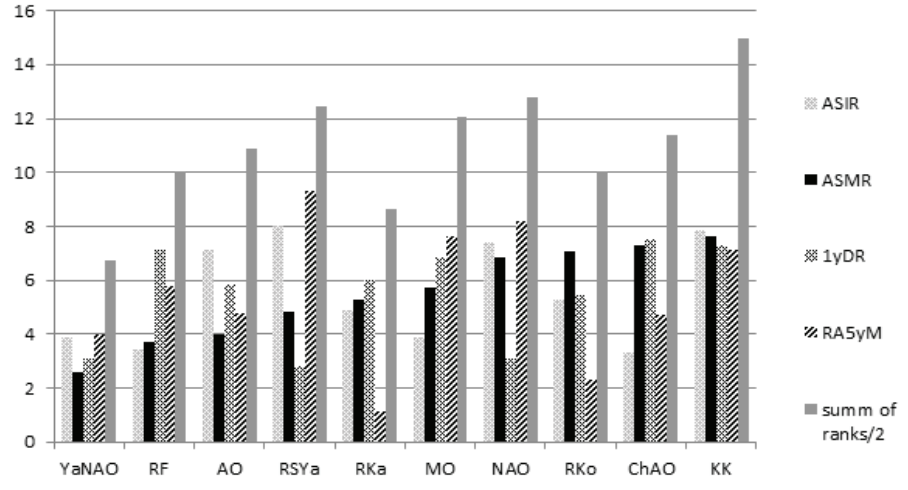
Results and their discussion. The analysis of CC indicators - ASIR, ASMR, 1yDR and RA5yM using the one-sample Kolmogorov-Smirnov criterion showed that their distribution does not correspond to normal ($0.997 \geq p \geq 0.330$) in all SEs of the AZRF and in the RF in the period 2016-2022. Annual values of CC indicators are presented in Table 1. Two-factor Friedman rank analysis revealed the presence of significant differences between these indicators depending on SE: for the ranks of ASIR, the differences have p=0.003, for ASMR - p=0.016, for 1yDR - p=0.004, for RA5yM - p=0.000. The ranks of CC indicators depending on the SE are shown in Figure1, the display has compiled in order of increasing values of ASMR ranks. Despite the fact that the 1yDR and the RA5yM indicators are used as indicators for evaluating the quality of oncological care, their values also depend on the quality of patient monitoring, the recording of deceased and withdrawn patients, as well as the timeliness of deregistration [5], and the rates of CC incidence may be associated with the quality of screening activities [10]. Therefore, in order to form a more clear vision of situation with CC in the SEs of Russia, whose territories classified as a part of the AZRF, CC ASMR was selected.

The CC incidence rates in almost all territories of the AZRF, with the exception of the ChAO, exceeded the all-Russian level. The highest rank of ASIR was observed in the RS(Ya), the lowest – in the ChAO. Mortality rates, as well as, incidence rates of cervical cancer, in almost all SE AZRF, with the exception of one region - in this case, the Yamalo-Nenets Autonomous Okrug, exceeded the all-Russian level. The highest rank of the ASMR was noted in the KK, the lowest – in the YaNAO. The 1yDR indicator had the highest level in the ChAO, the lowest – in the RS(Ya). Only in two regions – KK and the ChAO values were worse than the all-Russian ones. The ranking of another indicator for assessing the quality of oncological care - RA5yM, in which a higher value was assigned a lower rank, showed that in four regions, such as KK, MO, NAO and RS(Ya), values were worse than the all-Russian indicator. The worst values of RA5yM indicator were in RS(Ya), the best – in RKa.

If in 2020, compared to 2016, CC incidence in four SEs AZRF, such as RKa, RKo, RS(Ya) and YaNAO, as well as in Russia as a whole, significantly decreased [5], then in 2022, in contrast to the all-Russian indicator (T-test, $p<0.05$), there did not occur a significant decreasing the incidence compared to 2016 in all SEs AZRF. About similar picture observed in the analysis of mortality rates from CC: if in 2020, compared to 2016, in two SE AZRF - MO and RS(Ya), as well in Russia as a whole, they significantly decreased, then in 2022 only the all-Russian ASMR showed a significant decrease compared to 2016 (T-test, $p<0.05$).

A decrease the 1yDR indicator in 2022 compared to 2016, accompanied by rising the proportion of patients registered for 5 years or more (the RA5yM indicator), has observed in Russia as a whole, and only in three SEs of the AZRF - YaNAO, KK and RS(Ya) (Table 1).

Taking into account the set of values of the CC indicators selected for the study, it is noticeable, that in the eight of nine territorial units of the AZRF, with the exception of the YaNAO, the situation with CC is worse than in Russia as a whole in the period 2016-2022 (Fig. 1).



The ranks of CC indicators depending on the SE AZRF

The values of population' standard of living indicators included in the study, in Russia as a whole and in SEs of the AZRF in 2016-2022, PCI and PCI/SM have presented in Table 2. It is noticeable that during this period of time, the standard of living indicators rose. To determine their association with the indicators of cervical cancer, the Spearman correlation coefficient was calculated, the results of which are shown in Table 3. The analysis showed that there are no statistically significant associations between the CC incidence (ASIR) and PCI, as well as with PCI/SM. Mortality rates (ASMR) from CC are associated with the PCI and PCI/SM only at the all-Russian level - that is, the income growth of the Russian population is interrelated with decreasing CC mortality, but a similar association has not been observed in any subject of the AZRF. The 1yDR indicator is correlated only with PCI and only in the KK. The RA5yM indicator showed a greater number of links: with PCI and PCI/SM in the RKa, the RKo and the RS(Ya), and only with PCI - in the YaNAO, KK and the ChAO. None of the indicators of CC had a significant association with the standard of living of population in the NAO, the AO and the MO.

Of course, the delayed impact of an increase the standard of living on the improvement in CC incidence and mortality rates in the AZRF cannot be expelled, but one also cannot ignore the influence of the environment on CC incidence and mortality rates.

Quite often, environmental damage results from economic processes increasing living standards without taking into account ecological costs. It has also been established, that the CC incidence and mortality may be associated with social-demographic factors [11]. Using the example of skin cancer [12], which like CC, is caused by a human papillomavirus, a connection CC incidence and mortality with climatic and geographical features is not excluded. All this and much more is the subject of further research. At present, it is clear that the all SEs AZRF continue to be in dire need of preventive measures to combat CC, including immunization against the human papillomavirus, screening using modern methods, adjusting plans and developing new strategies for greater efficacy in early CC detection and treatment.

Conclusion. Thus, taking into account the values of the ASMR in combination with the values of the ASIR, 1yDR and RA5yM the CC situation has a tendency to continue deteriorate in the subjects of the AZRF, except for the YaNAO, in the period 2016-2022, especially as compared with the all-Russian indicators. A raise in standard of living in the AZRF, assessed by the PCI and PCI/SM, did not show a relationship with the CC incidence, and unlike in Russia as a whole, is not associated with significant decreasing of CC mortality. In three of the nine SEs, there is no one of the CC statistical indicators was associated with standard of living. In the remaining six SE AZRF, CC indicators are positively correlated mainly with the specific number of patients registered for clinic care for 5 years or more. At present, the population living in the AZRF continues to be in dire need of improving the effectiveness of existing and developing new approaches in the healthcare system for the CC prevention, eradication and control.

Table 2

The values of population' standard of living indicators in RF and in SEs AZRF in 2016-2022

		2016	2017	2018	2019	2020	2021	2022
RF	PCI	30 717	31 714	33 138	35 233	35 934	39 934	47 386
	PCI/SM	312.5	314.4	322.1	323.5	317.7	342.7	340.4
NAO	PCI	73 852	76 115	82 451	85 633	89 570	92 620	115 336
	PCI/SM	379.5	366.1	402.4	428.3	410.0	416.8	453.7
AO	PCI	31 201	32 381	34 133	36 377	37 728	41 307	49 347
	PCI/SM	255.4	276.8	287.9	286.3	281.1	298.1	305.6
MO	PCI	27 911	29 654	31 965	34 244	36 504	39 929	46 019
	PCI/SM	285.0	289.9	302.1	281.1	283.0	298.0	295.3
RKa	PCI	33 118	34 001	36 243	37 913	39 601	42 603	50 840
	PCI/SM	230.7	236.7	248.5	250.9	257.7	276.0	277.0
PKo	PCI	38 936	41 247	44 019	47 218	50 139	55 506	65 707
	PCI/SM	273.4	274.1	283.7	276.6	276.2	292.5	300.7
YaNAO	PCI	75 414	79 805	84 067	89 655	96 553	104 323	120 010
	PCI/SM	474.0	497.9	528.6	549.4	583.7	612.6	605.1
KK	PCI	27 851	28 777	29 972	31 694	32 801	36 004	43 183
	PCI/SM	253.4	253.6	257.4	254.0	251.3	268.5	279.5
ChAO	PCI	69 211	74 940	81 206	86 234	92 980	104 178	138 161
	PCI/SM	383.0	371.1	376.6	388.2	397.1	431.1	435.3
RS(Ya)	PCI	38 737	40 404	42 711	45 315	46 108	50 090	59 040
	PCI/SM	241.3	244.1	258.7	263.7	259.8	272.7	280.9

Note. The abbreviations are explained in the text of the article. PCI measured in rubles per month

Table 3

The values of Spearman correlation coefficient (rho) between CC indicators and the standard of living indicators in RF and in SEs AZRF in 2016-2022

		ASIR	ASMR	1yDR	RA5yM
RF	rho with PCI	-0.750	-0.964**	-0.991**	0.964**
	p	0.052	0.000	0.000	0.000
	rho with PCI/SM	-0.571	-0.893**	-0.883**	0.929**
	p	0.180	0.007	0.008	0.003
NAO	rho with PCI	-0.107	-0.054	-0.591	-0.464
	p	0.819	0.908	0.162	0.294
	rho with PCI/SM	0.000	0.018	-0.256	-0.571
	p	1.000	0.969	0.579	0.180
AO	rho with PCI	-0.143	-0.036	-0.108	-0.468
	p	0.760	0.939	0.818	0.289
	rho with PCI/SM	0.214	-0.250	0.324	-0.468
	p	0.645	0.589	0.478	0.289
MO	rho with PCI	-0.643	-0.643	-0.321	0.750
	p	0.119	0.119	0.482	0.052
	rho with PCI/SM	0.107	-0.286	0.321	-0.036
	p	0.819	0.535	0.482	0.939
RKa	rho with PCI	-0.750	0.667	0.685	1.000**
	p	0.052	0.102	0.090	0.000
	rho with PCI/SM	-0.750	0.667	0.685	1.000**
	p	0.052	0.102	0.090	0.000
PKo	rho with PCI	-0.321	0.107	0.357	0.964**
	p	0.482	0.819	0.432	0.000
	rho with PCI/SM	-0.179	0.179	0.143	0.821*
	p	0.702	0.702	0.760	0.023
YaNAO	rho with PCI	-0.214	-0.429	-0.321	0.793*
	p	0.645	0.337	0.482	0.033
	rho with PCI/SM	-0.464	-0.536	-0.250	0.667
	p	0.294	0.215	0.589	0.102
KK	rho with PCI	-0.357	-0.714	-1.000**	0.901**
	p	0.432	0.071	0.000	0.006
	rho with PCI/SM	-0.143	-0.036	-0.607	0.432
	p	0.760	0.939	0.148	0.333
ChAO	rho with PCI	-0.107	0.214	0.234	0.857*
	p	0.819	0.645	0.613	0.014
	rho with PCI/SM	-0.107	0.607	0.198	0.714
	p	0.819	0.148	0.670	0.071
RSYa	rho with PCI	-0.679	-0.429	-0.571	0.883**
	p	0.094	0.337	0.180	0.008
	rho with PCI/SM	-0.321	-0.357	-0.607	0.883**
	p	0.482	0.432	0.148	0.008

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POSTOPERATIVE COGNITIVE DYSFUNCTION: DEFINITION, CLASSIFICATION AND RISK FACTORS

One of the common and current adverse events following surgery is postoperative cognitive dysfunction (POCD). At the same time, there are no unified temporal and clinical criteria for its classification, and approaches to diagnosis and treatment are predominantly empirical. Based on a literature review, the leading risk factors for the development of both postoperative delirium (POD) and POCD itself have been identified, and factors that can reduce the likelihood of cognitive impairment after surgery have been highlighted. The pathophysiological mechanisms contributing to the development of POCD are discussed. The authors have established that POCD and POD are significant clinical problems requiring interdisciplinary efforts and a comprehensive approach to diagnosis, treatment, and prevention.

Keywords: postoperative cognitive dysfunction, postoperative delirium, surgery, anesthetics, cognitive impairment, dementia.

Introduction. According to Rosstat, in 2022, 9,446 thousand surgical interventions were performed in hospitals and 5,360 thousand operations in outpatient clinics in Russia [1]. Given the projected increase in the proportion of elderly and senile people both in the world and in Russia, it can be assumed that the number of operations performed will increase. One of the common and current adverse events following surgery is postoperative cognitive dysfunction (POCD) — a cognitive impairment that includes memory loss, attention deficit, executive dysfunction, and other cognitive changes occurring in both the early and late postoperative periods [43]. POCD is associated not only with medical but also with economic consequences. Thus, people with POCD have longer hospital stays, especially in intensive care units, are more likely to leave work, and have an increased risk of death within 1 year after surgery [8].

The purpose of this paper is to provide a comprehensive review of POCD, including its definition, classification, and consideration of risk factors, as well as prevention and treatment methods.

Definition and Classification. Literature review shows that there is no universally accepted classification for Postoperative Cognitive Dysfunction (POCD). Brodier E. and Cibelli M. propose a provisional classification of POCD: 1) postoperative delirium (up to 7 days); 2) prolonged neurocognitive recovery (up to 30 days); 3) postoperative neurocognitive disorder (up to 12 months) [12].

At the same time, many articles that will be referenced in this paper distinguish only postoperative delirium (POD) and POCD. The most comprehensive definition of POCD is provided in a 2024 article by Varpaei H. and colleagues based on a critical literature analysis: 1) manifestation following the acute phase (4-6 weeks); 2) subtle to extensive cognitive charge; 3) affects single or multiple cognitive domains; 4) reversible nature; 5) duration from several days to several years. They also emphasize that POD is an acute state of fluctuating and altered consciousness caused by internal and/or external factors, including acute confusion and disorientation post-surgery, and requiring immediate medical attention. While POCD involves dysfunction of memory and executive functions, POD leads to dysfunction of attention and consciousness [31].

It is possible that POD and POCD are components of a single continuum and are closely interconnected. POD is a risk factor for the development of cognitive impairments and dementia in the future, at least in elderly patients. For instance, Bickel H. and colleagues found that among patients aged 60 and older who underwent hip surgery, the occurrence of delirium increased the likelihood of persistent cognitive impairments (OR = 41.2; 95% CI: 4.3–396.2) and the need for long-term care (OR = 5.6; 95% CI: 1.6–19.7) [23].

Prevalence. A large-scale study on cognitive impairments following surgical intervention was conducted in China. A total of 8,783 patients were selected for the assessment of subjective cognitive impairments, and 5,700 patients were assessed for short-term memory. Cognitive function was evaluated at 1, 3, 6, and 12 months postoperatively using the AD8 scale and the 3-Word Recall Test (TRT). The authors found that after non-cardiac surgeries, the frequency of abnormalities according to the AD8 scale increased from 2.2% at 7 days to 17.1% at 6 months, and then remained stable. The TRT revealed a U-shaped pattern in short-term memory changes, with the most pronounced impairments observed at 7 days (in 38.9% of patients) and 12 months (in 49% of patients). Patients who underwent cardiac surgery exhibited similar patterns but with slightly more pronounced impairments. The authors also identified factors associated with aggressive cognitive decline following non-cardiac surgeries, specifically: 1) sleep disturbances with a Pittsburgh Sleep Quality Index index ≥ 16; 2) stay in the intensive care unit for 2 days or longer; 3) preoperative symptoms of depression [34].

Gruber-Baldini A. and colleagues conducted a study involving 674 patients aged 65 and older with hip fractures. By reviewing medical records and using the MMSE scale, the researchers identified a group of 486 individuals without cognitive impairment prior to surgery. Postoperatively, 149 patients (30%) developed cognitive impairments, which persisted in 40% of cases for at least 1 year [14].

Postoperative Delirium (POD) can develop in 4% to 53% of elderly patients following hip surgery. Delirium is not only a risk factor for the future development of dementia but also an independent risk factor for hospital mortality [39, 40].

Risk Factors. POCD is a multifactorial condition.

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Age. Age is one of the key risk factors for the development of POCD. A longitudinal study involving 1,064 patients aged 18 and older, who underwent neuropsychological testing before surgery, at hospital discharge, and 3 months postoperatively, showed that POCD was present in 36.6% of young adults, 30.4% of middle-aged patients, and 41.4% of elderly patients at hospital discharge. After 3 months, POCD was detected in only 5.7% of young adults, 5.6% of middle-aged patients, and 12.7% of elderly patients. The authors identified advanced age, lower education level, and the presence of cerebrovascular diseases without residual deficits as risk factors for the development of POCD [35]. POD is also associated with patient age. The frequency of delirium increased by 12% for every 10-year increase in age, reaching 22.2% in patients aged 65-75 years, 36% in patients aged 75-85 years, and 48.2% in patients aged 85-95 years [40].

According to Shnayder N.A., the prevalence of POCD in young patients with an unremarkable psychiatric and neurological history after upper and lower limb surgery under general anesthesia was 12.8% (95% CI: 10.6-14.9%) [6].

Type of Surgery. POCD is most associated with cardiac surgeries. A meta-analysis involving 91,829 patients showed that after coronary artery bypass grafting (CABG), cognitive impairments were observed in 43% of patients within 4 days postoperatively, in 39% within 1 month, in 25% within 4 months, and in 19% within 6 months. One year after CABG, the prevalence of cognitive impairments was 25%, and within 5 years, it increased to 40%. According to the same study, POD was identified in 18% of patients following CABG [15]. Another study found that the risk of POCD within 1-2 weeks was higher with traditional CABG compared to off-pump CABG (OR = 1.54 [95% CI 1.04, 2.27]) [13].

After non-cardiac surgeries, POCD is identified in 11.7% (95% CI: 10.9-12.5) of patients after 3 months, which is significantly lower than in cardiac surgeries [30]. Bordovsky S.P. and colleagues assessed the impact of spinal surgery under anesthesia on cognitive function in 20 middle-aged patients. Their results showed that 15% of patients developed POCD [3].

