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ANALYSIS OF PATHOGENIC VARIANTS OF THE MTDNA *MT-TS1* GENE IN PATIENTS WITH HEARING LOSS IN BURYATIA

Pathogenic variants of mitochondrial tRNA genes remain poorly understood in the context of the study of the etiology of hearing loss, despite the fact that they are one of the important causes of syndromic and non-syndromic hearing impairment as well as aminoglycoside-induced hearing loss. In this work, we searched for pathogenic variants of the mtDNA *MT-TS1* gene in patients with hearing impairments in Buryatia. One rare variant m.7445A>C was found in the *MT-TS1* gene out of five investigated variants in one patient (1/165; 0.6%). This variant is localized in the coding region of two genes the *MT-CO1* (H-chain) and *MT-TS1* (L-chain), but on different mtDNA chains. However, a pathogenetic role for the m.7445A>C substitution has been shown for the *MT-TS1* gene, but not for the *MT-CO1* gene. In databases, the m.7445A>C variant is associated with non-syndromic hearing loss, including those caused by aminoglycoside antibiotics. A comparative genotype-phenotypic analysis of our case and four cases with m.7445A>C of the *MT-TS1* gene described earlier in the literature showed that hearing loss in all cases is not congenital, but at the same time varies in severity with low penetrance. The results obtained indicate the involvement of other modulating factors in the clinical manifestation of hearing impairment associated with this variant. Thus, further study of rare variants of *MT-TS1* gene will contribute to our understanding of the pathogenetic mechanisms of mitochondrial forms of hearing loss.

Keywords: non-syndromic hearing loss, mtDNA, *MT-TS1*, m.7445A>C, Buryatia.

Introduction. Hearing impairment is one of the most common sensory pathologies. The worldwide prevalence of congenital hearing loss and deafness is estimated as 1 per 1000 newborns [6]. It is known that up to 50% of congenital deafness has an inherited etiology [18; 4]. Currently, more than 120 genes are known to be associated with hearing impairment [18; 4; 7]. About 75% of all cases of non-syndromic hearing loss are autosomal recessive forms, 10-15% – autosomal dominant and 1-2% – X-linked recessive and mitochondrial forms [18; 4; 15]. Despite the low contribution of pathogenic variants of the mitochondrial genome, they have wide clinical variability and are associated with various forms of hearing loss [2; 15], including hearing loss induced by aminoglycoside antibiotics [5; 16; 14; 22; 15].

The *MT-TS1* gene encodes the mitochondrial serine tRNA (UCN), which is involved in mitochondrial protein biosynthesis processes [11]. Currently, according to ClinVar database, 34 variants have been described in the *MT-TS1* gene, 12 of which are annotated as pathogenic and likely pathogenic https://www.ncbi.nlm.nih.gov/clinvar/?term=MT-TS1 [gene]). Among them, four variants are associated with non-syndromic deafness (OMIM:500008), MERF syndrome (OMIM:545000) and MELAS (OMIM:540000), mitochondrial cytochrome c oxidase deficiency with neurologic features (OMIM:590080.0003), palmoplantar keratoderma and deafness (OMIM:590080.0002), as well as exercise intolerance with muscle pain and lactic acidemia (OMIM:590080.0008). Most of the pathogenic variants of the *MT-TS1* gene (7 out of 12) are associated with hearing loss: m.7443A>G (rs397507452), m.7445A>T (rs199474818), m.7445A>C (rs199474818), m.7445A>G (rs199474818), m.7471dup (rs111033319), m.7510T>C (rs199474820) and m.7512T>C (rs199474817).

In the DNA diagnosis of hereditary hearing loss, pathogenic mitochondrial DNA variants are included in the research protocols in a limited number and in most cases search for only one mitochondrial variant m.1555A>G of the *MT-RNR1* gene. In Russia, analysis of the clinically relevant nuclear genes (*GJB2, SLC26A4*, and *STRC*), followed by a whole exome sequencing, is most commonly performed for DNA diagnosis of hereditary hearing loss [20]. Previously, mitochondrial variants of the *MT-RNR1* and *MT-TS1* genes were studied only in one research with a multi-ethnic sample of patients (n=410) with non-syndromic sensorineural hearing loss (Russians, Tatars, Bashkirs, Yakuts, Altaians, and Kazakhs) [1]. However, the pathogenetic role of the variants found in the *MT-RNR1* and *MT-TS1* genes, except for m.1555A>G of the *MT-RNR1* gene, remained undefined. In this regard, the aim of this study was to investigate pathogenic variants of the *MT-TS1* gene in patients with hearing impairment in the Republic of Buryatia.

Materials and methods. *Study samples.* A total of 165 hearing-impaired people were included in the study, with an average age 48.73 years old in the Republic of Buryatia. Nationality of the studied were represented in approximately equal proportions by Buryats (47.9%) and Russians (46%), the remaining 6.1% were Mongols, Nanai, Evenks, Chuvashes, Uzbeks and Germans.

Clinical and audiological analysis. Hearing impairment was determined by threshold tone audiometry using a MAICO ST 20 audiometer (Germany) by air conduction at frequencies 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 kHz and by bone conduc-

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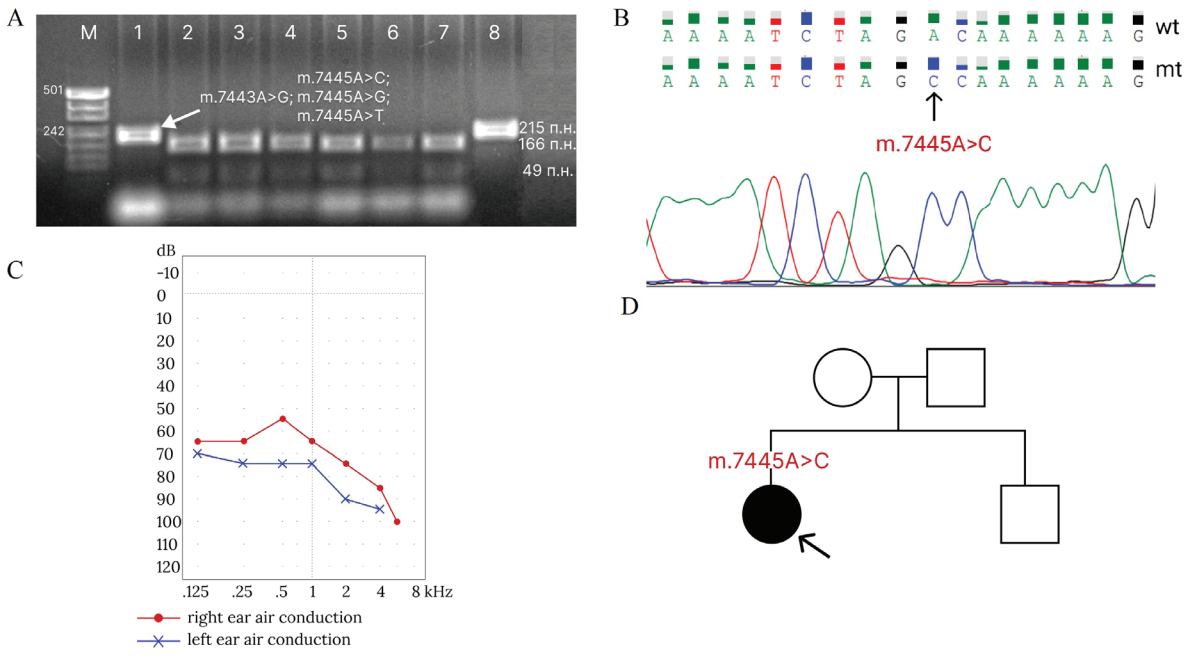

Fig. 1. Identification of the m.7445A>C variant in the *MT-TS1* gene in a patient with non-syndromic hearing loss.
Note. A - electrophoregram of RFLP analysis: M - molecular weight marker, 1 - sample with substitution in positions m.7443 A and m.7445A, 2-7 - samples without replacement, 8 - control sample not treated with XbaI enzyme; B - chromatogram section of *MT-TS1* gene sequence with m.7445A>C variant.; C - audiogram of proband; D - fragment of pedigree of patient with m.7445A>C in *MT-TS1* gene, proband marked by arrow.

tion and at frequencies 0.25, 0.5, 1.0, 4.0 kHz in 5.0 dB steps. Severity of hearing loss was defined by the average hearing threshold at 0.5;1.0;2.0;4.0 kHz, according to the WHO classification: mild - 26-40 dB, moderate – 41-70, severe – 71-90, profound - >90 dB.

Molecular genetic analysis. Genomic DNA samples were isolated from venous blood, using the phenol-chloroform method. The search for m.7443A>G (rs397507452), m.7445A>G (rs199474818), m.7445A>C (rs199474818) and m.7445A>T (rs199474818) variants was performed by PCR-RFLP using *Xba*I restriction endonuclease [10] (Fig. 1, A). Based on the results of PCR-RFLP analysis, Sanger sequencing was performed for samples lacking the *Xba*I restriction site at positions m.7443 and m.7445 (Fig. 1, B). Restriction endonuclease *Hinf*I was used to identify the m.7510T>C variant (rs199474820) by PCR-RFLP [19].

Ethical control. Surveys for this research were performed after informed written consent of the participants. This study was approved by the Local Committee on Biomedical Ethics at YSC CMP in 2019 (Yakutsk, Minutes no. 7 of 27 August 2019).

Results and discussion. In this study, among 165 patients with hearing loss in the Republic of Buryatia 5 of 7 known pathogenic variants of *MT-TS1* gene associated with non-syndromic hearing loss, including those induced by aminoglycoside antibiotics, were studied: m.7443A>G, m.7445A>C, m.7445A>G, m.7445A>T and m.7510T>C. The other two variants of the *MT-TS1* gene are not included in this study because the m.7512T>C variant is associated with MERF (OMIM:545000) and MELAS (OMIM:540000) syndromes, and the m.7471dup variant is associated with cytochrome c oxidase deficiency and neurologic features (OMIM:590080.0003). Only the m.7445A>C variant was found in one patient in the study sample, with an incidence of 0.6% (1/165). In the world, m.7445A>C occurs with a rather low frequency – in China from 0.04% (1/2651) [13] to 0.11% (1/887) [12], in Mongolia 0.42% (2/480) [8], in Russia 0.19% (1/520) [1].

The patient with the identified variant m.7445A>C was diagnosed with bilateral severe sensorineural hearing loss (Figure 1, C). The patient was 51 years old at the time of the study. From the anamnesis, it is known that the age of onset of hearing loss was 3 years after antibiotic treatment. Patient studied at a school for the deaf and hard of hearing (Ulan-Ude), does not wear hearing aids in daily life, and use speech and sign language in communication. Genealogical analysis of the patient with variant m.7445A>C showed the absence of other affected family members, which can be interpreted as a low penetrance of this variant (Fig. 1, D).

The pathogenic variant m.7445A>C in the *MT-TS1* gene is associated with non-syndromic mild hearing loss (OMIM:500008), including that caused by aminoglycosides (OMIM:580000) [14; 8; 17; 22]. Other substitutions at position m.7445, adenine (A) for guanine (G) and thymine (T), have also been described as pathogenic variants [3; 21; 9; 14; 17; 22]. Position m.7445A (Figure 2, A) is localized in the coding region of two genes: at the 3′-end of the *MT-TS1* gene (L-chain mtDNA) encoding the serine tRNA precursor (UCN) and at the 3′-end of the *MT-CO1* gene (H-chain mtDNA) encoding cytochrome c oxidase subunit 1 [21]. On the L-chain, position m.7445 is part of the 3′-endonuclease (3′-RNase Z) processing site, so replacing adenine with cytosine (A>C) leads to a failure in the serine tRNA precursor (UCN) processing (Figure 2, B) [21; 14; 17]. The exact pathogenic mechanism has been described for the m.7445A>G variant [21 and 9]. However, a similar failure of serine tRNA precursor (UCN) processing can occur with other nucleotide substitutions at the m.7445A position [14]. On the H-chain, in the *MT-CO1* gene, an adenine to cytosine substitution (A>C) results in the loss of the stop codon with the addition of three amino acids to the C-terminal of the polypeptide (Fig. 2, B), which is not thought to result in a functionally significant change in the protein [21; 14; 22].

The phenotypic effect of mitochon-

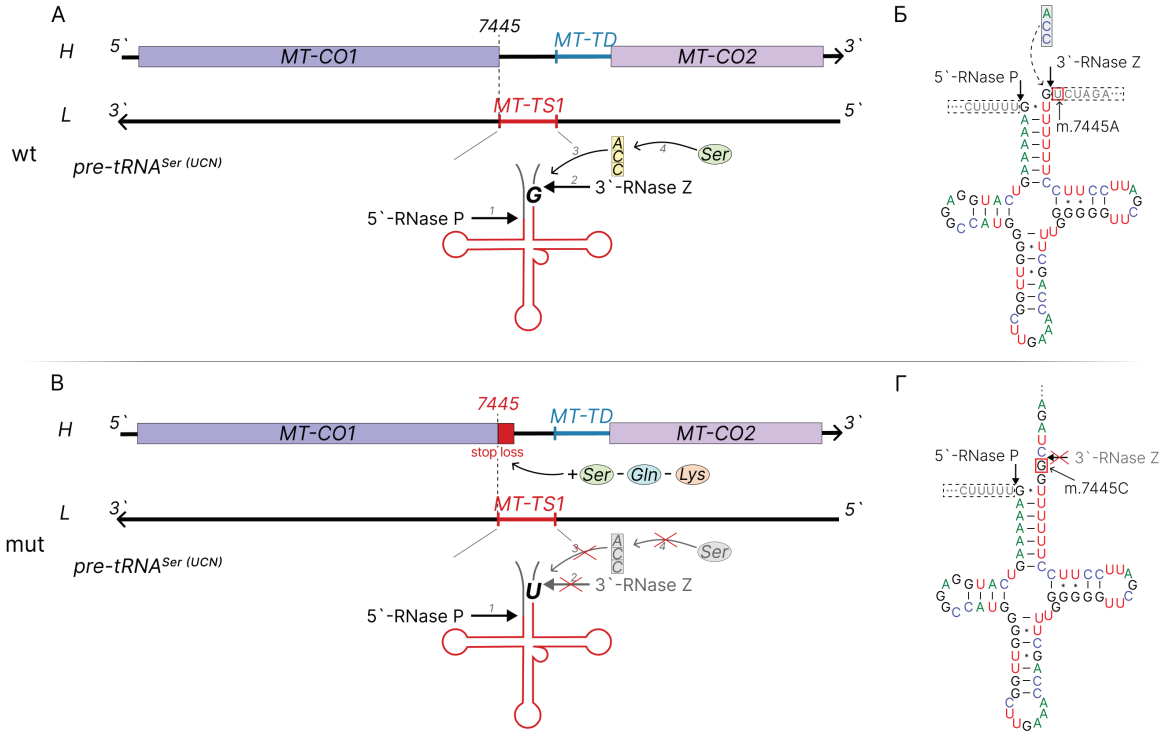

Fig. 2. Effects of adenine (A) to cytosine (C) substitution at position m.7445 for *MT-TS1* gene (L-chain) and *MT-CO1* gene (H-chain).
Note. A - Position of MT-CO1 (H-chain) and *MT-TS1* (L-chain) genes in normal, B - serine pre-tRNASer(UCN) processing and serine pre-tRNA structure in normal; C - Loss of stop codon in MT-CO1(H) gene at m.7445 substitution A>C and disruption of serine pre-tRNA processing; D - Structure of serine pre-tRNA when m.7445A>C is replaced. Figure adapted from [Guan et al., 1998 and Levinger et al., 2004].

Phenotypes of patients with the pathogenic variant m.7445A>C in the *MT-TS1* gene

Level of hearing impairment	Audiological curve configuration	Age at the time of the study (in years)	Age of manifestation (in years)	The cause of hearing loss	History of the use of aminoglycosides	Heteroplasmy/Homoplasmy	Penetrance	Frequency	Ethnicity	Literature
severe	NA	students	1-4	Due to disease	no	homoplasmy	NA	0.42% (2/480)	mongols (Mongolia)	[8]
mild	ravine	17	10	NA	no	homoplasmy	low	0.04% (1/2651) - 0.11% (1/887)	NA (China. Zhejiang Province)	[12-14]
severe	flat	19	1	NA	no	homoplasmy	low	NA	NA (China. Xingjiang Province)	[17]
moderate	NA	NA	NA	NA	NA	NA	high	0.19% (1/520)	Kazakh (Russia. Altai Republic)	[1]
severe	slope	51	3	Due to disease	yes	homoplasmy	low	0.6% (1/165)	Buryat (Russia. Republic of Buryatia)	Present study

drial variants on auditory function is highly heterogeneous and depends on the proportion of mutant and normal mtDNA copies in certain tissues, on the energy dependence of tissues, as well as on the role of modulators, in particular aminoglycosides [16]. Therefore, we performed a comparative analysis of the phenotypes of our case and four cases with m.7445A>C previously described in the literature (Table 1). In total, clinical data from five patients were included in the analysis [8; 14; 17; 1]. In most studies, the pathogenic variant m.7445A>C is found in the homoplasmy. The level of hearing impairment of patients ranged from mild to profound hearing loss with an age of manifestation ranging from 1 to 10 years. Only one patient in the present study had a history of antibiotic use. Hearing impairment due to the disease, however, has also been reported in patients from Mongolia, while no information about the disease or the use of medication has been described in other papers (Table 1). In general, for most families with m.7445A>C, the authors observed a low penetrance. According to some researchers, the biochemical defects associated with the m.7445A>C variant alone probably do not cause hearing impairment, which may be reflected in low penetrance. In this case, modifiers, in particular – antibiotics with ototoxic effects [14], associated with damage of hair cells as well as non-sensory cells modulating their function, leading to nerve damage and affecting auditory perception may play a significant role.

Conclusions. The m.7445A>C pathogenic variant in the *MT-TS1* gene was detected at a frequency of 0.6% in deaf patients from the Republic of Buryatia, which generally corresponds to the relatively low frequency of this variant in previously studied Asian regions (0.04% to 0.42%). Analysis of phenotypes of patients with this variant from different regions showed that hearing loss is not congenital in all identified cases, but varies in severity. For the majority of cases associated with m.7445A>C of the *MT-TS1* gene, low penetrance was shown, indicating the likely involvement of other modulating factors in the clinical manifestation of hearing loss. Thus, further study of rare *MT-TS1* gene variants will contribute to our understanding of the pathogenic mechanisms of mitochondrial forms of hearing loss.

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ANALYSIS OF POLYMORPHIC VARIANTS OF SEROTONIN AND GAMMA-AMINOBUTYRIC ACID RECEPTOR GENES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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An analysis of polymorphic variants of the serotonin receptor genes *HTRD rs674386, HTR1F rs56398417, HTR2A rs6313, HTR3A rs1062613, HTR2C rs6318* and the *GABRA2 rs279845* gene in T2D patients living in the Republic of Belarus was carried out. As a result of the study of 6 loci of neurotransmitter genes, protective markers *CT* and *CC* genotypes of the rs1062613 locus of the *HTR3A* gene (OR= 0.73, Pcor_FDR=0.0007) and *GC* and *CC* risk genotypes of the rs6318 locus of the *HTR2C* gene (OR=2.21, Pcor_FDR=0.0045) among women, the *CC* genotype is also risky for men (R=4.05, Pcor_FDR=0.0045). Analysis of combinations of genotypes and alleles revealed combinations of increased and decreased risk of T2D. The analysis of ROC curves showed that the studied loci and such variables as sex, age of the examined and BMI can be used to assess the prognostic significance of T2D AUC=83.4% (95% CI 83.5-87.4).

Keywords: type 2 diabetes mellitus, neurotransmitter system, serotonin receptors, gamma-aminobutyric acid receptor.

Introduction. Type 2 diabetes mellitus (T2D) is a metabolic disease characterized by elevated blood glucose levels; its development is due to the development of insulin resistance [2]. The prevalence of T2D is increasing worldwide, leading to a decrease in the quality of life and premature death [2]. Based on the concept of the psychobiosocial model of T2D pathogenesis and considering lifestyle as a trigger factor for the formation of T2D, it seems relevant and appropriate to study neurotransmitters in the development of T2D. One of the neurotransmitters of the central nervous system is serotonin (5-HT), which is mainly involved in the regulation of complex behavior such as aggression and appetite control [17]. Serotonin occurs in the body in two different pools, one in the central nervous system and the other in peripheral tissues. Approximately 90% of the total 5-HT present in the body is produced by the cells of the gastrointestinal tract; the released neurotransmitter is involved in the control of insulin secretion [11]. It has been established that altered serotonin functions cause dysfunction of pancreatic β-cells and ultimately lead to the development of T2D [4]. Bennet H., 2015 found that increased expression of the *HTR1D* and *HTR2A* genes in pancreatic β-cell tissue among T2D patients compared with healthy controls [4]. Studies of the relationship between T2D and the serotonergic system have revealed an association of polymorphic variants of the serotonin receptor genes *HTR2A, HTR2C* with the risk of developing type 2 diabetes in Caucasians [15,19], polymorphic variants of the *HTR3B* gene are associated with type 2 diabetes in Koreans [18], polymorphism of the HTR2C gene is associated with metabolic syndrome among the Greeks [3]. Polymorphic variants of the *GABRA2* gene encoding the α2 subunit of the gamma-aminobutyric acid receptor (GABA-α) have been associated with the risk of alcohol dependence [16]. Also, these receptors play an important role in the regulation of insulin secretion and glucagon release in pancreatic islet cells in both healthy and T2D patients [5]. Based on the results of GWAS studies among residents of the United Arab Emirates, markers of the risk of developing T2D were identified for GABA-α genes [6]. However, the role of neurotransmitters in the pathogenesis of T2DM remains poorly understood. In this regard, the analysis of polymorphic variants of the genes of the neurotransmitter system is an urgent problem. The aim of our study was to analyze polymorphic variants of the serotonin receptor genes *HTRD rs674386, HTR1F rs56398417, HTR2A rs6313, HTR3A rs1062613, HTR2C rs6318,* the gamma-aminobutyric acid receptor gene *GABRA2 rs279845* among patients with type 2 diabetes living in the Republic of Bashkortostan (RB).

Material and Methods Diagnosis of T2D was based on a set of ICD-10 codes, data on quantitative parameters that determine levels of T2D risk such as age, BMI, waist circumference, hip circumference, low-density lipoprotein, high-density lipoprotein levels, triglycerides. The characteristics of the groups are presented in Table 1. Statistics The correspondence between the frequency of genotypes and alleles and the Hardy-Weinberg equilibrium was assessed using the χ2 test. Analysis of associations with the development of T2D was performed using the PLINK v.1.9 program [14]. The Pcor_FDR comparison multiplicity correction was estimated using the online calculator https://www.sdmproject.com/utilities/?show=FDR. The association was considered significant when the Pcor_FDR level was less than 0.05, and the 95% confidence interval did not cross one. Analysis of associations calculated for the main group is presented in models: codominate and additive, as well as

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Table 1

Characteristics of the samples included in the study

Parameters	Healthy n=1096	T2D n=691	*P* value
Age, mean±Std.Dv	51.82±9.70	58.08±12.28	0.05
Men, n (%)	263 (23.9)	158 (22.2)	0.483
Women, n (%)	833 (76.1)	555 (77.8)	
Body mass index (BMI) (kg/m2), mean±SD	26.72±2.78	31.12±5.82	<0.0001
Obesity, n (%)	–	612 (85.8)	–
Duration of DM2, median [Q1;Q3]	–	7.23 [2; 15]	–
Arterial hypertension, n (%)	–	602 (84.5)	–
Cardiovascular disease, n (%)	–	256 (36.0)	–
HbA1C (%), median [Q1;Q3]	4.9 [3.8; 5.90]	9.20 [7.10; 14.00]	<0.0001
Fasting glucose (mmol/l), median [Q1;Q3]	4.80 [3.20; 5.90]	8.36 [8.31; 15.00]	<0.0001
Total cholesterol (mmol/l), median [Q1;Q3]	4.50 [3.30; 6.12]	5.30 [3.20; 10.30]	0.0008
LDL (mmol/l), median [Q1;Q3]	2.70 [0.79; 3.99]	3.20 [1.60; 7.09]	<0.005
HDL (mmol/l), median [Q1;Q3]	1.10 [0.87; 1.40]	1.10 [0.85; 1.30]	0.08
Triglycerides (mmol/l), median [Q1;Q3]	1.32 [1.10; 2.07]	1.67 [1.15; 2.17]	0.029

Note. LDL – low density lipoproteins, HDL – high density lipoproteins, Std. dv. – standard deviation.

in the form of an allelic test. Multiple logistic regression analysis and ROQ analysis were performed using SPSS v.22. Analysis of gene-gene associations with T2DM between allele and or/genotype was calculated using the APSampler 3.6.0 program (http://apsampler.sourceforge.net).

Results and discussion. To carry out the analysis of associations, we initially calculated whether the distribution of genotype frequencies of the studied polymorphic loci corresponded to the Hardy–Weinberg equilibrium, taking into account the rare allele frequency (MAF) among sick and healthy subjects (Table 2). The locus of the *HTR2C* gene located on the X chromosome was analyzed separately in women and men. The analysis was carried out in the codominant and additive models, and the allele test was also evaluated, the data are presented in Table 3. Statistically significant differences were obtained for the rs1062613 locus of the *HTR3A* gene in the codominant model for the *CT* and *CC* genotypes (OR=0.71 and OR=0.59, Pcor_FDR=0.004). In the additive model, the OR was 0.73, Pcor_FDR=0.0007. For the rs6318 polymorphic locus of the *HTR2C* gene, statistically significant differences were obtained in the group of women. In the codominant model, the association with the risk of developing T2D was determined for the *GC* and *CC* genotypes (OR=2.37 (95% CI 1.74-3.24), Pcor_FDR=0.0045, OR=2.77 (95% CI 0.93-8.25), Pcor_FDR=0.0045). Given that the confidence interval crossed 1 in the second case, the most statistically significant model is the additive OR=2.21 (95% CI 1.66-2.94), Pcor_FDR=0.0045). Among men, the CC genotype was also associated with the risk of developing T2D (OR=4.05, Pcor_FDR=0.0045). Analysis of the *rs279845* locus of the GABRA2 gene revealed a trend towards an increase in the frequency of the TT genotype among patients up to 37.2% compared with 31.0% in the control (OR=0.75 and OR=0.79, Pcor_FDR=0.046), respectively, for projective CT and CC genotypes.

As a result of the multilocus analysis of associations, five combinations of genotypes and alleles were identified that showed statistical significance with T2DM. The C allele of the rs1062613 locus of the HTR3A gene was included in two models of increased T2D risk, and the T allele was included in three reduced risk

Table 2

Description of the studied genes and the Hardy-Weinberg equilibrium

Polymorphism	Gene	Localization	P_{X-W} control	P_{X-B} patients	MAF (European)	MAF
rs279845	*GABRA2*	chr 4:46327706	0.1	0.045	44.8	44.0
rs1062613	*HTR3A*	chr11:113975284	0.061	0.42	22.6	25.05
rs6318	*HTR2C*	chrX:114731326	0.52	0.26	16.2	8.0
rs6313	*HTR2A*	chr 13:46895805	0.11	0.39	42.0	48.0
rs674386	*HTRD*	chr1:23192984	0.28	0.79	22.1	27.0
rs56398417	*HTR1F*	chr3:87975836	0.42	0.014	28.8	17.0

Note: PX-W level of significance in determining the Hardy-Weinberg equilibrium, MAF (European) frequency of the minor allele in the population of Caucasians (Project 1000 genomes), MAF – frequency of the minor allele in the control group.

Table 3

Association of studied polymorphic loci of serotonin and *GABBRA2* receptor genes

Gene, polymorphism	Model	Allele, genotype	T2D n=691 Individuals (%)	Control n=1096 Individuals (%)	OR (95 CI)	P	P_{FDR}
HTR1D rs674386	Co-dominant	*GG/AG/AA*	330 (47.8)/ 296 (42.9)/ 63 (9.1)	591 (53.9)/ 418 (38.1)/ 87 (7.9)	00 1.27 (1.04-1.56) 1.30 (0.91-1.84)	0.045	0.062
HTR1D rs674386	Allelic test	*G/A*	957 (69.0)/ 423 (31.0)	1600 (73.0)/ 592 (27.0)	1.19 (1.02-1.39)	0.01965	0.046
HTR1D rs674386	Additive	---	---		1.19 (1.03-1.38)	0.02067	0.046
HTR1F rs56398417	Co-dominant	*CC/CT/TT*	499 (72.3)/ 165 (23.9)/ 26 (3.8)	780 (71.2)/ 294 (26.8)/ 22 (2)	1.00 0.88 (0.70-1.09)/ 1.85 (1.04-3.30)	0.041	0.062
HTR1F rs56398417	Allelic test	*C/T*	1163 (84.0)/ 217 (16.0)	1854 (85.0)/ 338 (17.0)	1.02 (0.85-1.23)	0.843	0.932
HTR1F rs56398417	Additive		---	---	1.02 (0.85-1.23)	0.812	0.932
GABRA2 rs279845	Co-dominant	*TT/AT/AA*	257 (37.2)/ 307 (44.4)/ 127 (18.4)	340 (31)/ 542 (49.5)/ 214 (19.5)	1.00/ 0.75 (0.60-0.93) /0.79 (0.60-1.03)	0.023	0.046
GABRA2 rs279845	Allelic test	*T/A*	821 (59.0)/ 561 (41.0)	1222 (56.0)/ 970 (44.0)	0.86 (0.75-0.98)	0.034	0.055
GABRA2 rs279845	Additive		---	---	0.86 (0.76-0.99)	0.034	0.055
HTR3A rs1062613	Co-dominant	*CC/CT/TT*	440 (63.7)/ 227 (32.9)/ 24 (3.5)	604 (55.1)/ 435 (39.7)/ 57 (5.2)	1.00 0.71 (0.58-0.87) 0.59 (0.36-0.96)	0.0012	**0.004**
HTR3A rs1062613	Allelic test	*C/T*	1107 (80.0)/ 275 (20.0)	1643 (74.95)/ 549 (25.05)	0.74 (0.63-0.88)	0.0001	**0.00045**
HTR3A rs1062613	Additive		---	---	0.73 (0.64-0.88)	0.0002	**0.0007**
HTR2A rs6313	Co-dominant	*CC/CA/AA*	177 (25.6)/ 356 (51.6)/ 157 (22.8)	290 (26.5)/ 559 (51)/ 247 (22.5)	1.00 / 1.04 (0.83-1.31)/ 1.04 (0.79-1.37)	0.931	0.931
HTR2A rs6313	Allelic test	*C/A*	710 (51.0)/ 670 (49.0)	1139 (52.0)/ 1053 (48.0)	1.02 (0.89-1.17)	0.931	0.931
HTR2A rs6313	Additive		---	---	1.02 (0.89-1.17)	0.761	0.931
HTR2C rs6318	Co-dominant, female	*GG/GC/CC*	554 (68.7)/ 235 (29.1) / 18 (2.2)	341 (84)/ 61 (15)/ 4 (1)	1.00 2.37 (1.74-3.24)/ 2.77 (0.93-8.25)	0.0001	**0.00045**
HTR2C rs6318	Allelic test, female	*G/C*	1343 (83.0)/ 271 (17.0)	743 (92.0)/ 69 (8.0)	2.17 (1.64-2.87)	0.0001	**0.00045**
HTR2C rs6318	Additive, female		---	---	2.21 (1.66-2.94)	0.0001	**0.00045**
HTR2C rs6318	Male	*G/C*	114 (75.5) / 37 (24.5)	237 (92.6)/ 19 (7.4)	1.00/ 4.05 (2.23-7.35)	0.0001	**0.00045**

Note: Statistically significant differences are in bold.

models. In three models, the rs674386 locus of the HTRD gene was found, in this case, the A allele is represented in the increased risk model of the disease, the G allele was determined in the reduced risk models (Pcor_FDR=0.007 and (Pcor_FDR=0.001). In individual analysis, the association of the G allele was also more common among The most significant association was found for the combination of HTR3A rs1062613 allele C + HTR2A rs6313 allele A + HTRD rs674386 allele A + HTR1F rs55639841 CC genotype (OR=1.74, Pcor_FDR=0.0004).

When analyzing ROC curves to assess the prognostic significance of the identified risk values in the development of DM2, two models were built, for the first model only polymorphic loci were taken into account: *HTRD rs674386, HTR1F rs56398417, HTR3A rs1062613, GABRA2 rs279845*, the same loci were included in the second model, and also variables such as sex, age of the subjects and BMI. Prediction performance was measured using the area under the curve (AUC). ROC analysis showed an AUC of 56.7% (95% CI 53.9-59.4) for a model including only the studied polymorphs. For the second model, AUC was 83.4% (95% CI 83.5-87.4), indicating a high ability of the indicators included in the analysis to correctly classify individuals with T2DM and healthy individuals.

The rs10623613 polymorphic variant of the *HTR3A* gene demonstrated the largest number of associations. This polymorphism is located in the 5'UTR region of the gene; it was found that the C allele of this polymorphic locus affects the binding affinity of the transcription factor CTCF to the promoter region of

the *HTR3A* gene [12]. According to a number of authors, allele C is associated with low expression of the *HTR3A* gene [7] and a high level of methylation [13]. Low expression, in turn, causes a decrease in the level of serotonin in the central nervous system, leads to a change in eating behavior and the development of hyperphagia, and subsequently obesity, which provokes the development of T2D [2]. An association with the development of T2D was shown for the *rs6318* locus of the *HTR2C* gene. This polymorphism is due to the substitution of the amino acid Cys for Ser at position 23. It has been shown that the protein encoded by the Ser23 or C allele has a reduced affinity for serotonin [20]. A number of authors have established an association of this locus with the risk of developing depression [8], as well as obesity and DM2, which confirms our data [9, 10, 15, 19]. The *rs279845* locus of the *GABRA2* gene is associated with alcoholism; carriers of the *T* allele suffer from alcoholism to a lesser extent [16]. On the other hand, no relationship was found for the *rs279845* locus of the *GABRA2* gene when studying quantitative traits of personality, temperament, and character [1].

Conclusion. In this study, we assessed the effect of polymorphic variants of neurotransmitter genes on the risk of developing T2D by analyzing combinations of genotypes and alleles. It has been shown that a selected set of genetic variants and indicators such as gender, age, and BMI can be used to predict T2DM among residents of the Republic of Belarus.

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SPECIFIC FEATURES OF AORTIC WALL CALCIFICATION IN PATIENTS WITH THORACIC AORTIC ANEURYSM

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Histological assessment of calcification patterns in different sites of ascending aorta in patients with thoracic aortic aneurysm has been performed using alizarin red S staining. Biopsy specimens from 67 patients (47 males, 20 females, mean age 56,9±11,1 years) with thoracic aortic aneurysm from three different sites of ascending aorta were taken intraoperatively. Calcium content in aorta was calculated as the percentage of positively stained area using FiJi. Statistical data processing was performed using JASP 0.17.2.1. Calcific precipitates were diffusely distributed mainly in the *tunica media* of the vessel. The mean calcium percentage was: for the sinotubular junction (zone 1) - 7.85 [2.2; 15.4]%, mid-ascending aorta (zone 2) – 10.45 [3.83; 22.35]%, proximal aortic arch (zone 3) – 10.95 [4.65; 18.63]% (p=0.216). Patients with maximum calcification level in zone 3 were younger (53 [41; 62] years) than patients in whom the maximum calcification was detected in zone 2 (60 [55.25; 65] years) and zone 1 (64 [58; 68] years, p=0.035).

Keywords: thoracic aortic aneurysm, vascular calcification, alizarin red S.

Introduction. Vascular calcification is a process characterized by the accumulation of calcium salts in the vessel wall. Although calcification is thought to be a part of normal aging, it is associated with a high risk of morbidity and mortality [9].

While the blood vessel wall has three layers - *tunica intima, tunica media, tunica adventitia* - the phenomenon of calcification is described for the first two. Intimal calcification is associated with atherosclerotic disease; medial calcification is often, but not always, associated with diabetes, chronic kidney disease and aging. [16].

Atherosclerotic calcification is the most common form of vasculopathy. It occurs at a young age (already in the second decade of life) immediately after the stage of fatty streaks. Medial calcification is less common and develops along the elastic fibers. Calcium deposits are observed throughout *t. media*, and at later stages become circular, covering the entire circumference of the vessel. In some cases, maturation of osteocytes and bone trabeculae is observed [1].

Thoracic aortic aneurysm (TAA) – a progressive disease that is more likely to occur in older patients (>60 years) [2]. It is supposed that smooth muscle cells (SMCs) play a central role in the development of aortic aneurysms. Normally, they have a contractile phenotype that sometimes may switch to a synthetic. In response to various stress signals, SMCs can induce and enhance calcification through several mechanisms: increased apoptosis, release of extracellular vesicles, loss of natural inhibitors of calcification, such as matrix protein Gla, etc. [23].

Data on calcification of the main vascular beds (coronary/carotid arteries) and aorta is used in clinical practice to predict adverse cardiovascular events [22]. The accumulation of calcium in the coronary arteries correlates with that in the ascending aorta [19] which indicates the systemic nature of the pathological process. TAA calcification may also be a predictor of adverse cardiovascular events, so preoperative assessment of the intensity and volume of calcium deposits in the aortic wall may play a role in identifying risk groups among patients. [13].

Most studies describe a direct correlation between coronary artery calcification index and abdominal aortic diameter [3], however for the ascending aorta data on the association of its diameter with coronary calcium remains inconclusive and require further investigation [4, 8, 12]. Abovementioned studies utilized non-invasive diagnostic methods, and no histological assessment of calcium deposits in patients with TAA considering biopsy site has previously been performed. Thus, the aim of this study was to assess content and distribution of calcium in different sites of ascending aorta in patients with its aneurysm using alizarin red staining.

Materials and methods. The study included 67 individuals (47 males, 20 females) diagnosed with thoracic aortic aneurysm from Department of Cardiovascular Surgery, Cardiology Research Institute. All patients underwent surgical intervention in the period from 2013-2023. The inclusion criteria were: signed informed consent and age over 18. The mean age of the patients was 56.9 ± 11.1 years (minimum and maximum ages were 23 and 76 years, respectively). The mean diameter of the ascending aorta was 51.5 mm (minimum and maximum diameters were 42 mm and 65 mm, respectively).

Biopsy specimens from three different sites of ascending aorta (1 – sinotubular junction; 2 – mid-ascending aorta; 3 – proximal aortic arch, Figure 1) were taken intraoperatively. Fixation, processing, embedding were performed according to standard method. Histological sections

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4-5 μm thick were obtained using an automatic rotary microtome HM 355 S (Thermo Scientific, USA).

The sections were stained with alizarin red S (Dahl's method, 1952) and covered with Vitrogel mounting medium (BioVitrum, St. Petersburg). Light microscopy was utilized to examine the results (Axioskop 40, Carl Zeiss, Germany). Microphotographs of samples were obtained using a Canon G10 camera (Japan).

To assess the amount of calcium deposits in the aorta we measured the percentage of positively stained area using the FiJi program [15]. Up to 7 images (400x) were obtained from each slide, followed by calculation of mean value of the positively stained area (mean percentage of calcification). Statistical analysis was performed using JASP 0.17.2.1 software package. The normality of distribution was checked using Shapiro-Wilk test. Group comparison was performed using non-parametric tests. Results are presented as median, 1st and 3rd quartiles (Me [Q1; Q3]). Differences were considered significant at $p<0.05$.

Results and discussion. Calcific precipitates were diffusely distributed mainly in the *tunica media* of the vessel (Figure 2). Such localization may indicate an isolated process of calcium salt deposition, that is not associated with atherosclerosis, in which salts are located mainly in the subendothelial layer of the *tunica intima* [16]. Calcium density in the ascending aorta has previously been shown to be inversely correlated with the risk of cardiovascular events, as supported by several independent studies. [5, 18].

Medial calcification in TAA may be due to increased degradation of elastin, which is one of the main causes of pathological vascular dilation [20]. One of the possible mechanisms is that transforming growth factor-b (TGFb) in combination with products of elastin degradation stimulates osteogenic transformation of fibroblasts and accumulation of calcium ions in the culture of vascular SMC [21]. In addition, TGFb is known to be one of the key factors in vascular wall remodeling in TAA by inhibiting the proliferation of SMCs in the vessel wall and stimulating the formation of extracellular matrix, which subsequently leads to aortic dilatation [7].

In the present study, we compared the percentage of calcification in different sites of ascending aorta to assess the relationship of their embryonic origin with the degree of vascular calcification. It is known that the most proximal region of the aorta - the root - consists of pharyngeal mesoderm cells [11], aortic arch originates from neural crest cells [14], and the descending part (including both the thoracic and abdominal regions) comes from the somite mesoderm [10].

The mean calcium percentage was: for the sinotubular junction (zone 1) - 7.85 [2.2; 15.4]%, mid-ascending aorta (zone 2) – 10.45 [3.83; 22.35]%, proximal aortic arch (zone 3) – 10.95 [4.65; 18.63]% ($p=0.216$; Figure 3).

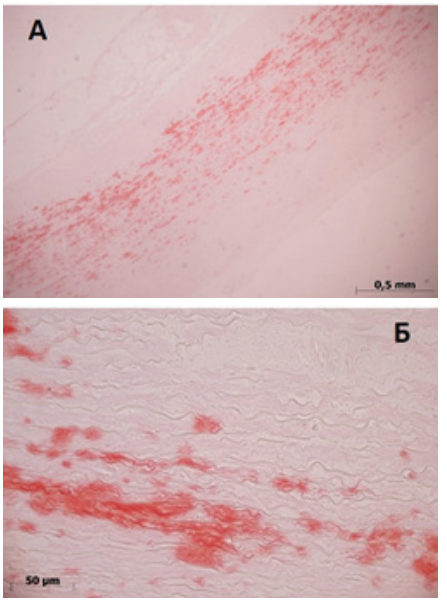

Fig. 2. Calcium precipitates in tunica media of aorta. А – 50x, Б – 400x

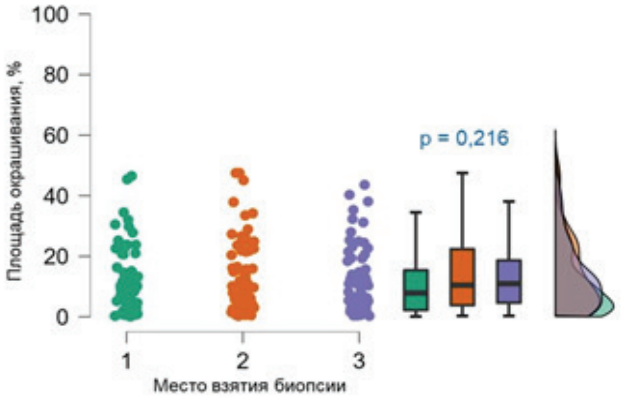

Fig. 3. Comparison of calcium percentage in different biopsy sites. 1 – sinotubular junction, 2 – mid-ascending aorta, 3 – proximal aortic arch

Fig. 1. Biopsy sites of aorta for histological examination. 1 – sinotubular junction, 2 – mid-ascending aorta, 3 – proximal aortic arch

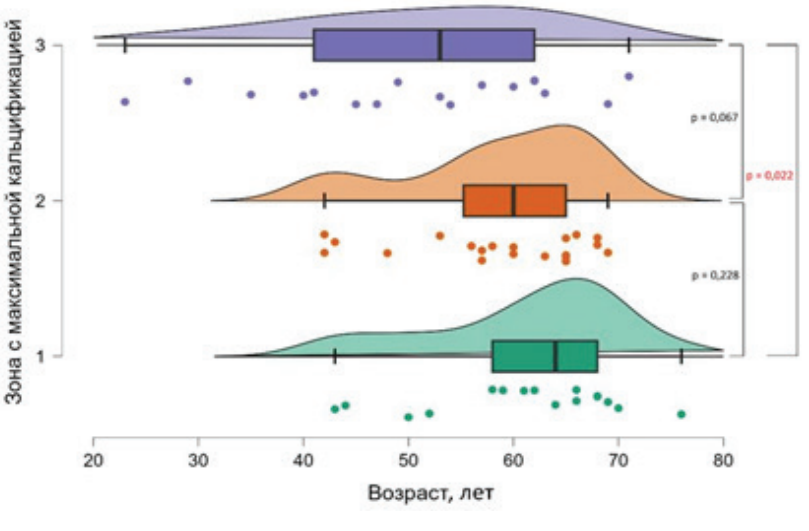

Fig. 4. Age difference in patients with different sites of maximal aortic calcification. 1 – sinotubular junction, 2 – mid-ascending aorta, 3 – proximal aortic arch

Based on mean calcium percentage among 3 zones of ascending aorta, we divided all patients with TAA into two groups with high (17.20 [13.78; 25.28]%) or low (2.2 [4.9; 6.3]%) calcium salts in *tunica media* of the aorta. The median value of calcification (10.3%) in the series of all observations was set as the threshold. Patients with a high percentage of calcification were older compared with patients with a low percentage of calcium deposits in the aorta (63 [56; 66] vs 57 [43;22], p=0.010). As previously shown, risk factors for calcification of the ascending aorta include, among others, older age and male gender [6]. Our results confirm the effect of age, but do not confirm the effect of gender on TAA calcification.

Patients with the maximum calcification in zone 3 were younger (53 [41; 62]) than those with maximum calcification in zone 2 (60 [55.25; 65]) or zone 1 (64 [58; 68]; p=0.035; Figure 4).

The fact that the youngest patients have a greater percentage of calcification in the most distal part of the ascending aorta may be the evidence that the first calcification of the ascending aorta occurs distally in the zone adjacent to the brachiocephalic trunk, and with age "descends" closer to the root. This is confirmed by experimental data: Leroux-Berger et al. in a series of *ex vivo* and *in vitro* experiments showed that the embryonic origin of SMCs affects their ability to mineralize. According to their results, the *tunica media* of the aortic arch, where SMCs are descendants of neural crest cells - calcifies much earlier than the descending aorta, where SMCs are of mesodermal origin [17].

Conclusion. In patients with thoracic aortic aneurysm calcium salt deposits are diffusely localized in the media of the vessel and distributed equally throughout the ascending aorta. Age is one of the factors affecting the calcification of media in patients with TAA. Younger patients with TAA have a greater percentage of calcification in the proximal aortic arch. Further study of calcification of the ascending aorta in patients with an TAA will complete our understanding of the molecular mechanisms of this pathology.

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HEMATOLOGICAL BLOOD PARAMETERS IN RESIDENTS OF YAKUTSK RECOVERED FROM CORONAVIRUS INFECTION COVID-19

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The study is devoted to a comparative analysis of the results of the effect of COVID-19 coronavirus infection on hematological blood parameters in patients who have been ill after three, six, nine and twelve months. Monitoring of hematological parameters is important for the identification and control of patients who have undergone COVID-19, who need additional assistance, and stratification of the risk of severe course of the disease. The study involved 161 residents of Yakutsk aged 20 to 72 years who had suffered COVID-19 in different periods of the pandemic. The study of hematological parameters showed that the average indicators of the morphological composition of red and white blood in people who have had COVID-19 correspond to generally accepted standards, with the exception of the tendency to increase monocytes, basophils, ESR and a slight decrease in MCHC indicators, which indicates a recently transmitted infectious disease.

Keywords: coronavirus infection, COVID-19, SARS-CoV-2, blood test, hematological parameters of blood.

Despite the fact that the COVID-19 pandemic is currently considered over, according to WHO and a number of authors, up to 1 million cases of this disease are observed in the world every month [2, 14]. In this regard, intensive study of the clinical and epidemiological features of the disease, the development of new means of its treatment and prevention is still ongoing. The most common clinical manifestation of a new variant of coronavirus infection is bilateral pneumonia (viral diffuse alveolar injury with microangiopathy).

Numerous studies indicate that the new coronavirus infection has a different effect on the human body, causing various symptoms and complications, and also causes disorders in the blood clotting system. Some patients develop hypercoagulation syndrome with thrombosis and thromboembolism, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems).

Based on the results of the analysis of publication activity, one of the most relevant in the study of this infection are hematological parameters that play an important role in the early diagnosis of the disease. The total number of leukocytes, the differential number of neutrophils, lymphocytes, eosinophils and monocytes, the number of platelets, the average volume of platelets and certain ratios of these parameters can be used as markers of inflammation in patients with COVID-19. The usual hematological changes observed in COVID-19 are: anemia, leukocytosis or leukopenia, neutrophilia, low levels of eosinophils or eosinophilia, thrombocytopenia and rarely thrombocytosis [11].

The purpose of this study is to study the effect of the new COVID–19 coronavirus infection on hematological blood parameters, depending on the duration and severity of the disease.

Materials and methods: The examination was carried out in the clinic of the Yakut scientific center for complex medical problems. 161 residents of Yakutsk, who suffered COVID-19 in different periods of the pandemic, aged from 20 to 72 years (including young people (20-44 years), were examined they were 56 people (34.8%); average (45-59 years old) – 53 people (32.9%); elderly (60-74 years old) – 51 people (31.7%) and senile (75-90 years old) – 1 person (0.6%) of age, respectively). There were 60 men (37.3%), 101 women (62.7%). All study participants gave voluntary informed consent to participate in the study according to the ethical standards of the Helsinki Declaration, which was approved by the decision of the local Ethics committee at the Yakut scientific center for complex medical problems, protocol No. 52 of March 24, 2021.

Four groups were formed, depending on the duration of the disease: the 1st group - up to 3 months, the 2nd group – up to 6, the 3rd group – up to 9, the 4th group - up to 12 months ago and according to the degree of lung damage by the type of "frosted glass", which were evaluated by the results of computed tomography (CT) obtained from discharge epicrisis: CT0 (zero) – absence of lung damage; CT1 (mild) – lung volume damage less than 25%; CT2 (moderate) – prevalence 25-50%; CT3 (severe) – 50-75%.

The material for the study was blood taken from the ulnar vein in the morning on an empty stomach. A general blood test was performed on a hematological analyzer "Sysmex KX-21N" (Japan), using reagents "CELLPACK" (Japan). The erythrocyte sedimentation rate (ESR) was determined by the Panchenkov method.

The analysis of the indicators was carried out as part of a one-stage study. Statistical processing of the results of the study was carried out using the Statistica 27 software package. The significance of the differences was assessed using the Student's t-test and ANOVA for independent samples with normal distribution and the Mann-Whitney test with abnormal distribution. A significance level of $p<0.05$ was established for all parameters. Correlation analysis of the data was carried out using the Pearson method.

Results and discussion. Hematological studies have shown that the average indicators of the morphological composition of red and white blood in people who have had COVID-19 correspond to generally accepted standards, with the exception of a tendency to increase monocytes, basophils, ESR and a slight

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decrease in MCHC indicators, which indicates a recently transmitted infectious disease.

According to the data obtained by us, depending on the duration of the disease, the platelet count was within the normal range, however, a statistically significant increase in platelet levels was noted only in group 4 in comparison with groups 1, 2 and 3 (p=0.001, p=0.044, p=0.010, respectively) (table 1). A direct correlation between the platelet level and the level of leukocytes (r=0.527; p<0.000), rod-shaped and segmented neutrophils (r=0.239; p<0.042 and r=0.278; p<0.007) and an inverse relationship with MCV and MCH (r=-0.239; p<0.022 and r=-0.266; p<0.010), with lymphocytes (r=-0.320; p<0.002) and monocytes (r=-0.23; p<0.027). According to literature data, after an infection, pronounced changes are determined by the content of platelets in peripheral blood. After a covid infection, there is a natural decrease in the content of platelets in peripheral blood during the first three months. Then there is a slow increase in their number. The number of these cells in the peripheral blood that is safe against hemorrhagic complications is achieved within 6 months of the postcovid period. It should be noted that normalization of platelet count is not achieved even after a year [1]. Thrombocytopenia is moderate, but more pronounced in the group of patients with severe course and subsequently died from COVID-19 [3, 8, 16].

A number of studies have shown that an informative criterion for identifying patients with severe forms of new coronavirus infection is the level of lymphocytes in the general blood test [12, 16]. The most frequent and characteristic feature is lymphopenia [3, 8]. According to the data obtained by us, the level of lymphocytes at all terms was within the normal range (Table 1). An inverse correlation was revealed with platelets (r=-0.320; p<0.002), leukocytes (r=-0.286; p<0.000), rod-shaped and segmented neutrophils (r=-0.189; p<0.038 and r=-0.786; p<0.000, respectively).

Comparative analysis of erythrocyte levels at all times revealed a significant increase in the first group in comparison with the 2nd, 3rd and 4th groups (p=0.06, p=0.042, p=0.021, respectively), however, the readings of erythrocytes were within the reference values (Table 1). Correlation analysis showed a direct relationship with hemoglobin (r=0.705; p<0.000) and leukocytes (r=0.295; p<0.00) and

Table 1

Hematological blood parameters depending on the duration of the disease

Indicator	I group up to 3 months	II group up to 6 months	III group up to 9 months	VI group up to 12 months	Significance
Leukocytes (4.0-9.0 x 10^9/l)	5.33 ± 0.34 n=15	6.13 ± 0.22 n=77	5.83 ± 0.24 n=49	5.84 ± 0.25 n=22	-
Erythrocytes (M. 4.0-5.1 x 10^{12} units/l, W. 3.7-4.7 x 10^{12} units/l	4.88 ± 0.09 n=15	4.68 ± 0.05 n=75	4.63 ± 0.05 n=49	4.56 ± 0.08 n=22	$p=0.06^{1-2}$ $p=0.042^{1-3}$ $p=0.021^{1-4}$
Hemoglobin (M. 132-164, W. 115-145)	140.73 ± 3.14 n=15	137.08 ± 1.56 n=75	134.35 ± 2.33 n=48	138.18 ± 2.34 n=22	-
Hematocrit, % (M. 40-48, W. 36-42)	44.45 ± 0.90 n=15	43.54 ± 0.43 n=75	43.14 ± 0.61 n=48	43.39 ± 0.65 n=22	-
MCV, fl (M. 81-93, Ж. 82-96)	92.26 ± 0.83 n=15	93.19 ± 0.58 n=75	92.72 ± 0.90 n=48	95.15 ± 0.67 n=22	$p=0.066^{3-4}$
MCH, pg (27-33)	29.21 ± 0.39 n=15	29.35 ± 0.23 n=75	28.94 ± 0.38 n=48	30.26 ± 0.27 n=22	$p=0.016^{3-4}$
MCHC, % (32,6-36,2)	31.65 ± 0.20 n=15	31.48 ± 0.11 n=75	31.12 ± 0.18 n=48	31.82 ± 0.12 n=22	$p=0.053^{2-3}$ $p=0.007^{3-4}$
Platelets, (150-400 x 10^9/l)	227.75 ± 5.83 n=48	259.69 ± 9.68 n=51	240.00 ±12.79 n=19	293.00 ±13.53 n=13	$p=0.001^{1-4}$ $p=0.044^{2-4}$ $p=0.010^{3-4}$
RDW-CV, % (11,5-14,5)	13.47 ± 0.12 n=15	13.44 ± 0.11 n=75	13.79 ± 0.22 n=48	13.25 ± 0.13 n=22	$p=0.064^{3-4}$
ESR, mm/h (M. 1.00-10.0, W. 2.0-15.0)	13.20 ± 1.59 n=15	18.91 ± 1.54 n=75	18.10 ± 1.59 n=48	15.86 ± 2.14 n=22	-
Basophils, % (0-1)	0.53 ± 0.40 n=15	0.23 ± 0.08 n=75	0.37 ± 0.12 n=49	0.14 ± 0.07 n=22	-
Eosinophils, % (0-5)	3.00 ± 0.44 n=12	3.37 ± 0.27 n=69	3.56 ± 0.46 n=43	3.76 ± 1.03 n=21	-
Stick - core, % (1-6)	2.41 ± 0.61 n=12	2.38 ± 0.28 n=55	1.89 ± 0.19 n=37	3.21 ± 0.67 n=14	$p=0.046^{3-4}$ $p=0.028^{3-4}$
Segmentonuclear, % (45-70)	53.07 ± 3.11 n=15	55.04 ± 0.84 n=75	54.52 ± 1.32 n=48	54.14 ± 1.66 n=22	-
Lymphocytes, % (18-40)	33.73 ± 2.39 n=15	30.29 ± 0.76 n=75	31.10 ± 1.03 n=48	30.23 ± 1.46 n=22	-
Monocytes, % (2-9)	8.73 ± 0.93 n=15	10.21 ± 053 n=75	9.52 ±.048 n=48	10.32 ± 0.84 n=22	-

Note. In Tables 1-2, n is the number of people who have been ill, p is the level of statistical significance.

feedback with MCV and MCH (r=-0.350; p<0.000 and r=-0.205; p<0.000) and the term of the transferred COVID-19 (r=-0.172; p0,029).

The average hemoglobin content at all terms was within the normal range and had no significant differences, but in the 2nd, 3rd and 4th groups there was a tendency to decrease this indicator (Table 1). According to literature data, the causes of a decrease in hemoglobin levels may be damage to the erythrocyte membrane by the SARS-CoV-2 virus due to the presence of angiotensin and proteins interacting with ACE2 on the surface of erythrocytes, a direct attack by the heme virus, a violation of the regulation of iron metabolism, blood loss that occurred during renal replacement therapy and gastrointestinal bleeding in patients with or without the use of anticoagulants, autoimmune hemolytic anemia during a cytokine storm [5, 13].

The hematocrit level was within the upper limit of the norm and did not differ depending on the duration of the disease (Table 1).

According to the MCV data obtained by us, MCH RDW-CV in the fourth group of patients significantly increased (p=0.066, p=0.016 and p=0.064) in comparison with the third group, but were within normal values (Table 1). The detection of RDW-CV in a patient above the normal range reflects the presence of anisocytosis, probably associated with the presence of small and/or large erythrocytes, whereas a decrease in the value of this indicator, as a rule, has no clinical significance [4, 15].

The MCHC level is slightly reduced at all times. Significant differences were revealed when comparing the indicators of the second and third groups (p=0.053) and the third and fourth groups (p=0.007) (Table 1). In rare cases, a decrease in this indicator is associated with infectious processes in the acute phase.

The results of the obtained data revealed that the average values of white blood in people who have had COVID-19 are within acceptable normal values. According to the data obtained by us, the leukocyte level was within the normal range regardless of the time after recovery (Table 1). According to the literature, the leukocyte level in most patients is within the normal range, a third has leukopenia [3, 7, 8]. The level of leukocytes had a direct correlation with hemoglobin (r=0.256; p<0.001), with platelets (r=0.527; p<0.000), rod-shaped and segmented neutrophils (r=0.232; p<0.011 and r=0.271; p<0.000, respectively) and an inverse relationship with RDW-CV (r=-0.214; p<0.006), lymphocytes (r=-0.286; p<0.000) and monocytes (r=-0.176; p<0.025).

When calculating the number of monocytes as a percentage of all leukocytes, there was a tendency to increase in the second, third and fourth groups (Table

Table 2

Hematological blood parameters depending on the severity of CT

Indicator	CT 0	CT 1	CT 2	CT 3	Significance
Leukocytes (4.0-9.0 x 10^9/l)	5.43 ± 0.32 n=27	5.90 ± 0.19 n=60	6.03 ± 0.31 n=42	6.23 ± 0.31 n=32	-
Erythrocytes (M. 4.0-5.1 x 10^{12} units/l, W. 3.7-4.7 x 10^{12} units/l	4.66 ± 0.08 n=27	4.62 ± 0.05 n=60	4.61 ± 0.05 n=42	4.84 ± 0.07 n=32	$p=0.013^{1-3}$ $p=0.011^{2-3}$
Hemoglobin (M. 132-164, W. 115-145)	135.81 ± 2.42 n=27	134.03 ± 1.97 n=60	136.46 ± 1.76 n=42	143.03 ± 2.46 n=32	$p=0.045^{0-3}$ $p=0.011^{1-3}$ $p=0.03^{2-3}$
Hematocrit, % (M. 40-48, W. 36-42)	43.18 ± 0.72 n=27	49.42 ± 6.54 n=60	43.31 ± 0.49 n=42	45.08 ± 0.61 n=32	-
MCV, fl (M. 81-93, W. 82-96)	92.77 ± 0.84 n=27	92.92 ± 0.78 n=60	94.01 ± 0.59 n=42	93.19 ± 0.93 n=32	-
MCH, pg (27-33)	29.19 ± 0.36 n=27	29.10 ± 0.34 n=60	29.61 ± 0.23 n=42	29.54 ± 0.35 n=32	-
MCHC, % (32,6-36,2)	31.44 ± 0.16 n=27	31.27 ± 0.16 n=60	31.49 ± 0.11 n=42	31.68 ± 0.18 n=32	-
Platelets, (150-400 x 10^9/l)	250.89 ± 26.05 n=9	251.93 ± 9.95 n=29	252.87 ± 9.26 n=32	275.19 ± 17.72 n=21	-
RDW-CV, % (11,5-14,5)	13.55 ± 0.21 n=27	13.57 ± 0.17 n=60	13.38 ± 0.15 n=42	13.57 ± 0.14 n=32	-
ESR, mm/h (M. 1.00-10.0, W. 2.0-15.0)	15.33 ± 1.77 n=27	18.27 ± 1.43 n=60	20.17 ± 2.24 n=42	15.53 ± 1.94 n=32	-
Basophils, % (0-1)	0.67 ± 0.27 n=27	0.28 ± 0.08 n=60	0.19 ± 0.12 n=42	0.09 ± 0.05 n=32	$p=0.049^{0-1}$ $p=0.021^{0-2}$ $p=0.009^{0-3}$
Eosinophils, % (0-5)	4.45 ± 0.83 n=22	3.28 ± 0.30 n=56	2.89 ± 0.28 n=37	3.73 ± 0.72 n=30	-
Stick - core, % (1-6)	1.89 ± 0.25 n=18	2.36 ± 0.32 n=44	2.54 ± 0.33 n=33	2.30 ± 0.41 n=23	-
Segmentonuclear, % (45-70)	52.85 ± 1.71 n=27	55.47 ± 0.98 n=60	54.78 ± 1.46 n=42	54.09 ± 1.41 n=32	-
Lymphocytes, % (18-40)	32.29 ± 1.61 n=27	30.15 ± 0.84 n=60	31.15 ± 1.12 n=42	30.56 ± 1.21 n=32	-
Monocytes, % (2-9)	9.88 ± 0.59 n=27	9.80 ± 0.62 n=60	9.82 ± 0.63 n=42	10.09 ± 0.61 n=32	-

1). The level of monocytes had an inverse correlation with platelets (r=-0.231; p<0.027), with leukocytes (r=-0.176; p<0.025), with rod-shaped and segmented neutrophils (r=-0,232; p<0.011 and r=-0.477; p<0.000).

The average content of rod-shaped and segmented neutrophils in the postcovid period was within the normal range. A significant difference was revealed when comparing the indicators of rod-shaped neutrophils in the third and fourth groups (p=0.028) (Table 1).

Erythrocyte sedimentation rate (ESR) is one of the oldest non-specific markers of quantitative determination of the inflammatory process. An increase in ESR is observed in the 3rd and 4th groups (Table. 1), which does not contradict the literature data [3, 8]. The erythrocyte sedimentation rate had an inverse correlation with erythrocytes (r=-0.390; p<0.000), hemoglobin (r=-0.414; p<0.000) and MCHC (r=-0.171; p<0.029).

The results of red blood tests – platelet, erythrocyte, hemoglobin, hematocrit levels, depending on the degree of lung tissue damage, also varied within the reference values. However, there was a tendency of an unreliable increase in platelet levels depending on the degree of lung damage. The level of erythrocytes in persons with T3 was increased in comparison with the data at K 1 (p=0.013) and KT2 (p=0.011). The hemoglobin content of COVID-19 patients with CT3 was also increased in comparison with CT0 (p=0.045), CT1 (p=0.011) and CT2 (p=0.03) (Table 2). Correlation analysis showed that the hemoglobin level had a direct relationship with the degree of lung damage (r=0.185; p<0.019). This confirms the dependence of hemoglobin changes on the severity of lung tissue damage in a new coronavirus infection [7, 10]. In addition, hemoglobin had a direct relationship with MCV, MCH, MCHC (r=0.354; p<0.000; r=0.528; p<0.000; r=0.670; p<0.000, respectively), as well as an inverse relationship with RDW-CV (r=-0.486; p<0.000). The hematocrit level changed unreliably.

According to the data obtained by us, the level of leukocytes, regardless of the degree of damage to the lung tissue of SARS-CoV-2, was within the normal range and had no significant differences (Table 2).

The average content of basophils varied within the reference values, but depending on the CT level, there was a decrease in CT1, CT2 and CT3 compared to CT0 (p=0.049, p=0.022 and p=0.009, respectively) (Table 2).

In our study, the level of the largest and most lysosomally filled phagocytes of the granulocyte series – monocytes was higher than normal in all groups and did not depend on the degree of lung tissue damage, but had no statistically significant differences (Table 2).

The erythrocyte sedimentation rate in patients with COVID-19, depending on the CT level, was increased in all groups, while the greatest increase was observed with CT1 and CT2, but had no statistically significant differences (Table 2). The increased erythrocyte sedimentation rate is another inflammatory biomarker that is increased with COVID-19 [2]. The exact reason is not known. However, since ESR depends on changes in the size, shape of red blood cells and plasma concentration, it is assumed that COVID-19 can cause a change in the characteristics of red blood cells or plasma, which leads to an increase in ESR [9].

Thus, in the individuals we examined after COVID-19, almost all hematological blood parameters were within the reference values and did not significantly differ from the duration of the disease and the degree of lung damage of SARS-CoV-2. Depending on the duration of the new coronavirus infection, there was a significant decrease in platelet levels after 3, 6 and 9 months compared to 12 months, which is a positive sign and indicates the recovery of the body. However, in all patients with a new coronavirus infection, inflammatory processes remained at a low level, since the level of monocytes and ESR remained elevated in all, regardless of the duration of the disease and the degree of lung damage. Also, a low MCHC content, most pronounced after 9 months, indicates signs of hypochromic iron deficiency anemia.

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COMPARATIVE CHARACTERISTICS OF CARDIOMETABOLIC DISORDERS IN THE WORKING POPULATION OF INDIGENOUS AND NON-INDIGENOUS NATIONALITIES OF YAKUTIA

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A pilot study was conducted in the expeditionary conditions of the working population of the Anabar and Aldan districts of the Republic of Sakha (Yakutia). Arterial hypertension was registered equally frequently in more than half of the respondents. More than half of the respondents had abdominal obesity, and it was more often detected in non-indigenous men and women of indigenous nationality. Abdominal obesity and arterial hypertension are associated with atherogenic dyslipidemia in the indigenous population, most often in women. In non-indigenous people, regardless of gender, obesity correlated with TG levels and blood glucose, arterial hypertension with the same indicators in non-indigenous women.

Keywords: arterial hypertension, abdominal obesity, lipid metabolism, indigenous and non-indigenous population, Yakutia.

Cardiovascular pathology and obesity pose a serious threat to the health of populations all over the world. Arterial hypertension (AH) is the most common cardiovascular pathology, its complications making a significant contribution to mortality. The scale of its spread in Russia has risen from 39.2% to 45.7% in a 20-year period of observations [2]. An epidemiological study conducted earlier in Yakutia revealed a 30.3% prevalence of hypertension in the population of the republic [5]. In recent years, studies have been conducted to research its spread mainly among the indigenous population, including indigenous small-numbered peoples, the frequency reached 54.3% [7; 9].

The prevalence of obesity in the world raises serious concerns. The scale of its spread is pandemic in nature. According to WHO, 650 million adults and 340 million children are obese [10]. According to the ESSE-RF study, its prevalence in Russia reaches up to 36.3% in men and 52.3% in women [4]. The study of the prevalence of obesity among the indigenous and non-indigenous population of the northern territories of Russia showed a lower prevalence among indigenous people [6]. The historically established way of life and the nature of nutrition among the indigenous peoples of the North have been undergoing global changes in recent decades. Considering the above, the study of cardiometabolic disorders in indigenous small-numbered peoples and non-indigenous residents of Yakutia is undoubtedly relevant.

Aim of the study: A comparative analysis of cardiometabolic disorders in the employed population of indigenous and non-indigenous nationalities in Yakutia.

Materials and methods. A single-stage pilot study of the employed population of the Republic of Sakha (Yakutia) was conducted. According to the employment lists, every third employee of the Aldan district (southern zone), where the mining industry is highly developed, and the Anabar district (northern zone), where diamond deposits have been mined in recent years, participated in the study. The response rate was 76%. The analysis was carried out, there were 380 study participants, including 180 non-indigenous and 200 indigenous people. In the Aldan district, the study was conducted among employees of an industrial enterprise, representatives of non–indigenous nationality (Russians, Ukrainians, etc.), in Anabar - social, housing and communal services employees of indigenous nationality, mainly represented by indigenous small peoples (Evenks and Dolgans). For comparative analysis, 2 groups were formed: indigenous and non-indigenous residents. The average age was 45.03±0.84 years for indigenous people, 44.37±0.86 years for non-indigenous people (p=0.587). In the group of people of indigenous nationality, there were 145 women, 55 men; in the group of non-indigenous nationalities 111 and 69, respectively. They were comparable in age for analysis. The average age of indigenous men was 45.07±1.82 years, non-indigenous 45.03±1.4 years (p>0.05), indigenous women 45.02±0.93 years, non-indigenous 43.95±1.10 years (p>0.05).

A comprehensive study of the population included a questionnaire, which reflected complaints, past illnesses, family history, living conditions, social status, diet, bad habits, etc.; an anthropometric study measuring height and weight, waist (WC) and hips circumference (HC). An examination by a general practitioner and a cardiologist with the measurement of blood pressure (BP) was carried out. Blood sampling from the vein was carried out on an empty stomach with a 12-hour fasting interval after the last meal. The study participants signed a voluntary consent form for the examination in accordance with the Protocol of the Ethics Committee of the YSC CMP.

Values of WC > 94 cm in men and > 80 cm in women indicate abdominal type of obesity [3].

Arterial hypertension was established (AH) at a blood pressure level≥140/90 mmHg or when constant use of antihypertensive drugs was prescribed [1;11].

Laboratory research methods included: determination of lipid metabolism (total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG)), and blood glucose.

Statistical data processing was carried out using the SPSS STATISTICS software package (version 26.0). Qualitative variables are described by absolute and

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relative frequencies (%), quantitative by means of the mean and standard error of the mean, median (Me) and interquartile range (Q1-Q3). The proportions between the groups were compared using the nonparametric Spearman criterion χ2. The odds ratio (OR) and 95% confidence interval (95% CI) were used to calculate the relationships. Spearman's coefficient was used for correlation analysis. The statistical significance of the differences (p) is less than 5%.

The work was carried out within the framework of the research of the YSC CMP "Regional specifics of normal and pathological biochemical, immunological and morphological indicators in the indigenous and non-indigenous population of the Republic of Sakha (Yakutia)" (FGWU-2022-0014).

Results and discussion. For the analysis of anthropometric indicators, the comparison of the average values of WC depending on ethnicity and gender was carried out. In men, the average WC index was higher with a statistical difference among representatives of non-indigenous nationality and amounted to 97.09±1.46 cm in comparison with indigenous men (91.84±1.58 cm) (p=0.017). As for the female population, the average WC index was above the reference values in both groups and had no statistical difference, for indigenous women it was 90.99±1.19 cm, for non-indigenous 88.69±1.47 cm (p=0.223).

More than half of the respondents have a high incidence of abdominal obesity (AO), for the indigenous population it was 70% (n=140), non-indigenous 66.7% (n=120) (OR 1.16; 95% CI [0.75-1.79], p=0.485). In gender comparison, AO was slightly more common in non-indigenous men compared to indigenous men - 62.3% and 47.3%, respectively (OR 0.54; 95% CI [0.26-1.11], p=0.094). In women, the opposite results were obtained, regardless of ethnicity, there is a high incidence of AO. Indigenous women were 1.5 times more likely to have AO without a statistically significant difference (78.1%), compared with non-indigenous women (70%) (OR 1.53; 95% CI [0.87-2.69], p=0.141).

Thus, the analysis of anthropometric data showed a high incidence of AO in both groups, which is most prominent in non-indigenous men and indigenous women. The global changes in lifestyle, traditional principles of nutrition, low physical activity are most characteristic of women, representatives of the indigenous peoples of Yakutia. The results are consistent with the studies of A.I. Kozlov, who showed the prevalence of obesity among the indigenous small-numbered peoples of the North, which is similar with the national data [8].