Scientists from the S.M. Kirov Military Medical Academy (Russia) propose to distinguish pathogenetic variants of brain damage during cardiac surgery: perioperative cerebral stroke, symptomatic delirium of the early postoperative period, and delayed cognitive impairment. According to their data, postoperative cerebral dysfunction generally occurs in 44% of patients and more often when using artificial circulation than during operations on a beating heart [2].

Type of Anesthesia. A systematic review that included 7 RCTs showed that the chance of developing POCD was higher in the general anesthesia group on the 1st and 3rd days postoperatively (OR = 3.86 [95% CI: 1.18-12.58] and OR = 2.0 [95% CI: 1.11-3.58], respectively). However, by the 7th day postoperatively and 3 months later, the relative odds of developing POCD did not differ based on the type of anesthesia [20].

A meta-analysis including 26 RCTs found no difference in the development of POCD in patients undergoing non-cardiac surgery depending on the type of anesthesia (general or regional). The author concluded that the results do not support the concept that general anesthesia agents can cause brain damage after a single exposure [22].

A Cochrane review compared the development of POCD in non-cardiac surgical patients over 60 years of age who received inhalational anesthesia with sevoflurane, desflurane, isoflurane, or halothane, versus total intravenous anesthesia (TIVA) with propofol. The review found no evidence of differences in the incidence of POD, the risk of death within 30 days, or the length of hospital stay depending on the type of anesthetic agents. However, the authors found weak evidence that TIVA with propofol may reduce the likelihood of POCD (OR = 0.52; 95% CI: 0.31-0.87) [26].

Neurophysiological studies are used to monitor the depth of anesthesia. It has been reported that bispectral index (BIS) monitoring can reduce propofol administration by 21% and inhalational anesthetics by up to 30%. In the postoperative period, the monitoring group experienced less frequent development of delirium (15.6% vs. 24.1%) and POCD at 3 months (10.2% vs. 14.7%) [11]. However, a meta-analysis based on 4 high-quality studies did not reveal a significant correlation between the depth of anesthesia and the development of POCD [46].

According to a meta-analysis, there is weak evidence of the protective effect of ketamine on the development of POCD (RR = 0.34, 95% CI [0.15, 0.73]), while there is no data on its effect on the development of delirium [25]. Dexmedetomidine, according to a meta-analysis, increases MMSE scores on the first postoperative day (SMD = 2.73, 95% CI: 1.33–4.12) and reduces the incidence of POCD (OR = 0.49; 95% CI: 0.39–0.63) [19].

Education Level. A systematic review and meta-analysis of 15 studies involving 5,104 patients confirms that a higher level of education reduces the risk of POCD. Each additional year of education was associated with a 10% reduction in risk. A categorical analysis revealed that individuals with secondary education were more likely to develop POCD compared to those with higher education (OR = 1.71; 95% CI: 1.30-2.25) [16].

Comorbid Conditions. Metabolic disorders can also increase the risk of developing POCD. Fayncol I. and colleagues studied the association between metabolic disorders and the risk of developing POD and POCD in elderly patients. The study included 765 participants, of whom 19.5% developed POD and 10.1% developed POCD. In patients with metabolic syndrome, the overall risk of POCD was 1.85 times higher (95% CI: 1.26–2.70). Each 1 mmol/L increase in HDL levels reduced the risk of POCD (RR = 0.47; 95% CI: 0.3-0.74), while each 1 kg/m² increase in body mass index (BMI) increased the risk of POCD by 1.09 times (95% CI: 1.02-1.16) [29].

A meta-analysis including seven studies and covering 2,673 patients showed that preoperative vitamin D deficiency increased the relative risk of developing POCD and POD by 1.54 times (95% CI: 1.21-1.97) [10].

Alcohol abuse in elderly patients poses a risk for POCD, particularly as these patients demonstrated poorer performance in visuospatial and executive function assessments [32].

Diabetes was associated with a 1.84-fold (95% CI: 1.14-2.97) increase in the likelihood of POCD according to three RCTs. At the same time, arterial hypertension and obesity were not associated with POCD [18].

Preexisting Cognitive Impairments. The presence of cognitive impairments before surgery can also increase the risk of developing POCD. Silbert B. and colleagues studied 300 patients scheduled for hip replacement surgery. All patients underwent a battery of eight neuropsychological tests before surgery, and at 7 days, 3 months, and 12 months postoperatively. Preoperative cognitive status, defined as a decline of more than 2 standard deviations in two or more neuropsychological tests, was classified as preexisting cognitive impairment (PreCI). POCD was identified in 25.3%, 14.9%, and 9.4% of patients with PreCI at 7 days, 3 months, and 12 months, respectively, whereas the corresponding rates

in patients without PreCI were 13.3%, 7.1%, and 1.1%, respectively. Using logistic regression, the authors found that the relative risk of developing POCD at 3 months increased by 2.41 times (95% CI: 1.06-5.49) in the presence of PreCI [36].

The risk of POD also increases in patients with preexisting cognitive impairment (OR = 2.53; 95% CI: 1.52-4.21). Postoperative delirium developed in 8.7% of patients with preexisting mild cognitive impairment or dementia, compared to only 2.6% of patients without cognitive impairment [33].

Pain. Morrison R. and colleagues conducted a prospective cohort study involving 541 patients with hip fractures. A high risk of developing POD was identified in patients who received less than 10 mg per day of morphine sulfate equivalents compared to those who received higher doses of analgesics (RR = 5.4, 95% CI: 2.4–12.3). This risk was higher than in patients with preexisting cognitive impairments (RR = 3.6; 95% CI: 1.8–7.2), abnormal blood pressure (RR = 2.3; 95% CI: 1.2–4.7), and heart failure (RR = 2.9; 95% CI: 1.6–5.3) [37]. Liu X. and colleagues also reported that a pain level of ≥ 4 on the Visual Analog Scale (VAS) is associated with the development of POD [40]. According to Shah B.N. and colleagues, optimizing perioperative pain management using various anesthesia techniques can reduce the incidence of POD from 62% to 5% [5].

Laboratory Markers. Several factors have been associated with POD. High preoperative and postoperative erythrocyte sedimentation rates and preoperative lactate levels were linked to a higher incidence of delirium [39]. According to the same study, delirium development was not influenced by levels of C-reactive protein, postoperative lactate, PaO2, PaCO2, glucose, or hemoglobin. However, two other studies found that high preoperative levels of C-reactive protein were strongly associated with the development of delirium [24, 28].

Brain Volume. A systematic review including RCTs with 269 surgical patients, 36 control group patients, and 55 healthy individuals provided weak evidence that reduced thalamic and hippocampal volumes and decreased cerebral blood flow may be associated with POCD, while preoperative and postoperative white matter pathology (leukoaraiosis, lacunes) may be linked to POD [21].

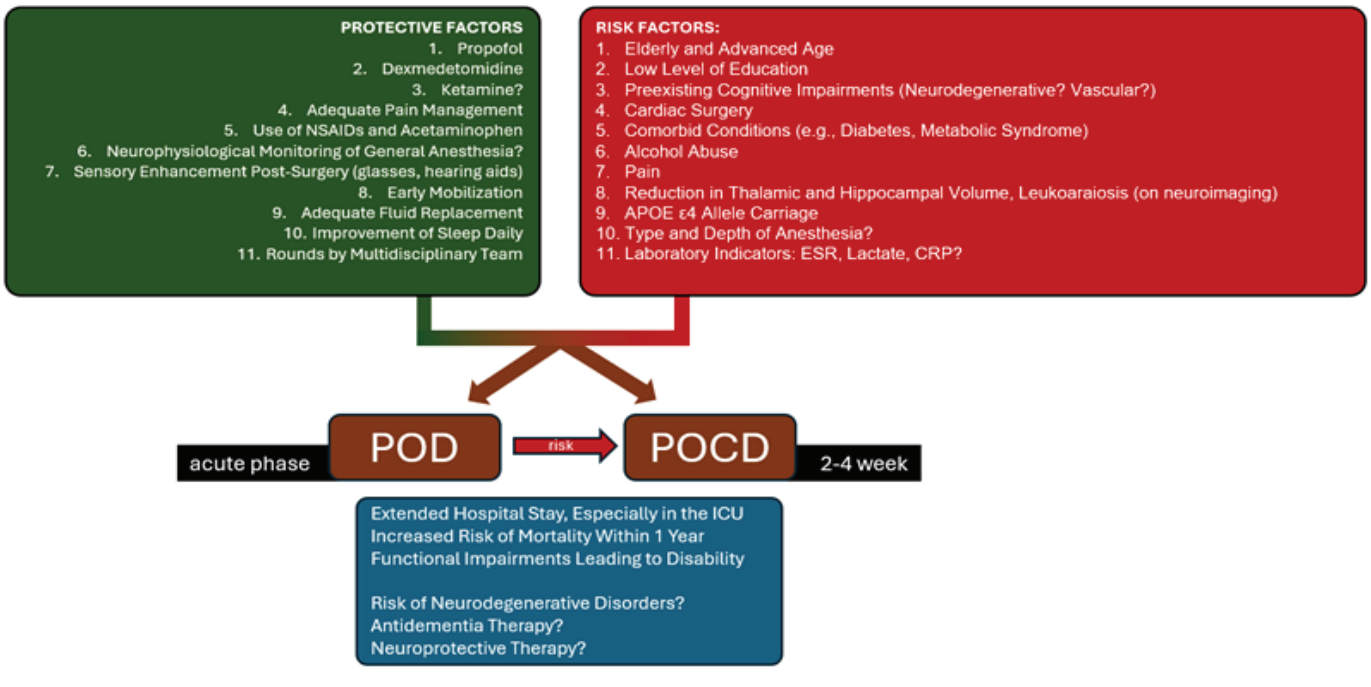
Genetic Factors. Genetic factors related to POCD are not well-studied. We found one study indicating more pronounced cognitive decline in men carrying the ε4 allele of the APOE gene [42]. It is well-known that carrying the ε4 allele of the APOE gene is also a risk factor for developing Alzheimer's disease, the most common neurodegenerative disorder [7].

NSAIDs and paracetamol. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol may reduce the risk of POD not only by alleviating pain but also possibly by reducing neuroinflammation. A retrospective cohort study involving over 1.5 million individuals showed lower odds of developing delirium with NSAIDs (OR = 0.85; 95% CI: 0.7-0.93) and COX-2 inhibitors (OR = 0.82; 95% CI: 0.77-0.89) [41].

The pathophysiology of POCD and POD remains unclear. However, it has been established that following general anesthesia and surgery, specific biomarkers of neuronal damage—such as light neurofilaments and tau protein—are detected in the blood plasma [9]. In patients who developed POD, a low level of Aβ42 in cerebrospinal fluid, a biomarker associated with Alzheimer's disease, was also identified [17]. Experimental data suggest that anesthetics may affect the blood-brain barrier, lead to endothelial inflammation, and subsequently cause neuroinflammation with the release of pro-inflammatory mediators (cytokines, chemokines, etc.) and activation of systemic immune competent cells [44]. This latter hypothesis might also explain the reduced risk of developing POD with the use of NSAIDs.

Diagnosis. Currently, there are no standardized criteria for diagnosing POCD, which likely contributes to the variability in reported prevalence rates of cognitive impairments following surgical procedures.

To assess cognitive decline, screening tools such as the MMSE, MoCA, TMT-A, TMT-B, Wechsler Memory Scale, and others are recommended [31].



Risk and protective factors and consequences of postoperative delirium and postoperative cognitive dysfunction. Abbreviations: NSAIDs – nonsteroidal anti-inflammatory drugs, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, POD – postoperative delirium, POCD – postoperative cognitive dysfunction, ICU – intensive care unit.

It is undoubtedly important to evaluate cognitive functions prior to surgery to predict the risk of developing POD and POCD. However, given time constraints, conducting neuropsychological testing on all patients may be impractical. The AD8 scale has been proposed as a brief tool to differentiate between mild dementia and normal aging. This scale assesses memory, orientation, thinking, and daily activities. It was found to be comparable to scales with up to 55 questions, and a score of 2 or higher with 74% sensitivity and 86% specificity effectively differentiated between participants with CDR 0 and CDR 0.5, in other words, between those without dementia and patients with very mild dementia [45].

Treatment. The most important strategy for preventing POD involves non-pharmacological methods, including sensory enhancement (e.g., glasses, hearing aids), mobility improvement (walking at least twice a day), cognitive stimulation, simple communication standards, nutritional and fluid replacement, sleep improvement, proper medication management, and daily rounds by an interdisciplinary team to reinforce interventions [39]. Late mobilization of patients is a risk factor for delirium; it has been established that delaying ambulation increases the likelihood of POD by 1.7 times daily [47].

In cases of POD, the first step is to assess and address potential causes, such as infection, pain, dehydration, metabolic disturbances, constipation, or urinary retention [37].

Pharmacological approaches include the use of antipsychotics. However, recent reviews indicate that administering antipsychotics not only fails to reduce the severity of delirium but also doubles the risk of death [27]. Thus, the optimal approach is to minimize the risk of developing POD and ensure adequate pain management for patients.

Regarding POCD, there is no data on effective treatment methods. The question remains whether basic anti-dementia therapy can be used.

Conclusion. POCD and POD represent significant clinical issues that require a comprehensive approach to diagnosis, treatment, and prevention. The development of POCD is associated with numerous factors, and effective management necessitates interdisciplinary efforts.

Figure illustrates the main risk and protective factors associated with POD and POCD, as well as their medical and social consequences.

Understanding and timely detection of POD and POCD are crucial for improving the quality of life in patients following surgical procedures. Modern diagnostic and treatment methods can significantly reduce the risk of developing these conditions. Continued research in the field of cognitive impairments after surgery is necessary, and the knowledge gained should be incorporated into clinical practice, particularly considering the limited research in the Russian Federation over the past 10 years.

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PANCREATIC CANCER MICROBIOME

Pancreatic cancer is one of the most lethal types of malignancies, with a very low survival rate (5-7%), which is related to the difficulty of early diagnosis and the aggressive nature of the disease. The progression of tumours and the process of metastasis are linked to a number of factors, one of which is the tumour microbiome. The microbiota plays a role in the formation of an immune-tolerant environment, which contributes to cancer development by inducing angiogenesis, chemoresistance, immune cell suppression, tumour invasion and metastasis. Modifications in the composition of tumour-associated microbes and alterations in immune function may ultimately influence the progression and outcome of the disease. Enhancing our understanding of the composition and pathways of microorganisms in tumours, such as pancreatic cancer, will facilitate the identification of predictive factors and potential therapeutic targets. The objective of this review to synthesise the current knowledge about the composition of the microbiota and its origins in pancreatic tumours.

Keywords: microbiome, pancreatic cancer, tumour microenvironment

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Introduction. Microorganisms have been identified as a contributing factor in the development of 20% of human malignant tumours. The microbiota plays a significant role in the tumour microenvironment, influencing oncogenesis and tumour progression at the local level. Of the 1012 different microbial species that have been identified to date, only 11 have been categorised as human carcinogens by the International Association of Cancer Registries [1, 2].

Pancreatic cancer (PDAC) is a highly invasive malignant disease with a five-

year survival rate of less than 9% (3). A number of risk factors have been identified as contributing to the development of PPC, including smoking, obesity, diabetes, chronic pancreatitis, and bacterial or viral infections. An additional critical factor is the occurrence of multiple genetic mutations, including KRAS (present in 85-100% of pancreatic cancers) and mutations in suppressor genes such as p16 (also known as CDKN2A), TP53, SMAD, and genes involved in the repair of damaged DNA, such as hMLH1 [5].

The pancreas has traditionally been regarded as a sterile organ, with the prevailing view being that the majority of microbes are unable to survive in pancreatic juice, which contains a multitude of proteases and is highly alkaline. Nevertheless, subsequent studies have documented the presence of bacterial DNA in pancreatic tissue samples from 76% of patients with PDAC and 15% of healthy individuals. A 1000-fold increase in the number of bacteria in intrapancreatic tissue was observed in patients with PDAC in comparison to normal pancreatic tissue [7, 8]. The mean relative proportions of a number of taxa differed between patients with PDAC, those with benign pancreatic neoplasms and a healthy cohort. The microbiome of pancreatic tumours is specific but independent of tumour localisation in the pancreas.

The objective of this review is to provide a comprehensive summary of the latest research on the composition and diversity of the pancreatic tumour microbiota over the past decade. This review encompasses not only the bacterial component of the intratumoural pancreatic microbiome but other aspects as well as pathways of microorganisms to the pancreas and their impact on pancreatic cancer progression. The following keywords were used to search for relevant literature: microbiome pancreatic cancer, pancreatic microbiota, pancreatic mycobiome, pancreatic viriome, tumour microenvironment. Fifty-five articles were selected for inclusion in this review, comprising clinical trials, meta-analyses, randomised controlled trials, and systematic reviews.

Pathways for microbial invasion into the PDAC. The sources of intratumoural microorganisms are diverse. The invasion of tumours by intraluminal microorganisms can occur when the tumour formation process results in mucosal destruction, thereby creating an opening for microorganisms to enter the tumour mass. Haematogenous spread can result in the transfer of microorganisms from the oral cavity and intestine to tumour foci [12-15].

The microbiota isolated from the pancreas exhibits similarities to the oral microbiota. A certain number of Clostridium species that originally colonised the oral cavity can be found in normal pancreatic tissues [17]. Compared with non-cancerous patients, patients with ampullary cancer or ductal adenocarcinoma of the pancreas have a significantly reduced number of Lactobacillus, while oral bacteria such as Porphyromonas, Clostridium and Prevotella are more abundant [18].

Additionally, bile is linked to bacterial colonization of the pancreas. A study of chronic pancreatitis and pancreatic cancer demonstrated that 29 pancreatic juice samples obtained from 20 patients with pancreatic cancer and 16 patients with duodenal or bile duct cancer, via drainage tubes following pancreatectomy, exhibited positive results for enterococcal DNA [6]. Furthermore, Enterococcus and Enterobacter species have been identified in bile samples, with Enterococcus faecalis detected in pancreatic tissue from patients with chronic pancreatitis and pancreatic cancer [6].

Additionally, bile duct obstruction and liver injury impact the microbiome. Bile duct obstruction and liver damage associated with PDAC disrupt the gut microbiome, leading to a decrease in many normal gut bacteria [19]. It has been postulated that bile microbiota, such as Escherichia coli, may affect the pancreatic microbiota. Some specific bacteria are capable to migrate from the gallbladder to the pancreas and induce a Th1-type immune response, which has a protective effect on the growth of PDAC. [20, 21] Furthermore, numerous clinical factors, including proton pump inhibitors, have been demonstrated to influence the composition of the microbiome in the pancreas and increase the risk of pancreatic cancer.