A correlation analysis of the conjugacy of WC with indicators of the lipid and carbohydrate spectrum, depending on gender and ethnicity, was carried out (Table 1). In indigenous men, significant conjugacy was obtained with LDL and TG, in the non-indigenous with TG and blood glucose. In women of indigenous nationality, a significant correlation was obtained with all indicators, except for TC. In non-indigenous women, as in men of the same ethnicity, WC positively correlated with the level of TG and blood glucose.

Correlation analysis showed the greatest association of AO with atherogenic dyslipidemia in the indigenous population, the most characteristic for women. In people of non-indigenous nationality, regardless of gender, AO correlated with TG levels and blood glucose. The close association of obesity with TG and glucose levels has also been confirmed in general population studies of ESSE-RF [4].

Given the epidemic nature of obesity among the study participants, a study was conducted on the presence of hypertension. It was revealed that more than half of the participants had hypertension, equally often in both indigenous and non-indigenous populations - 54.2% and 56.4%, respectively (OR 0.91; 95% CI [0.61-1.37], p=0.667). The mean systolic blood pressure (SBP) was 137.01±1.70 mmHg in the indigenous population with a significant difference compared to the non-indigenous population, whose SBP was 130.22±1.65 mmHg (p=0.004).

A gender comparison of the incidence of hypertension showed that men of non-indigenous nationality without significant differences were more likely to have hypertension compared to indigenous men (62.3% and 50.9%, respectively) (OR 0.62; 95% CI [0.30-1.28], p=0.202). In women, on the contrary, the opposite values were obtained. In indigenous women, hypertension was registered slightly more often (55.5%) compared with non-indigenous (52.7%) (OR 1.11; 95% CI [0.67-1.83], p=0.662).

Next, a correlation analysis of systolic blood pressure (SBP) with the parameters of lipid and carbohydrate metabolism, depending on gender and ethnicity, was carried out (Table 2). The indigenous male population has the greatest conjugacy with the level of TG, no correlation was obtained in non-indigenous men (p>0.05). As for the female population, the association of SBP with the levels of TC, LDL and TG was obtained in indigenous women. In non-indigenous women, SBP correlated with the con-

Table 1

Correlation analysis of WC with lipid spectrum and blood glucose by Spearman, depending on gender and ethnicity

WC			TC	HDL	LDL	TG	glucose
men	indigenous	r	0.095	0.100	0.312	0.253	0.126
		p	0.129	0.144	**0.000**	**0.000**	0.065
	non-indigenous	r	0.035	-0.078	-0.031	0.262	0.174
		p	0.510	0.138	0.561	**0.000**	**0.001**
women	indigenous	r	0.110	-0.418	0.201	0.479	0.369
		p	0.186	**0.000**	**0.015**	**0.000**	**0.000**
	non-indigenous	r	0.121	-0.167	-0.010	0.308	0.214
		p	0.207	0.081	0.917	**0.001**	**0.025**

Table 2

Correlation analysis of SBP with lipid spectrum and blood glucose by Spearman, depending on gender and ethnicity

SBP			TC	HDL	LDL	TG	glucose
men	indigenous	r	0.004	-0.013	-0.047	0.291	0.117
		p	0.999	0.925	0.736	**0.031**	0.397
	non-indigenous	r	0.009	-0.053	-0.011	0.198	0.133
		p	0.943	0.667	0.926	0.102	0.277
women	indigenous	r	0.433	0.108	0.402	0.262	0.160
		p	**0.000**	0.193	**0.000**	**0.001**	0.053
	non-indigenous	r	0.024	-0.101	-0.070	0.300	0.198
		p	0.803	0.296	0.468	**0.001**	**0.038**

centration of TG and blood glucose, no significant correlation was obtained for other parameters.

Thus, a high incidence of hypertension was revealed in both indigenous and non-indigenous populations, confirming the close relationship between hypertension and obesity, which was confirmed by earlier ESSE-RF studies [4]. When compared by gender, it was more often registered with an unreliable difference in non-indigenous men and indigenous women. AH correlates most significantly with lipid metabolism disorders in indigenous women.

Earlier studies conducted by Russian scientists proved a lower prevalence of obesity and hypertension in the indigenous population compared to non-indigenous residents of the northern and Arctic territories of Russia [6]. Our study showed the alignment and sometimes deterioration of some indicators of the cardiovascular system, obesity and lipid profile in the indigenous population of Yakutia.

Conclusion. The results obtained allow us to confirm that there is a change in the state of health of the indigenous peoples of the North. Our pilot study partially refutes the previously conducted research results on the most favorable profile of lipid disorders in the indigenous population compared with non-indigenous. Cardiometabolic disorders are equally common among the working population of Yakutia, regardless of ethnicity, and sometimes even more common among indigenous people. Arterial hypertension was registered with the same frequency in indigenous and non-indigenous populations. Abdominal obesity is more common in non-indigenous men and indigenous women. The relationship between the development of arterial hypertension with TC and its atherogenic fractions in representatives of indigenous peoples of the North, TG and blood glucose in non-indigenous women was obtained.

The male population in places of compact residence of indigenous small-numbered peoples of the North still retain occasional physical activity, engaging in reindeer husbandry, hunting, fishing. The health of the female population raises concerns due to a decrease in motor activity, changes in the traditional nature of nutrition (mainly carbohydrate-fat), an increase in the influence of gadgets in everyday life, etc. Further monitoring of the health status of the employed population with a comprehensive preventive approach to weight loss, promotion of healthy eating, sports, timely drug therapy of existing diseases of the cardiovascular system is required.

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DIAGNOSTIC AND TREATMENT METHODS

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SERUM BIOMARKERS IN DIFFERENT TYPES OF PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease of unknown origin with an average life expectancy of 3-5 years after diagnosis. The disease is accompanied by progressive pulmonary fibrosis, decreased lung function, poor response to therapy and early mortality. Various biomarkers, including serum biomarkers, are used for timely and differential diagnosis of idiopathic pulmonary fibrosis (IPF) and COVID-19-associated pulmonary fibrosis (PF), predicting the course of the disease and assessing the effectiveness of specific therapy. Target was to investigate the features of pulmonary fibrosis based on serum biomarkers in patients with ILF and COVID-19-associated fibrosis. Methods. Changes in serum concentrations of biomarkers CA15-3, LOXL2, TGFBR3 and periostin in patients with ILF (n=10), COVID-19-associated pulmonary fibrosis and controls were investigated. Results. Significant differences were found between LOXL2 concentrations in the control and ILF groups (p=0.003), ILF and COVID-19-associated fibrosis groups (p=0.036) and between periostin concentrations in the control and ILF groups (p=0.042). ROC analysis for LOXL2 revealed: in the ILF and control groups AUC=0.854 (95% CI 0.693-1.0; p<0.0001), with a sensitivity of 80.0% and specificity of 76.9%; in the ILF and COVID-19-associated LF groups AUC=0.773 (95% CI 0.556-0.989; p=0.014) with a sensitivity of 99.0% and specificity of 63.6%. For periostin: AUC=0.692 (95% CI 0.469-0.916; p=0.092) with a sensitivity of 50.0% and specificity of 84.6%. Correlation analysis in the pooled group showed a significant correlation for CA15-3 and periostin (rs=0.383; 95% CI 0.042-0.645; p=0.025), LOXL2 and periostin (rs=0.509; 95% CI 0.196-0.727; p=0.002), TGFBR3 and CA15-3 (rs=0.347; 95% CI 0.0-0.62; p=0.044). Conclusions. We found significant differences between serum levels of LOXL2 in ILF group and CG, ILF group and COVID-19-associated LF. ROC analysis yielded the values of the optimal points of group separation by serum LOXL2 and periostin levels. This allows differential diagnosis of different pulmonary fibrosis.

Keywords: pulmonary fibrosis, IPF, COVID-19, CA15-3, periostin, TGFBR3, LOXL2.

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Introduction. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial pulmonary disease of unknown origin with an average life expectancy of 3-5 years after diagnosis set up. The disease is accompanied by the development of progressive pulmonary fibrosis (PF), decreased respiratory lung function, poor response to therapy, and premature mortality [7]. In total, there are about 3 million patients with IPF in the world [9]. The estimated primary incidence rate in Europe is from 0.009 to 0.049 / 100,000 in population, in North America - 0.075-0.093, and the overall incidence rate is 0.033-0.251 in Europe and 0.24-0.298 – in North America [8].

When exposed to damaging environmental factors (cigarette smoke, viruses, dust) or as a result of an autoimmune process in IPF, the microdamage of the alveolar epithelium is initiated. Although the triggering mechanisms of the disease may vary, progression of PF is associated with growth factors activation, changes in the concentration of cytokines and chemokines, as well as epigenetic reprogramming of fibroblasts and vascular remodeling [5].

One of the most unfavorable complications of COVID-19 is the development of PF [15], which significantly decreases the quality of life and can subsequently lead to the death. In COVID-19-induced PF, a number of serum biomarkers, predictors of its unfavorable consequences, are being under investigation [1-3].

For the timely identification of patients with PF, as well as the determination of disease phenotypes, the use of serum biomarkers seems to be very promising. Given the common pathogenetic mechanisms of fibrosis, it is suggested that biomarkers of disease may be effective in identifying both IPF and COVID-19-associated PF. As a potential PF biomarkers and response to the antifibrotic therapy SP-D (surfactant protein D), MMP-1, MMP-8, KL-6, CRPM-1, CRPM-8, C3M, C1M, 5mC, mH2A1, TOLLIP and MUC5B [1, 10, 19], as well as CA15-3, TGFBR3, LOXL2 [16], and periostin are under consideration.

The objective was to study the diagnostic value of serum biomarkers LOXL2, periostin, TGFBR3 and CA15-3 in patients with IPF and COVID-19-associated fibrosis.

Methods. In longitudinal prospective non-randomized study 34 patients were enrolled: 1st group – patients with IPF (n=10), 2nd - COVID-19-associated PF (n=11), and 3d - control (CG) (n= 13). All patients were hospitalized in the Pulmonology or Thoracic Department of Bashkir State Medical University Clinic (Ufa). The diagnosis was established on the basis of a clinical examination, laboratory and instrumental studies, including high-resolution computed tomography, spirometry and video-assisted thoracoscopic lung biopsy. As part of the clinical and instrumental examination, body mass index and functional respiration parameters

(VC, FEV_1, FEV_1/VC) were assessed. In addition, for each group the proportion of smoking patients was determined by means of smoking index, as well as the proportion of patients with various concomitant diseases.

The concentration of biomarkers in blood serum was determined by enzyme immunoassay with further determination of optical density using a photoelectrocolorimeter with a wavelength 450 nm. The following reagent kits were used: RayBio® Human LOXL2 ELISA Kit (USA), RayBio® Human TGF-beta RIII ELISA Kit (USA), CHEMA® CA15.3 (M12)-ELISA (Russia), and Aviscera Bioscience® HUMAN PERIOSTIN/OSF- 2 ELISA KIT (USA).

The study was approved by the Local Ethical Committee of Bashkir State Medical University, protocol No. 3 from 21 September, 2022. All patients signed informed consent to participate in the study.

Statistical analysis was performed by means of STATISTICA program (version 10.0). Nonparametric statistics methods were used: data were presented as median (interquartile range Q1; Q3). To compare all three groups, the Kruskal-Walli's test was used, and Wilcoxon-Mann-Whitney U test - for paired comparisons. When determining the threshold values of biomarkers concentrations to differentiate the groups, ROC analysis was utilized with sensitivity and specificity calculation. A nonparametric correlation analysis was also carried out with the calculation of the Spearman correlation coefficient. A $p<0.05$ level was considered to be statistically significant.

Results and discussion. In the Table 1 the clinical and demographic characteristics of patients in the study groups, and in Table 2 – comparative results of determining the levels of biomarkers in the blood serum of the subjects are presented. The differences between groups were determined in age (less in control, 42.0 (33.0; 51.7) years versus 56.5 (51.8; 63.4) and 59.0 (52.5; 63.7) in IPF and COVID-19 LF groups, respectively), and in IPF group, the respiratory function parameters vital capacity (VC) (63.8% (54.3; 88.9)) and force expiratory volume (FEV_1, 57.0% (48.1; 93.4)), which were less than in other groups. COVID-19 group was more likely to consists males compared to IPF and control groups (30% vs. 54.5 and 42.0%, respectively). There were no significant differences between other parameters.When comparing the concentrations of the biomarkers, the significance levels of the U-test and the Kruskal-Walli's test are presented in Table. 3. Analyzing the results using the Kruskal-Walli's test, the significant differences between all three groups for LOXL2 ($p = 0.015$) were identified. Significant differences in LOXL2 levels in pairwise comparisons of IPF and CG groups ($p=0.003$) and IPF and COVID-19-associated PF groups were also found ($p=0.036$). Differences were also found for periostin in a pairwise comparison of the IPF and CG groups ($p=0.042$).

Further, the ROC analysis was performed for groups with significantly difference in biomarkers level. When dividing the IPF versus control group according to the LOXL2 level (Fig. 1), the AUC was 0.854 (95% CI 0.693-1.0, $p<0.0001$). The optimal LOXL2 group cut-off point was 20.6 pg/ml (sensitivity 80.0% and specificity 76.9%). When comparing IPF

Table 1

Clinical and demographic characteristics of patients

Indicator		IPF	COVID-19-PF	Control
(n)		10	11	13
Age, years		56.5 (51.8; 63.4)	59.0 (52.5; 63.7)	42.0 (33.0; 51.7)
Gender, n (%)	M	3 (30.0)	6 (54.5)	4 (30.8)
	F	7 (70.0)	5 (55.5)	9 (69.2)
BMI, kg/m^2		28.6 (24.9; 29.5)	28.4 (24.6; 34.2)	28.4 (24.6; 34.2)
Smoking, n (%)	Yes	1 (10.0)	6 (54.5)	4 (30.77)
	No	9 (90.0)	5 (55.5)	9 (69.23)
VC, % estimated		63.8 (54.3; 88.9)	85.74 (66.6; 92.6)	81.1 (52.0; 87.6)
FEV1, % estimated		57.0 (48.1; 93.4)	83.2 (73.2; 91.2)	86.97 (66.3; 94.1)
FEV1/VC, % estmated		104.7 (86.9; 114.1)	105.3 (94.5; 115.1)	100.7 (87.9; 108.3)
DM 2 type, n (%)		1 (10.0)	0	0
AH, n (%)		2 (20.0)	3 (27.3)	0

P.s.: BMI – body mass index, FEV – forced expiratory volume, FEV1/TL – Tiffeneau index, DM 2 type – diabetes mellitus of 2nd type, AH – arterial hypertension.

Table 2

Biomarker levels in the study groups

Indicator	IPF	COVID-19 PF	Control
Periostin, ng/ml	10.9 (6.6; 18.3)	6.9 (5.1; 13.1)	6.9 (4.1; 9.9)
CA 15-3, U/ml	3.6 (2.7; 6.1)	4.1 (3.1; 5.5)	3.3 (1.9; 5.0)
LOXL2, pg/ml	49.9 (23.4; 84.7)	13.8 (13.1; 62.2)	15.2 (12.6; 23.4)
TGFBR3, ng/ml	389.3 (330.5; 682.4)	472.1 (291.0; 859.6)	379.6 (223.9; 675.7)

Table 3

Significance levels of the Kruskal-Wallis p-test and the Wilcoxon-Mann-Whitney U-test when comparing biomarker levels in the studied groups

Indicator	Kruskal-Walli's test	U-criteria of IPF versus control	U-кcriteria of COVID-19 PF and control	U-criteria of IPF and COVID-19 PF
LOXL2	**0.015**	**0.003**	0.955	**0.036**
Periostin	0.145	**0.042**	0.631	0.512
TGFbR3	0.638	0.557	0.303	0.756
CA15-3	0.443	0.468	0.228	0.605

group versus COVID-19-associated PF group (Fig. 2), the AUC was 0.773 (95% CI 0.556-0.989, p=0.014). The optimal point for dividing the groups by LOXL2 level was 14.0 pg/ml (99.0% and 63.6%). When splitting the IPF group versus CG based on the periostin level (Fig. 3) the AUC was 0.692 (95% CI 0.469-0.916, p=0.092) and cut-off point between groups for periostin was 11.1 ng/ml (sensitivity 50.0% and specificity 84.6%).

Spearman's rank correlation coefficients were also calculated for biomarkers levels in the combined group of subjects. A significant positive correlation was found between the concentrations of LOXL2 and periostin (rs=0.51; 95% CI 0.20-0.73, p=0.002), TGFBR3 and CA15-3 (rs=0.35; 95% CI 0. 0-0.62, p=0.044), and CA15-3 and periostin (rs=0.38; 95% CI 0.04-0.65, p=0.025).

A special feature of our study was a comparative analysis of the diagnostic value of four current biomarkers of PF - LOXL2, periostin, TGFB3, CA15-3 in two groups of patients with different fibrosis diseases - IPF and COVID-19-associated PF. Despite the relatively small number of groups, significant intergroup differences and correlations in the levels of the studied biomarkers were found. The biomarker LOXL2 showed the biggest diagnostic significance, and seems to have a prominent role in the formation of fibrotic tissue. LOXL2 (lysyl oxidase-like protein 2) cross-links collagen fibers activates fibroblasts [11], promotes the synthesis and accumulation of collagen, and strengthens the intercellular matrix. Previously, the increased expression of LOXL2 gene was detected in patients with IPF compared to the control group [12]. An increase in the level of LOXL2 was also recorded in IPF [3, 13] and in fibrosis of other localizations – liver and cardiac fibrosis [11]. Serum LOXL2 concentrations greater than 700 pg/mL have been associated with higher risks of IPF progression [3]. The results of our study, where has shown the highest levels of LOXL2 found in patients with IPF and characterized by aggressive development of PF are consistent with the data from other studies. At the same time, significantly lower levels of LOXL2 in COVID-19-associated LF probably reflect the less malignant nature of the fibrotic process in this group of patients.

In our study, periostin has also confirmed its diagnostic value as a biomarker of PF. The increase in its expression level is observed during inflammation, resulting in remodeling and fibrosis of lung tissue in IPF, chronic obstructive pulmonary disease, bronchial asthma

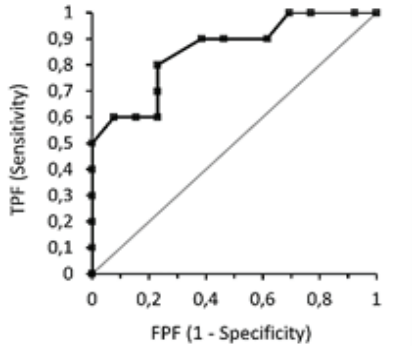

Fig. 1. ROC-analysis of LOXL2 on cut-off point between IPF and control group.

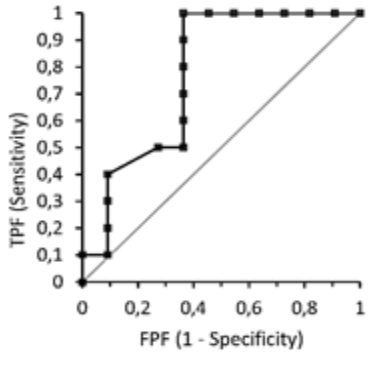

Fig. 2. ROC-analysis of LOXL2 on cut-off point between IPF and COVID-19-associated pulmonary fibrosis.

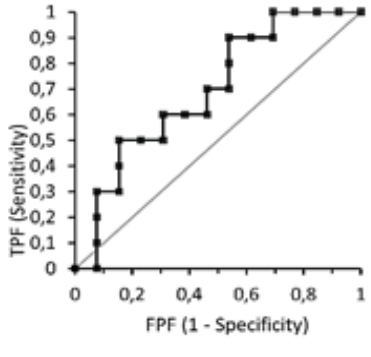

Fig. 3. ROC-analysis of periostin on cutt-off point between IPF and control group.

and lung cancer [14]. Monomeric periostin is one of the most sensitive and specific markers of IPF (AUC=0.958) [2]. At the concentration of 11.2 ng/ml, the sensitivity and specificity were 90.0% and 91.2%, respectively. In the total periostin the cut-off point was 77 ng/ml with AUC 0.843, sensitivity - 73.3% and specificity - 79.6% [2], which was superior to similar indicators of other important biomarkers of pulmonary fibrosis SP-D and KL-6 [20]. The increase in serum periostin concentrations greater than 117 μg/ml was associated with progression of IPF [3], deterioration of VC and DLCO diffusion capacity over six months [6].

Despite the fact that in our study the other two biomarkers TGFBR3 and CA15-3 did not reveal diagnostic significance, for a number of reasons they remain promising tool for diagnosing of PF and assessing other accompanying mechanism such as apoptosis. TGFBR3 is a type 3 transforming growth factor receptor TGF-β. Inhibition of TGFBR3 aggravates the development of pulmonary fibrosis [10]. Under certain conditions, TGFBR binds TGF-β [19], which leads to a decrease in the synthesis of smooth muscle actin-α (SMA-α), fibronectin, type I collagen due to inhibition of SMAD2/3, PI3K/Akt and MAPK signaling pathways TGF-β [1].

CA15-3 is a malignant antigen that is most actively expressed in breast location of cancer [4]. However, the increased concentration of CA15-3 was also observed in IPF [6]. According to d'Alessandro M. et al., the plasma concentration of CA15-3 in IPF was more than 5 times higher than in the control level [18]. In another study, estimation of CA15-3 levels enables to differentiate patients with different types of PF [17].

The discovered correlations between the studied biomarkers reflect their direct and indirect interaction as the links in the complex signaling pathways involved in PF [5]. On this basis, biomarkers of PF are considered not only as an important diagnostic and prognostic criteria, but also as the markers for highly effective targeted therapy in the future [12-14].

Conclusions. Significantly elevated levels of the biomarkers LOXL2 and periostin were found in IPF compared with both control and COVID-19-associated PF groups. The cut-off points to differentiate IPF versus COVID-19-associated LF groups, and IPF versus CG groups based on the LOXL2 level of 20.6 pg/ml and 14.0 pg/ml, respectively, were established. Similarly, for periostin, the cut-off point for IPF versus CG was 11.1 ng/ml. In the combined group of patients, the concentrations of periostin and CA15-3, periostin and LOXL2, TGFBR3 and CA15-3 were positively correlated with each other. Further studies of the plasma/serum concentrations of these biomarkers in patients with IPF and COVID-19-associated LF are needed, which in the future will increase the efficiency of diagnosis and prognosis of pulmonary fibrosis of various etiologies in order to determine the optimal treatment tactics.

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DIAGNOSTIC VALUE OF VERTICAL LINES OF LATERAL HEAD TELERADIOGRAPHS

Aim. To determine the diagnostic value of the vertical lines of lateral teleradiographs in the analysis of the gnathic section of the face and the position of the front teeth. **Material and methods.** A pilot retrospective study of 74 museum teleradiographs in the lateral projection was conducted. It is proposed to use the nasal-subnasal vertical. Parallel to the nasal-subnasal line, lines were drawn through the anterior superior alveolar point prosthion (Pr) and the anterior inferior point of the infradentale (Id). The position of the cutting edge of the incisors relative to the vertical diagnostic lines and the position of the contact point between the upper and lower incisors were evaluated. A visual analysis of the location of the anatomical details of the gnathic part of the face was carried out. **Results.** The result of the analysis of radiographs with a mesotrusion type of dental arches showed that in most cases the anterior alveolar vertical, crossing the prosthion point (Pr), passed through the cutting edge of the upper medial incisor, and the interstitial contact point was located in the middle, between the anterior and posterior alveolar lines. Regardless of the typological features of the dental arches in physiological occlusion, equality of vertical dimensions was noted, which was analyzed along five lines that passed perpendicular to the studied diagnostic verticals of the face. The upper horizontal line passed near the apical base of the upper jaw (point "A"), and the lower - through the point "B", which determines the position of the apical base of the lower jaw. **Conclusion.** Thus, the use of the proposed vertical diagnostic lines allows for a comparative analysis of dental arches of various trusion types, to assess the proportionality of parts of the gnathic section of the face and can be useful for diagnosing malocclusion in various directions, including vertical forms of occlusion and disocclusion.

Keywords: teleradiograph; physiological occlusion; pathological protrusion and retrusion of the incisors; occlusion anomalies.

Introduction. The introduction of modern technologies and equipment makes it possible to use a wider range of diagnostic measures in practical dentistry, not only to assess the risk of the underlying dental pathology, but also to identify concomitant somatic diseases. In particular, the peculiarities of oral cavity pathology in the presence of diabetes mellitus have been noted [1]. This paper presents modern methods of clinical and laboratory research, including radiological ones.

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One of the objective modern methods of radiological examination is cone-beam tomography with applied computer programs for analyzing the results [9]. However, despite the versatility and reliability of this method, there are some limitations for its daily use associated with the material expenditures of patients.

Along with CBCT, the method of teleradiography with numerous author's analysis methods has been widely used in the clinic of orthodontics and prosthetic dentistry [15]. In the present study the experts noted the features of morphometry using horizontal and vertical lines with the measurement of angles between them. The Dreyfus, Kantarovich, and Simon lines were separated from the vertical lines, which made it possible to consider the profile of the face taking into account Schwartz's recommendations. In addition, the typological features of the dentomaxillary arches are noted.

In turn, the types of dental arches, in particular, their protrusion and retrusion variants, affect the morphology of the bone structures of the mandibular joint [6, 17, 19]. Specialists note the peculiarities of the gnathic part of the face in people with congenital pathology, in particular, with cleft lip and palate [3, 18].

Taking into account the size of the head and face, odontometry methods have been proposed [10]. In the present study the authors determined the dependence of the sum of the width of the crowns of the four incisors of the upper arch, with the interzygomatic distance measured between the zygion points.

A comprehensive analysis of morphological dissertation studies of dental status in normal and pathological conditions was carried out, taking into account gender differences and periods of ontogenesis [8, 16]. The works present multifaceted information on the shape and size of the anatomical structures of the craniofacial complex. A comparative analysis of the dental parameters of arches of various types in the transversal, diagonal, and sagittal directions is given [4].

Researchers pay attention to the location of teeth in dentoalveolar segments, noting the location of the apical part of the root relative to the compact and spongy bone [2]. The greatest variability, according to the authors, is observed in the incisor group [7]. Particular attention in this study is paid to the position of the incisors in the anterior-posterior direction.

Based on the analysis of the proportionality of the parameters of the face and dental arches, algorithms for the diagnosis and treatment of patients with occlusal pathology, including the presence of defects in the dentition, have been proposed [5].

As a rule, the information obtained during morphometry determines the tasks of the orthodontist in carrying out therapeutic and dispensary measures [12].

A lot of information concerns the optimization of bite height determination methods, especially in people with vertical abnormalities [11]. Based on this principle, methods for diagnosing and treating patients of different ages with dental arch defects, including complete adentia, have been proposed [14,].

In addition, the use of modern methods of diagnosis and determination of the features of physiological occlusion are the criteria for the effectiveness of therapeutic and preventive measures [13].

The analysis of literature sources has shown that at present it is necessary to conduct additional research aimed at the development and implementation of modern methods for diagnosing teleradiograms, which formed the basis of the purpose of the work.

Aim. To determine the diagnostic value of the vertical lines of lateral teleradiography in the analysis of the gnathic part of the face and the position of the anterior teeth.

Material and methods of research. The pilot retrospective study was carried out on the basis of departmental materials and included the analysis of 74 lateral teleradiography, both with physiological norm and with various variants of abnormal occlusion.

In the course of the study, generally accepted landmarks were used to draw the plane of the skull base according to Schwartz, by connecting a point located in the middle of the entrance to the Turkish saddle (Se) with a nasal point on the bone (N). To construct the Dreyfus line, a skin point on the bridge of the nose (n) was used, through which a perpendicular was drawn to the plane of the base of the skull. In addition, diagnostic verticals were drawn (Fig. 1).

The main vertical was drawn through the cutaneous nasion point (n) and the subnasal point (sn). In the course of the study, the location of the nasal-subnasal line with the Dreyfus line was analyzed.

Parallel to the nasal-subnasal line, lines were drawn through the anterior upper alveolar point prostion (Pr) and the anterior inferior infradenthale (Id). The position of the cutting edge of the incisors relative to the vertical diagnostic lines and the position of the contact point between the upper and lower incisors were evaluated.

To assess the vertical dimensions of the gnathic part of the face, five lines were drawn perpendicular to the diagnostic verticals. The upper line departed from the subnasal point (sn), below it was the alveolar line from the point of prosthion (Pr), and the third line passed through the point of closure of the lips. The inferior alveolar line passed through the infradental point (Id) and the fifth line passed through the cutaneous supramental point (sm).

The trusion type of dental arches was assessed by the interincisor angle, which varied from 125 to 135 degrees in mesotrusion. An increase in the angle characterized the retrusive type, and a decrease – a protrusion variant of the dental arches.

Visual analysis of the location of anatomical details of the gnathic part of the face was carried out without morphometric analysis, which did not require static analysis of the study results.

Results and discussion. As a result of the study, attention was drawn to the fact that the Dreyfus line often did not coincide with the nasal-subnasal vertical and applying it could be useful for determining Schwartz facial profiles, taking into account the location of the subnasal landmark, which was located in front, behind or on the Dreyfus line.

In this regard, we consider it more rational to use the proposed diagnostic verticals when analyzing facial signs and, in particular, the gnathic part of the face.

Teleradiographs with physiological occlusion were divided into three groups. The first group included images in which the interincisor angle corresponded to the mesotrusive variant. In the second group, the protrusion version of the incisors predominated, and in the third group, the incisors closed in a retrusion pattern, corresponding to the signs of physiological occlusion.

The result of visual analysis of radiographs with the mesotrusion type of dental arches showed that in most cases the anterior alveolar vertical, crossing the prosthion point (Pr), passed almost through the cutting edge of the upper medial incisor, and the interincisor contact point was located in the middle, between the anterior and posterior alveolar lines.

Radiographs of the protrusion type of dental arches showed that in most cases the anterior alveolar vertical, crossing the prosthion point (Pr), also crossed the cutting edge of the superior medial incisor, which, as a rule, was located in front of the indicated line. The interincisor contact point was shifted from the center towards the anterior alveolar line.

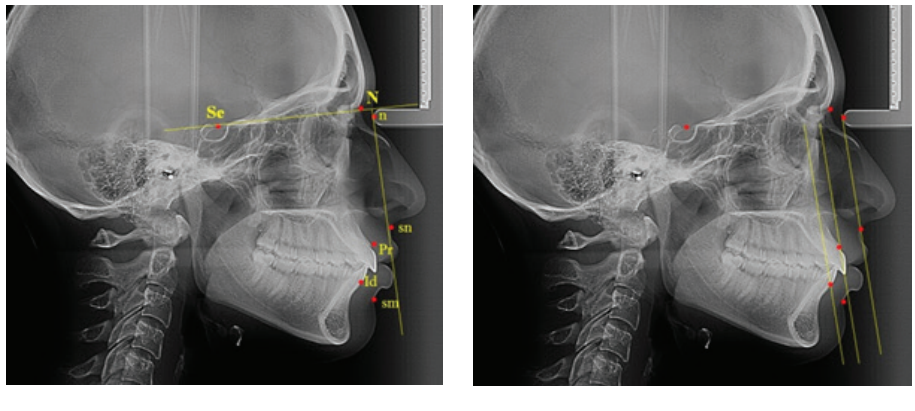
In the study of teleradiographs with the retrusion type of dental arches, it was noted that in most cases the anterior alveolar vertical, crossing the point of prosthion (Pr), did not reach the cutting edge of the superior medial incisor, which, as a rule, was located behind the indicated line. The interincisor contact point was shifted from the center towards the posterior alveolar line, sometimes even touching it (Fig. 2).

Regardless of the typological features of the dental arches in physiological occlusion, there was an equality of vertical dimensions, which was analyzed along five lines passing perpendicular to the studied diagnostic verticals of the face. The upper horizontal line passed near the apical base of the upper jaw (point "A"), and the lower line passed through point "B", which determined the position of the apical base of the mandible.

It is noteworthy that the line passing through the point of closure of the lips divided the interapical distance into almost two equal halves and corresponded to the location of the interincisor contact point. At the same time, the lines passing through the alveolar points bisected the upper and lower apical occlusal parts.

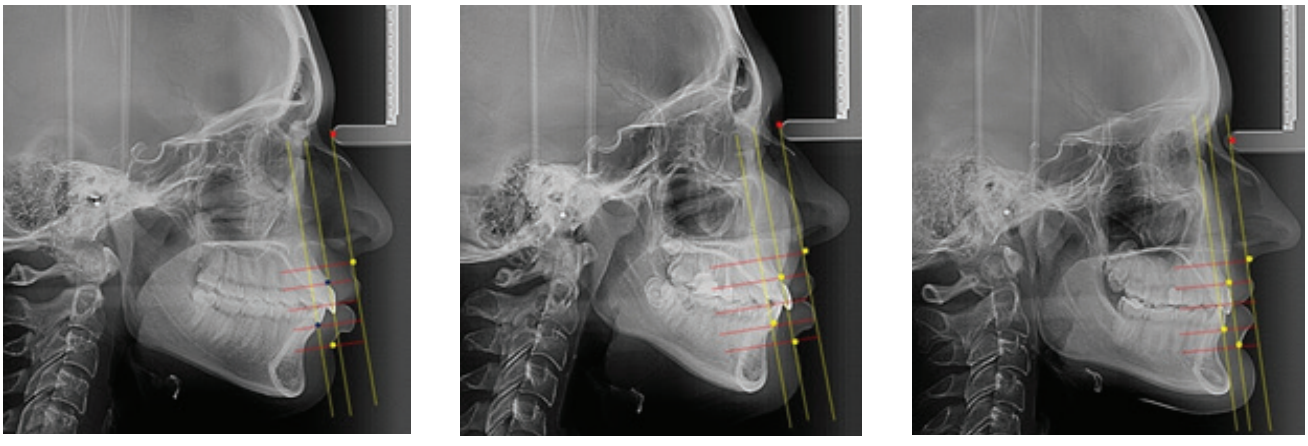
Thus, the use of the proposed vertical diagnostic lines allows for a comparative analysis of dental arches of various trussing types, to assess the proportionality of parts of the gnathic part of the face and can be useful for diagnosing malocclusion in various directions, including vertical forms of occlusion and disocclusion.

When analyzing the abnormal shapes of the anterior teeth, we divided the teleradiographs into two groups. In the first group, there were signs of pathological tooth retrusion, and in the second one



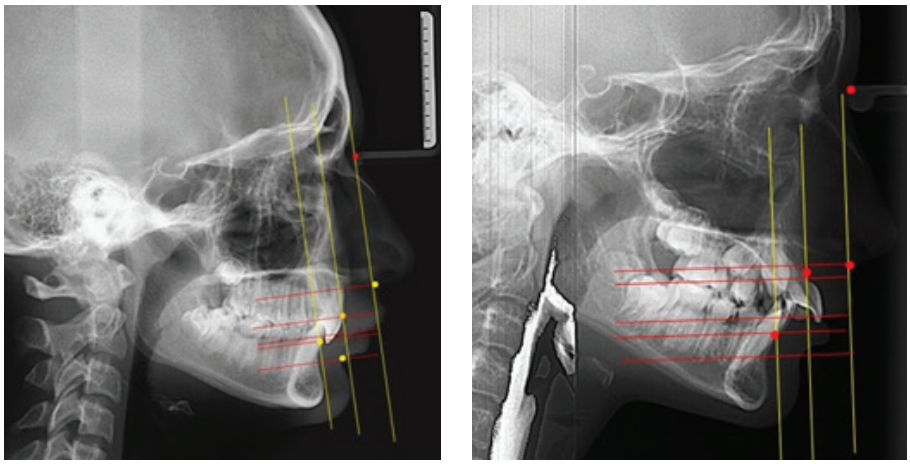
a b

Fig. 1. Main point landmarks with the Dreyfus line (a) and diagnostic verticals (b) on the teleradiograph in lateral projection



a b c

Fig. 2. Location of diagnostic verticals in mesotrusion (a), protrusion (b) and retrusion (c) of incisors in physiological occlusion



a b

Fig. 3. Location of incisors relative to diagnostic verticals in deep occlusion in combination with pathological retrusion (a) and pathological protrusion (b) of anterior teeth on teleradiograph fragments

there were signs of pathological incisor protrusion.

In both the first and the second variants, the change in the position of the incisors, as a rule, was combined with a decrease in occlusion height, which was also visually determined on the fragments of the gnathic part of the face of the studied teleradiography (Fig. 3).

In all variants of pathological incisor retrusion, the cutting edge of the medial incisors deviated significantly posteriorly from the anterior alveolar line and even reached the posterior alveolar vertical.

For variants of pathological incisor protrusion, the cutting edge of the medial incisors deviated significantly anteriorly from the anterior alveolar line. The position of the lower incisors was variable and depended on their protrusion or retrusion position, despite the protrusion of the upper incisors.

The inequality of parts of the gnathic part of the face is to be noted. The position of the labial line did not correspond to the location of the occlusal line and the contact point of the incisors was usually located above the specified landmark.

Thus, the use of the proposed diagnostic verticals can be useful for diagnosing anomalies of the dental arches and occlusion in general.

Conclusion. It is proposed to construct diagnostic vertical lines on a lateral teleradiography, which are based on the main nasal-subnasal vertical, parallel to which the anterior and posterior alveolar verticals pass. The nasal-subnasal vertical is used to construct perpendicular horizontals passing through landmarks generally accepted in clinical dentistry. This method of examination can be used to determine the occlusion height, both in normal and pathological conditions in prosthetic dentistry and orthodontics.

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SOME CRITERIA FOR DAMAGE TO THE CARDIOVASCULAR SYSTEM OF NEWBORNS DUE TO INTRAUTERINE HYPOXIA

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The results of laboratory and instrumental diagnostic methods in newborns with a history of intrauterine hypoxia were analyzed. Electrocardiographic features were revealed in the form of prolongation of the QT interval; diffuse secondary metabolic-hypoxic changes in the myocardium, such as myocardial hypertrophy, increased myocardial biopotentials from the right and left ventricles; severe overload of both atria. An important role in assessing the state of the cardiovascular system is assigned to the determination of markers for assessing the severity of damage: such as malondialdehyde (MDA) and brain natriuretic peptide (BNP) in the blood serum. As a result of the study, a significantly higher (1.2 times) MDA level was determined in newborns with antenatal hypoxia with NT-proBNP values 4 times higher than the reference laboratory values for the reagent kit. The results obtained suggest the importance of further research into the role of antenatal hypoxia in assessing the state of the cardiovascular system of children.

Keywords: intrauterine hypoxia, electrocardiogram, newborn, malondialdehyde (MDA), natriuretic peptide (BNP), cardiovascular system.

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Background: The characteristics and effects of intrauterine hypoxia on the cardiovascular system (CVS) of newborns and the consequences it causes continue to be a relevant topic for research, because CVS lesions occur, according to Russian authors, in 40–70% of cases [11], occupying second place in the list of pathological conditions of the perinatal period. It is generally accepted that the main cause of hypoxic heart damage in newborns is a decrease in energy production in the myocardial cell due to perinatal “hypoxic injury” and relative coronary insufficiency caused by the mismatch of the existing coronary blood flow with the functional needs of the heart, resulting from the high hemodynamic load on the ventricular myocardium during the period of postpartum adaptation blood circulation.

The cause of intrauterine hypoxia may be a decrease in oxygen content at the preplacental, placental and postplacental levels. A lack of oxygen supply can develop gradually and be chronic [2], leading to disruption of compensation mechanisms, resulting in activation of anaerobic glycolysis and centralization of blood circulation [6]. Fetal hypoxia leads to dis-

ruption of the mechanisms of automatism and contractility of the myocardium, and at later stages - the processes of repolarization and conduction along the His bundle [9]. With prolonged and pronounced hypoxemia in tissues, the mechanisms of anaerobic glycolysis are activated, acidic metabolic products accumulate [1], and foci of small focal necrosis are formed, located mainly in the subendocardial zone of the ventricular myocardium and papillary muscles [3].

Clinical and experimental research have shown the important role of fat peroxidation (LPO) in the development of oxidative stress, one of the end products of which is malondialdehyde (MDA). MDA is an endogenous aldehyde formed as a result of the metabolism of arachidonic and other polyunsaturated fatty acids. It has been established that the special role of MDA is the prognosis and control of treatment of cardiac pathology; the concentration of MDA correlates with some clinical signs of ischemic heart damage.

In the last decade, the prohormone brain-type natriuretic peptide (BNP), a member of the natriuretic peptide family, and its use as a marker in the diagnosis of heart failure (HF) have been actively studied [3]. There are different types of neurohormones in this family, but the most clinically relevant is brain natriuretic peptide (BNP), which is secreted by cardiomyocytes in response to increased intracardiac volume and pressure overload. Another source of BNP may be the intima of the coronary arteries under the influence of ischemia [14]. Currently, the determination of BNP and the N-terminal fragment of BNP (NT-proBNP) is widely used to diagnose heart failure, assess its severity, prognosis and monitor the effectiveness of therapy. In addition, studies have shown that high levels of BNP/NT-proBNP are an independent risk factor for atrial fibrillation (AF) as well as death in the general population [18]. There are studies [7] that allow the level of NT-pro-BNP in newborns on the first day of life to determine the degree of dysfunction of the cardiovascular system.

Diagnosis of heart damage is significantly difficult in the first days of life, which is due to the peculiarities of adaptation of the newborn's cardiovascular system. The search for a universal, reliable, reproducible method for diagnosing hypoxic heart damage determined the relevance of the study [10, 12].

Objective: To assess the significance of electrocardiographic parameters, the level of malondialdehyde (MDA) and B-type brain natriuretic peptide (NT-proBNP) in the blood serum as additional criteria for hypoxic damage to the cardiovascular system (CVS) in newborns.

Methods: In accordance with the inclusion and exclusion criteria, a random sampling method was used to analyze the clinical and laboratory data of 30 newborns whose prenatal period occurred against the background of antenatal fetal hypoxia.

The level of malondialdehyde (MDA) in blood taken at the time of birth from the umbilical cord artery was determined using the standardized thiobarbituric method.

On days 4-5 of life, an electrocardiographic study (ECG) was performed using a standard 12-lead technique and the concentration of the N-terminal fragment of the precursor of brain natriuretic peptide (NTproBNP) in the blood serum was determined using an ELISA kit of reagents for a one-step enzyme immunoassay determination of the concentration in the blood serum. The solid-phase sandwich ELISA method, "NT-pro BNP-ELISA-Best cat No. A-9102" was used. Laboratory equipment: ELISA analyzer "Alisei Q S".

The source of information was the developmental history of newborns (form No. 097-1/u-97), the results of the analysis of electrocardiograms and laboratory data.

The study did not include children with premature birth, manifestations of asphyxia at birth, infectious diseases, or severe condition at birth caused by any reasons.

Inclusion criteria for the study: gestational age 37 (0/7) – 41 (6/7) weeks of pregnancy, urgent vaginal delivery, diagnosis of "chronic fetal hypoxia" established during pregnancy, voluntary informed consent of the parents or legal representatives of the child for the procedure. examinations.

The ECG data obtained were compared with the results obtained in 30 apparently healthy newborns born without antenatal hypoxia.

Statistical analysis of the obtained data was carried out using standard statistical processing methods using Microsoft Office Excel 2013 and Statistica 6.0. The level of statistical significance when testing the null hypothesis was considered to be $p < 0.05$.

The study was approved by the local ethics committee at the Far Eastern State Medical University of the Russian Ministry of Health (protocol No. 10 of September 10, 2022), conducted in accordance with the ethical principles of medical research involving human subjects (Helsinki, 1964; revision - Scotland, October 2000).

Results: All children included in our study were relatively healthy at the time of the study, had no clinical manifestations of pathology of the cardiovascular system, and were born with average indicators of physical development corresponding to the gestational age. The Apgar score was 7.8±1.0 points in the first minute of life and 8.4±0.9 points in the fifth minute of life. All children were put to the mother's breast in the delivery room, stayed with their mother and were discharged from the maternity hospital in a timely manner.

When analyzing the MDA indicator, it was found that the results obtained (5.71±3.7) of all examined children did not correspond to the normal laboratory values specified in the method for the reagent kit; the MDA level exceeded the reference values 1.2 times ($p = 0.01$). Exceeding the MDA level is typical for intense physical activity in newborns and pregnant women, therefore, the indicators of activation of peroxide processes we obtained can be considered a reaction of the newborn's body to the intense effects of birth oxidative stress. The detected levels of MDA in newborns indicate oxidative stress, which makes this indicator a marker of the unfavorable course of the adaptation period in a newborn child.

The level of NTproBNP, determined on days 4-5 of life in the blood serum, turned out to be 813.39 ± 549.61 pg/ml with variability from 133.64 to 2117.92 pg/ml with the reference laboratory values specified in the method for the reagent kit, from 0.0 to 200.0 pg/ml. The indicators obtained in our study are in the range of normal values for the first day of life [7], but significantly, 4 times higher than the reference laboratory values for the set of reagents. The obtained data with a pronounced variability of the indicator (max 2117.92 pg/ml), a different age of the children during the study (4-5 days, the end of the period of acute adaptation) do not allow for an unambiguous assessment and suggest further research to clarify the diagnostic role of the NT-proBNP indicator in assessment of CVS damage during hypoxia.

The heart rate (HR) in the control group in most cases (93.3%) corresponded to the age norm and averaged 146-156 beats per minute (Table 1). In the group of children with intrauterine hypoxia, normal heart rate parameters were less common than in the control group (63.3% - $p=0.03$ OR=1.66). In every third case (36.6%), sinus tachycardia was di-

Some characteristics of the ECG of newborns (min-max, average value)

Groups	Heart rate (bpm)	EOS	P wave (ms)	PQ interval	QTs	QRS interval (V5) (ms)	R (V1) (mm)
Experimental group	156-190 (164)	-40/-80 (-65)	60-80	70-100 (85)	400-430 (425)	50-70 (60)	0-10
Control group	146-156 (150)	+78 /+180 (130)	60-70	100	400-410 (405)	50-60 (55)	0-17

agnosed with a heart rate averaging 175-190 beats per minute at rest [13]. The average duration of the P wave in children with antenatal hypoxia was 60-80 ms (56.6% - p=0.03 OR=1.4). In cases where sinus tachycardia was recorded, the P wave length was 40-60 ms (43.3% - p=0.02 OR=0.6). In the control group, the duration of the P wave averaged 60-70 ms (93.3% - p=0.01 OR=1.73), which is normal [16].

The duration of the PQ interval in children with intrauterine hypoxia averaged 90-100 ms (63.3% p=0.02 OR=1.83) with a norm of 70-140 ms [16]. A shortening of the length of the PQ interval in some children (36.6% - p=0.03 OR=1.56) was associated with an increase in heart rate and averaged 70-80 ms, which also corresponds to the conventional norm. In the control group, the length of the PQ interval averaged 100 ms (96.6% - p=0.04 OR=1.43) and was within the reference values [16]. The width of the QRS complex in all children we examined did not exceed 70 ms, with average values in children with intrauterine hypoxia in the group 50-60 ms (90% - p=0.04 OR=1.93), in the control group 50-70 ms (93.3% - p=0.03 OR=1.85), which is the age norm [15].

The T wave in the main (83.3% - p=0.03 OR=1.87) and control (90% - p=0.03 OR=1.75) groups had a low amplitude in the limb leads. In the right chest leads, the T wave was negative, in the left - positive, which is the norm for children in the first week of life [5].

It is known that the duration of the QT interval varies depending on the heart rate [4]; accordingly, to assess it, it is necessary to carry out a correction for a given heart rate - calculate the corrected QTc interval. In our study, the calculation was carried out using the Bazett's formula: QTc (c) = QT (c)/√RR (c) [17]. The average QTc duration in children with a history of antenatal hypoxia was 420-430 ms (60% - p=0.01 OR=1.83), with sinus tachycardia the QTc duration was 400-410 ms (40% - p=0.02 OR=1.56). In the control group, QTc duration was 380-400 ms (93.3% - p=0.05 OR=1.80). Newborns older than 4 days with a prolonged QT interval of more than 440 ms have a significantly higher risk of sudden death [17]. The values established during the study did not exceed 440 ms, however, some children with a history of intrauterine hypoxia were in the border zone in terms of QT level.

A feature of the electrical axis of the heart (ECA) in newborns is the right axis with an average value of 130° and variability from 55° to 200° [8]. In the control group, a shift of the EOS to the right was most often noted (86.6% - 26/30). In children with intrauterine hypoxia, a "levogram" was most often observed (76.6% - p=0.03 OR=1.06), in some cases (23.3% - p=0.02 OR=1.26) a shift of the EOS to the right.

Every second child with a history of antenatal hypoxia had diffuse secondary metabolic-hypoxic changes in the myocardium (56.6% - p=0.01 OR=1.73); myocardial hypertrophy (53.3% - p=0.04 OR=1.39); enhanced myocardial biopotentials from the right and left ventricles (46.6% - p=0.01 OR=1.21); severe overload of both atria (33.3% - p=0.02 OR=1.41).

Conclusion: Intrauterine fetal hypoxia causes disturbances in the state of the cardiovascular system, while the clinical picture may be absent, as in our study, or may be erased. The diagnostic significance of markers of CVS damage during hypoxia is different and requires the search for a universal and accessible test to assess the state of the CVS with minimally expressed clinical symptoms. In children with a history of intrauterine hypoxia, the electrocardiogram has a number of features in the form of a shift of the electrical axis of the heart to the left and hypertrophy of the myocardium of the left ventricle and left atrium (76.6%), an increase in the duration of the QTc interval (60% of cases), diffuse secondary metabolic-hypoxic changes in myocardium (56.6%), increased myocardial biopotentials from the right and left ventricles (46.6%), increased heart rate (36.6%), which can be regarded as a consequence of a lack of energy supply in the myocardial cell and a risk factor for the development of sudden death in children with a history of hypoxia.

Determining the level of MDA in the blood of newborns allows not only to assess the intensity of lipid peroxidation in tissues, but also to use this indicator to diagnose the severity of intrauterine hypoxia.

The determination of MDA and NT-proBNP is of particular interest for use in clinical practice as markers of intrauterine hypoxia with the possibility of predicting critical neonatal conditions. It is necessary to study the dynamics of indicators in the process of adaptation of newborns to extrauterine life under various pathological conditions.

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EFFICIENCY OF USING AUTOGENIC BONE IN COMBINATION WITH A XENOGENIC BONE MATERIAL FOR GUIDED BONE TISSUE REGENERATIONIN AN EXPERIMENT

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Currently, the search for effective methods of reconstructive interventions aimed at increasing alveolar ridge height and thickness remains a pressing issue in dentistry. However, the results of studies on the comparative assessment of the effectiveness of the use of autogenic bone from various donor sites are extremely small and ambiguous. **Aim.** Substantiate the effectiveness of using the optimal composition of autogenic bone chips (ABC) and xenogenic bone material (XBM) taking into account the anatomical localization of the donor zone in guided bone regeneration (GBR) according to the data of microhemodynamics of the experiment. **Research materials and methods.** The object of the study in the research was 84 sexually mature male rabbits of the chinchilla breed weighing 2500-3200 g. The materials of Cardioplant LLC (Penza) with registration certificates: Xenogenous bone material (XBM) "Xenograft Mineral" (medical device registration certificate No. RZN 2015/3086 dated 16.09.2015) and bioresorbable membrane "BioPLATE Barrier" (medical device registration certificate No. RZN 2016/4808 dated 26.01.2021). A defect in the mandible area was formed in the animals under study, which was then filled with osteoplastic material. Laser Doppler flowmetry (LDF) was used to monitor the state of microhemodynamics of gingival tissues in the area of surgery using a laser analyzer of capillary blood flow "LAKK-02," (NPP "Lazma," Moscow). Results and discussion. It was established that within the first two weeks after the intervention, optimal rates of microcirculation recovery in the surgical area are characteristic of osteoplasty using a mixture of XBM (75%) and ABC (25%) from the oral donor zone. On the 14th day after the operation, capillary blood flow was stabilized, which was manifested by a decrease in the studied parameters in all observation groups. However, the normalization of microvessel functioning was not the same in the study groups. At the same time, the normalization of capillary blood flow was optimal in animals of subgroup 3 in group II, with the microcirculation indicator at the level of 20,59±1,18 perf. units, and its intensity at the level of 2,31±0,12 perf. units by the 14th day. Starting from the 30th day of observation, microcirculation recovery proceeded at the same pace in all groups of animals, with the exception of a slight lag in animals of subgroup 3 in group III, however, by the 90th day and by the end of the observation period, significant differences in capillary blood flow levels could not be found.
Conclusion. The obtained results should be taken into account in outpatient dental practice when performing manipulations related to the use of the GBR technique.
Keywords: autogenic bone, donor zone, guided bone regeneration, microcirculation.

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Introduction. Currently, the search for effective methods of reconstructive interventions that contribute to an increase in the height and thickness of the alveolar ridge remains an urgent problem [5, 11, 12, 14, 15]. The need for such dental operations arises when there is insufficient bone level for the installation of implants, or incorrect ratio between the length of the implant and the height of the orthopedic structure, or in case of indications for such interventions in an aesthetically significant area [4, 8, 10, 13]. The predictability and successful outcome of surgical intervention largely depends on the material for augmentation of the alveolar ridges. Autogenic bone in combination with a membrane, not without reason, has the status of the "gold standard" during guided bone regeneration (GBR), however,

the difficulties associated with the trauma of the donor zone force researchers not to stop on the way to solving the issue of obtaining a sufficient volume of implanted bone material [2, 3, 7].

Analysis of the work of domestic and foreign researchers proves that the most appropriate way to reduce the invasiveness of guided bone regeneration (GBR) techniques is to use a combination of autogenic bone with xenogenic bone materials as a bone graft, however, information about the ratio of each of the components of such a combined material in the literature is extremely contradictory and requires more detailed study. The source of autogenic bone can be both intraoral (chin symphysis, mandibular branch, maxillary tubercle) and extraoral donor sites (iliac crest, cranial vault bones, scapula) [1, 6, 9]. However, the results of studies devoted to the comparative evaluation of the effectiveness of the use of autogenous bone from various donor sites are scarce and ambiguous. Taken the above into consideration, we have attempted a comparative assessment of the different ratio of compositions of xenogenous bone material (XBM) and autogenic bone chips (ABC) obtained from anatomically different donor sites.

Objective. Substantiate the effectiveness of using the optimal composition of autogenic bone chips and xenogenic bone material taking into account the anatomical localization of the donor zone in guided bone regeneration (GBR) according to the data of microhemodynamics of the experiment.

Materials and methods of research. The object of research in the work was 84 mature male chinchilla rabbits weighing 2500-3200 grams. During the experiment, we were guided by the recommendations of the ethics Committee established on the basis of the Saratov State Medical University named after V.I. Razumovsky" of the Ministry of Health of Russia (Protocol No. 10 of 11.05.2021). The materials of Cardioplant LLC (Penza) with registration certificates used in the work are xenogenic bone material (XBM) "Xenograft Mineral" and bioresorbable membrane "bioPLATE Barrier". General anesthesia was carried out by intramuscular administration of zoletil 100 (at the rate of 0.1 ml / kg of animal body weight) and xylazine (at the rate of 0.4 ml / kg of animal body weight), propofol was administered to maintain sleep (at a dose of 0.5 ml / kg of animal body weight per hour). Local anesthesia in the oral cavity was performed using a 4% solution of forte ultracaine. The animals formed a defect in the lower jaw area, after which it was filled with osteoplastic material. All animals were divided into three experimental groups: group 1 (n=12 animals) – XBM was used as an osteoplastic material; group 2 (n=36 animals) was divided into three subgroups, depending on the volume ratios of XBM and autogenous bone chips (ABC) obtained from the intraoral donor zone (angle of the lower jaw): subgroup 1 – a composition consisting of a mixture of 25% XBM and 75% ABC was used; subgroup 2 – a composition consisting of a mixture of 50% XBM and 50% ABC was used; subgroup 3 – a composition consisting of a mixture of 75% XBM and 25% ABC was used; group 3 (n=36 animals) was divided into three subgroups, according to the principle similar to the second group: subgroup 1 of group 3 – a composition consisting of a mixture of 25% XBM and 75% ABC was used; 2 subgroup 2 of group 3 – a composition consisting of a mixture of 50% XBM and 50% ABC was used; subgroup 3 of group3 – a composition consisting of a mixture of 75% KKM and 25% ABC was used. At the same time, in the third group, the source of ABC was the extraoral donor zone – the iliac bone. Laser Doppler flowmetry (LDF) was used to monitor the state of microhemodynamics of gum tissues in the area of surgery using a laser analyzer of capillary blood flow "LAKK-02", (NPP "Lazma", Moscow). The integral characteristic of capillary blood flow (indicator M), the characteristic of erythrocyte flow, reflecting statistically significant fluctuations in the velocity of erythrocytes (σ), as well as the ratio between tissue perfusion and the magnitude of its variability (K) were recorded. The results were presented in the form of databases, which were subsequently subjected to statistical processing using the application packages "Statistica V.10" and "Microsoft Excel for Windows" (2007).

Results and discussion. During the study, it was found that the initial values of the microcirculation index (M) in experimental animals of the first (control) group were 17.15 ± 0.13 perf.units, its intensity (σ) was 1.94 ± 0.09 perf. units, the coefficient of variation (Kv) was 11.33 ± 0.54%. On the 3rd day after surgery, a significant increase in capillary blood flow was noted, which was confirmed by a significantly significant increase in comparison with the initial values of the microcirculation index (M) by 76.03%, the values of the mean square deviation by 98.87%, and an increase in the coefficient of variation (Kv) by 11.03% was also marked. On the 14th day after surgery, there was a tendency to tissue blood flow normalization. Compared with the previous observation period, the microcirculation index (M) decreased by 19.31% and amounted to 24.36±1.24 perf. units. The intensity of blood flow (σ) in the study area decreased by 24.21%, vasomotor vascular activity (Kv) decreased by 5.72% and amounted to 11.86 ± 0.72%. On the 30th day, there was also a tendency to restoring the studied parameters. Thus, the blood flow level (M) was at the level of 19.64 ± 0.04 perf. units, the average square deviation (σ) was 2.33±0.06 perf. units, the coefficient of variation (Kv) was 11.87 ± 0.30%. On the 90th and 180th days of observations, microcirculation parameters were noted that did not have statistically significant differences from the values obtained before the experiment. Thus, by the end of the observation period, the microcirculation index (M) was 17.11 ± 0.17 perf. units, the intensity of blood flow was 1.85 ± 0.03 perf. units, the coefficient of variation was 10.79± 0.31%.

It should be noted that before the operation, microhemodynamic parameters in all subgroups of the second group were characterized by similar values. However, three days after the operation, there was a different severity of hemodynamic disorders provoked by surgical trauma. In animals of the first subgroup, the microcirculation index increased from 17.32±1.08 to 29.39±0.64 perf.units, in animals of the second subgroup – from 17.41±0.27 to 30.21±1.11 perf. units, in animals of the third – from 17.32± 0.54 to 27.41±0.84 11 perf. units. It should be noted that normalization of the studied parameters began to be noted by the 14th day of postoperative observations, while the slowest rates of restoration of the functional state of the microcirculatory bed were detected in the first subgroup of this group.

On the 3rd day after surgery, an increase in the values of microhemodynamic parameters due to the reaction to surgery was noted in all subgroups of the third group. Thus, the microcirculation index in the 1st subgroup increased by 52.91%, in the 2nd subgroup – by 58.96%, in the 3rd subgroup – by 61.59%. There was also a sharp increase in the intensity of blood flow, which is confirmed by an increase in the values of the mean square deviation in the first subgroup by 70.81%, in the 2nd subgroup – by 64.95%, in the 3rd subgroup – by 72.50%. In addition, there was an increase in vasomotor vascular activity in all subgroups. On the 14th and 30th days after surgery, all indicators of capillary blood flow showed the dynamics of recovery and by the 90th day of observations returned to their orig-

inal values, remaining stable for the entire period of the study.

The study of hemomicrocirculation parameters according to LDF data at the stages of the experimental study revealed different dynamics of restoration of capillary blood flow in the area of surgical intervention in experimental animals. So, before the surgical intervention, the blood flow level (M) in the groups varied from 17.15 ±0.13 to 17.41±0.27 perf. units, the intensity of blood flow (σ) was in the range from 1.85±0.08 to 2.14±0.09 perf. units, vasomotor activity of microvessels (Kv) ranged from 10.63±0.48% to 12.33±0.55%. It should be noted that there were no significant differences in these indicators before the start of the experiment (p0.05). On the 3rd day after the intervention, statistically significant changes in microcirculation parameters were observed in all the studied groups of animals compared with the values obtained in the groups before the experiment. Thus, a significant increase in tissue blood flow was observed in all animals, which was expressed by a statistically significant increase in the integral indicator of microcirculation (M) and the indicator of blood flow intensity (σ). There was also an increase in the mechanisms of modulation of tissue blood flow, which was manifested by a tendency to increase the values of the coefficient of variation (Cv). At this stage of observations, it was possible to establish an important trend in the dynamics of changes in the studied indicators. Thus, it was noted that a more pronounced reaction of the microcirculatory bed to traumatic intervention was noted in groups of animals implanted with XBM and XBM in combination with ACS from the nutrient donor zone. However, in our opinion, the reason for such a pronounced reaction to intervention in these groups has a different origin. It can be assumed that the use of XBM as an osteoplastic material leads to a more pronounced tissue reaction due to the increased immunological load caused by the use of xenogenic material. In the case of combined use of XBM and ABC, in all likelihood, there is a decrease in the immunological response of tissues to the bioimplant, however, the reaction of microvessels increases as a result of additional traumatization of the donor zone located in anatomical proximity to the operated area.

The volume of the intraoral donor zone also, in our view, affects the nature and severity of the microvascular reaction to the intervention, which was confirmed by the dynamics of the level of capillary blood flow and its intensity in experimental animals of group 2. Thus, on the 3rd day after surgery, there was a tendency to lowering values of the microcirculation index (M) in subgroup 3 of animals with an implanted mixture of XBM (75%) and ABC (25%) from an intraoral source (27.41±0.84 perf. units) compared with similar indicators in the subgroups with an implanted mixture of XBM (25%) and ABC (75%) (the value of M was 29.39±0.64 perf. units), and the subgroup with an implanted mixture of XBM (50%) and ABC (50%) (30.21±1.11 perf. units) of the same inside the blood flow zone. The tendency to increase the intensity of tissue blood flow (σ) in study group 2 was also lower in subgroup 3 of animals with an implanted mixture of XBM (75%) and ABC (25%) from an intraoral source. On the 14th day after the operation, the stabilization of capillary blood flow was noted, which was manifested by a decrease in the studied indicators in all observation groups. However, the normalization of the functioning of microvessels was not the same in the study groups. It should be noted that normalization of capillary blood flow was at an optimal rate in animals of subgroup 3 of group 2, in which by the 14th day the microcirculation index was determined at the level of 20.59 ± 1.18 perf. units, and its intensity was at the level of 2.31 ± 0.12 perf. units. Starting from the 30th day of observation, the restoration of microcirculation proceeded at the same pace in all groups of animals, with the exception of a slight lag in subgroup 3 of group 3, however, by the 90th day and by the end of the observation period, it was not possible to detect significant differences in the levels of capillary blood flow.

Conclusion. The study of the parameters of hemocirculation according to LDF data at the stages of the experimental study revealed different dynamics of restoration of capillary blood flow in the area of surgical intervention. Monitoring of the functional state of the microcirculatory bed suggested that the restoration of capillary blood flow in the intervention area depends on a number of factors. Firstly, the use of xenogenic bone material as a monomaterial in osteoplasty is accompanied by a more pronounced reaction of the microcirculatory bed to surgery compared with the use of mixtures of XBM and ABC. Secondly, the anatomical proximity of the donor zone when using intraoral sources of autostasis enhances the reaction of the microcirculatory bed. A comparative analysis of the dynamics of capillary blood flow in experimental animals allowed to establish that in the first two weeks after the intervention, the optimal rates of restoration of microcirculation in the surgical area are characteristic of osteoplasty using a mixture of XBM (75%) and ABC (25%) from the intraoral donor zone. The data obtained coincided with the results of a histological study of the processes of neosteogenesis conducted during the experiment. The conclusions drawn from the results of the work should be taken into account in outpatient dental practice when carrying out manipulations related to the use of the GBR technique.

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ASSESSMENT OF THE EFFECT OF LOCAL TREATMENT ON THE FREQUENCY OF CELLS WITH NUCLEAR ABNORMALITIES IN THE CYTOGRAM OF BUCCAL EPITHELIUM IN PATIENTS WITH AN EROSIVE AND ULCERATIVE FORM OF LICHEN PLANUS OF THE ORAL MUCOSA (PART 1)

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Oral Lichen Planus (OLP) is a common chronic inflammatory disease with a high risk of malignization. Early diagnostic tests of erosive and ulcerative form (ECF) of the LP, timely pharmacotherapy are the key to success in the treatment of this form of dermatosis. The cytologic research method is one of the methods by means of which it is possible to obtain the results and adjust the scheme of medication symptomatic treatment in the future. **The aim of research** is to determine the effect of local treatment on the frequency of cells with nuclear abnormalities in the cytogram of buccal epithelium obtained from the reticular mesh area and from the surface of erosions in patients with the erosive and ulcerative form of the Lichen Planus in the oral cavity mucosa lining. **Materials and methods.** In the cytogram of buccal epithelium, cytogenetic indicators (micronucleus, tongue-type protrusion, and broken egg-type protrusion), indicators of nucleus destruction (karyopyknosis, karyorrhexis, karyolysis), and indicators of nuclear proliferation (notching) were assessed. **Results.** The developed method of local treatment of the erosive and ulcerative form of the Lichen Planus contributed to a more significant decrease in the frequency of cells with nuclear proliferation in the form of notches, compared to the group of patients treated according to clinical recommendations ($p=0.05$), and significantly decreased the frequency of cells with micronuclei ($p<0.01$), the frequency of degenerative change of the nucleus at $p<0.05$. Both methods of local treatment were effective, however, in clinical subgroups of patients with high titers of Candida spp. detected in the oral microbiota, the effect of local treatment in the form of ozone therapy, contributed to a decrease in the frequency of the cytogenetic indicator in the form of micronucleus protrusion (at $p<0.1$), nucleus notching (at $p<0.01$), the indicator of completion of nuclear destruction ($p<0.1$). Cytologic examination of the buccal epithelium is a non-invasive method that provides clear information about the status of the epithelial cells, in particular their DNA damage, the proliferative potential of basal cells and cell death, which are considered basic principles of cancer alertness.

Keywords: erosive and ulcerative form of Lichen Planus, buccal cytogram, ozone therapy, hyaluronic acid, corticosteroids, hyaluronic acid gel, Ora-Aid self-adhesive patch.

Introduction. The Lichen Planus (LP) involving the oral cavity mucosa lining (OCML) is a T-cell-mediated chronic inflammatory disease, with characteristic periods of relapses and remissions, and occurs as one of six variants. The reticular and erosive types of the LP are the most common in the OCML [14]. The etiological factors of the disease have not yet been discovered, although it is known that it is based on an autoimmune mechanism [20, 22].

Causes may include bad habits, somatic pathology [19, 24], menopause, depression and stress [10, 22]. The lesions are most often prevalent in females, the location on the OCML is symmetrical, and the buccal mucosa is involved in 28.1% of cases [18].

When diagnosing pathologic processes on the oral cavity mucosa lining in the form of white and/or erosive and ulcerative elements, it is necessary to screen for cancer alertness. Due to the similarity of clinical manifestations, it is sometimes difficult to distinguish benign white lesions from their pre-malignant or malignant analogues [1, 17], and the risk

of malignant transformation of the erosive and ulcerative form of the LP in the OCML according to the data represented by Iocca O. et al. (2020) is extremely low, that is 1.4% - 10% [15], the treatment and preventive measures of this form are not always effective [11].

Modern approaches to the diagnosis of pathology of the oral cavity mucosa lining include the use of various methods aimed at early screening of inflammation, as well as malignization [7]. The Buccal Micronucleus Cytome Assay (BMN Assay) provides a platform to identify individuals at high risk of malignancy by assessing markers of nuclear damage at the earliest microinvasive stage possible [23]. Histopathological examination of the involved tissue is a prerequisite for any type of OCML changes. In the research, chromosomal aberrations in the form of micronucleated cells were detected in patients with the presence of Lichen Planus clinical findings with localization on the OCML [12].

Thus, cytologic examination in cancer diagnosis of OCML pathology becomes important for choosing a rational treatment regimen. This paper considers the diagnostic criteria of the erosive and ulcerative form (EUF) of the LP in the OCML based on cytologic examination of buccal epithelium.

The goal of research is to assess the frequency of cells with nuclear abnormalities in the buccal cytogram obtained from the reticular mesh surface, hyperemia area and erosive and ulcerative elements in patients with the erosive and ulcerative form of the Lichen Planus in the oral cavity mucosa lining before and after local treatment.

Materials and methods of research. This two-center, prospective observational non-controlled study was conducted with the effective collaboration of two dermatovenerology centers of Ufa and Omsk. Patients were selected on the basis of discrete clinical features: the presence of prominent linear or reticular papules, erosive and ulcerative elements, and the presence of high titers of Candida yeast-like fungi in the oral microbiota. The record of complex dental examination included an assessment of the clinical state of the oral cavity mucosa lining, the presence of typical papules and/or erosive and ulcerative elements on the cheek mucosa, which made it possible to make a diagnosis according to ICD-10 as the erosive and ulcerative form (EUF) (L43.82) and typical (L43.80) form of the LP in the OCML. Consent for the histologic study was obtained from each patient and his/her attendants. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Bashkir State Medical University (FSBEI HE BSMU) of the Ministry of Health of the Russian Federation (Order No. 11 dated December 17, 2019).

All patients with the EUF of the LP (L43.82) in the OCML (n=86) were divided into two main clinical groups. In the composition of microbiota of erosive and ulcerative elements in patients of I (n=46) and II (n=40) main clinical groups there is a difference in the quantitative content of *Candida spp*.: in 26.08% of cases the amount from 3.0 to 5.0 Lg CFU/u, and in 47.5% of cases from 4.0-6.0 Lg CFU/u respectively.

The main clinical groups were divided into equal clinical subgroups Ia (n=23), IIa (n=23), Ib (n=20), IIb (n=20). The developed, implemented and patented complex of local treatment was used [6] (described below) for the main Ia and IIa clinical subgroups, and in the main Ib and IIb clinical subgroups the method of treatment according to the federal clinical recommendations [3] was used as a comparison. The comparison group included 25 patients with the typical form of the LP (L43.80) in the OCML and was a relative criterion of norm in the whole period of dynamic observation.

Local treatment of the EUF (L43.82) of the LP in the OCML included the use of ozone therapy on the Prozone device, applications of 0.2% hyaluronic acid gel (Hy + Al Gel), 0.5% Prednisolone ointment and Ora-Aid self-dissolving patch, which together have antiseptic, anti-candida, and anti-inflammatory properties increasing the rate of epithelialization and promoting mucosal regeneration. Erosive and ulcerative elements on the mucosa lining were treated using a preparation containing a broad-spectrum antiseptic, that is cetalkonium chloride (1 application, duration: 60 sec., 7 days), ozone therapy with the Prozone device (7 procedures, exposure duration: 6 sec., mucosa distance: 1-2 mm), as well as treatment of their surface with 0.5% Prednisolone ointment (3 times a day, 7 days). At home, the patients independently dried the mucosal surface and closed it with Ora-Aid self-adhesive patch 3 times a day until its complete dissolution, having anti-inflammatory and analgesic properties due to the active substance, that is cetalkonium chloride accelerating epithelization and mucosal regeneration due to vitamin E, 3 times a day for 6 days.

The efficacy of the local treatment complex in patients with the EUF of the LP in the OCML was assessed based on the leveling of subjective perceptions (burning, tingling and tension), changes in the composition of microbiota of the surface of erosive and ulcerative elements and pH of oral fluid. In the comparison group with a typical form of the LP in the OCML, dynamic observation was carried out, including correction of oral cavity hygiene and sanation, and elimination of traumatic factors.

Before and after local treatment (on average on day 21), we conducted a comparative cytologic study of the composition of buccal epithelium obtained by scraping with a wooden spatula from the cheek mucosa in the area of Wickham's reticular mesh (Wickham's striae) and/or the area of erosive and ulcerative elements. The level of cytoplasmic and karyological abnormalities was assessed in buccal epithelial cells. Then the following cells in the buccal cytogram were calculated: those with micronuclei, protrusions, binuclear cells (including those with twin nuclei), with chromatin condensation, karyorrhexis, karyopyknosis, karyolysis, and apoptotic corpuscles. Material for buccal epithelium examination was sampled on the first day of the study and at the end of local treatment on day 21.

Romanowsky-Giemsa staining was used for coloring. Isolated cells were selected and photographed. From 100 to 1000 isolated cells with continuous edges were analyzed. The preparations were examined at x630 magnification with immersion on a Leica DM 2500 microscope (Germany) (Fig. 1-4).

Based on the sample size, the nonparametric Mann-Whitney U test was used to match the differences between the hyperemia area and the area of erosive and ulcerative elements, which was a justifiable criterion in the context of small group size (<160 observations). For intragroup comparisons before and after local treatment, the nonparametric Wilcoxon test applied for comparison of dependent samples was used. It was considered that there were statistically significant differences in the data of the indicators of cytograms studied of buccal epithelium if the p-level of rejection of the null hypothesis was less than 0.05. The statistics and their corresponding significance levels were calculated using the 'stats' library of the R open source statistical computing environment (version 4.3.1).

Research results and discussion. The statistical analysis of nuclear aberrations in the form of cytogenetic abnormalities, indicators of destruction completion, and nuclear proliferation in the cytogram of buccal epithelium obtained from the

Table 1

Dynamics of the frequency of cells with nuclear abnormalities in the cytogram of buccal epithelium (from the reticular mesh and hyperemia area) in patients of I and II main clinical subgroups before and after the complex of local treatment

Indicators	Ia main clinical subgroup of the EUF of the LP in the OCML (suggested treatment) (n=23)	Ib main clinical subgroup of the EUF of the LP in the OCML (treatment according to federal clinical recommendations)) (n=23)	IIa main clinical subgroup of the EUF of the LP in the OCML (suggested treatment) (n=20)	IIb main clinical subgroup of the EUF of the LP in the OCML (treatment according to federal clinical recommendations)) (n=20)	Comparison group. typical form of the LP in the OCML (n=25)
1	2	3	4	5	6
Comparisons: Comparisons between groups Ia. Ib. IIa. IIb and a comparison group before treatment according to the Mann-Whitney U test *(p)*. intergroup comparisons between group Ia and Ib. IIa and IIb before treatment according to the Mann-Whitney U test (p_1). intergroup comparisons between group Ia. Ib. IIa and IIb after treatment and a comparison group according to the Mann-Whitney U test (p_2). intra-group comparisons according to the Wilcoxon test for Ia. Ib. IIa and IIb subgroups before treatment and after treatment (p_3). intergroup comparisons between group Ia and Ib. IIa and IIb after treatment according to the Mann-Whitney U test (p_4).					
Cytogenetic abnormalities					
Micronucleus before treatment	2.16±0.37 p=0.225	2.12±0.23 p=0.289	2.18±0.37 p=0.218	2.27±0.25 p=0.204	1.82±0.47
	Z=0.245, p_1=0.806		Z=0.256, p_1=0.798		
Micronucleus after treatment	1.91±0.09 p_2=0.565, p_3=0.183	2.17±0.23 p_2=0.276, p_3=0.456	1.85±0.15 p_2=0.865, p_3=0.423	2.19±0.16 p_2=0.233, p_3=0.827	
	Z=0.938, p_4=0.348		Z=1.138, p_4=0.255		
Micronucleus protrusion before treatment	1.10±0.05 p=0.149	0.92±0.34 p=0.274	1.19±0.45 p=0.254	1.17±0.36 p=0.247	0.75±0.35
	Z=0.650, p_1=0.516		Z=0.150, p_1=0.881		
Micronucleus protrusion after treatment	0.81±0.19 p_2=0.615, p_3=0.189	0.93±0.07 p_2=0.487, p_3=0.934	0.79±0.23. p_2=0.891, p_3=0.401	0.93±0.05. p_2=0.435, p_3=0.455	
	Z=0.357, p_4=0.721		Z=0.877, p_4=0.384		
(Tongue-type) Micronucleus protrusion before treatment	0.43±0.17 p=0.163	0.37±0.15 p=0.101	0.43±0.17 p=0.163	0.85±0.11 p=0.201	0.69±0.11
	Z=0.215, p_1=0.829		Z=1.178, p_1=0.239		
(Tongue-type) Micronucleus protrusion after treatment	0.66±0.24 p_2=0.799, p_3=0.207	0.71±0.29 p_2=0.786, p_3=0.160	0.68±0.40 p_2=0.898, p_3=0.417	0.71±0.23 p_2=0.842, p_3=0.472	
	Z=0.182, p_4=0.856		Z=0.384, p_4=0.701		
Indicators of nucleus destruction completion					
Karyopyknosis before treatment	6.03±0.47 p=0.812	5.87±0.41 p=0.741	6.43±0.40 p=0.399	6.40±0.33 p=0.316	6.03±0.17
	Z=0.420, p_1=0.674		Z=0.209, p_1=0.834		
Karyopyknosis after treatment	6.02±0.06 p_2=0.982, p_3=0.941	6.32±0.28 p_2=0.453, p_3=0.234	5.99±0.03$^{\&}$ p_2=0.822, p_3=0.254	6.18±0.06 p_2=0.259, p_3=0.804	
	Z=0.420, p_4=0.674		Z=1.972, p_4=0.049		
Karyorrhexis before treatment	2.95±0.34 p=0.806	2.94±0.27 p=0.814	3.85±0.14‡ p=0.009	3.67±0.21 p=0.066	2.93±0.26
	Z=0.193, p_1=0.847		Z=0.706, p_1=0.480		
Karyorrhexis after treatment	2.39±0.31 p_2=0.209, p_3=0.199	2.69±0.31 p_2=0.498, p_3=0.494	2.89±0.06*** p_2=0.877, p_3<0.001	2.85±0.05*** p_2=0.846, p_3<0.001	
	Z=0.654, p_4=0.513		Z=0.551, p_4=0.582		
Karyolysis before treatment	0.52±0.30 p=0.910	0.57±0.31 p=0.912	0.85±0.10 p=0.096	0.82±0.20 p=0.108	0.55±0.14
	Z=0.111, p_1=0.912		Z=0.091, p_1=0.927		
Karyolysis after treatment	0.56±0.12 p_2=0.977, p_3=0.895	0.67±0.15 p_2=0.569, p_3=0.589	0.56±0.13* p_2=0.932, p_3=0.048	0.72±0.15 p_2=0.132, p_3=0.299	
	Z=1.202, p_4=0.229		Z=1.389, p_4=0.165		

Окончание табл. 1

Indicators of nuclear proliferation					
1	2	3	4	5	6
Nucleus notching before treatment	4.67±0.55 p=0.802	4.41±0.42 p=0.765	4.67±0.15 p=0.741	4.96±0.05 p=0.126	4.51±0.49
	Z=1.655, p_1=0.098		Z=1.603, p_1=0.109		
Nucleus notching after treatment	4.55±0.13 p_2=0.888, p_3=0.731	4.64±0.26 p_2=0.707, p_3=0.567	4.49±0.02$^{\&}$ p_2=0.913, p_3=0.109	4.71±0.09 p_2=0.798, p_3=0.099	
	Z=0.330, p_4=0.741		Z=1.958, p_4=0.05		
Apoptotic Index (AI)					
Amount of abnormalities of the AI before treatment	17.86±2.25 p=0.811	17.21±2.13 p=0.901	19.57±1.78 p=0.420	20.14±1.51 p=0.199	17.28±1.73
	Z=0.405, p_1=0.685		Z=0.331, p_1=0.741		
Amount of abnormalities of the AI after treatment	16.90±1.14 p_2=0.309, p_3=0.405	18.13±1.59 p_2=0.367, p_3=0.355	17.25±0.66 p_2=0.908, p_3=0.211	18.29±0.79 p_2=0.261, p_3=0.349	
	Z=1.116, p_4=0.264		Z=1,715. p_4=0.086		

Note: ‡ - differences before treatment are statistically significant as compared to the comparison group indicators at p<0.01; *, **, *** - differences after treatment are statistically significant as compared to pre-treatment indicators at significance level p<0.1, p<0.05, p<0.01 and p<0.001 respectively; $^{\&}$, $^{\&\&}$, $^{\&\&\&}$ - differences are statistically significant after treatment between the main Ia and Ib, IIa and IIb clinical subgroups at p<0.1, p<0.05 and p<0.001 respectively.

surface of the reticular mesh and the hyperemia area showed that significant differences before the local treatment complex between typical and erosive and ulcerative forms of the Lichen Planus in the oral cavity mucosa lining were observed only in the indicator of completion of nuclear destruction, manifested in the disintegration of the cell nucleus into parts, and these manifestations are more evident in the II main clinical group with the predominance of *Candida spp.* in the oral microbiota (Table 1).

Local treatment provided using the developed method or according to clinical recommendations did not reveal statistical differences (*p>0.1*) in the frequency of cells with nuclear abnormalities in the cytogram of buccal epithelium in patients with erosive and ulcerative and typical forms of the LP in the OCML.

As a result of the local treatment, the cytograms of buccal epithelium showed a dynamic decrease in the frequency of cells with disintegration of part of the nucleus obtained from patients of the II main clinical group *(p<0.001)*. For patients with predominance of high titers of *Candida spp.* in the oral microbiota, the developed complex of the local treatment contributed to a significant decrease in the occurrence of cells with a degenerative change of the nucleus *(p<0.05)* in the cytogram of buccal epithelium obtained from the area of the reticular mesh and the hyperemia area. The developed method of local treatment in this category of patients also contributed to a more significant decrease in the frequency of cells with nuclear proliferation in the form of notches in the cytogram of buccal epithelium as compared to the group of patients treated according to clinical recommendations *(p=0.05)* (Table 1).

In general, according to the results of calculation of the amount of apoptotic index aberrations in the cytogram of buccal epithelium obtained from the surface of the reticular mesh and the hyperemia area, its value after treatment with the developed method was significantly lower at the level *p<0.1* as compared to the treatment according to the federal clinical recommendations. The dynamics of stabilization of the amount of the apoptotic index aberrations in the cytogram of buccal epithelium is more evident in patients with the prevalence of high titers of *Candida spp.* in the oral microbiota (Table 1).

The analysis of cytograms of buccal epithelium before and after local treatment showed that the treatment contributed to significant differences in the index of nucleus destruction, manifested in the disintegration of the cell nucleus into parts for the first and second main clinical subgroups regardless of the method applied, but for the patients of the II main clinical group with predominance of high titers of Candida spp. in the oral microbiota the effect was more pronounced (p<0.001). The effect of the developed method of local treatment was a criterion for the decrease in the frequency of nucleus destruction in the cytogram of buccal epithelium, manifested in the disintegration of the cell nucleus into parts as compared to the treatment according to clinical recommendations: for patients of the I main clinical subgroup at p<0.05, for patients of the II main clinical group at p<0.001.

The greatest effect of the developed method of local treatment was observed in patients of the IIa main clinical subgroup with predominance of high titers of Candida spp. in the oral microbiota. In the cytogram of buccal epithelium obtained after local treatment, the frequency of cells with micronuclei significantly decreased (p<0.01), and the frequency of degenerative change of the nucleus decreased at p<0.05.

In Ia and IIa clinical subgroups of patients with Candida spp. detected in the oral microbiota, in the cytogram of buccal epithelium there was observed a decrease in the frequency of a cytogenetic indicator in the form of micronucleus protrusion (at p<0.1), nucleus notching (at p<0.01), and these indicators when applying the developed method of local treatment are more significant (at p<0.1 and at p<0.001 respectively) as compared to the treatment according to clinical recommendations.

The decrease in the frequency of occurrence of the index of nuclear destruction completion in the cytogram of buccal epithelium was achieved only in the group of patients with predominance of Candida spp. in the oral microbiota and those who obtained the developed method of local treatment (IIa subgroup) at the significance level p<0.1.

When calculating the amount of the abnormalities of the apoptotic index, its

Table 2

Dynamics of changes in the frequency of cells with nuclear abnormalities in the cytogram of buccal epithelium (from the surface of erosive and ulcerative elements) in patients of I and II clinical subgroups with the erosive and ulcerative form (L43.82) of the Lichen Planus (LP) in the oral cavity mucosa lining (OCML) before and after the treatment

Indicators	Ia main clinical subgroup of the EUF of the LP in the OCML (suggested treatment) (n=23)	Ib main clinical subgroup of the EUF of the LP in the OCML (treatment according to federal clinical recommendations) (n=23)	IIa main clinical subgroup of the EUF of the LP in the OCML (suggested treatment) (n=20)	IIb main clinical subgroup of the EUF of the LP in the OCML (treatment according to federal clinical recommendations)) (n=20)
Comparisons: Intergroup comparisons between group Ia and Ib, IIa and IIb according to the Mann-Whitney U test (p_1), intra-group comparisons according to the Wilcoxon test for subgroups Ia and Ib, IIa and IIb before treatment and after treatment (p_2), intergroup comparisons between group Ia and Ib, IIa and IIb before treatment according to the Mann-Whitney U test (p_3).				
Cytogenetic abnormalities				
Micronucleus before treatment	2.35±0.25	2.33±0.18	2.92±0.17	2.84±0.19
	Z=0.134. p_1=0.893		Z=0.206. p_1=0.837	
Micronucleus after treatment	1.84±0.09, p_2=0.204	2.05±0.13, p_2=0.223	1.99±0.14$^{**,\&}$, p_2=0.002	2.54±0.09, p_2=0.199
	Z=1.007, p_3=0.314		Z=2.095, p_3=0.036	
Micronucleus protrusion before treatment	1.18±0.32	1.24±0.28	1.27±0.26	1.19±0.25
	Z=0.201, p_1=0.841		Z=0.245, p_1=0.806	
Micronucleus protrusion after treatment	0.74±0.05, p_2=0.187	0.79±0.04, p_2=0.202	0.77±0.06, $^{\&}$, p_2=0.055	0.98±0.06, p_2=0.093
	Z=0.177, p_3=0.860		Z=1.945, p_3=0.052	
(Tongue-type) Micronucleus protrusion before treatment	0.64±0.04	0.60±0.07	0.95±0.05	0.85±0.11
	Z=0.145, p_1=0.885		Z=1.178, p_1=0.239	
(Tongue-type) Micronucleus protrusion after treatment	0.68±0.02, p_2=0.877	0.68±0.03, p_2=0.819	0.70±0.04**, p_2=0.004	0.68±0.05, p_2=0.220
	Z=0.024, p_3=0.981		Z=0.181, p_3=0.856	
Indicators of nucleus destruction completion				
Karyopyknosis before treatment	6.51±0.39	6.67±0.40	6.90±0.33	6.89±0.28
	Z=0.311, p_1=0.756		Z=0.108, p_1=0.914	
Karyopyknosis after treatment	6.14±0.06, p_2=0.314	6.29±0.05, p_2=0.345	6.18±0.06, $^{\&}$, p_2=0.078	6.44±0.07, p_2=0.312
	Z=1.412, p_3=0.158		Z=1.962, p_3=0.049	
Karyorrhexis before treatment	4.06±0.28	4.18±0.21	5.67±0.21	5.79±0.18
	Z=0.821, p_1=0.412		Z=0.760, p_1=0.447	
Karyorrhexis after treatment	3.14±0.08$^{**,\&\&}$, p_2=0.009	3.59±0.08*, p_2=0.05	3.35±0.09$^{***,\&\&\&}$, p_2<0.001	4.39±0.16***, p_2<0.001
	Z=2.212, p_3=0.027		Z=3.451, p_3<0.001	
Karyolysis before treatment	0.72±0.15	0.71±0.10	1.08±0.13	1.04±0.14
	Z=0.094, p_1=0.921		Z=0.181, p_1=0.856	
Karyolysis after treatment	0.64±0.06, p_2=0.377	0.66±0.07, p_2=0.404	0.72±0.08*, p_2=0.011	0.89±0.06, p_2=0.211
	Z=0.164, p_3=0.869		Z=1.093, p_3=0.274	
Indicators of nuclear proliferation				
Nucleus notching before treatment	4.62 ± 0.09	4.70±0.07	5.16±0.09	5.27±0.08
	Z=1.003, p_1=0.316		Z=1.062, p_1=0.288	
Nucleus notching after treatment	4.55±0.07, p_2=0.234	4.59±0.07, p_2=0.310	4.65±0.07$^{***,\&\&\&}$, p_2<0.001	5.03±0.04*, p_2=0.045
	Z=0.217, p_3=0.828		Z=3.319, p_3<0.001	
Apoptotic Index (AI)				
Amount of abnormalities of the AI before treatment	20.08±1.52	20.43±1.31	23.95±1.24	23.87±1.23
	Z=0.211, p_1=0.833		Z=0.205, p_1=0.838	
Amount of abnormalities of the AI after treatment	17.73±0.43$^{\&}$, p_2=0.234	18.65±0.47, p_2=0.453	18.36±0.54$^{***,\&}$, p_2<0.001	20.95±0.53, p_2=0.069
	Z=1.678, p_3=0.093		Z=2.478, p_3=0.013	

significant decrease after local treatment (at $p<0.1$) was observed for the group of patients with candidiasis regardless of the method of treatment, but this effect was more pronounced with the developed complex (at $p<0.001$), and its differences in significance after treatment in IIa and IIb subgroups reaching $p<0.05$.

Thus, in patients with the EUF of the LP in the OCML the influence of the developed method of treatment contributed to the decrease in the frequency of micronucleus abnormalities in the cytogram of buccal epithelium, as well as in the indicators of nucleus destruction completion.

Discussion. During the examination of 139 male and female patients living in Ufa and Omsk, clinical manifestations of various forms of the Lichen Planus (typical, erosive and ulcerative, hyperkeratotic, bullous and atypical) were revealed on the oral cavity mucosa lining, the age of the patients varied from 31 to 60 years, 111 patients with the erosive and ulcerative (L43. 82) form of the LP in the OCML (n=86) and typical form (L43.80) (n=25) were further clinically examined by selection, which contradicts the data obtained by Irani S. et al. [16].

There are several studies investigating the frequency of micronuclei in patients with the EUF (L43.82) of the LP in the OCML, but they only assess micronuclei. Analysis of cytogram data of buccal epithelium obtained from the area of the reticular mesh and erosive and ulcerative elements before treatment showed a statistically significant increase of cells with micronuclei by 1.42 times from the surface area of erosions and ulcers in the EUF (L43.82) of the LP than from the reticular mesh area in typical form of the LP (L43.80) in the OCML ($p<0.05$). Our data are close to those obtained by Sanchez-Siles M. et al. [21].

According to the data of Serikova O. V. et al., in cytological preparations the total number of cells with abnormalities, as well as the frequency of occurrence of some nuclear aberrations (micronuclei, karyorrhexis, karyopyknosis) is higher in the EUF (L43.82) of the LP in the OCML, and the frequencies of occurrence of some indicators of nucleus destruction (karyolysis and perinuclear vacuoles) were lower than in the control group ($p<0.05$). On the surface of the erosive and ulcerative elements, the number of cells with abnormalities prevailed as compared to the area without abnormalities ($p<0.01$) [1, 2, 4]. In a study of patients with a clinical diagnosis of the EUF of the LP in the OCML, Buajeeb et al. (2007) also found a significantly increased frequency of micronuclei [9]. During clinical and laboratory research we took into account the data of cytograms of buccal epithelium obtained in 86 patients with the EUF (L43.82) of the LP in the OCML. When analyzing the data of cytograms of the reticular mesh surface and hyperemia area before and after local treatment significant differences in the index of nuclear destruction completion were obtained, manifested in the disintegration of cell nucleus into parts, and the studied index was more obvious in patients of the II main clinical group with predominance of Candida spp. in the oral microbiota. The effect of the developed method of local treatment [6] was an important criterion contributing to the decrease in the frequency of nucleus destruction in the cytogram of buccal epithelium for patients of the I main clinical group at $p<0.05$, and for patients of the II main clinical group at $p<0.001$. In the cytogram of buccal epithelium the frequency of cells with karyological aberrations, that is micronuclei ($p<0.01$), degenerative change of the nucleus at $p<0.05$ significantly decreased. In cytograms obtained from the surface of erosive and ulcerative elements of patients of Ia and IIa clinical subgroups with Candida spp. detected in the oral microbiota, there was observed a decrease in the frequency of the cytogenetic index in the form of micronucleus protrusion (at $p<0.1$), nucleus notching (at $p<0.01$), and these indicators when applying the developed method of local treatment were more significant (at $p<0,1$ and at $p<0.001$ respectively), the decrease in the frequency of the index of nuclear destruction completion was achieved only in IIa clinical subgroup at significance level $p<0.1$.

Manifestation of chronic inflammation on the oral cavity mucosa lining in the EUF (L43.82) of the LP mainly has signs of a macrophage response and is subjected to oxidative stress, which contributes to the production of endogenous reactive oxygen and nitrogen species, and their imbalance has a direct toxic effect on tissues. This induces a proliferative response, which in turn promotes genetic damage, increasing the degree of error probability in DNA replication by increasing genetic instability in it [13], which is consistent with our data.

Assessment and analysis of cytogenetic abnormalities, proliferation and apoptosis in the cytogram of buccal epithelium can be used as a differentiated approach in the diagnosis, and control of the course of various forms of the Lichen Planus in the oral cavity mucosa lining and adherence to the principles of cancer alertness [5].

Karyopyknosis, karyorrhexis and karyolysis is the terminal stage of epitheliocyte destruction. The decrease in the number of these cells in the main clinical groups with the developed method of local treatment correlates with the decrease in the degree of hyperkeratosis and restoration of the structure of the oral mucosa.

Conclusion. The effect of the developed method of local treatment, including a complex of ozone therapy on the Prozone device, applications of 0.2% hyaluronic acid gel (Hy + Al Gel), 0.5% Prednisolone ointment and closure of the surface of erosive and ulcerative elements with Ora-Aid self-dissolving patch contributes to the decrease in the frequency of cells with proliferation of the nucleus in the form of notches, decreased frequency of cells with micronuclei ($p<0.01$), degenerative changes of the nucleus ($p<0.05$) as compared to the group of patients treated according to clinical recommendations ($p=0.05$). In clinical subgroups of patients with prevalence of high titers of Candida spp. in the composition of the oral microbiota, the influence of the developed method contributed to the decrease in the frequency of micronucleus protrusion (at $p<0.1$), nucleus notching (at $p<0.01$), and the index of nuclear destruction completion ($p<0.1$).

In conclusion, cytologic examination of buccal epithelium is a sensitive, non-invasive method that provides clear information on the status of epithelial cells, in particular their DNA damage, the proliferative potential of basal cells and cell death, which are considered basic principles of cancer alertness.

Thus, cytogenetic monitoring of patients with dermatosis is of special importance as it allows to control the dynamics of the frequency of occurrence in the cytogram of buccal epithelium of the indicator of nucleus destruction, that is karyopyknosis and karyorrhexis, and allows of their clinical observation in the process of local treatment and screening of the EUF (L43.82) of the LP in the OCML.

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HEALTHY LIFESTYLE. PREVENTION

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CHICKENPOX AND HERPES ZOSTER: DYNAMICS OF INCIDENCE AND APPROACHES TO PREVENTION

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The dynamics of the incidence of chickenpox and herpes zoster in the population of the Irkutsk region and the city of Irkutsk against the background of ongoing selective vaccination was studied. A descriptive epidemiological study was conducted according to state statistical reporting based on materials from the Irkutsk region and the city of Irkutsk for 2013-2022. The calculation of predictive values was made using regression equations, the statistical significance of differences in intensive indicators was assessed by 95% CI. Against the background of a decrease in the incidence of chickenpox, in 2021-2022. There was an increase in the indicator among different age groups of the population, the most significant among children under 6 years of age. According to the forecast, in 2023 the incidence rate will not change significantly. Selective vaccination tactics do not significantly affect the incidence of chickenpox (p = -0.217; -0.7; p>0.05). The incidence of shingles in the region exceeds the national level. Taking into account the continuing epidemiological trouble for chicken pox in the region and the data of forecast calculations, it is necessary to adjust the existing vaccination programs, including gradually expanding the contingents to be vaccinated.

Keywords: chicken pox, shingles, incidence, vaccination.

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Introduction. Chickenpox and herpes zoster (HZ) are two independent and at the same time different in clinical manifestations nosological forms, the etiolog-

ical agents of which are the same pathogen: human herpes virus type 3 (Varicella Zoster virus). Chickenpox belongs to the group of highly contagious acute viral diseases with airborne transmission, often leading to serious complications [2, 5]. Every year, in terms of economic damage, chickenpox leads among infectious diseases [9]. The ubiquitous spread of the pathogen, a high incidence rate, insufficiently effective preventive measures, and an increase in the frequency of herpesvirus infections in immunocompromised individuals determine the relevance of the problem of these diseases [7, 11]. The causative factor in the development of HZ in individuals with defects in the immune system is chickenpox suffered in childhood. In the Russian Federation, statistical recording of cases of acute illness has been introduced since 2019.

In the Russian Federation, vaccine prevention of chickenpox has been introduced into the calendar of preventive vaccinations for epidemic indications since 2014; children and adults from risk groups are subject to vaccination, including persons subject to conscription for military service, who have not previously been vaccinated and have not had chickenpox. Some subjects of the Russian Federation successfully carry out routine vaccination in accordance with the current regional calendars of preventive vaccinations and regional vaccination programs [3, 6, 12].

One of the main documents defining the state policy in the field of development of immunization in the Russian Federation is the Strategy for the development of immunoprophylaxis of infectious diseases until 2035. One of the directions for solving the tasks of the Strategy is the improvement of the national vaccination calendar, including the inclusion in it of a vaccine for the prevention of chickenpox for cohort vaccination. However, taking into account the regional characteristics of epidemiologists chickenpox, it is necessary to reconsider approaches to organizing vaccination.

The purpose of the study: to study the dynamics of the incidence of chickenpox and herpes zoster in the population of the Irkutsk region and the city of Irkutsk against the background of ongoing selective vaccination.

Materials and methods of research. A retrospective descriptive epidemiological study was conducted for the period 2013–2022. based on materials from the Irkutsk region. The incidence of chickenpox among different age groups of the population of the Irkutsk region and the city of Irkutsk was calculated according to the reporting form of the Rospotrebnadzor Department No. 2 "Information on infectious and parasitic diseases." The dynamics of the number of vaccinated people is presented according to reporting form No. 5 "Information on preventive vaccinations" for 2014-2022.

The incidence rates of chickenpox and herpes zoster by year were calculated using the size of different age groups and the total population of the Irkutsk region and the city of Irkutsk at the beginning of the calendar year according to the data of the Territorial body of the Federal State Statistics Service for the Irkutsk region (Irkutskstat).

To calculate the forecast indicators of chickenpox for 2023 in the compared territories, a statistical forecasting method was used, the basis of which was the assessment of time series, the selection of a trend line according to the level of approximation reliability (R2), and the construction of a trend line with a smoothed curve. The calculation was made using the regression equation.

To assess the statistical significance of differences in relative indicators, confidence intervals were calculated with a significance level of 95% (95% CI). Regression equations, correlation coefficients, graphical data processing were performed using Excel (Windows 2010).

Results and discussion. During the observation period, the incidence rates of chickenpox in the total population in the Irkutsk region were unevenly distributed. The long-term average indicator (MAI) was 593.2 [521.5÷673.9] per 100 thousand, the average annual rate of decline was 0.9%. Period 2014–2020 was characterized by a decrease in the incidence level: from 833.4 [822.0÷844.8] to 507.6 [498.6÷516.6], with a subsequent increase to 813.7 [802.2÷825.2] per 100 thousand in 2022 (Fig. 1).

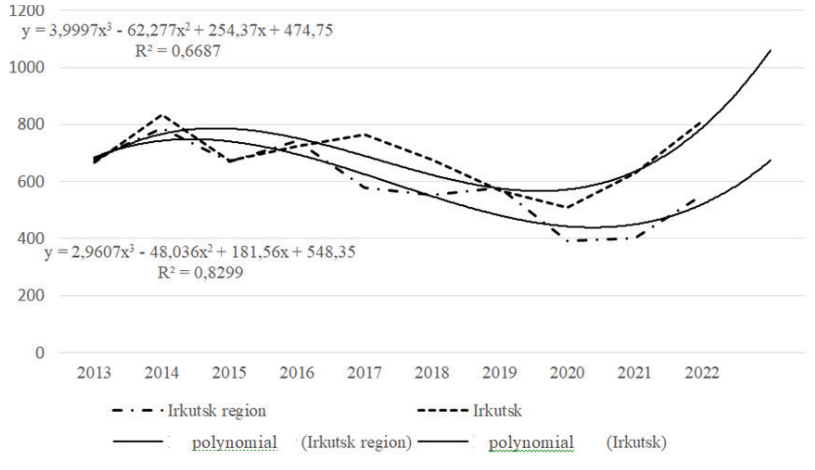

Fig. 1. Dynamics of chickenpox incidence in the total population of the Irkutsk region and Irkutsk in 2010-2022 with a forecast for 2023. (per 100,000 population)

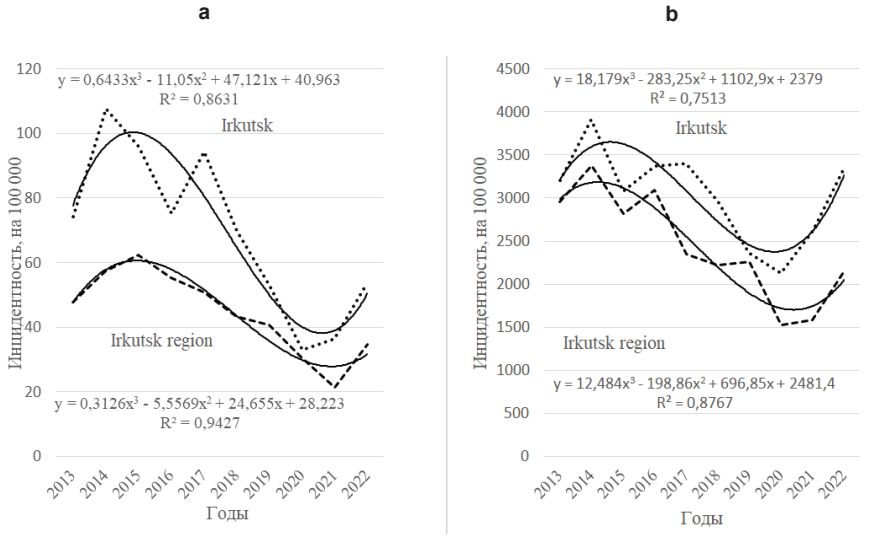

Fig. 2. Dynamics of the incidence of chickenpox in adults (a) and children (b) in the Irkutsk region and Irkutsk in 2013-2022. (per 100,000 population)

Table 1

The incidence of chickenpox among different age groups of the population of the Irkutsk region and Irkutsk for 2020-2022 (per 100 thousand) taking into account 95% CI

age groups	Год					
	2020		2021		2022	
	Irkutsk region	Irkutsk	Irkutsk region	Irkutsk	Irkutsk region	Irkutsk
total population	391.9 [366.8÷417.0]	622.1 [602.5÷641.7]	402.0 [394.0÷410.0]	628.2 [608.4÷648.0]	552.2 [542.8÷561.6]	813.7 [793.0÷834.4]
adult population (over 18 years old)	30.4 [27.1÷33.7]	33.1 [28.0÷38.2]	21.5 [19.3÷23.7]	36.5 [31.2÷41.8]	34.6 [33.7÷37.3]	53.5 [47.0÷60.0]
children 0 – 17 years old, of them:	1522.2 [1490.7÷1553.7]	2129.9 [2054.6÷2205.2]	1586.2 [1554.1÷1618.3]	2620.7 [2537.4÷2704.0]	2153.8 [2116.2÷2191.4]	3342.1 [3249.0÷3435.2]
0 – 6 years	2827.9 [2613.3÷3042.5]	4035.4 [3881.3÷4189.5]	3132.0 [3059.9÷3204.1]	5060.1 [4886.1÷5234.1]	4203.6 [4118.5÷4288.7]	6478.8 [6280.3÷6676.7]
7 – 17 years	631.6 [547.8÷715.4]	595.5 [541.4÷649.6]	605.7 [580.0÷631.4]	779.5 [718.7÷840.3]	1056.4 [1023.1÷1089.7]	1111.6 [1040.5÷1182.7]

Note: the cells where the intergroup differences are statistically significant over the years in the compared territories are highlighted in color

Children under 17 years of age prevailed in the structure of cases in the region; the long-term average was 91.1±0.2%. Chickenpox was registered among all age groups of the child population: the proportion of children under 1 year was 3.1±0.05%; children aged 1–2 years – 14.2±0.4%, a significant contribution was made by children aged 3–6 years – 62.4±0.5%; the proportion of children 7–14 and 15–17 years old was 20.3±0.3% and 2.8±0.1%, respectively.

Chickenpox was recorded unevenly among municipalities of the Irkutsk region. A comparative analysis of the long-term dynamics of incidence in the Irkutsk region and in the city of Irkutsk showed that in different years the incidence level of the total population of Irkutsk exceeded the regional average values, while unidirectional trends were noted (Fig. 1). The incidence of the adult and child population in Irkutsk was higher than the regional average: 69.3 [53.6÷85.0] versus 44.4 [36.4÷52.4] and 3039.3 [2707.3÷3371.3] versus 2434.2 [2050.2÷2818.2] per 100 thousand, respectively. Period 2014–2020 was characterized by a persistent decrease in indicators in the compared groups in the compared territories ($p<0.05$). A significant increase in incidence was registered in 2022 among children in Irkutsk; the rate increased compared to the previous period by 1.6 times, exceeding the SMP (Fig. 2).

According to the forecast calculation, in 2023 the incidence level of chickenpox among the total population in the compared territories will not change signifi-

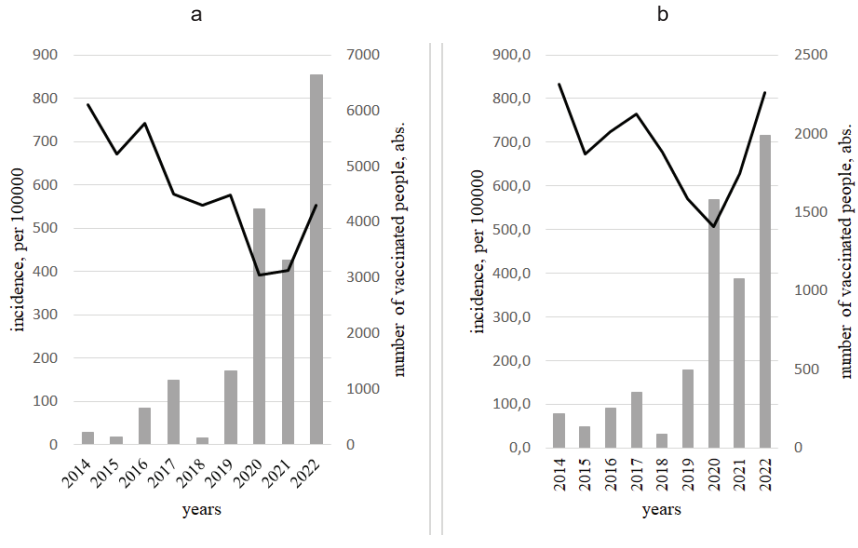

Fig. 3. Dynamics of chickenpox incidence in the total population in the Irkutsk region (a) and in Irkutsk (b) (per 100 thousand) and the number of vaccinated against chickenpox (abs. values) in 2014-2022.

Table 2

The incidence of shingles in the total population of the Irkutsk region, Irkutsk and the Russian Federation (per 100 thousand), taking into account 95% CI

territory	years			
	2019	2020	2021	2022
Russion Federation	13.1 [12.9÷13.3]	10.3 [10.2÷10.4]	9.2 [9.1÷9.3]	11.4 [11.2÷11.6]
Irkutsk region	20.1 [18.4÷21.8]	24.8 [22.8÷26.8]	24.1 [22.2÷26.0]	37.6 [35.1÷40.1]
Irkutsk	10.6 [8.1÷13.1]	6.5 [4.6÷7.4]	10.0 [7.5÷12.5]	27.4 [23.3÷31.5]

cantly. In the Irkutsk region the indicator will be 521.2 per 100 thousand population (in the range from 479.9 to 562.5 per 100 thousand); in the regional center – 790.5 per 100 thousand population (ranging from 758.0 to 823.0 per 100 thousand) (Fig. 1).

In 2021-2022 the incidence of chickenpox exceeded the 2020 level in different age groups in the compared territories, the differences are statistically significant ($p<0.05$) (Table 1).

From 2014 to 2022, vaccination volumes in the region increased significantly. During the analyzed period, 17,787 people were vaccinated, which amounted to 0.8% of the population. Of these, more than 6,000 were vaccinated in Irkutsk (0.9% of the city's population). Despite the increase in vaccination volumes (primarily conscripts contacted in epidemic foci were vaccinated in the compared territories), an inverse, high, statistically insignificant relationship was noted between the number of vaccinated and those sick with chickenpox ($p = -0.7$; $p>0.05$) in the Irkutsk region and the inverse weak connection is statistically insignificant ($p = -0.217$; $p>0.05$) in Irkutsk (Fig. 3).

Herpes zoster deserves special attention as an independent nosological form. Over the course of four years, the incidence of herpes zoster among the total population in the Irkutsk region increased by 1.8 times and exceeded the all-Russian values, the differences are statistically significant ($p<0.05$) (Table 2). The structure of cases was dominated by persons over 18 years of age, whose proportion was 85.6±1.4%. During the analyzed period, 291 cases of the disease were registered in children under 17 years of age, of which 194 cases (66.6%) were in children 7–17 years of age. The incidence rate of herpes zoster in Irkutsk was lower than regional values and the level for the Russian Federation as a whole.

In the Irkutsk region, as in the Russian Federation, signs of epidemiological problems with chickenpox remain – a consistently high incidence rate in different age groups of the population with a tendency to increase. A significant decrease in the indicator in 2020 was due to the implementation of large-scale anti-epidemic measures during the period of epidemic rise in the incidence of COVID-19 infection [9]. In 2021–2022 the incidence level increased in the compared territories and in the Russian Federation as a whole.

The age group at risk for chickenpox remains children under 6 years of age [6]. At the same time, the incidence of children aged 7–17 years is registered at a high level (595.5-1111.6 per 100 thousand). With the continuing trend, the risk of introducing the pathogen into children's groups (preschool and educational institutions) remains quite high and significant resources will be required to eliminate foci of infection [10].

In the Russian Federation, the volume of vaccination against chickenpox increases annually [6, 9]. A similar trend is typical for the Irkutsk region. However, due to the uneven distribution of incidence among municipalities, it is advisable, first of all, to provide the vaccine to areas with a high incidence rate. Even so, selective vaccination would not have a significant effect on chickenpox incidence rates ($p = -0.2217$ – -0.7, $p>0.05$).

The analysis of the incidence of the population of OL in the Irkutsk region and in the city of Irkutsk demonstrated an excess of the all-Russian indicator in the region; involvement in the epidemic process mainly of persons over 18 years of age (85.6%); and among children – the group of 7–17 years old (58.0 – 90.2%). This is consistent with data from other territories [8, 9, 13].

The massive incidence of chickenpox, significant economic damage, and the increasing incidence of herpes zoster, including in children, determine the need to optimize approaches to the prevention of the infections being studied. According to experts, economic benefits can only be obtained through universal vaccination of the population [4, 11, 14]. Calculations to assess the economic efficiency of mass vaccination against HE of children, carried out earlier in the region, showed the possibility of obtaining a significant economic effect [1]. There is no specific prevention of herpes zoster in the Russian Federation. Consequently, to control the epidemic process of this infectious disease, the leading anti-epidemic measures are early detection and isolation of patients [8].

Conclusion. Taking into account the ongoing epidemiological problems in the region and data from forecast calculations indicating a high level of incidence, it is necessary to adjust the existing vaccination programs against chickenpox, including gradually expanding the populations subject to immunization. When conducting epidemiological control over herpes zoster, special attention should be paid to the timeliness and effectiveness of primary anti-epidemic measures.

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THE ROLE OF PREVENTIVE EXAMINATIONS IN THE EARLY REHABILITATION OF MUSCULOSKELETAL DISEASES OF CHILDREN AND ADOLESCENTS

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Based on the analysis of the results of preventive examinations of children and adolescents of the Astrakhan region for the period from 2015 to 2021, it was revealed that, despite the steady increase in detected cases of diseases of musculoskeletal system (MSS), the percentage of those placed on dispensary registration is constantly decreasing, which violates the target requirements of current regulatory documents at both federal and regional levels.Together with the negative impact of covid restrictions on the volume of preventive examinations, it seriously worsens the situation with the timely implementation of rehabilitation measures for MSS diseases.The negative consequences for the health of the sick will progress as they grow up, which will lead to serious economic damage to society as a whole.

It is proposed to increase the percentage of children being registered at the dispensary with MSS diseases, even if at the time of the examination they have the form of functional abnormalities with the risk of transition to the chronic phase; to expand the rehabilitation infrastructure by creating a specialized center, or significantly improving the equipment of existing medical institutions, to promote measures of self rehabilitation and prevention of MSSdiseases among children and youth.

It is proposed to increase the proportion of children with MSS diseases taken under observation at the early stages of the disease, even if at the time of preventive examination they have only the form of functional abnormalities with the risk of transition to the chronic phase; to expand the rehabilitation infrastructure by creating a specialized center, or significantly improving the equipment of existing medical institutions, to promote measures of self-rehabilitation and prevention of MSS diseases among children and youth.

Keywords: preventive examination, dispensary registration, rehabilitation, effectiveness, children, musculoskeletal system.

Introduction. The urgency of the problem lies in the fact that there is a causal relationship between the quality of preventive examinations in childhood and the level of health of a person's MSS throughout life, as well as financial damage to the state from such diseases.

Preventive examinations are the most comprehensive and regular health monitoring, giving an objective picture of the prevalence of diseases and pathological conditions. It is during the preventive examination that diseases and functional disorders of the MSS are most often diagnosed for the first time. According to the results, the placement of a child on a dispensary registrationincreases the likelihood of timely initiation of treatment and rehabilitation. Thus, the risk of severe complications is reduced, which in turn reduces economic losses for society.

The aim of the study is to assess the role of preventive examinations in the early rehabilitation of children and adolescents with diseases of the musculoskeletal system

To achieve the intended goal, it is necessary to solve the following tasks:

1) to assess the specifics of diseases of the musculoskeletal system among children and adolescents;

2) to assess the importance of occupational examinations for the early detection of MSS diseases;

3) to assess the dynamics of the timeliness of the coverage of newly identified patients with diseases of the musculoskeletal system by dispensary observation.

Materials and methods. The research uses the following methods: statistical analysis, analytical, the study of scientific literature and the regulatory framework, expert assessments of medical organizations. The study used "Information on preventive medical examinations of minors" for 2015-2021 in the Astrakhan region in the form of statistical reporting No. 030-PO/0-17, orders and instructions of the Ministry of Health. The object of the study were residents of the Astrakhan region 0-17 years old who underwent a preventive examination from 2015 to 2021, including for diseases of the musculoskeletal system. In addition to the traditional indicators of the effectiveness of preventive examination (coverage, pathological lesion, the number of diseases detected for the first time to the number of examined), it is also proposed to calculate the proportion of patients who are registered at the dispensary. The indicator is the most important in the national project "Health", measured as a percentage and calculat-

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ed by dividing the number of residents registered for a particular disease by the total number of identified residents with this disease [1, 2].

Results and discussion. Effective strengthening and preservation of the health of children and adolescents can be realized only with regular large-scale and periodic monitoring in the form of preventive examinations, which should ensure early detection of the disease and possible further rehabilitation. This fully applies to diseases of the musculoskeletal system.

The key trend for the coming years to increase the economic efficiency of healthcare should be the reorientation of the industry to preventive and rehabilitation measures. This direction is also supported in legislative acts at the level of the whole country [3].

Based on the study of current scientific publications on the subject, the following conclusions were made during the study regarding the specifics of diseases of the musculoskeletal system among children and adolescents, which should be taken into account during preventive examinations and rehabilitation:

1) The widest prevalence (priority in many age categories) [4].

2) Influence on the rest of the body's systems (respiratory, cardiovascular, sexual, etc.) [5].

3) Steadily progressing course of the disease and, accordingly, consistently deteriorating the quality of human life and, as a consequence, increasing economic costs and losses of society.

4) Fundamentally different genesis of MSS diseases. Most of the cases, with all their diversity, can be reduced to three: firstly, congenital and, as a rule, detected at birth or in the first months of life, secondly, acquired as a result of injuries or the consequences of other diseases, and finally, thirdly, arose and gradually developed due to the impact of a complex of social and genetic factors.

5) Often, for the latter type of diseases, a complex of rehabilitation measures can be effectively carried out independently, or with minimal participation of medical personnel. Also in this case, as a rule, there is a high rehabilitation potential, directly proportional to how early the disease was diagnosed [6].

6) The measures used both in rehabilitation and in the prevention of MSS diseases are similar in many situations, especially when the disease is at an early stage or problems, in general, are detected only at the level of functional abnormalities [7].

Regular preventive examinations of children for the detection of diseases, including MSS, is the leading process for placing them on dispensary registration (taking under dispensary supervision) for this disease [8].

During the analysis of the results of preventive examinations in the Astrakhan region from 2015 to 2021 , the following key indicators were analyzed in dynamics:

1) The percentage of coverage of children living in the territory with preventive examination plans;

2) The proportion of children who have passed a preventive examination relative to the plan;

3) The percentage of children with newly diagnosed MSS diseases based on the results of a preventive examination in comparison with the proportion of the prevalence of this disease in the same sample before the start of a preventive examination;

4) Comparison of the proportion of those under dispensary supervision in connection with the diagnosis of MSS disease before the preventive examination with the proportion of those taken on dispensary registration among those who had this disease for the first time diagnosed directly after the examination.

First of all, it is necessary to estimate the number of children and adolescents in the Astrakhan region. From 2015 to 2018 it steadily grew from 220.3 thousand people to 227.7 thousand people, thus, the increase was 3.4%. Then there was a gradual decline in the number, and by 2021 it decreased by 0.7%, reaching 226.0 thousand people.

The number of children subject to routine preventive examination from 2015 to 2019 grew from 78.8 thousand people to 193.9 thousand people, then by 2021 this figure decreased by 4.4 thousand people. The first rapid growth occurred in 2016, when the indicator immediately increased by more than 2 times to 162.3 thousand children compared to 78.9 thousand in 2015. If we compare the plans for medical examination with the total number of the corresponding population group, the planned coverage increased immediately from 35.8% to 72.4%. Then in 2018, the plans for professional examination increased by 10%, and in 2019 by another 7%, reaching a maximum of 193.9 thousand people (85.2%). By 2021, the planned coverage rate was 189.5 thousand people, or 83.8% of the total number of children and adolescents in the Astrakhan region. It should be noted that from 2015 to 2019, the proportion of children and adolescents who actually passed a preventive examination regarding the medical examination plan exceeded 95% annually. However, in 2020, due to COVID-19, the indicator decreased by more than 3 times to 29.2%, and even with the improvement of the epidemiological situation in 2021 it reached only 80.5%.

From 2016 to 2021, there was an increase in the detection of children with diseases of the musculoskeletal system from 8.1% in 2016 to 14.5% in 2021, which was characterized by a pronounced and statistically significant trend (R2=0.97; p=0.003). In such situations, there is usually a dilemma about the reasons: is the health of the younger generation deteriorating so rapidly or have the methods, qualifications and equipment for better diagnostics improved. At the same time, in any case, according to the results, more than 22 thousand children and adolescents in the region with a diagnosis of MSS diseases are detected annually.

During the same 6-year period, the newly detected incidence of MS directly during the preventive examination of children and adolescents is also characterized by a pronounced and statistically significant trend, increasing from 1.6% in 2016 to 3.6% in 2021 (R2=0.84; p=0.01). Among other things, the explanation for such a sharp increase in the detection of diseases of the musculoskeletal system in 2021 may also be the fact that in 2020 more than 60% of children did not undergo a preventive examination.

Most scientists explain the progressive spread of MSS diseases primarily by behavioral factors: decreased motor activity, poor nutrition, incorrect posture and gait, hours of use of gadgets, etc.[9].

The urgency of the problem was assessed at the federal level, and the key indicator for this area was presented in the regulatory documentation of the national project "Healthcare".: "The proportion of children aged 0-17 years taken under medical supervision with diagnoses of diseases of the musculoskeletal system and connective tissue for the first time in their lives (%)" [10]. In accordance with the Presidential Decrees, the Government of the Astrakhan Region also adopted a Resolution, paragraph 6.6 of which, by analogy with federal legislation, states an increase in the coverage of dispensary observation of children with diseases of the musculoskeletal system and connective tissue for the first time in their lives to 90% [11].

It is assumed that with the increase in the detection of the incidence of children with MSS diseases in the Astrakhan region, both during occupational examina-

tions, and in general, taking into account the strict requirements of legislation, the coverage of dispensary observation of this pathology should grow. At the same time, the trend was the opposite: for 6 years from 2016 to 2021, the indicator of those under dispensary supervision relative to the number of children with detected MSS diseases before the start of a new dispensary steadily and significantly decreased, with the exception of one year out of trend (2019), decreasing during this period from 68.0% to 45.7% (R2=0.95; p=0.005).

A similar negative trend and even lower rates for taking under dispensary supervision are also observed when the disease is detected directly following the results of a preventive examination, which also does not meet the above-mentioned goal of 90%. If in 2016-2019 the indicator fluctuated between 50.5% and 56.1%, then in 2020 and 2021 it fell below 40.0% (R2=0.63; p=0.058). It is worth noting that, unlike the above dependencies, this relationship of parameters is not strong, but moderate, and is on the border of statistical significance (p<0.05), nevertheless it can be considered reliable (p<0.1).

When comparing the proportion of children taken under dispensary observation after the detection of MSS disease during a preventive examination, with the proportion of children already placed on such observation before a preventive examination based on the results of previously detected MSS diseases, it is clear that the second indicator was higher in each year of the analyzed period (2015-2021). Presumably, this is due to the fact that the most obvious cases of the disease, for example, congenital diseases and the consequences of serious injuries are almost always put under medical supervision, and if the negative consequences are not so obvious yet, then only in less than half of the cases.

Unfortunately, the generalized nature of reporting № 030 – PO/o-17 does not allow us to analyze the health groups of children in the context of specific diseases, including the musculoskeletal system. When considering the overall picture, according to the results for 2021 in the Astrakhan region, only 22.0% of children are recognized as healthy (health group I), 56.8% have functional abnormalities (health group II), 21.2% have chronic diseases (III-IV-V health groups).

It is known from interviewing employees of medical institutions that the majority of children referred for MSS treatment and, mainly, rehabilitation corresponded to those who were taken under medical supervision. It can be assumed that the more children would be taken under medical supervision, the more they would be sent to rehabilitation. The study of such dependence is expected in future studies.

Carrying out high-quality rehabilitation of children and adolescents before the completion of the formation of the skeleton and muscle frame can reduce the risk of negative effects of MSS diseases throughout life [12]. Thus, for effective rehabilitation, it is important how early the disease was detected. As indicated in the Methodological Recommendations on the algorithms for calculating the indicators of the National Project "Healthcare", it is "the timeliness of taking under dispensary supervision of children aged 0-17 years with a diagnosis of musculoskeletal system and connective tissue diseases for the first time in their lives and constant dynamic monitoring will reduce the risk of developing the consequences of these diseases" [13].

Conclusion

Based on the results of the study , the following conclusions were formulated:

1. The number of detected cases of MSS diseases among children and adolescents of the Astrakhan region is steadily growing every year.
2. The proportion of children placed on dispensary registration from the number of detected MSS diseases falls annually despite the increase in morbidity and the targets of the authorities, which have so far remained unattainable.
3. Covid restrictions had a negative impact on the number of timely detected cases of MSS diseases and the number of cases registered at the dispensary, due to which preventive examinations were not carried out in full for 2 years.

Based on the stated conclusions, it is proposed:

1. To increase the proportion of MSS registered at the dispensary for the detection of the disease to 90%, primarily due to children with the 2nd group of MSS health according to the results of a preventive examination.
2. To expand the infrastructure base of rehabilitation for MSS diseases for all three of its stages by creating a specialized center or significantly improving the equipment of existing medical institutions.
3. To expand the practice of self-rehabilitation and prevention of MSS diseases by children themselves, parents and educational institutions with remote control of medical personnel.

The proposed measures will make it possible to use the results of preventive examinations to detect MSS diseases to a greater extent for the health of the future of the nation.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

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EPIDEMIOLOGICAL SITUATION AND ORGANIZATION OF SPECIALIZED MEDICAL CARE FOR INFECTIOUS DISEASES IN THE REPUBLIC OF SAKHA (YAKUTIA)

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The article presents a content analysis of the epidemiology of infectious diseases in the Republic of Sakha (Yakutia) in the period from 2020-2023. An increase in the incidence of infectious pathology in the Republic of Sakha (Yakutia) by 20 nosological forms was revealed. Taking into account the epidemiological situation, as well as the available capacities of medical facilities and staffing, recommendations are proposed to improve the organization of specialized medical care for infectious diseases in the Republic of Sakha (Yakutia).

Keywords: infectious diseases service, morbidity, infectious diseases, pandemic, mortality, bed stock, staffing, Yakutia.

Introduction. The coronavirus pandemic has shown society's vulnerability to infectious threats. The measures taken in the Russian Federation partially prevented the scale of losses for society, but showed the need to improve the healthcare system in the fight against epidemics [1, 2, 4, 5]. This was especially acute in the regions of the Arctic zone of the Russian Federation and the Far Eastern Federal District.

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In this regard, an analysis of indicators of infectious pathology, reflecting the state of the infectious disease health service in the regions of the Russian Federation, can be the basis for developing directions for modernizing the infectious disease service. The state of the infectious disease service may largely reflect the problems that have developed in the healthcare system. Problems identified in the organization of specialized medical care for patients with infectious diseases require management decisions aimed at providing staff and beds in hospitals, introducing modern diagnostic and treatment technologies, with a corresponding increase in funding [3, 6, 7].

Purpose of the study: to conduct a content analysis of the main performance indicators of the infectious disease service of the Republic of Sakha (Yakutia) and determine the main directions for development.

Materials and methods of research: the reporting data of medical organizations and the Ministry of Health of the Republic of Sakha (Yakutia) for 2021-2022, data on the demographic situation and morbidity structure, statistical data of the main morbidity indicators in the Russian Federation were studied.

Results and discussion. Epidemiological situation in the Republic of Sakha (Yakutia). Compared to 2021, in 2022, an increase in the incidence of infectious pathology in the Republic of Sakha (Yakutia) was observed in 20 nosological forms: salmonellosis - by 48.2%, dysentery - by 10.9 times, rotavirus infection - by 6.8%, acute intestinal infections of unknown etiology - by 39.2%, enterovirus infection - by 8.3 times, acute hepatitis - by 2.0 times, incl. acute hepatitis C - by 2.2 times, chronic hepatitis B - by 11.1%, chronic hepatitis C - by 37.8%, scarlet fever - by 4.9 times, chicken pox - by 1.5 times, tick bites - by 1.7 times, pediculosis - by 25.5%, infectious mononucleosis - by 1.6 times, syphilis - by 36.1%, gonorrhea - by 22.8%, HIV infection - by 9.6%, ARVI - by 15.7%, flu - 5 times, COVID-19 - 2.1 times.

The situation in the republic remains tense regarding the incidence of chronic viral hepatitis. According to the register "Chronic viral hepatitis in the Republic of Sakha (Yakutia)" in 2022, 14,781 people were registered, including 484 people with liver cirrhosis of viral etiology, and 47 people with primary liver cancer. (Table 1). Due to viral hepatitis in the region in 2022, 188 people died. At the same time, 113 people (60.1%) hepatitis was the main cause of death.

The situation regarding HIV infection is very tense. The spread of the human immunodeficiency virus among the population and the increase in the cumulative number of infected and sick people continues. The incidence rate of HIV infection was 16.7 people per 100 thousand people, which is 9.6% higher than in 2021 (15.2 people per 100 thousand people, or 149 cases). The highest prevalence of this infection is observed in industrial areas, where there are a large number of migrants coming for seasonal work.

Since 2001, an annual increase in tick attacks on humans has been recorded. From 2019 to 2022, the number of calls due to tick bites increased by more than 2.5 times - from 221 to 565 cases per year.

For 2020-2022, a decrease in the population mortality rate among people over working age from infectious diseases was recorded by 28.7% (from 25.4 to 18.1 people per 100 thousand people), but at the same time the mortality rate from tuberculosis increased – by 37.1% (from 3.5 to 4.8 per 100 thousand population).

The COVID-19 pandemic has affected the overall infectious and parasitic morbidity of the population. At the end of 2022, 651,876 residents of the Republic of Sakha (Yakutia), of which 50.2% were children, suffered from infectious and parasitic diseases. Compared to 2021, there was an increase in infectious morbidity by 30.8%, and among children under 14 years old - by 19%. In 2022, in the structure of general infectious morbidity, the share of ARVI and influenza was 70.2%, coronavirus infection (CVI) - 26.3%. It should be noted that the decrease in the level of dispensary observation during the period of restrictive measures due to COVID-19 not only caused a subsequent increase in complications from viral hepatitis, HIV infection and tuberculosis, but also reduced the official morbidity rates.

Organization of specialized medical care for infectious diseases. As of January 1, 2023, the infectious disease service of the Republic of Sakha (Yakutia) employs 89 infectious disease doctors, of which 77 people work in practical healthcare. (86.5%). 58 people (65.2%) work in Yakutsk, 31 people work in the districts. (34.8%). In total, in practical health care there are 24 infectious disease doctors with the highest qualification category (31.1%); with the first category - 4 (5.2%); with the second category – 8 (10.4%), the total categorization was 40.4%. The number of specialists of retirement age (over 50 years old) is 27 people (35.0%), people under 50 years old - 62 (80.5%), of which 31 people (50%) are under 35 years old. The average age of infectious disease specialists in practical healthcare is 36.5 years. On the basis of the Medical Institute of the North-Eastern Federal University, training and advanced training of medical personnel is carried out through residency (10 people) and postgraduate studies (5 people).

The number of people with chronic viral hepatitis who are undergoing dispensary observation in the Republic of Sakha (Yakutia), 2022

Index	Chronic hepatitis				
	B	C	D	mixed	Total
absolute number, people	6260	6779	1241	501	14781
mass fraction, %	42.4	45.9	8.3	3.4	100
people/per 100 thousand population	0.63	0.68	0.12	0.05	1.48

Primary specialized health care is provided in 30 infectious diseases rooms of city and regional medical organizations. There are 23.7 full-time positions of infectious disease doctors, 84.2% are occupied, and the actual number of doctors in clinics is 27 people.

Specialized medical care is provided in the State Budgetary Institution of the Republic of Sakha (Yakutia) "Children's Infectious Diseases Clinical Hospital", the infectious diseases department of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital", the infectious diseases hospital of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Mirny Central district hospital" and infectious diseases departments of 29 district and city medical organizations. In the region, the number of infectious disease beds in 2022 is represented by 676 beds (annual average), of which there are 301 adult beds, 128 children's beds, and 247 mixed beds. The increase in the number of adult and children's beds is primarily due to their repurposing for the treatment of patients with COVID-19 throughout the republic.

In 2022, 9 temporary infectious diseases hospitals were deployed for patients with COVID-19, the maximum number of beds reached 533 units, of which 160 beds were with oxygen supply, 210 with non-invasive ventilation, 42 with access to invasive ventilation. The average annual bed occupancy for 2022 is 270 days. Availability of beds for 10 thousand of us. increased by 2022 from 2.28 to 5.96 - 2 times, however, taking into account the climatic and geographical characteristics of the region and the transport accessibility of medical organizations in certain territories of the republic, a further increase in the bed capacity is required. Today, 12 infectious diseases departments require major overhaul; departments in 7 districts of the Republic of Sakha (Yakutia) need reconstruction.

There are only 34 full-time infectious disease doctors to work in hospitals, of which 91.2% are employed; 28 individuals work in infectious disease departments with an estimated number of 1 doctor for 15 patients.

Since 2021, the Republican Hepatology Center began operating on the basis of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakut Republican Clinical Hospital" - an organizational structure that combines the stages of dispensary observation, hospital and organizational and methodological center. In connection with the unfavorable situation in the territory of Yakutia regarding the incidence of viral hepatitis and their consequences (cirrhosis and liver cancer), a draft target program "Improving methods of providing medical care to patients with chronic hepatitis B, C and D for 2022-2024" has been prepared. in the Republic of Sakha (Yakutia)" with a complex of preventive, diagnostic and therapeutic measures, which will reduce the morbidity and mortality from viral hepatitis and its consequences, such as cirrhosis and liver cancer, leading to disability and premature mortality. The routing of patients with chronic viral hepatitis in the region is regulated by orders of the Ministry of Health of the Republic of Sakha (Yakutia) "On the organization of medical care for patients with chronic viral hepatitis in the Republic of Sakha (Yakutia)", "On the Commission for the selection of patients with chronic viral hepatitis for etiological therapy".

During 2022, 351 people with chronic hepatitis underwent a course of antiviral therapy, 86% were with hepatitis C, the rest with HBV infection, including 47 patients who began antiviral therapy for HD hepatitis with the drug "Bulevirtide". In the future, it is planned to increase the coverage of patients with chronic hepatitis C with etiotropic therapy to 60% by 2025.

Over the past 12 years, 95 orthotopic liver transplantations have been performed in patients with chronic viral hepatitis with cirrhosis (76.8%) and liver

cancer (23.2%). 80 transplants were performed in federal clinics, 15 transplants in the republic.

In 2022, 329 telemedicine consultations on coronavirus infection were conducted, 73 patients with COVID-19 from remote areas of the region were hospitalized, and 34 teleconsultations on other infectious diseases were organized.

Scientific and scientific-practical conferences are systematically held in the republic, including traditional republican schools of hepatologists, well known outside of Yakutia. The event has been held for 22 years with the invitation of leading experts from Moscow, St. Petersburg, Vladivostok, Chelyabinsk and other cities of the country. In total, 891 specialists with higher medical education were trained as part of CME in infectious diseases in 2022. Schools for patients with viral hepatitis are held quarterly at the NEFU clinic; educational work is carried out on an ongoing basis in the media, social networks, and television.

In the Republic of Sakha (Yakutya) February 27, 2023 a comprehensive action plan has been adopted to prevent the spread and treatment of hepatitis C until 2030, which provides for measures to improve the system for identifying and preventing chronic hepatitis C, ensuring registration and provision of medical care, raising awareness and conducting additional professional education for workers of medical organizations and laboratory services, prevention of infection with the hepatitis C virus during the provision of medical care.

The work plan of the Ministry of Health of the Republic of Sakha (Yakutia) “On approval of the Comprehensive Departmental Plan (Road Map) for reducing the mortality rate of the population from infectious diseases in the Republic of Sakha (Yakutia) for 2023-2024” was adopted.

Based on the above, to further limit the spread of infectious diseases and reduce mortality from their consequences, it is necessary:

- implementation of a set of measures to achieve target indicators for the implementation of state programs on HIV infection, tuberculosis;

- ensuring increased infectious alertness in connection with the increase in external biological risks and increased migration flows;

- ensuring readiness for an increase in the incidence of natural focal diseases through vaccination within the framework of calendar according to epidemic indications;

- improvement of diagnosis, observation and recording of patients with infectious pathology;

- integration of testing and treatment of socially significant infectious diseases with other services, decentralization of medical care;

- increasing drug provision for patients with chronic viral hepatitis using all possible sources of financing, incl. within the framework of a regional program;

- increasing the availability of beds and effective management of beds.

Conclusion. The situation with infectious diseases in the Republic of Sakha (Yakutia), despite achievements in the field of healthcare in recent years, remains unstable; there is an increase in the incidence of 20 infectious nosologies. Due to the difficult situation regarding infectious pathology, it is necessary to gradually implement a comprehensive plan for the development of the infectious disease service of the republic with the construction of an infectious diseases hospital and the reconstruction (overhaul) of 95% of the bed capacity. Reorganization of departments is required to increase boxed departments with subsequent redistribution of bed capacity.

There is a need for effective interaction between government agencies and medical organizations at all levels, including with regard to the introduction of restrictive measures and the effective management of forces and resources.

Comprehensive measures are needed to eliminate the personnel shortage, this includes increasing the prestige of the infectious disease doctor profession, creating comfortable working conditions, increasing wages, improving the system of training personnel in infectious diseases, and increasing the number of targeted areas.

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ESTABLISHING PAIN THERAPY MANAGEMENT FOR CANCER PATIENTS IN THE REPUBLIC SAKHA (YAKUTIA)

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One of the most challenging and unresolved problems in modern oncology is the provision of medical care to incurable patients. Chronic pain syndrome is one of the most common phenomena causing severe and agonizing suffering to patients with malignant neoplasms.

As part of the implementation of the comprehensive national program for the development of palliative care in the Russian Federation (Order of the Ministry of Health of the Russian Federation and the Ministry of Labor and Social Protection of the Russian Federation dated May 31, 2019, No. 345n/372n), the authors have developed a project for the establishment of a Pain Management Center at the Yakutsk Oncological Dispensary and pain management rooms at the Ambulatory Oncology Center (AOC).

The regulatory and legal framework has been studied, and a calculation of patients requiring adequate pain relief at the end of life for the year 2022 has been conducted. In this project, the relevance of the topic is demonstrated, and the medical and social significance is justified. A SWOT analysis of the project has been carried out, evaluating the main risks of the project and proposing methods to eliminate and minimize negative consequences.

Keywords: chronic pain syndrome, pain treatment center, pain management office, interventional methods, organizing pain treatment, pain treatment.

Introduction. As of today, despite remarkable achievements in the diagnosis and treatment of malignant neoplasms (MN), according to the projected data from the World Health Organization (WHO), an increase in the incidence and mortality of MN is expected. As a result, there will be a noted rise in patients experiencing pain syndrome [5, 9].

It has been established that chronic pain syndrome (CPS) is encountered in the majority of cases in oncological practice. According to specialized literature, at the initial stages of the tumor process, 35–50% of patients report experiencing pain syndrome, with the progression of the disease, this figure rises to 75% of patients, and in the terminal stage, it reaches 95–100% [5, 7].

According to the Federal Law of November 21, 2011 No. 323-FZ “On the fundamentals of protecting the health of citizens in the Russian Federation,” the Ministry of Health of the Russian Federation (MH RF) approved a regulation on the organization of palliative care [1,2]. In Russia and worldwide, palliative medical care (PMC) as an independent direction in healthcare originated in oncological practice, considering that patients suffering from malignant neoplasms (MN) were in greater need of pain relief [5].

In many developed countries around the world, there has been a specialized pain management service for many years [10-12]. Providing pain relief to those suffering from CHD involves several gradations of levels when this assistance is provided.The gradation of levels is directly related to the specialization of medical professionals and the capabilities of healthcare institutions. It has been observed that the proportion of patients decreases as they move up the hierarchy. For example, in Canada, at the primary care stage, physiotherapists and psychologists work with patients [12]. A specialized guide for primary care physicians on the diagnosis and treatment of CPS has been prepared in France (Agence Nationale d’Accréditation et d’Évaluation en Santé — ANAES). Specialized care for patients with CPS in Canada is provided by neurosurgeons, anesthesiologists, and orthopedic surgeons. In turn, in France, there are algological units, which are interdisciplinary advisory services consisting of three specialists [13]. If it is not possible to provide the necessary assistance, the patient is referred to the next stage in an interdisciplinary pain clinic.

According to the literature, there are approximately 15 pain management centers in the Russian Federation. It has also been established that Russia lags behind European countries in the development of pain management centers and the training of specialists by 20-25 years [6]. In the Sakha Republic, like in all regions of Russia, the organization of pain management is not implemented to its full extent. There are no pain management rooms for both oncological and non-oncological patients in the region, highlighting the relevance of this work.

Materials and Methods: in the Sakha Republic in 2022, there were 2614 cases of newly diagnosed malignant neoplasms (MN), with 1291 (49.4%) in men and 1323 (50.6%) in women. By the end of 2022, 13,286 patients were registered in RS (Y) (compared to 12,560 in 2021). The prevalence rate was 1339.2 per 100,000 population. The distribution of newly diagnosed malignant neoplasms by stages was as follows: Stage 1 — 26.3%, Stage 2 — 22.9%, Stage 3 — 18.6%, Stage 4 — 27.1%. According to the Federal State Statistics Service (Rosstat), the mortality rate from MN in the Sakha Republic remains lower than the national average.

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According to preliminary data from Rosstat in the Republic of Sakha (Yakutia), the mortality rate from malignant neoplasms for 2022 was 126.3 per 100 thousand population (the total number of deaths from cancer was 1201 patients, of which 790 were men, 411 women) [8].

By the Order of the Ministry of Health of the Russian Federation No. 345n and the Ministry of Labor of Russia No. 372n dated May 31, 2019, *"On the Approval of the Regulation on the Organization of Palliative Medical Care, including the Procedure for Interaction between Medical Organizations, Social Service Organizations, and Public Associations, and Other Non-Profit Organizations Operating in the Field of Health Protection"*, indications for the provision of palliative medical care (PMC) to oncological patients have been approved. These indications include the presence of metastatic lesions with a minimal response to specialized therapy or the presence of contraindications to its implementation, the presence of metastatic lesions in the central nervous system, liver, lungs, and the presence of pain and other severe manifestations of the disease [1].

Currently, in oncological practice, determining the need for palliative medical care (PMC) requires taking into account data on the incidence, prevalence, and mortality rates of malignant neoplasms (MN) at the territorial level, as well as the number of MN cases diagnosed at stage IV [6].

As part of this project for the establishment of a Pain Management Center at the Yakutsk Oncological Dispensary and pain management rooms at the Ambulatory Oncology Center (AOC), a calculation was made of the number of oncology patients in need of primary care at the end of life according to WHO recommendations (Global Atlas of Palliative Care at the End of Life. London/Geneva: Worldwide Palliative Care Alliance and World Health Organization, 2014) [5].

$$C = A \times B/100,$$

where A is Overall mortality from diseases (malignant neoplasms), B is Pain prevalence (84%, fixed number), C is Number of patients in need of palliative care

$$C = 1201 \times 84\ \% / 100 = 1009.$$

Based on the data provided, it has been established that in 2022, 1009 end-of-life patients were in need of adequate pain management.

As part of the organizational project to establish a Center and pain management rooms in medical organizations of the Sakha Republic, the authors conducted an analysis of the regulatory and legal framework for providing pain therapy to oncological patients.

A comprehensive set of government documents aimed at expanding the accessibility of pain relief was adopted. These include:

- Federal Law dated December 31, 2014, No. 501-FZ: *"On Narcotic Drugs and Psychotropic Substances"*
- Federal Law dated March 6, 2019, No. 18-FZ: *"On Amendments to the Federal Law on the Basics of Citizens Health Protection in the Russian Federation on Issues of Providing Palliative Medical Care"*
- Government Resolution of the Russian Federation dated August 6, 2015, No. 807: *"On Amendments to Certain Acts of the Government of the Russian Federation on Issues Related to the Circulation of Narcotic Drugs, Psychotropic Substances, and their Precursors"*.

This resolution also includes the recognition of the obsolescence of paragraph 3 of the Regulation on the Use of Narcotic Drugs and Psychotropic Substances in Veterinary Medicine [2, 3, 10].

An analysis of the availability of pain relief in providing palliative medical care, including the use of narcotic drugs and psychotropic substances in the Sakha Republic, has been conducted. The organization authorized to engage in activities involving the circulation of narcotic drugs and psychotropic substances in the Sakha Republic is the Sakhafarmatsiya LLC.

As of 2022, there are 343 organizations in the Sakha Republic that dispense narcotic and psychotropic substances to individuals. These points are organized across 33 administrative-territorial entities, including 158 rural health posts, 10 paramedic posts, and 175 medical outpatient clinics [5].

As of today, there is a trend towards an increase in the number of patients in the Stage 4 clinical group among all patients under dispensary observation in oncological institutions in the Russian Federation. It should be noted that based on this trend, the number of patients in need of palliative medical care will steadily grow [6, 10].

Results: In the context of this scientific work, a project has been developed by us for the establishment of a Center and pain management rooms in medical organizations of the Sakha Republic for oncological patients. This initiative is proposed to be implemented at the Yakutsk Oncological Dispensary and the Ambulatory Oncology Center. Figure 1 shows the organizational model of the project.

The project's Strengths and weaknesses of the project were determined using a SWOT analysis (Table 1).