Approximately 25% of the pancreatic cancer microbiome is constituted by bacteria originating from the gut, which are absent in normal adjacent tissue. This indicates that the gut microbiome is able to specifically colonise pancreatic tumours. This assertion was validated by Riquelme and colleagues, who transferred the microbiome of advanced-stage PDAC patients into the intestines of mice. Following a designated period, the researchers observed the presence of human donor bacteria within the mice's tumours. The donor bacteria constituted less than 5% of the intratumoural microbiome. Moreover, notable alterations in the bacterial constitution of the mouse intratumour microbiomes were observed following transplantation. These findings indicate that the gut microbiome has the capacity to modulate the intratumoural microbiome, and that such modifications can be achieved by modifying the intratumoural bacterial composition.

The sources and mechanisms of microorganism's invasion in pancreatic tumours are now being progressively investigated, thereby furthering our understanding of the dynamics and behaviour of the intratumoural microbiota in cancer tissues. A comparison of the intratumoural microbiota composition with microbiota from other body sites can identify key microorganisms associated with different tumours, thereby offering valuable insights for cancer prevention strategies. The molecular mechanisms of how microbes penetrate the tumour microenvironment remain a fascinating and important area of research.

Microbiota of the pancreatic cancer Bacteria. Investigations have demonstrated that the composition of bacteria in pancreatic cancer tissue differs from that observed in normal pancreatic tissue. Pushalkar et al. [7] sequenced the 16S region of ribosomal RNA (rRNA) in 12 pancreatic ductal adenocarcinoma tissues and identified 13 different types of bacteria. The most prevalent were Proteus (45%), Bacteroides (31%), Firmicutes (22%) and Actinobacteria (1%), present in all samples. Furthermore, members of the genera Pseudomonas and Elizabethkingia were present in considerable quantities. Geller et al. [25] identified the class Gammaproteobacteria as the most prevalent group in pancreatic cancer tissues, with Enterobacteriaceae and Pseudomonas representing the majority. This suggests that the bacteria colonise the pancreas and are part of the tumour microenvironment in pancreatic cancer.

Gnanasekaran et al. discovered that Porphyromonas gingivalis is capable of surviving within pancreatic cancer cells, a process that is facilitated by hypoxia, a prominent feature of pancreatic cancer. The proliferation of tumour cells was found to be associated with the level of intracellular persistence, and infection of tumour cells with P. gingivalis resulted in enhanced growth in vivo.

The relationship between Helicobacter pylori and pancreatic cancer remains a topic of contention in the scientific community. To date, case-control studies, prospective cohort studies and meta-analyses have demonstrated that H. pylori infection is associated with an elevated risk of developing PDAC [29, 30]. Nevertheless, some studies have indicated

that there is no correlation between these two factors (31). In a Swedish study, the presence of H. pylori DNA was identified in pancreatic tumour tissue and/or surrounding tissues in 60% of patients with pancreatic cancer, indicating a potential role for H. pylori in the development of this disease [32]. Additionally, H. pylori DNA has been undetected in pancreatic juice and tissue samples from patients with chronic pancreatitis and PDAC, indicating that H. pylori does not directly colonize the pancreas and may indirectly contribute to pancreatic carcinogenesis. Further investigation is required to ascertain whether H. pylori colonize the pancreas and the impact of such colonization on the immune microenvironment of pancreatic tumours.

Recent studies have demonstrated a correlation between the intratumoural microbiota and the survival of patients with PDAC. The alpha diversity of the tumour microbiome in patients with long survival is significantly higher than in patients with short survival. Furthermore, patients with high alpha diversity have been observed to significantly increase overall survival. Therefore, tumour alpha diversity can be used as a predictor of survival in patients with surgically resected prostate cancer. The enrichment of Proteobacteria (Pseudomonas), Saccharopolyspora and Streptomyces was observed in tumour tissues of patients with long survival, whereas non-dominant bacteria were identified in patients with short survival [24, 34].

Fungi. The limited abundance of intestinal fungi and the absence of a well-characterised reference genome have resulted in the fungal flora's influence on pancreatic cancer progression being a relatively new and understudied area of research. The migration of certain fungi from the gut to the pancreas has been linked to the development of pancreatic cancer [35, 36]. A study conducted in Taiwan demonstrated that infection with Candida fungi can significantly elevate the risk of cancerous growths. These fungi are capable of producing compounds such as nitrosamines - carcinogenic substances that play a role in causing oral cancer. An earlier study indicated that Candida albicans can promote cancer development through a pro-inflammatory response mediated by an increase in cytokine production and adhesion molecule expression.

Aykut et al. conducted an experiment in which fungal strains labelled with green fluorescent protein (GFP) were injected into the intestines of mice. The fungi migrated into the pancreas within 30 minutes, indicating that they can colonise the pancreas. In human pancreatic tumours and mouse models, the number of fungi was 3,000 times higher than in normal pancreatic tissues, and species composition also differed. For example, the most abundant species in the mouse pancreas was Malassezia, whose relative abundance was significantly higher compared to the intestine.

The binding of mannose-binding lectin (MBL) by pathogenic fungi in pancreatic tumour tissue has been observed to activate the complement C3 cascade, thereby promoting the progression of pancreatic cancer. MBL is a soluble lectin of the innate immune system, produced by the liver and secreted into the bloodstream. Its function is to activate the complement lectin pathway, enhance the phagocytosis of microorganisms by leukocytes, and regulate inflammation. The complement system plays an important role in regulating the immune response, and its interaction with cancer cells has been observed to promote various processes associated with tumour growth, including proliferation, epithelial-mesenchymal transition, migration and invasion [43, 44]. MBL recognises the carbohydrate structure produced by Malassezia and activates the C3 protein, triggering an inflammatory immune response via the complement cascade. Complement activation stimulates cell proliferation and migration and promotes tumour growth [45]. Deletion of MBL/C3 in the extratumoural compartment or knockdown of C3aR in tumour cells can suppress tumour growth. Therefore, further studies of the fungal flora as a potential prognostic tool for early diagnosis of this cancer are warranted.

Viruses. Viruses are a component of the microbiota that may have a significant impact on the process of pancreatic oncogenesis. Many viruses have been implicated in carcinogenesis, including human papillomavirus (cervical cancer), Epstein-Barr virus (nasopharyngeal carcinoma), and hepatitis viruses (liver cancer).

A recent study by the Pan-Cancer Analysis of Whole Genomes Consortium, which examined whole genome sequencing data from 38 cancer types, found a high prevalence of known tumour-associated viruses [46]. In pancreatic cancer in particular, the most common viruses found in the tumour were roseoloviruses, lymphocryptoviruses and gamma retroviruses.

It is noteworthy that there is a potential association between hepatitis B virus (HBV) and hepatitis C virus (HCV) and pancreatic cancer. HBV and HCV are hepatotropic viruses, meaning that they are specific to the liver and can also be detected in the pancreas. The precise pathophysiological mechanisms by which these hepatotropic viruses enter the pancreas remain unclear. The potential mechanisms include anatomical proximity of the pancreas and liver, common origin of the blood vessels and bile ducts of these organs, common origin of hepatocytes and pancreatic cells from multipotent endodermal cells, and risk of transformation when cultured under specific conditions (in the pancreas). Furthermore, chronic inflammatory changes may occur, with the potential for progression to metaplasia and subsequent malignant transformation. Additionally, HBV-DNA integration at the cellular level, chromosomal instability and alterations in gene expression have been observed [48, 49].

Some researchers have identified the presence of hepatitis B virus (HBV) in pancreatic acinar cells and pancreatic juice, with a correlation between this presence and the development of pancreatitis [50]. Furthermore, research has demonstrated that individuals with hepatitis B or C virus (HBV or HCV) infection exhibit an elevated risk of developing pancreatic cancer compared to those without hepatitis [51, 52]. The potential mechanisms by which HBV and HCV contribute to pancreatic cancer may include persistent chronic inflammation and alterations in tissue elasticity. Some researchers have proposed that the HBx protein expressed by HBV may induce carcinogenesis via the PI3K/AKT signalling pathway. Nevertheless, this induction can only account for a limited aspect of the underlying mechanism, and further research is required to investigate the intrinsic links between viruses and pancreatic cancer.

Human papillomavirus (HPV) has been linked to various cancers, including cervical, anal and oral cancers [54]. Recently, the HPV-16 strain of HPV was detected in mucinous neoplastic cysts of the pancreas, indicating a potential role in the carcinogenesis of pancreatic cancer [55].

Impact of the intratumoural microbiome on tumour progression of PDAC. The bacterial composition and diversity of normal and cancerous pancreas differ, as do the compositions of the pancreatic microbiome in early-stage disease and in advanced-stage PDAC. These findings suggest that cancer progression is associated with changes in the microbiome. In particular, the prevalence of Malassezia species was markedly elevated in PDAC, and the introduction of Malassezia fungi, but not Candida,

Aspergillus or Saccharomyces species, into the mycobiome of Kras-ablated mice markedly accelerated the progression of pancreatic cancer [41].

Using of mouse models has demonstrated that bacterial colonisation in pancreatic cancer can reset immune tolerance and promote tumour progression via bacterial metabolites [7, 25]. Conversely, research has indicated that certain microorganisms present in tissues (e.g., Alphaproteobacteria, Sphingobacteria, and Flavobacteria) may facilitate an antitumour immune response by enhancing the recruitment and activation of CD8+ T cells, which is associated with a favourable prognosis. It is noteworthy that long-term survival in pancreatic cancer is linked to heightened bacterial diversity within tumours, along with elevated numbers of mature CD8+ T cells and granular B cells [24]. There is compelling evidence that the tumour microbiota plays a pivotal role in development and progression. Consequently, the investigation of therapeutic strategies targeting these microorganisms represents a significant frontier in scientific inquiry.

Conclusion. The PDAC microbiome is associated with the occurrence, progression, response to treatment, and survival period in pancreatic cancer. Modulation of the pancreatic microbiome, either via its elimination or augmentation, is associated with enhanced survival in patients with PDAC, augmented responsiveness to chemotherapeutic agents and reduced tumour burden.

The mechanism of the effect of the microbiome on the tumour microenvironment, as well as immunotherapy approaches, requires further investigation to provide additional evidence to explain the complex relationship between the microbiome and PDAC. Appropriate studies targeting the microbiome may provide insights into the mechanisms of the development and progression of PDAC, improve treatment efficacy, and improve the overall prognosis of patients.

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MULTIPLE PRIMARY NON-HEREDITARY MALIGNANT NEOPLASMS

Multiple primary malignant tumors are independent occurrence and development of two or more neoplasms in one patient. In this case, not only different organs of different systems can be affected, but also paired organs, as well as one organ multicentrically. Carcinogenesis is based on a multistage process of changes, malignant transformation and progression, which includes DNA damage and dysfunction of the immune system. Damage to certain parts of genes involved in mitosis, cell death or DNA repair is reflected in an increase in the mutation load. After accumulation of a sufficient number of mutations, control over cell function is disrupted, which leads to the development of cancer. In recent years, an increase in the frequency of multiple primary neoplasms has been noted. The review presents the main risk factors that to one degree or another affect the development of polyneoplasia.

Keywords: multiple primary malignant neoplasms, polyneoplasia, risk factors

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Definition of multiple primary malignant tumors, study history. Primary multiple tumors are the simultaneous or sequential occurrence of tumor growth points that are pathogenetically unrelated to each other [8]. The term multiple primary malignant tumors or neoplasms (MPMTs, MPMN) refers to the presence or consideration of only tumor growth points with a malignant phenotype [28].

The problem of MPMTs development is multifaceted and very complex. The urgency of studying the regularities of the development of polyineoplasias is gaining momentum, including due to a significant increase in their prevalence: in Russia, from 2015 to 2023. The incidence of MPMTs and the proportion of patients with polyneoplasias from the total number of cancer patients increased by 97.0% (from 26.8 to 52.8 $^{0}/_{0000}$) and 56.8% (from 4.4 to 6.9$^{0}/_{0000}$) [1].

The first mention of MPMTs is considered to be the case description of consecutive occurrence of both mammary glands carcinomas and uterus by the London surgeon D. Pearson in 1793 [6]. In 1889, the German surgeon T. Billroth was the first to propose the criteria for PMMT, which O. Goetze adapted for clinical practice in order to uniformly accumulate data [6, 7]. The first Russian study to analyze world literature data on MPMTs was performed by G.G. Nepryakhinym with an attempt to classify them. In 1974, V.G. Bebyakin (Table) proposed a classification that included benign formations [6]. From the very first classification to the

Multiple primary tumors classification (V.G. Bebyakin)

	Classification feature		Tumor type
I	By combination (mani-festation type)	1	benign
		2	benign and malignant
		3	malignant
II	By detection sequence	1	synchronous
		2	metachronous
		3	synchronous-metachronous
		4	metachronous-synchronous
III	By functional relationships	1	functional-dependent
		2	hormone-dependent
		3	unsystematic
IV	By tissue affiliation	1	one tissue affiliation
		2	different tissue affiliation
V	By histological structure	1	one histological structure
		2	different histological structure
VI	By localization	1	single and paired organs
		2	the same system different organs
			different systems organs

present, the criteria for MPMTs remained approximately the same: tumors must have a malignant phenotype, be located separately from each other, and must not be metastases of one tumor [7, 4].

Interpretation of the MPMTs is based on two main recommendations: The Surveillance, Epidemiology, and End Results (SEER) Program, as revised in 2012, and the 2005 International Agency for Research on Cancer (IARC) classification used in most European countries [27]. Both recommendations are aimed at uniform presentation of MPMTs statistics with a general definition of the time interval for metachronism characterization (6 months or more) and indicateаниемthat tumors prone to multipleтиorgan damage should not be registered as primary multiple neoplasms (Kaposi's sarcoma, leukemias and lymphomas). [27, 23].

Etiology and pathogenesis of multiple primary malignant tumors. From the point of several authors view, the phenomenon of MPMTs occurrence, can be largely explained from the perspective of the "tumor field" theory of W. Willis (1967). Theory describes the occurrence likelihood of malignant growth multiple points as a result of the "field" creation by one carcinogen, as a result of which several sites may appear malignant growth [7].

Risk factors for the development of MPMTs can be divided into hereditary and non-hereditary. Hereditary causes include at least 29 familial tumor syndromes [29] with the most common combinations of gastrointestinal polyneoplasia [18, 19], which, however, are themselves among the most frequently diagnosed.

In addition to standard screening for Lynch syndrome by comparing the Amsterdam II criteria or other original criteria, one of the predictors was the phenotype of microsatellite instability on histological examination [2].

Non-hereditary neoplasms are caused by the influence of urbanization and industrialization, habitual intoxications (alcohol, smoking), immunodeficiency states, oncovirus infections, radio-, chemotherapy of the first neoplasms, external sources of ionizing radiation and the presence of a malignant neoplasms history. However, it is noted that in these cases, patients must have predisposing genetic characteristics [7, 5, 41].

The diagnostic and therapeutic capabilities in modern oncology are extensive, which undoubtedly affects the survival rate of cancer patients [32] and the risk of the emergence of other sites of tumor growth. It has been shown that the presence of one malignant neoplasm in the anamnesis increases the chance of developing a subsequent tumor by 23%, and in the case of two or more – by 47% [7, 10].

The MPMTs development is enhanced by carcinogenic environmental agents that contaminate through inhalation, water and nutritional routes, the regular impact of which, especially on city residents, is associated with the repeated development of tumor transformations [11].

Scientists attribute the carcinogenic role of chemotherapy and radiation therapy to the associative factors of MPMTs [7, 9, 42] with an increase in the likelihood of polyneoplasia up to 5-8% 5 years after treatment with a significant increase in risk with the simultaneous use of these methods [9].

A correlation has been identified between the development of a "second" tumor in organs anatomically adjacent to the affected organ and local radiation exposure to the tumor, for example, with the development of rectal carcinoma during radiotherapy for prostate cancer [33]. However, a large meta-analysis involving 1.6 million women with breast cancer who underwent radiation therapy did not confirm a statistically significant risk of developing lung cancer [33].After treatment of breast cancer patients with cyclophosphamide, cisplatin and tamoxifen, a dose-dependent increase in the likelihood of inducing the development of recurrent malignant endometrial tumors within 5 years was shown [44]. A dose-dependent increase in the likelihood of inducing the development of recurrent malignant tumors (kidney carcinoma, bladder carcinoma and leukemia) has been shown after treatment with cyclophosphamide.

It was noted that the degree of occurrence risk, including recurrent tumors, in association with alcohol consumption is dose-dependent. Studies on the role of alcohol (low - up to 12.5, moderate - 12.5-50 and high - more than 50 g/day) in carcinogenesis have demonstrated an increased risk of developing squamous cell carcinoma of the esophagus (regardless of the consumption volume), colorectal cancer (with moderate and high consumption) and insignificantly for breast cancer [15, 43, 12, 13, 37].

The main target sites for malignant neoplasms caused by smoking are: the oral cavity, pharynx, larynx and lungs [37, 36, 17, 35]. Carcinogenesis occurs even after treatment of the first tumor - through nicotine derivatives benzopyrene and nitrosamines, which cause mutations in the k-ras and p53 genes: nitrosamines are stronger ligands of n-cholinergic receptors than nicotine itself [37, 35]. Smokers have a higher risk of developing metachronous tumors than never smokers, with a proven dose-dependence [14, 31].

The mutual potentiation of various factors of carcinogenesis was noted using the example of the radon influence, asbestos fibers and smoking on lung tissue. Increasing the duration of carcinogenic substances exposure to lung tissue enhances their de novo mutagenic activity (spontaneously arising under DNA replication during cell division) with the induction of persistent resistance to apoptosis and infiltration clones tumor [39, 24].

For many years, the carcinogenic potential of viruses has been studied, with an increasing likelihood of their influence on the re-development pathology cancer. Oncoviruses include: hepatitis B and C viruses, Epstein-Barr virus, T-cell leukemia virus 1, human papillomavirus (HPV), herpes virus-8, Merkel cell polyomavirus [5, 34, 26, 20, 40]: from 400 HPV types known, the carcinogenic role of 12 has been proven: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 [40, 30].

By binding to the DNA of the host cell, HPV realizes its oncogenic potential through the E6 and E7 proteins. E6 causes degradation of p53, E7 - pRB, thereby blocking one of the apoptosis mechanisms [30]. At the same time, heterogeneity by gender was noted - with a higher risk of developing a subsequent tumor in men. A statistically significant probability of developing "recurrent" tumors were cancers of the esophagus, larynx, nasal cavity, lungs and bladder [16]. However, the authors emphasize the likelihood of developing increased risk MPMTs of these localizations due to the patients habitual intoxication (alcohol and smoking). Among those not associated with modifiable risk factors, MPMTs should be noted data on a significant increase in the developing polyneoplasia risk in patients with esophagus squamous cell carcinoma [21].