To achieve our project's goal, we need to complete the following tasks:

1. Developing a complex of organizational and methodological measures, including:

- Approving local regulatory acts on the organization of pain management rooms and the Pain Management Center
- Issuing and approving an organizational order
- Obtaining a license for providing palliative medical care.
- Approving job responsibilities for staff
- Adjusting the staffing schedule

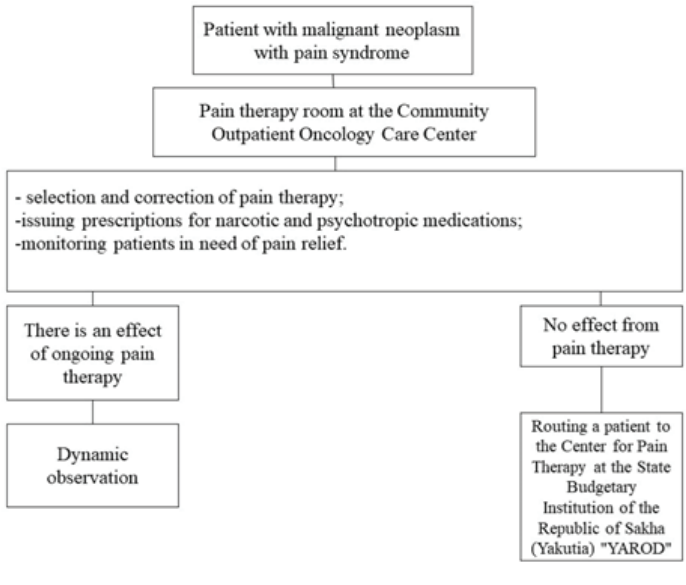

Fig. 1. Project organizational model

of the Ambulatory Oncology Center and the Yakutsk Oncological Dispensary

- Approving the patient routing algorithm for patients with oncological chronic pain to the Pain Management Center at the Yakutsk Oncological Dispensary

2. Establishing the organization's material and technical base:

- Allocating and preparing pain management rooms
- Equipping the rooms (procuring the necessary equipment and inventory)

3. Organizing the Pain Management Center and rooms at the Yakutsk Oncological Dispensary and the Ambulatory Oncology Center in the Sakha Republic:

- Staff training (training programs for professional development in leading scientific centers of the Russian Federation through on-site, distance, and mixed forms of training)
- Approving the operation of pain management rooms and the Pain Management Center (working hours, scheduling)
- Implementing new methods of minimally invasive surgical treatment of chronic pain syndrome to enhance pain management services

Additionally, within the project management framework, we have conducted an assessment of foreseeable risks and methods for their mitigation (see Table 2).

In the pain management rooms at the Ambulatory Oncology Center, appointments will be conducted by general practitioners or oncologists who have undergone advanced training courses in Palliative Care or courses in pharmacotherapy for chronic pain syndrome in oncology patients. At the Pain Management Center at the Yakutsk Oncological Dispensary, appointments will be handled by a surgeon or neurosurgeon who has completed advanced training in Palliative Care. Interventional surgical methods for treating chronic pain syndrome will be carried out in the day hospital of the Radiosurgical Diagnostic and Treatment Methods Department (RDTMD).

The treatment of pain syndrome in patients with malignant neoplasms will

Table 1

Project's SWOT analysis of the project to create a Center and Pain Management Rooms at the Yakutsk Oncological Dispensary and the Ambulatory Oncology Center

Strengths	Weaknesses
Yakutsk Oncological Dispensary Structural Unit	Lack of a state program for the study and treatment of CPS in cancer patients
Current lack of pain managements centers or rooms in the Sakha Republic	Lengthy bureaucratical process of coordinating all organizational issues when creating a pain management service
Modern medical equipment in the Yakutsk Oncological Dispensary for conducting interventional surgical methods for the treatment of CPS	Lack of regulations regarding pain management services
Inclusion of CPS into ICD-11 as a standalone disease	Lack of funding sources
Guaranteed influx of patients with CPS	Insufficient number of qualified specialists and lack of state specialized centers/rooms for chronic pain syndrome management
Highly qualified medical personnel	Lack of reliable information among the population about the causes of chronic pain, as well as methods of its prevention and treatment
High-tech medical services for the treatment of chronic pain syndrome	Vast territory of the Sakha Republic

Table 2

Risk Assessment when Organizing a Center and Pain Management at the Yakutsk Oncological Dispensary and the Ambulatory Oncology Center

Risk	Assessment	Ways to Eliminate and Minimize Negative Consequences
External Risks		
Risk of failure to obtain relevant government approvals	High	Compliance with all requirements for medical services
Internal Risks		
Decreased quality of services as a result of insufficient staff experience	Medium	Hiring only highly qualified personnel
Lack of own funds to finance the project	Medium	Maintaining a minimum monetary reserve
Equipment failure	High	Acquiring warranty service agreements
Lack of an effective management system or decreasing quality of management	Low	Constant monitoring of the Medical Center's activities
Difficulties with recruiting qualified personnel	Medium	Maintaining high salary levels
Energy outages	Low	Installing an uninterruptible power supply system
Inventory decline	Medium	Maintaining the minimum required amount of inventory

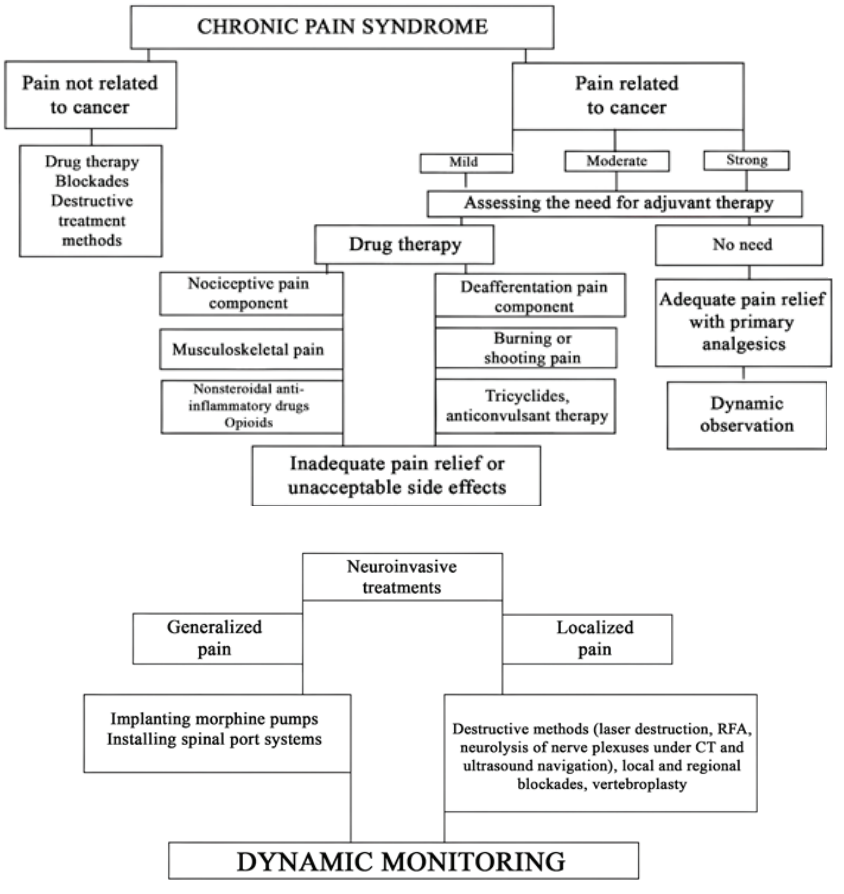

Fig. 2. Algorithm of interventional methods of surgical treatment of chronic pain syndrome in cancer patients

be provided at both early and advanced stages of the disease, as well as during the postoperative period and throughout the entire course of treatment for the primary illness. Additionally, treatment for pain syndrome unrelated to the primary disease will be administered.

Pain Management Rooms are tasked with the following responsibilities:

1. Treating chronic pain syndrome and other severe manifestations associated with malignant neoplasms
2. Selecting analgesic therapy, prescription of medications, including narcotic and psychotropic drugs
3. Monitoring patients in need of pain management
4. Referring patients to the Pain Management Center at the Yakutsk Oncological Dispensary for persistent pain syndrome resistant to pharmacotherapy to provide interventional surgical treatment for chronic pain syndrome.

The Pain Management Center will primarily focus on selecting patients for interventional surgical methods, and the list of interventions performed is indicated in Figure 2.

Also, within the framework of this project, tasks have been formed that must be completed to implement this work:

1. Developing the financial plan for the project
2. Calculating the expenses required for organizing the training of medical personnel and equipping workplaces
3. Establishing telemedicine consultations for the Pain Management Center and Rooms

As follows, this scientific work on organizing pain management for oncology patients in the Sakha Republic requires refinement in terms of assessing economic efficiency and legal protection before being implemented in practical activities.

Conclusion: the project we have presented for organizing pain management for oncology patients in the Sakha Republic is designed to improve the quality of life for patients and their families in the region. The effective work of this project will make it possible to receive specialized pain care in remote and hard-to-reach areas of the Republic of Sakha (Yakutia).

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PRIMARY MORBIDITY IN THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA) FOR THE PERIOD 2005-2021

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The article presents an analysis of the primary morbidity of the population in the Republic of Sakha (Yakutia). The purpose of the study was to conduct a comparative assessment of primary morbidity indicators for the entire population of the Republic of Sakha (Yakutia) by disease class with similar average Russian indicators. At the same time, the morbidity rate for the period 2005-2021 was analyzed. The percentile method was used to determine morbidity levels. As a result, classes of diseases were identified that had high levels throughout the Russian Federation during the period under review. In this regard, the following classes of diseases are distinguished: diseases of the nervous system, eyes and its appendages, diseases of the respiratory and digestive organs, diseases of the skin and subcutaneous tissue, injuries, poisoning and some other consequences of external causes. The points for applying the efforts and resources of health care authorities and medical organizations of the republic to improve public health indicators are becoming obvious.

Keywords: primary morbidity, primary morbidity by disease class, Republic of Sakha (Yakutia), morbidity in the population of the Russian Federation.

Introduction. State and regional authorities of the Russian Federation are making considerable efforts to improve the health status of the population. This is evidenced, in particular, by the currently existing National Health and Demographic Projects and the State Health Care Development Program until 2024. At the same time, identifying those classes and types of diseases that are problematic in certain regions is of no small importance. We have set this task for our republic. At the same time, the following goal of the study was determined: to conduct a comparative assessment of primary morbidity indicators of the entire population of the Republic of Sakha (Yakutia) by disease class with similar average Russian indicators.

Materials and methods of research. The materials of official statistics were analyzed: the Federal State Statistics Service (Federal State Statistics Service or Rosstat) and the Yakut Republican Medical Information and Analytical Center (YRMIAC) [1, 2]. When analyzing population morbidity, the percentile method was used. According to this method, regions with indicators up to the 10th percentile were classified as territories with a low level of one or another morbidity indicator, from the 10th to 25th percentile - with a level below average, from 75 to 90th - above average and above 90- th percentile – with a high level. It is obvious that regions with indicators ranging from the 25th to 75th percentiles belonged to groups with average values.

Results and discussion. The analysis revealed the level of primary morbidity of the entire population for 2005 and 2010-2021 for the main classes of diseases [1, 2]. Table 1 presents primary morbidity indicators for the entire population of the Russian Federation and the Republic of Sakha (Yakutia) (registered diseases in patients diagnosed for the first time in their lives).

As stated, morbidity rates were determined using the percentile method for all subjects of the Russian Federation, including the Republic of Crimea and the city of Sevastopol since 2014, and the Arkhangelsk and Tyumen regions were assessed without taking into account the autonomous okrugs. We conducted similar studies earlier [3].

Thus, if in 2005 the republic was among the territories with an above-average level of primary morbidity in general, then in 2010-2019 was already at a high level. At the end of 2017, this figure in the Republic of Sakha (Yakutia) was 31.2% higher than the Russian average.

For infectious and parasitic diseases during the period under review, the morbidity rate in the republic was average, not counting 2012 and 2020 (the level was below average). For neoplasms, an average morbidity rate is noted for all years, not including 2020.

For diseases of the blood and hematopoietic organs, the morbidity rate in 2005 and in 2010-2014 was above average. And for diseases of the endocrine system, a motley picture emerges: in 2005, 2010-2011, 2013 there was a high level, in 2012 and 2014 - above average, in 2016 and 2021 - below average, and in 2017-2018 and in 2020 – a low morbidity rate for this class of diseases.

For diseases of the nervous system in 2005, 2010-2016 there was a high morbidity rate, and in 2017-2019 and in 2021 the level is above average. Eye diseases: only in 2017-2018. and in 2020, the indicator can be attributed to the average level for the country; in the remaining years under review, levels above average and even high were noted (2010, 2013-2014). For ear diseases, the picture is more favorable, and in some years (2011-12 and 2016-2018) the morbidity rate was below average.

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Table 1

Primary morbidity of the entire population of the Russian Federation and the Republic of Sakha (Yakutia) in 2005. 2010-2021. (per 1000 people)

	2005	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Primary morbidity per 1000 population													
RF	743.7	780.0	796.9	793.9	799.4	787.1	778.2	785.3	778.9	782.1	780.2	759.9	857.1
RS (Y)	881.7	1023.4	1047.4	1066.5	1107.0	1098.1	1026.6	1043.8	1021.1	1015.3	1032.9	899.6	1053.8
Some infectious and parasitic diseases													
RF	37.3	32.8	32.4	32.1	30.9	30.8	28.1	27.9	27.3	27.0	26.6	20.5	21.4
RS (Y)	32.6	30.5	27.0	27.9	34.7	32.6	26.7	28.2	26.9	29.1	26.3	16.2	18.0
Neoplasms													
RF	9.5	10.8	11.1	11.6	11.4	11.6	11.4	11.4	11.4	11.6	11.9	9.8	10.2
RS (Y)	9.1	10.7	11.3	11.9	12.1	11.1	12.2	10.4	10.5	9.5	10.6	6.9	9.1
Diseases of the blood. hematopoietic organs and certain disorders involving the immune mechanism													
RF	4.5	4.9	4.7	4.7	4.7	4.7	4.7	4.7	4.5	4.3	4.2	3.3	3.5
RS (Y)	6.1	5.8	5.6	5.3	6.1	5.6	4.8	4.3	3.3	3.8	4.1	2.7	3.6
Endocrine system diseases. nutritional disorders and metabolic disorders													
RF	9.6	10.2	10.3	10.6	10.6	11.2	13.3	13.9	14.0	13.1	14.4	11.0	11.4
RS (Y)	15.7	16.7	15.9	14.7	20.3	15.7	12.6	9.2	6.6	8.2	13.1	6.4	8.4
Nervous system diseases													
RF	15.3	16.4	16.5	16.3	16.5	16.2	15.4	15.2	15.0	14.8	14.8	12.5	13.5
RS (Y)	27.8	32.0	32.6	33.9	36.7	36.6	28.7	22.7	18.7	18.7	19.1	14.6	18.5
Diseases of the eye and its adnexa													
RF	33.6	33.0	33.3	35.2	35.0	34.7	33.3	32.6	31.6	31.4	30.0	23.9	24.9
RS (Y)	46.0	49.5	47.3	49.6	50.2	52.9	40.2	39.5	33.3	32.8	34.2	22.9	29.3
Diseases of the ear and mastoid process													
RF	24.1	27.1	27.8	28.2	28.0	27.7	26.6	26.3	25.9	25.5	25.0	20.5	21.3
RS (Y)	22.5	25.4	23.8	24.0	24.9	26.7	25.6	21.5	21.1	21.0	23.6	15.0	17.6
Diseases of the circulatory system													
RF	23.0	26.1	26.6	26.6	29.9	28.8	31.2	31.7	32.1	32.6	35.0	29.4	30.5
RS (Y)	26.8	29.8	30.1	31.8	37.6	33.2	25.9	22.0	20.2	24.2	32.8	18.9	22.8
Respiratory diseases													
RF	294.4	324.0	338.8	330.9	338.4	333.4	337.9	351.6	353.5	359.8	356.2	370.6	407.1
RS (Y)	351.2	461.5	488.8	491.5	490.6	493.9	500.4	538.5	565.6	570.0	579.8	500.1	559.0
Digestive diseases													
RF	35.4	33.4	33.3	34.8	35.2	36.6	35.3	35.6	34.0	33.1	32.0	26.3	26.9
RS (Y)	71.0	77.7	83.1	87.0	95.9	94.4	78.6	71.0	58.3	55.7	51.3	43.4	49.1
Diseases of the skin and subcutaneous tissue													
RF	49.7	48.2	47.5	48.0	47.0	46.3	44.0	42.5	41.0	40.3	40.7	34.0	35.6
RS (Y)	56.7	60.2	62.7	62.2	63.9	62.2	55.4	55.6	51.6	45.2	43.3	33.5	37.9
Diseases of the musculoskeletal system and connective tissue													
RF	33.3	33.5	33.6	33.2	32.3	31.8	30.1	29.5	29.5	29.8	30.3	25.0	26.7
RS (Y)	33.9	36.7	36.6	40.4	40.9	38.7	26.9	31.0	24.5	25.6	26.3	23.7	30.1
Diseases of the genitourinary system													
RF	46.1	47.9	49.3	49.6	49.8	49.0	46.4	45.6	44.8	44.8	44.5	36.0	36.9
RS (Y)	50.1	50.9	51.5	52.2	59.4	59.0	49.7	47.4	37.3	35.8	36.2	27.8	30.7
Congenital anomalies (malformations). deformations and chromosomal disorders													
RF	1.7	2.1	2.1	2.1	2.1	2.1	2.0	2.1	2.0	2.0	2.0	1.7	1.7
RS (Y)	2.1	2.2	2.1	2.7	3.1	3.0	2.7	2.4	1.8	1.6	2.8	1.7	2.3
Injuries. poisoning and some other consequences of external causes													
RF	90.0	91.7	92.8	93.8	92.6	90.2	90.4	89.1	88.2	89.0	90.4	81.3	83.6
RS (Y)	93.7	104.0	101.8	106.5	103.1	105.0	105.3	112.6	117.7	112.2	107.1	95.9	101.5

Legend:

20.3	high morbidity rate
15.7	morbidity rate is above average
8.4	Morbidity rate is below average
6.4	low morbidity rate

Table 2

Primary morbidity of the entire population in the Russian Federation and the Republic of Sakha (Yakutia) in 2016 2017. (per 100,000)

Classes of diseases	RF		RS (Yakutia)	
	2016	2017	2016	2017
Mental and behavioral disorders	442.5	416.9	483.8	380.5
Pregnancy, childbirth and the postpartum period*	6307.9	6072.5	6504.8	5407.3
Symptoms, signs and abnormalities identified during clinical and laboratory tests, not classified elsewher	92.1	95.6	4.8	-

* The indicator is calculated for the female population (10-49 years old)

The picture regarding diseases of the circulatory system is ambiguous. So, if in 2012-2013 the morbidity rate was above average, then in 2016-2018 and in 2020 the level became below average or even low. The situation with respiratory diseases is more clear: only in the mid-2000s the level was above average, in other years since 2010 it was high. And for diseases of the digestive system, everything is clear: for all years there has been a high morbidity rate, with the exception of 2020, when the level was above average.

Diseases of the skin and subcutaneous tissue: during 2010-2017. There are above average and high (2013-2014) morbidity rates. For diseases of the musculoskeletal and genitourinary systems, the indicators are within average values, excluding 2013-2014, when the level was above average for both classes. For congenital anomalies, above-average rates were observed not only in 2013-2014, but also in 2019 and 2021.

In the class “Injuries, poisonings and some other consequences of external causes”, recent years have caused concern: since 2016, indicators have been above average, and in 2017 there was even a high level of injuries and poisonings.

For a number of other classes, we previously assessed the morbidity rate according to the data of the Ministry of Health of the Russian Federation (Table 2) [3]. Thus, for mental disorders and behavioral disorders, as well as for complications of pregnancy, childbirth and the postpartum period, the indicators were within the average level. And in the class “Symptoms, signs and deviations from the norm, identified during clinical and laboratory tests, not classified in other headings,” which largely characterizes the quality of all medical care in a particular region, the republic’s indicators were not bad - the level was low.

Conclusion. Thus, based on the comparative characteristics of the levels of primary morbidity of the population of the Republic of Sakha (Yakutia) with similar indicators of all regions of the Russian Federation for the period 2005, 2010-2021. The following conclusions can be drawn.

1. In terms of primary morbidity of the entire population, the Republic of Sakha (Yakutia) is consistently among the subjects of the federation with the most unfavorable level of this indicator, and in 2010-2019. The republic was part of the group of regions with a high morbidity rate.

2. By disease class (entire population): relatively high rates are observed in such classes as diseases of the blood, hematopoietic organs and endocrine system (2005, 2010-2014), diseases of the nervous system (2005, 2010-2019 and 2021), respiratory and digestion (2005, 2010-2021), diseases of the skin and subcutaneous tissue (2010-2017), eye diseases (2005, 2010-2016, 2019 and 2021), congenital anomalies (malformations) (2013-2014, 2019 and 2021), injuries and poisonings (2015-2021). In addition, for diseases of the musculoskeletal and genitourinary systems in 2013-14 higher than average morbidity rates were observed.

3. Thanks to the efforts of the republic’s health authorities and institutions, relevant specialized services and specialists, it was possible to correct the situation and improve indicators in the second half of the 2010 and the beginning of the 2020 for the following classes of diseases: Diseases of the endocrine system, nutritional disorders and metabolic disorders; Diseases of the circulatory system.

4. We hope that the presented data will help to apply the efforts and resources of health authorities, institutions and services to the most problematic issues of public health in the Republic of Sakha (Yakutia).

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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CONTENT OF HORMONES IN THE POPULATION OF SOUTH YAKUTIA WORKING IN AN AREA WITH NATURAL RADIATION

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A study of the level of hormones in the blood serum was carried out in 173 residents of the Aldan region aged from 22 to 75 years, of which 65 (39.8%) were men and 108 (60.2%) women, the average age was 44.0 (35. 0; 52.0) years. In the working population, there is functional tension of the pituitary-thyroid link, characterized by a higher frequency of occurrence of thyroid hormone levels below the normal T3total. in 27.2%, T3f. in 19.3% and T4f. in 11.6% of people, more pronounced in women. Increased concentrations of thyroid hormones T3f., T4f. and T4tot. observed with age, T3total and T4total in people with an increased body mass index. The presence of increased levels of antibodies to thyroid peroxidase in 18 (10.4%) people indicates a strained immune system, therefore it is recommended to include endocrinological examinations in periodic medical examinations

Keywords: radon, endocrine system, thyroid hormones, cortisol, South Yakutia.

Introduction. The largest uranium ore deposit in Russia is located in the Aldan region. The study and development of the territories of the Central Aldan gold-uranium mining region, in which the Elkon gold-uranium, Lebedinsky and Kuranakh gold mining nodes are identified, with the extraction of minerals has led to the emergence of centers of radioactive contamination (uranium ore dumps, mine workings). The ecological and geological assessment of the area is characterized as satisfactory for 53.5% of its territory, tense for 39.6% and crisis for 6.9%.

The maximum values of the exposure dose rate of gamma radiation in some areas are 1600-2150 μR/h (micro-roentgen per hour), the specific effective activity of natural radionuclides is 20441-23640 Bq/kg, and the uranium content is 1637-1888·10-4 mg/ kg2, which exceeds the background levels by almost 1000 times [12]. In the mountain taiga landscapes of the region, radiation varies from 30 to 50 μR/hour (in Central Yakutia the normal radiation background is 15 μR/hour) and contamination of wild plants (moss, berries and mushrooms) with natural radionuclides uranium - 238 and radium - 226 is noted [5 ,13]. Regular consumption of forest products with a high content of radionuclides can result in higher doses of internal radiation in individual citizens [8].

In the air of 46 premises located on the territory of the Aldan region, an excess of sanitary standards for radon content was noted (Rn222-429±86 Bq/m3) [14].

Radon is a radioactive gas and is a carcinogen; its radioactive particles, when accumulated in the body, can negatively affect human health, damage the DNA structure of cells, cause pathological processes, lung cancer, hormonal changes and increase mortality [1; 17]. It has been established that in the settlements of the Aldan mining region there has been a steady trend of deterioration in the health of the population [13].

The impact of climatic and environmental factors among residents of the North is accompanied by tension in adaptation processes, which is particularly manifested in the activation of the pituitary-thyroid system [9]. Thyroid hormones (T4 and T3) play an important role in maintaining the homeostasis of the internal environment, the normal functioning of all organs and systems (growth, development of the body, energy supply to organs and tissues, myocardial contractility, intestinal motility, etc.) [4]. Changes in the levels of thyroid hormones can disrupt the functioning of most organs and systems (musculoskeletal, cardiovascular and nervous systems, gastrointestinal tract) [2].

Therefore, for the timely development and implementation of measures for the prevention of chronic non-infectious diseases, the study of the state of the pituitary-thyroid system in residents living in areas with natural radiation is relevant.

The purpose of the study was to assess the level of thyroid hormones and cortisol in residents of the Aldan region.

Materials and methods. The study involved 173 residents from the city of Aldan and the city of Tommot, Aldan district, aged from 22 to 75 years, the average age was 44.0 (35.0; 52.0) years, of which 65 were men (39.8%) and women - 108 (60.2%), average age - 45.0 (35.0; 53.0) years, and 42.0 (36.0; 51.0) years, respectively. The study was carried out within the framework of the research work at the Federal State Budgetary Scientific Institution "Yakut Scientific Center for Medical Problems" "Regional characteristics of biochemical, immunological and morphological parameters in the indigenous and newcomer population of the Republic of Sakha (Yakutia) in health and pathology" (FGWU-2022-0014) and

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the research work of the Academy of Sciences of the Republic of Sakha (Yakutia) "Evaluation levels of exposure of the population of the Aldan region due to natural sources of exposure and recommendations for carrying out protective measures to reduce them." The study was carried out with the informed consent of the subjects and was approved by the decision of the Local Ethics Committee at the Federal State Budgetary Institution "YSC KMP".

Blood sampling from all subjects was carried out in the morning (8-11 a.m.) on an empty stomach from the ulnar vein into a vacutainer with a coagulation activator, in a state of relative muscle rest.

Analysis of the levels of thyroid hormones (triiodothyronine-T3free, T3total, thyroxine-T4total, T4free), thyroid-stimulating hormone (TSH), thyroglobulin (TG), antibodies to thyroglobulin (anti-TG), antibodies to thyroid peroxidase (anti-TPO) and cortisol was carried out in blood serum by enzyme-linked immunosorbent assay (ELISA) on a Uniplan photometer using standard Vector Best kits (Russia), according to the manufacturer's instructions.

Body mass index (BMI) was calculated using the formula: BMI (kg/m²) = body weight (kg)/height (m²) [11].

Statistical processing of the data was carried out using the IBM SPSS Statistics 23 application package. Standard methods of variation statistics were used: calculation of average values (M), error of the average (m). The normality of distribution was checked by the Kolmogorov-Smirnov method. In the case of a normal distribution of quantitative indicators, the t-Student test was used to evaluate statistical hypotheses, and in the case of deviation from the normal distribution, the Mann-Whitney U test was used. The assessment of relationships between variables was carried out using the paired correlation method using Pearson (for metric variables) and Spearman criteria (for variables measured on a rank scale), where r is the correlation coefficient, p is the significance of the result.

Results and discussion. An analysis of the hormone levels in the residents of Aldan and Tommot in the pituitary-thyroid system showed that the average hormone level in the examined residents of the Aldan region varied within the reference values and did not have significant differences by gender (Table 1).

However, the levels of T3tot., T3st. were shifted to the lower limit of normal, which may be a criterion for a decrease in thyroid reserves. In residents of the North, the tension in the functional state of the pituitary-thyroid system can be contributed to by a natural lack of iodine, which is characteristic of the population of Siberia [7]. Inhibition of the functional activity of the thyroid gland (increased concentration of thyroid-stimulating hormone, decreased level of thyroxine, triiodothyronine), according to literature data, was noted among the population of patients with nodular goiter who were exposed to radiation in the past. [6].

Quantity T3tot. is often indicative of questionable results of T3 light tests, which are carried out to determine thyroid dysfunction in humans. The level of free hormones is less than 0.1% of their total amount, but it is the free fraction of hormones that is the most biologically active and it is this fraction that provides all the effects of thyroid hormones. The main point of application for triiodothyronine is DNA in combination with its receptors in the cell nucleus. Here, T3 activates transcription, synthesis of RNA and enzyme proteins involved in the body's most important metabolic reactions, including under stress; with its direct and irreplaceable participation, the processes of cell proliferation and differentiation occur [9].

Thyroxine is the main thyroid hormone and is produced only by thyroid cells. T4general is a total indicator of bound and free fractions of thyroxine. Most of T4 is in a state bound to transport proteins and is biologically inactive. All the main functions are performed by T4, circulating in the plasma in free form: it increases basal metabolism, supports energy metabolism, stimulates and normalizes processes in the central nervous system,

Table 1

Indicators of hormone levels in residents of the Aldan region

Indicator	Average value (M±m)		
	Total n=173	Men n=65	Women n=108
T3tot.(1.3-3.0 n/mol/l)	1.6±0.45	1.55±0.05	1.64±0.07
T3free (4-8.6 pmol/l)	4.82±0.104	5.04±0.16	4.54±0.14
T4total (52-155 nmol/l)	103.36±2.26	101.39±2.96	106.44±2.97
T4free (10.3-24.5 pmol/l)	15.13±0.28	15.29±0.37	14.66±0.45
TG (<50ng/ml)	7.16±1.11	5.81±1.85	9.13±1.69
TSH (0.4-5 mIU/l)	2.19±0.18	1.98±0.14	2.42±0.32
Anti-TG (up to 100IU/ml)	8.15±1.23	6.77±1.52	9.39±1.87
Anti-TPO (up to 30 U/ml)	15.63±3.56	11.62±5.12	18.07±4.81
Cortisol(190-690 nmol/l)	388.86±13.10	422.57±23.23	352.31±16.45 p=0.019

Table 2

Hormone levels depending on age

Indicator	Age group		
	1 group n=93	2 group n=64	3 group n=16
T3tot.(1.3-3.0 n/mol/l)	1.56±0.47	1.67±0.10	1.44±0.05
T3free (4-8.6 pmol/l)	4.51±0.13	5.03±0.19 p_{1-2}=0.037	4.69±0.20
T4tot. (52-155 nmol/l)	99.26±2.44	108.52±3.76	121.86±7.38 p_{1-3}=0.012 p_{2-3}=0.075
T4free (10.3-24.5 pmol/l)	14.50±0.34	15.25±0.60	16.81±0.54 p_{1-3}=0.012
TG (<50ng/ml)	7.06±1.49	8.63±2.35	6.49±1.33
TSH (0.4-5 mIU/l)	1.89±0.10	2.73±0.47 p_{1-2}=0.022	2.03±0.30
Anti-TG (up to 100IU/ml)	6.79±1.24	8.74±2.33	14.83±6.76
Anti-TPO (up to 30 U/ml)	12.73±4.60	20.84±6.52	12.49±10.12
Cortisol(190-690 nmol/l)	360.69±19.1	386.79±21.58	448.00 ±44.24

Note: 1-young (20-44 years old); 2-middle age (45-59 years); 3-elderly (60-74 years old)

and promotes bone tissue renewal. The effect of thyroid hormones on various parts of endocrine regulation depends on their concentration: in physiological doses they have an anabolic effect, in large doses they have a catabolic effect [16].

Thyroid-stimulating hormone is synthesized by the anterior pituitary gland and is the main regulator of the thyroid gland. TSH stimulates the synthesis of T3 and T4 by thyroid cells and their release into the blood. The synthesis and secretion of TSH is stimulated by thyroliberin, a hypothalamic peptide that is produced when the level of thyroid hormones in the bloodstream is low. Elevated levels of T3 and T4 suppress TSH secretion through a classical negative feedback mechanism [10]. This mechanism maintains a constant level of thyroid hormones, as well as metabolic stability. When connections between the thyroid gland, hypothalamus and pituitary gland are disrupted, the functioning of the endocrine glands is disrupted. Situations arise when, with high levels of T3 and T4, thyroid-stimulating hormone continues to increase.

The average TSH concentration varied within normal limits, elevated levels of TSH and TG were noted in 2 (1.2%) and 5 (2.9%) people, respectively, while elevated anti-TG levels of more than 100 IU/l were not detected. (Table 4), which is a favorable sign for the diagnosis and treatment of malignant neoplasms of the thyroid gland.

It has been proven that elevated TSH levels are associated with a higher risk of developing well-differentiated thyroid cancer and its more aggressive clinical course, manifested by a higher frequency of advanced stages of the tumor. A long-term increase in TSH stimulates the growth of residual thyroid tissue and tumor foci [3;18].

Thyroglobulin is a protein that is produced by the follicles of the thyroid gland. TG contains iodine, from which two main hormones are subsequently synthesized - thyroxine and triiodothyronine. Normally, the thyroid gland produces a small amount of TG. A significant increase in the level of TG in the blood is observed during tumor processes in the thyroid gland, so this indicator in some cases can serve as a tumor marker. Determination of serum TG biomarkers together with anti-TG is the only clinically recommended method for timely diagnosis of relapse of thyroid malignancies and treatment monitoring [3]. In benign diseases characterized by dysfunction of the thyroid gland (inflammation of the thyroid tissue - thyroiditis, Graves' disease or Basedow's disease, Hashimoto's thy-

Table 3

Hormone levels depending on body mass index

Indicator	Body mass index				
	1 group n=48	2 group n=62	3 group n=36	4 group n=14	5 group n=6
T3tot.(1.3-3.0 n/mol/l)	1.48±0.04	1.62±0.11	1.60±0.07	1.92±0.11 p_{1-4}=0.026	1.63±0.17
T3free (4-8.6 pmol/l)	4.35±0.19	4.86±0.18	5.15±0.23 1-3=0.033	4.57±0.48	4.46±0.32
T4tot. (52-155 nmol/l)	98.40±3.40	100.93±3.56	114.37±4.22 p_{1-3}=0.010 p_{2-3}=0.036	113.27±9.85	108.94±11.89
T4free (10.3-24.5 pmol/l)	14.19±0.47	15.48±0.61	15.78±0.52	12.39±0.97 p_{2-4}=0.025 p_{3-4}=0.011	15.36±1.55
TG (<50ng/ml)	6.23±2.59	7.82±1.96	5.01±1.47	16.75±6.95 p_{1-4}=0.025 p_{3-4}=0.019	15.18±6.18
TSH (0.4-5 mIU/l)	1.93±0.15	2.39±0.41	2.12±0.23	2.95±1.40	2.45±0.24
Cortisol (190-690 nmol/l)	363.62±26.46	381.94±23.09	426.62±30.33	341.13±29.87	308.72±60.1

Notes: 1-normal weight, BMI < 25; 2-overweight, BMI 25–29.9; 3-obesity I degree, BMI 30–34.9; 4-class II obesity, BMI 35–39.9; 5—grade III obesity, BMI >40.

Table 4

Frequency of hormonal imbalances in men and women in Aldan region, n/%

Indicator	Total	gender		Pearson chi-square	df	p
		Men	Women			
T3tot.(1.3-3.0 n/mol/l)						
1	47/27.2	20/30.8	27/25.0	1.231	2	0.540
2	125/72.3	45/69.2	80/74.1			
3	1/0.6	-	1/0.9			
T3free (4-8.6 pmol/l)						
1	33/19.1	8/12.3	25/23.1	5.121	2	0.077
2	139/80.3	57/87.7	82/75.9			
3	1/0.6	-	1/0.9			
T4tot. (52-155 nmol/l)						
1	-	-	-	0.929	1	0.335
2	164/94.8	63/96.9	101/93.5			
3	9/5.2	2/3.1	7/6.5			
T4free (10.3-24.5 pmol/l)						
1	20/11.6	4/6.2	16/14.8	3.584	2	0.167
2	152/87.9	61/93.8	91/84.4			
3	1/0.6	-	1/0.6			
TG (<50ng/ml)						
1		-	-	0.663	1	0.416
2	169/97.1	64/98.5	104/96.3			
3	5/2.9	1/1.5	4/3.7			
TSH (0.4-5 mIU/l)						
1	-	-	-	1.207	1	0.272
2	171/98.8	65/100	106/98.1			
3	2/1.2	-	2/1.9			
Anti-TPO (up to 30 U/ml)						
1	-	-	-	1.474	1	0.225
2	155/89.6	60/92.3	95/88.0			
3	18/10.4	5/7.7	13/12.0			
Anti-TG (up to 100IU/ml)						
2	173/100	64/100	109/100			

Note: 1-level below normal; Level 2 is normal; 3-level above normal.

roiditis), the TG level can also increase, and the disease can be accompanied by a decrease (hypothyroidism) or an increase (hyperthyroidism, thyrotoxicosis) in thyroid function. TG synthesis is under the control of TSH.

Antithyroglobulin antibodies (anti-TG) are specific immunoglobulins directed against the precursor of thyroid hormones. They are a specific marker of autoimmune thyroid diseases (Graves disease, Hashimoto's thyroiditis). The cells of the thyroid gland are collected in follicles, in which a protein specific only to this organ accumulates - thyroglobulin, which contains iodine. Subsequently, thyroid cells produce thyroxine and triiodothyronine from it. Sometimes thyroglobulin becomes a target for the immune system: antibodies (anti-TG) begin to be produced against it - the reason for this process is still precisely unknown. As a result, the normal synthesis of thyroid hormones from this protein is significantly disrupted: in some cases it decreases, in others it increases.

Correlation analysis showed a direct connection between the levels of T3free, T4free., T4tot. with age (r=0.190; p=0.012), (r=0.227; p=0.003), (r=0.202; p=0.007) and T3tot., T4tot. with body mass index (r=0.168; p=0.031), (r=0.216; p=0.005)

Depending on age, the subjects were divided into 3 groups: 1 - young (20-44 years), 2 - middle age (45-59 years), 3 - elderly (60-74 years). An increase in hormone levels was noted in the 2nd age group: T3 free by 10.3% (p=0.037) and TSH and 30.7% (p=0.022) compared with the 1st (Table 2), in the 3rd age group T4total. and T4 free by 18.54% and 10.9% in comparison with the 1st and 2nd age groups, respectively (Table 2).

Depending on body mass index, the subjects were divided into 5 groups: 1-normal weight, BMI < 25, 2-overweight, BMI 25–29.9, 3-I degree obesity, BMI 30–34.9, 4-obesity II degree, BMI 35–39.9, 5-obesity III degree, BMI >40. The average content of hormones in blood serum in all groups varied within the reference values. However, in persons of the 3rd group there is a slight increase in the concentration of some hormones: T3f. by 19.8%, T4tot. by 13.7% compared to group 1 and T4tot. by 11.7%, compared with group 2 (Table 3).

In the 4th group, an increase in T3total was noted. by 22.9%, TG by 62.8% in comparison with the 1st group and TG by 70% in comparison with the 3rd group. Level T4f. in this group with II degree obesity was the lowest, in comparison with the 2nd, 3rd groups by 20 and 21.5%, respectively (Table 3).

Analysis of the frequency of occurrence of hormonal disorders showed that the most pronounced deviations in the content of T3total. (reduced in 47 people (27.2%)), T3f. (reduced in 33 people (19.1%)), T4f. (decreased in 20 (11.5%)), anti-TPO (increased in 18 (11.5%)) (Table 4).

The frequency of disorders according to gender distribution did not have statistically significant differences, however, the increase in the frequency of occurrence of hormonal changes was more pronounced in women (Table 4). The number of indicators below generally accepted norms was noted T3total. in 20 (30.8%) men and 27 (25.0%) women, T3f. in 8 (12.3%) men and 25 (23.1%) women, T4f. in 4 (6.2%) men and 16 (14.7%) women. An elevated level was determined by T4tot. in 2 (3.1%) men and 7 (6.4%) women, T3 St free. and T4 free. – in 1 (0.9%) woman, TG – in 1 (1.5%) man and 4 (3.7%) women, TSH in only 2 (1.9%) women and anti-TPO in 5 (7.7%) men and 13 (12%) women (Table 4).

Antibodies to thyroid peroxidase are protein compounds whose action is directed against the enzymes responsible for the formation of the active form of iodine necessary for the synthesis of thyroid hormones. If anti-TPO is elevated, this is a marker of the presence of autoimmune thyroid diseases in the body. As a result of immune failure, a deficiency of thyroid hormones may develop.

The level of the stress hormone cortisol corresponded to the reference values, but in the group of men it was slightly higher by 16.6% (p = 0.019) (Table 1), which may be due to an increase in psycho-emotional stress. Cortisol concentrations also tended to increase with age (Table 2). In residents of northern latitudes, there was a twofold increase in the level of the stress hormone cortisol and psycho-emotional stress by 19.4%, compared with healthy residents of middle latitudes [15].

Thus, in the Aldan region, residents of the cities of Aldan and Tommot show changes in the content of thyroid hormones, which is characterized by a higher frequency of occurrence of low T3total levels. at (27.2%), T3free at (19.3%) and T4free at (11.6%), more clearly manifested in women. Increased concentration of hormones T3f., T4f. and T4total, observed with age. An increase in T3total and T4total levels is observed in people with an increased body mass index. The presence of elevated levels of antibodies to thyroid peroxidase in 18 (10.4%) people indicates a strained immune system, therefore it is recommended to include endocrinological examinations in periodic medical examinations.

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DETECTION OF HIGH-RISK HUMAN PAPILLOMA VIRUS IN WOMEN WITHIN THE FRAMEWORK OF THE SECOND STAGE OF THE PILOT PROJECT "ОНКОПОИСКСАХА.РФ" IN YAKUTIA

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The study was conducted in 2022 as part of the implementation of the second stage of the pilot project "ОНКОПОИСКСАХА.РФ" (ONCO-SEARCH) at the Yakut Republican On-cology Dispensary, which is part of the national project "Healthcare". The project involved 798 women from 10 districts of the Republic of Sakha (Yakutia). The comprehensive examination included cytological testing, detection and genotyping of high carcinogenic risk human papillo-mavirus (HCR-HPV) using polymerase chain reaction, and assessment of viral load. The territori-al distribution of HCR-HPV types was demonstrated. The overall infection rate among women ranged from 6.9% (Tomponsky district) to 25.0% (Oymyakon district), with an average of 14.8%. The majority of infections were of the episomal - non-integrated form of HPV. Differ-ences in infection rates among women of different age groups were observed. The highest pro-portion of HCR-HPV carriers, including integrated forms, was found in the age groups of 20-30 and 31-40 years. High-grade squamous intraepithelial lesions (HSIL) were diagnosed in 2.5% of the examined women, while low-grade squamous intraepithelial lesions (LSIL) were found in 1.8%. One woman was diagnosed with squamous cell carcinoma. The study showed a correlation between viral load, integrated forms of HPV, and cervical intraepithelial neoplasia (CIN). The integrated form of genotype 16 made the largest contribution (50%) to CIN lesions among HCR-HPV-infected individuals.

Keywords: human papillomavirus, screening, age distribution, integrated forms, cervical cancer, cervical intraepithelial neoplasia.

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Introduction. Human papillomavirus (HPV) is one of the most common sexually transmitted infections in Russia and many other countries [5, 7]. High-risk HPV is capable of integrating its genome into human DNA and rapidly spreading, leading to cell transformation and the development of malignant tumors [9,13,14,17]. Studies conducted in different regions of the world have shown that HPV is the main risk factor for cervical cancer (CC) development. Epidemiological observations conducted in numerous areas confirm this association [6, 8]. Cervical cancer is a relatively common disease among women, ranking fourth in terms of cancer incidence worldwide. In Russia, according to data from 2021, cervical cancer accounted for 4.9% of all cancers in women [4].

The main methods of combating cervical cancer include vaccination, screening, diagnosis, and subsequent treatment with assessment of treatment outcomes. The most optimal strategies to combat this disease are mass vaccination of girls before the age of 15, periodic screening of older women, and subsequent treatment in case of detection of morphological changes in tissues [23].

Early-stage treatment is more effective and can only be achieved through periodic screening, as women generally do not exhibit symptoms and there are no reasons for examination. Screening not only leads to more effective treatment outcomes but also proves to be more cost-effective overall, as the costs of preventive screening are significantly lower than expensive future treatments. Cervical screening involves diagnostic tests using cytology and PCR methods to detect morphological changes [12].

To determine type-specific risk and predict disease incidence, it is necessary to study the geographical distribution and characteristics of HPV types, as well as investigate infection rates in the region. This is because HPV infection rates can vary by region, and therefore, preventive and treatment algorithms may differ [6, 8].

The Yakut Republican Oncology Dispensary has launched the pilot project "ONKOPOISKSAKHA.RF" as part of the national project "Healthcare". In 2021, the first stage of mass HPV screening for women in Yakutia was conducted. Medical teams traveled to different settlements and regions to examine the population and collect samples for laboratory testing. In the first stage, 724 women from 5 districts (Zhigansky, Verkhoyansky, Churapchinsky, Namsky, Srednekolymsky) of the Republic of Sakha (Yakutia) and the city of Yakutsk with its suburbs were examined. The studies determined the overall infection rate, identified differenc-

es in infection rates among women of different age groups, and demonstrated the territorial specificity of different HCR-HPV genotypes distribution [2]. However, a significant part of the regions remained uncovered, and in some indicators, such as infection rates in the age groups of 20-30 and over 70 years, the sample size needed to be expanded for statistical significance.

The Purpose of the Study: To continue mass screening testing, including cytological examinations, analysis of HPV genotype distribution, and characteristics of viral load of 14 oncogenic HPV types in women residing in 10 districts of the Republic of Sakha (Yakutia) that have not been previously covered by the study.

Material and Methods. In the voluntary screening study of the second stage of the pilot project "ONKOPOISKSAKHA.RF," women residing in 10 districts of the Republic of Sakha (Yakutia) participated. These districts include Allaykhovsky, Anabarsky, Verkhnekolymsky, Gorny, Lensky, Neryungrinsky, Oymyakonsky, Tomponsky, Ust-Maysky, and Khangalassky. The age range of the participants was from 20 to 87 years (n = 798). The average age of women in the final overall sample was 48.0±9.6 years.

The material for the study consisted of epithelial cells collected from cervical and cervical canal swabs, which were placed in a liquid-based cytology transport medium. The collected material was analyzed using liquid-based cytology on an automated system called CellPrepPlus (Korea). The slides with the biomaterial were stained using the Papanicolaou method. The results of liquid-based cytology were interpreted according to the Bethesda System terminology (2014).

For DNA extraction, the "AmpliSens® DNA-Sorb-D" kit was used, which is designed for total DNA extraction. For simultaneous amplification and detection of HPV DNA regions (multiplex PCR), the "AmpliSens® HPV VKR Screen-Titer-14-FL" test system was used. This test system allows for the detection of 14 highly oncogenic types of HPV:

- for genotypes 16, 31, 33, 35, 52, 58 – region E1 gene
- for genotypes 18, 39, 45, 56, 59, 66, 68 – region E2 gene
- for genotype 51 – region E7 gene

The E6 gene region was detected separately for genotypes 16, 18, and 45 (Table 1). The detection of the E6 region in the absence of the E1/E2 region indicated viral integration into the human genome. The presence of the E6 region in the presence of the E1/E2 region was interpreted as a mixed form, while the absence of the E6 region in the presence of the E1/E2 region indicated a non-integrated, episomal form of the virus.

To determine the genotype and viral load concentration, the "AmpliSens® HPV HCR Genotype-Titer-FL" reagent kit was used. Amplification was performed on a 6-channel real-time PCR detection system with a 96-well block, the "Real-time CFX-96 Touch" from Bio-Rad (USA). The amplification setup and analysis of the obtained results were conducted using the "FRT-Manager" software (version 3.7). The obtained result with a specific viral load concentration was interpreted according to the instructions (Table 2).

The statistical analysis of the data was performed using the "Statistica" 6.0 software. To determine the statistical significance of differences in the distribution of frequencies of qualitative variables between groups, a four-fold contingency table analysis was used [24]. The level of significance was determined using the χ2 (chi-square) test. The strength of the association between the risk factor and the outcome was assessed using the normalized value of the Pearson coefficient (C'). The risk assessment of the outcome based on a binary variable was performed using the odds ratio (OR) with a 95% confidence interval.

Results and Discussion. The overall prevalence. It is known that the prevalence of HPV in Russia is approximately 20-30%. However, different studies have shown highly variable results between regions and social groups, indicating a focal nature of HPV transmission [7]. Previously, using the example of 5 districts of the Republic and the city of Yakutsk, we showed that the overall prevalence of HPV HCR among women can vary across geographical areas, ranging from 4.7% to 11%, which is a difference of more than 2 times [2].

Table 1

Distribution of Fluorophores by Detection Channels

Channel for Fluorophore	FAM	JOE	ROX	Cy5	Cy5.5
Target DNA	HCR HPV DNA Genotype 16	HCR HPV DNA Genotype 18	Genotypes **16,18,31,33,35, 39,45,51,52,56, 58,59,66,68**	Plot DNA β -Globin Gene (Internal Control Sample Glob)	HCR HPV DNA Genotype 45
Amplification Region	E6 Gene	E6 Gene	E1 Gene (for genotypes 16, 31, 33, 35, 52, 58)/ E2 gene (for genotypes 18, 39, 45, 56, 59, 66, 68)/ E7 gene (for genotype 51)	β-Globin Gene	E6 Gene

Table 2

Interpretation of lg results (HPV per 100,000 cells)

Virus concentration, HPV genome equivalents, n*lg/10^5 cells	Interpretation
<3	Clinically insignificant value
3–5	Clinically significant value. Dysplasia cannot be ruled out, there is a risk of developing dysplasia
>5	Clinically significant, elevated value. High chance of dysplasia

Table 3

Structure of HCR HPV Infection

Ulus (Village)	HPV 16[1]	HPV 18[1]	HPV 45[1]	HCR[2]	Mixed (Geno-types), Persons	Negative, Persons	Total, Persons/(%)	Infected, Per-sons/(%)
Allaihovsky	-	-	-	9	**1** (18[1].52[2])	78	88	10 (11.4)
Anabarscy	1	-	-	7	**1** (16[1].51[2]) **1** (16[1].39[2].56[2]. 31[2]. 59[2])	52	62	10 (16.1)
Verhnekolymsky	1	-	1	7	-	52	61	9 (14.8)
Gorny	2	1	-	19	-	111	133	22 (16.5)
Lensky	9	3	1	13	**1** (16[1].18[1].45[1])	125	152	27 (17.8)
Nerungrinsky	2	1	-	2	-	37	42	5 (11.9)
Oimyakonsky	1	1	-	3	-	15	20	5 (25.0)
Tomponsky	-	-	-	2	-	27	29	2 (6.9)
Ust-Maisky	4	-	-	17	**1** (16[1].51[2].16[2])	135	157	22 (14.0)
Khangalassky	1	-	-	5	-	48	54	6 (11.1)
Total:	21	6	2	84	5	680	798	118 (14.8)

1 – genotypes – region E6 gene (likely integrated into the human genome);
2 – genotypes 16, 31, 33, 35, 52, 58 – E1 gene region, genotypes 18, 39, 45, 56, 59, 66, 68 – E2 gene region, geno-type 51 – E7 gene region.

In the studies conducted during the second stage of the pilot project "ОНКОПОИСКСАХА.РФ" (2022), HPV HCR infection was detected in 118 women, with a prevalence rate of 14.8% (n=798) (Table 3). Among the 10 districts of the Republic of Sakha (Yakutia) that were studied, the highest prevalence rates were observed in the following districts: Oymyakonsky - 25.0%, Lensky - 17.8%, Gorny - 16.5%, and Anabarsky - 16.1%. The lowest prevalence rate was found in Tomponsky district, where it was 6.9%. However, due to the small sample size of n=20 for Oymyakonsky and n=29 for Tomponsky districts, it is expected that the prevalence values will be adjusted when expanding the number of participants in future studies.

The integration of HPV DNA into the human cell DNA structure is a key event in the transformation of infected cells [10]. The integrated form of the virus stimulates cell proliferation, induces genomic instability, and can lead to the development of mutations [18,19,22]. The most frequently integrating HPV genotypes are 16 and 18, where the E1/E2 region is disrupted but the oncogenes E6/E7 are preserved [15, 21]. Thus, cervical cancer is a unique example of virus-associated carcinogenesis, where the constant presence of exogenous HPV genetic information in tumor cells plays an important role in their transformation.

Figure 1 shows the distribution of integrated HPV HCR forms and overall virus infection rates across districts. The average infection rate across the 10 districts was 14.8%, with integrated virus forms accounting for 4.3% of cases.

The highest proportion of integrated virus forms was observed among the surveyed women in the Oymyakonsky (10%), Lensky (9.2%), and Neryungrinsky (7.1%) districts. Interestingly, cases of co-infection with two or more HPV HCR genotypes, combined with integrated forms, were recorded among women from 4 districts (Table 3). In Allaykhovsky district, a combination of integrated HPV-18 and non-integrated episomal HPV-52 forms was detected. In Anabarsky and Ust-Maysky districts, combined infection of integrated HPV-16 forms with episomal forms was found. In Lensky district, there was one case of infection with three integrated virus forms of genotypes 16, 18, and 45. It should also be noted that among all the surveyed women, the prevalence of the episomal (non-integrated) form of virus infection (HCR[2], Table 3) with detectable E1/E2/E7 gene region of HPV HCR predominates.

The age structure of infection. The dependence of infection and disease prevalence on the age of the surveyed individuals is of particular interest in sci-

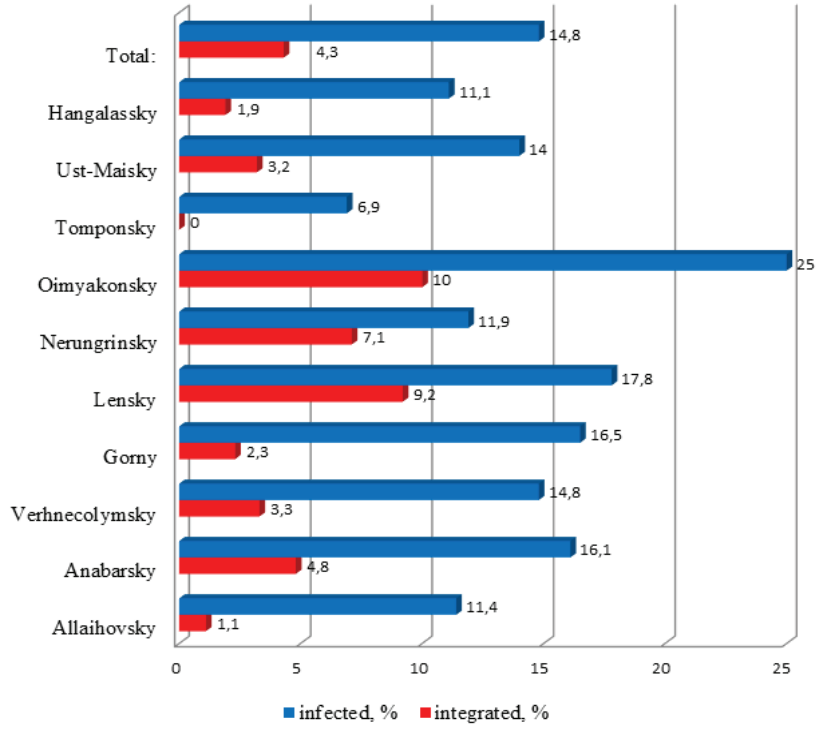

Fig. 1. Structure of the Territorial Distribution by Uluses of General Infection and HPV Forms Integrated into the Human Genome (%)

entific research on virus prevalence. It is believed that virus prevalence correlates with the age range of active sexual life [11,20]. The highest peak of virus infection is observed in the age group of 15-20 years. The peak of precancerous cervical conditions is registered with a shift of 10 years, and the peak of the prevalence of invasive cancer occurs at the age of 40-50 years [20]. In Yakutia, according to research, the peak incidence of cervical cancer is observed in the age group of 40 to 54 years [1], which generally corresponds to global indicators.

To identify age-related distribution patterns of HPV in the Republic of Sakha, we combined data from 2022 with the results of studies from 2021 [2]. To understand the age structure of the distribution among all surveyed individuals, further analysis was conducted based on 6 age groups (Fig. 2). The largest proportion of surveyed women was in the age group of 41-50 years, accounting for 30%. The smallest groups were women aged 20-30 and over 70 years, accounting for 6.5% and 4.1%, respectively. Considering that screening examinations were conducted after widespread public awareness through mass media and were voluntary in nature, the highest medical participation in the «ОНКОПОИСКСАХА.РФ» program was observed among women aged 41-50 years, while medical passiveness was more prevalent among women aged 20-30 and over 70 years.

The analysis of HPV HCR distribution showed that the highest proportion of carriers was observed among women aged 20-30 years (16.7%) and 31-40 years (10.7%) (Fig. 3). The lowest infection rate was observed in the group aged over 70 years, accounting for 6.8%. As mentioned earlier, the study had smaller sample sizes in the younger (20-30 years) and older (over 70 years) age groups, with n=162 and n=103, respectively.

The maximum proportion of integrated HPV HCR forms was also found in the age groups of women aged 20-30 years (6.2%) and 31-40 years (3.6%). In descending order, the next groups were women over 70 (2.9%), 41-50 (2.7%), 51-60 (2.2%), and the lowest number of cases (0.5%) of integrated virus forms were detected in women aged 61-70 years, which generally corresponds to global indicators.

Cervical intraepithelial neoplasia (CIN). The studies conducted using liquid-based cytology (n=798) identified intraepithelial lesions of various degrees (CIN) in 35 women (4.3%). Among them, 14 (1.8%) were diagnosed with low-grade squamous intraepithelial lesions (LSIL), and 20 (2.5%) had high-grade squamous intraepithelial lesions (HSIL) of the flat epithelium (Table 4). One woman (0.13%) was diagnosed with morphological changes characteristic of squamous cell carcinoma. The age of women with detected intraepithelial lesions of various degrees ranged from 20 to 63 years. In terms of age distribution, the highest proportion of CIN was found in the 20-30 age group, accounting for 9.1%, while the lowest proportion of CIN changes was observed in women over 60 years old (1.1%). In the other age groups, the proportion of CIN did not differ statistically: 31-40 years (5.0%), 41-50 years (4.8%), 51-60 years (5.1%).

To determine the relationship between HPV HCR infection and intraepithelial lesions, a comparative analysis of the obtained results was conducted. Among HPV-positive women (n=118), the number of women with morphological changes in the cervix was 14 (11.9%), while among HPV-negative women (n=680), it was 21, or 3.1%. The differences between the groups were statistically significant ($p<0.001$); the odds ratio (OR) with a 95% confidence interval (95% CI) was 4.22 (0.158-0.667). Thus, HPV HCR-infected women have more than a 4-fold higher risk of developing intraepithelial lesions of the flat epithelium.

The study [16] demonstrates that without screening, the average mortality rate from cervical cancer is 8.3 cases per 1000 women. However, systematic cervical screening can reduce this rate to 0.76 when using cytological examination and to 0.29 when utilizing HPV testing as the primary analysis. Despite the high sensitivity of PCR testing, our data confirms the necessity of comprehensive screening that includes both PCR testing and cytological screening.

High viral load can be used as a prognostic risk factor for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. In the two cases of detected CIN changes and in the case of diagnosed squamous cell carcinoma, high viral loads (>3 genome equivalents) were observed in HPV-positive women, which are interpreted as clinically significant (Table 2), indicating a risk of developing dysplasia. In 10 cases, the viral load was >5 genome equivalents, indicating a high likelihood of dysplasia development. In the entire sample of HPV-positive women, a viral load >3 genome equivalents was detected in 36 surveyed women. Statistical analysis of the four-fold contingency table showed a significance level of $p<0.001$ based on the $\chi 2$ (chi-square) criterion. The measure of association between the risk factor (concentration >3 genome equivalents) and the outcome (intraepithelial le-

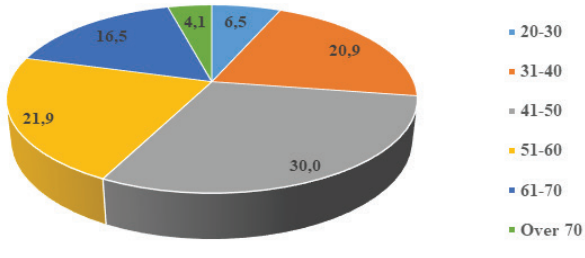

Fig. 2. Structure of the Distribution of the Studied by Age Groups (%)

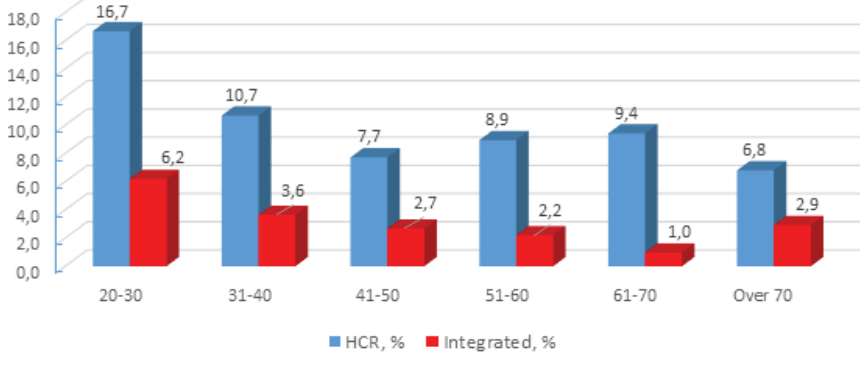

Fig. 3 Distribution of HCR HPV and Integrated Forms of the Virus by Age Groups
X-Axis: Age (Years);
Y-Axis: Infection (%)

Table 4

Prevalence of infection in women with detected intraepithelial lesions

HCR HPV	(n)/genotypes	Detection region	Quantity HPV genome equivalents, n*lg/10^5 cells
Low-grade squamous intraepithelial lesion (LSIL)			
HPV-18	1	E2	5.2
HPV-31	2	E1	5.0/5.7
HPV-39	1	E2	5.6
Negative	10	-	-
High-grade squamous intraepithelial lesion (HSIL)			
HPV -16	4	E6	4.7-6.3
HPV -31	1	E1	6.2
HPV -51	1	E7	4.7
HPV-16/ HCR	(1) / HPV 16/39/56/31/59; (1) / HPV-16/51/16; (1) / HPV-16/51	E6/ E2/ E1/; E6/ E7/ E1; E6/ E7	4.8/3.8/5.2/6.0/3.3; 6.1/4.2/5.3; 6.1/5.8
Negative	11	-	-
Squamous cell carcinoma			
HPV-51	1	1 (E7)	4.7

sions) had a strong association strength (C' = 0.685). Our findings confirm a direct correlation between high viral concentrations and the risk of developing cervical intraepithelial lesions of various degrees.

In the study [3], the authors provide data indicating that high viral load of HPV-16 increases the probability of its integration into the cellular genome. From our obtained data (Table 4), it can be seen that in 7 out of 14 cases of CIN in HPV-positive women, HPV-16 is diagnosed in an integrated form (detected in the E6 gene region), both as a mono-infection (4 women) and in mixed forms with episomal variants (3 women). Other HPV genotypes detected in women with CIN were relatively rare. For example, HPV-51 was detected in two cases, including squamous cell carcinoma, HPV-31 and HPV-39 in 3 and 1 case, respectively. In the statistical evaluation, three cases of mixed genotypes, including integrated (HPV-16) and episomal forms of the virus, were classified as integrated forms due to the predominance of this risk factor. In the overall sample of HPV-positive women, genotype 16 was detected in 40 cases, with 25 of them in an integrated form (Table 3). The analysis of the obtained data showed a level of statistical significance ($p < 0.05$). The measure of association between the risk factor (integrated form of HPV-16) and the outcome (intraepithelial lesions) was relatively strong, with C' = 0.475. Thus, based on the results of our study, the maximum contribution to the structure of detected HPV genotypes associated with cervical lesions was made by genotype 16 in an integrated form.

As a result of implementing the first and second stages of the pilot project "ONKOPOISKSAKHA.RF," we obtained data for the first time on the prevalence of HPV HCR, including integrated forms, in 15 districts of the Republic of Sakha. The association between HPV HCR infection and the risk of developing cervical intraepithelial neoplasia and cervical cancer was investigated. In order to obtain more accurate statistical data in areas with insufficient population coverage and to study the prevalence of the virus across the entire territory of the Republic of Sakha (Yakutia), further continuation of mass screening HPV testing is required, expanding the geographic scope of the research.

Conclusion. It has been established that the overall infection rate in the 10 studied districts ranges from 6.9% to 25%, with an average of 14.8%. The highest infection rates were found in the Anabar district - 16.1%, Gorny district - 16.5%, Lensky district - 17.8%, and Oymyakon district - 25.0%. The maximum proportion of integrated forms of the virus was observed among surveyed women in the Oymyakon district (10%), Lensky district (9.2%), and Neryungri district (7.1%). In terms of prevalence, the most common integrated genome forms were HPV genotype 16 (2.6%), followed by HPV 18 (0.8%) and HPV 45 (0.25%).

According to the aggregated results for 2021-2022, the highest proportion of HPV HCR carriers was found in the age groups of 20-30 years (16.7%) and 31-40 years (10.7%). These same age groups also had the highest proportion of integrated forms of the virus, at 6.2% and 3.6%, respectively. The lowest number of cases (1.0%) of integrated forms of the virus was observed in the age group of 61-70 years, and the lowest infection rate was found in women over 70 years old. The highest participation in the survey was among women aged 41-50 years (30%), while the lowest participation was among women aged 20-30 years (6.5%) and over 70 years old (4.1%).

Among the surveyed women, a high grade (HSIL) of squamous epithelial lesions was diagnosed in 2.5%, a low grade (LSIL) in 1.8%, and one woman (0.13%) was diagnosed with squamous cell carcinoma. The maximum proportion of CIN was found in the age group of 20-30 years, accounting for 9.1%, while the minimum proportion of CIN changes was observed in women over 60 years old (1.1%). It has been shown that HPV HCR infection increases the risk of intraepithelial squamous epithelial lesions by more than 4 times. A direct correlation between viral load and integrated forms of HPV with cervical intraepithelial neoplasia has been identified. The integrated form of genotype 16 contributes to 50% of CIN lesions among HPV HCR -infected women.

All identified cases of infection, with a high probability, can lead to cervical

cancer. All infected individuals have been registered and referred for further investigation and treatment at the Yakut Republican Oncology Dispensary under the pilot project "ОНКОПОИСКСАХА.РФ".

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TOPICAL ISSUE

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ANALYSIS OF VACCINE EFFECTIVENESS AGAINST COVID-19 ON THE EXAMPLE OF RESIDENTS OF TWO CITIES OF EASTERN SIBERIA

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The analysis was conducted of 14,578 patients vaccinated against coronavirus infection in Krasnoyarsk and Zelenogorsk. As a result of the study, the effectiveness of vaccination against the SARS-Cov-2 coronavirus was proven. It was found that of all vaccinated people, 49.5% did not get sick with COVID, and the majority of vaccinated patients had a mild course of the disease. Mortality in the study group from a new coronavirus infection was 3.9% in Krasnoyarsk, 2.9% in Zelenogorsk (p = 0.0005). The median age of patients who died from a new coronavirus infection in Krasnoyarsk was 68.0 [61.0; 72.5] years, among women 68.5 [61.5; 77.0] and in Zelenogorsk among men 72.5 [62.0; 83.0] years, among women 78.0 [71.0; 83.0] years.

Among patients with severe and extremely severe severity, 24 patients were vaccinated, which accounted for 7.9% of all patients with severe and extremely severe severity. Among the deceased patients, 21 (7.8%) patients were vaccinated. In 18 (6.8%) patients who died, infection with a new coronavirus infection occurred within 10 days from the date of vaccination.

Keywords: coronavirus infection, SARS-Cov-2, vaccination against COVID-19, effectiveness of vaccination, mortality from coronavirus infection.

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Introduction. Coronavirus SARS – Cov -2 has become an extraordinary shock throughout the world [1]. The pandemic has disrupted the usual way of life of society and resulted not only from an increase in morbidity and mortality of the population, but also from the destabilization of international political and economic relations, increased unemployment, and social upheaval.

Official information about an outbreak of pneumonia of unknown etiology in Wuhan City, the capital of Hubei Province of China, first appeared on December 31, 2019. According to the World Health Organization (WHO) Center in China (WHO China Country Office) from On January 3, 2020, this new disease was confirmed in 44 patients [2]. And on March 11, 2020, WHO recognized COVID-19 as a pandemic [11].

Among the most frequent symptoms with which patients with suspected COVID-19 were hospitalized, the following were noted: fever (98-98.6%), unproductive cough (76-82%), shortness of breath (43%); myalgia and fatigue (44%). Much less frequently, patients complained of headache (up to 9%), hemoptysis (5%), productive cough (28-37%), diarrhea (up to 14%), nausea (up to 14%) and vomiting (5%). These symptoms at the onset of infection were also observed in the absence of fever [1].

Analysis of the database of 5700 patients with COVID-19 (average age 63 [52; 75] years, 39.7% of women) admitted to 12 New York City hospitals between March 1 and April 4, 2020 showed that the most common comorbidities were hypertension (3,026; 56.6%), obesity (1737; 41.7%) and diabetes mellitus (1808; 33,8%). Also S. Tai et al. in their study, they determined the relationship between the severe course of coronavirus infection and the patient's history of cardiovascular diseases (CVD), in the structure of which arterial hypertension took the leading position. Of 332 patients with mild COVID-19 (mean age 51 [40; 59] year, 61.2% of women) 48 (14.5%) patients had CVD. Of these, 23 (47.9%) had a severe course and required hospitalization. The level of intensive care requirement among these patients also increased compared to the group without concomitant cardiac pathology (47.92 and 12.4%, respectively, p < 0.001) [2;4; 6].

Mortality at COVID-2019 is proportional to the age of patients: from 0% in children under 9 years old to 14.8% in people over 80 years old. Approximately 10-15% of the lungs and 81-82% of the moderate cases from all infected go to severe. About 15-20% of severe cases become very severe. The category of high risk of mortality from COVID-2019 should include elderly patients with concomitant diseases, especially those with damage to the cardiovascular system [1].

In this regard, it became necessary to take the most effective measures that will help stop the coronavirus epidem-

ic. Despite a certain decline in infection with coronavirus infection, measures are needed to manage the epidemic, which necessarily include specific immunoprophylaxis. In January 2020, several organizations and institutions began work on the creation of a vaccine against SARS-CoV-2 based on the published genome [7]. Vaccination is the most effective measure that reduces morbidity and deaths. Back in the 18th century, the introduction of smallpox vaccination showed its exceptional effectiveness. The consequence of success was the disappearance of smallpox as an actual viral infection. [13].

To date, the following vaccines have been registered in the Russian Federation for vaccination against COVID-19: combined vector vaccines "Gam-COVID-Vac", "Gam-COVID-Vac-Lio", "Gam-COVID-Vac-M" and "Gam- COVID-Vac" (nasal drops), vaccines based on peptide antigens "EpiVacCorona" and "AURORA-CoV", inactivated whole-virion concentrated purified coronavirus vaccine "CoviVac", vaccine for the prevention of COVID-19 "Sputnik Light", subunit recombinant vaccine "Convasel" " Of the foreign vaccines, the most popular are: AZD1222 (ChAdOx1 nCoV-19) or Covishield - a vaccine developed by Oxford University and AstraZeneca, Pfizer/BioNTech - a vaccine produced by the German biotechnology company BioNTech in collaboration with the American Pfizer and Chinese Fosun Pharma, mRNA-1273 - COVID-19 vaccine being developed by Moderna [9; 12].

There is strong evidence that vaccines against SARS-CoV-2 infection are clinically effective in preventing infections and are also effective in reducing the likelihood of hospitalization and death [14].

Gam-COVID-Vac has proven its effectiveness not only in the Russian Federation, but also in the countries that have used this vaccine. According to some reports, the effectiveness exceeds 95%. The effectiveness of vaccines developed by BioNTech from Pfizer, Covishield from the University of Oxford and mRNA-1273 from Moderna ranged from 91% to 94%. According to a study conducted in the Krasnoyarsk Territory, the incidence of COVID-19 among vaccinated individuals is 8 times lower than among unvaccinated individuals. It has been convincingly proven that among patients with COVID-19 who fell ill after vaccination, compared with unvaccinated patients with COVID-19, hospital treatment is required 1.3 times less often, and artificial ventilation is required 2.2 and 2.0 times less often, respectively. hospitalization in intensive care units, patients are 1.5 times less likely to be in serious and extremely serious condition. An important aspect is also that among vaccinated COVID-19 patients, deaths are 1.6 times less common compared to COVID-19 patients who were not vaccinated at the time of illness [10].

To date, 64.4% of the world's population has received at least one dose of a COVID-19 vaccine. In some countries, the proportion of vaccinated people reaches high values, for example, in the UAE - 99%, Portugal - 95%, China - 88%, Canada - 86%, Brazil - 85%, Italy - 84%, Vietnam - 81%, Japan – 81%, France – 80%, Great Britain – 77%, USA – 55%, Germany – 76%, India – 71%, and at that time in Russia this figure does not exceed 55% [5]. The population of pregnant women who have had infection and/or been vaccinated against COVID-19 deserves special attention [3]. According to published data from the US Department of Veterans Affairs health database (34 thousand fully vaccinated patients and 113 thousand unvaccinated participants who had COVID-19), among fully vaccinated patients who had COVID-19, the risk of death within the next 6 months is significant lower than in unvaccinated people (risk ratio (RR) was 0.66). According to a study in Khabarovsk, in the cohort of those effectively immunized in relation to the unvaccinated, the following was noted: a decrease in the incidence of coronavirus infection by 4.3 times; reduction in the frequency of hospitalization of patients by 57.7 times; reduction in the specific gravity of severe and critical forms by 84 times [8].

The purpose of our study was to analyze the effectiveness of vaccination against COVID-19 in Krasnoyarsk and Zelenogorsk of patients who applied to medical institutions of the Federal State Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia, the structure of the incidence of coronavirus infection in the study group.

Research materials and methods. An analysis of the database of patients in Krasnoyarsk and Zelenogorsk, who are served at the Federal Siberian Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia, was carried out. Krasnoyarsk and Zelenogorsk are located at a distance of 155 km from each other. Both cities have a similar natural and climatic zone: Krasnoyarsk is a large industrial center of Eastern Siberia, Zelenogorsk has the status of a closed administrative-territorial entity. During the vaccination process, a register was compiled that included 28,762 patients who were vaccinated in medical institutions of the Federal State Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia in Krasnoyarsk and Zelenogorsk for the period from 2020 to 2022. We took into account gender, age, the drug used for vaccination, the diseases for which the patients sought medical help, the severity of these diseases and the place of treatment of these patients.

Statistical analysis of the material was carried out on a personal computer using nonparametric methods of statistical analysis. The quantitative and qualitative characteristics included in the study formed a computer database. To describe quantitative characteristics, medians and interquartile ranges (Me, 25th and 75th percentiles) were calculated. Qualitative variables are presented as absolute values and as percentages. To compare independent data series based on quantitative characteristics, the Mann-Whitney test was used.

Analysis of the statistical significance of differences in qualitative characteristics was carried out using the $\chi 2$ test. In all statistical analysis procedures, the critical significance level (p) was taken to be 0.05 or less.

Results and discussion. For immunization against the new coronavirus infection, Russian-made vaccines Gam-COVID-Vac 26,638 (92.7%), CoviVac 322 (1.1%), EpiVacCorona 638 (2.2%), Sputnik Light 1,164 (4.0) were used %). The majority of patients completely completed the course of vaccination, which amounted to 92.8% (26,699). Of the 26,638 patients, only 2,063 (7.2%) patients received only one component of the Gam-COVID-Vac vaccine for any reason.

We analyzed 14,578 patients (50.6%) from the registry who sought medical attention for respiratory symptoms and subsequently received outpatient or inpatient treatment in medical institutions depending on the severity of the disease. The register includes residents of Krasnoyarsk (8,263 people) and Zelenogorsk (6,315 people). Of these, 4,159 (50.3%) men and 4,104 (49.7%) women were included in Krasnoyarsk, and 2,654 (42.0%) men and 3,661 (58.0%) in Zelenogorsk women. The median age of these patients was 53.0 [40.0; 65.0] years in Krasnoyarsk and 56.0 [41.0; 67.0] years in Zelenogorsk. Table 1 presents the diseases with which patients were observed in health care facilities.

When comparing the detection of SARS-Cov-2 among men and women in Krasnoyarsk and Zelenogorsk, it was re-

vealed that infection with the virus among the female population is significantly higher than in men (p<0.001). The diagnosis of new coronavirus infection was established in 5880 (45.3%) men and 7104 (91.5%) women.

Depending on the severity, patients were observed on an outpatient or inpatient basis (Table 2).

When comparing the detection of SARS-Cov-2 among men and women in Krasnoyarsk and Zelenogorsk, it was found that infection with the virus among the female population is significantly higher than that of, respectively (p < 0.001). The diagnosis of a new coronavirus infection was established in men 5880 (45.3%) and 7104 (91.5%) women.

Depending on the severity, patients were observed in outpatient or inpatient settings (Table 3).

The study revealed that most often patients received outpatient treatment both in Krasnoyarsk and Zelenogorsk - 4,635 (56.1%) and 4,628 (73.3%), respectively. Table 4 shows the distribution of diseases depending on severity.

The course of coronavirus infection in most patients was mild, both in Krasnoyarsk (5,932 (71.8%)) and in Zelenogorsk (5,305 (84.0%)). Moderate severity of the disease was diagnosed in 1,987 (24.1%) patients in Krasnoyarsk and 910 (14.4%) patients in Zelenogorsk. Patients with severe and extremely severe severity were in the ICU in 267 (3.2%) patients in Krasnoyarsk and 37 (0.6%) in Zelenogorsk. Of these, 251 patients were on mechanical ventilation. Among patients with severe and extremely severe severity, 24 patients were vaccinated, which accounted for 7.9% of all patients with severe and extremely severe severity. The severe course of the new coronavirus infection in vaccinated patients is due to decompensation of comorbid pathology, and in patients without comorbid pathology it is due to infection with the Delta variant of SARS-CoV-2. Among the deceased patients, 21 (7.8%) patients were vaccinated. In 18 (6.8%) patients who died, infection with a new coronavirus infection occurred within 10 days from the date of vaccination.

The duration of treatment in Krasnoyarsk was 14 [10; 20] days and 13 [11; 17] days in Zelenogorsk (p=0.04). Moreover, there are no significant differences in the duration of the disease between men and women.

Mortality from the new coronavirus infection was 324 (3.9%) patients in Krasnoyarsk, 180 (2.9%) in Zelenogorsk (p = 0.0005). It comprised equal shares among men and women in both localities. The median age of patients who died from a new coronavirus infection in Krasnoyarsk was 68.0 [61.0; 72.5] years, among women 68.5 [61.5; 77.0] and in Zelenogorsk among men 72.5 [62.0; 83.0] years, among women 78.0 [71.0; 83.0].

The leading cause of death among patients included in the registry in both cities was the new coronavirus infection, in both men and women. A postmortem diagnosis of coronavirus infection was established in 269 patients, which amounted to 83.1% of all deaths in Krasnoyarsk, of which 130 (40.2%) were men and 139 (42.9%) women. In Zelenogorsk, 86 patients died from coronavirus infection, which was 47.7%, of which 42 (23.3%) were men and 44 (24.4%) women. A large proportion of deaths from SARS-Cov-2 were registered in 2020 before the start of mass vaccination and were not vaccinated with a full course.

Table 1

Structure of acute respiratory diseases with which vaccinees were observed by residence

Diagnosis	Krasnoyarsk (n = 8263)		Zelenogorsk (n = 6315)		p
	n	%	n	%	
J12.8-J18.9	502	6.1	256	4.1	p= 0.046
U 07.1	7 060	85.4	5 924	93.7	p= 0.001
U 07.2	701	8.5	137	2.2	p= 0.001

Table 2

Distribution of patients diagnosed with a new coronavirus infection among men and women in Krasnoyarsk and Zelenogorsk

	men (n=5880)		women (n=7104)		
Krasnoyarsk	3 398	26.2	3 662	28.2	
Zelenogorsk	2 482	19.1	3 442	26.5	
Total	5 880	45.3	7 104	54.7	p<0.001

Table 3

Place of treatment for patients with respiratory symptoms depending on gender and place of residence

Treatment	Gender	Krasnoyarsk		Zelenogorsk		
Outpatient treatment	men	2 185	26.4	1 896	30.0	
	women	2 450	29.7	2 732	43.3	
	Total	4 635	56.1	4 628	73.3	p<0.001
Inpatient treatment	men	1 974	23.9	758	12.0	
	women	1 654	20.0	929	14.7	
	Total	3 628	43.9	1 687	26.7	p<0.001

Table 4

Distribution of patients with coronavirus infection depending on severity in Krasnoyarsk and Zelenogorsk

Degree of severity	Krasnoyarsk		Zelenogorsk		p
	n	%	n	%	
Easy	5 932	71.8	5 305	84.0	p<0.001
Average	1 987	24.1	910	14.4	p<0.001
Heavy	120	1.5	61	1.0	p= 0.0107
Extremely heavy	224	2.7	39	0.6	p<0.001

Table 5

Structure of post-mortem diagnoses among men and women in Krasnoyarsk and Zelenogorsk

Diagnosis	Krasnoyarsk				Zelenogorsk			
	men		women		men		women	
	n	%	n	%	n	%	n	%
B20[1]	3	0.9	1	0.3	0	0	0	0
C18-C91[2]	2	0.6	2	0.6	5	2.8	2	1.1
E11[3]	0	0	1	0.3	0	0	1	0.6
G31-46[4]	1	0.3	0	0	1	0.6	0	0
I21-46[5]	6	1.8	2	0.6	32	7.7	33	18.4
I61-67[6]	3	0.9	4	1.2	5	2.8	6	3.3
J12-18[7]	16	5.0	14	4.4	4	2.2	5	2.8
U07[8]	130	40.2	139	42.9	42	23.3	44	24.4

Note:1 - B20 - Disease caused by human immunodeficiency virus [HIV]; 2 - C18-C91- Malignant neoplasms; 3 - E11 – Diabetes mellitus; 4 - G31-G46 – Damage to the nervous system; 5 - I21- I46 – Heart diseases (AMI, cardiac arrest); 6 - I61-I67 – Intracerebral hemorrhages; 7 - J12-18 – Community-acquired pneumonia; 8 - U07 – Coronavirus infection.

Conclusion. Thus, the main vaccine for immunization against the new coronavirus infection of the adult population is the Russian-made Gam-COVID-Vac vaccine. An analysis of the register showed that the bulk of cases occurred in 2020 before mass vaccination of the population. Of all those vaccinated, 49.5% did not get sick with coronavirus infection. The vaccinated patients had a mild course of the disease - 5932 people from Krasnoyarsk (71.8%) and 5305 patients from Zelenogorsk (84.0%). The disease was of moderate severity in 1987 (24.1%) patients in Krasnoyarsk and 910 (14.4%) patients in Zelenogorsk. In vaccinated patients, a severe and extremely severe course of the disease, which led to death, is due to decompensation of severe comorbid pathology. In 6.8% of deceased patients, infection with a new coronavirus infection occurred before 10 days from the date of vaccination. The severe course of the new coronavirus infection in vaccinated patients without comorbid pathology is caused by infection with the Delta variant of SARS-CoV-2.

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A CLINICAL CASE OF CONCURRENT COURSE OF THE NOVEL CORONAVIRUS INFECTION COVID-19 AND ACUTE MYOCARDIAL INFARCTION

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COVID-19 is a severe acute respiratory infection caused by the SARS-CoV-2 coronavirus primarily affecting the respiratory system and leading to pathological changes in the cardiovascular system. The aim of the research is to analyze the clinical course of the new coronavirus infection in patients with comorbid conditions and the development of heart damage associated with COVID-19.

Materials and Methods: A clinical case of a patient belonging to a high-risk group is described, having comorbidities (such as chronic heart failure, type 2 diabetes mellitus, arterial hypertension), an age of 77 years, and female gender. Despite the patient's late presentation for medical assistance, resulting in worsening of myocardial infarction, which occurred in combination with severe acute respiratory distress syndrome, timely identification of the risk of cardiovascular complications was carried out during the hospitalization stage, and specific targeted therapy was initiated. However, 11 months after discharge, the patient experienced a second myocardial infarction, followed by a third one after 3.5 months (both with favorable outcomes).

Results of the Study: The presented clinical case confirms the existence of pathogenetic interaction between cardiovascular diseases and COVID-19, wherein the SARS-CoV-2 virus penetrates lung cells, heart, and other organs, affecting the endothelium of blood vessels, leading to partial destruction and damage to cardiac tissue.

Keywords: COVID-19, clinical case, arterial hypertension, myocardial infarction, risks of cardiovascular complications.

Background. COVID-19 is a severe acute respiratory infection caused by the SARS-CoV-2 coronavirus, not only affecting the respiratory system but also causing pathological changes in the cardiovascular system. The presence of concomitant cardiovascular diseases (CVD) determines a wide variability in the clinical course of COVID-19, rapid development of severe complications, and risks of a fatal outcome.

Research Objective: Analyzing the clinical course of the new coronavirus infection in patients with comorbid conditions and the development of heart damage associated with COVID-19.

Materials and Methods. A retrospective analysis of a patient's medical history was conducted who was hospitalized in May 2021 at the Yakutsk Republican Clinical Hospital (YRCH) with a confirmed diagnosis of "new coronavirus infection". A clinical example of a severe course of COVID-19 with the development of cardiovascular complications at different stages of the patient's illness was demonstrated. The patient belonged to a high-risk group: having 3 comorbid conditions (chronic heart failure, type 2 diabetes mellitus, arterial hypertension), being over 65 years old, and female.

Clinical Case. The patient U., 77 years old, was admitted complaining of pronounced shortness of breath, nausea, and dull chest pains. She considered herself ill since May 13, 2021, experiencing general weakness and shortness of breath during regular physical exertion. She did not seek medical help and did not take any medications. On May 18, 2021, due to worsening shortness of breath, increasing weakness, and the onset of chest pains, she consulted her local therapist. Her medical history included type 2 diabetes treated with insulin, ischemic heart disease (IHD), a previous myocardial infarction in 2019, and hypertension. On the same day, U. was hospitalized at the district Central Regional Hospital with suspected severe acute respiratory distress syndrome (SARDS) and community-acquired pneumonia. On May 19, 2021, a CT scan of the chest revealed bilateral lower lobe bronchopneumonia, and the treatment prescribed included levofloxacin, dexamethasone, interferon, heparin, Lasix, and Actrapid.

On May 21, 2021, 8 days after the onset of the illness, based on a telemedicine consultation, she was airlifted for inpatient treatment at YRCH, to the pulmonary department for COVID-19 patients, with the diagnosis: "Primary diagnosis: New coronavirus infection COVID-19, virus identified, moderate-severe form. Community-acquired bilateral multisegmental pneumonia, severe course."

From the epidemiological history, it is known that the patient had not previously contracted COVID-19, lives alone, received a flu vaccine in October 2020, and had not been vaccinated against pneumococcal infection or COVID-19.

Upon admission, her condition was assessed as severe. Her body temperature was 36.5°C. She had pronounced shortness of breath, a respiratory rate of 24-26 breaths per minute, SpO2 at 96% with the administration of supplementary oxygen at a rate of 15 liters per minute (without oxygen, saturation decreased to 80%). She had elevated blood pressure at 180/90 mmHg, a heart rate of 81 beats per minute. She was admitted to the intensive care unit (ICU) where she received oxygen therapy through nasal cannulas at a rate of 15 liters per minute, prophylaxis against thromboembolic complications, correction of acid-base balance and fluid-electrolyte balance, antibiotic therapy, hormonal preventive therapy, and adjustment of hypoglycemic and antihypertensive medications.

Upon examination at admission: PCR for COVID-19 was positive, the blood test showed anemia (hemoglobin 83.10 g/L), marked leukocytosis 23.5010⁹/L, thrombocytosis 599.010⁹/L, accelerated ESR 53.0 mm/h. Biochemical blood analysis revealed elevated liver transaminases activity, lactate dehydrogenase, hyperglycemia, and inflammatory response (glucose - 15.3 mmol/L; ALT- 75.9 IU/L; AST- 81.4 IU/L; lactate dehydrogenase- 399.1 IU/L, C-reactive protein-110.6 mg/L).

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On the chest CT scan from May 21, 2021: signs of bilateral multisegmental interstitial pneumonia. High probability of COVID-19. Severity of lung involvement on CT scan is more than 75%. CT-4. Differential diagnosis includes pulmonary edema. Basal segments of lower lobes on both sides show compressive atelectasis. CT signs of mediastinal lymphadenopathy (Figure 1).

ECG from May 21, 2021: Sinus rhythm, HR=64 bpm. In leads II, III, AVF, V5-V6 (inferior, lateral wall), there is observed ST segment depression with a positive T wave (Figure 2). A high-sensitivity troponin was measured: elevated result of Troponin I up to 1.340 ng/mL.

According to the echocardiogram (May 22, 2021): "Areas of local contractility impairment: hypokinesis in the basal anterior-septal, mid posterior-septal, basal posterior-septal regions.

Conclusion: Global left ventricular contractility reduced EF - 34% (C). Aortic wall and valve leaflets thickening. Mitral valve regurgitation - 1-2 degrees, tricuspid valve - 1 degree, aortic valve - 2 degrees. Left atrium and pulmonary trunk dilatation. Pulmonary hypertension - 1 degree." Based on the examination results, the clinical diagnosis was established: Primary diagnosis: U07.1 - New coronavirus infection COVID-19, virus identified, moderate-severe form. Community-acquired severe-grade bilateral multisegmental pneumonia, CT-4.

Background: Type 2 diabetes, on insulin. Diabetic microangiopathy. Diabetic macroangiopathy.

Concomitant conditions: Ischemic heart disease. Post-infarction cardiosclerosis (2019). Grade 3 hypertension. Stage 2 arterial hypertension. Left ventricular hypertrophy. Cardiovascular risk - 4. Secondary atrial enlargement. Relative tricuspid valve insufficiency - 2 degrees, mitral valve - 1-2 degrees. Pulmonary hypertension - 1 degree. Bilateral hydrothorax. Chronic heart failure with low ejection fraction (34%) 2B stage. Moderate anemia. Chronic cholecystitis, not in exacerbation.

Considering the suspicion of acute coronary syndrome, a cardiologist was consulted, and coronary angiography with PCI-1 stent in RCA No.2-CIMP was performed. Anti-anginal, antiplatelet, diuretic, antiarrhythmic therapy was prescribed, along with recommendations for monitoring, clinical analysis, and ECG control. In the subsequent course, anginal pain, dyspnea, and biochemical blood parameters increased: ALT increased to 85 IU/L, AST to 100.5 IU/L, creatine phosphokinase. Total creatine kinase: 262.7 IU/L (26-192); Troponin I up to 1.650 ng/mL; also LDH: 528.0 IU/L (135-214). Amid intensive therapy, C-reactive protein decreased to 62.7 mg/L, in CBC: leukocytosis slightly decreased to 20.1210^9/L (4-10); low hemoglobin persisted (HGB): 85.80 g/L (110-160); erythrocytes - 3.510^{12}/L, platelets - $616*10^{9}$/L. ECG recorded negative dynamics with the appearance of ischemic changes (Figure 3).

Based on the results of measuring the Na-uretic peptide, an elevated BNP level of 1520 pg/mL was detected, indicating the presence of chronic heart failure in the patient. On May 22, 2021, a diagnosis of "acute myocardial infarction with Q-wave formation in the anterior-septal wall, presumably from May 21, 2021" was established by the cardiologist. The patient was transferred to Cardiac Center No.1 - Clinical Emergency Medical Center (CERC) on May 23, 2021, where a selective coronary angiography was performed: Atherosclerosis of the coronary arteries. Stenoses: Left main coronary artery (LMCA) 70%, proximal left anterior descending artery (LAD) 80%, proximal circumflex artery (Cx) 90%, distal Cx 50%, ostial right coronary artery (RCA) 50%, proximal posterior descending artery (PDA) 70%, distal PDA 80-70-80%, obtuse marginal artery (OM) 70%. Right dominance of myocardial blood supply. Due to complex multivessel coronary artery disease, stable hemodynamics, and a high Syntax score (53 points), a decision was made to refrain from percutaneous intervention. After two weeks, the patient was discharged in satisfactory

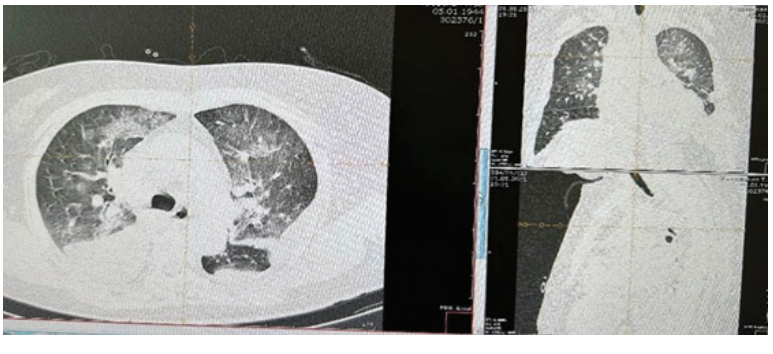

Fig. 1. Bilateral multisegmental interstitial pneumonia, 8th day from the onset of the first symptoms of the illness.

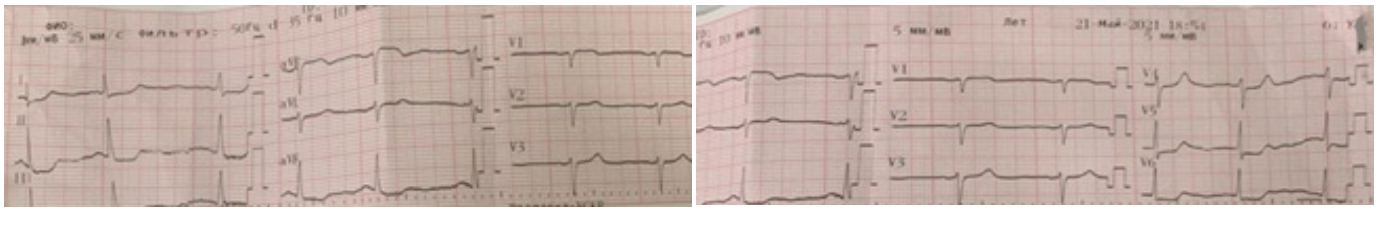

Fig. 2. ECG of patient U. upon admission

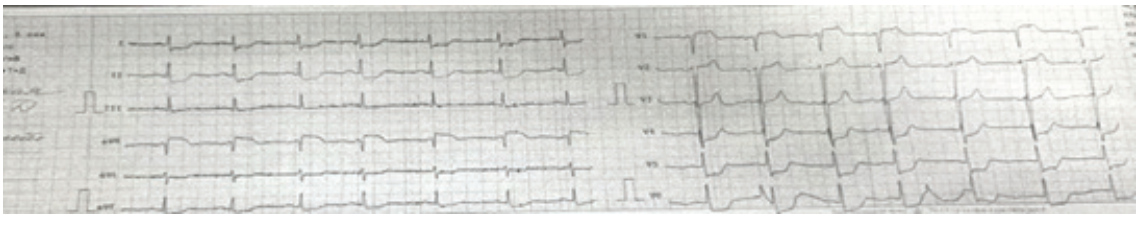

Fig. 3. ECG of patient U. one day after admission

condition, and a follow-up chest CT scan showed a reduction in the extent of damage to CT-2. However, after 11.5 months, in April 2022, the patient presented with clinical signs of a recurrent myocardial infarction and acute left ventricular failure at the Central District Hospital of the Momsky District. Diagnostic coronary angiography (April 20, 2022) revealed multivessel atherosclerotic coronary artery disease: Left main artery stenosis 70%, left anterior descending artery stenosis 70% at the ostium, 50% in the proximal third, 80% in the mid-third; diagonal branch stenosis 50%; circumflex artery 90%; obtuse marginal artery 50% at the ostium, 60% in the mid-third; right coronary artery stenosis 90% in the proximal third, 80% in the mid-third, 90% in the distal third; posterior descending artery 70%. No endovascular treatment was administered. Considering negative cardiac markers and stabilized hemodynamics, the patient continued with conservative therapy. Despite following all recommendations, the patient experienced acute decompensation of heart failure on August 1, 2022: worsening dyspnea and pronounced weakness, which the patient attributed to increased physical exertion the day before. On the same day, the patient was hospitalized in the therapeutic department of the district hospital. Examinations revealed a positive qualitative troponin test, consistent ECG changes: ST segment depression in the anterior-lateral and inferior walls of the left ventricle, ST segment elevation in aVR. Additionally, moderate anemia was diagnosed and corrected through blood transfusion. After coordination through telemedicine consultation, the patient was transferred for further treatment to a Regional Cardiac Surgical Center Oncology (RKCS ONC). After stabilization, the patient was transferred to a general ward. Subsequently, the patient underwent coronary angiography with stenting of the coronary artery (PCI with stenting of the posterior descending artery (PDA) using Resolute Integrity stents sized 3.030mm (distally p=16 atm.), 3.026mm (mid-section p=16 atm.), and 3.0*30mm (proximally p=18 atm.) on August 17, 2022. Conservative management was recommended, including adherence to antiplatelet therapy and anticoagulants. With improved condition, the patient was discharged for further treatment and follow-up at home, with a scheduled follow-up coronary angiography after 12 months.

Discussion. The presented example demonstrates that COVID-19 in comorbid patients can lead to the development of combined complications caused by the infection, in this case - non-hospital bilateral pneumonia and acute myocardial injury. The situation was complicated by the fact that in the district hospital, due to the lack of appropriate facilities, timely ECG, troponin test, and EchoCG were not performed, and timely anti-anginal and antiplatelet therapy for myocardial infarction was not administered. In addition to ECG and Echo-cardiography, the acute myocardial necrosis in the patient was indicated by elevated levels of troponin and cardio-enzymes (lactate dehydrogenase, liver transaminases, creatine phosphokinase). Considering the patient's heart failure, coronary artery disease, and stage 3 hypertension, it was reasonable to prescribe medications with anti-anginal, antiarrhythmic, antiplatelet, and antihypertensive effects. Severe COVID-19 progression can lead to cardiac pathology even after the patient's recovery - as in this case, leading to two myocardial infarctions occurring 11 months after discharge with a 3.5-month interval. The mechanism of cardiac involvement is primarily linked to the SARS-CoV-2 virus penetrating the ACE2 protein found in the endothelium of blood vessels and cells of the heart, lungs, and other organs, causing partial destruction and damage to the cardiac tissue. Studies [3, 5] have indicated involvement of the renin-angiotensin-aldosterone system among molecular and pathophysiological mechanisms since SARS-CoV-2 tropism is associated with angiotensin-converting enzyme 2, leading to altered neuromuscular response to SARS-CoV-2 tropism. This leads to abnormal functioning of the smallest blood vessels, endothelial inflammation, microthrombosis, vessel wall damage, and increased permeability. As a result, the risk of coronary artery disease leading to myocardial infarction increases. The presence of type 2 diabetes in the patient, which contributed to the recurrent myocardial infarctions, led to characteristic systemic inflammatory shifts, immune system function disturbances, metabolic changes, resulting in severe pneumonia with persistent oxygen deprivation, high hyperglycemia, systemic inflammatory disorders, and decreased tolerance for physical exertion. The onset and development of acute cardiac damage in COVID-19 are likely associated with the virus's spread from the respiratory tract through the bloodstream or the lymphatic system, as suggested by Italian researchers [6]. There is currently no confirmed evidence of detecting SARS-CoV-2 RNA in the heart. However, there are observations of the direct impact of SARS-CoV-2 on the cardiovascular system, eliciting an excessive inflammatory response that damages the myocardium [1]. The comorbid conditions of anemia and severe hypoxia due to SARS-CoV-2-induced pneumonia contributed to oxidative stress, myocardial damage, and irreversible destructive processes due to increased myocardial oxygen demand.

Conclusion. Thus, the presence of cardiovascular diseases may be associated with an increased risk of severe complications and outcomes of COVID-19. This is due to the characteristics of the modern population with cardiovascular diseases, dominated by the elderly and comorbid conditions. Conversely, COVID-19 can have an acute and chronic damaging effect on the cardiovascular system. It is anticipated that the COVID-19 pandemic will trigger a new wave of non-infectious diseases, primarily cardiovascular diseases, as their common pathogenesis is the chronic pro-inflammatory status [2].

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QUALITY OF HEALTH OF HOSPITALIZED COVID-19 PATIENTS IN THE POST-COVID PERIOD: TWO-YEAR FOLLOW-UP STUDY

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Accumulating evidence indicates a high prevalence of long-term negative consequences of COVID-19. Their final assessment is possible only after their complete disappearance, which, given the ongoing registration of negative assessments of the health status of some hospitalized COVID-19 patients, is impossible in the near future. Taking this into account, further study of post-Covid consequences in dynamics is relevant. **The purpose of the study** was to determine the quality of life and health of patients in the long-term period (24 months) after hospitalization for COVID-19-associated pneumonia. **Material and methods.** The study was conducted on data from 158 patients with moderate and severe severity who were hospitalized during the first wave of coronavirus infection in the period 09/01/2020-11/30/2020. To assess the quality of life in the post-Covid period the VR-12 questionnaire was used. The study involved conducting structural and frequency analysis, assessing the consistency of answers to the questionnaire using Cronbach's alpha and the chi-square test, calculating the nonparametric Spearman rank correlation coefficient, and non-serial correlation coefficients. To identify factors influencing health assessments, a linear regression model was built. Ordered logistic regression was estimated to identify factors influencing the distribution of responses to additional questions. **Results.** The analysis showed an insignificant difference between the physical component summary (PCS) and mental component summary (MCS) of the respondents. A connection was found between age and the risk of deterioration in self-esteem of health. It was possible to identify a significant difference in the self-assessment of the quality of physical and mental health in men and women, taking into account adjustment for age, two years after suffering from pneumonia, and also to substantiate the non-significance of RDS during hospitalization, given the significance of a high percentage of lung damage for the lower self-assessment of health of persons who had suffered coronavirus infection of moderate and severe severity. **Conclusion.** The results are largely consistent with studies conducted in other countries, indicating an uneven change in post-Covid consequences and emphasizing the importance of individual recovery programs taking into account the severity of the disease, age and gender of patients.

Keywords: post-Covid consequences, long-COVID, VR-12, mental health index, physical component summary, mental component summary.

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Introduction. The COVID-19 coronavirus pandemic has led to a significant increase in the number of hospitalizations, deaths and related complications in the acute period of the disease [5]. Long-term symptoms were already shown in the first year of the disease, such as persistent anosmia, weakness, fatigue, shortness of breath and others, which were detected in 80% of cases after the disease and significantly reduced life expectancy [15]. Cases of persistence of these symptoms for more than 2 months after more than 3 months from the moment of illness began to be isolated separately and were subsequently defined as long-COVID syndrome [4]. In addition to the noted symptoms, patients with long-COVID were more likely to experience adverse pulmonary events such as progression of pulmonary fibrosis and respiratory failure, as well as cardiovascular consequences - an increase in the frequency of sudden deaths, atrial fibrillation, heart failure, myocardial infarction and strokes [14, 18]. These consequences together determined a lower quality of life and more frequent use of medical care after discharge in people with long-COVID compared with those without long-term symptoms [13]. However, , a small proportion of those who were unable to fully return to work remains even after two years [26]. All this leads to higher estimates of the economic burden, determined not only by rising health care costs, but also by declining labor productivity.

A particular challenge in research on long-COVID syndrome arises from its heterogeneous clinical picture and corresponding symptoms [21]. Systematic reviews [20, 23] and meta-analyses [8] contribute to the synthesis of the results of numerous studies. In order to study the long-COVID syndrome more deeply, both diagnostic studies in outpatient settings and various surveys (EQ-5D-5L, SF-36, VR-12, PHQ-9 and others [19]) were conducted on purpose of better understanding quality of life and psychological status of COVID-19 survivors. It is believed that post-Covid symptoms persist from 3 months to 2 years in 80% of patients [9]. Recent studies compare the conditions of people who have had COVID over the past two years [22]. After 2 years, most studies report improvement in the condition of COVID survivors [11], but still worse than in the control group [19]. However, those with severe disease course, and especially those who required hospitalization and intensive care unit stay,

had a higher incidence of persistent symptoms [25]. Moreover, at a 2-year follow-up, the number of difficulties/problems at work decreased in comparison to the 1-year follow-up period [26].

It should be noted that both the presence of post-Covid complications and long-COVID symptoms significantly reduce the quality of life of patients [6]. At this point in time, in the Russian Federation there is an insufficient number of studies on this topic [2].

The aim of the study: to study the quality of life and health of patients in the long-term period (24 months) after hospitalization for COVID-19-associated pneumonia.

Methods. The study included 400 patients hospitalized at the BSMU clinic in 2020 for COVID-19-associated pneumonia of moderate and severe severity in the period 01.09.-30.11.2020 in the first wave of coronavirus infection. To assess the quality of life in the post-Covid period of patients hospitalized for COVID-19, the international questionnaire VR-12 was used. The choice of this scale as the main analysis tool was due to three reasons: firstly, the questionnaire allows you to assess both the physical and mental health of the respondent, and secondly, it is quite short - it includes only 12 questions, unlike broad surveys VR-36 or SF-36, thirdly, the questions have multiple answer options corresponding to a three-point to six-point Likert scale, which increases the reliability of the survey results.

Official permission was obtained from the authors for the use of the VR-12 scale in this study [12]. The VR-12 questionnaire “The Veterans RAND 12 Item Health Survey (VR-12)” is a standardized questionnaire developed based on the RAND 36 Veterans Health Survey (VR-36), which in turn was developed based on the RAND SF-36 MOS version 1.0 ." VR-12 contains 14 questions, 12 of which are basic and constitute an assessment of the health status of the respondent. Based on the answers to 6 questions of the questionnaire (1, 2a, 2b, 3a, 3b, 5), after recoding, a summary indicator of physical health (PCS index) was determined, taking into account both the respondent’s general perception of his health and physical limitations and problems, including presence of physical pain. Based on responses to the other 6 questions (4a, 4b, 6a, 6b, 6c, 7), a mental health composite score (MCS index) was calculated, taking into account role limitations due to emotional problems, energy fatigue, social functioning and mental health. Both indices (PCS and MCS) could take a value in the range of 0-100 points, where 100 corresponded to an absolute indicator of health, and 0, on the contrary, to the absence of health in the questionnaire. If the respondent refused to answer any of the questions, then some of the answers could be restored: for pairs of answers 2a and 2b, 3a and 3b, 4a and 4b, 6a and 6b, if one of them was missed, the score was restored according to the answer to the second question.

Even more, additional questions 13 and 14 should be noted (8 and 9 in the questionnaire), that are not taken into account in the health quality assessment indices, which made it possible to modify them in comparison with the original questions of the VR-12 scale, based on the purpose of the study: 8. “How would you assessed your health now compared to what it was immediately after being discharged from the Covid hospital?”; 9. “How would you rate your emotional problems now compared to what they were like immediately after leaving the Covid hospital? (for example, a state of depression or anxiety).” To answer these questions, five options were offered according to a Likert scale.

Based on the data from electronic medical records of patients at the BSMU clinic in Ufa who were hospitalized during the period 09.01.2020-11.30.2020 for viral pneumonia caused by COVID-19, an electronic database was created. The observational study was a continuous retrospective one. The following information was collected for the selected patients: gender, age, body mass index, duration of hospitalization, presence of respiratory distress syndrome, percentage of lung damage based on computer tomography data, transfer of the patient to invasive or non-invasive ventilation, presence of concomitant diseases (arterial hypertension, diabetes mellitus, chronic renal failure, chronic heart failure, history of stroke or myocardial infarction, chronic obstructive pulmonary disease). The assessment of health quality based on the VR-12 questionnaire was carried out in the period 1.11.2022-25.11.2022 through a telephone survey. To make it easier to fill out the questionnaire and increase the speed of the survey, special software was developed, implemented using the cross-platform execution environment “Nodejs” in the JavaScript language. To interact with the database, the SQL Server database management system was chosen; access was achieved by creating an external tunnel using the ngrok service.

As a result, out of 400 selected patients, it was not possible to reach 157 by telephone, and 42 patients refused to answer the questionnaire; 11 patients were reported by relatives about their death. Of 190 remaining respondents who began the survey, only 152 answered all questions in the survey. For 6 respondents, it was possible to restore the missing answers according to the rules of the questionnaire. As a result, complete information according to the VR-12 questionnaire was collected on 158 patients (68 men and 90 women) hospitalized two years ago with viral pneumonia in the COVID hospital.

The study was conducted in compliance with the Declaration of Helsinki and was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education BSMU of the Ministry of Health of Russia, protocol No. 5 of May 20, 2020. All patients signed informed consent to participate in the study.

For statistical analysis of the obtained questionnaire data, we used the capabilities of the statistical data analysis environment R (version 4.3.1), namely the libraries “MASS”, “caTools”, “erer”, “dplyr”, “DescTools”. To assess the distribution of the PCS and MCS indices, the frequency of responses to the questionnaire, and the analysis of demographic and clinical characteristics of the respondents, the median (me), interquartile range (IQR: Q1 – Q3) and frequency of occurrence were calculated, respectively. To visualize the distribution of answers to questions, a hitmap and distributions of PCS and MCS indices – histograms and boxplots – were built. The assessment of the consistency of answers to questionnaire questions forming indices of physical and emotional (mental) health was checked using Cronbach's α, considering that if its value is statistically significantly different from zero, then the answers are consistent. To assess differences in the distribution of answers to questions 8 and 9 of the VR-12 questionnaire, the chi-square test was used.

To assess the relationship between the PCS and MCS indices and various factors (age, body mass index and percentage of lung damage), the nonparametric Spearman rank correlation coefficient was calculated; to evaluate the relationship between the index values and gender, the presence of respiratory distress syndrome (RDS), non-sirial correlation coefficients were calculated. It was considered that a relationship between characteristics was present if the corresponding p-value of deviation of the null hypothesis that the correlation coefficient

was equal to zero did not exceed 0.05.

To identify factors influencing the values of the PCS and MCS health assessment indices, linear regression equations were built; to identify factors influencing the distribution of answers to additional questions 8 and 9, ordered logistic regression equations were built. The statistical significance of regression coefficients and latent variable cut points (in ordered regression) was tested using a t-criterion according to the determined standard error (SE) of the coefficients. To parameterize the regression coefficients, we used: for linear regression – the least squares method, for ordered logistic regression – the maximum likelihood method. The interpretation of the modeling results for linear regression was carried out on the basis of incremental analysis, for ordered logit regression - based on the calculation of the marginal effects of the influence of each factor.

Results. After processing the data from the VR-12 questionnaire in order to to assess the quality of health of patients hospitalized 24 months ago for viral pneumonia, physical and mental health indices were separately calculated: PCS and MCS, respectively. Table 1 presents the results of the epidemiological and sociological analysis for VR-12 respondents.

Analysis of physical and mental health indicators (PCS and MCS indices), calculated two years after hospitalization for covid pneumonia, indicates the relative well-being of respondents: there is a significant shift to the right (towards high assessments of health quality) for both indices. This is clearly visible in the histograms and boxplots of the PCS and MCS indices (Fig. 1 and 2, respectively). The results of the correlation analysis (n=158) confirmed the consistency of the physical and mental health indices - the Spearman correlation coefficient was r=0.75 (p<0.001).

All responses to questions were consistent: Cronbach's α calculated for responses forming the PCS and MCS indices, respectively, were α=0.74 (p<0.001) and α=0.69 (p<0.001). This indicates the reliability of the results obtained and the validity of the conclusions drawn from the analysis of the results of the VR-12 survey.

Correlation analysis carried out on the basis of calculating Spearman's correlation coefficients (r) and biserial correlation coefficient (rb) to assess the influence of demographic and epidemiological indicators of the respondent on the values of the PCS and MCS indices revealed the presence of a connection between the indices and age (p<0.001), gender (p<0.001), the presence of arterial hypertension (p<0.001); between the PCS index and the presence of diabetes mellitus (p<0.01), between the MCS index and the % of lung damage on CT (p<0.05) (Table 2).

For a convenient interpretation of the impact of factors on health quality indicators, taking into account their cross-influence, multifactor linear regression equations were constructed. Since the objective of the study was to analyze how viral pneumonia due to infection with COVID-19 affected the quality of health after 2 years, the main regressors in the models were considered the % of lung damage (according to CT) and the presence of RDS, adjusted for the gender and age of the respondent. Table 3 summarizes the assessment results for each of the health indices separately: the coefficient of the regressor ± standard error (SE), p-level of deviation of the null hypothesis that the coefficient is equal to zero. Table 3 also provides an indicator of the quality metric for assessing the regression equation (R2, coefficient of determination), which provides information on how much the identified factors explain changes in health indices.

The regression analysis showed the presence of a negative effect of age (p<0.001) on the assessment of the quality of health two years after suffering from "covid" pneumonia: thus, an increase in the respondent's age by one year compared to the average age (56.5 years) reduces the assessment of physical health in on average by 0.8 points, and mental health assessment by 0.5 points. It is noteworthy that the male gender of the respondent on average provides an increase in the physical health score by 11.5 points, and mental health by 9.5 points (p<0.001). The presence of respi-

Table 1

Clinical and demographic characteristics of the surveyed patients

Continuous features: median (me) and interquartile range (*IQR: Q1 – Q3*)		Frequency characteristics: absolute frequency (proportion in %)	
Age. years	56.5 (45.75-66.5)	Gender (male)	68 (43)
PCS index	75 (51.04-91.67)	Availability of RDS	16 (10.1)
MCS Index	74.17 (58.54-85.83)	AH	54 (34.6)
Body mass index	28.68 (25.57-32.01)	CHF	13 (8.3)
Height. m	1.65 (1.6-1.74)	CRF	9 (5.8)
Weight. kg	80 (70-90)	History of myocardial infarction	4 (2.6)
% lung damage (according to CT)	40 (28-49)	History of stroke	4 (2.6)
		COPD	4 (2.6)
Duration of hospitalization. days	11 (9-13)	Diabetes	28 (18)
		Mechanical ventilation/ NIV	0 (0)

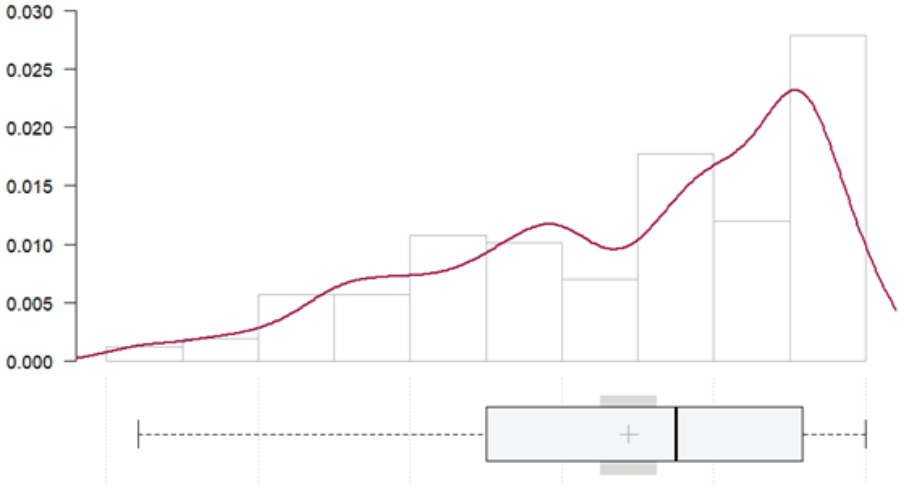

Fig. 1. Distribution histogram and boxplot of the PCS physical health index according to the VR-12

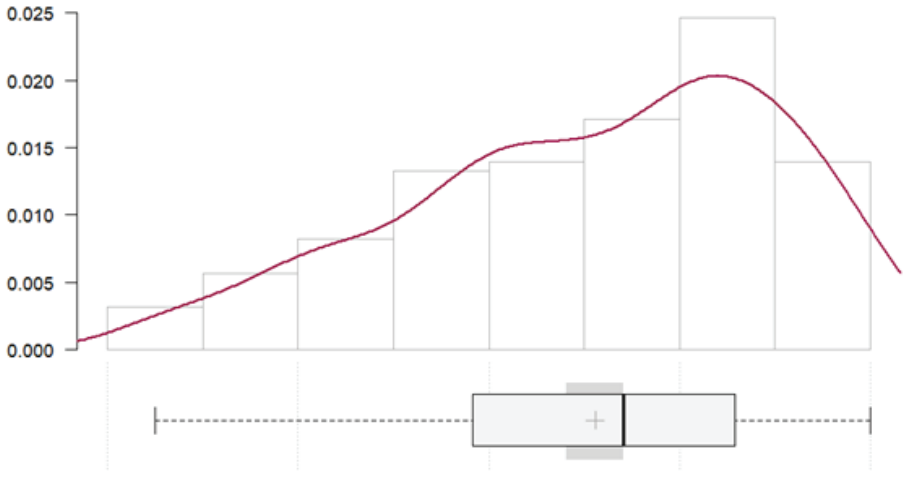

Fig. 2. Distribution histogram and boxplot of the MCS mental health index according to the VR-12

ratory distress syndrome during hospitalization for COVID-19 does not affect the self-assessment of the mental and physical health of the respondent in any way (p>0.2). The degree of development of COVID-19-associated pneumonia during hospitalization affects only the mental health indicator (p<0.05), where a 1% increase in the area of lung damage reduces the MCS score by an average of 0.15 points.

Frequency analysis of answers to additional questions 8 and 9 of the VR-12 questionnaire is presented in Table 4. According to the chi-square test, there were no differences in the distribution of answers to questions (p>0.1). The overwhelming majority of respondents responded that they felt better two years after hospitalization: for physical health - 86%, for mental health - 79.7%. However, 2.6% of respondents noted a significant deterioration in their health.

The modeling carried out on the basis of ordered logistic regression of answers to questions 8 and 9 of the VR-12 questionnaire made it possible to identify the influence on the probability of answer only of the age of the respondent (p<0.001), the other factors considered (male gender, the presence of RDS and the area of lung damage (%)) did not provide (p>0.15). The results of estimating the ordered regression coefficients using the maximum likelihood method are summarized in Table 5 – the coefficient of the regressor ± standard error (SE), p-level of rejection of the null hypothesis that the coefficient is equal to zero.

Since only the age of the respondent had a significant impact on the probability of choosing a certain answer to questions 8 and 9, the marginal effects were calculated only for this factor. Increasing the age of the interviewee by 1 year compared to the average age reduced the probability of hearing the first answer option in questions 8 and 9 by 0.017 and 0.012 points, respectively. Hearing the second answer option, on the contrary, increased the probability by 0.01 and 0.005 points, respectively, the third option increased the probability by 0.05 and 0.05 points, the fourth option increased the probability by 0.001 and 0.002 points, the fifth option increased the probability by 0.001 and 0.001 points, respectively.

Table 2

Values of Spearman correlation coefficients (*r*) and biserial correlation coefficient (*rb*) for PCS and MCS indices, *p*-level

Index	Age	BMI	% lung damage	Presence of AH	Presence of DM	Presence of RDS	Male gender
PCS	r=–0.44 p<0.001	r=–0.13 p=0.125	r=–0.08 p=0.334	r_b=0.56 p<0.001	r_b=0.31 p=0.005	r_b=0.09 p=0.499	r_b=0.60 p<0.001
MCS	r=–0.33 p<0.001	r=–0.07 p=0.394	r=–0.21 p=0.041	r_b=0.64 p<0.001	r_b=0.12 p=0.124	r_b=–0.07 p=0.542	r_b=0.54 p<0.001

Table 3

Results of linear regression assessment of physical (PCS) and mental health (MCS) indices according to the VR-12

Influence factor	PCS	MCS
	Regression coefficient±SE, *p*-level	
Age	–0.79±0.13**. p<0.001	–0.49±0.10**. p<0.001
Gender (male)	11.48±3.46**. p<0.001	9.51±2.79**. p<0.001
RDS (availability)	0.91±5.78. p=0.875	–0.08±4.67. p=0.985
% lung damage (CT)	–0.11±0.09. p=0.265	–0.15±0.07*. p=0.045
Free member of society	104.39±8.11**. p<0.001	89.32±6.55**. p<0.001
R^2	0.267	0.207

*, ** - coefficient is statistically significant at p<0.05 and p<0.001, respectively.

Discussion. Our use of the VR-12 scale to assess the quality of physical and mental health 24 months after hospitalization for COVID-19 showed a slight difference between the mental health index (MCS) and the physical health index (PCS) of respondents (74 points versus 75), and MCS<PCS. Similar differences using the same VR-12 scale were found in another study [17], where out of 304 participants surveyed, depression, post-traumatic stress and fatigue were more often observed between 9 and 26 months after the onset of the disease, and these symptoms manifested themselves less strongly 26 months later than after 9 months from the onset of the disease. A longitudinal study [22], conducted on the basis of the health questionnaire (GHQ-12) in the period 1 and 2 years after the illness, also noted the emergence of mental and physical health problems in 45 respondents who had COVID-19, and after 2 years these problems become less pronounced. In another study [26], based on a survey of patients admitted to the intensive care unit for pneumonia associated with COVID-19, according to the health quality assessment scales CIS-8, CFQ-14, HSDS after 1 and 2 years, it was shown that if the physical health problems of the respondents do not change over time, then with regard to mental health the situation only significantly worsens. In general, the VR-12 scale has been quite successfully used

Table 4

Distribution of answers to questions 8 and 9 of the VR-12

Answers	Question 8: How would you rate your health now compared to what it was like immediately after being discharged from the Covid hospital?	Question 9: How would you rate your emotional problems now compared to what they were like immediately after leaving the Covid hospital? (for example, feeling depressed or anxious)	*p*-level
Much better now than after hospitalization	95 (60.1%)	83 (52.5%)	*p*=0.174
Slightly better than after hospitalization	41 (25.9%)	43 (27.2%)	*p*=0.799
On the same level	14 (8.9%)	22 (13.9%)	*p*=0.157
Slightly worse than after hospitalization	4 (2.6%)	6 (3.8%)	*p*=0.521
Much worse now than after hospitalization	4 (2.6%)	4 (2.6%)	*p*=1.0

to assess health status in the post-Covid period, allowing one to show changes in self-assessed health status after an infection [16, 17].

Many studies devoted to assessing the quality of life and health in the post-Covid period use linear regression tools to assess the influence of various factors on the health score, measured according to various scales (VR-12, EQ-VAS, EQ 5D 5L, etc.) after various periods after the illness (3-6-12 and 24 months), an adjustment for the patient's age is always taken into account, since at an older age, other things being equal, the self-assessment of the quality of health is always lower than that of younger people. For example, in one study [10], age was a statistically significant risk factor for a decrease in the health quality score assessed according to the EQ-5D-3L scale. In our study, both when examining the assessment of physical and mental health according to the PCS and MCS scales, respectively, and when examining differences in the assessment of general condition 2 years after hospitalization (according to questions 8 and 9), age was a risk factor for deterioration in self-assessment of one's own health.

Our study revealed a significant difference in self-assessment of the quality of physical and mental health in men and women, adjusted for age, two years after COVID-19 - associated pneumonia (by 11.5 and 9.5 points, respectively). Similar results were obtained by many scientists studying the impact of COVID-19 on the quality of health in the post-Covid period. For example, in a study by Kuryllo T. et al (2023) they did not find gender differences in physical weakness during an observation period of 3 to 6 months after an infection, but after 6-12 months of observation they recorded significant gender

Table 5

Results of the ordered logistic regression assessment of answers to questions 8 and 9 according to the VR-12

Influence factor	Answer to question 8	Answer to question 9
	Regression coefficient±SE, *p*-level	
Age	0.071±0.015*. *p*<0.001	0.048±0.013*. *p*<0.001
Gender (male)	0.062±0.352. *p*=0.860	0.056±0.329. *p*=0.866
RDS (availability)	–0.049±0.567. *p*=0.930	0.212±0.491. *p*=0.666
% lung damage (CT)	–0.014±0.010. *p*=0.164	–0.009±0.008. *p*=0.342

* - coefficient is statistically significant at p<0.001.

differences in the assessment of physical health [24]. In particular, the authors noted that women experienced greater impairment in physical functioning, including decreased strength, walking shorter distances, and higher neurological load, even 1 year after hospitalization. A study by Huang L. et al (2021) showed that the use of corticosteroid therapy, widely used in the treatment of viral pneumonia in the first wave of COVID-19, contributed to the development of fatigue syndrome or muscle weakness 12 months after hospitalization specifically in women [3]. A Russian study based on a survey of 84 people found that women were more likely to report symptoms associated with deteriorating health 12 months after contracting COVID-19 [1]. Finally, a systematic review conducted by Sylvester S.V. et al. in 2022 led to the conclusion that, in general, female patients were more likely to have long-COVID-19, that is, female gender was a risk factor for chronic fatigue and symptoms of mood/behavioral disorders and other symptoms in the post-Covid period [23].

Our study showed that the presence of RDS during hospitalization did not predict the risk of deterioration in mental and physical health assessments two years after COVID-19. This result is consistent with a study by Heubner L. et al (2022), which showed that although RDS was associated with in-hospital mortality, in the medium term, RDS occurring during hospitalization was not a predictor of death [7]. At the same time, the authors showed that the presence of RDS influenced a decrease in quality of life, but this conclusion was made on the basis of an examination of patients 1 year after discharge, and not 2 years, as in our study. In addition, in our study there was no transfer to mechanical ventilation in any of the surveyed patients who had RDS. In the above study, on the contrary, in people with RDS in 27% of cases, not only mechanical ventilation was required, but also extracorporeal membrane oxygenation. It is noteworthy that in the work of Heubner L. et al. (2022), the percentage of lung damage was not a predictor of low physical health assessment (according to the VR-12 scale) 2 years after hospitalization for COVID-19 [7]. Similar results were obtained by Gulyaev P.V. et al (2022), who showed that the severity of the viral disease did not affect the physical condition after 12 months [1]. At the

same time, we found that a high percentage of lung damage, on the contrary, was a predictor of lower self-esteem of mental health according to the MCS scale even 2 years after hospitalization. This may be due to the fears and anxiety that arose after suffering COVID-19 in severe and moderate forms, which requires separate additional research.

Conclusion. The burden of COVID-19 is determined not only by the high mortality rate during infection, but also by the severity and long-term persistence of its complications. Our analysis of the quality of life showed that even after two years after the illness, some patients still have low self-esteem of their health. At the same time, there is a significant difference in the self-assessment of the quality of physical and mental health in men and women, taking into account adjustment for age - the indicators of the quality of life of women were lower. It was found that the presence of RDS during hospitalization is not a predictor of the risk of worsening mental and physical health scores two years after COVID-19, while age is a risk factor for worse self-esteem of one's own health, and a high percentage of lung damage is a risk factor for lower self-esteem mental health according to the MCS scale even 2 years after hospitalization. The study expands the understanding of the recovery trajectory of patients with COVID-19 and emphasizes the importance of individual recovery programs taking into account the severity of the disease, age and gender of patients.

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ALZHEIMER'S DISEASE IN THE REPUBLIC OF SAKHA (YAKUTIA): REALITIES AND EXPECTATIONS

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Introduction. Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline, primarily loss of memory for recent events. Despite the widespread prevalence of AD in the world, in Russia there is a high level of deficiency in diagnosing the disease. The Republic of Sakha (Yakutia) is a large subject of the Russian Federation; at the beginning of 2023, the population of the Republic was 997,565 people, and over the past 20 years, the share of elderly people (60 years and older) has increased 1.86 times (from 8.3% to 15 ,5%). The **aim of the research:** to assess the level of diagnosis of Alzheimer's disease and predict the likely number of patients in the Republic of Sakha (Yakutia). **Materials and methods:** to estimate the number of patients with AD, reports from neurologists of the Republic of Sakha (Yakutia) and official data on the disease provided by the Yakut Republican Medical Information and Analytical Center were analyzed (YRMIAC). To predict the number of patients in the city of Yakutsk and the regions of the Republic of Sakha (Yakutia) for each age group of the population, the maximum and minimum proportions of people who could potentially suffer from AD were calculated. Based on various epidemiological studies, three forecast scripts have been identified: "Chinese", "Japanese" and "American". **Results and discussion.** According to official data, 45 patients diagnosed with AD are registered in the Republic of Sakha (Yakutia), of which 36 (80%) people live in Yakutsk. According to reports from neurologists for 2022, only 7 people are registered at the dispensary with a diagnosis of Alzheimer's disease. If we extrapolate world data for the Republic Sakha (Yakutia), then the minimum number of patients with Alzheimer's disease should be 4,166.4 people and observed under the "Chinese" script, and the maximum number of patients – 8,428.5 people – under the "American" script. The largest number of patients is predicted in the industrial districts of the republic (Neryungri, Mirny and Aldan). The smallest number of patients with Alzheimer's disease is predicted in the Arctic and Northern districts, especially in Eveno-Bytantaysky and Anabarsky. **Conclusion.** Alzheimer's disease is one of the leading medical and social problems of the modern world. At this stage in the Republic of Sakha (Yakutia), improved diagnosis of the disease is required for the timely initiation of symptomatic therapy. The predicted number of patients determined by us in the city of Yakutsk and the districts of the Republic can serve as a guideline when screening patients for cognitive impairment.

Keywords: dementia, Alzheimer's disease, cognitive impairment, mind.

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline, primarily loss of memory for recent events [9]. AD is not only the leading cause of dementia, but also leads to significant mortality in the population. According to the 2023 Alzheimer's Disease Facts and Figures, the number of deaths from AD increased 145.2% from 2000 to 2019, making the disease the sixth leading cause of death among older adults in USA [8].

AD is based on the earlier extracellular accumulation of beta-amyloid and the later intracellular accumulation of tau protein, with amyloid plaques disrupting interneuronal communication at synapses, and intracellular tau protein blocks the transport of nutrients for the normal functioning of the neuron [3, 11, 21].

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According to leading neurologists, in Russia there is an extremely low detection rate of Alzheimer's disease: only 9 thousand patients are officially registered, while the expected number of patients is about 1.2 million people [1, 4, 6]. The disease is detected mainly only at the stage of severe dementia [2].

Age is one of the key risk factors for the disease. In the United States, 5.3% of people aged 65-74 years, 13.8% of people aged 75-84 years, and 34.6% of people over 85 years old have dementia due to Alzheimer's disease [17]. With regard to early-onset Alzheimer's disease, a large meta-analysis estimated that the prevalence of Alzheimer's disease among persons 35-64 years of age was 41.1 per 100,000 population, much higher in Europe than in the United States (54.1 vs. 31.8 for 100,000). In the age groups 35–39 years, 40-44 years, 45-49 years, the prevalence is only 0.1 for 100,000 people, while in the groups 50-54 years, 55-59 years, 60-64 years it increases and equals 1.5; 6.9 and 24.8 for 100,000 people, respectively [14].

Ethnicity is also likely to play a role in the development of Alzheimer's disease. Study of 10,342 participants from the United States showed that 18.6% of African Americans, 14.0% of Hispanic Americans and 10% of Caucasian Americans suffered from Alzheimer's disease [17]. According to another study, the lowest prevalence of dementia is found in Japanese Americans - 6.3% among people 65 years of age and older [15]. Almost similar data were obtained during a 10-year follow-up of 2034 people in Japan itself: the proportion of patients with AD dementia among people 65 years of age and older was 7.2% [24]. According to a meta-analysis, a high prevalence of AD is observed in China. Thus, among people 65-69 years old it occurs in 12.7%, and among people 95-99 years old – 48.2% [13].

The Republic of Sakha (Yakutia) is the largest subject of the Russian Federation, located in the North-West of the Far East, the area is 3102.2 thousand km2. If in 1990 the population of the Republic was 1,111,480 people, then in subsequent years there was a population decline, reaching a minimum number in 2003 - 948,636 people. Since 2004, there has been a slight annual increase in population and at the beginning of 2023 the population of the Republic was 997,565 people, incl. 48.3% are men and 51.7% are women. Yakutia has a unique multinational composition: more than half of the population (55.3%) are Yakuts, 32.6% are Russians, the remaining share (12.1%) is made up of Evenks, Evens, Kyrgyz, Ukrainians and other nationalities. As for the age structure, over the past 20 years the proportion of elderly people (60 years and older) has increased by 1.86 times (from 8.3% to 15.5%) (Fig. 1) [7].

The **aim of the research** is to assess the level of diagnosis of Alzheimer's disease and predict the likely number of patients in the Republic of Sakha (Yakutia).

Materials and methods. The study was conducted at the Department of Neurology and Psychiatry of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov and the Laboratory of Neurodegenerative Diseases of the Yakut Scientific Center for Complex Medical Problems. To estimate the number of patients with Alzheimer's disease, reports from neurologists of the Republic of Sakha (Yakutia) for 2022 and official data on the disease provided by the Yakut Republican Medical Information and Analytical Center (YRMIAC) were analyzed. To predict the number of patients in the city of Yakutsk and districts of the Republic of Sakha (Yakutia) for each age group of the population, the maximum and minimum proportions of people who could potentially suffer from Alzheimer's disease were calculated. Age groups of the population were formed from open data of the Territorial Authority of the Federal State Statistics Service for the Republic of Sakha (Yakutia) [7]. Based on various epidemiological studies [13,15,17], three forecast scripts have been identified: “Chinese”, “Japanese” and “American”.

Results. According to official data from YRMIAC for 2022, 45 patients diagnosed with Alzheimer’s disease are registered in the Republic of Sakha (Yakutia), of which 36 (80%) people live in Yakutsk, the rest in the central districts and in the Vilyui group of districts. Of the Arctic regions, only one patient was registered in the Abyisky district.

The results of the analysis of reports from neurologists are radically different from the YARMIAC data. According to reports from neurologists for 2022, only 7 people are registered at the dispensary with a diagnosis of Alzheimer’s disease: three patients in Yakutsk, two patients in the Tattinsky district and one patient each in the Verkhnevilyuysky and Nyurbinsky districts.

Table 1 shows the forecast for the number of patients with Alzheimer's disease among people 65 years of age and older in the city of Yakutsk and regions of the Republic of Sakha (Yakutia).

Based on Table 1, the minimum number of patients with Alzheimer's disease in the Republic of Sakha (Yakutia) should be 4,166.4 people. and be observed under the “Chinese” script, and the maximum number of patients is 8,428.5 people. – in the “American” script. The largest number of patients is predicted in the industrial districts of the republic: Neryungri (302.0-671.1 people), Mirny (196.2-429.6 people) and Aldan (173.3-365.9 people). In the central (Khangalassky, Namsky, Gorny) and trans-river districts (Ust-Aldansky, Churapchinsky, Tattinsky, Amginsky, Ust-Maisky) the projected number of patients with Alzheimer's disease ranges from 45.8 to 249.9 people, in the Vilyui group of districts (Vilyuisky, Verkhnevilyuysky, Nyurbinsky, Suntarsky) - from 74.5 to 167.6 people. The smallest number of patients with Alzheimer's disease is predicted in the Arctic and Northern districts, especially in Eveno-Bytantai (6.9-11.1 people) and Anabar (4.8-10.5 people) (Fig. 1).

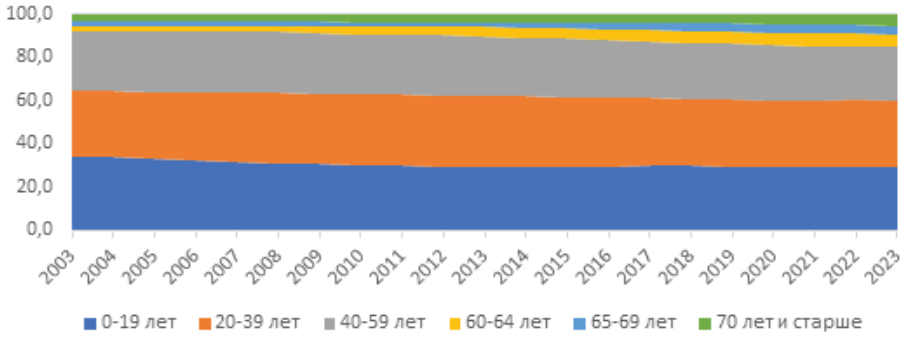

Fig. 1. Age structure of the population of the Republic of Sakha (Yakutia) from 2003 to 2023.

Table 1

Projected number of patients with Alzheimer's disease in the Republic of Sakha (Yakutia) among persons 65 years of age and older

	Сценарий		
	"Chinese" script	"Japanese" script	"American" script
Population of the Republic of Sakha (Yakutia), human.	992 115		
Population of the Republic of Sakha (Yakutia) aged 65 years and older, people.(%)	94 470 (9.52%)		
Predicted number of patients in the Republic of Sakha (Yakutia), people.	4 166.4	5 951.6	8 428.5
Predicted number of patients in Yakutsk, people.	1 499.4	1 947.1	2 908

Discussion. According to the results of our study, it follows that there is an extremely high level of underdiagnosis of Alzheimer's disease in the Republic of Sakha (Yakutia). The diagnostic deficit is 99%! The reason for low diagnosis, in our opinion, may be:

1. failure to timely seek medical help in the early stages of AD;
2. insufficient awareness of primary care physicians about the early manifestations of AD;
3. misunderstanding of dementia only as complete functional dependence on others (in fact, severe dementia);
4. lack of routing of patients with AD;
5. lack of highly sensitive biomarkers available in clinical practice.

The population of the Republic of Sakha (Yakutia) is heterogeneous by age group, which will certainly affect the number of patients with Alzheimer's disease in different districts. In 2022, the share of the population aged 60 years and older in the Republic was 15.5% (among women - 18.4%, among men - 12.4%). In six northern districts, the proportion of people of this age is less than 10% (Olenek-sky - 6.8%, Anabarsky - 6.8%, Eveno-Bytantaisky - 7.4%, Bulunsky - 8.7%, Zhigansky - 9.0%, Momsky – 9.3%). In three districts there is a large proportion

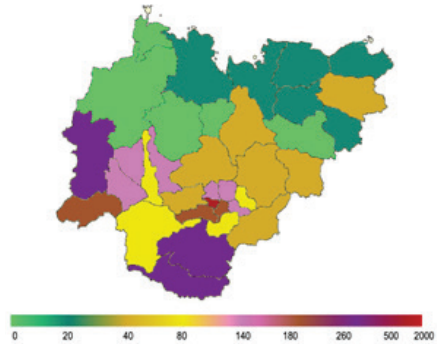

Fig. 2. Map of the projected number of patients with Alzheimer’s disease in the city of Yakutsk and regions of the Republic of Sakha (Yakutia), abs.

Table 2

Characteristics of cognitive decline in Alzheimer's disease

MCI in Alzheimer's disease	There are biomarkers of Alzheimer's disease and subtle problems with memory, speech and thinking. These disturbances are noticeable to the patient, family members, friends, but not to others and do not interfere with daily activities.
Mild dementia	People are able to function independently in many areas, but require assistance with some activities (especially managing finances and paying bills). Patients can still drive, work, and do business on their own.
Moderate dementia	People experience even greater problems with memory and speech, there may be episodes of disorientation, and it is difficult to perform multi-step tasks (bathing, dressing). Urinary incontinence may occur at times, and personality and behavior changes may begin, including suspiciousness and agitation. There may be problems recognizing loved ones.
Severe dementia	Patients almost completely lose the ability to communicate, require round-the-clock monitoring, and are often bedridden. Possible complications such as thrombosis, skin infections, sepsis, dysphagia, aspiration pneumonia

of people aged 60 years and older (> 20%): Verkhnekolymsky - 20.3%, Tattinsky - 20.6%, Ust-Maysky - 20.8%. The proportion of elderly women was higher than the proportion of men in the corresponding group by an average of 6.0%, the largest difference was found in the Aldan (8.6%) and Khangalass (8.0%) districts, the smallest difference was in the Anabar district (0,5%).

Dementia in Alzheimer's disease does not develop acutely and, in its development, overcomes the stage of moderate cognitive impairment. According to a systematic review, the conversion rate of AD in MCI ranges from 10.6% to 37.8% over 5 years [16]. The importance of identifying MCI is dictated by the fact that at this stage of cognitive impairment, 53.4% may have an improvement in cognitive functions, although for the amnestic type of MCI the proportion of patients with improvement is only 6.3% [17]. MCI is detected in 6.7% of the population aged 60-64 years, this figure increases and in the group of 80-84 years old reaches 14.8% [18]. Table 2 shows the characteristics of patients with varying degrees of cognitive decline in AD [1].

Of the identified genes, the APOE4 gene has the greatest influence on the development of AD. The APOE4 protein is involved in cholesterol transport. The greatest risk is observed in patients with the ε4/ε4 genotype (8-12 times higher), while the ε2/ε2 genotype is associated with a reduced risk, and the e3/e3 genotype has a neutral effect [10]. According to a large meta-analysis that included studies from 1985 to 2010, the distribution of heterozygous and homozygous carriage of the APOE4 gene in patients with AD differs depending on geographic location. The lowest prevalence of carriage was found in Asia (heterozygotes ε4 - 41.9%, homozygotes ε4/ε4 - 7.7%) and Southern Europe (heterozygotes ε4 - 40.5%, homozygotes ε4/ε4 - 4 .6%); on the contrary, in Northern Europe there was the largest number of carrier patients (heterozygotes ε4 - 61.3%, homozygotes ε4/ε4 - 14.1%) [19].

Despite hereditary burden, modifiable risk factors play a role in the development of AD. A study of more than 22,000 people showed that the cognitive performance of people aged 40–79 years who did not have risk factors for dementia was similar to that of people 10–20 years younger who did have risk factors [22]. It was found that a high level of education reduces the relative chance of developing AD (odds ratio = 0.64, confidence interval = 0.56-0.74), and also delays the time of development of cognitive impairment (OR = 0.76, CI = 0.67 -0.85) [22]. This is explained by a higher level of cognitive reserve in people whose work is associated with continuous education and intellectual activity [5].

One of the protective effects among the indigenous population of the Republic of Sakha (Yakutia) may be bilingualism. In China, the effect of bilingualism on AD was studied in Cantonese and Mandarin monolinguals as well as bilinguals. Scientists have found that bilinguals have a later onset of AD (70.93 years versus 63.9 years and 63.4 years) and an initially high level of MMSE (16.43 points versus 12.25 points and 15.75 points) [23].

Conclusion. Thus, AD is one of the leading medical and social problems of the modern world. At this stage in the Republic of Sakha (Yakutia), improved diagnosis of the disease is required for the timely initiation of symptomatic therapy. The predicted number of patients determined by us in the city of Yakutsk and the regions of the Republic can serve as a guideline when screening patients for cognitive impairment.

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EMERGENCY SURGICAL AID TO PATIENTS WITH COLORECTAL CANCER IN THE REPUBLIC OF SAKHA (YAKUTIA)

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УДК 616-01/-099:619.9:66-053.34

The article presents materials of the coloproctology department of the Republic hospital №2 - Emergency Medical Center for the last five years (2018-2022). Diagnosis and treatment of 399 patients with complicated colorectal cancer admitted by emergency indications were analyzed. 115 patients (28.8%) were delivered from the districts of the Republic by air ambulance. The remaining 284 patients (71.2%) were hospitalized from Yakutsk and its suburbs. 90% of patients were operated by emergency. The mortality rate after emergency surgical interventions amounted to 20.2%.

Keywords: neoplasms, colon, colorectal cancer, surgical treatment.

Introduction: Emergency surgical care in the Republic of Sakha (Yakutia) has its own peculiarities related to the vast territory, sparsely populated areas, transportation scheme and weather conditions [3]. There is a certain number of patients with complicated colorectal cancer among emergency surgical patients, who are admitted urgently to the surgical departments, as well as to the coloproctology department of the Republic hospital №2 - Emergency Medical Center. Specialized oncological care in the Republic is provided by the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republic Oncological Dispensary".