One of the most important application points in the MPMTs carcinogenesis is psychological stress, first described by G. Selye, accompanying the oncological patient life, is a decrease in the immune system reactivity, DNA repair systems inhibition , apoptosis and acceleration aging cellular [22, 3, 38, 25].

Conclusion. At the moment, literature data indicate mainly the similarity risk factors influence on the development of both single and multiple tumor processes with continued influence on the body: there is still no comprehensive information about the polyneoplasia predictors special characteristics, the relationship

between the influence of hereditary and non-hereditary carcinogenesis mechanisms. It is interesting to conduct a detailed non-hereditary mechanisms synergy study and its molecular basis, which will allow us to identify specific tumor markers with the forming risk groups possibility for the development of primary multiple tumors for the further necessary preventive measures development, taking into account the additional examination methods during observation use.

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PHYTOCHEMICAL ANALYSIS AND ANTIOXIDANT PROPERTIES OF EXTRACTS OF PLANTS OF *THE ROSACEAE* FAMILY

The article presents data on the content of biologically active compounds and total antioxidant capacity of extracts of plants of the family Rosaceae - Crataegus dahurica Koehne ex Scheid., Sanguisorba officinalis L., Rosa acicularis Lindl. growing in Yakutia. The quantitative content of flavonoids, phenylpropanoids, and the total content of phenolic compounds was analyzed in water-ethanol extracts of leaves from the studied plants, according to Folin-Chokalteu. It was shown that among the plants, a high content of flavonoids (2.51 mg%) and total phenolic compounds (42.34 mg%) were found in Rosa acicularis extracts, while phenylpropanoids (2.26 mg%) were predominant in Sanguisorba officinalis leaves.

To evaluate the total antioxidant capacity, the chemiluminescence assay method was used in a horseradish peroxidase, hydrogen peroxide, and luminol system. The highest antioxidant capacity values were found in Rosa acicularis leaf extracts (9.77 units), which correlates with the increased content of phenolic compounds in this plant. Rosa acicularis leaves are more promising for searching for sources of antioxidants.

Keywords: plant extracts, antioxidants, total antioxidant capacity, phenolic compounds, phenylpropaniodes, flavonoids, chemiluminescence.

Introduction. *Rosaceae* is an important family of plants that includes many species containing valuable biologically active substances: tannins, polysaccharides, flavonoids, etc. The *Rosaceae* family includes about 100 genera distributed worldwide [43]. In Russia and CIS countries, the family is represented by about 55 genera [8], of which 25 genera and 93 species grow in Yakutia [9].

Some of the most common species of plants of the *Rosaceae* family growing in the central part of Yakutia are *Crataegus dahurica* Koehne ex Scheid., *Sanguisorba officinalis* L., *Rosa acicularis* Lindl. Medicinal raw materials of the above plant species are used in folk medicine in many nations, and they are also included in the State Pharmacopoeia of the Russian Federation. Modern research notes that these plants contain a unique composition of biologically active substances with strong antioxidant activity and a wide range of other pharmacological properties. *Crataegus dahurica* leaves contain significant amounts of hyperoside, quercetin, and vitexin [45]; *Sanguisorba officinalis* leaves contain gallic, chlorogenic, and ellagic acids as well as catechins [33]; *Rosa acicularis* leaves are rich in phenolic compounds such as ellagotannins and flavonoids [39].

One of the most essential features of phenolic compounds is their synergistic action. The interaction of flavonoids and phenylpropanoids enhances their antioxidant and anti-inflammatory effects [55]. Thus, the combination of hyperoside, vitexin, and chlorogenic acid results in enhanced antioxidant action. Such synergistic effects make phenolic compounds promising components for use in complex preparations aimed at combating oxidative stress and inflammatory processes [26]. Oxidative stress is considered an important pathogenetic link in the development of more than 200 diseases [22,28].

In connection with those mentioned above, nowadays, the task of searching for local medicinal plant raw materials with a high content of phenolic compounds with the best antioxidant activity to inhibit oxidative processes becomes the most urgent.

The work aimed to evaluate the antioxidant capacity of aqueous-alcoholic extracts of leaves of plants of the *Rosaceae* family: *Crataegus dahurica*, *Sanguisorba officinalis*, and *Rosa acicularis*.

Materials and methods. Water-ethanol extracts from leaves of wild plants - *Crataegus dahurica*, *Sanguisorba officinalis*, and *Rosa acicularis* collected in Yakutia were used as research objects. The collection and storage of raw plant materials were carried out according to the requirements of the State Pharmacopoeia of the Russian Federation. Plant raw materials were stored at 18°C in a place protected from light. Extraction was carried out with 60% ethyl alcohol at a ratio of 1:30.

Spectrophotometric studies were carried out on the spectrophotometer SF-2000 (OKB Spektr, St. Petersburg): the method of quantitative determination of phenolic compounds according to Folin-Chokalteu [29], the method of quantitative analysis of flavonoids using

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aluminum chloride [1,2], and the method of quantitative analysis of phenylpropanoids [4].

The total antioxidant capacity of leaf extracts of the studied plants was evaluated using chemiluminescence analysis in a horseradish peroxidase, hydrogen peroxide, and luminol system. Chemiluminescence was recorded on a chemiluminometer Lum-1200 (Russia) using the attached software PowerGraph 3.3 [10]. All experiments were performed in fourfold repetition. The results were statistically processed using the Statistica 10 program. Differences between groups were evaluated using the Mann-Whitney U-test. Correlations were determined using Spearman rank correlation. A value of $p<0.05$ was considered a statistically significant difference.

Results and discussion. As a result of spectrophotometric and chemiluminescent studies, data on the quantitative content of phenolic compounds, phenylpropanoids, flavonoids, and total antioxidant capacity in the leaves of *C. dahurica*, *S. officinalis*, *R. acicularis* growing in Yakutia were obtained. It was found that leaves of *C. dahurica*, *S. officinalis*, and *R. acicularis* plants contain various biologically active substances.

Phenolic compounds of plants belong to the group of secondary metabolites involved in adaptation processes [24]. In the human body, phenolic compounds of plant origin play an essential role in maintaining health by exerting antioxidant action, reducing blood coagulation, reducing capillary fragility and permeability, and improving metabolic processes. [44].

The results of the present work showed that the total content of phenolic compounds in the leaves of the studied plants varies depending on the plant species (Table 1). We observed the highest content of phenolic compounds in *R. acicularis*, 42.34±0.21 mg%. At the same time, almost 1.4 and 2.0 times less were found in the leaves of *S. officinalis* and *C. dahurica* compared to *R. acicularis*.

Phenylpropanoides are phenolic compounds containing one or more phenylpropane moieties in their structure. Most phenylpropanoids are known to have antioxidant and immunomodulatory properties [7].

The content of phenylpropanoides in the studied plants was carried out in terms of caffeic acid. A high level of phenylpropanoides in the leaves of *S. officinalis* was observed, was equal to 2.26±0.08 mg%, which was about 1.2 and 1.6 times higher than in other analyzed plants *R. acicularis* and *C. dahurica*, respectively.

Flavonoids have a polyphenolic structure antioxidant, and antibacterial, antiviral properties [11].

The quantitative content of flavonoids in the studied plants was measured using the specific redemption ratio of the dominant flavonoid (in terms of rutin, quercetin, and hyperoside). The high flavonoid content was observed in the leaves of *R. acicularis* - 2.51±0.09 mg%, and low, 2.3, and 2.4 times less, *C. dahurica* and *S. officinalis*, respectively.

The chemiluminescence method was used to estimate the total antioxidant capacity of plant water-alcoholic extracts. The method is based on the registration of chemiluminescence kinetics occurring in the system: hydrogen peroxide, horseradish peroxidase, and luminol, according to the mechanism shown in Figure.

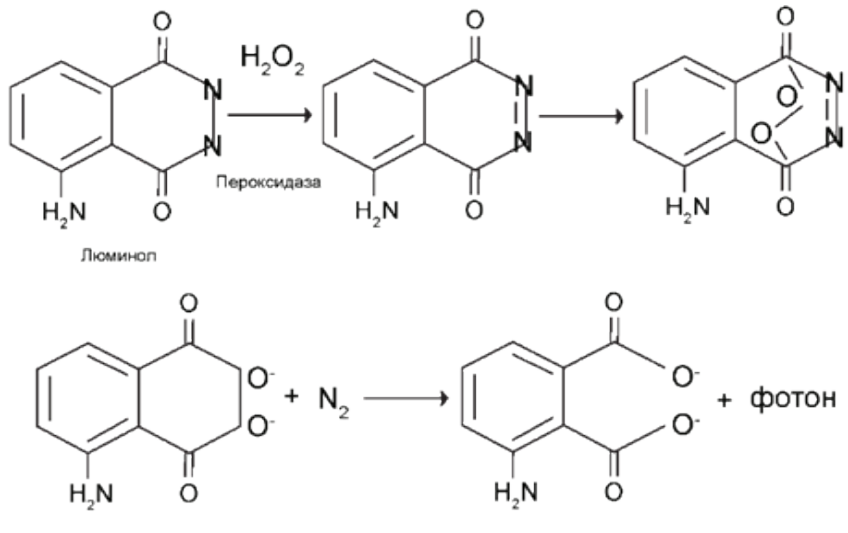
In this system, hydrogen peroxide served as a source of reactive oxygen species, horseradish peroxidase was an inducer of free-radical oxidation, and luminol was used as a substrate that emits a photon during oxidation. Adding the studied plant extracts to the system led to a decrease in the intensity of chemiluminescence due to the neutralization of reactive oxygen species by antioxidants present in the samples. Chemiluminescence was recorded using a chemiluminescence analyzer under fixed temperature and time conditions. The results were

Table 1

Phytochemical analysis of leaf extracts of the studied plants. M±δ

Object of research	Phenolic compounds. mg%	Phenylpropanoides. mg%	Flavonoids. mg%
Crataegus dahurica	22.84±0.15	1.40±0.04	1.08±0.04 (converted into hyperoside)
Sanguisorba officinalis	29.61±0.32	2.26±0.08	1.06±0.05 (converted into quercetin)
Rosa acicularis	42.34±0.21	1.91±0.05	2.51±0.09 (converted into rutin)

Note: The values of phenylpropanoides are given in terms of caffeic acid.



Mechanism of chemiluminescence reaction in the system of luminol and hydrogen peroxide in the presence of horseradish peroxidase

Table 2

Total antioxidant capacity of leaf extracts of the studied plants, M±δ

Object of research	*Crataegus dahurica*	*Sanguisorba officinalis*	*Rosa acicularis*
AOC•10^{-6}, relative units	7.23±0.31	8.37±0.25	9.77±0.38

Note: AOC is total antioxidant capacity.

expressed through a decrease in the light sum of chemiluminescence, which directly correlated with the antioxidant activity of the samples.

The study of the total antioxidant capacity of water-alcohol extracts of *C. dahurica*, *S. officinalis*, and *R. acicularis* leaves showed that all samples have antioxidant activity (Table 2). *R. acicularis* extract showed high antioxidant capacity (9.77±0.38 units), while in *S. officinalis* and *C. dahurica* extracts, the antioxidant capacity was 1.16 and 1.35 times less, respectively.

The correlation analysis showed that the total antioxidant capacity was significantly correlated with the total content of phenolic compounds (r=0.98; p=0.000...). In the plants we studied, the total content of phenolic compounds probably makes a greater contribution to the antioxidant capacity.

The data of the present study indicate that *R. acicularis* contains more phenolic compounds and flavonoids than *C. dahurica* and *S. officinalis*. The literature reveals that the main phenolic compounds in *R. acicularis* leaves are ellagic acid, kaempferol, and quercetin [39].

Randomized clinical trials have shown that ellagic acid, due to its antioxidant and anti-inflammatory properties, can reduce symptoms of some diseases: depression in patients with multiple sclerosis [25], improved sleep quality in patients with irritable bowel syndrome [36], reduced metabolic disorders in women with polycystic ovary syndrome [31], and affected oxidative stress and inflammation in patients with type 2 diabetes [23].

It was shown that kaempferol inhibits apoptosis in acute liver failure and tumor diseases [37,56]. An experimental model of hypoxia in vitro showed that kaempferol in mouse neurons provides protection against ferroptosis by activating the Nrf2 signaling pathway [57].

Studies by foreign authors using molecular docking have established that quercetin is a potent inhibitor of the RNA-dependent RNA polymerase SARS-CoV-2 and also inhibits the main protease 6LU7 of the virus (SARS-CoV-2), thereby preventing the process of its replication [18].

Studies by foreign authors show that the high content of phenylpropanoids in *S. officinalis* leaves is mainly due to coumaric and ferulic acids [61].

Coumaric acid is a promising adjuvant therapy compound. *In vitro* studies on the glioblastoma (U87Mg) model showed that it stops the cell cycle in the G2/M phase and activates apoptosis [40]. Also, coumaric acid exhibits protective properties in rat ovarian tissues under cisplatin-induced oxidative stress [14].

Ferulic acid exhibits antithrombotic, neuroprotective, and anti-inflammatory properties [34]. Studies have emphasized its low toxicity due to its metabolization ability in the human body [54].

Recent studies have shown that ferulic acid alleviates anxiety and depression by regulating changes in the gut microbiome, highlighting its potential use as a novel antidepressant [17]. In addition, ferulic acid has been found to alleviate sciatica in rats by inhibiting neuroinflammation through the TLR4/NF-κB pathway, promoting sciatic nerve repair [60].

Although *C. dahurica* leaf extract, showed low antioxidant capacity and low values of total phenolic compounds, phenylpropanoids and flavonoids, is a valuable subject for further study because it contains flavonoids: hyperoside and vitexin. Hyperoside has been known to exhibit neuroprotective properties. However, recent studies have shown that it can reduce β-amyloid toxicity by reducing neuronal death *in vitro* and *in vivo* models [19,50]. Vitexin has anti-inflammatory and antioxidant properties [49].

Thus, the comparative phytochemical analysis showed that the water-ethanol extract of R. acicularis leaves contained the highest concentration of phenolic compounds and flavonoids. In contrast, the water-ethanol extracts of *S. officinalis* leaves had a high content of phenylpropanoids. Extracts of *C. dahurica* leaves were characterized by a low content of phytochemicals considered by us. Total antioxidant capacity showed the highest results in *R. acicularis* leaf extracts, compared to *S. officinalis* and *C. dahurica* leaf extracts.

Conclusion. The present work has shown that *R. acicularis* leaves are a promising object for further studies related to the effect of water-ethanol extracts of plants on model systems *in vitro*, in studying the processes of free radical oxidation of lipids, as well as possibly activation of the immune system and apoptosis, in various diseases since extracts of this plant showed high values of antioxidant capacity (9.77±0.38 units) and flavonoid concentration (2.51±0.09 mg%), compared to *S. officinalis* and *C. dahurica*.

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GENETIC FACTORS AFFECTING SKIN HEALTH

Skin is the largest organ in the human body, performing a barrier function to maintain homeostasis of the body. Skin aging is a complex process influenced by hereditary and environmental factors. Properties such as hydration, elasticity and antioxidant capacity play a key role in the skin aging process. Genetic variations can affect the production of collagen and elastin, the level of antioxidants and the integrity of the barrier function of the skin. Identification of genetic markers that affect skin condition will allow us to develop recommendations for correcting signs of aging, and may also become an effective and affordable method for treating many skin diseases in the future. This review summarizes and presents current data on genetic factors and molecular mechanisms affecting the health and appearance of the skin.

Keywords: skin, genes, polymorphism, dermatology, cosmetogenetics

Introduction. The psycho-emotional state of a person is affected not only by physical and social factors, but also by appearance. With the development of quality of life and medicine in modern society, both women and men pay special attention to their appearance. Today, thanks to the development of genomic association studies (GWAS), researchers can accurately identify specific loci, genes and proteins associated with aging and appearance [35].

The condition of the skin plays an important role in appearance. Unlike others, the skin is the main organ through which the body interacts with the environment and its aging is most noticeable. Aging is determined by internal factors such as changes in hormone levels, decreased ability to repair deoxyribonucleic acid (DNA), accumulation of mutations in DNA caused by free radicals or ultraviolet (UV) radiation, and external environmental factors such as air pollution, lack of nutrients and vitamins in the diet, exposure to UV radiation, smoking, etc. [13].

According to researchers, the external parameters of skin aging have a strong ethnic and genetic basis. It has been found that different populations have different characteristics of the skin and its aging, for example, among representatives of the Caucasian race, there is an earlier onset and more pronounced signs of wrinkling and sagging skin than among representatives of other races. There are also differences in the severity of wrinkles in different areas of the face among Chinese, Japanese, Thai and European women [26]. It is also known that skin color and phototype influence the degree of photoaging, with people with a dark phototype typically having more "hypertrophic reactions" such as deep wrinkles, coarsening, and lentigines, while people with a light phototype typically have fewer wrinkles with epidermal atrophy, focal depigmentation, and dysplastic changes such as actinic keratosis, non-melanoma, and melanoma skin cancer [17].

Clinical manifestations of skin aging include dehydration, loss of elasticity, increased extensibility and the appearance of wrinkles [2]. Wrinkles are a typical symptom of skin aging caused by loss of elasticity, which is determined by a decrease in the amount of collagen associated with the elasticity of the dermal tissue of the skin. Collagen is closely associated with skin elasticity, as it protects against external irritants and provides it with tension and strength. The use of an increasing number of molecular genetic methods and the identification of genes predisposing to skin aging using GWAS allows for the development of personalized skin care recommendations based on nutrigenomics and cosmetology. Thus, in the study by Naval J et. al. (2014), 13 SNPs were selected in genes encoding proteins that play a role in skin properties associated with aging, namely, susceptibility to oxidative stress, elasticity and hydration, and genotyped in a sample of 120 women. Based on the collective contribution of a set of polymorphisms to the biochemical and metabolic properties of the skin, they identified 10 genotypic groups with different skin care needs [33].

Genes associated with photoaging. UV radiation exposure is a major risk factor for skin inflammation, immune changes and premature skin aging and is also a major risk factor for cancerous degeneration [8]. Photoaging depends primarily on the degree of sun exposure and pigmentation (melanin production), which contributes to protection from UV radiation [34]. Important regulators of melanogenesis are α-melanocyte-stimulating hormone (αMSH) and adrenocorticotropic hormone (ACTH) [1]. Melanocytes, which are stimulated by α-MSH, modulate pigment metabolism via the melanocortin 1 receptor protein (MC1R) and synthesize the black pigment eumelanin, which has photoprotective properties [8]. Several studies have linked mutations in the melanocortin-1 receptor gene (*MC1R*) to phenotypic traits such as tanning [29, 30], fair skin, freckles, and photoaging [17, 43], as well as an increased risk of melanoma, other skin cancers, and breast cancer [28].

Also, pigmentation is affected by the interferon regulatory factor 4 (IRF4) gene, which influences the expression of the gene encoding the pigmentation enzyme tyrosinase (TYR). The rs12203592 polymorphism of the *IRF4* gene is associated with tanning and skin aging characteristics, the risk of sunburn, and malignant skin tumors [36].

In the study by Sigrid et al. (2013) established the association of SNP rs322458, which is closely linked to the intronic SNP of the *STXBP5L* gene, with skin photoaging. They also found that this SNP affects the expression of the *FBXO40* gene in the skin, which is responsible for regulating the cell cycle and response to DNA damage [4].

UV radiation promotes various mutagenic and cytotoxic DNA lesions, which are detected and repaired by activation of complex multiprotein pathways [11]. X-ray repair cross-complement protein 1 (XRCC1) is involved in DNA repair and plays a role in the repair of single-strand breaks induced by ionizing radiation. SNP rs25487 in the *XRCC1* gene affects the central domain of the enzyme

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required for activation of base excision repair (BER), which in turn leads to hypersensitivity to ionizing radiation [39].

In the study, Rahmouni M et al. (2022) identified new metabolic pathways and genes, some of which are likely to determine skin aging, such as the *WNT7B, PRKCA*, and *DDB1* genes [23]. The WNT7B protein, encoded by the *WNT7B* gene, is responsible for establishing the cortico-medullary axis of epithelial organization. The *PRKCA* gene (protein kinase C alpha) is involved in cell proliferation and cell growth arrest by positively and negatively regulating the cell cycle. The *DDB1* gene encodes a large subunit of the DNA damage binding protein, regulating numerous important processes in the cell, including DNA repair and replication, chromatin remodeling, and more [22].

Genes Associated with Skin Elasticity. The main proteins that affect the elasticity and firmness of the skin are extracellular matrix proteins (collagen, elastin and fibrin). The genes encoding these proteins play a key role in the synthesis, remodeling and degradation of collagen and elastin.

In the *COL1A1* gene, single nucleotide polymorphisms (SNPs) have been described that can alter the expression of *COL1A1* and, therefore, affect the properties of type I collagen. Among the various polymorphisms in the *COL1A1* gene, the most frequently studied polymorphism is the +1245G/T polymorphism (rs1800012), located in the first intron of the *COL1A1* gene, affecting the properties of type I collagen and leading to susceptibility to injury [24] and the formation of wrinkles on the skin [19].

Elastin is the main component of elastic fibers that provide reversible stretchability to connective tissue. Mutations in the elastin gene (*ELN*) can lead to disturbances in elastin metabolism, which leads to fragmentation of elastin and, thus, to a decrease in skin elasticity. In the studies of Tung et al. (2013), it was found that the elastin gene polymorphism rs7787362 may be associated with a decrease in the expression of functional elastin, which in turn contributes to the development of striae [21]. However, in further studies of this polymorphism, Kasielska-Trojan et al. (2018) and Pietrusiński et al. (2019) did not reveal differences in the distribution of alleles between women with and without striae [10, 38].

Matrix metalloproteinases (MMPs) are zinc-dependent proteolytic enzymes that promote the degradation of the extracellular matrix. Matrix metalloproteinase 1 (MMP-1) and matrix metalloproteinase 3 (MMP-3) can degrade extracellular matrix collagen types I, II, and III, which contributes to skin aging. The *MMP-1* gene is located on the long arm of chromosome 11 (11q22.3), spans 8 kb, and is expressed in a wide variety of normal cells such as fibroblasts, chondrocytes, endothelial and epithelial cells, as well as in various tumor cells [7]. The *MMP3* gene encodes matrix metalloproteinase 3, also known as stromelysin-1. The rs3025058 polymorphism in this gene affects the expression of MMP-3 and can lead to increased collagen degradation [18], which in turn negatively affects the elasticity and health of the skin. Thus, in the study by Vierkötter A et al. (2015), an association was established between the rs1799750 polymorphism of the *MMP-1* gene and the rs3025058 polymorphism of the *MMP-3* gene with skin aging [31].

Genes associated with skin hydration. The skin is the main organ that performs a barrier function to maintain homeostasis and also regulates water loss [25]. In cold conditions, the skin responds by constricting blood vessels to protect the body from losing excess heat. Sustained low temperatures reduce sebum secretion, which leads to dryness and irritation of the skin. Disturbances in the complex interactions of genes of environmental and host susceptibility, skin barrier function and the immune system can lead to the development of dermatitis [12].

The *FLG* gene encodes profilaggrin, a protein necessary for the formation and hydration of the skin barrier. Various mutations of the *FLG* gene significantly predispose Europeans to atopic dermatitis [16] and ichthyosis, but they are usually specific to different populations, so a low incidence of European mutations was found in African American, Japanese and Iranian populations [15]. In a recent study of Europeans from Central Russia, Churnosov M et al. (2022) found an association between atopic dermatitis and ten *FLG* gene polymorphisms (rs61816761, rs12130219, rs77199844, rs558269137, rs4363385, rs12144049, rs471144, rs6661961, rs10888499, rs3126085), which have different effects on 38 genes in different tissues and organs [37].

Aquaporin 3 (AQP3), a member of the aquaglyceroporin subfamily, is expressed in the epidermis and suprabasal layers and functions in the transport of water and glycerol, thereby playing an important role in skin hydration [3]. AQP3 has been attributed key roles in various processes underlying keratinocyte function and differentiation [6]. Also, decreased AQP3 expression in vitiligo skin may contribute to the pathogenesis of vitiligo through impaired keratinocyte differentiation and adhesion along with decreased keratinocyte survival, which may contribute to melanocyte death, thereby having a potential role in hypopigmentation [45]. AQP3 plays an important role in various skin diseases such as psoriasis, vitiligo, atopic dermatitis, non-melanoma skin cancers, basal cell and squamous cell carcinomas, bullous pemphigus, dyshidrotic eczema, acrokeratoderma and may also play a role in scleroderma [5].

The ability to maintain proper skin hydration levels in Caucasians is influenced by the rs17553719 polymorphism of the *AQP3* gene, while in Asians it is influenced by the rs71625200 polymorphism of the *FLG* gene, rs2496253 polymorphism of the *TCHH* gene, rs4278906 polymorphism of the *ADAM17* gene and rs11103631 polymorphism of the *FCN1* gene [27].

Trichohyalinin (TCHH) is involved in the interfilament crosslinking of keratin intermediate filaments and functions as a major reinforcement protein for the cell membrane barrier structure, associated with various hair or epidermal growth disorders such as trichothiodystrophy and keratinization diseases of the skin [46]

ADAM17 (disintegrin and metalloproteinase 17) is a membrane-anchored metalloproteinase that cleaves membrane-bound tumor necrosis factor (TNF)-α, affecting the epidermal barrier [42].

FCN1 gene encodes the plasma protein ficolin-1, classified in the immunoglobulin superfamily, plays a critical role during infection and inflammation, promoting the destruction of pathogens, thereby participating in the inflammatory response and immune defense mechanisms of the skin barrier [32]

Genes associated with antioxidant capacity. The skin, due to its location, is involved in many important processes in the body, including redox reactions and circadian rhythms [40]. Excessive amounts of reactive oxygen species in the skin cause degradation of the dermal extracellular matrix and are characterized by increased oxidative damage [9]. To counteract the increased potential for oxidative stress, skin cells have several lines of defense, including protective enzymes such as catalases (CATs), glutathione peroxidases (GPxs), and superoxide dismutases (SODs), as well as low-molecular-weight antioxidants such as vitamins A, C, and E; melatonin; and glutathione (GSH) [40].

The rs4880 polymorphism of the *SOD2* gene is characterized by the replacement of alanine with valine and is

associated with a decrease in enzyme activity, which manifests itself in a decrease in the antioxidant defense of the cell [41]. In the study by Soerensen M et al. (2009) established an association of the rs4880 polymorphism of the *SOD2* gene and rs1050450 of the *GPX1* gene with life expectancy, functional and cognitive abilities in old age [44]. In the study of Katsarou M-S et al. (2018) of ten polymorphisms of 8 genes involved in oxidative stress, it was found that residents of the Caucasian race from the south-eastern region of Europe may have higher protection against oxidative stress than northern, central, north-western and south-western Europeans [20].

In the study of Sepetiene R. et al. (2023) from the Lithuanian University of Health Sciences found significant correlations of genetic variants of *CAT* (rs1001179), *GPX1* (rs1050450), *NQO1* (rs1800566), *IL1Beta* (rs1143634) and *COL1A1* (rs1800012) with liver enzymes ALT and AST, as well as with white blood cell count, highlighting their potential role in maintaining liver health and supporting the immune system [19].

Conclusion. Currently, there is no consensus on the definition of the degree of skin aging and methods for assessing its condition, except for visual ones. Since the degree of pigmentation and elasticity of the dermis are individual characteristics, the use of a genetic approach to skin care can affect the rate and efficiency of penetration, absorption and sensitization of cosmetics and drugs.

Understanding the influence of genetic features on skin properties in combination with environmental factors and lifestyle can become a valuable tool for the design and creation of personalized skin care products, preventive medical and cosmetic correction of signs of aging, and can also become an effective and affordable method for treating many skin diseases in the future.

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POINT OF VIEW

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THYROID HORMONE LEVEL IN MEN AND WOMEN OF SOUTH YAKUTIA DEPENDING ON THE TYPE OF WATER CONSUMED

In order to compare the level of thyroid hormones and antibodies depending on the use of filtered or untreated water, a survey of residents of the Aldan district of South Yakutia was conducted. As a result of the study, more pronounced changes in the level of thyroid hormones were revealed in women of Aldan. The frequency of violations of low levels of T3free, T3total, T4free is noted in people who use filtered water, which requires additional comparative study of the chemical composition of purified and untreated water consumed by the population.

Keywords: thyroid hormones, drinking water, South Yakutia

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Currently, in the Aldan district of South Yakutia there are gold mining facilities located on the territory of the Kuranakh ore field on the watershed of three rivers (B. Kuranakh, Seligdar and Yakokut) flowing into the Aldan River. As a result of the activities of gold mining enterprises, unfavorable factors are formed, which, being a powerful source of pollution of water bodies, soil, atmospheric air, flora and fauna, can have a negative impact on the human body. High concentrations of toxic elements of heavy metals As, Cr, Pb, Zn were found in the soil of 5 settlements of

the Aldan district. The highest level of soil contamination is recorded in the city of Aldan [4]. An additional factor influencing morbidity is the radiation factor [6].

In drinking water sources and in the indoor air of the Aldan district, there is an increased level of radon, which enters the water, soil and air from radium and is associated with the geological structure of the region. It should be noted that according to data obtained by specialists of the Territorial Administration of Rospotrebnadzor in the Republic of Sakha (Yakutia) in the Aldan district, in different seasons of 2017, the specific activity of radon in the water of water intake wells in the city of Aldan was higher and amounted to 54-181 Bq / l, in the city of Tommote (including the Alekseyevsk microdistrict) - 55-99 Bq / l.

The problem of wastewater treatment in industrial areas (Aldan, Ust-Nera, Chersky) continues to be relevant, since treatment facilities do not cope with the task and do not provide a good degree of purification.

The endocrine system is one of the central links in the adaptation process. Therefore, the assessment of the endocrine system provides important prognostic information on pre-clinical diagnostics of health disorders. [5, 3, 9].

Changes in the hormonal profile of the pituitary-thyroid system can cause the development of various diseases, endocrine pathology, so timely diagnostics and prevention remain relevant.

The aim of the study was to assess the level of thyroid hormones in residents of the Aldan district who consume filtered and untreated water.

Materials and methods of research: A survey of 173 people of working age of the Aldan district was conducted: 116 people from the city of Aldan (58 men and 58 women, the average age was 44 (33; 52) and 39 (32; 45), respectively, from the city of Tommot 57 people (7 men and 50 women), the average age of men was 62 (41; 64), women 48 (37-59) years. The study was approved by the decision of the Local Ethics Committee at the Federal State Budgetary Scientific Institution "Yakutia Scientific Center for Clinical and Medical Research". The study participants were informed in advance about the goals and nature of the study, and all of them provided written voluntary consent for its implementation.

Blood sampling was performed before 11 a.m., with a 12-hour interval from the last meal. Determination of the concentration of hormones free triiodothyronine (T3free), total triiodothyronine (T3total), total and free thyroxine (T4total and T4free), thyroid stimulating hormone (TSH), thyroglobulin (TG), antibodies to thyroglobulin (anti TG), antibodies to thyroid peroxidase (anti TPO) was performed in blood serum by a solid-phase enzyme immunoassay (TIFA) on a Uniplan photometer using Vector Best kits (Russia), according to the manufacturer's instructions.

Statistical data processing was performed using the IBM SPSS Statistics 23 software package. The data are presented as median (Me) and interquartile range [Q25; Q75]; for categorical indicators, as absolute and relative values - n (%). The nonparametric Mann-Whitney U-test was used to compare two independent samples. The normality of distribution was tested using the Kolmogorov-Smirnov method. Differences were considered statistically significant if the level of significance was $p < 0.05$.

Results and discussion. Statistical analysis of hormone levels by ethnicity and place of residence showed that the average hormone levels in men and women from Aldan and Tommot varied within the normal range, except for T3total, the level of which was shifted to the lower limit of the norm. Women from Aldan had higher free T3 levels, by 15.9% (p=0.012) compared to women from Tommot and by 16.4% (p=0.015) compared to men from Aldan. Women from Tommot had the highest total T4 levels, by 15.2% (p=0.000) compared to women and men from Aldan and 20.8% (p=0.000), respectively. Free T4 level in women from Tommot, it was also higher in comparison with women (p=0.000) and men (p=0.005) from Aldan. In women from Aldan, free T4 was increased by 9.1% (p=0.003) in comparison with men from Aldan and by 19.3% (p=0.003) in comparison with men from Tommot.

In men of Aldan and Tommot, the average hormone level did not differ, but was lower in comparison with women (Table).

The levels of TG, TSH, Anti-TPO and Anti-TG by gender distribution and place of residence did not differ significantly.

Analysis of the frequency of hormonal disorders by place of residence and gender showed that in Aldan the number of women with thyroid hormone levels below the norm is higher and amounted to: T3total. (11) 19.3%, T3free. (21) 36.2%, T4free. (14) 24.1%, in Tommot - T3total in (16) 32.0%, T3free. in (4) 8%, T4free. in (2) 4.0%, respectively. An increase in the concentration of T3free. above the norm was detected in one woman in Aldan (1.7%), T3total. in one woman 2% in Tommot. The level of T4total was higher than the norm in two (3.4%) women in Aldan and in (5)10% in Tommot. In men in Aldan, the level of T3total, T3free, T4free below the norm was detected in (19)32.8%, (8)13.8%, (4)6.9%, in Tommot only T3total was found in (1)14.3%.

Thyroid hormone levels in men and women cities of Aldana and Tommot

Indicators	Aldan		Tommot	
	Men n=58	Women n=58	Men n=7	Women n=50
	1	2	3	4
T3total (1.3-3.0 n/mol/L)	1.46 (1.16; 1.72)	1.49 (1.42; 1.62)	1.48 (1.29; 1.87)	1.48 (1.18; 1.85)
T3free (4-8.6 pmol/L)	4.72 (4.20; 5.73)	5.65 (4.51; 6.39) p=0.015[1-2] p=0.012[2-4]	4.11 (3.29; 4.68)	4.75 (4.36; 5.23)
T4total (52-155 nmol/L)	93.57 (88.97; 100.24)	100.31 (98.77; 129.47)	92.54 (84.44; 114.16)	118.28 (92.39; 135.44) p=0.000[1-4] p=0.000[2-4]
T4free (10.3-24.5 pmol/L)	15.31 (13.68; 16.97)	16.84 (15.85; 18.75) p=0.003[1-2] p=0.003[2-3]	13.58 (10.01; 16.73)	17.04 (15.31; 18.07) p=0.005[1-4] p=0.000[2-4]
TG(<50ng/mL)	1.94 (0.76; 3.92)	9.8 (3.10; 12.37)	1.12 (0.16; 7.42)	5.73 (2.78; 10.66)
TSH(0.4-5.0 mIU/L)	1.60 (1.11; 2.79)	1.55 (1.15; 2.57)	1.78 (1.09; 2.61)	1.77 (1.10; 2.32)
Anti-TPO (up to 30 U/ml)	0.27 (0.00; 1.94)	0.00 (0.00; 1.83)	0.42 (0.00; 2.25)	0.00 (0.00; 2.45)
Anti-TG (up to100 IU/ml)	2.88 (0.57; 5.78)	3.75 (2.88; 4.62)	2.88 (0.42; 10.02)	4.33 (2.30; 6.49)

The TG level was elevated in (4) 6.9% of women and (1) 1.7% of men only in Aldan. Elevated TSH levels were detected in one woman (1.7%) from Aldan and the second from Tommot (2%). Anti-TPO concentrations were higher than normal in (5) 8.6% of women in Aldan and (8) 16.0% in Tommot. Changes in almost all hormonal parameters were noted in one woman in Aldan, a decrease in the level of total T3, free T3, and free T4, and an increase in the levels of TG, TSH, and Anti-TPO, who was previously diagnosed with primary hypothyroidism. Among residents of Tommot, T3 free and free T4 values below normal were noted in one woman. Increased hormone levels were noted in two women, one with total T3 and total T4, and the other with total T4, free T4. and Anti-TPO diagnosed her with grade 1 nodular goiter.

Statistical analysis of changes in hormone levels depending on the place of residence and type of water consumed showed that the average level of T3total, T3free, TG, TSH, Anti-TPO and Anti-TG in residents of Aldan and Tommot varied within the normal range and did not differ significantly. However, residents of Tommot, who consumed both filtered and untreated water, had higher levels of T4total and T4free, compared to the data of residents of Aldan (Fig. 1, 2).