According to the researches [2], colorectal cancer ranks the 3rd position in the structure of oncologic morbidity in developed countries after lung cancer and gastric cancer, and accounts for 4-6% of the total oncopathology. There is an increase in the level of primary morbidity of malignant neoplasms by 13.4% according to the data of Yakutsk oncological dispensary for the last 10 years in the Republic of Sakha (Yakutia). 2506 cases of malignant neoplasms were detected in 2021 in the Republic for the first time. It is established that the age of patients with first detected colorectal cancer is predominantly older than 50 years old, and women are 1.5 times more often than men. [6]. Colorectal and rectosigmoid cancer occupies leading positions in morbidity and mortality among other malignant tumors due to clinical statistics. 45277 new cases of colorectal cancer were registered in 2019 in Russia, 23593 patients died from this disease [1]. Colorectal cancer was 14.0 per 100 thousand population, and rectosigmoid-rectal cancer was 12.2 per 100 thousand population in the Republic of Sakha Yakutia in 2019 according to L.N Afanasyeva and co-author study [2]. The mortality rate was 5.3 deaths per 100,000 population for colorectal cancer, and 3.0 per 100,000 population was for rectosigmoid-rectal cancer. The main problem in colorectal cancer is the occurrence of various complications in 8-30% of patients, first of all

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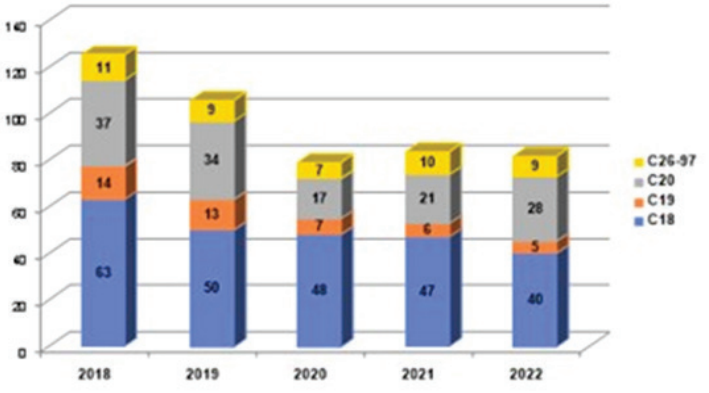
stenosis, manifested by acute obturation colonic obstruction, bleeding and perforation (8). Lethality in these complications ranges from 7.6 to 55.5%. [4] [5].

Materials and Methods. 399 patients with colorectal malignant neoplasms underwent emergency surgical treatment in the coloproctology department of Republic hospital №2 from 2018 to 2022. There were 103 patients in 2018, 85 - in 2019, 59 patients - in 2020, 51 - in 2021 and 101 patients - in 2022. There was a decrease in the number of patients in 2019 and 2020 due to the COVID-19 pandemic. As for gender, there were more females than males yearly, ranging from 4% in 2022 to 12% in 2020. In the age distribution, the largest number of patients were over 60 years old. All patients on admission were examined in the emergency room: examination of specialists with history taking, general and biochemical tests, ultrasound of abdominal cavity organs, radiography of abdominal cavity review, CT and MRI as indicated. After diagnosis and indications for emergency surgical treatment, preoperative preparation was carried out, for some patients - in the intensive care unit. The surgeon's tactics were specified on the operating table after laparotomy and revision of abdominal cavity organs.



Localization of neoplasms

Table 1

Distribution of patients with ZNO who were urgently hospitalized in the coloproctology department of RB2-CEMP for emergency indications, by year

Year	Total patients	Primary		They are registered in YAROD	
		abs.	%	abs.	%
2018	104	78	75	26	25
2019	85	70	82	15	18
2020	59	51	86	8	14
2021	51	40	78	11	22
2022	101	78	78	23	23

Table 2

Distribution of operations by type, n(%)

Year	Total operations	Hemicolectomy on the right	Hemicolectomy on the left	Sigma resection	Rectal resection	Preventive colostomy	Others
2018	103 (100)	17 (16,5)	21 (20)	23 (22)	7 (7)	17 (16)	17 (16)
2019	85 (100)	18 (21)	11 (13)	19 (22)	4 (5)	19 (22)	14 (16)
2020	59 (100)	14 (24)	7 (12)	19 (32)	2 (3)	13 (22)	4 (7)
2021	51 (100)	17 (33)	10 (20)	16 (31)	3 (6)	3 (6)	2 (4)
2022	102 (100)	24 (23)	21 (20)	24 (23)	7 (7)	12 (12,3)	15 (15)

Results and Discussion. As a result of disease neglect, 399 (100%) patients were hospitalized in the Republic hospital №2 as an emergency with complicated forms of colorectal cancer. According to the coding peculiarities of colorectal disease in ICD-10 (International Statistical Classification of Diseases and Health Related Problems) patients were divided into the following groups (Fig.1). C18 - malignant neoplasms of the colon, C19 - malignant neoplasms of the rectosigmoid, C20 - malignant neoplasms of the rectum, C26-97 - other malignant neoplasms. When divided by gender, there were more women than men in each year, ranging from 4% in 2022 to 12% in 2020. In the age distribution, the greatest number of patients were over 60 years old. Elderly patients had comorbid pa-

Table 3

Histological verification of complicated colorectal cancer

Year	Total	Highly differentiated adenocarcinoma	High-grade adenocarcinoma	Low-grade adenocarcinoma	GIST tumor	Nonspecific T-cell lymphoma	Ring-shaped cell carcinoma	Mucinous adenocarcinoma	Squamous cell carcinoma
2018	103	14 (14%)	85 (82%)	2 (2%)	1 (1%)	1 (1%)			
2019	85	9 (10%)	71 (83%)	4 (5%)			1 (1%)		
2020	59	7 (12%)	49 (83%)	3 (4%)				1 (1%)	
2021	51	5 (10%)	43 (84%)	1 (2%)				1 (2%)	1 (2%)
2022	101	21 (21%)	69 (68%)	5 (5%)				3 (3%)	3 (3%)

thology, which determined the severity of the condition in the postoperative period. As for nationality, 53% were native inhabitants and 47% were the immigrant population. Out of the 399 patients who were admitted to the emergency room of the Republic hospital №2, and hospitalized in the coloproctology department for emergency indications, 307(61.5%) patients were diagnosed with primary cancer: in 2018 - 78(75%), in 2019 - 70(82%), in 2020 -51(86%), in 2021 - 40(78%) and in 2022 78(77%) patients (Fig.2).

Our data show that the most frequent complication of colorectal cancer was obturation intestinal obstruction in 2018 - 61(59%), 51(61%) - in 2019, 43(73%) - in 2020, 32(57%) - in 2021 and 60(59%) cases in 2022. The second place in complications of malignant neoplasms was occupied by bleeding due to tumor decay with vascular arrosion, in 2018 - 19(18%), in 2019 - 13(15%), in 2020 - 7(12%), 2021 - 2 (9%) and in 2022 12(12%) patients. Then inflammatory complications (perforations, abscesses, peritonitis) in 2018 - 10(10%) , in 2019 - 8(9%), in 2020 - 3 (5%), in 2021 - 12(9%) and in 2022 - 11(11%), this complication has the highest mortality (see Fig. 7).

Nowadays, surgical intervention remains the method of choice in the treatment of colorectal cancer, especially in emergency admissions; the performed surgical intervention should not only comply with all oncologic principles of surgery, but also not reduce the patient's quality of life [7,8]. The hospitalized patients underwent the following surgical interventions on an emergency basis: hemicolectomy on the right side - 90(22.5%), hemicolectomy on the left side - 70(17.5%), Hartmann type surgery and sigmoid colectomy - 101(25.3%), removal of preventive ileostomy or colostomy - 64(16.0%), rectal resection - 23(5.7%) and other operations opening of abscesses, paraproctitis - 51(13.0%) (Fig. 4).

Moderately differentiated adenocarcinoma -317(79,4%) occupied the first place in histologic verification of complicated colorectal cancer. Highly differentiated adenocarcinoma 56(14,0%), then low-differentiated adenocarcinoma - 15(3,75%) mucinous adenocarcinoma - 5(1,2%) and squamous cell cancer were found in 4(0,7%) cases. And 1(0.2%) each GIST tumor, T-cell lymphoma and persistent cell carcinoma were detected. (Figure 5).

The mortality by complicated colorectal cancer was -16(15.5%) in 2018 , 10(11.7%) in 2019, 15(25.4%) in 2020, 14(27.4%) in 2021 and 22(21.3%) in 2022. Mortality averaged 20.2% over the five years.

Conclusion: The complicated colorectal cancer remains urgent problem and requires special attention. In the Republic of Sakha (Yakutia) emergency care for patients with colorectal cancer is provided in surgical departments of hospitals and in the coloproctology department of the Republic hospital №2- Emergency Medical Center, where patients are admitted from Yakutsk and suburbs, as well as after telemedicine consultation and from the regions of the Republic by air ambulance. According to the research results, 307 (76.9%) patients were diagnosed with colorectal cancer with complications, which had not been diagnosed earlier. It should be noted that complications due to tumor growth may occur even in case of previously confirmed diagnosis, so 83 (20.8%) patients were registered in Yakutsk oncological dispensary. All patients were operated on for emergency indications after preoperative preparation, surgical tactics was specified intraoperatively. Radical tumor removal at emergency operations was performed in 261 (65.4%) patients. The lethality was 20.2% among the patients with colorectal cancer operated on emergency indications.

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PREVALENCE OF SOCIAL RISK FACTORS AND ITS TRENDS IN THE POPULATION OF WOMEN OF REPRODUCTIVE AGE AT THE TERRITORIAL LEVEL

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Introduction. Tumours affecting the reproductive organs are diagnosed in women of fertile age in 20–40% of cases. Therefore, the current situation not only affects the quality and life expectancy of patients, but also leads to a decrease in the reproductive potential of the country. **Relevance of Research.** The authors' research aims to obtain new theoretical data regarding the risks of malignant neoplasms in the female genital system correlated with various ratios of risk factors at the territorial level. **Materials and Methods.** During the initial research stage, the authors employed the analytical method to gather data on risk factors for oncological malignancies identified through content analysis of both domestic and foreign literature sources. During the second research stage, data were collected regarding the incidence of cancer risk factors classified as social and hygienic factors. The data were collected retrospectively for the period of 1995–2020 (n = 36935). The data processing programme comprised the calculation of the prevalence rate of the risk of malignant neoplasms of the reproductive system in women of reproductive age. Research methodical specifics involved constructing parallel chronograms of each cancer risk factor and new onsets of malignant cancer diseases broken down by years of the research period. These data were used as evidence of effectiveness of cancer risk management procedures within the territory. **Conclusion.** The data obtained bolster the correlation between malignant reproductive diseases in women and social and hygienic risk factors. This substantiates the suggestion to incorporate such risk factors as maternal smoking, late first pregnancy and maternal age over 40 years, early sexual activity and large number of sexual partners in the set of indicators for assessing the risk burden in the territory.

Key words: public health, social risk factors, social determinant, systemic approach, reproductive age, malignant diseases of reproductive system organs in women, risks of malignant neoplasms of female genital system.

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Introduction. Patients with cancer in Russia make up 2.4% of the population. In 2018, their total number was over 3.5 million, including more than 600,000 patients diagnosed with new-onset malignant neoplasms (MNDs). In 2021, a total of 580,415 cases of malignant neoplasms were newly diagnosed in the Russian Federation, with over half of them occurring in female patients. In comparison to year 2020, there was a rise of 4.4% in this metric. Furthermore, the prevalence of malignant neoplasms in the Russian population surpassed the 2011 level by 32.6%. [18]. In 2020, the crude morbidity marker per 100 thousand people in Russia amounted to 379.7, with an increase of 20.5% over the 10-year period. This can largely be attributed to the unfavourable demographic trends in the population, which have led to its ageing. Breast cancer is the most prevalent MND among females worldwide, accounting for more than 20% in the cancer morbidity distribution [19]. Despite comparable global and Russian incidence rates of breast cancer (with over 1.5 million cases diagnosed worldwide annually and over 68,000 in Russia), the mortality rate from this disease is higher in the latter country than elsewhere [21, 32]. The relationship between the stage of a neoplastic process and the effectiveness of treatment and survival rates is widely acknowledged. Currently, the Russian Federation reports detection rates of 2.0–2.5 cases of breast cancer at the in situ stage per every 100 newly diagnosed malignant neoplasms [19]. Uterine body cancer (UBC) is the most prevalent malignant tumour of the female reproductive system in developed countries and the second most prevalent malignant tumour after cervical cancer (CC) worldwide [13, 19]. UBC ranks third in the distribution of the disease among the female population in Russia. More than 20,000 new cases are reported each year. Between 2006 and 2017, the increase in adjusted incidence rate per 100,000 female population was 23.54% [15]. In Ivanovo Oblast, the incidence of UBC surpasses the national average consistently. During the last decade, there has been a noticeable upward trend in the disease incidence from 25.94 per 100,000 women in 2010 to 45.7 per 100,000 women in 2020, making this matter especially pressing for the region. The incidence of CC within the country stood at 19.75 per 100,000 women in 2020, denoting an increase of 12.4% over the last 5 years. The high neglect rate for cervical cancer in Russia, which was 34.1% in 2021 and 33.6% in 2020, highlights the importance of giving priority to timely diagnosis of neoplastic processes. Meanwhile, the detection rates for preinvasion and early stage cases, where organ preservation treatment is possible, are still unsatisfactory. The

incidence of in situ cervical cancer was 33.6 cases per 100 new cases of cervical malignancy diagnosed in 2021, indicating an increase from 30.8 cases in 2020 [4]. In 20–40% of cases, reproductive organ tumours (ROTs) are diagnosed in women of fertile age. Therefore, the current situation not only affects the quality and life expectancy of patients, but also leads to a decrease in the reproductive potential of the country.

Relevance of Research. The relevance of our research lies in the acquisition of new theoretical data regarding the risks of malignant neoplasms in the female genital system at a territorial level. Our objective is to confirm trends and practical work scope in the healthcare system that concentrate on the female population in the region, taking into account the obtained risk characteristics and dynamic trends.

Research Materials and Methods. The research methodology utilised a systemic approach to examine the risk factors for female reproductive organ malignancies. This approach draws on data from both domestic and foreign researchers highlighting the significant incidence of comorbid gynaecological pathologies in patients with breast diseases, breast cancer, endometrial cancer, ovarian cancer, preinvasive diseases and CC [5,6]. Several authors consider the condition of mammary glands a marker of reproductive health [3, 5, 6, 14]

The identified interrelationships allowed us to merge risk factors for the emergence of specific forms of malignant neoplasms into a unified set of risk factors for the development of malignant neoplasms in the reproductive system. We also examined patterns in its condition and trends at a territorial level.

During the initial research stage, the authors employed the analytical method to gather data on risk factors for oncological malignancies identified through content analysis of both domestic and foreign literature sources. During the second stage, we acquired data on the frequency of cancer risk factors within the social and hygienic factors group. These factors are related to both family and non-family characteristics, and were identified among the risk factors for perinatal and maternal mortality. The data were obtained from the system that monitors the health and medical surveillance of women who are pregnant or have recently completed pregnancy (on the example of one constituent entity of the Russian Federation). The data were collected retrospectively for the period of 1995–2020 (n = 36935). The data processing programme comprised the calculation of the prevalence rate of the risk of malignant neoplasms of the reproductive system in women of reproductive age (number of risk cases per 1,000 women) as well as the prevalence rates of individual risk factors (number of cases of risk factor registration for malignant neoplasms affecting the reproductive system in cases per 1,000 women). The research analysed the number of women of reproductive age over the course of several years (five-year periods in 2000, 2005, 2010, 2015, and 2020) and made a medium-term forecast using extrapolated data from the multi-year trend. Data on the occurrence and composition of malignant tumours affecting reproductive organs were sourced from Russian and regional statistics. Research methodical specifics involved constructing parallel chronograms of each cancer risk factor and new onsets of malignant cancer diseases broken down by years of the research period. These data were used as evidence of effectiveness of cancer risk management procedures within the territory.

Results and Discussion. Based on the statistical data collected, the incidence rates of malignant neoplasms affecting the reproductive organs of women residing in Ivanovo Oblast have been consistently higher than the national average for the past decade and display an increasing trend, as depicted in diagrams 2 and 3. Consequently, further investigation into this problem remains a priority.

In line with the research programme, we analysed the risk factors for malignant neoplasms of the reproductive system in women identified by domestic and foreign researchers. For this purpose, a literature

Table 1

Look-up table of risk factors for malignant neoplasms of the reproductive system in women (based on systemic analysis of special literature)

Factor name	Source number in the reference list
Harmful habits (smoking, alcohol)	23, 30, 35, 37
Occupational hazards	2, 36
Environmental factors	24, 34, 36
Late first labour	2, 5, 6, 10, 20, 26
Cervical diseases and destructive interventions	1, 11, 38
Gynaecological diseases	1, 5, 9, 12
in vitro fertilisation	16, 33
Endometriosis	7, 40
Uterine and ovarian tumours	22, 39
Parovarium surgeries	17, 29
Infertility	17
HPV infection	9, 11
Abortions	27
Obesity	25
Diabetes mellitus	8
Thyroid diseases	10
Liver diseases	10
Psychological factors, stress	28

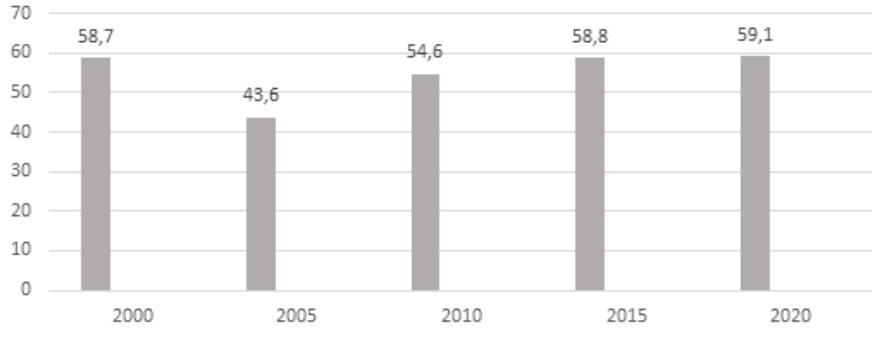

Fig. 1. Frequency of women of childbearing age at risk of malignant neoplasms of reproductive organs at the territorial level

review was conducted to investigate the risk of developing malignant reproductive system pathologies in women of reproductive age. The search depth covered 10 years, the number of works analysed on the problem amounted to 264, including 32 monographs, 198 articles and 34 dissertations.

The search outcomes were collated in a table (Table 1) that classifies risk factors contributing to female reproductive system cancer via alphabetical order and by origin (societal environment, lifestyle, living conditions, somatic, gynaecological, psychological, reproductive, and genetic health).

The evaluation of literature on malignant neoplasms affecting the reproductive system in women of reproductive age reveals numerous studies confirming the existence of risk factors for the development of these malignant neoplasms. The scholarly importance of this information establishes the basis for conduct-

Table 2

Frequency of social risk factors for malignant reproductive neoplasms in women of reproductive age at the territorial level

Name	2000		2005		2010		2015		2020	
	Abs.	Cases per 1.000	Abs.	Cases per 1.000	Abs.	Cases per 1.000	Abs.	Cases per 1.000	Abs.	Cases per 1.000
Habits that are harmful to the mother: smoking	586	25.83	526	21.19	902	25.74	1011	28.75	617	20.7
Occupational hazards adversely affecting the mother	172	7.58	84	3.38	32	0.91	22	0.63	20	0.67
Environmental factors at the woman's place of residence	74	3.26	61	2.46	41	1.17	32	0.91	1	0.03
Maternal age over 40 years	57	2.51	36	1.45	81	2.31	147	4.18	186	6.24
Habits that are harmful to the mother: alcohol abuse, drug addiction	39	1.72	44	1.77	78	2.23	95	2.70	13	0.44
Maternal age of 35–40 years, primipregnancy	16	0.71	124	5.00	572	16.32	830	23.60	976	32.75
Marital status (single, divorced, common-law marriage)	4167	183.71	3585	144.45	3498	99.81	2720	77.35	1776	59.6
Financial situation	1805	79.58	952	38.36	860	24.54	320	9.10	136	4.53
Unintended pregnancy	806	35.53	409	16.48	167	4.77	255	7.25	188	6.31
Conflict within the family (unwanted child)	320	14.11	124	5.00	46	1.31	28	0.80	10	0.34
Early sexual activity (before 19)	172	7.58	124	5.00	81	2.31	95	2.70	75	2.52
More than 3 sexual partners	39	0.17%	36	1.45	32	0.91	83	2.36	63	2.11

Table 3

Social risk factor structure for malignant reproductive system neoplasms in women of reproductive age over time for the period from 2000 to 2020

Name	2000		2005		2010		2015		2020	
	Abs.	D%	Abs.	D%	Abs.	D%	Abs.	D%	Abs.	D%
Harmful habits (maternal smoking)	586	7.10	526	8.62	902	14.12	1011	18.23	617	15.15
Occupational hazards adversely affecting the mother	172	2.08	84	1.38	32	0.50	22	0.40	20	0.49
Environmental factors at the women's place of residence	74	0.90	61	1.00	41	0.64	32	0.58	13	0.32
Maternal age over 40 years	57	0.69	36	0.59	81	1.27	147	2.65	186	4.57
Habits that are harmful to the mother (alcohol abuse, drug addiction)	39	0.47	44	0.72	78	1.22	95	1.71	13	0.32
Maternal age of 35–40 years, primipregnancy	16	0.19	124	2.03	572	8.95	830	14.97	976	23.96
Marital status (single, divorced, common-law marriage)	4167	50.49	3585	58.72	3498	54.74	2720	49.05	1776	43.60
Financial situation	1805	21.87	952	15.59	860	13.46	320	5.77	136	3.34
Unintended pregnancy	806	9.77	409	6.70	167	2.61	255	4.60	188	4.62
Conflict within the family (unwanted child)	320	3.88	124	2.03	46	0.72	28	0.50	10	0.25
Early sexual activity (before 19)	172	2.08	124	2.03	81	1.27	63	1.14	75	1.84
More than 3 sexual partners	39	0.47	36	0.59	32	0.50	22	0.40	63	1.55
Total	8253	100,0	6105	100,0	6390	100,0	5545	100,0	4073	100,0

ing further research on the risk factors associated with malignant neoplasms in reproductive organs. Concurrently, we consider researching the incidence of each identified risk factor in the female population of a specific area, tracking this metric over time and correlating it to dynamic primary morbidity rates of malignant neoplasms to be a vital aspect of the study of the problem in women of reproductive age.

To examine the occurrence of neoplastic conditions in the reproductive organs of women of reproductive age (Table 2), we gathered pertinent data and conducted an analysis at the territorial level employing the risk factor look-up table created during the initial stage of the research. We followed the methodology detailed in the Materials and Methods section.

Figure 1 illustrates the incidence of malignant neoplasms of the reproductive system in women of reproductive age.

The table displays the frequency of risk factors associated with malignant neoplasms of the reproductive system in women of reproductive age at the territorial level, as identified by researchers (Table 3).

Table 5 displays the structure of specific risk factors associated with malignant neoplasms of the reproductive system in women of reproductive age who have performed reproductive function in 2000, 2005, 2010, 2015, and 2020. The fidelity assessment of these indicators has been conducted by determining the t-test.

The proportion of the insufficient financial security risk factor among the survey participants decreased over the examined period. There has been a notable reduction in the proportion of environmental factors as a component of cancer risk factors from 2000 to 2020. The share of unstable marital status as a component of cancer risk factors had a pronounced unidirectional downward trend over the entire study period. Unfortunately, these favourable changes in the structure of socio-hygienic factors were not translated into the dynamics of cancer incidence in women's reproductive organs.

The proportion of late first pregnancies has risen steadily from 0.07% in 2000 to 3.35% in 2020, correlating with rising rates of endometrial, breast and cervical cancer by 2015. The reduction in the occurrence of gynaecological cancer in 2020, according to our viewpoint, cannot be attributed to genuine progress, but rather to a decline in the identification of tumour diseases due to the difficulties in arranging screening and preventive examinations in the context of the coronavirus infection pandemic. Between 2005 and 2020, there was a significant rise in the ratio of pregnant women over the age of 40 who were surveyed.

The proportion of harmful habits in a pattern of risk factors over the period 2000–2015 was not reliably different. However, there was a substantial reduction in the incidence of this factor in 2020. The proportion of women who reported having more than three sexual partners in surveys conducted between 2000 and 2015 declined gradually. However, in 2020, this indicator experienced a significant increase.

The proportion of unintended pregnancies among those surveyed was highest in 2000. It then decreased significantly, reaching its lowest level in 2010, after which it increased again in 2015–2020, although the analysed indicator remained significantly lower than the baseline. The

Table 4

The structure of specific risk factors for malignant neoplasms of the reproductive system among populations of women of reproductive age who performed reproductive function between 2000 and 2020

Analysed factor	Fidelity assessment (D)	Year				
		2000	2005	2010	2015	2020
Occupational hazards	D%	2.08	1.38	0.5	0.4	0.49
	previous year t		3.27	5.05	0.85	-0.68
	base year t		3.27	8.78	9.45	10.99
Financial situation	D%	21.87	15.59	13.46	5.77	3.34
	previous year t		9.66	3.39	14.52	5.78
	base year t		9.66	13.48	29.15	47.14
Environmental factors at the place of residence	D%	0.9	1	0.64	0.58	0.32
	previous year t		-0.62	2.21	0.45	1.91
	base year t		-0.62	1.77	2.2	5.33
Marital status	D%	50.49	58.72	54.74	49.05	43.6
	previous year t		-9.84	4.49	6.21	5.31
	base year t		-9.84	-5.12	1.66	8.15
First pregnancy in the age of 35-40	D%	0.19	2.03	8.95	14.97	23.96
	previous year t		-9.83	-17.29	-10.07	-10.93
	base year t		-9.83	-24.30	-30.68	-35.50
Maternal age over 40 years	D%	0.69	0.59	1.27	2.65	4.57
	previous year t		0.75	-3.97	-5.38	-4.89
	base year t		0.75	-3.45	-8.37	-11.69
Habits that are harmful to the mother (alcohol abuse, drug addiction)	D%	0.47	0.72	1.22	1.71	0.32
	previous year t		-1.88	-2.86	-2.22	7.13
	base year t		-1.88	-4.77	-6.53	1.54
More than 3 sexual partners	D%	0.47	0.59	0.5	0.4	1.55
	previous year t		-0.95	0.67	0.85	-5.45
	base year t		-0.95	-0.24	0.67	-5.41
Unintended pregnancy	D%	9.77	6.7	2.61	4.6	4.62
	previous year t		6.71	10.83	-5.76	-0.04
	base year t		6.71	18.68	11.98	13.44
Conflict within the family (unwanted child)	D%	3.88	2.03	0.72	0.5	0.25
	previous year t		6.62	6.27	1.51	2.11
	base year t		6.62	13.3	14.48	24.24

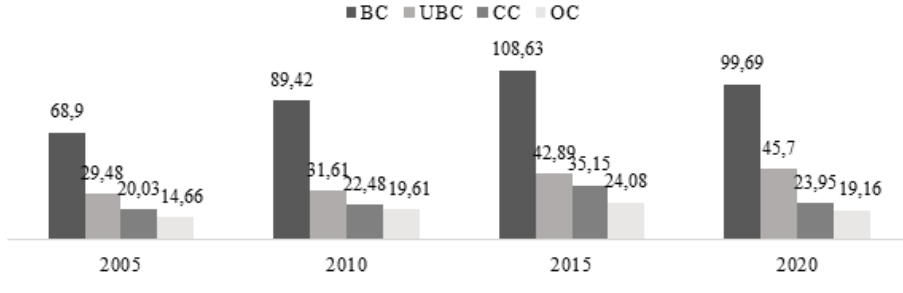

Fig. 2. Dynamics of MND incidence per 100,000 female population

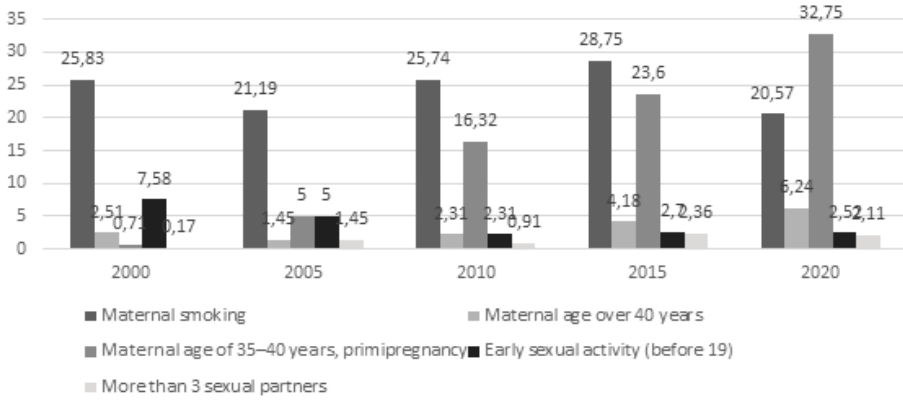

Fig. 3. Prevalence data on social and hygienic risk factors for malignant reproductive system cancer and incidence rates in women of reproductive age between 2000 and 2020 within the same constituent entity of the Russian Federation (Ivanovo Oblast)

incidence of conflicts arising within families due to the birth of an unwanted child demonstrated a distinct and consistent decline throughout the analysed period.

It was relevant to analyse the data concerning the risk of malignant neoplasms in the reproductive system of women of reproductive age, with regard to evaluating the evidence supporting the significance of risk factors. To meet this aim, we undertook a comparative analysis of the extended-term trend in social factors and indicators of recently diagnosed malignant cancers in a specific area, utilising graphical analysis.

We examined statistical data on the occurrence of primary malignant neoplasms in women of reproductive age and compared them with data on the prevalence of risk factors for malignant cancer of the reproductive system in the same region over a twenty-year period. Figure 2 presents the trend in the occurrence of malignant neoplasms (MND) affecting reproductive system organs in the region.

Figure 3 presents the prevalence data on social and hygienic risk factors for malignant reproductive system cancer and incidence rates in women of reproductive age between 2000 and 2020 within the same constituent entity of the Russian Federation (Ivanovo Oblast).

The data obtained indicate that within the group of social and hygienic risk factors, there is a mutually reinforcing relationship between the incidence rate of malignant oncopathology of the reproductive system in women and several risk factors, including maternal smoking, late first pregnancy, maternal age over 40 years, early sexual activity, and large number of sexual partners.

This allows to incorporate these factors into a set of 12 social and hygienic indicators to evaluate the risk burden of malignant neoplasms in women residing in the area.

Conclusion. The data obtained bolster the correlation between malignant reproductive diseases in women and social and hygienic risk factors. This substantiates the suggestion to incorporate such risk factors as maternal smoking, late first pregnancy and maternal age over 40 years, early sexual activity and large number of sexual partners in the set of indicators for assessing the risk burden in the territory.

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ASSESSMENT OF CARBOHYDRATE-LIPID BALANCE IN PEOPLE UNDERGONE COVID-19 AMONG THE RESIDENTS OF YAKUTSK

An assessment was made of the biological constant, consisting of the sum of glucose and total cholesterol levels in 161 residents of Yakutsk aged 20 to 72 years who had recovered from COVID-19.

The increase in this biological constant in the post-Covid period is most acutely expressed in individuals with morbid obesity. At the same time, there was a statistically significant tendency to increase the constant, as the disease worsened. Its significant increase to 12.25 mmol/l was noted in the post-ovoid period, in the group of patients with severe lung damage. The imbalance of harmony occurs due to an increase in glucose concentration, i.e. it is associated with a violation of carbohydrate metabolism. The results of our study indicate that patients who have suffered from SARS-CoV-2 coronavirus infection are at high risk of developing cardiovascular diseases in the postcovid period.

Keywords: coronavirus infection, glucose, total cholesterol, biological constant, body mass index, fatness.

Introduction. The rapid outbreak of coronavirus disease 2019 (COVID-19) has negatively impacted the quality of life of people around the world. According to WHO epidemiological data, up to December 2021, a total of 270,155,054 confirmed cases have been reported with a total of 5,305,991 deaths, with a mortality rate of 2.18% and hospital mortality of 15% to 20% [4].

During the pandemic, people's eating behavior has changed significantly. According to literature data, 5% of patients with COVID-19 who were treated in a hospital had a decrease in appetite, severe weight loss, a feeling of fullness, a change in taste, and a lack of smell [5, 8, 9]. Malnutrition compromises immunity and the inflammatory response, so a nutritional support system may be necessary to reduce complications caused by SARS-CoV-2, disease progression, and even death [3]. Decreased appetite and caloric intake have been reported to be associated with increased synthesis of pro-inflammatory interleukins, mainly TNF-alpha, leading to cachexia [7, 9].

Obesity is a major factor in the development of type 2 diabetes mellitus, and its global prevalence contributes to increased cardiovascular morbidity and mortality [2]. Body weight is regulated by the interaction of a number of processes, including homeostatic, environmental and behavioral factors [2, 6].

According to I.M. Rosly (2020), the total amount of cholesterol and glucose is equal to a rigid biological constant (10 mmol/l), which is necessary to assess the degree of changes in carbohydrate and lipid balance [1]. Disturbances in lipid metabolism caused by COVID-19 may persist in the post-Covid period, causing the development of cardiovascular diseases.

The purpose of the work was to study changes in glucose and total cholesterol levels in people who have had COVID-19, depending on body mass index and the severity of lung damage.

Material and methods. A survey was carried out on 161 people in Yakutsk, 60 men (37.1%) and 101 women (62.7%), who had recovered from COVID-19, with varying degrees of lung damage, aged from 20 to 72 years. The average age of the surveyed men was 50.5 [40.0; 61.7], women - 53.0 [42.0; 61.5] years. Patients with signs of ARVI at the time of the study were excluded from the group.

All examined patients, depending on their body mass index (BMI), were conditionally divided into 5 main groups according to the generally accepted WHO classification; the first group included persons with normal weight with a BMI of 18.5-24.9, the second group included those with a BMI of overweight - 25-29.9, the third person with class 1 obesity with BMI - 30-34.9, the fourth with class 2 obesity with BMI - 35-39.9 and the fifth person with class 3 obesity (morbid) with BMI above 40. Body mass index (BMI) or Quetelet II index was calculated using the formula:

BMI, kg/m2 = body weight, kg/height, m2.

To determine the frequency of lipid metabolism disorders, the Russian recommendations of the VII revision of the Russian Society of Cardiology 2020, compiled taking into account the European recommendations 2019, were used. Hypercholesterolemia (HCH) was defined as a total cholesterol level ≥ 5 mmol/l (190 mg/dl) taking into account the SCOR scale. Hyperglycemia was defined as glucose ≥ 5.6 mmol/L. The value of the hard biological constant was assessed by the level of total cholesterol and glucose, the values of which should not exceed 5 mmol/L and a total of 10 mmol/L.

Depending on the degree of lung damage, all subjects were divided into four groups: the first group with CT 0 (no lesion), the second group with CT 1 (with mild damage), the third - CT 2 (with moderate-severe damage) and the fourth with CT 3 (severe damage), confirmed by the result of X-ray computed tomography (X-ray CT).

Biochemical indicators - the level of glucose, total cholesterol, triglycerides and lipoproteins, were determined on an automatic biochemical analyzer "Labio - 200" (Mindray, China), using Biocon reagents. Blood sampling was carried out in the morning, on an empty stomach, from the cubital vein. Laboratory studies were performed using blood serum.

The study was conducted with the informed consent of the subjects, approved by the decision of the ethical committee of the Federal State Budgetary Institution "Yakut Scientific Center for Complex Medical Problems".

The obtained data were processed using the statistical program SPSS Statistics 19. Data are presented as Me (median), Q1 and Q3 (25 and 75% quartiles). The significance of differences in mean values was assessed using Student's t-test and ANOVA, for independent samples with a normal distribution and the Mann-Whitney test with a non-normal distribution. Correlation analysis of data was carried out using the Pearson and Spearman method. The critical value of the level of statistical significance of differences (p) was taken equal to 5%.

Results and discussion. The results of our study revealed statistically significant changes in the biological constant in people sick with COVID-19, depending on the covid period (from the moment of admission to the hospital and discharge after treatment) and the post-covid period. The period from the moment of recovery ranged from 3 months to 1 year.

A significant increase was observed in patients infected with the SARS-CoV-2 virus in the post-Covid period, and amounted to 11.51±0.16 mmol/l. The equilibrium shift was shifted towards carbohydrate metabolism, since the levels of glucose and total cholesterol were above the norm of 5 mmol/l and amounted to 6.07±0.13 mmol/l and 5.44±0.08 mmol/l (Table 1). As a percentage, the excess of the concentration of total cholesterol from the norm was 8% and glucose - 7%, respectively.

Our analysis showed that upon admission to the hospital, the biological constant in patients with COVID-19 was 10.65±0.44 mmol/l. At discharge, this hard-biological constant was 10.78±0.72 mmol/l. The average total cholesterol value in patients with COVID-19 upon admission and discharge was within the physiological norm. At the same time, changes in the components of the biological constant were multidirectional: the glucose concentration in patients upon admission to the hospital was higher than at discharge, and the content of total cholesterol, on the contrary, at discharge was increased (Table 1).

In the post-Covid period, the content of total cholesterol in patients increased statistically significantly, compared with similar indicators in patients upon admission and upon discharge, and amounted to 5.44±0.08 mmol/l. The serum glucose level was characteristically high on admission to hospital compared with that on discharge and was 6.41±0.27 mmol/l (p=0.01). In the post-Covid period, this figure increased again (Table 1). The data presented indicate an imbalance and disruption of biological phenomena in patients upon admission to the hospital in general due to a decrease in glucose levels. The trend toward normalization of biological constants after treatment tends to occur in the post-Covid period.

Thus, the highest average value of the sum of glucose and total cholesterol was observed in the group of patients in the post-Covid period, exceeding the normal value by 15%, due to an increase in cholesterol levels by 9% and glucose by 8.4% from the normal level. An excess of

Table 1

The content of glucose and total cholesterol in the blood serum at different periods after infection with SARS-CoV-2.

Biochemical indicator	Upon admission 1	At discharge 2	The Postcovid period 3	p
Glucose, mmol/l	6.41±0.27** n=62	5.89±0.31 n=51	6.07±0.13 n=161	$p^{1.2}$=0.011 $p^{1.3}$=0.578 $p^{2.3}$=0.238
Total cholesterol, mmol/l	4.27±0.17** n=29	4.40±0.20** n=21	5.44±0.08** n=161	$p^{1.2}$=0.089 $p^{1.3}$=0.000 $p^{2.3}$=0.015
Biological constant, mmol/l	10.65±0.44 n=29	10.78±0.72 n=21	11.51±0.16 n=161	$p^{1.2}$=0.489 $p^{1.3}$=0.114 $p^{2.3}$=0.190

Note. In table 1 and 2 ** - differences are significant at p<0.05.

the constant by more than 10 mmol/l indicates the severity of metabolic disorders. Glucose plays a major role in metabolism, as it is the main source of energy.

The biological constant in patients infected with SARS-CoV-2 in the post-Covid period was higher than normal and depended on the severity of lung damage (Table 2).

At the same time, there was a statistically significant tendency towards an increase in the constant depending on the degree of lung damage. Its significant increase was noted in the group of patients with CT 3 and amounted to 12.26±0.41 mmol/l. Moreover, its increase is accompanied by a significant increase in glucose levels by 17%, compared with the group of patients with CT 0 (Table 2). In this group of patients, the constant was the smallest and equaled 10.97±0.32 mmol/l. It was observed that the concentration of glucose and the level of total cholesterol in the blood serum in patients who had recovered from COVID-19, regardless of the degree of lung damage, remained statistically significantly higher than the reference values (Table 2). In the group of patients with CT 2 and CT 3, this coefficient was 11.99±0.40 mmol/l and 12.26±0.41 mmol/l, respectively.

The results of our study revealed changes in glucose levels depending on BMI in the post-Covid period (Fig. 1). There was a statistically significant trend toward increased glucose levels in the more obese groups. The median glucose in patients with SARS-CoV-2 infection with normal body weight did not exceed the reference values and was equal to 5.40 [5.10; 5.80] mmol/l. In patients with excess body weight in the post-Covid period, the median was 5.71 [5.35; 6.15] mmol/l, when compared with patients with normal body weight (p=0.015). Meanwhile, in the group of patients with obesity of 1 and 2 degrees, the glucose level was 5.83 [5.50; 6.70] (p=0.001)

Table 2

Glucose and cholesterol levels depending on the severity of CT

Biochemical indicator	CT 0 n=27 1	CT 1 n=60 2	CT 2 n=42 3	CT 3 n=32 4	p
Glucose, mmol/l	5.62±0.12**	5.85±0.13**	6.29±0.36**	6.62±0.42**	$p^{1.3}$=0.076 $p^{2.4}$=0.036
Total cholesterol, mmol/l	5.34±0.26**	5.19±0.11**	5.70±0.14**	5.63±0.20**	$p^{1.4}$=0.043 $p^{2.3}$=0.007 $p^{3.1}$=0.049 $p^{3.2}$=0.007
Biological constant, mmol/l	10.97±0.32**	11.05±0.18**	11.99±0.40**	12.26±0.41**	$p^{1.3}$= 0.025. $p^{2.4}$=0.015 $p^{4.1}$=0.014 $p^{1.4}$=0.051

and 5.85 [5.46; 6.45] mmol/l, compared with patients with normal BMI (p=0.019). In two patients with a BMI over 40, the median glucose was 12.75 [5.40; 20.10] mmol/l, but due to the small number of subjects studied, the difference is not statistically significant.

According to our data, in the post-Covid period, the content of total cholesterol in the blood serum, regardless of BMI, was higher than the reference values (Fig. 2). The highest level of total cholesterol was observed in the group of patients with stage 2 obesity with a median of 5.47 mmol/l [4.64; 6.14]. In patients with morbid obesity, the median total cholesterol was 5.20 mmol/l [4.77; 5.78]. In the group of patients with normal and overweight, the concentration of total cholesterol was increased by 7-8% of the reference value.

Thus, the results of our study indicate that patients who had COVID-19 experienced an imbalance of the biological constant associated with impaired carbohydrate metabolism. In all study groups, the biological constant was higher than normal. At the same time, a tendency for the constant to increase with increasing body weight was revealed. Thus, in persons with normal body weight, this constant was increased by 8%, with overweight by 10.9%, with class 1 obesity by 12%, with class 2 obesity by 13% and with morbid obesity by 79%.

Correlation analysis showed that the sum of total cholesterol and glucose is positively correlated with the level of triglycerides, LDL cholesterol, VLDL cholesterol, Ka and has a positive relationship with BMI (Table 3). In turn, a high coefficient of atherogenicity is associated with excess body weight. Table 3 shows the relationship of body mass index with lipid metabolism fractions and glucose. An increase in body weight is accompanied by a significant increase in primarily TG, VLDL, Ka, and glucose. Among all the biochemical parameters associated with lipid metabolism, the antiatherogenic lipid fraction of HDL cholesterol, which negatively correlated with BMI, is of greater importance. The low level of antiatherogenic lipid fraction indicates that these patients are in the group with the highest risk of developing cardiovascular diseases.

In the post-Covid period, an increase in the biological constant occurs due to a metabolic disorder in carbohydrate metabolism. Perhaps the increase in blood glucose levels is due to poor carbohy-

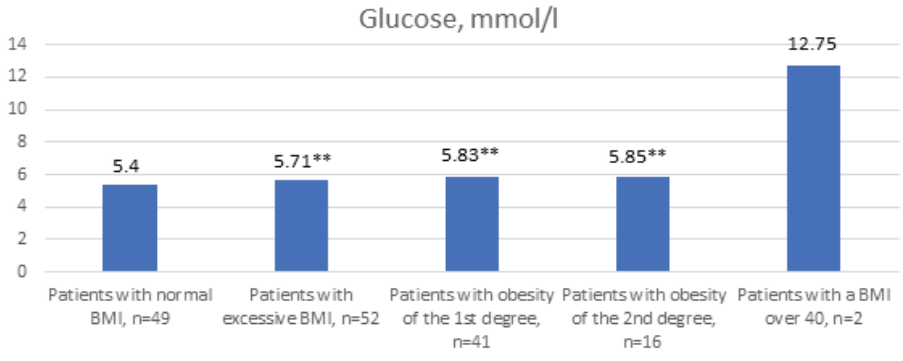

Fig. 1. Median serum glucose in patients with COVID-19 in the postcovid period, where, ** is the level of statistical significance p≤0.05

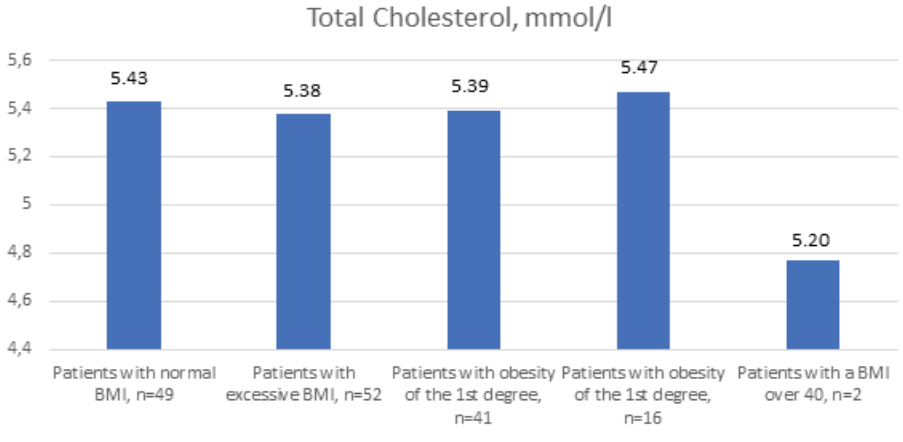

Fig. 2. Median total serum cholesterol in patients with COVID-19 in the postcovid period, where ** is the level of statistical significance p≤0.05

Table 3

Correlation of BMI of lipids and glucose in the blood serum of the subjects in the postcovid period

	TG	TCH	HDLP	LDLP	VLDLP	C_a	Glucose	TCH+ Glucose
BMI	0.378** 0.000		-0.241** 0.000		0.366** 0.000	0.232** 0.000	0.233** 0.000	0.155** 0.01
TG		0.255** 0.000	-0.290** 0.000	0.166** 0.002	0.983** 0.000	0.436** 0.000	0.275** 0.000	0.365** 0.000
TCH			0.153** 0.004	0.758** 0.000	0.255** 0.000	0.209** 0.000		0.585** 0.000
HDLP	-0.290** 0.000	0.153** 0.004			-0.280** 0.000	-0.640** 0.000	-0.152** 0.005	
LDLP		0.758** 0.000			0.160** 0.003	0.297** 0.000		0.524** 0.000
VLDLP						0.425** 0.000	0.266** 0.000	0.358** 0.000
C_a		0.209** 0.000					0.198** 0.000	0.267** 0.000
Glucose						0.198** 0.000		0.522** 0.000

Note: ** - correlation is significant at 0.01 (two-way).

drate-dominant nutrition: an addiction to sweets and a deficiency of complete proteins.

Under conditions of severe energy deficiency, the conjugation of these two components is triggered: an increase in glucose levels leads to a decrease in cholesterol levels and vice versa. Exceeding the constant (10 mmol/l) indicates the severity of metabolic disorders. At the same time, the detected increase in glucose and cholesterol levels can be considered as an indicator of the risk of cardiovascular diseases, atherosclerosis and liver diseases.

The data we obtained are consistent with the literature data of other researchers, overwhelmingly foreign ones, and reflect the general trend: the greater the weight, the more aggravated the disease [5, 6, 10].

Conclusion. The features of changes in glucose and total cholesterol levels in individuals during the post-Covid period identified in our study depend on the degree of obesity and lung damage. Hypercholesterolemia and hyperglycemia were expressed in all study groups, regardless of the severity of the disease and body weight. The peak incidence of hyperglycemia is up to 56% in patients with SARS-CoV-2 infection with morbid obesity and up to 15% in people with severe lung damage (50-75%) compared to patients without lung damage. In all groups of patients in the post-Covid period, the value of the constant remained high, due to a significant increase in the concentration of glucose in the blood on an empty stomach, which indicates liver dysfunction, or complete depletion of the internal substrate-energy reserves of the body, which indicates inhibition of the mechanisms of lipid breakdown and dominance in general bioenergetics carbohydrate metabolism. An increase in glucose activity and a decrease in cholesterol indicates a gradual transition from the use of predominantly fat to the use of glucose. Thus, all patients who have had COVID-19 in terms of the sum of total cholesterol and glucose have an increased biological constant of ten, and are at risk of developing cardiovascular diseases, so these patients need further observation, treatment and rehabilitation.

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ARCTIC MEDICINE

K.O. Pashinskaya, A.V. Samodova, L.K. Dobrodeeva

THE RELATIONSHIP OF THE CONTENT OF BLOOD TRANSPORT PROTEINS WITH THE STATE OF THE IMMUNE SYSTEM IN PRACTICALLY HEALTHY INHABITANTS OF THE SVALBARD ARCHIPELAGO DURING THE POLAR DAY

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The article presents data on the content of transport proteins of the blood system in relation to the state of the immune system in people living in extremely unfavorable conditions of the Svalbard archipelago. It has been established that the inhabitants of Spitsbergen have an activation of cell migration into tissues in case of insufficient oxygenation of tissues. A decrease in the level of lymphocytes in the circulation causes a violation of the regulation of immune reactions with the accumulation in the blood of extracellular forms of receptors, circulating immune complexes. People living in Svalbard have an increased need for transport components of the blood system: haptoglobin, transferrin and IgM.

Keywords: neutropenia, lymphopenia, free forms of cell receptors, immune complexes, haptoglobin, transferrin, immunoglobulins, Svalbard archipelago.

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Introduction. Physiological, biochemical and immunological reactions in the human body, as a rule, occur against the background of quantitative changes in the content of transport components of the blood system, including albumins, lipoproteins, haptoglobin, transferrin, a2-macroglobulin and immunoglobulins. The influence of the complex of unfavorable factors of the North and the Arctic is manifested in changes in the internal environment of the human body, including changes in the content of transport proteins and parameters of the blood system. Northern tissue hypoxia, low air temperature, lack of illumination, ionomagnetic disturbance voltage have an ambiguous effect on adaptive adjustments and can lead to depletion of the body's reserve capabilities [2,3,4]. The change in the content of components of blood transport systems is associated with the functional state of the human body and is aimed at maintaining homeostasis with participation in the regulation of the immune system.

Conducting research in the Svalbard archipelago is difficult and few, which leads to insufficient data on the risks to human health.

Purpose of the work – to establish the state of the transport components of the blood system and the immune system in people living and working in extremely unfavorable conditions of the Svalbard archipelago.

Material and methods. The paper presents the results of studying the immunological parameters of 75 residents of the Barentsburg settlement of the Svalbard archipelago, 46 of them women and 29 men and 79 residents of the Arkhangelsk region 58 of them women and 21 men aged 20 to 60 years, practically healthy of the survey, at the during the polar day (July-August 2017). All research was conducted with the consenot of the volunteers and in accordance with the requirements of the World Medical Association's Declaration of Helsinki (2013). The work was approved and approved by the Commission on Biomedical Ethics at the N. Laverov Federal Center for Integrated Arctic Research of the

Ural Branch of the Russian Academy of Sciences (Protocol No. 5 of 11.02.2022).

The complex of immunological parameters included the study of hemogram, phagocytic activity of neutrophils in blood smears stained according to Romanovsky–Giemsa, isolation of mononuclear cells from peripheral blood by the method of A. Boymn [12]. The content of mature T-lymphocytes (CD3+), T-helpers (CD4+), cytotoxic T-lymphocytes (CD8+), precursors of B-lymphocytes (CD10+), B-lymphocytes (CD19+), T-lymphocytes with transferrin receptor (CD71+)), T-lymphocytes with the receptor for the Fc fragment of immunoglobulins (CD23+), lymphocytes prepared for apoptosis with the Fas-R receptor (CD95+) were studied by the method of indirect immunoperoxidase reaction using monoclonal antibodies (MedBioSpectrum, Sorbent, Moscow) in residents of the Svalbard archipelago in connection with research in difficult expeditionary and climatic and geographical conditions and flow cytometry using the Epics XL apparatus from Beckman Coulter (USA) with reagents from Immunotech a Beckman Coulter Company (France) in residents of Europe in the North of the Russian Federation. Regardless of the method of lymphocyte phenotyping, the obtained results were in fact completely consistent (when comparing two methods of lymphocyte phenotyping in residents of the European North).

The contents of haptoglobin, transferrin, immunoglobulins (IgM, IgG, IgA, IgE), cytokines (IL-1β, TNF-α, IL-6, IL-10), free forms of transferrin receptors (sCD71), intercellular adhesion molecules L-selectin (sCD62L) and receptors involved in apoptosis (sApo-1/Fas), Fas-ligands (sFasL) were studied by enzyme immunoassay on the Evolis automatic analyzer (Bio-RAD) using diagnostic kits. Serum was obtained by centrifugation of venous blood for 20 minutes at 1500 rpm. in plastic tubes with a coagulation activator after settling in a vertical position and stored at -70°C in Eppendorf tubes until analysis. The concentration of circulating immune complexes (CIC) was determined by precipitation using 3.5; 4.0; 7.5% PEG-6000.

The mathematical and statistical analysis of the research results was carried out using the software package "Microsoft Excel MX" and "SPSS Statistics 21.0".

Results and discussion. Residents of the Svalbard archipelago, compared with residents of the European North, have a higher frequency of registration of elevated hemoglobin concentrations (29.8 vs. 7.6%), erythrocytosis (57.6 vs. 31.6%), thrombocytosis (23.7 vs. 5.1%), which indicates the presence of a risk of hypoxic state formation as a result of accelerated erythropoiesis in combination with an increase in fetal hemoglobin content in the conditions of the North and the Arctic [5].

The examined residents living in extremely uncomfortable conditions of the Svalbard archipelago are characterized by a high frequency of leukopenia (21.3 vs. 8.9%), neutropenia (32.4 vs. 10.1%), lymphopenia (18.7 vs. 16.4%), monocytopenia (29.3 vs. 1.27%), p <0.01-0.001 (Fig. 1), this indicates increased migration of blood cells into tissues with the development of tissue hypoxia.

The increase in lymphocyte migration into tissues is confirmed by a higher frequency of registration of deficiency of mature T-lymphocytes (CD3+), T-helper cells (CD4+), lymphocytes with transferrin receptor (CD71+) and lymphocytes with apoptosis receptor (CD95+) in 92.1; 45.3; 88.1; 89.3%. Against the background of insufficient content of mature T-cells in the inhabitants of the Svalbard archipelago were found elevated levels of cytotoxic lymphocytes (CD8+), lymphocytes capable of proliferation (CD10+), B-lymphocytes (CD19+) in 10.7; 13.4; 16.0%, respectively (Fig. 2).

People living in extremely unfavorable conditions of the Arctic have a high frequency of increased concentrations of circulating immune complexes (CIC) in 56-100%. A high level of CIC is associated with the insufficiency of the complement system, phagocytic protection [3]. However, for the examined persons living in the Svalbard archipelago, 30.9% were characterized by an increased level of phagocytic activity of neutrophils 91.0 ± 1.38% with phagocytosis intensity of 17.9 ± 1.75 pcs., the deficiency of active phagocytes was established at 13.3%.

It is known that activation of phagocytosis occurs during the polar day. During the polar day, residents of the Svalbard archipelago have higher phagocytic activity compared to residents of the European North (69.25± 1.19 vs. 46.05± 0.69%, p <0.001), which confirms the data on the increase in the level of phagocytic activity as the severity of the climatic and geographical conditions of the territory increases [2]. Unfavorable environmental

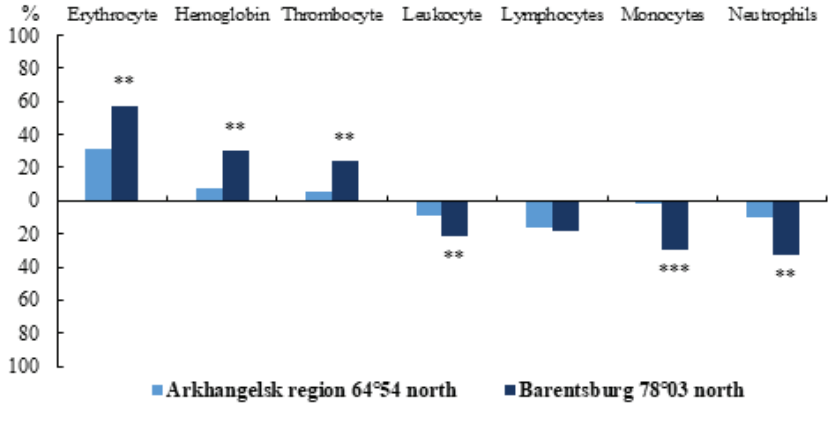

Fig. 1. Frequency of registration of elevated and decreased levels of blood system parameters in persons living in the Svalbard archipelago. Note: the significance of the difference compared to the inhabitants of the European North ** - p <0.01; *** - p <0.001

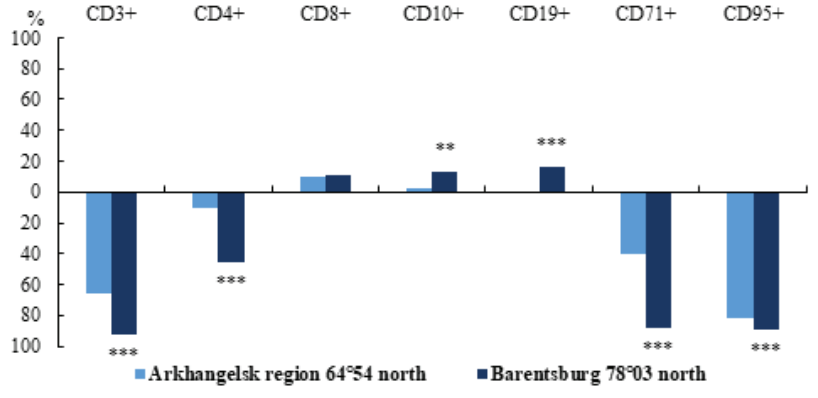

Fig. 2. The frequency of registration of elevated and decreased levels of lymphocytes of the main phenotypes in the inhabitants of the Svalbard archipelago. Note: the significance of the difference compared to the inhabitants of the European North ** - p <0.01; *** - p <0.001

factors in the early stages increase the activity of phagocytes, but in the future, depletion of reserve capabilities may manifest itself by a decrease in the activity of phagocytosis and its intensity [1].

In the extremely unfavorable conditions of the Arctic, compared with the inhabitants of the European North, there is a higher registration of the extracellular pool of receptors for transferrin sCD71 (70.6 vs. 40.5%), the intercellular adhesion molecule sCD62L (53.3 vs. 27.8%), the free pool of receptors involved in the formation of apoptosis of sAPO-1/Fas immunocompetent cells (28.1 vs. 16.5%) and sFasL (13.6 vs. 7.6%) p <0.05-0.001. The accumulation of an extracellular pool of receptors indicates the shedding of receptors in the absence of the need or ability of cells to respond to a biologically active substance or signal [3].

In the examined inhabitants of the Svalbard archipelago, the levels of proinflammatory cytokines IL-1ß (11.86±3.22 pg/ml), IL-6 (5.40±0.29 pg/ml), TNF-α (14.05±0.70 pg/ml) are within physiological limits, elevated levels were not detected.

Thus, the state of the immune system in people living in extremely unfavorable conditions of the Arctic is characterized by the activation of migration processes in conditions of tissue hypoxia and a high level of CIC, free forms of receptors.

The inhabitants of the Svalbard archipelago, compared with the inhabitants of the European North, have a higher level of content and frequency of registration of elevated concentrations of haptoglobin, transferrin and IgM (Fig. 3.).

The average level of haptoglobin in the blood is higher in the inhabitants of the Svalbard archipelago compared to the inhabitants of the European North (1865.12±22.18 vs. 1194.86 ±32.25 mg/l; p < 0.001) with a frequency of increased concentrations of 17.3% versus 1.26%, respectively (Fig. 3.). The increase in haptoglobin content is explained by the need to bind hemoglobin, which is released during the lysis of erythrocytes in circulation with a decrease in their energy supply or violation of the integrity of the membrane [6,10]. In conditions of hypoxia, the increased breakdown of erythrocytes is compensated by intensive hematopoiesis [5,6].

Residents of the Svalbard archipelago have a higher average transferrin content (496.05±57.02 vs. 295.60±3.65 mg/dl; p <0.01) and the frequency of elevated concentrations (43.6% vs. 31.8%, respectively) (Fig. 3.). An increase in the transferrin content in the blood is associated with an increase in the concentra-

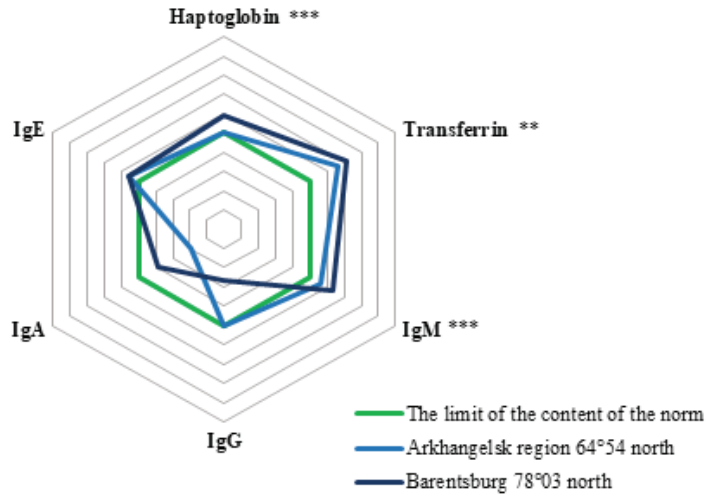

Fig. 3. Matrix of changes in the content of transport components of the blood system in the inhabitants of the Svalbard archipelago. Note: ** - p <0.01; *** - p <0.001 - the reliability of differences when comparing indicators with practically healthy residents of the European North of the Russian Federation.

Table 1

The content of lymphocyte phenotypes in the blood with an increase concentrations of transferrin in the residents of the of the Svalbard archipelago

Parameters	Normal serum content of transferrin	Elevated serum concentrations of transferrin	Reference limits of content
Transferrin level, mg/dl	222.0±4.72	558±8.96***	170–340
The content of lymphocytes, 10^9 cl/ l	2.37±0.25	1.88±0.18**	1.5–4.0
CD3+, 10^9 cl/l	0.79±0.14	0.56±0.08*	1.0–2.0
CD10+, 10^9 cl/l	0.46±0.05	0.41±0.04	0.05–0.6
CD4+, 10^9 cl/l	0.66±0.06	0.42±0.07*	0.4–0.8
CD8+, 10^9 cl/l	0.43±0.09	0.33±0.04	0.2–0.6
CD19+, 10^9 cl/l	0.72±0.07	0.32±0.04**	0.1–0.7
CD71+, 10^9 cl/l	0.47±0.11	0.28±0.05*	0.5–1.0
CD95+, 10^9 cl/l	0.43±0.07	0.28±0.03*	0.5–1.12

Note: * - p<0.05; ** - p<0.01 – the reliability of differences in the content of lymphocyte phenotypes at elevated serum concentrations of transferrin in the residents of the Svalbard archipelago

Table 2

The content of lymphocyte phenotypes in the blood with an increase concentrations of IgM in the residents of the of the Svalbard archipelago

Parameters	Normal serum content of IgM	Elevated serum concentrations of IgM	Reference limits of content
The content of IgM, g/l	1.52±0.06	2.84±0.12***	0.70–1.9
The content of lymphocytes, 10^9 cl/l	2.09±0.07	2.31±0.09*	1.5–4.0
CD3+, 10^9 cl/l	0.58±0.03	0.74±0.07*	1.0–2.0
CD10+, 10^9 cl/l	0.41±0.02	0.49±0.06	0.05–0.6
CD4+, 10^9 cl/l	0.44±0.02	0.54±0.06	0.4–0.8
CD8+, 10^9 cl/l	0.34±0.02	0.48±0.04*	0.2–0.6
CD19+, 10^9 cl/l	0.39±0.03	0.54±0.05*	0.1–0.7
CD71+, 10^9 cl/l	0.27±0.02	0.41±0.04**	0.5–1.0
CD95+, 10^9 cl/l	0.32±0.02	0.37±0.04	0.5–1.12

Note: * - p<0.05; ** - p<0.01 – the reliability of differences in the content of lymphocyte phenotypes at elevated serum concentrations of IgM in the residents of the Svalbard archipelago.

tion of the serum transferrin receptors sCD71 (from 3770±134 to 6960±199 ng/ml; p <0.05), which indicates an increase in the transport of the necessary amount of iron to maintain erythropoiesis at high latitudes. The marked activation of iron redistribution with an increase in the serum transferrin receptors indicates a reduction in the reserve capabilities of activating the immune system in conditions of tissue hypoxia.

With an increase in transferrin content in the inhabitants of the Svalbard archipelago, a decrease in the total level of lymphocytes was found mainly due to mature T-lymphocytes CD3+, T-helper cells CD4+, B-lymphocytes CD19+, lymphocytes with transferrin receptor CD71+ and lymphocytes labeled with apoptosis CD95+ (Table 1). In 90.9% of the surveyed residents of the Svalbard archipelago, an increase in transferrin concentration was associated with a decrease in the content of lymphocytes with a membrane receptor for transferrin (CD71+), which reflects the processes of self-regulation by the type of feedback at the level of changes in the receptor sensitivity of cells or shedding into the intercellular medium.

Photoperiodicity and the intensity and intensity of the magnetic environment are specific factors of high latitudes, affecting the immune system. The Svalbard archipelago is located in the region of the Earth with the maximum intensity of the geomagnetic field [7]. It has been shown that under the influence of magnetic disturbances, the functional activity of cellular receptors is inhibited by changing the distance between ligands and receptors with a decrease in blood T-lymphocytes with CD3+, CD5+, CD71+, CD95+ receptors. It was found that on magnetically disturbed days, the content of CIC increases sharply with the absence of changes on the part of serum immunoglobulins [2,8].

In the inhabitants of the Svalbard archipelago, the concentrations of IgM (1.74±0.09 g/l), IgG (7.56±0.34 g/l), IgA (1.98±0.08 g/l) and IgE (63.60±10.47 IU/ml) are within the physiological limits with a shift of the IgM to the upper limit of the norm and IgA, IgG to the lower limits of the content. Elevated concentrations of IgM and IgE were found in the 26.7% and 12.0%, respectively. Deficiency of IgA and IgG content is registered in 22.7 and 46.7% (Fig. 3.). An increase in IgM content against the background of IgG deficiency indicates an inhibition of switching the synthesis of Ig class M to G (Fig. 3.). Deterioration in the production of high-affinities IgG occurs when B-lymphocytes are reprogrammed for glycolytic metabolism in hypoxia [9,13].

A decrease in the level of IgA in the blood serum is a negative shift in the inhabitants of the North and the Arctic under the influence of climatogeographic factors (Scheme 1). Insufficient oxygen density in the atmosphere, increased humidity correlates with a low level of IgA [2].

In the inhabitants of the Svalbard archipelago, an increase in IgM concentrations is associated with an increase in the level of lymphocytes mainly due to increase of mature T-lymphocytes CD3+, cytotoxic lymphocytes CD8+, B-lymphocytes CD19+ and lymphocytes with transferrin receptor CD71+ (Table 2).

Increased concentrations of immunoglobulins can lead to a damaging effect due to the activation of cytokine synthesis and antibody-dependent cytotoxicity with an increase in tissue and cell damage products. An increase in IgM concentration, coupled with an increase in the level of CIC against the background of an imbalance of serum immunoglobulins in the inhabitants of the Svalbard archipelago, reflects the risk of disruption of adaptive rearrangements. Increased concentrations of CIC in the blood are caused by a violation of their clearance efficiency, which leads to their deposition on membranes, vessel walls with impaired microcirculation [2,3].

Conclusion. In the extremely unfavorable conditions of the Arctic, in the body of the inhabitants of the Svalbard archipelago, cell migration into tissues is activated due to tissue hypoxia. The decrease in the content of circulating neutrophils and monocytes is compensated by an increase in the activity and intensity of phagocytosis. A decrease in the level of lymphocytes, mainly mature T-lymphocytes, T-helper cells, lymphocytes with a transferrin receptor and lymphocytes with a receptor for apoptosis causes the risk of developing an immunodeficiency condition.

In the body of the inhabitants of the Svalbard archipelago, there is a need to increase the transport proteins of the blood system. The increase in haptoglobin content is explained by insufficient tissue oxygenation with an increase in erythrocyte lysis. An increase in the transferrin content associated with an increase in the concentration of the serum transferrin receptor sCD71 indicates an increase in the transport of the necessary amount of iron to maintain erythropoiesis at high latitudes.

An increase in the IgM content reflects to a certain extent the activation of autoantibody formation. IgM belong to autoantibodies, performing regulatory functions to preserve homeostasis, but on the type of feedback inhibits antibody formation on other antigens [11]. The activity of autoantibody synthesis depends on the level of autoantigens [3]. An increase in autoantigens in the residents of the archipelago Svalbard may be caused by a violation of membrane permeability due to the damaging effect of increased concentrations of CIC [8]. An increase in IgM concentration associated with an increase in the level of CEC in the residents of the archipelago Svalbard displays the risk of disruption of adaptation restructuring.

In the inhabitants of the Svalbard archipelago, an increase extracellular forms of lymphocyte receptors in the blood indicate shedding of receptors in the absence of the ability to respond to a signal, including as a result of a change in the distance between ligands and receptors with a violation of their interaction. An increase in the extracellular pool of receptors against the background of a deficiency of active phagocytes indicates the risk of insufficient utilization of the products of adaptive reactions.

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DYNAMICS OF THE MAIN MEDICAL AND DEMOGRAPHIC INDICATORS OF MATERNAL AND CHILD HEALTH CARE IN THE ARCTIC REGIONS OF THE REPUBLIC OF SAKHA (YAKUTIA)

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The analysis of the main medical and demographic indicators of maternal and child health care in 13 Arctic regions of the Republic of Sakha (Yakutia) is presented in the article. It is demonstrated that the studied period is marked by a decrease in population size, and despite this, there are high birth rates, as well as high rates of total mortality, a significant decrease in the infant mortality rate, and high rates of child morbidity.

Keywords: demography, birth rate, mortality, morbidity, Arctic, Yakutia.

Introduction. The industrial development of the Arctic territories of Russia is one of the priorities of the state development. In the current geopolitical conditions, it acquires special significance [3,4]. In this regard, the development of such an important area of medicine as Arctic medicine requires consolidation and cooperation [1,6]. It is possible to determine the initial situation of health care in the Arctic territories by analyzing the main medical and demographic indicators that are public health parameters [2,5,6]. The state of health of children and adolescents in the Arctic has always been a priority. In recent years, extensive federal programs for the protection of women's and children's health in the Russian Federation have been approved and implemented. All this has significantly affected the availability and quality of medical care in the regions of the Arctic zone of the Russian Federation. And this program should be continued. After all, healthy children are the future of the Arctic.

Purpose of the study: to analyze the dynamics of the main medical and demographic indicators in the Arctic regions of the Republic of Sakha (Yakutia) in 2000-2022 in order to establish the main directions for improving the system of maternal and child health care.

Materials and Methods: The dynamics of the main medical and demographic indicators of maternal and child health protection in 13 Arctic regions of the Republic of Sakha (Yakutia) according to the data of the YARMIAC for the period of 2000-2022 was analyzed. Two time periods (2000 and 2022) were taken. The methodology of calculating the indicators of the dynamic series is used.

Results. Since 2000, the population in the Arctic regions of the Republic of Sakha (Yakutia) has decreased by 30%. Moreover, in 4 Arctic districts the population has decreased by more than 40%:

Allaihovsky, Verkhnekolymsky, Nizhnekolymsky and Ust-Yansky districts. The smallest population decline is in the Anabarsky District. The population growth is registered only in two districts namely Oleneksky and Eveno-Bytantaysky districts (3 and 4% respectively).

Certainly, the decrease in the population should be reflected in the number of children, but this trend does not fully correlate with the number of children. This is another point in the demographic development of the population, primarily due to the large number of children and the presence of 3 or more children in families. As shown in Table 1, the number of children in the Arctic regions of the Republic of Sakha (Yakutia) decreased by 33% between 2000 and 2022. In 5 districts, the number of children decreased by 40% or more: Abyisky, Allaikhovsky, Verkhnekolymsky, Verkhoyansky and Nizhnekolymsky districts. The lowest rate of decline in the number of child population was in 3 districts: Zhigansky, Oleneksky and Eveno-Bytantaysky districts (5%, 2%, 2% respectively).

As shown in Table 2, despite the rather serious population decline, the average birth rate in the 13 Arctic regions remains at the level of 14.4‰. Compared to 2000, the birth rate decreased by 0.1 unit and the rate of decline was only 1%. The stable high birth rates are observed in the same districts where the population size is preserved, these are Anabarsky and Bulunsky districts. The birth rate increased in the following districts: Allaihovsky (18%), Verkhnekolymsky (24%), Zhigansky (20%), Oleneksky (39%) and Ust-Yansky (70%). The largest decrease in the birth rate in two districts: Bulunsky (27%), Momsky (36%).

The mortality rate is stably higher than the national one and has no tendency to decrease. For 2000-2022 this indicator decreased by 0.3‰, the rate of decline amounted to only 3%. The high growth rate of mortality rate is observed in Abyisky (36%), Allaihovsky (54%), Verkhnekolymsky (41%), Oleneksky (16%), Srednekolymsky (20%), Ust-Yansky (21%) Districts. The mortality rate decreased in 3 districts: Anabarsky (-39%), Bulunsky (-21%), Eveno-Bytantaysky (-37%).

As shown in Table 3, the mortality rate of the child population increased significantly during the period under study. Thus, the highest rate of increase is in the following districts: Nizhnekolymsky, Ust-Yansky, Allaihovsky.

The modernization and improvement of the pregnancy routing allowed for a 23-year period to reduce significantly the infant mortality rate in the country as a

Table 1

Child population in the Arctic regions of the Republic of Sakha (Yakutia)

Districts	Population of children		Absolute growth (by how many units the 2022 indicator > or < that of the 2000 indicator)	Growth rate, %
	2000 г.	2022 г.		
Abyisky	1541	783	-758	-49
Allaikhovsky	1072	638	-434	-40
Anabarsky	1256	1029	-227	-18
Bulunsky	2812	1986	-826	-29
Verkhnekolymsky	1659	745	-914	-55
Verkhoyansky	4229	2357	-1872	-44
Zhigansky	1352	1282	-70	-5
Momsky	1735	1253	-482	-28
Nizhnekolymsky	1892	1016	-876	-46
Oleneksky	1517	1488	-29	-2
Srednekolymsky	2966	2047	-919	-31
Ust-Yansky	2952	1791	-1161	-39
Eveno-Bytantaysky	799	787	-12	-2
Average for Arctic regions	25782	17202	-8580	-33
RS (YA)	306208	224438	-81770	-27

Table 2

Birth rate in the Arctic regions of the Republic of Sakha (Yakutia)

Districts	Birth rate (per 1000 of population)		Absolute growth (by how many units the 2022 indicator > or < that of the 2000 indicator)	Growth rate. %
	2000 г.	2022 г.		
Abyisky	15.4	13.3	-2.1	-14
Allaikhovsky	15.3	18.1	2.8	18
Anabarsky	19.7	19.4	-0.3	-2
Bulunsky	14.6	10.6	-4	-27
Verkhnekolymsky	10.0	12.4	2.4	24
Verkhoyansky	15.0	13.0	-2	-13
Zhigansky	12.6	15.1	2.5	20
Momsky	17.3	11.0	-6.3	-36
Nizhnekolymsky	11.6	10.4	-1.2	-10
Oleneksky	11.6	16.1	4.5	39
Srednekolymsky	13.9	12.1	-1.8	-13
Ust-Yansky	9.0	15.3	6.3	70
Eveno-Bytantaysky	22.6	20.2	-2.4	-11
Average for Arctic regions	14.5	14.4	-0.1	-1
RS (YA)	13.5	11.9	-1.6	-12

whole and in a number of Arctic regions. In general, the infant mortality rate in all Arctic regions decreased by 72% and amounted to 7.9‰ in 2022. Thus, according to Table 4, eight districts did not allow infant mortality in 2022. The infant mortality rate increased only in Verkhnekolymsky Raion. We can safely say that these indicators demonstrate the origins of the phenomenal vitality of the people in the sharply continental conditions of life in the Arctic. A huge reserve for preserving the health of the population in the Arctic has been revealed in the creation and organization of an effective system in practical perinatology and pediatrics. Evidently, this is not the limit.

As shown in Table 5, the average morbidity rate of the child population in the Arctic regions of the Republic of Sakha (Yakutia) increased by 24%. However, when considering the dynamics of the indicator for the period under study, its range is very wide. There are even districts in which the incidence rate of the child population in 2022 decreased significantly: Bulunsky, Verkhnekolymsky, Verkhoyansky, Zhigansky, Eveno-Bytantaysky districts. In general, the dynamics shows an increase in the morbidity rate of the child population in the Arctic regions of the Republic of Sakha (Yakutia). Taking into account the fact that the morbidity indicator is formed on the basis of data on the population turnover, it can be assumed that it is difficult to present a real picture of the health status of the child population on the basis of its data.

Discussion. The analysis of the dynamics of the main medical and demographic indicators in the 13 Arctic regions of the Republic of Sakha (Yakutia) in 2000-2022 has shown the following trends:

1. A clear downward trend in population and child population in general (by 30 and 33%, respectively).
2. High birth rate (in 2022 -14.4‰).
3. High rates of total mortality (only 3% decrease) and mortality of the child population (3-fold increase).
4. Infant mortality rates have been significantly reduced (by 72%).
5. Morbidity among the child population has increased by 24%.

The improvement of the system of women's and children's health care in the Republic of Sakha (Yakutia) affects the main indicative medical and demographic indicators, but when analyzing the situation in the Arctic regions, the following trend is quite worrying: an increase in child mortality and child morbidity, which require urgent detailed analysis, the development of regional programs and

Table 3

Child mortality rate in the Arctic regions of the Republic of Sakha (Yakutia)

Districts	Mortality rate in children of 0-17 ages (per 10 000 of child population)		Absolute growth (by how many units the 2022 indicator > or < that of the 2000 indicator)	Growth rate, %
	2005 г.	2022 г.		
Abyisky	4.0	0	-4	-100
Allaikhovsky	2.2	12.7	10.5	477
Anabarsky	7.3	15.8	8.5	116
Bulunsky	0.7	0	-0.7	-100
Verkhnekolymsky	-	21.8		
Verkhoyansky	2.8	0	-2.8	-100
Zhigansky	-	0		
Momsky	0.6	0	-0.6	-100
Nizhnekolymsky	0.7	16.7	16	2286
Oleneksky	2.5	12.0	9.5	380
Srednekolymsky	2.1	4.1	2	95
Ust-Yansky	2.1	14.6	12.5	595
Eveno-Bytantaysky	-	11.0		
Average for Arctic regions	1.9	8.4	6.5	342
RS (YA)	1.3	4.6	3.3	254

Table 4

Infant mortality rate in the Arctic regions of the Republic of Sakha (Yakutia)

Districts	Infant mortality rate per 1000 of live births		Absolute growth (by how many units the 2022 indicator > or < that of the 2000 indicator)	Growth rate, %
	2000 г.	2022 г.		
Abyisky	25.0	0	-25	-100
Allaikhovsky	30.8	20.2	-10.6	-34
Anabarsky	95.9	14.1	-81.8	-85
Bulunsky	13.8	0	-13.8	-100
Verkhnekolymsky	15.9	20.8	4.9	31
Verkhoyansky	20.4	0	-20.4	-100
Zhigansky	12.5	0	-12.5	-100
Momsky	22.7	0	-22.7	-100
Nizhnekolymsky	22.5	0	-22.5	-100
Oleneksky	27.4	14.3	-13.1	-48
Srednekolymsky	7.1	0	-7.1	-100
Ust-Yansky	22.5	0	-22.5	-100
Eveno-Bytantaysky	54.1	33.9	-20.2	-37
Average for Arctic regions	28.5	7.9	-20.6	-72
RS (YA)	17.6	3.9	-13.7	-78

Table 5

Childhood morbidity rate in the Arctic regions of the Republic of Sakha (Yakutia)

Districts	Morbidity in children (per 1000 of population)		Absolute growth (by how many units the 2022 indicator > or < that of the 2000 indicator)	Growth rate, %
	2000 г.	2022 г.		
Abyisky	1783.3	2742.7	959.4	54
Allaikhovsky	1518.7	2656.4	1137.7	75
Anabarsky	1163.9	2102.0	938.1	81
Bulunsky	1443.5	1120.9	-322.6	-22
Verkhnekolymsky	1753.4	1284.4	-469	-27
Verkhoyansky	1384.4	994.7	-389.7	-28
Zhigansky	1853.3	1202.4	-650.9	-35
Momsky	1564.9	1828.0	263.1	17
Nizhnekolymsky	1562.7	2889.5	1326.8	85
Oleneksky	1941.1	2635.0	693.9	36
Srednekolymsky	2570.4	2941.8	371.4	14
Ust-Yansky	1157.5	2717.1	1559.6	135
Eveno-Bytantaysky	1525.5	1168.6	-356.9	-23
Average for Arctic regions	1632.5	2021.8	389.3	24
RS (YA)	1658.3	2507.5	849.2	51

changes in the ideology of medical care for children in the Arctic regions, and interdepartmental work to reduce child mortality.

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RISK FACTORS FOR CHRONIC KIDNEY DISEASE IN THE ARCTIC ZONE OF THE REPUBLIC OF SAKHA (YAKUTIA)

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To date, there is a worldwide trend of increasing morbidity and mortality in patients with chronic kidney disease. Given the secondary nature of kidney damage, prevention and early detection of risk factors are the main priority of modern medicine.

The purpose of our work was to conduct a screening study of the population of the Momsky district (5 settlements) of the Republic of Sakha (Yakutia) for early detection of damage and decreased kidney function.

Results. The study involved 222 people, of whom 14 (6,3%) had chronic kidney disease (GFR less than 60 ml/min/1.73 m2). An early predictor of the development of chronic kidney disease, albuminuria was found in 70 (31.5%) of the examined patients. The main risk factors affecting the development of chronic kidney disease were hypertension (54.3%), burden of cardiovascular diseases (50%) and obesity (37.1%), burden of kidney diseases were in 11 (15.7%) of the examined patients.

Keywords: chronic kidney disease, Arctic zones, albuminuria, glomerular filtration rate, risk factors.

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Introduction. Currently, it can be stated that the global burden of chronic kidney disease (CKD) is only increasing [2,12]. Being one of the most common pathologies of non-infectious nature, CKD causes not only social, but also economic damage to the medical field. The prevalence of CKD increases exponentially, being the consequences of diseases such as diabetes mellitus and cardiovascular diseases. In the epidemiological study of GBD Chronic Kidney Disease Collaboration, The Lancet, by 2017, the number of patients with various stages of CKD reached almost 700 million, while if the mortality rate at the diagnosis of CKD led to 1.2 million deaths in 2017, the number of which is projected to grow to 2.2 million by 2040 at best and up to 4.0 million in the worst case [12].

Data on the prevalence of CKD differ in countries with a higher standard of living, depend on income and public awareness of the outcomes of cardiometabolic diseases. In addition to regional peculiarities, the formation of CKD is influenced by age, gender, impaired plasma glucose levels, hypertension, high body mass index, high sodium content in food [2,5,12].

In Russia, general population studies of the prevalence of CKD at the predialysis stages have not been conducted, but the results of individual epidemiological studies confirm the high prevalence of pathology [1,2].

Thus, according to the All-Russian register as of 31.12.2020, the number of patients with stage 5 CKD and receiving renal replacement therapy was 60,547 [1]. In addition to epidemiological problems, the cost of treatment in this group of patients should also be attributed, since the costs of renal replacement therapy make up a significant part (2-5%) of health budgets in developed countries, while the proportion of patients is no more than 0.7% of the total number of patients [6]. Although the diagnosis of CKD is quite simple, there is insufficient detectability at the outpatient level, namely the difficulty of registering albuminuria, albumin-creatinine ratio, glomerular filtration rate (GFR) [8].

In the multicenter observational study "CKD screening" conducted in 12 regions of Russia, the aim was to study the prevalence of CKD in patients who visited primary health care institutions who had not previously been diagnosed with CKD [3]. It was found that among the 1.2 million patients who presented to primary health care facilities, 13.2% had previously undiagnosed CKD, 72% of whom had C3a-C3b CKD. At the same time, the main causes of CKD were arterial hypertension, chronic heart failure and obesity.

Considering that the majority of CKD is secondary nephropathies on the background of diabetes mellitus and cardiovascular diseases, the relevance of diagnosis, treatment and, most importantly, prevention of CKD has become an interdisciplinary therapeutic problem.

Thus, considering the impact on the quality of medical care for patients with CKD of such factors as the availability of laboratory methods, awareness of the population, the influence of "urbanized" risk factors on the formation of kidney pathology, we have begun a study of the adult population of remote Arctic regions of the Republic of Sakha (Yakutia).

In total, 13 districts belong to the Arctic zone of the republic. According to the data of the Yakut Republican Medical Information and Analytical Center (YARMIAC) on the incidence of the genitourinary system (ICD-10) among the adult population of the Arctic regions of the Sakha Republic (glomerular, tubulointerstitial kidney diseases, other kidney and urinary tract diseases) have a significant tendency to decrease over the past 10 years, which may indicate not only the migration of the population, but also improving the quality of medical care provided. So, in 2013, 649 patients were registered with a newly diagnosed diagnosis for this group of diseases, and in 2022 only 108 people (per 1000 population, this indicator was 13.3 and 2.3, respectively). With respect to renal insufficiency (ICD-10, N18), the total incidence of the adult population in 2013 was 19 people, increasing to 78 by 2022 (0.4 to 1.8 per 1000 population, respectively). As for the primary morbidity, 3 patients were diagnosed with renal insufficiency in 2013, and 15 in 2022 (0.06 and 0.32 per 1000 population, respectively).

In our study, we used screening methods for CKD risk factors among the adult population in one Arctic region – Momsky district.

According to YARMIAC, the total incidence of renal insufficiency in the adult population of Momsky district in 2013 and in 2022 was 2.5 per 1000 population (7 patients each). In 2013, the primary incidence of renal insufficiency was not registered, in 2022 it was diagnosed in 1 person, which was 0.4 per 1000 population.

Material and methods. This study was conducted free of charge based on a screening program designed to identify individuals with an increased risk of kidney disease and to motivate individuals to regular medical examination, as well as correction therapy. Eligible participants in the study were men and women over the age of 18, as far as free circulation. Participants who received regular dialysis treatment or were diagnosed with CKD were excluded from this study.

Data on demographic characteristics of participants, personal and family medical history, as well as health behaviors were collected [4]. Blood and urine samples were collected and processed to determine serum creatinine and urine albumin levels.

Potential risk factors for CKD included age, gender, obesity (body mass index over 30 kg/m2) and nationality. The age was determined by the stated date of birth at the time of screening and was divided into three groups: 18-44, 45-59 and 60 and older according to the criteria of the World Health Organization [6].

The glomerular filtration rate (GFR) was determined using the initial serum creatinine value recalculated by the CKD-EPI formula 2009 [13]. Urine samples were collected and tested for albuminuria using Combilyzer (Human GmbH, Germany). Criteria for CKD were albuminuria > 30 mg/g and/or eGFR < 60 mL/min/1.73 m2 based on the KDIGO 2012 Clinical Guidelines for CKD [13].

The population in the Momsky district in 2022, according to Rosstat, amounted to 3991 people, there is a decrease in the population (in 2021 – 4021 people) [14]. Out of 6 naslegs (settlements) of the Momsky district, the population of 5 settlements and a separate settlement of reindeer herders were examined by a simple screening method. In the Indigir national nasleg (Buor-Sasy village) the total population is 342 people, of whom 40 have been examined; in the Moma national nasleg (Khonu village) - 2295 people, 56 were examined; 255 people live in Sobolokh national nasleg (Sobolokh village), 42 have been examined; in Tebulakh national nasleg (Chumpu-Kytyl village) out of 214 people, 21 were examined; In the Ulakhan-Chistai national nasleg (Sasyr village + reindeer herders' settlement), 63 out of 673 people were examined. The study did not include the Chybagalakh national nasleg (Kulun-Elbut village).

Results. A total of 222 people were screened from February 2023 to May 2023. There were significantly fewer men in the study - 57 (25.7%) than women - 161 (72.5%). The data for the determination of eGFR were available for all 222 (100%) and formed our main research part. CKD (a decrease in eGFR of less than 60 ml/min/m2) was detected in 14 (6.3%) of the studied. Data for the determination of albuminuria among the study population were available for 181 (81.5%) of the total, while high level of albuminuria (A2, A3) was detected in 70 (31.5%) people.

In the age group older than 60 years, 13 (5.9%) showed reduced eGFR, while in the young group (18-44 years) there was no decrease in eGFR (Table 1). We also see a tendency to increase the prevalence and albuminuria with the age of patients (16.2%), but there is a fairly high percentage and in the young age group (13%).

In terms of settlements, most of the participants were in the village of Sasyr with a settlement of reindeer herders, where 63 people were examined, a smaller number of participants in the village of Chumpu-Kytyl were examined 21. At the same time, the percentage of stage 3 CKD (eGFR less than 60 ml/min/m2) among the participants in the localities was the highest among those examined in the village. Buor-Sasy in 5 (12.5%) out of 40 participants and also 5 people (9%) out of 56 in the village of Khonu.

In the study of an early marker of kidney damage, a high detection rate of albuminuria was observed in 36 out of 63 (57.1%) patients studied in the village of Sasyr with a settlement of reindeer herders, which exceeds the detection rates of albuminuria among the population of the district center of the village of Khonu (34%). At the same time, a decrease in eGFR was detected in only one person in the village of Sasyr.

According to the distribution of patients by categories of CKD (eGFR and albuminuria), the following features were revealed (Table): eGFR ≥90 ml/min/1.73 m2 was detected in 131 patients, of which 44 (33.6%) had albuminuria; eGFR 60-89 ml/min/1.73 m2 in 77 patients, albuminuria in 20 (26%) patients. 13 people had stage 3 CKD (6 patients with albuminuria) and 1 with stage 4 CKD (without albuminuria).

To determine the significance of the influence of risk factors, we assessed age, sex, nationality, obesity, diabetes, hypertension, and smoking, as well as available data on heredity – burden of diabetes, hypertension (cardiovascular diseases) and kidney disease (Table 1).

Patients with diabetes accounted for 31 (14% of the total number studied), and among those who had a eGFR < 60 ml/min/1.73 m2, diabetes was detected in only 3 (9.7)%.

Of all the studied 98 (44.1%) people, arterial hypertension was detected, of which albuminuria was detected in 31 patients (31.6%). The distribution by albuminuria and eGFR is presented in Table.

Obesity (BMI more than 30 kg/m²) was observed in 65 (29.3%) of all patients, among this group of patients, albuminuria with normal eGFR was detected in 14, with eGFR 60-89 ml/min/1.73 m2 in 7, eGFR < 60 ml/min/1.73 m2 in 5.

Among 63 smokers and previous smokers (28.4% of the total number studied), normal eGFR was observed in 61, a decrease in eGFR < 60 ml/min/1.73 m2 in 1, and albuminuria in 21 (9.5% of the total number studied).

A history of diabetes was observed in 32 (14.4%) people according to the questionnaire, while 12 had significant albuminuria. Cardiovascular diseases (CVD), including hypertension, accounted for 101 (45.5%) and albuminuria was detected in 35 in this group. The burden of

Identification of risk factors for CKD in subjects depending on albuminuria and glomerular filtration rate

Criteria	Albuminuria > 30 mg/g in individuals with eGFR ≥ 90 mL/min/1.73 m2 (CKD G1)	Albuminuria > 30 mg/g in individuals with eGFR 60-89 mL/min/1.73 m2 (CKD G2)	eGFR 30-59 mL/min/1.73 m2 *regardless of* albuminuria (CKD G3)	eGFR 15-29 mL/min/1.73 m2 *regardless of* albuminuria (CKD G4)
Albuminuria (> 30mg/g)	44	20	6	0
Age, year old				
18–44	22	7	0	0
45–59	10	2	1	0
Старше 60	12	11	12	1
Gender,				
Men	15	10	1	0
Women	29	10	12	1
Nationality				
Yakuts	27	11	8	1
Evens	14	2	0	0
Evenki	1	2	2	0
Russians	2	3	2	0
Undefined	0	2	0	0
Obesity (BMI 30 kg/m2)	14	7	4	1
Diabetes mellitus	5	1	3	0
Arterial hypertension	17	10	10	1
Smoking	15	5	1	0
History of diabetes mellitus	7	1	3	1
History of cardiovascular disease	23	6	5	1
History of kidney disease	7	2	2	0

kidney disease occurred in 41 (18.5%) of the examined, albuminuria in 11 of them.

It is noteworthy that many of the subjects found it difficult to answer the questionnaire regarding high blood sugar levels and a history of hereditary burden.

In the study of national characteristics, no significant differences were revealed.

Discussion. According to a large epidemiological study [12], CKD is a highly prevalent disease, a burden that has not decreased as much as many other important noncommunicable diseases over the past 27 years.

In our study, 70 (31.5%) of the 222 patients examined had significant albuminuria. 14 (6.3%) had a decrease in eGFR < 60 mL/min/1.73 m2, 93% of whom were in the older age group.

When analyzing the influence of risk factors on renal injury (patients with albuminuria > 30 mg/g), it was found that 38 (54.3%) had arterial hypertension, 35 (50%) had CVD and hypertension, and 26 (37.1%) had obesity. Among the studied patients in the stage 3-4 CKD group, renal injury is probably more associated with the presence of hypertension (11 patients out of 14) than with diabetes (3 patients). In general, the prevalence of arterial hypertension is quite high - 98 (44.1%), while various forms of diabetes were detected in 31 (14%). Modifiable risk factors have a fairly high prevalence, for example, obesity occurs in about a third of all studied and in 37.1% patients with albuminuria.

In addition, I would like to note the high prevalence of smoking (30%) as a known risk factor for renal damage [17] in the group of patients with albuminuria.

Our study also has some limitations, such as free recourse for examination, there may be an overestimation of the prevalence of albuminuria in a young group of patients (38.6%) who do not have predictors of CKD. In the future, we plan to cover all 13 regions of the Arctic zone of the Republic of Sakha (Yakutia).

It is important to note that slowing the progression of CKD in its early stages provides economic benefits [6, 16] and prevents the development of cardiovascular complications, which are the leading cause of death in patients with CKD. A comprehensive action plan should include effective management of CKD risk factors at the primary health care level, improved detection among at-risk groups, and development of routing (inter-hospital transport, telemedicine technologies) in remote areas for the treatment of patients with confirmed disease.

A characteristic feature of the Arctic regions of the republic is not only a small population, but also a low population density, on the other hand, this can be seen as a positive side. For example, the physician is informed in more detail about the health status of each patient and, knowing the risk factors for the development of CKD, prevention coverage can be of better quality. Thus, according to the YARMIAC, the incidence and primary diagnosis of renal failure has increased, which may indirectly confirm that the diagnosis of CKD in the region has improved.

Further research in the field of prevention and early diagnosis of CKD opens up great prospects for the development of innovative approaches in the prevention, prognosis and treatment of severe socially significant and economically burdened end-stage CKD.

Conclusion. Identification of early predictors of the development of CKD, the introduction of more convenient preclinical diagnosis and documentation of CKD predictors for primary health care, as well as a patient-centered approach considering the inaccessibility of medical care are important to ensure the optimization of population-significant diseases in the residents of the Arctic regions of the Republic of Sakha (Yakutia).

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SCIENTIFIC REVIEWS AND LECTURES

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BIOLOGICAL MARKERS IN PREDICTING THE COURSE OF SPINAL MUSCULAR ATROPHY AND THEIR IMPORTANCE IN ORGANIZING MEDICAL CARE

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A correlation between the levels of blood biomarkers and clinical manifestations of SMA in patients of the main regional healthcare institution of the Samara region was carried out.

Differences in creatinine, creatine phosphokinase, and lactate dehydrogenase levels among patient groups and their association with motor impairment did not show statistical significance. Differences in CPK levels between groups may be related to age, weight, gender, and levels of physical activity of patients. The data obtained from the study of the history of repeated hospitalizations do not provide reliable information due to the limited sample and heterogeneity of the data. The results of this work indicate the ineffectiveness of assessing the levels of creatinine, CPK and LDH in order to monitor and predict the course of SMA, as well as the inappropriateness of repeating these laboratory studies in patients with SMA 5q.

Keywords: creatine phosphokinase, creatinine, neurofilament, neuromuscular diseases, nusinersen, hereditary disease, pathogenetic therapy, risdiplam, spinal muscular atrophy.

Introduction. Spinal muscular atrophy (SMA) is a genetically heterogeneous group of CNS disorders characterized clinically by the loss of motor skills, progressive symmetric peripheral paralysis due to degeneration of motor neurons, and resultant atrophy of striated muscles, which leads to difficulty in swallowing, general paralysis, and respiratory failure. SMA predominantly develops in childhood and is a major hereditary cause of infant mortality (Araujo et al. 2009). The worldwide prevalence of SMA is estimated to be 8.5-10.3 per 100,000 newborns, with carrier frequencies ranging from 1 in 35 to 1 in 60 (Kimizu et al. 2021). SMA is most commonly caused by autosomal inheritance mutations, resulting in a roughly equal distribution among both genders, although the gender frequency differs slightly according to SMA type (Verhaart et al. 2017, Gayduk & Vlasov 2019). The most common forms, known as SMA 5q, have no clear association with cognitive

and affective disorders in numerous studies, which have nonetheless highlighted the lack of detailed information about neuropsychiatric status (Mix et al. 2021, Zappa et al. 2021, Rivière et al. 2007, Gayduk et al. 2022).

The genetic nature of SMA 5q variants calls for molecular-genetic research methods as essential tools for confirming the diagnosis. Here, the most relevant method is testing for the copy numbers of *SMN1* and *SMN2* using multiplex ligation-dependent probe amplification (MLPA) (Hong et al. 2020, Mercuri et al. 2018, Feng et al. 2020, Lopez-Lopez et al. 2020). At the time of writing, laboratory diagnostic methods other than MLPA do not accurately determine the presence of the disease or provide predictions regarding its progression and severity. However, some studies suggest that certain nonspecific biomarkers hold promise for monitoring disease progression and assessing treatment effectiveness (Alves et al. 2020, Freigang et al. 2021, Yuan et al. 2017, Kobayashi et al. 2013, Kolb et al. 2016, Gayduk et al. 2022). These biomarkers include plasma levels of creatine phosphokinase (CPK), creatinine, and neurofilaments (NF). For instance, a study involving 238 patients demonstrated an inverse between serum creatinine levels and disease severity in children and adolescents, with correction for age and muscle mass (Alves et al. 2020). Creatinine levels were highest in patients with type III SMA and lowest in patients with type I, but decreasing with age regardless of clinical subtype.

A study population of 22 infants diagnosed with preclinical SMA underwent repeated measurement of plasma creatinine levels and evoked potentials electromyography (EMG) over the course of a year (Alves et al. 2020). Results showed decreasing creatinine levels and evoked potential amplitudes during the first three months, in consideration of earlier findings that decreasing creatinine levels preceded the decline in evoked potential amplitudes in 8 of 12 type III SMA patients. Another study conducted with adult patients demonstrated a correlation between plasma CPK and creatinine levels and disease severity, indicating their potential utility in predicting treatment efficacy (Freigang et al. 2021).

NF are cytoskeletal proteins that provide structural integrity to neurons, particularly in their axons. Elevated levels of NF are present in blood and cerebrospinal fluid during ongoing neurodegenerative processes in several diseases and in traumatic brain injury. In the case of SMA, plasma levels of NF are more indicative for disease prognosis and treatment monitoring in children than in adult patients (Yuan et al. 2017).

Broader research on SMA biomarkers has revealed other analytes that correlate with the degree of motor function impairment; the Biomarkers for SMA (BforSMA) study published in 2013 identified 200 plasma markers correlating with motor and other impairments in infants with SMA up to two years of age (Kobayashi et al. 2013). The authors selected the most significantly correlating plasma metabolites to create the commercially available diagnostic panel known as SMA-MAP. Further studies with the SMA-MAP panel revealed statistically significant deviations in infants with SMA compared to healthy infants up to 6 months of age (Kolb et al. 2016).

Serum lactate dehydrogenase (LDH) is a cytoplasmic enzyme, which serves as a common indicator of tissue damage (Zhang et al. 2012). Despite its broad application at many local healthcare institutions, there is scant evidence for the fitness of LDH as a biomarker for SMA.

As noted above, EMG is among the most effective instrumental diagnostic methods for evaluating neuromuscular function (Querin et al. 2018). Changes in electrophysiological parameters in SMA patients correlate with the number of *SMN2* copies, SMA type, motor function assessment results, and patient age. EMG results also serve for assessing the patient's response to specific therapies (Weng et al. 2021, Kariyawasam et al. 2020). The application of techniques such as EMG with motor unit number index (MUNIX) and motor unit size index (MUSIX) enables the detection of subtle electrophysiological changes, which is valuable for identifying specific patterns for differential diagnosis and therapy monitoring (Querin et al. 2018, Nandedkar et al. 2010). However, at the time of writing, there are no universal and cost-effective diagnostic and prognostic EMG-based tools, which poses a major challenge in providing medical care to SMA patients in Russia and around the world.

Thus, the currently most available and widely used blood biomarkers (serum creatinine, CK, and LDH) have the potential for utilizing as a tool for disease course monitoring. This approach is considerably cheaper than SMA-MAP (USD 500 per test), and calls for lower labor input than tests involving motor unit examinations.

The aim of this study was to investigate differences in an abbreviated panel of blood biomarkers (serum creatinine, CK, and LDH), EMG data, and clinical manifestations (including psychological/psychiatric impairments), among SMA patients at the main regional healthcare institution in the region of Samara, Russia Federation. Our goal was to obtain data that could contribute to the development of a practical and effective method for predicting the course of the disease, with potential application as an endpoint in intervention/treatment studies.

Materials and Methods. In a retrospective study of archived data from the V.D. Seredavin Samara Regional Clinical Hospital (SRCH), we assembled 112 medical records from 58 patients from hospitalizations spanning from January 2008 to February 2022. Patients were divided into groups based on gender, age (children under 18 years and adults), and the ICD-10 diagnostic categories (G12.0, G12.1, G12.8, and G12.9). When available, we included data from subsequent hospitalizations. The analysis included clinical data from general and neurological examinations, laboratory test indicators (LDH, CK, creatinine levels), and instrumental diagnostic methods (EMG). Statistical analysis was performed using MedCalc and IBM SPSS Statistics (Version 27, license from Samara State Medical University, 2022) with descriptive statistics and non-parametric methods due to the small sample size and non-normal distributions of the data. The Kruskal-Wallis test, a non-parametric equivalent of one-way analysis of variance (ANOVA), was used to compare median values between groups, with pairwise comparisons adjusted for multiple comparisons using the Dunn method. The data were described using the median, first and third quartiles, absolute frequencies, and percentages (indicated in parentheses).

Results. From January 2008 to February 2022, 58 SMA patients (38.4 [quartiles 13.7, 55.0] years old) had been registered at SRCH, of whom 32 (55.2%) were female. Among the 58 patients, 21 were children (12.3 [6.6, 13.9] years old), including 14 (24.1%) girls. The diagnosis of "Infantile spinal muscular atrophy, Type I, Werdnig-Hoffmann" (G12.0) was established in 7 patients (12.0%), all of whom were children: 5 (8.6%) girls and 2 (3.4%) boys. The oldest such patient was 14.3 years old, and the youngest was 4.8 years old (median of 7.7 [6.8, 12.7] years). The diagnosis of G12.1, encoding SMA II, III, and IV, was assigned to 43 patients (74.1%) (median age of 37.3 [14.5, 55.6] years), including 14 (24%) children, 9 (15.5%) of whom were girls, and 29 (50.0%) adults, 13 (22.4%) of whom were women. The diagnosis of

G12.8 was assigned to 6 adult patients: 3 (5.2%) women and 3 (5%) men, with mean age 59.3 [37.3, 62.1] years. Two women, aged 40 and 52 years, were diagnosed with G12.9, "Unspecified spinal muscular atrophy."

According to the general and neurological examinations, all patients included in the study were clinically stable, in a satisfactory condition, and not on mechanical ventilation. Data on motor impairments were obtained from the results of neurological examinations recorded in all medical records. Motor impairments ranged from mildly expressed proximal lower paraparesis (n=13, 22.4%) to severely pronounced tetraparesis (n=7, 12.1%) (Table). Assessment of the mental status primarily involved evaluating the level of consciousness and rapport using the clinical-psychopathological method, without the use of neuropsychological tests. All patients were responsive, and could understand and accurately follow instruc-

Socio-demographic, clinical and laboratory characteristics of the study sample of patients with SMA, depending on the nosological category

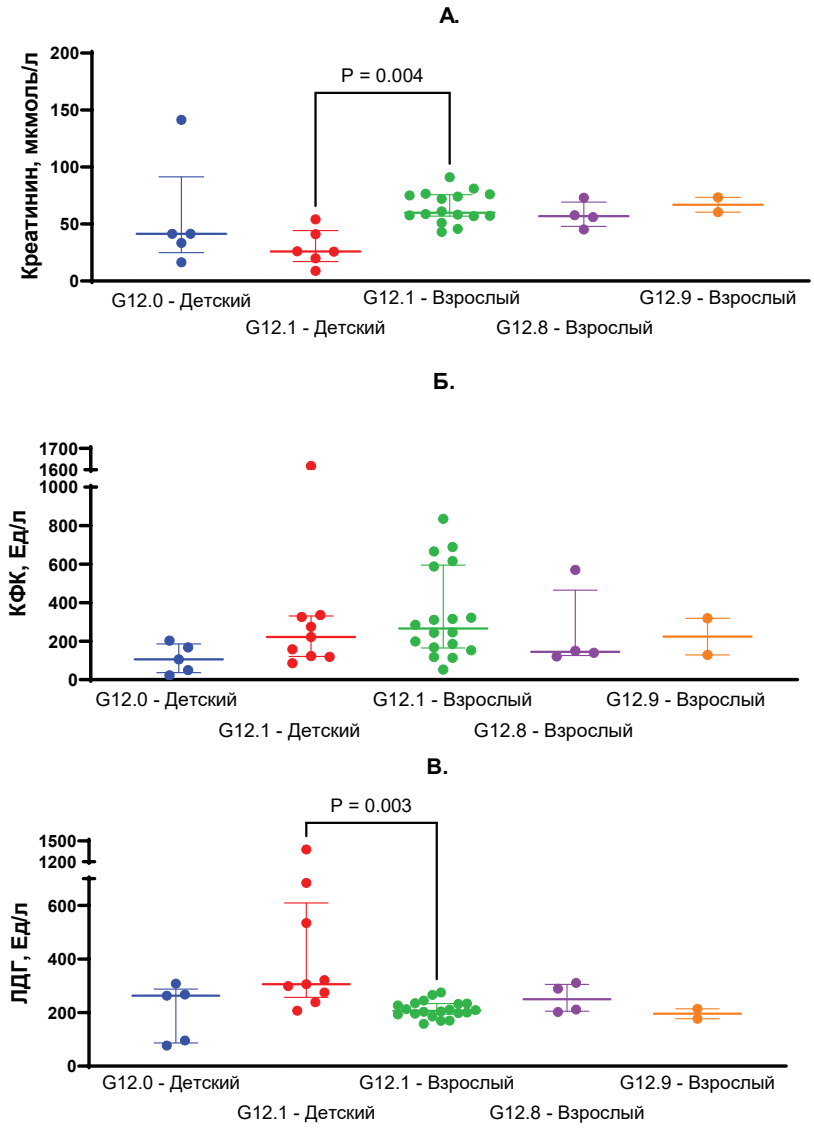
Diagnostic categories according to ICD-10	G12.0	G12.1		G12.8	G12.9	Всего		Статистика
Age Group Gender	Children	Children	Adults	Adults	Adults	Children	Adults	
Socio-demographic indicators of the sample Sample size, n (%)								
W:	5 (8.6%)	9 (15.5%)	13 (22.4%)	3 (5.2%)	2 (3.4%)	14 (24.1%)	18 (31.0%)	χ2=4,163, df=4, p=0.384, for gender distribution between groups
M:	2 (3.4%)	4 (6.9%)	16 (27.6%)	3 (5.2%)	0	6 (10.4%)	19 (32.8%)	
Total:	7 (12.1%)	14 (24.1%)	29 (50.0%)	6 (10.4%)	2 (3.4%)	21 (36.2%)	37 (63.8%)	
Age - Median (Interquartile interval), years								
W:	7.7 (4.2)	13.2 (7.8)	50.8 (19.69)	63.6 (16.3)	45.8 (6.2)	11.8 (7.7)	51.4 (22.9)	KW=40.125, df=4, p<0.001 to compare the age between groups
M:	10.2 (3.7)	12.7 (8.7)	47.1 (30.0)	55.0 (8.9)		12.7 (8.0)	48.6 (28.5)	
Total:	7.7 (5.8)	12.9 (8.3)	49.1 (24.8)	59.3 (15.5)	45.8 (6.2)	12.3 (7.4)	50.8 (24.1)	
Assessment of motor functions during neurological examination, graduation taking into account the sum of the scores of the four limbs								
W:	6.3	14.3	13.4	12	15.3	11.5	13.4	KW=14.196, df=4, p=0.007 to compare the amount of points between groups
M:	2	11.8	13.2	16.7		9	13.7	
Total:	5.1	13.4	13.3	14.3	15.3	10.6	13.6	
Bulbar syndrome								
W:	1 (1.7%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7%)	0 (0)	χ2=5,418, df=4, p=0.247 to distribute cases of bulbar syndrome between groups
M:	1 (1.7%)	0 (0)	2 (3.4%)	0 (0)	0 (0)	1 (1.7%)	2 (3.4%)	
Total:	2 (3.4%)	0 (0)	2 (3.4%)	0 (0)	0 (0)	2 (3.4%)	2 (3.4%)	
Laboratory and instrumental indicators								
Creatinine is the Median (Interquartile gap), mmol/l								
W:	41.4 (54.0)	25.9 (5.4)	74.1 (15.1)	65.4 (7.6)	66.9 (6.5)	33.4 (18.6)	73.1 (14.6)	KW= 15.0324, df=4, p=0.005 to compare creatinine between groups
M:	28.9 (12.5)	31.4 (22.6)	57.9 (6.1)	50.6 (5.3)		28.9 (30.0)	57.4 (7.4)	
Total:	41.4 (8.0)	25.9 (15.9)	61 (18.9)	56.9 (8.3)	66.9 (6.5)	33.4 (18.5)	60.4 (17.5)	
KFC - Median (Interquartile interval), Units/l								
W:	168.0 (48.4)	190.0 (129.9)	222.5 (157.7)	345.3 (224.4)	224.05 (94.9)	168.0 (138.7)	222.5 (189.7)	KW=6. 460, df=4, p=0.167 to compare CFCs between groups
M:	36.4 (13.5)	972.0 (3341.5)	303.6 (453.5)	144.4 (5.0)		206.0 (1236.2)	264.6 (390.7)	
Total:	106.1 (118.1)	248.4 (201.7)	265.6 (349.3)	144.4 (119.8)	224.0 (94.9)	168.0 (188.2)	245.0 (236.9)	
LDH is the Median (Interquartile interval), Units/l								
W:	267.5 (22.5)	287.0 (56.2)	211.0 (39.4)	299.7 (10.8)	195.5 (18.5)	275.0 (44.4)	214.0 (70.4)	KW= 14.2622, df=4, p=0.006 to compare LDH between groups
M:	86.2 (9.2)	684.1 (421.0)	204.0 (26.9)	206.7 (4.2)		534.0 (588.7)	204.0 (15.3)	
Total:	263.0 (172.1)	305.7 (259.0)	206.5 (37.7)	250.0 (85.5)	195.5 (18.5)	287 (72.9)	210 (37.4)	

tions, within the constraints of their motor capabilities. Some pediatric patients showed emotional lability (n=6, 10.3%), fatigue (n=10, 17.2%), and tearfulness (n=3, 5.2%).

During their examinations, all patients underwent a biochemical blood analysis to measure creatinine, CK, and LDH levels (Table). Diagnosis confirmation through molecular-genetic testing conducted by the laboratories of the Federal State Budgetary Scientific Institution "Medico-Genetic Scientific Center named after Academician N.P. Bochkov," was performed on 10 children and 2 adult patients at the time of data collection. EMG was performed on all patients with limb muscles using surface or needle electrodes. Specific electromyographic changes characteristic of SMA were detected in all patients, but quantitative descriptions of these changes were often lacking, which hindered establishing correlations between the EMG findings and other clinical results. The research results are presented in Table. There were no statistically significant differences in creatinine and CK medians between the G12.0, G12.1, G12.8, and G12.9 groups, nor were there any significant associations with motor impairments (Figure). However, we did detect subgroup differences in LDH levels between the G12.1 Children and G12.1 Adult subgroups: G12.1 Children VS G12.1 Adult (median [1 and 3 quartiles]): 305.7 [275.0, 534.0] VS 206.5 [195.0, 233.0], mean rank difference = 16.84, Dunn's p=0.003.

Analysis of archival medical records of patients (n=4, 6.9%) with repeated hospitalizations showed highest CK levels (up to 9000 U/L) in patients of the G12.1 group at clinical onset, followed by a decline in subsequent 3-17 months, depending on the records date. Individual data from cases with repeat hospitalizations also indicated increased CK levels in patients of the G12.0 and G12.1 groups upon initiating disease-modifying therapy with nusinersen or risdiplam. Archival data did not reveal significant correlations between CK levels, disease stage, and the age at start of therapy.

Discussion. The total number of patient records is greater than the number of persons due to inclusion of elderly patients with a milder course of the disease, who had been regularly hospitalized for the 14 years of record collection. Statistical analysis of laboratory test results and neurological examination data obtained from 112 archival medical records of 58 SMA patients diagnosed with G12.0, G12.1, G12.8, and G12.9 codes did not show any associations between creatinine and CK levels with diagnostic categories. Numerically higher CK levels in the G12.1, G12.8, and G12.9 groups compared to the G12.0 group were not statistically significant and were more likely related to age, weight, gender, and the level of physical activity of the patients. These factors were also likely to have been associated with the corresponding group differences in LDH levels. Due to limited sample size and heterogeneity of the data, results for patients with repeat hospitalizations did not support strong conclusions about time-dependent individual changes biomarker levels. Similarly, the collected data on the patients' mental status was insufficient to identify group differences or establish associations with biomarker levels; emotional lability, fatigue, and tearfulness are not specific symptoms.



Levels of creatinine (А), CPK (Б) and LDH (В) in patients with diagnoses G12.0, G12.1, G12.8 and G12.9, taking age into account

Conclusions. Routine laboratory diagnostic methods for SMA, particularly the measurement of creatinine and CK levels, did not reveal differences between the ICD subgroups, nor any association with severity of motor impairments. Although serum LDH levels did show significant differences among the groups, these differences were likely related to body weight and age rather than disease progression and motor impairments. Therefore, we cannot draw strong conclusions regarding the effectiveness of assessing creatinine, CK, and LDH levels for evaluating and predicting the course of the disease. As such, we do not recommend these laboratory tests as part of current clinical practice. Further research is needed to identify possible correlations between baseline CK levels and clinical presentation dynamics, and response to

pathogenetic therapies such as nusinersen, onasemnogen abeparvovec, and risdiplam. Results also highlight the need for prospective investigations of the possible relationship between psychiatric impairments or symptoms, motor manifestations of SMA 5q, and the three widely accessible biomarker levels.

Limitations. The study included archival material from the main regional institution, therefore omitting data from SMA patients residing in the greater Samara Oblast who have not undergone diagnosis and treatment at our hospital. Additionally, the advanced age of some patients in the sample raises concerns about the accuracy of their diagnosis; genetic confirmation was only available in 12 subjects. The study is subject to the typical limitations of a retrospective design. The limited amount of data also does not allow for a comprehensive assessment of the dynamic changes in present blood biomarker levels in individual patients.

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3D MODELS FOR THE ANALYSIS OF TUMOR INFILTRATION BY MONOCYTE-MACROPHAGES

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An analytical review of literature data of modern studies of monocyte migration (movement) in tumor microenvironment using various three-dimensional models of monocyte migration in tumor microenvironment is presented. The given literature data can serve as a characteristic of three-dimensional models as an optimal platform for studying the functions of both individual cell populations of immune cells and whole cell ensembles in the development and therapy of malignant neoplasms. One of the most important characteristics of a three-dimensional model, which has a significant impact on its prognostic ability, is the cellular composition used. The given data clearly demonstrate the importance of the diversity of cell types of the used models, including the introduction of stromal cells (in particular, fibroblasts). Various cell types form a complex system of interactions, thus forming three-dimensional models closest to native organismal conditions. Different types of tumor cells and their individual cell lines are of no less high importance for prognostic ability. For example, tumor spheroids that contain different types of cancer cells show a different secretory profile. As such, the pattern of monocyte infiltration and polarization may differ depending on the type of tumor cell line. In addition to the components themselves used to create the 3D model, the nature of the organization of the above components (different cell types and populations, as well as structural extracellular components) is important. Therefore, this analytical review contains a separate structural section including the analysis of the diversity of structural groups of three-dimensional tumor models. Among the variety of the mentioned structural groups the following should be mentioned: suspensions of multicomponent cancer spheroids, various variants of microfluidic systems and a separate group of organoids - miniature models of native organs and tissues. Thus, this analytical review demonstrates the importance of further optimization of three-dimensional tumor models in order to obtain even more effective means of reproducing the native structure of the tumor microenvironment.

Keywords: three-dimensional matrix, monocytes, tumor microenvironment.

Introduction: The study of the complex structure of the tumor microenvironment includes the analysis of interactions between cancer cells, stromal component and immune system cells. In turn, studies using three-dimensional models allow a more accurate analysis of the structure of the tumor microenvironment and the interactions of its individual elements with each other compared to classical two-dimensional models. Numerous studies convincingly demonstrate the relationship between the nature of intercellular interactions and the progression of malignant solid tumors [32]. In recent years, the complexity of the tumor microenvironment has been reproduced in advanced three-dimensional cell culture-based models. While *in vivo* models are expensive and time-consuming to develop, classical 2D *in vitro* models cannot sufficiently replicate the spatiotemporal dynamics characteristic of physiological conditions *in vivo* [3], 3D models have the ability to reproduce to a greater extent the architecture and metabolism of the original tissue [16]. Moreover, there is a continuous improvement and specialization of three-dimensional models depending on the initial data and ultimate goals of research, among which we can mention the inclusion of different extracellular matrix proteins or the addition of different types of supporting cells and the creation of angiogenic environment [19, 15, 23].

As a rule, existing three-dimensional models of tumor microenvironment focus on the interaction of cancer cells and their derivatives with stromal cells such as fibroblasts, but the accumulation of more and more new data shows the significant relevance of studies of the interaction between elements of the immune system and the tumor microenvironment [32]. Indeed, modern multicomponent three-dimensional cell culture models may be an optimal platform to study the role of the immune system in malignancies. A clear example of this is the study by K. Heungnam using three-dimensional models of mesothelioma, which reproduces changes in complex networks of biomarkers associated with immune response and apoptosis [21].

The role of different cell populations for the prognostic ability of three-dimensional tumor models. The development of malignant neoplasm promotes qualitative changes in cells of innate and adaptive immunity. It is known that monocytes can differentiate into two functionally distinct subtypes of macrophages: classical anti-inflammatory macrophages known as M1-like and M2-like macrophages, which are known to be associated with tumor progression through remodeling of the extracellular matrix and stimulation of angiogenesis [32]. In the context of the present study, the results of using existing three-dimensional cellular models to analyze the complex system of interactions between monocytes, macrophages, cancer cells and their microenvironment are of considerable interest.

Currently, the classical type of three-dimensional models is spherical

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cellular structures (spheroids). According to the origin of cells, the following types of spheroid models are distinguished: multicellular tumor model using cell lines, oncospheroids from cells of dissociated solid tumor, tissue tumor spheres formed by partial dissociation of solid tumor, and organotypic multicellular spheroid models, which differ from the previous model by the absence of tissue dissociation. The latter two models involve a blurring between the terms "spheroid" and "organoid". Nevertheless, the term "spheroid" is the most used term for three-dimensional cell cultures including multicomponent suspensions of primary cells or cell lines [8].

Analysis of three-dimensional spheroid models of human colon cancer cell culture (cell line HRT-18) formed in agarose wells showed association of macrophages with the spheroid surface within 24 hours, with their subsequent infiltration and disintegration in the absence of pronounced cytotoxicity after 5 days of co-culture. Also, cancer spheroids showed intensified migration in the presence of anti-inflammatory macrophages compared to anti-inflammatory and resident macrophages in collagen substrate [32]. Analysis of peripheral blood monocyte recruitment using three-dimensional spheroid models of fibroblasts in agarose wells showed that monocyte infiltration was characteristic of cancer spheroid models of fibroblasts, whereas normal spheroid models of fibroblasts showed a low degree of infiltration [35]. Equally, a higher rate of monocyte migration was shown for spheroid models of breast cancer cells containing fibroblasts relative to models without them [17], raising the question of cancer and stromal cells as bases for recruitment of immune cells. However, these results were not confirmed in studies of head and neck squamous cell carcinoma (hereinafter referred to as HNSCC), as no significant differences in the intensity of infiltration by peripheral blood mononuclear cells (hereinafter referred to as PBMCs) of fibroblast spheroidal models of HNSCC cells and spheroidal models of HNSCC cells without fibroblasts were recorded. At the same time, when the amount of MPCs increased, their concentration on the surface of spheroidal models increased without further infiltration. Nevertheless, experimental suppression of epithelial growth factor receptor expression resulted in increased infiltration [5].

Studies using three-dimensional spheroid models of breast cancer cells (cell line SUM159PT) showed a significant infiltrative capacity of macrophages mediated by the activity of matrix metalloproteinases. Breast cancer cell spheroids themselves were largely capable of infiltrating in type I fibrillar collagen medium, but they lost any pronounced infiltration capacity in the substrate of murine extracellular matrix extract (Matrigel1). Incorporation of macrophages both as part of cancer spheroids and directly into the substrate of murine extracellular matrix itself significantly improved the infiltrative ability of breast cancer cell spheroids, but did not increase the invasiveness in the medium of fibrillar collagen [33].

M2-type macrophages promote invasiveness of three-dimensional spheroidal models of breast cancer cells in Gultrex1 basal membrane extract through paracrine signaling as well as through direct intercellular interactions during co-culture in type I collagen substrate [14, 11]. Fibroblasts, which are part of the cancer microenvironment and cancer cells themselves, promote M2-differentiation of macrophages by secreting such factors as interleukin-6 (IL-6) and stromal growth factor-1 (SDF-1) [22].

Studies of three-dimensional spheroid models of cell cultures using the alginate porous platform AlgiMatrix™ showed that the cultivation of mouse breast cancer cells with fibroblasts alone had a negative effect on the formation of cancer spheroids, whereas co-culture with macrophages alone inhibited their growth. In turn, only co-culture of macrophages, fibroblasts and cancer cells resulted in an increase in the number of spheroids [31]. Addition of macrophages to a rat tail collagen substrate that included a layer of dermal murine fibroblasts on top of which murine squamous cell carcinoma cells were cultured resulted in the polarization of macrophages into an M2-like phenotype followed by active invasion of carcinoma cells into the collagen substrate by increasing the collagenolytic activity of metalloproteinases (MMP2 and MMP9). The researchers confirmed the obtained result by analyzing the co-culture of human squamous cell skin cancer cells, primary human dermal fibroblasts and macrophages derived from human monocytes [20].

These results indicate a significant influence of the composition of the three-dimensional matrix on the interaction between immune cells and cancer cells. In addition, the above confirms the significant influence of immune cells in the interaction between cancer cells and their microenvironment.

The significance of different tumor cell types and their individual cell lines for the prognostic ability of three-dimensional tumor models. Tumor spheroids including different types of cancer cells also show differences in secretory profile. Accordingly, the intensity of monocyte infiltration and the pattern of monocyte polarization may differ depending on the type of tumor cell line. In particular, a recent study showed the highest infiltrative activity of monocytes for spheroids created using MIA and PaCa-2 (pancreatic cancer) cell lines, while the lowest infiltrative activity was demonstrated by monocytes in MCF-7 breast cancer spheroid models [24]. Moreover, the above results are consistent with other studies [25, 17]. 1BR.3.G fibroblasts were also found to improve the stability of spheroids and enhance the overall physiological relevance of the models. When 1BR.3.G fibroblasts and MIA PaCa-2 cancer cells were co-cultured together, the formation of smaller and more compact spheroids was observed. However, their degree of stability often remained low [24], which seems to be a common problem for this cancer cell line [25, 6], indicating that active infiltration and polarization of monocytes are not associated with the fibroblast cell line.

The results of analyzing the effects of CSF1R inhibitors and antibodies administered simultaneously to monocytes in similar three-dimensional models of MCF-7, HT-29 (colorectal cancer), PANC-1 (pancreatic cancer), and MIA PaCa-2 cell lines should not be overlooked, as here, too, a heterogeneous pattern of reduction in monocyte infiltrative capacity was shown between the models in question in response to exposure to CSF1R antibodies and inhibitors. A visible decrease in monocyte infiltrative capacity was shown for models including MCF-7 and MIA PaCa-2 cell lines, while spheroids of HT-29 and PANC-1 cell lines show a slight decrease in infiltrative capacity [18].

As a result of cancer cell type-dependent polarization of monocyte precursors, researchers observe different phenotypic manifestations of tumor-associated macrophages, as clearly captured by analysis of 3D models. Specifically, MIA PaCa-2 spheroids polarize infiltrating monocytes into M2-like macrophages, whereas bone marrow-derived macrophages polarized by MCF-7 spheroid models exhibit an M1-like phenotype. Among other models generated using HT-29 and PANC-1 cell lines, a mixed type of polarization is observed with a predominance of macrophages of M2-like phenotype and expression of markers of M1-like phenotype. Noteworthy differences be-

tween macrophages determined by the tumor microenvironment and bone marrow-derived macrophages polarized by co-culture with tumor spheroid models are worth noting. The present results suggest a specific role for cell-cell interactions between cancer cells and monocytes [24], and also correlate well with data on a more pronounced development of a phenotype associated with tumor development for macrophages embedded directly in tumor spheroids compared to macrophages that are diffusely dispersed throughout the collagen substrate [7].

Analysis of the secretion profile of the considered tumor cell models showed marked differences already before co-culture with monocytes, confirming the ability of cancer cells to influence infiltrating monocytes depending on their individual secretion profile. Generally, MCF-7 spheroids exhibited an overall low level of soluble factor secretion. On the other hand, the microenvironment of MIA PaCa-2 spheroids exhibited a distinct pro-inflammatory profile combined with high secretion of the anti-inflammatory cytokine IL-10 and pro-angiogenic factors. However, secretion of most soluble factors was significantly increased when monocytes were added to the spheroid cultures. Common to all models was an increase in the levels of CCL2, CCL22, CCL24, and IL-10. CCL2, CCL22 and CCL24 were associated with M2-like polarization and significantly associated with poor prognosis in cancer patients. A concomitant decrease in the secretion of IL-12, a key factor in the antitumor immune response, was observed. For models including HT-29, PANC-1 and MIA PaCa-2 cell lines, high levels of VEGF secretion have been shown to be associated with the expression of CCL2 and IL-4 factors necessary for monocyte recruitment, in addition to transforming the immune microenvironment into an immunosuppressive state [24]. On the other hand, monocytes infiltrating HT-29 spheroids may also possess antitumor activity, since their characteristic secretion of CXCL10 and CXCL11 has been associated with tumor suppression [24, 13].

Histological analysis of the models showed the following structural features: fibroblasts in the three-dimensional model of HT-29 cell line are structurally connected with necrotic nucleus, for spheroids of MCF-7 cell line direct interaction with MCF-7 cells with subsequent formation of differentiated structures was shown.

Similar results were found already with different breast cancer cell lines: the highest intensity of monocytic infiltration was shown for three-dimensional spheroid models of cell line Hs578T (ER-negative carcinoma); spheroid models of cell line T47D showed a moderate degree of monocytic infiltration; the lowest degree of monocyte infiltration was shown for spheroid models of cell lines BT549 (ductal carcinoma), BT474 (ductal carcinoma) and MCF7 (ER-positive adenocarcinoma) [17], which indicates the ability of three-dimensional models of cell cultures to reliably reproduce the processes of tumor development down to differences at the molecular level. Based on the analysis of spheroid models of two different breast cancer cell lines (MCF-7 and MDA-MB-231) with different aggressiveness, fundamentally different effects of interaction between monocytes and cancer cells were shown. On the one hand, for spheroid models of the less aggressive MCF-7 cell line, the presence of monocytes reduced the expression of tumor malignancy markers such as metalloproteinase 9, urokinase plasminogen activator, cyclooxygenase-2, and osteopontin. On the other hand, co-culture of monocytes with three-dimensional spheroid models of the aggressive cell line MDA-MB-231 increased the expression of matrix metalloproteinase genes, as a result of which cancer cells and monocytes showed greater joint infiltrative capacity in the substrate of murine extracellular matrix extract (Matrigel1) [22].

Similar results were shown for dendritic cells derived from peripheral blood cells by exposure to IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) when co-cultured with spheroids of different tumor cell lines. The character of dendritic cell modulation differed depending on the tumor cell line [18].

There are studies that demonstrate a correlation between monocytic and neutrophil infiltration. For example, infiltration of spheroids with CD14+ monocytes resulted in a subsequent decrease in neutrophil infiltration. In contrast, prior infiltration with neutrophils did not affect subsequent monocyte infiltration, and tumors with macrophage depletion in mice showed higher neutrophil infiltration [28].

Thus, three-dimensional cell models are a feasible means to study the infiltrative capacity of monocytes and the polarization of tumor-associated macrophages down to the specificities of different tumor types and their individual cell lines, allowing its use as a susceptible screening tool for anticancer compounds *in vitro*.

Diversity of structural groups of three-dimensional tumor models. In order to create *in vitro* tumor models of non-small cell lung cancer (NSCLC) that include the myeloid compartment, Sofia P. Rebelo et al. prepared three-dimensional cell culture models encapsulated in alginate microcapsules with an average diameter of 652 ± 26 μm. This three-dimensional model included three cellular compartments: spheroids of NMSL cells (NCI-H157 cell line), cancer-associated fibroblasts (CAF), and the monocytic cell line THP-1. The microencapsulated models were maintained in suspension culture under constant agitation for three weeks. Each cell type exhibited high viability throughout the culturing time. Cell proliferation was uniform in all compartments and resulted in a tenfold increase in tumor cell concentration by week 3, which was comparable to the increase in tumor monocultures and double co-culture control groups (NSCLC cells were cultured with either tumor-associated fibroblasts or the THP-1 monocytic cell line). These results indicate that co-culture of stromal and monocytic cells had no significant effect on tumor proliferation [2].

During the culture period, the models composed of the three components contained numerous spheroids and cell clusters comprising all cell types (NSCLC, CAF, and THP-1 cells). In contrast, one to three large spheroids were found in the microcapsules of tumor monocultures, which had a loose shape and consisted of N-cadherin and vimentin positive cells (NCI-H157 retain their typical mesenchymal phenotype when microencapsulated). Moreover, in the observed multicomponent models there was an intense accumulation of extracellular matrix proteins: fibronectin, collagens of the first and fourth types, which, together with multiple cell clusters and single cells, formed a tissue-like model. At the periphery of alginate microcapsules, there was an intensive accumulation of extracellular matrix proteins, in which cells demonstrating a migratory phenotype were located, indicating active cell movement within microcapsules and the formation of a more invasive phenotype [2].

Single CD45+ positive cells and their small clusters were found around larger tumor spheroids both in three-dimensional models with three compartments and in immunocyte-tumor models. Such a distribution of CD45+ cells in the models considered indicates an enhancing activity of the tumor microenvironment with respect to the infiltration of myeloid cells into tumor spheroids. A similar distribution is shown for CD68. High expression of CD68 indicates active differentiation

of monocytes into macrophages. Moreover, high levels of CD163+ cells were recorded in three-compartment models and paired control models (THP-1/CAF and THP-1/NMRL), while CD163+ cells were recorded at residual levels in monocytic monocultures. This indicates the ability to stimulate monocytic cell differentiation towards an M2-like phenotype for both tumor cells and CAFs. The ratio of CD163+/CD68+ cells, which characterizes the proportion of M2-like macrophages, is approximately 15-20% for the three-compartment 3D model and the "THP-1/NMRL" control model and only 2% in the "CAF/THP1" culture. The high degree of polarization was confirmed using three-dimensional models with peripheral blood monocytes (PBM) of donor origin. On average, after 4 days of culturing, 70-80% of CD45+ cells expressed M2-like markers (CD206 and CD163) in complete models, whereas only 2-6% expressed M2-like markers (CD206 and CD163) in microencapsulated PBM monoculture.

The high proportion of CD163+ cells indicates that the presented model (three-dimensional spheroidal structure of three compartments encapsulated in an alginate shell) promotes cell migration similar to myeloid infiltration in human lung cancer under physiological conditions. At a significantly lower level, CD163+ cells were observed in control cultures with "THP-1/NMRL" and "THP-1/CAF". This is consistent with previous reports of high CAF activity in the context of monocyte recruitment associated with a marked change in secretory profile and high production of extracellular matrix proteins. Moreover, in models of co-culture of blood monocytes with breast cancer cell spheroids and tumor-associated fibroblast (CAF) spheroids, monocyte migration was higher towards CAF spheroids, for which CCL2 overexpression has been shown [17]. The high importance of CAF is confirmed in studies using classical cancer models. Within the tumor microenvironment, CAFs promote monocyte recruitment and differentiation into immunosuppressive M2 macrophages via interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF) synthesis [10], and into myeloid-derived suppressor cells (MDSC) via signal transduction and activation of transcription 3 (STAT3) [26].

An important feature of the shown three-dimensional model is the use of an inert framework, since the introduction of physiologically relevant extracellular matrix proteins remains a fundamental problem for *in vitro* tumor analysis [30]. The considered alginate microcapsules allow to accumulate collagen types I and IV and fibronectin, forming collagen fibers with single cellular inclusions, which contributes to the formation of tissue-like structures [29].

The use of classical three-dimensional models allows obtaining relatively reliable results in the context of tumor microenvironment analysis. However, these models themselves have low predictive power with respect to the dynamic parameters of tumors *in vivo*. This problem has been addressed by combining standard 3D models with controlled dynamic environments. An interesting illustration of this approach is a three-dimensional multicomponent cell model (breast cancer cells, CAF, endothelial cells) cultured on a microfluidic chip. The architecture of the above model involves the flow of medium from peripheral chambers populated by breast cancer cells and PBMCs through a central chamber occupied by CAFs. The analysis of the presented model confirms the ability of CAF to modulate immune cells, reducing the time of their contact with tumor cells [8].

Microfluidic systems are three-dimensional models with high throughput and the possibility of automated processing of multiple samples, allowing the creation of mimetic media according to the properties of the studied organ and tissue [27]. Analysis using three-dimensional microfluidic models has shown the high importance of interferon regulatory factor (IRF-8) for the ability of immune cells to limit the invasiveness of cancer cells, which is supported by *in vivo* studies [4, 9]. A curious result was shown using three-dimensional microfluidic systems to reproduce and analyze the interaction between cancer cells and the tumor vasculature in the presence of immunocytes. Two channels populated with human breast carcinoma cells (MDA231) and endothelial cells (HUVEC) were connected by a three-dimensional hydrogel structure based on extracellular matrix, resulting in endothelial cells forming a layer on the surface of the extracellular matrix and tumor cells actively infiltrating it. As a result of tumor canal repopulation by murine macrophages (RAW264.7), a significantly higher rate of intravasation into the endothelial layer was observed [34].

The following study uses a three-dimensional model that represents a microfluidic system of channels filled with medium and collagen substrate that include hepatocellular carcinoma cells. Operation of this model involves the migration of fluorescent dye-labeled immune cells from the peripheral media-filled channels into the central channel filled with collagen substrate and hepatocellular carcinoma cells. In addition, the inclusion of so-called dead and live discriminatory dyes in the substrate composition allows to detect the dynamics of cell death [3]. The above three-dimensional tumor model was adapted by increasing the cellular diversity of the microfluidic system by including primary human monocytes. Monocytes were suspended together with aggregates of target cells in collagen gel, injected into the central hydrogel region of the microfluidic device and cultured overnight. The final arrangement of cells in the microfluidic platform mimics some features of the tumor microenvironment *in vivo*, which allows the analysis of numerous intercellular interactions [12]. In addition to increasing cellular diversity as a qualitative change in 3D models, some researchers suggest the importance of a proportional ratio of different cell groups, as this may contribute to the mimetic nature of the developed models [8].

A separate group of three-dimensional models, close in their properties to classical spheroidal models, includes so-called organoids, which are miniature models of organs embedded in extracellular matrix and formed from stem and poorly differentiated cells obtained by mechanical or enzymatic cleavage of primary donor tissue. Organoids reproduce the architecture as well as the diversity of cellular compartments and organization of the original tissue, allowing for a significant reproduction of physiological conditions. Patient-derived organoids allow for three-dimensional culture of cancer cells isolated from primary treated tissues, which can result in the loss of stromal and immune compartments. After formation of a research model of patient-derived organoids, peripheral blood mononuclear cells or other immune and stromal cell groups can be introduced as a co-culture [8].

Conclusion. The data presented above provide a clear picture of the importance of further optimization of 3D tumor models in order to obtain optimal means of reproducing the full variety of structures and conditions of the tumor stroma. The evaluation of therapeutic compounds in classical 2D models may allow a relatively reliable study of the diverse effects of antitumor agents on immune cells outside the context of the tumor microenvironment. However, the effects of antitumor agents on the infiltration and modulation of immune cells in conjunction with the tumor microenvironment cannot be adequately studied by classical 2D models. This probably

explains the relatively low success rate of anticancer immunotherapies preclinically tested on 2D models [1, 2]. Tumor 3D cellular models appear to be an optimal means to study the infiltrative capacity of monocytes and the subsequent polarization of tumor-associated macrophages. It is necessary to note the high level of sensitivity of three-dimensional models, allowing to capture a complex set of changes according to different cell populations and cell lines, which allows using it as a susceptible screening tool for anticancer compounds *in vitro*.

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THE ROLE OF PROINFLAMMATORY CYTOKINES IN THE DEVELOPMENT OF CHRONIC DISCOGENIC PAIN SYNDROME

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The purpose of this review is to update the knowledge of neurologist doctors about the role of pro-inflammatory cytokines in the evelopment and chronicity of discogenic pain syndrome in patients with intervertebral disc degeneration.

Keywords: cytokines; cytokine status; disk degeneration; biomarker; chronic inflammation, discogenic pain syndrome.

Introduction: Intervertebral disc degeneration (IDD) is a multifactorial chronic recurrent pathological process that primarily affects the nucleus pulposus (NP) of the intervertebral disc and then spreads to the annulus fibrosus (AF) and other elements of the spinal motion segment (SMS). The pathogenetic mechanism manifests itself under certain conditions in various (reflex, compression, compression-reflex and reflex-compression) neurological syndromes [1]. The new International Classification of Diseases, 11th revision (ICD XI), has a separate block for coding discogenic pathology - block FA80 "Degeneration of the intervertebral disc with and without involvement of the nervous system." The new ICD-11 does not provide for the use of the terms "dorsopathy" and "dorsalgia". The term "Dorsopathy" can only be used in the case of category FB1Z - "conditions associated with the spine, unspecified." Non-discogenic back pain (not associated with damage to the intervertebral disc (IVD)) can be coded as ME84 - "back pain, the sources of which are muscles, nerves, bones, joints or other structures of the spine" or MG30.3 "chronic secondary musculoskeletal pain." Other categories that are directly related to IVD are highlighted separately. They are presented in table 1 [2].

One of the main mechanisms of IDD is the loss of proteoglycans [3], which results in a decrease in osmotic pressure in the disc matrix and loss of water molecules, which is manifested by a change in the mechanical properties of the IVD. Gradually, these processes lead to protrusion and a decrease in the height of the IVD. The loss of proteoglycans promotes the movement of serum proteins and cytokines into the extracellular matrix (ECM), which affect the PN cells and accelerate the process of IDD [3]. The activity of matrix metalloproteinases (MMPs) and cathepsins plays an important role in the denaturation and breakdown of collagen, fibronectin and proteoglycans. The consequence of this process is osteoarthritis degeneration, protrusion of ligaments into the spinal canal with compression of neural structures [39]. The degenerative cascade involves the roots of the spinal nerves, which causes chronic pain mainly due to their compression and partly due to neoangiogenesis (ingrowth of the smallest nerve endings into the degenerating IVD and their activation due to the constant release of inflammatory mediators, including proinflammatory cytokines) [36].

In recent years, cytokine imbalance is considered as one of the most important mechanisms for the formation of persistent vertebrogenic pain syndrome [41], which consists in a shift in the balance of cytokines towards an increase in the content of pro-inflammatory cytokines and the maintenance of chronic inflammation in the degenerating IVD and surrounding tissues [7]. The release of a large number of pro-inflammatory cytokines is mediated by NP and AF cells, as well as macrophages, neutrophils, T- and B-lymphocytes. Proinflammatory cytokines cause a chain of pathophysiological reactions leading to degeneration [12,25], oxidation [12,18], autophagy [19,34], aging [31,38] and apoptosis [34] of IVD cells (Table 2).

Accordingly, the delicate balance between pro-inflammatory and anti-inflammatory cytokines determines the overall effect of the inflammatory response in patients with IDD and the expected therapeutic response to prescribed drugs [26], as well as the possibility of using more high-tech treatment methods in case of severe IDD and persistent discogenic back pain [17].

Damage caused by proinflammatory cytokines in intervertebral disc degeneration. Cytokines (interleukins (IL), lymphokines, monokines, interferons and chemokines) are important components of the immune system (Fig. 1) [7]. They act in conjunction with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Imbalances in cytokine production or cytokine receptor expression and/or dysregulation of cytokine balance contribute to the development and progression of IDD. Cytokines are classified into two large groups: pro-inflammatory and anti-inflammatory. Time-dependent imbalance of pro- and anti-inflammato-

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Table 1

Coding of intervertebral disc degeneration according to ICD-11 and ICD-10

ICD-11 block/code	Block/code name		ICD-10 block/code
FA80	"Intervertebral disc degeneration"	“Other dorsopathies associated with damage to the intervertebral disc”	M50-M53
8B93.6 8B93.8 8B42	"Radiculopathy due to damage to the IVD" "Radiculopathy due to spondylosis" "Myelopathy in spondylosis"		M50-M53 M47.1 M47.2
FA8Z	"Spondylosis"		M47
ME84	"Back pain"	"Dorsalgia"	M54
MG30	"Chronic pain"		-
FB1Z	"Spine-related conditions, unspecified"		-

ry cytokines determines the outcome of the inflammatory response as one of the main mechanisms for the development of IDD [7].

Pro-inflammatory cytokines play a central role in the development of IDD, are produced predominantly by activated macrophages and are involved in enhancing inflammatory reactions, serve to contain and eliminate inflammatory foci by activating local and systemic inflammatory reactions, and can directly modulate cell activity in various structures of the IVD, including the NP, AF and ECM [25]. The main proinflammatory cytokines responsible for early responses are interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α). Other proinflammatory mediators include members of the IL-20 family, IL-33, leukemia inhibitory factor (FIL), interferon gamma (IFN-γ), oncostatin M (OCM), ciliary neurotrophic factor (CNTF), transforming growth factor beta (TGFR-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-11, IL-12, IL-17, IL-18, as well as other chemokines that chemoattract inflammatory cells. IL-1, IL-6 and TNF-α manifest their action as endogenous pyrogens that enhance the synthesis of secondary mediators and proinflammatory cytokines by macrophages and mesenchymal cells, stimulating the production of acute phase proteins or attracting inflammatory cells. IL-1β, TNFα, IFN-γ, IL-12 and IL-18 are well characterized as proinflammatory cytokines [7].

Interleukin 1β – IL-1β is one of the key pro-inflammatory cytokines that is involved in the regulation of the innate immune response [28]. Apoptotic macrophage cells release only IL-1, but not IL-6 or TNF-α, suggesting that *in vivo* apoptosis of macrophages in the IVD is the source of cytokine release. IL-1β may promote the expression of matrix metalloproteinases in the IVD. IL-1β stimulates disintegrin and metalloprotease with thrombospondin-1-like domains (ADAMTS), which may regulate the production of ADAMTS-4 and ADAMTS-5 in the IVD, promoting ECM loss and development of IDD [24]. There is a connection between IL-1β and premature stress-induced aging of IVD cells. In IL-1β stimulated NP cells, the levels of β-galactosidase are significantly increased [38], which leads to an increase in the number of senescent IVD cells and a decrease in the ability of cell self-renewal. IL-1β promotes the production of pro-apoptotic proteins, including cleaved caspase 3 (apoptosis coordinator enzyme) and Bax (apoptosis promoter protein), and reduces the production of anti-apoptotic content in the IVD. IL-1β stimulation dramatically increased caspase-3 activity, cell apoptosis rate, and production of cleaved PARP (poly(ADP-ribose) polymerase), Bax, caspase-3, and cleaved caspase-3, but decreased the level of B-cell lymphoma 2 (Bcl- 2 - apoptosis inhibitor protein) in the IVD of rats. Stimulation of IL-1β leads to a sharp increase in the rate of apoptosis in rat AF due to increased caspase-3 activity, which is also suppressed by 17β-estradiol [44].