The concentration of T4free in residents of Tommot who consume filtered water was increased by 7.3% (p=0.000) compared to those in Aldan who consume untreated water and by 15.2% (p=0.000) filtered water (Fig. 1). In residents of Tommot who consume untreated water, the level of T4total was increased by 5.3% (p=0.041) and 9.6% (p=0.015) compared to residents of Aldan who consume untreated and filtered water, respectively. Tommot residents who drink filtered water have a T4total level. was increased by 13.8% (p=0.012), compared with residents of Aldan drinking untreated water and by 17.8% (p=0.000) drinking filtered water (Fig. 2).

The analysis of the frequency of occurrence of changes in the pituitary-thyroid axis depending on the type of water consumed showed that low hormone levels were more often observed in people drinking filtered water, in residents of the city of Aldan T3total in 30.8%, T3free in 29.7%, T4free in 16.5%, in residents of the city of Tommot in 33.3%, 6.7% and 2.2%, respectively.

In women of the European North, low values of T3total were observed with an increase in the content of T3free and a decrease in the level of adaptation potential, also in the Caucasian population with

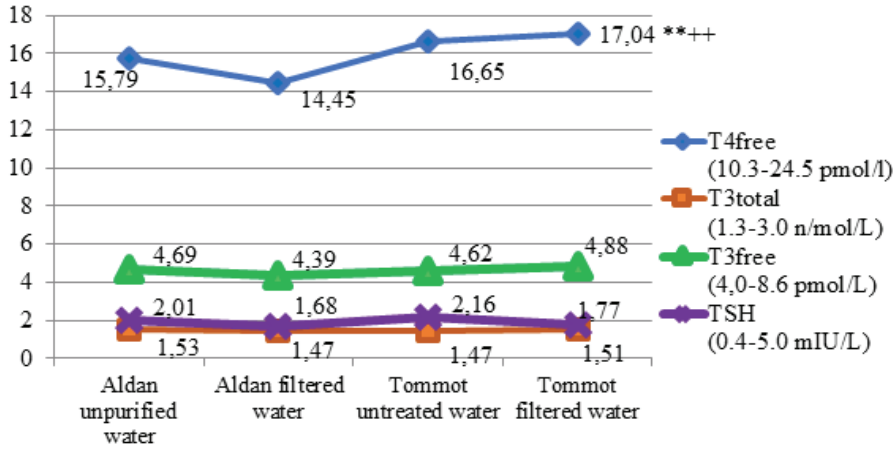

Fig. 1. Level of thyroid hormones in city residents. Aldan and Tommot depending on the type of water used.
Note: **-p<0.00 in comparison with residents of Aldan drinking untreated water; ++-p<0.000 in comparison with residents of Aldan drinking filtered water.

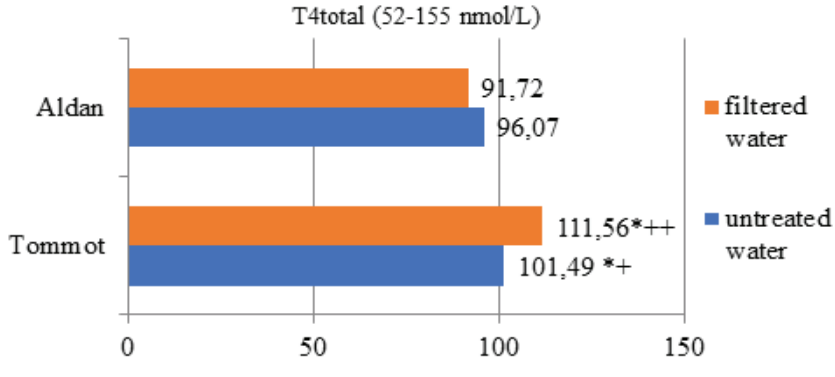

Fig. 2. T4 total level. (nmol/l) among residents of the city Aldan and Tommot depending on the type of water used.
Note: * - p < 0.05 in comparison with residents of Aldan drinking untreated water; + -p<0.05 in comparison with residents of Aldan drinking filtered water; ++-p<0.000 in comparison with residents of Aldan drinking filtered water.

adaptation stress, significant changes in the thyroid status were revealed, manifested by a decrease in the concentrations of T4total and an increase in TSH and T3free, in comparison with the sedentary aboriginal population [3].

According to literary data, thyroid diseases in residents of the Penza region had a positive correlation with the content of minerals in water and soil [8].

In healthy residents of the Arkhangelsk region, low values of the thyroid index ITI, T3free and T3 /T4 free ratios were found in individuals with an increased level of anti-TPO and anti-TG, which indicates a decrease in the index of tissue conversion of thyroxine into its more biologically active metabolite against the background of higher activity of the thyroid gland, which is confirmed by higher levels of T4 [1].

Thus, more pronounced changes in the level of thyroid hormones were noted in women of Aldan. The frequency of violations of low levels of T3free, T3total, T4free is noted in people drinking filtered water, which requires additional comparative study of the chemical composition of purified and unpurified water consumed by the population.

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RELATIONSHIP OF NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH ARTERIAL HYPERTENSION TO CERTAIN CARDIO-METABOLIC RISK FACTORS

A study was conducted by type "case" (n=29) and "control" (n=69) among the non-indigenous population in south Yakutia with arterial hypertension (AH) in the presence and absence of non-alcoholic fatty liver disease (NAFLD). The groups were comparable in age. Patients in the main group had statistically significantly high systolic blood pressure, average BMI and WC values compared with patients without NAFLD. In hypertensive patients in combination with NAFLD, the chance of developing obesity is more than 4 times higher compared to the control. Hypertensive patients with NAFLD had a significantly high incidence of atherogenic dyslipidemia. The conducted ROC analysis showed the prognostic significance of risk factors such as BMI, WC, TG and blood pressure levels with the risk of developing NAFLD in patients with hypertension.

Keywords: arterial hypertension, non-alcoholic fatty liver disease, obesity, dyslipidemia, predictive significance

Arterial hypertension (AH) is currently the most common cardiovascular pathology, and its prevalence is increasing every year [1, 14]. There is also a steady increase in the prevalence of non-alcoholic fatty liver disease (NAFLD) worldwide, according to preliminary data, affecting more than a quarter of the adult population [3, 15]. NAFLD, same as AH, is a predictor of metabolic syndrome, often having common pathophysiological mechanisms of development. As for the effect of NAFLD on the risk of hypertension, it remains unclear and widely discussed in the scientific community [8, 16]. The NHANES cross-sectional multicenter study [16] and meta-analysis of a large-scale 11-cohort study in the pre-pandemic period revealed a correlation between the development of hypertension and the risk of developing NAFLD [6, 9, 11, 12]. However, the causal relationship between them remains unclear.

The aim of the study was to identify the relationship of non-alcoholic fatty liver disease in patients with arterial hypertension with certain risk factors for cardiovascular diseases in the territory of southern Yakutia.

Materials and methods of research. An expeditionary survey of people of working age of non-indigenous nationality in southern Yakutia was conducted with the participation of general practitioners and specialists, as well as specialists of the auxiliary service. A total of 200 people were invited to the study from the list of employees of an enterprise, 174 of them participated, the response rate was 87%.

98 people with established essential hypertension were selected for further study. Blood pressure levels of ≥ 140/90 mmHg or constant use of antihypertensive drugs were assessed as hypertension according to clinical recommendations for the diagnosis and treatment of hypertension [1, 14].

For further research, two groups of people with elevated BP were formed: the main group (case), consisting of people with diagnosed hypertension in combination with NAFLD (29 people) and the control group (control) - hypertension without NAFLD (n=69).

Exclusion criteria: hypertension of the

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3rd grade, 3rd stage, secondary arterial hypertension, other liver diseases (viral hepatitis, cirrhosis of the liver, liver cancer, alcoholic hepatitis), diabetes mellitus, oncological diseases.

The research was guided by the ethical principles of the Helsinki Declaration of the World Medical Association (2008), as well as the protocol of the Bioethics Committee at the Yakutsk Scientific Center for Complex Medical Sciences.

The diagnosis of "Non-alcoholic fatty liver disease" was made on the basis of an ultrasound examination of the liver on an empty stomach and the report of a general practitioner. The echo signs were distal attenuation of the echo signal, diffuse increased echogenicity of the liver compared to the kidneys, blurred or depleted vascular pattern. The exceptions were alcoholic liver damage, chronic viral hepatitis and cirrhosis. We were guided by the clinical recommendations for the diagnosis and treatment of NAFLD in 2022 [3].

The body mass index (BMI) or Quetelet II index was calculated using the formula: BMI (kg/m2) = body weight (kg)/ height (m2). Overweight was established at a BMI value of ≥25 and <30 kg/m2, obesity at a BMI of ≥ 30 kg/m2 [4].

To identify the type of obesity and its severity, waist circumference (WC) is measured. WC is measured in a standing position, patients should only wear underwear. The measurement point is the midpoint of the distance between the apex of the iliac crest and the lower lateral edge of the ribs. It does not necessarily have to be at the navel level. WC > 94 cm in men and > 80 cm in women, it can be assumed that the patient has abdominal type of obesity [2].

Laboratory research methods included: determination of lipid metabolism (total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG)), and blood glucose.

Russian clinical guidelines were used to determine the frequency of lipid metabolism disorders. Lipid metabolism disorders in 2023 [5]. Fasting hyperglycemia (HG) was established at a glucose level of ≥ 6.0 mmol/L.

Statistical processing of the obtained results was carried out using the IBM SPSS Statistics program (26.0). Qualitative variables are described by absolute and relative frequencies (%), quantitative variables are described using the mean and standard error of the mean, as well as the median (Me) and interquartile range (Q25-Q75). Frequency comparison was performed using Spearman's χ2 test with Yates correction, odds ratio (OR) and 95% confidence interval (95% CI). Spearman's coefficient was used to analyze the correlation. The statistical significance of the differences (p) was assumed to be less than 0.05. The predictive significance between quantitative indicators was also carried out using logistic regression and ROC analysis.

Table 1

Clinical and demographic characteristics of patients with hypertension

Indicator	Main group (AH+NAFLD)	Control group (AH)	P
Age, years, Me (Q25; Q75)	49 (42.5; 54)	49 (40.5; 57)	0.792
Gender m/f,n (%)	11/18 (37.9/62.1)	30/39 (43.5/56.5)	0.611
Stage 1 AH, n (%)	5 (17.2)	21 (30.4)	0.177
Stage 2 AH, n (%)	24 (82.8)	48 (69.6)	
Grade 1 AH, n (%)	7 (24.1)	26 (37.7)	0.195
Grade 2 AH, n (%)	22 (75.9)	43 (62.3)	
SBP, mmHg (M±m)	152.07±2.45	143.33±2.63	**0.048**
DBP, mmHg,(M±m)	91.21±1.52	88.48±1.27	0.217
BMI, kg/m2, (M±m)	34.07±0.82	29.51±0.56	**<0.001**
WC, cm, (M±m)	106.45±1.91	94.90±1.47	**<0.001**

Note: SBP – systolic blood pressure, DBP – diastolic blood pressure

Table 2

Average median values of blood metabolic indicators in hypertensive patients with and without NAFLD

Indicators	Main group (n=29)		Control (n=69)		P
	Me	Q25; Q75	Me	Q25; Q75	
TC	5.01	4.85; 5.61	5.01	4.84; 6.04	0.205
LDL	2.61	1.81; 3.11	2.37	1.45; 2.35	0.833
HDL	1.62	1.36; 1.87	2.01	1.51; 2.47	0.003
TG	2.18	1.56; 2.88	1.58	1.15; 2.80	0.539
glucose	5.3	4.8; 6.0	5.2	4.9; 5.7	0.818

Table 3

Comparative analysis of lipid-metabolic disorders in hypertensive patients with and without NAFLD

Indicators	Main group n(%)	Control n(%)	χ^2	TC [95%CI]	P
HCS	15 (51.7)	35 (50.7)	0.008	1.041 [0.437-2.479]	0.928
LDL HCS	19 (65.5)	29 (42.0)	0.776	2.621 [1.063-6.463]	0.036
Hypo-α-CS	2 (6.9)	1 (1.4)	2.042	5.037 [0.438-57.880]	0.153
HTG	21 (72.4)	32 (46.4)	5.574	3.035 [1.183-7.784])	0.018
HG	11 (37.9)	21 (30.4)	1.375	1.397 [0.563-3.465]	0.241

Results and discussion. A comparative analysis of clinical and demographic indicators of patients with AH with NAFLD (main group) and without NAFLD (control) was carried out. The results of the analysis are shown in Table 1. The comparison groups were comparable in age. But at the same time, patients in the main group had statistically significantly high systolic blood pressure, average BMI and WC values compared to patients without NAFLD, showing the importance of combination with comorbid pathology. Our

data are consistent with literary sources, where the risk of developing NAFLD increases with BMI and WC [15, 16].

For correlation analysis, we have carried out a parallel of the strength and direction of the relationship between systolic blood pressure (SBP) and anthropometric data in hypertensive patients, depending on the presence or absence of comorbidity. The correlation with anthropometric indicators was determined in both comparison groups. In both the main group and the control group, SBP and diastolic blood pressure (DBP) were statistically significantly correlated with BMI: in patients with hypertension with NAFLD (r=0.425, p=0.022; r=0.418, p=0.024; respectively); in the control group (r=0.264, p=0.028; r=0.263, p=0.029; respectively).

In the AH+NAFLD group, the vast majority of patients had a BMI exceeding 30 kg/m2, which was 82.8% (n=24), 5 people or 17.2% were overweight. As for people with isolated hypertension, 52.2% of them were obese in BMI (n=36), 20 people or 29% - overweight, the remaining 13 people or 18.8% of them had a normal BMI. The risk of developing obesity in the main group was more than 4 times higher (OR 4,400 [95% CI 1,505-12,867] (p=0.018).

A positive correlation with waist circumference was obtained in both groups, the strongest in the group of hypertensive patients with NAFLD (r=0.436, p<0.001), average strength in the group of hypertensive patients without NAFLD (r=0.241, p=0.036). AO was observed in all persons of the main group (100%), in the control group - in the majority (82.6%), the differences between them were statistically significant (χ^2=5,747, p=0.017).

Thus, the key link influencing the association of hypertension with NAFLD was obesity, both in BMI and abdominal type with a significant difference. Our results confirm the results of large-scale studies of NHANES [16] and PROSPERO [13].

To determine the comorbid effect of NAFLD on hypertension, we conducted a comparative analysis of metabolic disorders in hypertensive patients with and without NAFLD.

The average concentrations of metabolic indicators in the compared groups were characterized (Table 2). In hypertensive patients with NAFLD, the median concentrations of TC, LDL cholesterol, and TG were statistically slightly higher than those of the control groups. The median TG in the main group exceeded the reference values. The median HDL cholesterol was statistically significantly lower in the main group compared with the control.

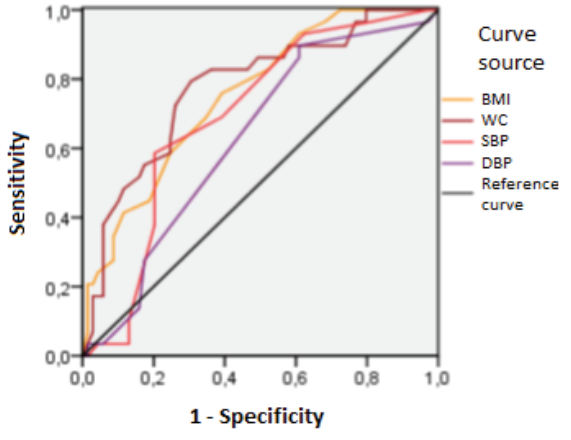

Fig. 1. ROC curve of dependence of BMI, WC, BP in predicting the risk of NAFLD

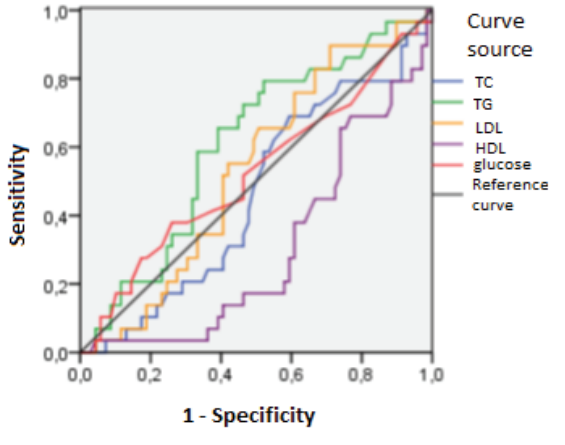

Fig.2. ROC curve of parameters of lipid and carbohydrate metabolism in predicting the risk of NAFLD

Further analysis was carried out to determine whether the existing essential hypertension is aggravated by comorbid pathology on the part of the liver. As shown in Table 3, metabolic disorders were most often detected in the group of hypertensive patients with concomitant comorbid pathology, and had statistically significant differences in the incidence of atherogenic fractions of dyslipidemia, in particular with respect to LDL HCS and HTG (p<0.05). If the overall medians of these indicators did not have significant differences, then exceeding their reference values in the main group showed the effect of NAFLD on the risk of aggravation of atherosclerosis and possible vascular complications in the future.

A correlation analysis of SBP with the lipid and carbohydrate spectrum was carried out. In the main group, significant correlations of SBP were obtained only with TC (r=0.368, p=0.049), the conjugacy with other blood parameters was insignificant: TG (r=0.137, p=0.479), HDL (r=0.041, p=0.834), HDL (r=0.301,p=0.112), blood glucose (r=0.305, p=0.108). In hypertensive patients without NAFLD, SBP had no significant correlation with any indicator of lipid and carbohydrate metabolism (p>0.05).

To assess the prognostic significance, determine the causal relationships between hypertension, risk factors and NAFLD, a sensitivity and specificity analysis of models or ROC analysis was performed.

To analyze the relationship with the development of NAFLD in hypertensive patients, a logistic regression of ROC analysis with anthropometric indicators and levels of systolic and diastolic blood pressure was performed (Fig.1). The area under the curve with good informativeness is most sensitive for WC, whose AUC (AreaUnderCurve) was 0.776±0.052 [95% CI: 0.674-0.877], with statistical significance (p<0.001), and for BMI with AUC]0.753±0.051 [95% CI: 0.654-0.852] (p<0.001). The average quality of the predictive power of the models was obtained for systolic and di-

astolic blood pressure, where the AUC was 0.693±0.055 [95% CI: 0.586-0.801] (p=0.003), and 0.626±0.059 [95% CI: 0.512-0.741] (p=0.049), respectively.

As for the indicators of lipid and carbohydrate metabolism, as shown in Figure 2, no prognostic significance was obtained with respect to the risk of developing NAFLD, except for TG with satisfactory informativeness, where the AUC was 0.608±0.061 [95% CI: 0.489-0.727] (p=0.092).

Thus, the ROC analysis showed the prognostic significance of risk factors such as BMI, WC, TG and blood pressure levels with the risk of developing NAFLD in patients with hypertension.

Conclusion. NAFLD, having common pathophysiological mechanisms of development with hypertension, exacerbates the course of the disease, since hypertension itself is a predictor of the development of complications from the cardiovascular system. This confirms that in the group of comorbid patients, significantly high rates of systolic blood pressure, BMI obesity, abdominal obesity, LDL HCS and HTG were noted. Sedentary lifestyle and overeating create conditions for the epidemic spread of obesity and, consequently, NAFLD. NAFLD itself, by potentiating hypertension, can lead to the development of metabolic syndrome and type 2 diabetes mellitus, and an increase in mortality from cardiovascular disasters. Long-term NAFLD under the influence of a number of factors can sooner or later lead to the development of steatohepatitis, liver fibrosis, decompensated cirrhosis and further hepatocellular carcinoma. Programs are needed to raise awareness of the presence of NAFLD, timely implementation of a strategy for lifestyle changes, weight loss, increased physical activity among the population, a diet with a reduced content of carbohydrates and fats, hepatoprotective treatment, which may help, if not reverse, then slow down the course of the disease.

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CLINICAL CASE

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BLAND-WHITE-GARLAND SYNDROME: CLINICAL FEATURES OF THE COURSE AND TREATMENT IN A YOUNG PATIENT

Bland-White-Garland syndrome (SBUG) is a rare, high–risk fatal outcome in infancy and sudden death in adults, an anomaly of the divergence of the left coronary artery (LCA) from the pulmonary artery (PA) (ALCAPA - abnormal left coronary artery arising from the pulmonary artery). In 85-90% of cases, children without radical surgical treatment do not live up to a year. In our clinical case, in a 36-year-old patient, the disease debuted with recurrent ventricular arrhythmias, Imaging diagnostic methods coronary angiography, spiral computed tomography, magnetic resonance imaging of the heart revealed in the patient, in addition to the pathology of the LCA, individual anatomical features of the coronary bed, which provided adequate myocardial perfusion and maintained sufficient myocardial reserve. A combined operation was performed on a patient at the "Federal Center for Cardiovascular Surgery" of Khabarovsk: prosthetics of the LCA trunk with a vascular prosthesis "Vascutek PTFE" № 6. Plastic surgery of the pulmonary trunk (PT) with a patch from the autopericardium. Mitral valve repair (MV) on the "MedInj" support ring № 28. The postoperative period was uneventful. The period of dynamic observation was 22 months. Currently, the patient is in a satisfactory condition and is able to work. Given the different clinical variants of SBUG, specialists providing primary health care - district pediatricians, internists, cardiologists - should be wary of this rare but life-threatening congenital malformation.

Keywords: Bland-White-Garland syndrome, anomaly of the left coronary artery, ALCAPA.

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Introduction. Bland-White-Garland syndrome (SBUG) is a rare congenital heart disease in which the left coronary artery (LCA) departs not from the left coronary sinus, but from the trunk of the pulmonary artery (PA) (ALCAPA – abnormal left coronary artery arising from the pulmonary artery). SBUG is more often observed in female patients who die in early infancy or in adulthood from sudden death [3]. In 1886, H. St. J. Brooks made the first description of the congenital anomaly of LCA, then A.I. Abrikosov, the founder of the Russian and Soviet schools of pathological anatomy, in 1911. For the first time, at an autopsy in a 5-month-old child, he discovered and described this pathology [6]. Further in 1933, E. Bland, P.D. White and J. Garland presented clinical and electrocardiographic (ECG) signs of this defect [8].

The risk factors and causes of the formation of this congenital anomaly in the fetus are still debatable. According to L.A. Bokeria, the incidence of congenital anomalies of the coronary arteries (CA) is 1.3% among patients who underwent coronary angiography (CAG). SBUG accounts for 0.25-0.5% of all anomalies [1].

There are 4 variants of this anomaly, when the LCA, the right coronary artery (RCA), both the LCA and the RCA or the accessory coronary artery can depart from the PA. Depending on the variant of the coronary artery anomaly, damage to three segments of the myocardium to which non-oxygenated blood is delivered is characteristic. SBUG undergoes 3 main pathophysiological phases in its development: in the 1st phase in the prenatal period, high pressure in the PA ensures adequate blood flow to the LCA; the 2nd phase is critical, associated with a drop in pressure in the PA and the development of intercoronary anastomoses; Phase 3 is characterized by high systolic pressure in the RCA than in the abnormal LCA [4].

The clinical picture depends on the type of SBUG. The "infantile" type proceeds with "angina pectoris" with the appearance of sudden anxiety, tachypnea, cough, pallor, acrocyanosis in the child. Seizures can also be provoked by crying, defecation. The increasing deterioration of myocardial blood flow in a child leads to unstable angina and myocardial infarction (MI). After undergoing it, ischemic cardiomyopathy develops. In 85-90% of cases, children without radical surgical treatment do not live up to a year [9]. If this life-threatening period passes, then stabilization of the condition may occur. In the "adult" type of SBUG, sudden cardiac death often occurs, often without previous signs of heart failure.

We present our clinical observation of SBUG in a young patient. The patient has received informed consent to the publication of the medical history.

Clinical observation. Patient S., 36 years old, was urgently delivered by ambulance to the Republican Cardio-vascular Center (RCvC) in September 2022. From the anamnesis of the disease, it

was found out that at night the husband found his wife unconscious with wheezing breathing. Immediately, calling an ambulance, he began to perform indirect heart massage. Ventricular fibrillation (VF) was registered on the ECG. Cardiopulmonary resuscitation, defibrillation, and tracheal intubation were performed. According to the mother, up to 3 years old, she was worried about frequent seizures: her lips turned blue, and her heart periodically "stopped". She was sent to Meshalkin National Medical Research Center, Novosibirsk, where dilated cardiomyopathy (DCM), mitral valve insufficiency (MV) 2 art. was diagnosed and a heart transplant was recommended. But from that time until the age of 16, seizures were rarely bothered. The patient is married. 1 pregnancy that ended in cesarean delivery at the age of 23.

The patient underwent emergency CAG: the type of blood supply is right-handed. The trunk of the LCA is not visualized in a typical place. The RCA is passable, hypertrophied, up to 6.5 mm in diameter; without signs of stenosis. There is a contrast between the anterior interventricular branch (LAD) and the envelope branch (EB) due to intersystem overflows and discharge of contrast material from the trunk of the LCA into the PA.

According to the EHO-CG: Dilation of the left ventricular cavity (LV): CDS 6.4 cm, CSS 4.9 cm. CDV 102 ml, CSV 52 ml, IV 50 ml. MV: the valves are compacted, regurgitation 3 art. Hypokinesis of the anterior, anterolateral, anterior chin wall in the basal and middle segments. The ejection fraction (EF) is 48% (Simpson).

On the 8th day, the patient lost consciousness, and resuscitation measures were initiated. On an ECG - VF, defibrillation was performed with restoration of the sinus rhythm. Considering episodes of bradycardia, a temporary cardiac pacemaker (TCP) was implanted.

To determine the anatomical and functional state of the coronary bed, a multispiral computed tomography (MSCT) of the heart was performed in angiography with contrast: an increase in the size of RA, LA, LV. Trunk PA 2.9 cm; right PA - 1.9 cm; left PA - 1.8 cm. LV: CDV 188.89 ml; CSV 89.5 ml; IV 99.38 ml. Hypokinesis in the anteroposteroid (13), apical-septal (14), basal lower lateral (15) segments. Hypoperfusion in the middle anterior (7), anterolateral (13) segments. The right-hand type of blood supply. There are 2 arteries extending from the right coronary sinus: RCA and an additional twisted branch along the front wall. The trunk of the LCA departs from the pulmonary trunk (PT). 3 permanent residence LAD, anterior branch (AB) and EB depart from the trunk. A branch departs from the EB into the left coronary sinus. The coronary arteries are hypertrophied, have a convoluted course, without signs of stenosis. There are no calcium inclusions. There are small collateral vessels from the descending aorta (Fig 1).

In order to assess the severity of ischemic myocardial damage and its reversibility, valvular structures, and hemodynamic parameters, a magnetic resonance imaging of the heart was performed: moderate expansion of LA, LV, and RA. The zone of hypokinesis in the area of segment 7. EF 39%; IV 66.8 ml; CO 5.5 l/min; CDV 172.6 ml; CSV 105.6 ml. No pathological lag was detected during perfusion examination. On delayed scans after contrast administration, there is an accumulation of contrast in the area of the middle anterior segment (7) measuring 0.8-0.4 cm with local thinning of the myocardium. In T1 mapping, the Epsilon value is 32.5% (the reference value is 30%).

Telemedicine consultations (TmC) were conducted with the Federal State Budgetary Institution "Meshalkin National Medical Research Center" of the Ministry of Health of the Russian Federation, Federal State Budgetary Institution "Federal Center for Cardiovascular Surgery" of the Ministry of Health of the Russian Federation Khabarovsk, Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences", Federal State Budgetary Institution " National Medical Research Center of Cardiology named after Academician E. I. Chazov " of the Ministry of Health of the Russian Federation. A positive response was received from the "Federal Center for Cardiovascular Surgery" of Khabarovsk: surgical treatment in the volume of surgical revascularization of the coronary basin is indicated. In October 2022, the patient underwent a combined operation: prosthetics of the LCA trunk with a vascular prosthesis "Vascutek PTFE" № 6. Plastic surgery with an autopericardial patch. Plastic surgery of the mitral valve on the «MedInj» support ring № 28. On the control CAG: The trunk of the LCA: the prosthesis is passable. No occlusive stenotic lesion was detected in RCA, LAD, EB. Myocardial revascularization is not shown (Fig.2).

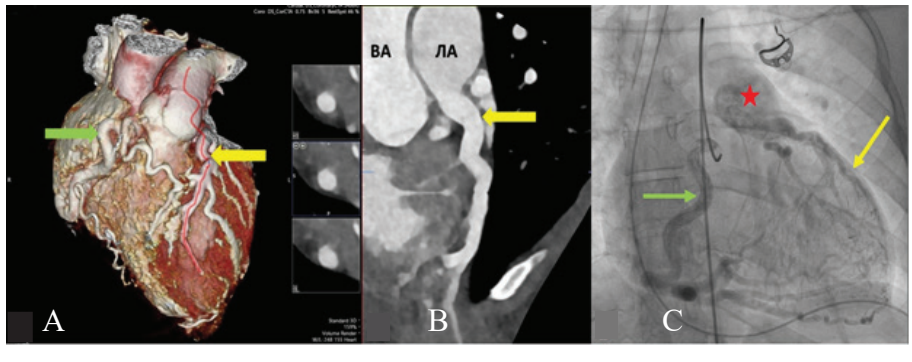

Fig. 1. Preoperative CT of the heart and CAG: A and B - the trunk of the LCA departs from the PA (yellow arrow), RCA (green arrow); C – enlarged RCA (green arrow) retrograde fills the LCA basin (yellow arrow) and the pulmonary artery (red asterisk). BA is the ascending aorta, ЛА is the pulmonary artery

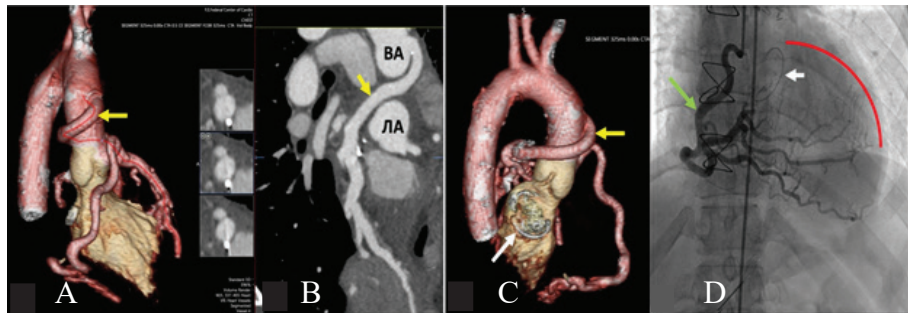

Fig. 2. Control CAG and SCT: A, B and C – prosthetic trunk of the LCA (yellow arrow) passes between the aorta and the pulmonary trunk, the support ring of the mitral valve (white arrow); D – RCA of a smaller diameter (green arrow), there is no retrograde filling of the LCA basin (red line), the shadow of the support mitral valve rings (white arrow). BA is the ascending aorta, ЛА is the pulmonary artery

The early postoperative period was uneventful. The observation period is 22 months. He does not make any active complaints. The patient is able-bodied, committed to the prescribed therapy.

Discussion. The clinical picture of the "adult" type of SBUG is multifaceted, including an asymptomatic course that can be detected during medical examinations [7.10]. In our patient, the manifestation occurred with VF paroxysms. According to the results of imaging diagnostic methods, individual features of the coronary bed were identified, which provided adequate myocardial perfusion. An important fact is that the patient, despite LV remodeling, showed no signs of heart failure. In this regard, the functioning of Viessen-Tebesia vessels, which are located intramurally and anastomose with both arterial and venous vessels, thereby providing compensatory perfusion of ischemic myocardium, is not excluded [5]. The restoration of LV size and volume can be explained by the phenomenon of chronic hibernation with long-term coronary mole deficiency [2].

Conclusion: in SBUG, the only treatment method is surgical restoration of arterial coronary blood flow to reduce the risk of fatal arrhythmias in ischemic LV remodeling. The example of this case demonstrates qualified treatment at all stages of medical care: 1 help, specialized ambulance, cardiac resuscitation, specialized cardiology, high-tech cardiac surgery, which were carried out according to absolute vital indications. Given the various clinical variants of SBUG, specialists providing primary health care - district pediatricians, internists, cardiologists - should be wary of this rare but life-threatening congenital disease.

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A CLINICAL CASE OF ALBINISM IN A TWELVE-YEAR PATIENT

The article presents a clinical case of oculocutaneous albinism type 1A. The albinism type and concomitant diseases are determined. Oculocutaneous albinism is an inherited autosomal recessive disorder which is characterized by hypopigmentation of the skin and hair besides ocular albinism.

Keywords: oculocutaneous albinism type 1A, reduced visual acuity, pigmentation, Yakutia, the Arctic

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Introduction. Albinism is inherited autosomal recessive disorder which is associated with insufficiency or absence of melanin production in ectoderm that result in hypopigmentation of the skin, hair and eyes. The disorder is characterised by disturbance of melanin production in the melanocytes which results from tyrosinase inactivity [1,2,6]. Nowadays, the genetic researchers have revealed that almost all types of oculocutaneous albinism (OCA) are inherited by autosomal recessive type, while ocular albinism is inherited only by X-linked type. Thus, the following classification was agreed:

– Tyrosine-dependent OCA (type 1), which includes 1A – tyrosine negative and 1B – tyrosine positive;
– P-gene dependent OCA (type 2), which includes A – P-gene dependent oculocutaneous albinism (OCA), B – P-gene 'partial' albinism, C – 'brown' albinism;
– TRP-dependent OCA (type 3).

Moreover, the classification contains such syndromic forms as the Germansky-Pudlack syndrome, Chediak-Higashi syndrome, X-linked recessive ocular albinism, syndromes with the skin hypopigmentation associated with or without deafness, ocular hypopigmentation and Angelman syndrome [3,4,9,13].

Today, 12 clinical genetic types of OCA are recognized. OCA type 1 is most common one. It has two subtypes: 1A is caused by complete absence of tyrosinase activity and 1B is caused by partial reduction of tyrosinase activity [1,10,12]. The clinical manifestations of the both subtypes are almost similar, but the first one is considered to be more severe due to absence of positive prognosis with the increasing age. Thus, OCA 1A is characterized by a complete absence of melanin. The worldwide occurrence of the case is from 1:17000 to 1:20000. The tyrosinase works by hydrolizing the change in the amino-acid L-tyrosine to L-DOPA and then oxidizing L-DOPA to DOPA-quinone. Loss of that function results in inability to synthesize melanin. These children phenotypically have very pale skin, fair hair, light or red irises, they are susceptible to ultraviolet lights and should be lifelong cautious as they are at risk of skin cancer development [3,7,11].

Ocular pathology seems to be a most severe clinical manifestation of albinism. The affected individuals have visual problems manifested by hypopigmentation or lack of pigmentation of retina and iris, decrease of vision acuity, nystagmus, strabismus, photophobia and misrouting of the optic nerves in optic chiasm [5,6,10].

No specific treatment of albinism is available, it is treated only symptomatically. Treatment is focused on correction of the eyesight [eye care] and prevention of the skin disorders.

A clinical case: A female patient A., aged 12, Evenk by nationality, follows up regular care at the Medical genetic consultation center of the M.E. Nikolaev Republican hospital #1, National health center, from the age of 1, she has been followed up since 2012. She is regularly hospitalized to the Pediatric center of the M.E. Nikolaev Republican hospital #1, National health center, complaining of overweight, poor eyesight and absence of secondary sexual characters.

From a case history: The child is born from the third pregnancy. Weight at birth was 5000 gr, height was 57 cm. She was born with abnormal pale skin, fair hair, eyelashes and eyebrows, horizontal nystagmus. The patient is overweight since her early childhood, the condition has been progressing in the last two years. She is prescribed permanent astigmatism eyeglasses, the lenses were corrected in April, 2023. She follows up regular check-ups at her local polyclinic with diagnosis of partial atrophy of the optic nerve disk. Appetite is increased, sleep is disturbed. She has suffered from upper respiratory diseases, viral infections of the upper respiratory tract and chicken-pox at her early childhood. No traumas and surgeries as well as allergies are registered. A full complex of medical examination was not carried out as it was impossible to go out from the residential community.

Objective medical status: height – 152cm, weight – 69 kg, BMI=29.8 kg/m2 (normal weight is 18.0 – 18.4); BMI SDS+2.7 (normal weight +-1.0 BMI SDS). She has proportional constitution. The head shape is round. Skin surfaces and visible mucous membranes, hair, eyelashes and eyebrows are hypopigmented. Subcutaneous fat is utterly expressed in the region of the abdomen, skin defects presented by the stretch marks are noticed on the abdomen and thighs. The muscles are hypotonic. The feet are valgus. The face is symmetrical. The neck is short and wide. No abnormalities are noticed in the chest. The abdomen is enlarged. The liver and the spleen are not enlarged. The limbs are symmetrical. The sexual development is of the female character. Stool and urination are normal.

The following laboratory and instrumental investigations are carried out:

Complete blood count, 28.01.2024, anemia, lymphocytosis, monocytosis, neutrophilia. ESR by Panchenkov's micromethod – 26 mm/hr (normal value is 1-15 mm/hr).

Biochemical blood test and hormone status, 23.11.2024, were within the normal values.

Blood test for growth hormone, 23.01.2024, the insulin-like growth factor – 520.2 ng/mL (/normal values/ referential indices 123-396 ng/mL), somatotropic hormone – 0.16 ng/mL (normal value is 0.12-8.08 ng/mL).

Glucose tolerance test: 7.00=4.72 mmol/L; 8.00=9.79 mmol/L; 9.00=7.91 mmol/L.

Electroencephalogram, 23.01.2024, showed bioelectrical activity of the brain according to the age. No pathology of epileptomorphic activity was revealed.

Ultrasound scan of the thyroid gland, 24.01.2024, showed no abnormalities.

The digital X-ray of the hand, 19.01.2024, taken in two projections, determined that the bone age was 11-11.5.

The gynecological examination, 14.01.2024, revealed mammae 1, axillaris 0, pubis 0, mensis 0. Puberty is retarded.

She was consulted by the geneticist. The diagnostic report was: oculocutaneous albinism type 1A. The proband and her family members are recobmmended to be followed up at the medical genetic consultation center and use whole-exome sequencing (WES) or whole-genome sequencing (WGS).

A genetic test by the method of seguencing in the TYR gene revealed OCA1A, OMIM#203100. The test reported oculocutaneous albinism of 1A type.

The ophthalmologist consultation, 19.01.2024, revealed that vision acuity with the correction was OD: 0.05sph+3.0, cyl-2.0 ax0=0.05; OS: 0.05sph +2.5 cyl-1.0 ax0=0.07. Local status: eye fundus OU: pendular waveforms in the horizontal plane with moderate slow phase, nystagmus angles at +15 degrees. The cover test shows that nystagmus alternates and misalignment is neutralised, the movement of the open eye is complete when the other one is closed. Eyelids show no abnormalities, the lacrimal points are within the norm. Conjunctiva is calm. Cornea is transparent. The front chamber is of medium depth. Moist of the front chamber is transparent. Pupil is round, mydriasis medicamentosus is 6mm. Iris examination revealed the loss of iris pigment epithelium, iris transillumination is detected. The eye lens is transparent. Vitreos humor shows no abnormalities. Retina is bright pink colour with no pigmentation, the vessels are transilluminated, choroids. Medical decision is lack of pigmentation in the iris and fundus, hypoplasia of fovea of the 3rd - 4th degree. Reduction of visual acuity is revealed. Diagnosis: OU – partial inherited descending atrophy of the optic nerve associated with albinism. There were noticed hypermetropy of the moderate severity and direct astigmatism. Conjugated secondary non-accomodative alternating chiasmus is revealed.

According to the results of investigations a clinical diagnosis was made. The main clinical diagnosis was oculocutaneous albinism type 1A, obesity of the 2nd -3rd degree. Concomitant diagnosis was partial inherited descending atrophy of the optic nerve associated with albinism. Hypermetrophy of the moderate degree, direct astigmatism were noticed. Conjugated secondary non-accomodative alternating chiasmus was revealed.

Discussion. We have represented the clinical case of the congenital oculocutaneous albinism type 1A. The child was followed up at the medical genetic consultation center since birth, but she

has passed a full genetic examination recently which determined the type of albinism. Moreover, a complete ophthalmological examination which revealed all eye disorders has been carried out for the first time.

According to the researches one third of such children with oculocutaneous albinism may suffer from speech inhibition. The disturbance in the vision may result in disturbed social and relational perceptions [8,14]. The patient shows no inhibition in her intellectual ability, she progresses in studies.

It is known that albinism is a rare genetic disorder which is characterized by inherited disorders of many kinds. Moreover, there are manifestations of the syndromic forms of albinism and this pathology is not well known. The genes, mutations in which seem to be possibly affected by the synthesis of melanin, are being studied. According to the researches there are eight forms of oculocutaneous albinism of different phenotypes.

Early diagnosis is important to identify the severity of the eye affection and due time optic correction, and to enhance the life quality. The patients with albinism should be regularly followed up by the ophthalmologist and the dermatologist for a lifelong period and if it is necessary they have to be followed up by the other medical specialists, too.

The children with albinism should also have special environment to live. Further difficulties might be associated with job finding and child bearing. Thus, the research of this problem seems to be relevant at all times. The study of the clinical symptoms and peculiar characteristics of the disorder will be of great interest for the practicing pediatricians and oculists.

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CLINICAL CASES OF ENDOSCOPIC REMOVAL OF ENDOBRONCHIAL TUMORS

Endoscopic removal of 2 cases of benign tumors and 1 malignant tumor of the bronchus was performed in the endoscopy department of the Republican Hospital No. 1 – National Center of Medicine named after M.E. Nikolaev. The choice of the technique was based on the histological conclusion and videobronchoscopy materials. 2 formations were removed by loop electroexcision and 1 by argonoplasmic coagulation. All patients, without exception, had airway clearance restored with adequate ventilation of previously switched-off lung sections. Endoscopic methods are highly effective in the treatment of patients with bronchial tumors.

Keywords: benign tumors, lung cancer, endoscopic treatment, bronchial recanalization, diagnosis of neoplasms, tracheobronchial tree.

Introduction. The problem of identifying and treating patients with tumors in the bronchi remains important. The main symptoms of obstruction and compression of local structures of the bronchial tree play a key role in the clinical picture, manifested by coughing, wheezing or chest discomfort. [8].

Lung cancer (RL) is the most common malignant tumor disease in the global population, constantly occupying the first place. According to the International Agency for Research on Cancer, more than a million new cases of RL are diagnosed worldwide every year [4]. At the same time, exophytic tumor growth occurs in about 43% of cases [2].

Benign endobronchial tumors are particularly rare clinical manifestations with significant variability in etiology and manifestation [3]. Bronchial lipomas and leiomyomas are quite rare tumors. According to some studies, it is known that there are about 100 reports about bronchial lipomas in the world's literary records [5]. In contrast, leiomyomas occurring inside the lung parenchyma are relatively common, while endobronchial ones are extremely rare. Mainly, that both lymphoma and lung lymphoma usually exhibit benign clinical progression. [3]. The radiological manifestations of these lesions are often vague, including atelectasis, bronchiectasis, recurrent pneumonia or mediastinal displacement, which makes it difficult to distinguish them from malignant tumors [7, 8].

Of all diagnostic methods, the bronchoscopic method is of the greatest importance in the recognition of bronchial tumors. This method is an indispensable study that makes it possible to see direct or indirect signs of a tumor, get an idea of its localization, prevalence and morphological structure. Over the past three decades, there has been a significant shift towards the adoption of endoscopic treatments for patients with certain types of benign tumors. These minimally invasive procedures have emerged as the gold standard of radical treatment [1]. Endoscopic interventions play a key role in restoring bronchial patency and can be performed using either rigid or flexible bronchoscopes, or in combination with both [1]. Endobronchial treatment of central RL offers a viable alternative to traditional open surgery. This approach may be particularly suitable for cases associated with intraepithelial bronchial carcinomas of stage 0 (TisN0M0), in which additional interventions are not required. In addition, endoscopic treatment can be considered as the method of first choice when surgical intervention is not possible due to factors such as the patient's advanced age, concomitant diseases or multiple organ failure [6]. Currently, this is often the preferred option for airway obstruction caused by tumor growth, thereby alleviating associated symptoms and restoring airflow through the tracheobronchial tract [1].

The aim of the study is to present the results of successful treatment of two cases of benign bronchial tumors and one case of malignant bronchial tumor. It should be noted that all three cases were observed one after the other with an interval of about 1.5 months.

Materials and methods. Here are the cases of two endoscopic extractions of benign bronchial tumors and one removal of a malignant bronchial tumor performed for the first time in the Republican Hospital No. 1 – M.E. Nikolaev National Center of Medicine.

The first case: Patient A., 66 years old. It is known from the anamnesis that about 2 years ago, complaints of coughing with sputum and shortness of breath during physical exertion first appeared. During the treatment of NKVI in 2022, the formation of the left main bronchus was revealed on CT of chest organs (CO). With a control CT scan of the CO, an increase in the size of the formation was revealed after 1 year, the patient was referred for consultation to the Clinical and Advisory Department of the Clinical Diagnostic Center of the Republican Hospital No. 1 - National Center of Medicine (RHN№1-NCM). Bronchoscopy was performed on an outpatient basis: at the level of the left main bronchus, the bronchial lumen almost completely encircles a polypoid formation on a short leg, up to 2.0 cm in size. pale pink color. The patient was admitted to the hospital, where endobronchial ultrasonography was performed under ETN and the formation on the pedicle was removed by electroexci-

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sion using a diathermic loop. Conclusion of the pathomorphological examination: histological picture of bronchial submucosal lipoma. The postoperative period proceeded without any peculiarities, the patient was discharged a day later in a satisfactory condition.

The second case: Patient D., 56 years old. It is known from the anamnesis that a few months before hospitalization, there were complaints of coughing with difficult-to-separate sputum. She was sent to the Yakut Republican Oncology Dispensary, underwent a comprehensive examination, and a biopsy revealed leiomyoma at the mouth of the upper lobe bronchus. On CT scan of the CO in the lingual segments of the left lung, a site of fibrosis of a severe nature, in the central parts of which foci of calcification are determined, the left upper lobe bronchus has an air column defect associated with this consolidation. Sent for consultation in RB No. 1-NCM. She was hospitalized for endobronchial removal of the formation. On bronchoscopy, the mouths of the lingual bronchi (B4, B5) of the left lung are not traced, they are completely covered with a dirty pink color, up to 1.0 cm in size. spherical shape with a "false" leg formation. The consistency of the tumor is dense. The formation was partially removed at the first stage under intravenous anesthesia by endoscopic loop electroexcision. After 5 days, complete removal of the formation. The postoperative period proceeded without any peculiarities and a day after the last intervention, the patient was discharged in a satisfactory condition.

Case of malignancy: Patient P., 73 years old. He was on inpatient treatment in RHN№1-NCM, where the patient underwent stenting in the proximal third of the posterobasal branch of the right coronary artery for coronary sclerosis. The second stage, after 2 weeks, was aortofemoral bypass surgery. The postoperative period was smooth. Then the patient gradually developed a feeling of lack of air, vomiting, increased blood pressure, and a rapid increase in respiratory failure. CT scan of the CO revealed an obturation of the right main bronchus. Fibrobronchoscopy with biopsy was performed, where a dirty gray tumor with endobronchial growth was determined, completely obstructing the lumen of the right main bronchus. After 2 days, for the purpose of recanalization under ETA, a videobronchoscope was introduced through a rigid bronchoscope No. 18, the formation in the area of the upper lobe bronchus spur was cut off by argonoplasmic coagulation. There were no complications after surgery. Histological examination: squamous cell carcinoma G2 with small foci of keratinization. The patient was transferred to the Yakutsk Republican Oncological Dispensary for further treatment.

Results and discussion. The procedures were performed for the radical removal of the tumor or for the purpose of palliative treatment to restore the patency of the bronchial tree. Tumor removal using a flexible bronchoscope through an intubation tube under general anesthesia was performed in one patient, in one through tracheal intubation with a rigid bronchoscope, in one under intravenous anesthesia. Electroexcision of the tumor was applied in two patients, one had argonoplasmic excision, and in all cases complete restoration of patency was achieved. There were no postoperative complications and no repeated interventions were required.

Conclusion. These clinical cases demonstrate the effectiveness of endoscopic surgical methods in maintaining respiratory function in patients with benign tumors. Taking into account the endobronchial nature of tumor growth, the use of endoscopic surgery made it possible to avoid traumatic resections, thereby improving the overall quality of life in these patients. In addition, endoscopic interventions in patients with malignant bronchial tumors contribute to the effective and relatively safe restoration of airway patency.

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PATHOLOGICAL FISTULA OF THE SMALL INTESTINE FORMED BY MAGNETIC FOREIGN BODIES

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Magnetic foreign bodies of the gastrointestinal tract are not uncommon in children. A feature of the magnetic foreign bodies of the intestine is their tendency to stick together with each other with the development of intestinal perforation, intestinal fistulas or obstruction.

The purpose of this article is to show the development of a serious complication of magnetic foreign bodies in a child without clinical manifestations.

Foreign bodies of the gastrointestinal tract were discovered accidentally during an X-ray examination for another pathology. The duration of exposure to magnetic foreign bodies is unknown. The child's condition remained satisfactory. A fixed location of foreign bodies in the abdominal cavity was revealed, and the child underwent emergency and delayed surgery. The operation revealed a pathologically formed fistula between the lower horizontal branch of the duodenum and the initial section of the jejunum. The fistula was disconnected and the walls of the hollow organs were sutured. The patient was discharged with recovery.

Keywords: foreign bodies of the intestine, children, magnets

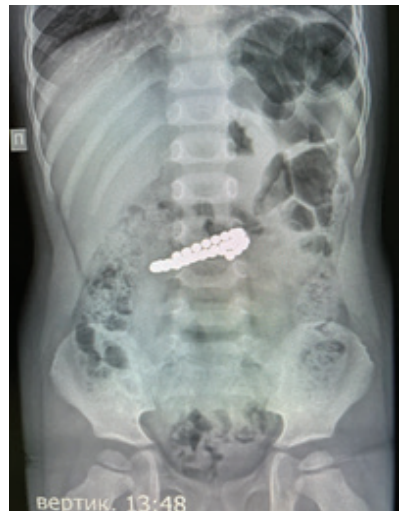
According to many authors [5], even a single magnetic foreign body cannot always be freely evacuated from the child's gastrointestinal tract. Multiple magnetic foreign bodies can cause serious complications in a short time [7]. Clinical symptoms of complications of magnetic foreign bodies of the intestine are non-specific, which can create difficulties in timely diagnostics for a long time. Rarely, such foreign bodies can proceed asymptomatically, even with the development of formidable complications. The purpose of demonstrating a clinical case is to draw attention to the asymptomatic course of a pathologically formed interintestinal anastomosis.

Child K., 3 years old, underwent chest X-ray on 09/06/23 due to a positive reaction to the Mantoux test. Since the film captured an image of both the chest and abdominal cavity, magnetic foreign bodies in the form of a "chain" in the projection of the mesogastrium were accidentally discovered. The duration of the presence of foreign bodies in the intestine is unknown, the parents do not remember swallowing magnets. The child's condition is satisfactory, he is active, has no complaints, the abdomen is soft, painless, pathological formations in the abdominal cavity are not palpable. Stool is self-acting.

With a referral diagnosis of foreign magnetic bodies in the small intestine, a child was admitted to the surgical department of the Pediatric Center for inpatient examination and treatment on September 8, 2023; he was delivered by ambulance from the Central District Hospital. The following diagnostic tests were performed: abdominal ultrasound did not reveal any pathological changes; fibroesophagogastroscopy revealed - congestive gastropathy. A plain radiograph of the abdominal cavity in a direct projection was performed upon admission: pneumatized loops of the large intestine are determined; a cluster of radiopaque shadows in the form of a chain is determined at the level of L3.4, each up to 4 mm in diameter; there are no levels of fluid or free gas in the abdominal cavity. Conclusion: a bracelet-shaped chain of small foreign bodies in the projection of the abdominal cavity (Fig.). Complete blood count upon admission: L - 7.1; ER-4.15; HB-97 g / l; t/c – 263, p/y-1; s/y-36; eos-8; l/c-53; m/c-2; ESR- 12 mm/h.

Taking into account the anamnesis, stable general status of the patient, absence of complaints, satisfactory state of health, soft painless abdomen without symptoms of peritoneal irritation, blood test without inflammatory changes, it was decided to prepare the child for delayed surgical treatment.

On 10.09.23, a control plain radiography of the abdominal cavity was performed - no changes. Over the weekend, the child's condition was satisfactory, active, no complaints, the abdomen is painless, stool is self-acting. The day before the operation, preparation was prescribed - table 1a, infusion therapy, 40 minutes before the operation, perioperative antibiotic prophylaxis was performed with ampicillin sulbactam at the rate of 150 mg / kg / day intravenously slowly. On 11.09.23, a midline laparotomy was performed, during revision below the ligament of Treitz by 10 cm, a formed interintestinal fistula was found



Overview X-ray of the abdominal cavity upon admission

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between the lower horizontal branch of the duodenum and the initial section of the jejunum, foreign bodies were palpated in the lumen. Dissection of the fistula was performed, foreign bodies were removed - round multi-colored magnetic balls with a diameter of 0.3 cm, linked together, in the amount of 34 pieces. Intraoperative X-ray control of the abdominal cavity was performed - no other foreign bodies were found. The wall of the duodenum and jejunum was sutured with a two-row suture of PDS 4/0 thread. The surgical wound was sutured layer by layer, leaving drain tube in the area of fistula suturing. The postoperative period was uneventful, fasting for two days, drinking was started on the second day. On the third postoperative day, the patient was transferred to the general ward for mother's care, enteral loading was started, drain tube from the abdominal cavity was removed. He was discharged on the 11th postoperative day in a satisfactory condition.

Discussion. Foreign bodies of the gastrointestinal tract are a common pathology in young children and can cause serious complications, especially in the presence of multiple magnetic foreign bodies. The absence of specific clinical symptoms prevents timely diagnosis of pathologically formed interintestinal anastomoses. According to the authors [1,3], an indication for surgical treatment is not only the increase in abdominal pain syndrome and signs of intestinal obstruction, but also the absence of natural movement of magnetic foreign bodies along the digestive tract. Treatment tactics for swallowing magnetic balls depend on the localization, time from the moment they enter the lumen of the digestive tract and the presence of complications [6]. With fixed magnets in the digestive tract, the tactics should be active. The authors [1] proposed an algorithm of tactics in the presence of magnetic foreign bodies in the gastrointestinal tract of a child - in the case of an asymptomatic course of the disease, dynamic observation in a surgical hospital with X-ray control after 4-6 hours is indicated. In the absence of advancement of magnetic foreign bodies, an urgent operation is indicated. Magnetic foreign bodies are classified as physically active foreign bodies that have a compressive effect on the wall of a hollow organ [2, 4], as a result of which a pathological interintestinal fistula can form in a short time.

Conclusions:

1. The presence of magnetic foreign bodies in the child's gastrointestinal tract should alert the patient to the possibility of developing surgical complications.

2. In the absence of clinical complaints from the abdominal cavity, the presence of fixed magnetic foreign bodies in the intestine according to X-ray examination is an indication for emergency-delayed surgery and revision of the gastrointestinal tract.

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