Also, IL-1β is associated with pyroptosis, a form of inflammatory programmed cell death associated with the secretion of IL-1β. The process of pyroptosis is pro-inflammatory and is triggered by the inflammatory domain NOD-like receptor 3 (NLRP-3) family pyrin (NLR family

Table 2

Theories about the role of cytokines in the development of intervertebral disc degeneration

Theory	Cytokines involved	Sources
Theory of structure degra-dation extracellular intervertebral disc matrix	IL-1β, IL-6, IL-8, IL-17, IL-18, IL-21, IL-23, TNF-α, IFN-γ	[8,12,25]
Oxidation theory	IL-1β, IL-6, IL-8, IL-17, IL-18, TNF-α, IFN-γ	[14,18]
Mechanical Load Theory	IL-1β, IL-6, IL-8, IL-17, TNF-α	[9,16]
Theory of programmed cell death (apoptosis)	IL-1β, IL-6, IL-17, IL-18, TNF-α	[19,30,33,35]
Theory of cell proliferation	IL-1β, IL-17, TNF-α	[11,22]
Theory of premature aging	IL-1β, IL-6, IL-18, TNF-α	[31,38]
Autophagy theory	IL-1β, IL-17, TNF-α, IFN-β1	[19,34]
Theory of angiogenesis and neoinnervation	IL-1β, IL-17, TNF-α	[10,14]
Theory of hypoxia	IL-1β, TNF-α	[12]
Cell cycle disruption theory	IL-1β, IL-17, TNF-α	[44]

Note: IL-1β – interleukin 1 β; IL-6 – interleukin 6; IL-8 – interleukin 8; IL-17 – interleukin 17; IL-18 – in-terleukin 18; IL-21 – interleukin 21; IL-23 – interleukin 23; TNF-α – tumor necrosis factor alpha; IFN-γ – interferon gamma; IFN-β – interferon beta.

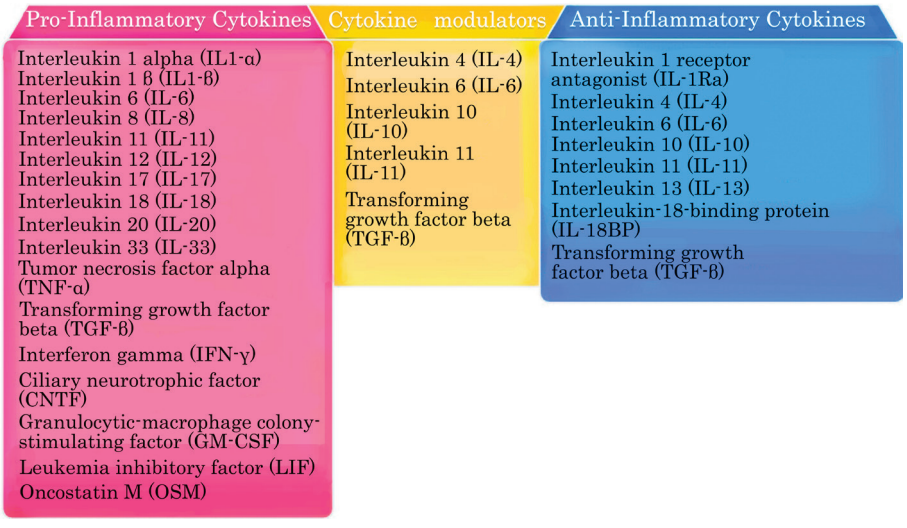

Fig. 1. Main groups of cytokines.

pyrin domain 3 (NLRP3)), which depends on the formation of oligomers of apoptosis-associated speck proteins known as pyroptosomes [35]. In addition, pyroptosis has been found to be associated with IDD mediated by the propiobacterium P. acnes. Increased levels of NLRP3, IL-1β, caspase-5, caspase-1 and gastermin D (a tumor suppressor) were found in NP cells after co-culture with P. acnes [40].

Many factors have been found that can modulate the proliferation of NP cells, such as thymosin beta-4, insulin-like granulocyte growth factor 1 (IGF-1) and leptin. IL-1β stimulation significantly suppresses IVD proliferation [11].

The processes of neoinnervation and neoangiogenesis likely increase the severity and rate of development of IDD. Overexpression of the most important proangiogenic factor, vascular endothelial growth factor (VEGF), leads to acceleration of IDD [14], as well as overexpression of neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BNF) [10].

Interleukin 2 – IL-2 is produced by mature T cells; this cytokine is involved in the maturation of T cells and B cells, functioning as a growth factor for them. Serum levels of IL-2 in patients with low back pain were significantly lower than in controls, similar to other factors including IL-6, IL-4, and MMP-1 [37]. It should be recognized that the role of IL-2 in the development of IDD is still being studied.

Interleukin 8 – IL-8 is produced by macrophages, T lymphocytes, neutrophils, and other cells in response to antigen; IL-8 is the most potent of the human chemokines [7]. IL-8 causes hyperalgesia by triggering local production of sympathetic amines, which increase the sensitivity of pain receptors [36]. Oxidative/nitrosative stress and mechanical

Table 3

The role of pro-inflammatory cytokines in the pathogenesis of intervertebral disc degeneration

Cytokine	Gene: OMIM	Role in the intervertebral disc	Clinical role	Sources
IL-1β	*IL1B*: 147720	Initiation of inflammatory, oxidative, degenerative, apop-totic cascades. Association with premature aging and cessation of cellular growth. Overexpression of VEGF, NGF, BNF.	+++	[24,35,38]
IL-8	*CXCL8:* 146930	Increased migration of neutrophils, T cells and monocytes. Indirect increase in oxidative stress, which can lead to IVD cell death. Participation in the pathogenesis of acute neuropathic pain.	+/-	[8,9,16,36]
IL-12A	*IL12A*: 161560	Stimulation of proliferation. Activation and increase in cytotoxicity of natural killer cells and T cells. Stimulation of Th-1 differentiation. Induction of secretion of IFN-γ and TNF-α, synergism with pro-inflammatory cytokines.	++	[7]
IL-17	*IL17A*: 603149	Initiation of the inflammatory and degenerative cascade. Association with cell growth arrest. Stimulation of angiogenesis.	+++	[19,43]
IL-18	*IL18:* 600953	Initiation of the inflammatory and degenerative cascade (activation of IFN-γ). Initiation of apoptotic and oxidative cascade. Association with premature aging of IVD cells.	+++	[42]
TNF-α	*TNF:* 191160	Initiation of inflammatory, apoptotic, oxidative and de-generative cascades of IVD cells. Association with premature aging and cessation of cell growth. Autophagy promoter.	+++	[7,24,35]
IFN-γ	*IFNG:* 147570	Initiation of the inflammatory and degenerative cascade in IVD cells. Participation in the pathogenesis of acute neuropathic pain in IDD.	++	[20]

Note: (+/-) – questionable prognostic role in the development of intervertebral disc degeneration (IVD); (+) – low prognostic role in the development of IDD; (++) – moderate prognostic role in the development of IDD; (+++) – significant prognostic role in the development of IDD; IFN-γ – interferon gamma; IL-12 – interleu-kin 12; IL-17 – interleukin 17; IL-18 – interleukin 18; IL-1β – interleukin 1β; IL-8 – interleukin 8; BNF - brain-derived neurotrophic factor; NK cells – natural killers; T cells – T lymphocytes; Th1 – T-helper type 1; TNF2 – tumor necrosis factor 2; TNF-α – tumor necrosis factor alpha; NGF – nerve growth factor; VEGF - vascular endothelial growth factor.

damage lead to increased levels of IL-8 in degenerating IVDs [9].

Unfavorable mechanical stress on human NP and AF cells and acute mechanical trauma ex vivo of the human IVD induces an increase in IL-8 expression [16]. An increase in the level of IL-8 after sterile inflammation of the IVD has been shown, including activation of toll-like receptors type 2 (TLRe2) in NP cells [13], TNFα treatment of NP cells, IL-1β treatment of NP cells with TPRe2 activation [5].

Interleukin 12 – IL-12 is secreted by macrophages and dendritic cells as a response to bacterial cell wall components. IL-12 causes stimulation of proliferation, activation and increased cytotoxicity of natural killer cells (NK cells) and T cells, participating in their differentiation into T-helper type 1 (Th-1) [7], which also plays a role in the development IDD. IL-12 induces the secretion of IFN-γ, TNF-α and has a synergistic effect with IL-18 [7]. IL-12 functions together with cytokines such as IFN-γ, and differences in the levels of these cytokines in IVD herniated fragments and in degenerating IVD cells have been noted [21]. Accordingly, both IL-12 and IFN-γ, as well as other cytokines (IL-4, IL-6) showed higher levels in IVD herniated fragments. Although, on the other hand, the expression levels of these cytokines obtained from the IVD at autopsy in patients with IDD did not have significant differences with their levels in the NP and AT in clinically healthy people [20].

Interleukin 17 – IL-17 is produced by Th-17, accelerates the development of IDD by stimulating the secretion of pro-inflammatory cytokines by macrophages [7], promotes ECM degradation, enhancing the inflammatory response, inducing neoangiogenesis and inhibiting autophagy and proliferation of NP cells.

High levels of IL-6, IL-17A and TNFα were noted in the blood of patients with lumbar spinal root lesions compared with patients with neuropathic pain syndrome, and the level of Th-17 was increased in the venous blood in patients with lesions of the lumbar spinal roots, compared with patients with neuropathic pain syndrome [43]. In an *in vitro* study, treatment of NP cells isolated from the IVD with IL-17A showed that IL-17A inhibits cell proliferation and ECM synthesis [22]. Treatment with IL-17A and anti-IL-17A neutralizing antibodies significantly reduces the response to IL-6, cyclooxygenase 2 (COX-2), MMP-3, and MMP-13. IL-17A can inhibit autophagy in human NP cells by activating the PI3K/Akt/Bcl-2 signaling pathway (the classical anti-apoptosis pathway in cells) (PI3K - phosphoinositide 3-kinase inhibitors; Akt - protein kinase B). Based on the protective role of autophagy in IDD, it can be concluded that IL-17A contributes to the development of IDD by inhibiting autophagy [19].

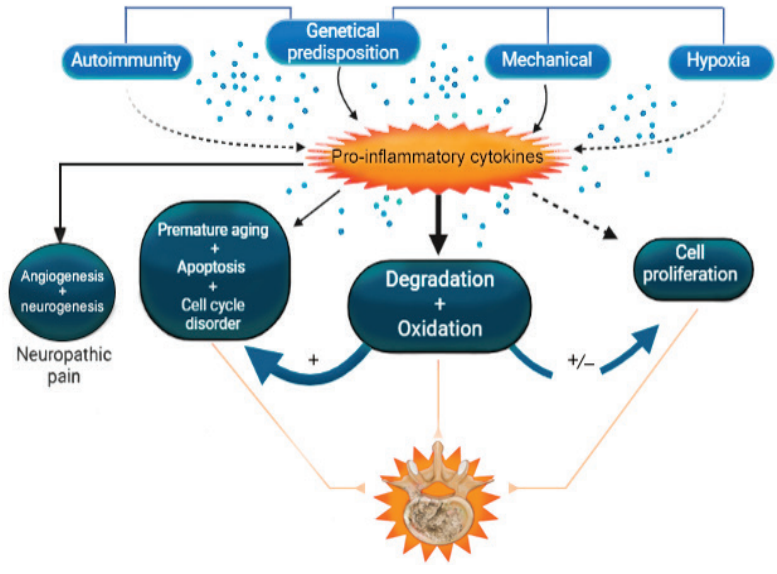

Fig. 2. Mechanisms of intervertebral disc degeneration [6]. Effects of proinflammatory cytokines in intervertebral disc degeneration (IDD). Note: (+) — interconnected mechanisms of development of IDD; (+/-) – possible connection between the mechanisms of development of IDD.

Interleukin 18 – IL-18, a member of the IL-1 superfamily with a structure similar to IL-1β, is a highly regulated proinflammatory cytokine that is cleaved by caspase-1 to produce a biologically active molecule. The level of IL-18 increases during inflammatory processes in the body [4]. The activation of T cells and NK cells mediated by this cytokine leads to the secretion of gamma interferon (IFN-γ), activation of macrophages secreting cytokines such as TNF-α and IL-1, which, in turn, cause increased degradation matrix both directly and through the activation of proteinases like MMPs [27].

IL-18 activates caspase-1 and the inflammasome system, increasing the production of reactive oxygen species in cells, which leads to further IL-18 production and neuronal apoptosis [30]. IL-18 can increase the level of anti-apoptotic proteins BCL-2 and BCL-XL (very large B-cell lymphoma) [33], and also cause inflammatory reactions in synoviocytes and chondrocytes, increasing the expression of pro-inflammatory factors such as TNF-α, prostaglan -din E2 (PGE-2) and COX-2, contributing to the acceleration of cartilage degeneration and the development of osteoarthritis [42].

Tumor necrosis factor alpha – TNF-α, as the most important pro-inflammatory cytokine, enhances the expression of COX-2 in IVD cells, and also increases the production of PGE-2 (which regulates the activity of various signaling pathways through the prostaglandin receptors of the G-protein family), which stimulates the work of the Wnt signaling pathway (intracellular signaling pathway regulating embryogenesis, cell differentiation and the development of malignant neoplasms) TNF-α-PGE-2 through the prostaglandin E3 receptor (EP3 receptor). TNF-α activates the p65, Janus kinase (JNK) and p38 sites of the mitogen-activated protein kinase (MAPK) signaling pathway in NP cells in the IVD. At the same time, stimulation of proliferative processes carried out through TNF-α depends on the interaction of NF-κB, JNK and p38 signaling pathways. Short-term exposure to TNF-α stimulates proliferative processes through the MAPK pathway without the involvement of extracellular signal-regulated kinases ½ (ERK1/2) [8]. In addition, TNF-α is involved in the activation of NLRP-3 inflammatory pathways [35].

Stimulation of TNF-α promotes the production of proinflammatory cytokines IL-8 and IL-6 in IVD AF in adults. The result of TNF-α stimulation is an increase in the level of substance P (SP), as well as induction of the expression of IL-1β, IL-6 and IL-8. TNF-α stimulates the synthesis of reactive oxygen species, which is subsequently associated with the severity of IDD. IL-17 and TNF-α can induce the secretion of inflammatory mediators in AF and NP cells in patients with surgery for IDD, including IL-6, NO and PGE2. IL-17 and TNF-α increase the level of intercellular adhesion molecule (ICAM (InterCellular Adhesion Molecule)-1) in IVD cells

[8]. TNF-α leads to stimulation of the expression of multiple MMPs and ADAMTS, inducing their expression through activation of the NF-κB/MAPK signaling pathway. TNF-α has a positive effect on the synthesis of MMP-1, MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5 in the IVD *ex vivo*, leading to the degradation of aggrecan and collagen in the NP. Due to stimulation of TNF-α, the levels of MMP-3 and ADAMTS-5 significantly increase, and the production of type II collagen, on the contrary, decreases [24].

Interferon gamma – IFN-γ is a soluble cytokine that is predominantly released by Th-1, cytotoxic T lymphocytes and natural killer cells [7]. This is a pro-inflammatory cytokine activated in the IVD nucleus, which influences tissue-specific macrophages in NP cells in IDD. Any structural change in the gene encoding IFN-γ, which leads to an increase in the level of its expression, can theoretically participate in the pathogenesis of the disease, due to the activation of this cytokine during neuroinflammation, as well as its effect on the nociceptor system of the body [23].

Discussion. A summary of the role of proinflammatory cytokines in the development of DMD is presented in Table 3.

Effects of proinflammatory cytokines in intervertebral disc degeneration (IDD). Note: (+) — interconnected mechanisms of development of IDD; (+/-) – possible connection between the mechanisms of development of IDD.

Passive and active immune privileged barriers are both damaged during the development of IDD and various mechanisms are involved [29], disrupting the immune balance in the microenvironment of the degenerating IVD. This additionally involves various specific and non-specific immune cells in the IVD, which, together with cytokines secreted by the IVD cells, aggravate the pathological process, interfere with recovery and contribute to the development of acute and chronic discogenic pain syndromes. An increase in the expression of growth factors and pro-inflammatory cytokines in the area of the autoimmune reaction of the IVD contributes to the activation of neovascularization and neurogenesis [36]. Elevated levels of pro-inflammatory cytokines accelerate the development of IDD, enhance the degradation of aggrecan and collagen, contributing to changes in the phenotype of IVD cells and their microenvironment [15]. Moreover, proinflammatory cytokines can cause IVD cell death and degradation of ECM cells in degenerating IVDs, promoting further progression of IDD. Thus, although the inflammatory response may be involved in the onset of disease, it is also critical for maintaining tissue homeostasis. For example, with an optimal cytokine balance, it can promote restoration/regeneration of IVD tissue [32].

Conclusion: This narrative review provides new insight into the role of proinflammatory cytokines in the pathogenetic mechanisms of IDD, which, in turn, sets new targets for the future development of promising therapeutic strategies for patients with this pathology and with IDD-associated pain syndromes.

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POINT OF VIEW

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COMPARISON OF THE NANO-SIZED PARTICLES NUMBER IN BLOOD PLASMA AND ON THE ERYTHROCYTES SURFACE USING SCANNING ELECTRON MICROSCOPY IN A CERVICAL CANCER PATIENT

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To explain the more productive isolation of HPV DNA from the blood component compared to plasma in cervical cancer patients, using scanning electron microscopy images of venous blood were studied. It was revealed that there are more nanosized bioparticles on the erythrocytes surface than in plasma. It has been suggested that among them there may be tumor extracellular vesicles carrying HPV DNA. To confirm that the erythrocyte fraction of blood is a more productive biological sample for isolating HPV DNA, continued studies are needed.

Keywords: human papillomavirus, screening, extracellular vesicles.

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Despite widespread screening in Russia to prevent cervical cancer, mortality from it remains high and has not decreased significantly. Residents of the regions of the Arctic zone of the Russian Federation (AZRF) feel this to a greater extent [11]. In the territories of the Russian Arctic there are difficulties in solving government tasks to improve the standard of living of the population and provide them with quality goods and services. It is believed that the main reasons are the weather conditions, the size of the territory, insufficient or even absence of transport infrastructure, significant dispersion of settlements, low population density, nomadism, etc. [8].

These reasons also negatively affect the use and effectiveness of traditional methods of screening for cervical pathology in women living in the Arctic. Therefore, there is an urgent need to develop simple tests applicable in hard-to-reach settlements of the Russian Arctic, that

represent an alternative to traditional screening for cervical pathology. In this regard, identifying cervical pathology and cervical cancer using a blood test is, in our opinion, the optimal choice. Indeed, blood sampling is easy, it can be carried out at the patient's location, and one container for blood is needed. While for traditional screening the collection of biomaterial requires an equipped obstetrician-gynecologist's office and a larger number of consumables - a gynecological speculum, a cytobrush, glass slides , vial, etc.

Currently, as early markers of cervical cancer, researchers suggest using some special characteristics of blood identified by such methods as, for example, measuring red cell distribution width (RDW) [14], differential scanning calorimetry [7], Raman spectroscopy [6], etc. Scientific directions searching for the cervical cancer markers in the blood also include studies of the proteome, metabolome, transcriptome and genome [15,20].

In our opinion, the studies on the detection of tumor DNA in the blood are especially promising as a cervical cancer early marker. It is known that the cause of cervical cancer is the human papillomavirus (HPV), and HPV DNA fragments detected in the blood can be attributed to cervical cancer tumor DNA [18]. But tumor DNA circulating in the blood is highly fragmented, its concentration can be extremely low [5], the half-life ranges from 30 minutes to two hours [1]. This explains the complexity and still low sensitivity of cervical cancer detecting tests based on the isolation of circulating tumor DNA in the blood.

Plasma or serum are using as a biological sample to isolate cervical cancer tumor DNA in the vast majority of studies. However, it has been shown that HPV DNA fragments can be detected in the erythrocyte component of blood [10, 12], and in this component they are found more often than in plasma [12]. Now we suppose that the isolation of cervical cancer tumor DNA from the erythrocyte component of blood may be more productive than from whole blood, plasma and serum.

Tumor DNA circulating in the blood may be cargo in extracellular vesicles secreted by tumor cells [4]. One of the methods for studying extracellular vesicles is scanning electron microscopy [9,14]. Biological nanosized particles of endogenous origin were visualized on the surface of erythrocytes in cervical cancer patients by scanning electron microscopy [14]. Among which, probably, there may be tumor extracellular vesicles.

The purpose of this study was to examine cervical cancer patient's blood images using scanning electron microscopy to compare the number of nanosized particles in the blood plasma and on the surface of red blood cells. The presence of a larger number of nanosized particles on the erythrocytes surface than in plasma, albeit indirectly, may explain the more productive isolation of HPV DNA from the erythrocyte component of blood than from plasma.

Materials and methods. Smears for imaging were made from the venous blood of a patient at the Yakut Republican Oncology Center with newly diagnosed cervical cancer. The patient gave written informed consent to the study. Venous blood was collected in the morning, on an empty stomach, into a vacuum blood container with K3-EDTA. A drop of the resulting blood was smeared in a thin even layer on a clean fat-free glass slide and air-dried at room temperature for 24 hours. Blood images were obtained using a high-resolution scanning electron microscope JSM-7800F (JEOL, Japan) by detecting secondary electrons with a lower detector at an accelerating voltage of 1 kV and a focal length of 4.2 millimeters. Glass substrates with blood smears were fixed by using carbon tape. The image magnification of blood samples ranged from 500 to 20,000 times.

Results and discussion. A series of images of venous blood from a patient with cervical cancer were obtained with magnification from 500 to 20,000 times. Clear visualization of nanosized particles became possible with magnifications of 5,000 times or more (Figure 1). The surface area of erythrocytes and the area of blood plasma located between them have approximately equal proportions in the resulting image. Nanosized particles are characterized by a white color; a study of their elemental composition in a previous study showed the content of carbon, nitrogen and oxygen in them, which confirmed their organic origin [14]. In Figure 1, some of the nanosized particles are marked with white arrows, and it can be seen that they are much more common on the surface of red blood cells than in plasma. The particle sizes in the images were approximately 70 nm (Fig. 2), this value is within the size range of extracellular vesicles.

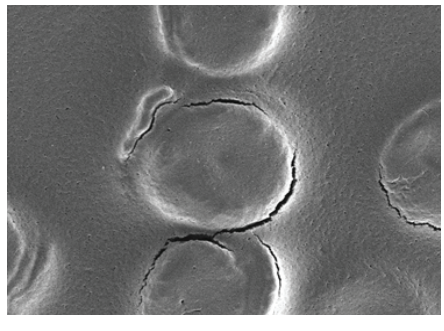

Fig. 1. SEM image of a venous blood sample from a patient with cervical cancer at 5,000x magnification

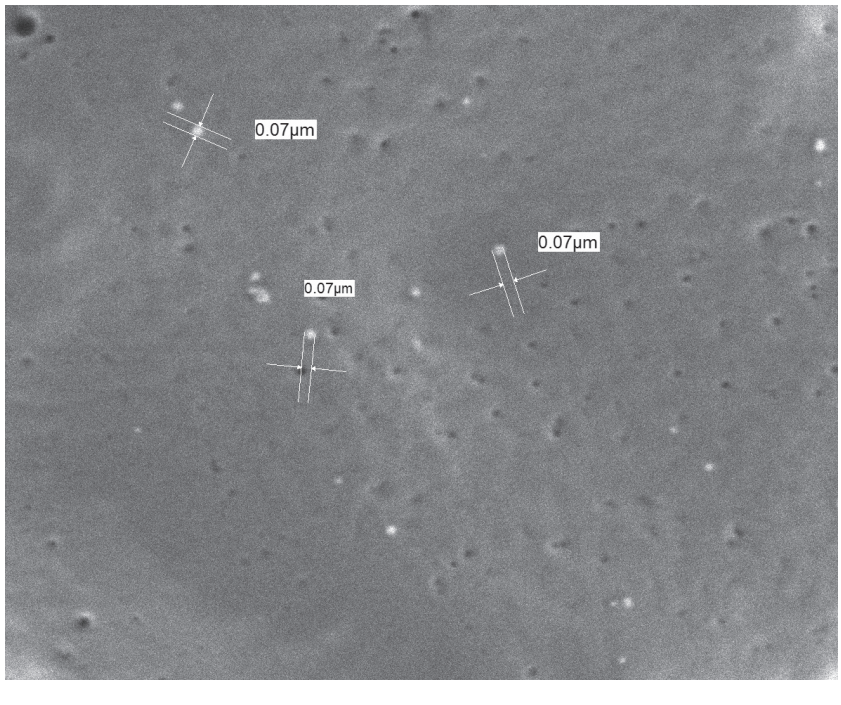

Fig. 2. SEM image of the surface of a red blood cell from the venous blood of a patient with cervical cancer at a magnification of 20,000 times

Extracellular vesicles are secreted by almost all mammalian cells, including cancer cells, and there is high variation in their secretion rates between different cell types. Extracellular vesicles are bounded by a bilipid outer layer and contain a wide range of bioactive molecules that play a critical role in regulating a variety of natural processes in the human body, as well as in pathological processes such as viral infection, the development of cancer and its metastases [4].

It has been established that DNA incorporation into extracellular vesicles is important for maintaining cellular homeostasis; inhibition of their secretion leads to the accumulation of nuclear DNA in the cytosol, provoking a senescence-like phenotype, leading to cell cycle arrest and ultimately to apoptosis. Secretion of DNA through extracellular vesicles protects tumor cells from the inflammatory response. It is assumed, that higher DNA concentrations are associated with more larger sizes of extracellular vesicles, and a greater amount of DNA is contained in extracellular vesicles of tumor cells compared to normal cells. DNA included in extracellular vesicles of tumor cells reflects their genome and is protected from nucleases [4].

Of course, extracellular vesicles observed on the surface of erythrocytes can be secreted by the erythrocytes themselves and adhere to their surface [16]. But it is known that many of the erythrocyte adhesion receptors are similar to those of other cells [19]. Extracellular vesicles also have adhesion receptors, with the help of which they interact with recipient cells [2]. In addition, it has been established that the lipid and protein profiles of erythrocyte membranes in healthy patients and cancer patients differ, and the differences are not associated with the nutritional characteristics of patients [3,17]. That is, the possibility of adhesion of extracellular vesicles, including produced those by tumor cells, on the surface of erythrocytes cannot be ruled out.

We recognize, that the significant predominance of the number of nanosized particles on the surface of erythrocytes compared to blood plasma, which we detected using scanning electron microscopy in the images of the venous blood of the cervical cancer patient, does not directly confirm that the erythrocyte component of blood is a more productive biological sample for isolating cervical cancer tumor DNA. Further molecular genetic studies are needed to establish this. It is necessary to note that modification of the scanning electron microscope with a thermal field Schottky cathode and a superhybrid lens at low accelerating voltages made it possible to study blood samples without applying a conductive coating to them, which distorts the image of surfaces in the nanometer range. Using this modification allowed us to visualize nanosized particles in blood samples and determine their location and size.

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CLINICAL CASE

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CLINICAL CASE OF GLYCOGENOUS DISEASES TYPE III IN A CHILD

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Glycogenosis type III (Cori disease) is one of the most common glycogen storage diseases in the world. The disease is associated with a disorder of carbohydrate metabolism: glycogen metabolism, leading to disruption of its synthesis or breakdown and is characterized by excessive accumulation of this polysaccharide in the organs and tissues of the body, most often in the liver or muscles. This article presents a clinical case of glycogen storage disease type III.

Keywords: glycogenosis, storage diseases, glycogen accumulation, children, liver, hypoglycemia, diagnosis, treatment.

Introduction. Glycogenous disease (GD, synonym: glycogenosis, glycogen storage disease, ICD10 - E 74.0) is a group of hereditary diseases of carbohydrate metabolism disorder – glycogen metabolism, leading to disruption of its synthesis or breakdown and accompanied by excessive accumulation in the liver or muscles. Currently, 15 types of GB have been described [1,3,4]. Hepatic forms of GB include types I, III, VI and IX.

The frequency of GB type III is 24% of all types of GB. It is characterized by an autosomal recessive type of inheritance, resulting from mutations of the AGL gene and deficiency of the enzymes amylo-1,6-glucosidase and 4a-glucanotransferase. An enzyme defect leads to the accumulation of glycogen of an abnormal structure in the liver or muscles. Clinically manifested by: cardiomyopathy, muscle weakness, muscle atrophy, states of acute hypoglycemia from birth, general intoxication, nosebleeds, growth retardation in combination with excess body weight. The formation of liver adenomas and cases of left ventricular hypertrophy have been described; in rare cases, life-threatening rhythm disturbances can be recorded. Damage to the diaphragm can cause frequent pneumonia with the development of cor pulmonale [2,5,6,7].

The main methods of confirming the diagnosis are biochemical - determining the activity of the enzyme in leukocytes, erythrocytes or fibroblasts. It is also possible to conduct molecular genetic studies [4,5].

No specific treatment has been developed. The main thing in the treatment of GB is strict adherence to the diet and a specialized diet to prevent glucose levels from falling below acceptable values. Great importance is attached to the organization of fractional meals [3].

Purpose of the study: to describe the clinical and laboratory picture of glycogen disease type III in a 9-year-old child.

A retrospective analysis of the medical history of a patient who was hospitalized in the Department of Pediatric Endocrinology and Gastroenterology of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "RB No. 1-NCM named after. M.E. Nikolaev". The department conducted a full in-depth examination. Laboratory tests were performed (general blood and urine analysis, biochemical blood test, glycemic profile study, immune status, thyroid hormone analysis) and instrumental studies (ultrasound of the internal organs, ECG, ECHO-CG, FEGDS, chest radiography, computed tomography of internal organs, hepatoscintigraphy, liver biopsy, tandem MAS spectrometry).

Clinical example. Child D., 9 years old, girl, Sakha, was admitted with complaints of nosebleeds, frequent and prolonged acute respiratory viral infection (ARVI), episodes of hypoglycemia, moodiness, tearfulness, difficulties in learning at school.

Anamnesis of life. The child is from the second pregnancy, which proceeded physiologically. First birth, on time, natural. Birth weight: 4080 g, body length 56 cm. Apgar score 8/9 points. Attached to the breast for 1 day, breastfed until 1 year 1 month. Psycho-motor development: walking with a delay from 1 year 8 months, speech development according to age. She received preventive vaccinations on an individual schedule due to frequent acute respiratory viral infections. Mother is 39 years old, father is 48 years old, no chronic diseases. They have a child who is 5 years old and healthy.

Anamnesis of the disease. At the age of 5 months, the mother noticed an increase in the size of the child's abdomen, but due to the remoteness of her place of residence, she did not seek medical help or examination.

In April 2015 a girl with suspected pneumonia was hospitalized at the Central District Hospital, where a biochemical blood test revealed high cytolytic activity and elevated triglyceride levels. With suspicion of viral hepatitis, she was transferred to the Children's Infectious Clinical Hospital in Yakutsk, where this diagnosis was excluded. The child was hospitalized in the gastroenterology department of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "RB No. 1-NCM named after. M.E. Nikolaev".

Upon admission, complaints of severe sweating, abdominal enlargement, rashes, anxiety, tearfulness.

In the department, the child underwent a complete clinical, laboratory and instrumental examination. Viral hepatitis, yersiniosis, and CMV infection were excluded. According to the results of FEGDS, no changes were detected; sigmoidoscopy revealed catarrhal proc-

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titis. Ultrasound of the liver revealed an increase in its size, increased echo density, and splenomegaly. According to CT scan of the abdominal cavity, no signs of biliary or portal hypertension were detected. In order to clarify the diagnosis, a liver biopsy was performed; fibrosis of the portal tracts, with areas of bridging fibrosis, and moderate infiltration of lymphocytes, hysteocytes, and single eosinophils were revealed. Index of histological activity excluding fibrosis according to Knodell: 5. Stage of fibrosis 1. A preliminary diagnosis was made: Congenital fibrosis of the liver. Treatment provided: ursosan, hofitol, infusion therapy with glucose-salt solutions, aminoven.

Repeated hospitalization after 2 months due to the lack of positive dynamics in the child's condition, the abdomen increased, tearfulness and sweating persisted. Upon examination, the liver dimensions were +9+9+8 cm, spleen +3 cm. In the biochemical blood test, ALT/AST 596/1169 U/l, GGT 270 U/l, alkaline phosphatase 417.5 U/l, LDH 1036 U/l l, glucose 2.74 mmol/l, TG 4.71 mmol/l, cholesterol 5.59 mmol/l, cortisol 484.8 nmol/l, insulin 6.0 cd/l, growth hormone 42.28 ng/ml.

The child was additionally examined by geneticists, and tandem MAS spectrometry was performed. No aminoacidopathy was detected, and no defects in mitochondrial beta-oxidation were detected. In therapy she received heptor, viferon, ambroxol. With suspicion of glycogen storage disease, the girl was sent to the Federal State Institution "National Medical Research Center for Children's Health" of the Ministry of Health of the Russian Federation (Moscow) to clarify the diagnosis.

In the Federal State Institution "National Medical Research Center for Children's Health" of the Ministry of Health of the Russian Federation, the department of gastroenterology, the child was from 10/06/15 to 10/20/15, a clinical diagnosis was established: Glycogen disease (type 1b?), moderate to severe course.

Conducted research. Blood test for mutations in the G6PC, SLC37A4 genes, corresponding to glycogen storage disease type 1, results in the work. Three-day monitoring of blood glucose levels did not reveal any episodes of hypoglycemia.

The liver biopsy was reviewed, description: low quality materials. Serial sections of liver puncture biopsy, staining with hematoxylin and eosin according to Van Gizzon, according to Masson, PAS reaction. The biopsy is 1.4 cm long and very thin. In the section, up to 6-7 complete and incomplete portal tracts, 2-3 central veins are identified. The portal tracts are fibrotic, with multiple porto-portal septa. 1 porto-central septum, areas of perihepatocellular fibrosis. In the portal tracts there are scanty infiltrates of lymphocytes, histiocytes with an admixture of a few eosinophils. The border plate is preserved. Hepatocytes are round in shape, of various sizes, some are large, the beam structure is not distinguishable. The cytoplasm of hepatocytes is very light, fine-grained, and vacuoles are visible in some hepatocytes. The nuclei are small, shifted to the periphery, the membrane is clearly contoured. When carrying out the PAS reaction, there is an uneven accumulation of PAS-positive substance. Conclusion: Low quality of materials. Liver preparations contain signs of chronic periportal hepatitis of low histological activity without taking into account sclerosis. Sclerosis index according to Desmet 3 points (severe), perihepatocellular fibrosis. The detected changes do not contradict the diagnosis of glycogen storage disease; a final conclusion can be made after preparing additional materials. Therapy performed: glycogen diet, corn starch, heptral intravenously, Elcar, Reamberin, Polydexa, calcium D3 nycomed, leucostim 5 mcg/kg-75 mcg subcutaneously on 10/13/15 and 10/19/15. The child was discharged with recommendations to follow a diet excluding sugar, lactose, limiting fat, and taking medications.

During the next hospitalization in the gastroenterology department of the Federal State Institution "National Medical Research Center for Children's Health" of the Ministry of Health of the Russian Federation in April 2016, the final clinical diagnosis was confirmed: Glycogen disease type III, mutation c.3980G>A, pW1327* in a homozygous state in the AGL gene.

The girl is regularly observed in the department of pediatric endocrinology and gastroenterology of the Pediatric Center of the State Autonomous Institution of the Republic of Sakha (Yakutia) "RB No. 1-NCM named after. M.E. Nikolaev", follows a diet, receives leukostim subcutaneously, hepatoprotectors. The dynamics are stable. Height 128 cm, weight 34 kg. The condition is of moderate severity due to the underlying disease. The increase in abdominal size due to hepatomegaly persists.

Conclusion: This clinical case confirms the need for further research to develop optimal management tactics for patients with clear recommendations on the frequency and scope of laboratory and instrumental examinations in order to identify complications. The creation of a national registry of patients with GB is required. Conducting of children with glycogenosis requires the vigilance of specialists in many fields: pediatricians, gastroenterologists, endocrinologists, hematologists, geneticists, etc. Timely diagnosis and initiation of adequate therapy will significantly improve the quality of life of patients, the prognosis of the disease and reduce the development of complications.

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POSSIBILITIES FOR CONTROLLING BILATERAL TONIC-CLONIC SEIZURES USING THE APPLICATION EpiTapp® FOR RESISTANT EPILEPSY WITH THE DEVELOPMENT WITH ARTERIOVENOUS MALFORMATION

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Patients with drug-resistant epilepsy (DRE) due to an arteriovenous malformation (AVM) located in a functionally significant area of the brain experience a significant decrease in quality of life and require additional non-drug rehabilitation methods aimed at controlling epileptic symptoms.

Aim. To present a clinical observation of the use of the Epi-Tapp® application in a 29-year-old patient with an AVM. Materials and methods. We used the author's wrist tapping method EpiTapp® (RF patent No. 2606489 dated January 10, 2017). Results. Using the EpiTapp® application allowed a 29-year-old man with an AVM to reduce the severity and duration of focal seizures in 85% of cases and prevent secondary bilateral transformation of incipient bilateral tonic-clonic seizures in more than 50% of cases. Conclusions. This clinical case demonstrates the possibility of effectively using the EpiTapp® application in a patient with drug-resistant epilepsy as an element of a rehabilitation program aimed at controlling epileptic seizures.

Keywords: epilepsy, wrist tapping, EpiTapp®, rehabilitation.

Introduction. Arteriovenous malformations (AVMs) are congenital vascular anomalies that result from shunting between high-capacity arteries and low-capacity venous vessels, forming a dysplastic vascular lesion in the brain parenchyma [10]. The prevalence rate of cerebral AVMs in the population varies from 1.12 to 1.42 cases per 100 thousand population. However, one of the most common complications of all primary brain AVMs (up to 68% of cases) is hemorrhage [8]. The second most common complication of AVM, which occurs in 20–45% of patients, is the development of structural focal epilepsy (SFE). The mechanisms of occurrence of epilepsy in AVM are diverse. On the one hand, epileptic seizures can develop directly as a result of hemorrhages and hemosiderosis, on the other hand, the cause may be the phenomenon of vascular brain steal [5]. The absolute indications for invasive treatment of AVM are hemorrhage due to rupture of the malformation. The issue of treatment of unruptured AVMs is still controversial. In neurosurgical practice, the classification according to Spetzler-Martin (1986) (Table 1) is widely used, which allows one to assess the possible risk of surgical intervention.

Today, symptomatic therapy and observation, endovascular embolization, microsurgical removal of the malformation and radiosurgery are used to treat patients with AVMs. The opinions of neurosurgeons often differ on the tactics of managing patients with AVMs. According to some experts, patients with AVM always require surgical intervention, other experts choose conservative treatment tactics, and others argue that this group of patients should simply be observed, since the risk of negative consequences

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Table 1

Classification of AVM (according to Spetzler-Martin, 1986)

To size: Less than 3 cm – 1 point 3 – 6 cm – 2 points More than 6 cm – 3 points *By localization:* Outside the functionally significant zone* – 0 points Within a functionally significant area – 1 point *ABM division by nature дренирования:* Absence of deep draining veins – 0 points Presence of deep draining veins** – 1 point	Using this classification, most neurosurgeons determine the degree of operability of the malformation. There are 5 gradations of malformation: with gradation I (1 point), the risk of surgical intervention is insignificant, with gradation V (5 points), great technical difficulties arise, and the risk of severe disability and death is high.

* Functionally significant areas - sensorimotor area, Broca's and Wernicke's centers, occipital lobes, thalamus, deep structures of the temporal lobe, brainstem.
** Deep venous collectors are draining veins that flow into the system of the great cerebral vein, the straight sinus.

Table 2

Study design of the author's EpiTapp® wrist tapping method in patient A. 29 years old

Event	Visit 1 randomization	Visit 2 inclusionin the study	Visit 3 in 3 months	Visit 4 via 6 months
Anamnesis of life	+	-	+	+
History of the disease	+	-	+	+
Analysis of the seizure diary	+	+	+	+
Neurological examination	+	+	+	+
EEG video monitoring	+	-	-	+
MRI of the brain according to the Epilepsy protocol	+	-	-	-
Therapeutic drug monitoring of AEDs in the blood	+	-	-	-
Scale for assessing the quality of life of patients with epilepsy "Quality of life in epilepsy - QOLIE - 31"	-	+	+	+
Author's scale for assessing the effectiveness and safety of EpiTapp® "Research on the effectiveness of the EpiTapp® wrist tapping method"	-	-	+	+
EpiTapp® training	-	+	-	-
EpiTapp® session	-	+	+	+

of using any invasive treatment methods exceeds the risks natural course of the disease [9]. It is known that all methods of invasive treatment are aimed at completely eliminating the AVM from the bloodstream in order to eliminate the risk of hemorrhage, eliminate the phenomenon of brain stealing, reduce or regress neurological deficit, and control epileptic seizures [3]. The literature describes data that total shutdown of the AVM using open surgery provides effective control over epileptic seizures with seizure freedom in more than 70% of cases [4]. Considering the fact that structural epilepsy in patients with AVMs is almost always pharmacoresistant, which is associated with the presence of a functioning AVM, the only and most effective way to treat this disease is total resection neurosurgical treatment. However, when an AVM is localized in a functionally significant area (3 - 5 points on the Spetzler-Martin grading scale), great technical difficulties may arise during invasive intervention, and the risk of profound disability and death increases. Thus, this group of patients experiences a significant decrease in quality of life due to drug-resistant epilepsy and needs additional non-drug rehabilitation methods aimed at being able to control epileptic seizures.

The goal is to present a unique clinical observation demonstrating the ability to control bilateral tonic-clonic seizures using the EpiTapp® application in

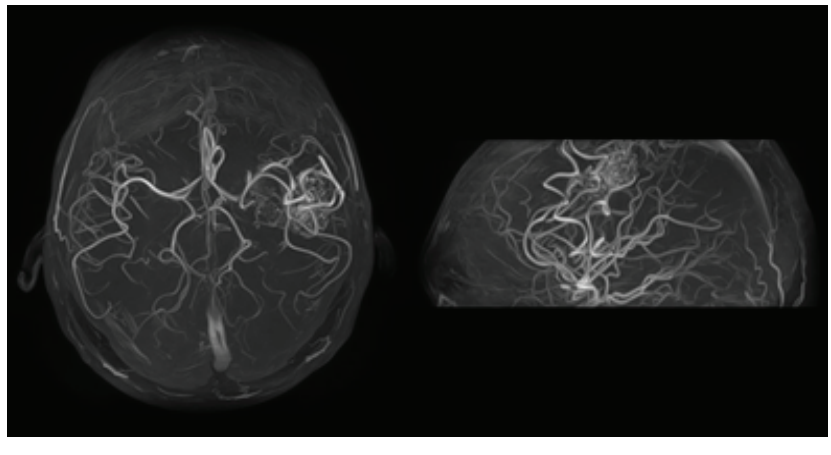

Fig. 1. Magnetic resonance angiography of the brain of patient A. (29 years old): AVM in the territory of the left middle cerebral artery

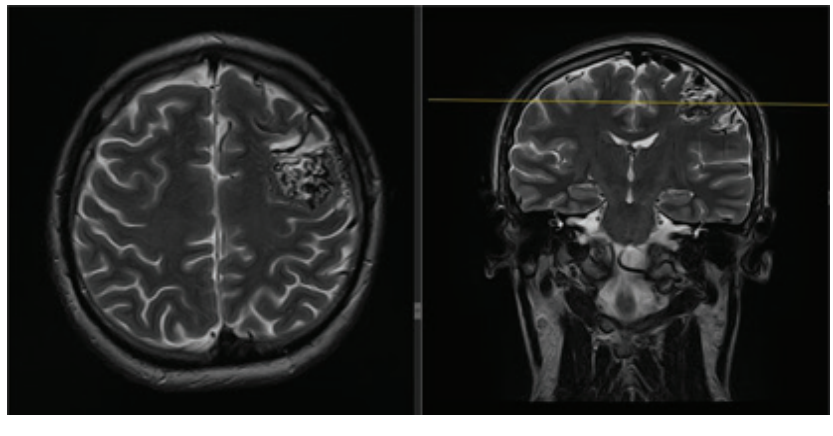

Fig. 2. Magnetic resonance imaging of the brain of patient A. (29 years old): Condition after partial embolization of AVM.

a 29-year-old patient with drug-resistant structural focal epilepsy that developed against the background of an AVM located in a functionally significant area of the cerebral cortex.

Materials and methods. The work used the author's wrist tapping technique (RF patent No. 2606489 dated January 10, 2017) in the form of the EpiTapp® application for a smartphone. The patient regularly used the EpiTapp® application as an outpatient SFE rehabilitation during the onset of a focal motor hemifacial seizure, or during the focal onset of a bilateral tonic-clonic seizure. Previously, the patient underwent an electroencephalographic study (EEGA - 21/24, elite version "Encephalan - 131 - 03", modification 10 and 11 (Russia) with three-dimensional localization of sources of epileptiform activity (Brain Loc)) and training by a neurologist - epileptologist in the use of the EpiTapp® application on your own at home. The study also used: the quality of life scale in epilepsy - QOLIE - 31 and the effectiveness scale of the author's wrist tapping technique.

Research procedure. The patient was installed the EpiTapp® application on a mobile device based on Android OS. The patient then completed three self-calibration tests to automatically configure the application in a therapeutic self-help mode. During the onset of the first signs of an incipient epileptic seizure, the patient independently launched the application and tapped the index or middle finger of the subdominant (left) hand on the smartphone screen, simultaneously with the automatic delivery of sound and vibration signals by this device, programmed by the attending physician in rhythm mode healthy person (1.13 Hz) without epileptic seizures [6].

The design of the present study included 4 patient follow-up visits (Table 2).

Ethical considerations. The conduct of this study was approved by the local ethical committee of the Krasnoyarsk State Medical University named after Professor V.F. Voino-Yasenetsky, Krasnoyarsk (protocol No.77/2017 dated June 26, 2017). The patient signed a voluntary informed consent before starting the study. The patient did not receive any remuneration for participating in this study. The researchers did not receive any remuneration for conducting this study.

Results and discussion. Patient A. at the age of 15 (2009) underwent surgical neurosurgical intervention for a malignant neoplasm (astrocytoma) of the brain. After this, he underwent annual control magnetic resonance imaging of the brain (MRI brain). In 2015, during a routine MRI of the brain, an AVM was discovered in the territory of the left middle cerebral artery (Figure 1). Considering the location of the AVM in a functionally significant area (left frontal and parietal lobes of the brain) of grade III according to Spetzler-Martin, the patient was denied open-access neurosurgical treatment.

In 2018, patient A., aged 24 years, was consulted by neurosurgeons in Novosibirsk. The patient was offered staged partial embolization of the AVM. A year later, in 2019, the first stage partial embolization of AVM occurs. From 2019 - 2022 The patient underwent a total of six staged partial embolizations. At the beginning of July 2022, the last, 6th embolization occurred, after which the patient was recommended for further radiosurgical treatment (Figure 2).

At the end of July 2022, the first focal motor hemifacial epileptic seizure develops. On September 15, 2022, the first bilateral tonic-clonic seizure (BTCS) occurs. Two weeks later, the patient's

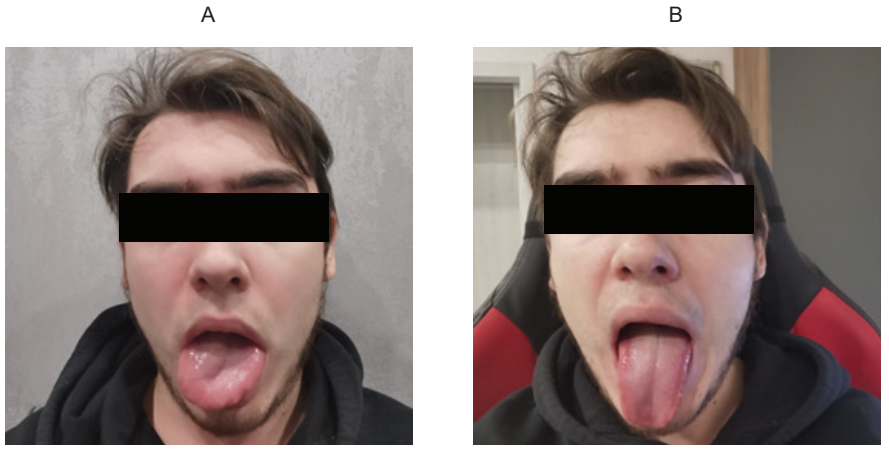

Fig. 3. Todd paresis of the tongue muscles after a focal motor hemifacial epileptic seizure: A – immediately after the seizure; B – 15 minutes after the seizure.

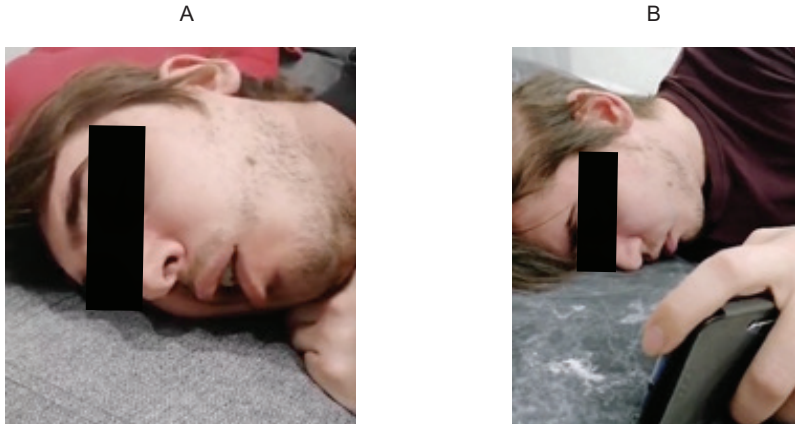

Fig. 4. Use of the EpiTapp® application by patient A. (29 years old) at home, as an element of urgent self-help in the event of BTCS with focal motor hemifacial onset in the right half of the face: A – onset of focal motor hemifacial seizure; B – stopping an seizure using the EpiTapp® application

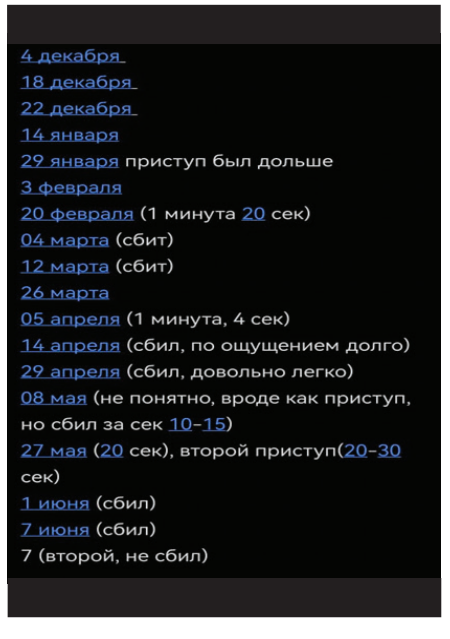

Fig. 5. Fragment of the seizure diary provided by patient A. after adjusting the antiepileptic therapy regimen and starting to use the EpiTapp® application

health worsens, repeated BTCS develops, and hemifacial and focal motor seizures become daily. In this regard, patient A. was consulted by an epileptologist with subsequent prescription of antiepileptic therapy (valproic acid 1000 mg per day). No obvious positive effect was observed. Frequent focal motor and bilateral tonic-clonic seizures bothered the patient daily (up to 3-4 times a day), the patient's quality of life and ability to work decreased significantly. Thus, according to the analysis of the results of the questionnaire on the "Quality of Life in Epilepsy - QOLIE - 31" scale as modified by the authors (Narodova E.A. et al. 2021), patient A. had a significant decrease in quality of life due to epilepsy (4 points according to five-point subscale, where 5 points is the worst result). The man rated his health status low (12 points on a 100-point subscale, where 100 points is the best result). Frequent epileptic seizures did not allow the patient to engage in usual work activities, despite the fact that, as a professional programmer, he had the opportunity to work at home.

In October 2022, the patient underwent repeated radiological treatment, after which his dose of valproic acid was increased to 1250 mg per day, and a new generation drug was added - perampanel at a dose of 6 mg per day (with slow titration). Against this background, positive dynamics were observed. However, BTCS continued to bother the patient up to 4 times a month. The focal onset at this time was short-lived (up to 3 seconds) and the patient did not have time to take measures aimed at preventing trauma against the background of the subsequent development of a generalized tonic-clonic seizure. The patient also continued to have frequent focal motor seizures up to 5-10 times a week (Figure 3).

In February 2023, at an appointment with an epileptologist, it was decided to add disease-modifying therapy (Dibufelon at a dose of 400 mg per day, followed by an increase to 800 mg per day according to the regimen) [2], [7], [1] , and also recommended the use of the EpiTapp® application at the first signs of an incipient focal seizure as a rehabilitation program for the self-management of epileptic seizures.

According to the inclusion/exclusion criteria, the patient was included in the study. The date the patient started using the application is February 18, 2023. The duration of using the technique is 7 months. The patient used the EpiTapp® application for focal motor seizures as emergency self-help (at home, on the street, in transport, in a store).

After just a week of regular use of the EpiTapp® application, the patient was able to stop an incipient focal motor seizure. Moreover, against the background of correction of drug therapy, already after 2 weeks the patient experienced a change in the nature of the BTCS, in the form of a lengthening of the focal motor onset. Therefore, the patient was advised to actively use the EpiTapp® app not only during focal seizures, but also during focal motor onset of BTCS (Figure 4).

Figure 4 - Use of the EpiTapp® application by patient A. (29 years old) at home, as an element of urgent self-help in the event of BTCS with focal motor hemifacial onset in the right half of the face: A – onset of focal motor hemifacial seizure; B – stopping an seizure using the EpiTapp® application.

According to the diary of self-observation of seizures, the patient was able to stop the incipient BTCS at the stage of focal onset in more than 50% of cases, which significantly improved the patient's quality of life (Figure 5).

Discussion. At visit 4 (6 months from the start of using the EpiTapp® application), according to the study design, patient A. was given a final survey on the scale of the effectiveness and safety of the author's wrist tapping method. Analysis of the data obtained showed that while using the application, the patient noted an improvement in quality of life by 58% due to the ability to stop vocal seizures (FS) and prevent the development of BTCS in more than 50% of cases. In this regard, the patient was able to return to work, and it became possible to work not only at home, but also to travel to the office. In 85% of cases, the patient was able to stop an incipient focal seizure, reducing its severity and duration.

Conclusion. Thus, the use of the EpiTapp® application allowed a young man with treatment-resistant FES to reduce the severity and duration of focal seizures in 85% and in more than 50% of cases to prevent secondary bilateral transformation of incipient BTKP. This clinical example demonstrates the possibility of effective use of the EpiTapp® application in a patient with drug-resistant structural focal epilepsy associated with an AVM as an element of a rehabilitation program aimed at controlling epileptic seizures.

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CHARGE SYNDROME IN CHILDREN

The article presents a clinical case of CHARGE syndrome in a 4-year-old child. Literature data and a description of the clinical observation of CHARGE syndrome are given. CHARGE syndrome (Hall–Hittner syndrome; ICD-10:Q87.8) is a rare hereditary disease. The name of the syndrome is made up of the first letters of the main malformations characteristic of the disease. CHARGE: Coloboma (coloboma — a defect of the membranes of the eye), Heart disease (heart disease), choanal Atresia (hoan atresia — overgrowth of the posterior parts of the nasal cavity), growth and mental Retardation (delay in physical and mental development), Genital anomalies (anomalies of the genitourinary system).

Keywords: CHARGE syndrome, children, coloboma, hoan atresia, congenital heart disease, developmental abnormalities, clinical case.

Introduction. The syndrome was first described in 1979 by the authors of Hitter and Hall, who independently revealed phenotypic features in this syndrome [1,3,7]. In 1981, it was proposed to combine the main signs of the manifestation of the disease into an abbreviation. In 2004, Vessers L.E. and co-authors identified pathological changes in the gene in patients with CHARGE syndrome, thereby determining the genetic cause of the disease [5,7,8]. CHARGE syndrome is a genetic disorder caused by a mutation of the CHD7 gene, inherited in an autosomal dominant manner. In children, it occurs with a frequency of 1:12,000 to 1:15,000 among newborns around the world [1,2,10]. When a child has signs that cause suspicion of a given syndrome, a genetic study is carried out to confirm the diagnosis. Due to the wide range of outcomes in children, CHARGE syndrome is difficult to establish. To do this, the main symptoms and less specific symptoms to confirm the diagnosis are identified (Tab. 1).

The diagnosis is made if the child has 4 or 3 basic and 3 less specific signs. If there are less than 3 or 2 signs, it is believed that CHARGE syndrome is possible [1,8,10]. However, making this diagnosis has great difficulties, since a genetic test is not always available and not all patients with CHARGE syndrome will confirm the mutation of the CHD7 gene.

Treatment is required from the early neonatal period, as it is associated with serious health problems – complicated breathing, heart defects, other birth defects, nutrition problems, etc. Subsequently, it is necessary to pay attention to the hearing, vision and general development of the child [6,10]. Speech therapy and psychotherapy are recommended, as well as lifelong immunocontrol [4,10,11].

In the literature, russian and foreign, this syndrome is not so often described, due to a rare occurrence.

Purpose of the study: description of the clinical case and features of the diagnosis of CHARGE syndrome.

Material and methods. A retrospective analysis of the case histories of a patient who was on inpatient treatment in the pathology of newborns was carried out, and subsequently in the psycho – neurological department – 1 (PND – 1) and the psych- - neurological department – 2 (PND – 2) of the Pediatric Center of the Republican Hospital №1 – National Center of Medicine named after M.E. Nicolaev.

Clinical example. Patient A., child from 5 pregnancies, 5 births. Pregnancy occurred in 1 half – without features, in 2 half – against the background of anemia. During pregnancy, ultrasound examination of the fetus revealed multiple malformations from the cardiovascular and nervous system – arachnoid cyst of the brain with ventriculodilation, pyeloectasia on the right, tricuspid valve regurgitation, pericardial fluid. Mother refused to terminate the pregnancy. Childbirth at term. Birth weight – 3700g, height – 52cm. The condition at birth is satisfactory, the Apgar score is 7 – 8 points. On the 2nd day after birth – difficulty breathing and swallowing. Child transferred to intensive care unit with increasing shortness of breath. She was in the department of pathology of newborns diagnosed with perinatal damage to the central nervous system. Hearing impairment. Open arterial duct. Up to 4 month – probe nutrition, due to severe bulbar syndrome. The child developed with a gross delay in physical and neuropsychiatric development, recurrent diseases of the bronchopulmonary system.

She was repeatedly admitted for examination and treatment at PND – 1 with a diagnosis of perinatal brain damage, severe, gross delay in static – motor and psycho – speech development. Grade 2 hypotrophy. Developmental microanomalia. Genetic disease is not excluded. Microdeletion (microduplication) syndrome. Complication: Heart failure in a newborn, pulmonary hypertension grade 2.

At the age of 2, she was admitted to inpatient treatment at the PND – 2, where the diagnosis was established: Perinatal lesion of the central nervous system. Gross defeat. On examination: height – 76cm, weight – 7,7kg, BMI – 13,33, HP – 84, BP – 90/40 mm hg.

Saturation 99%. The childs condition is closer to satisfactory. Mucous membranes are clean, of ordinary color. Peripheral lymph nodes are not enlaged. The skin is clean, usually colored. Breathing is carried out in all fields, there are no wheezing. The tones of the heart are clear, rhythmic, there are no noises. The abdomen during palpation is soft, painless. Urination is free, painless. The chair is decorated, regular.

Gastroscopy: Superficial gastritis.

Ultrasound of the heart: open ductus arteriosus – 0,24 – 0,25cm. open oval window – 0,25cm. Mitral valve insufficiency 1st degree. Sealing of the walls of the atrioventricular valve with minimal regurgitation. Regurgitation on the tricuspid valve is minimal – 1degree. Right atrial dilation – 2,7cm and pulmonary artery trunk – 1,43 – 1,46cm. Slight expansion of the root of the aortic valve – 1,6 – 1,7cm, the right ventricle – 1,4cm. Ejection fraction – 69,3%.

Based on the results of the examination and in order to exclude genetic dis-

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eases, a DNA study was carried out by genetic sequencing. As a result, a mutation was detected in the CHD7 gene (locus 8q12.2), which encodes the DNA – binding protein 7 of chromodomain helicase DNA binding protein 7.

Ophtalmologists consultation: Retinal angiopathy.

Consultation with a cardiologist: Congenital heart disease. Open arterial duct. Mitral valve insufficiency grade 1. Chronic heart failure grade 2.

Surgical treatment for congenital heart disease is recommended.

In August 2021 in the Federal Center for Cardiovascular Surgery (Khabarovsk), an operation was performed – Spiral Embolization of the open arterial duct.

One year after the operation on the control ultrasound of the heart: condition after the operation: embolization of the open arterial duct. No additional ducts were identified in the aircraft trunk. Open oval window – 0,25cm. Arterial valve insufficiency 1st degree. Tricuspid valve regurgitation grade 1. Expansion of cavities of right atrium (RA), right ventricle (RV), left ventricle (LV), aortic root. Additional trabecules in the LV cavity. Ejection fraction – 70%.

At the age of 4, she was hospitalized in a PND – 2 with complaints of weakness in the muscles – does not sit, does not stand. Upon admission, the condition was assessed as conditionally satisfactory. Crying, inspection is difficult. Height – 83,5cm, weight – 9,3kg. Breathing rate – 28 per minute, heart rate – 120 per minute. Saturation – 98%. The physique is asthenic. The skin is pink, there is no cyanosis. Peripheral lymph nodes are not enlarged. Pharynx without features. Puerile breathing in the lungs, no wheezing. The cardiac area was not changed. There is no shaking. The boundaries of the percussion are not expanded. Heart tones are clear, rhythmic, systolic noise on the 4 intercostal areas on the left. The abdomen is soft, painless. Liver, spleen not enlarged. There are no edema. The head is tilted forward. Head turns in full. “short neck”. The spine line is curved in the pectoralis. Doesn’t sit. Walks with support. The foot support is complete. Lower limb length D=S. Movements in the joints in full, painless during flexion. Muscle tone is reduced uniformly.

CBC (HGB) – 86 g/l (115 - 145 g/l); RBC - 4,37x10^{12}/l (3,7-4,9x10^{12}/l); PLT - 350 10^9/l (150 – 400x10^9/l); WBC -11,8x10^9/l (5,5 – 14.5x10^9/l); LYMF – 29.1% (19-37%); monocytes - 0,4x10^9/l (0,05 - 0,4x10^9/l); rod – nucleated neutrophils - 2% (1-6%); segmented neutrophils - 69%, (32 - 55 %); eosinophils – 0% (0-5%); determination of ESR by Panchenkov – 11mm/h (1 – 15mm/h). Conclusion: hypohemoglobinemia, lymphocytosis.

Immunogram results: immunoglobulin A – 4,2g/l (0,7 – 3,0g/l); Immunoglobulin M – 3,2 mg/ml (0,6 – 2,00 mg/ml); immunoglobulin G – 17,2 mg/ml (8,00 – 16,26mg/ml); immunoglobulin E – 122U/ml (0 – 100U/ml). Conclusion: increase in all indicators.

Blood chemistry: AlAt – 10,3U/l (00 – 29,00U/l), AsAt – 29,4U/l (00 – 36U/l), albumin – 35,5g/l (38,00 – 54,00g/l), total bilirubin – 9,00mmol/l (3,4 – 7,1mmol/l), ferritin – 9,77mcg/l (7,00 – 140,00mcg/l), phosphorus – 1,67mmol/l (1,46 – 1,78mmol/l), total protein – 68,9g/l (60,00 – 80,00g/l), urea – 5,8mmol/l (1,8 – 6,4mmol/l), glucose – 3,08mmol/l (3,3 – 5,6mmol/l), ferrum – 3,7mmol/l (8,95 – 21,48mmol/l), total calcium – 2,4mmol/l (2,2 – 2,7mmol/l). Conclusion: decreased serum blood ferrum and albumin.

Radiography of the spine: enhanced kyphosis of the thoracic spine, smoothed lordosis of the lumbar spine.

The child was examined by a cardiologist: Condition after surgery: embolization of the open arterial duct. Open oval window 0,25 see degree 1 circulatory insufficiency. Cardiomyopathy in the background of the underlying disease.

Examination of traumatologist – orthopedist: congenital malformation of the cervical spine. Crank. Grade 1 C-shaped thoracolumbar scoliosis. Osteoporosis. Cerebral palsy. Atonic – astatic form. Gross delay in development. Myotonic syndrome. Flat – valgus feet of the 2nd degree.

Ophthalmologists examination: Hypermetropia of mild OU grade. OU retinal angiopathy.

Examination by an otolaryngologist: Severe bilateral sensorineural hearing loss. Tubootite. Congenital laryngomalacia.

Clinical diagnosis: CHARGE syndrome. Severe perinatal brain damage, gross delay of static-motor and psycho-speech development. Grade 2 hypotrophy. Developmental microanomaly. Congenital heart disease. Open arterial duct. Mitral valve insufficiency grade 1. Chronic heart failure grade 2. Complication: Heart failure in a newborn, pulmonary hypertension grade 2.

Diagnostic criteria for CHARGE syndrome in children

Basic	Less specific
Coloboma (defect of one or more eye structures); Heart defect; Atresia of the choanae; Discreased or no breathing; Facial paralysis (unilaterial or bilaterial); Ear anomalies	Cleft lip; Esophageal atresia; Kidney abnormalities; Low growth; Altered facial features (square face, broad forehead and bridge of nose); Delayed puberty; Foot hand abnormality

Thus, a comprehensive examination revealed in this patient 3 main and 3 less specific signs characteristic of CHARGE syndrome from the central nervous system, cardiovascular, respiratory systems, musculoskeletal system, hearing and vision organs.

Discussion. The manifestations of CHARGE syndrome are most dangerous in the neonatal period, since hoan atresia causes respiratory distress syndrome, which we observe in this clinical case. According to literature, impaired swallowing and aspiration in CHARGE syndrome occur due to abnormalities of IX-X cranial nerve pairs [3,4,9].

Among all the described cases of children with CHARGE syndrome, congenital heart defects were a common sign. 70-80% of children with this pathology are found [1,5]. Coloboma is diagnosed with the same frequency, in this case, the absence of this sign was a feature of the manifestation of the syndrome.

Hearing loss, auricle abnormalities, facial nerve paresis are also characteristic of the disease [1,4].

Half of patients with CHARGE syndrome have endocrine pathology, most often hypogonadotropic hypogonadism. In boys, micropenis and cryptorchism are noted at birth, in girls it manifests itself only during puberty [2,7].

Approximately 30% of patients have abnormalities of the hands and feet in the form of polydactyly, forking of the phalanges of the fingers on the hands and feet, extra vertebrae, scoliosis. In the described case, the child was diagnosed with chest kyphosis and lordosis of the lumbar spine.

Treatment of children with CHARGE syndrome is symptomatic, with an emphasis on hormone replacement and surgical methods [2,4,6].

Conclusion. CHARGE syndrome is a

rare disease difficult to diagnose. Patients with this syndrome need lifelong medical and psychological support. Timely diagnosis and treatment, as well as effective care will help improve their quality of life.

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A CLINICAL CASE OF ELIMINATION OF OBSTRUCTIVE JAUNDICE CAUSED BY *ASCARIS LUMBRICOIDES*

The article presents a clinical case of elimination of obstructive jaundice caused by Ascaris lumbricoides. The patient was admitted with a clinic of obstructive jaundice, presumably caused by choledocholithiasis against the background of a long history of cholelithiasis, chronic calculous cholecystitis. After two attempts of lithoextraction in the lumen of the common bile duct, a round parasite was detected, which extracted and sent for laboratory was testing, where the diagnosis of ascariasis was confirmed. The clinic of obstructive jaundice was dropped out.

Keywords: ascariasis, obstructive jaundice.

Introduction. Ascariasis is one of the most common helminthiases, according to WHO, more than 1.4 billion people are infected with ascariasis in the world. Every year, up to 100 thousand people die from ascariasis and its complications [1]. At the same time, ascariasis rarely gives surgical complications. We applied the principles of writing a systematic review of PRISMA to evaluate the statistics of surgical complications of ascariasis. In the Pubmed database over the past 10 years, 33 publications were found for the keywords "ascariasis", "Ascaris lumbricoides" and "surgical complications", while only one publication is a meta-analysis, the rest were clinical observations of various rare complications. 3 meta-analyses and 336 studies since 1998 were found in the Cochrane database for the keywords "ascariasis", "Ascaris lumbricoides", and "surgical complications". At the same time, less than ten studies are devoted to the systematic study of surgical complications and there is not a single meta-analysis on this issue, and the existing studies are devoted to intestinal obstruction, as the most common complication, the rest of the complications are described in the form of clinical cases. Most surgical complications are caused by a large number of nematodes in the intestinal lumen, which is the fate of third world countries, where there are poor social and living conditions, a high risk of massive contamination by the fecal-oral route [1]. The most common surgical complication of ascariasis is intestinal obstruction [1, 2]. Other complications are published in the literature as clinical cases due to their rarity, such as acute appendicitis due to obstruction of the lumen of the appendix by a parasite [3], perforation of the small intestine [4], as well as complications from the hepatopancreatobiliary system, such as acute pancreatitis, obstructive jaundice and hepaticolithiasis [5, 6].

We considered it necessary to present a clinical example of the treatment of a rare complication of ascariasis, obstructive jaundice, in an adult patient who denies a typical history of STH infection.

A 67-year-old patient was hospitalized in the Department of Surgery of the City Hospital No. 5, Barnaul, with complaints of heaviness and periodic pain in the right hypochondrium and epigastrium for two days. Social and living conditions are satisfactory, he lives in an apartment building with a central sewerage system. Contact with unwashed food from the ground, water not from the sewer denies. In histo-

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ry for many years suffers from cholelithiasis, chronic calculous cholecystitis. When contacting the clinic at the place of residence, an ultrasound examination of the abdominal cavity, magnetic resonance imaging with intravenous contrast was performed, which revealed signs of biliary hypertension, choledocholithiasis, calculi of the left hepatic duct. After further examination, she was sent to the Department of Surgery for treatment.

On admission, the patient's condition was satisfactory. Skin and mucous membranes of physiological color. Pulse - 78 beats per minute, BP-132/84 mm Hg. Art. Tongue moist, not coated. The abdomen is soft, symmetrical, participates in the act of breathing, not swollen, soft, painless. The size of the liver according to Kurlov is 9*8*6 cm. The gallbladder and spleen are not palpated. Peritoneal symptoms are negative. Pasternatsky's symptom is negative. Stool is dyed. Urine is light. Laboratory examination in the scope of the general blood test, taking markers of bilirubinemia, cytolysis, cholestasis, renal dysfunction, electrolytes and blood amylase, general urinalysis, coagulogram did not reveal any violations.

Ultrasound examination of the abdominal organs revealed:

Liver: oblique vertical size of the right lobe 164 mm, craniocaudal size 100 mm, contours are clear, even, the edge is sharp, the structure is fine-grained, heterogeneous, echogenicity is moderately increased. Volumetric formations were not revealed. The diameter of the portal vein is 11 mm, the inferior vena cava is 18 mm. Gallbladder: located in the usual projection, dimensions 120*45 mm, with a constriction in the body and an inflection in the lower third, walls up to 4 mm, increased echogenicity, no calculi, a small amount of sludge in the cavity, calculi are not convincingly located. Intrahepatic ducts are dilated: right lobar up to 8 mm, left lobar up to 10 mm, confluence is preserved, segmental up to 3 mm on the right, up to 4 mm on the left. Hepaticocholedochus is expanded to 15 mm, has a non-straight course, is visualized up to the head of the pancreas. In the lumen of the hepaticocholedochus, formations of increased echogenicity with dimensions of 8.3 * 5 mm and 4 * 4 mm are located, without a clear acoustic track. Pancreas - located in the usual projection, dimensions: Head: 25 mm, body 14.5 mm, tail 23 mm. The contours are fuzzy, even, the structure is heterogeneous, increased echogenicity, the Wirsung duct is not dilated. Spleen: in the usual projection, 110 * 37 mm, the structure is homogeneous, the splenic vein is not dilated. Kidneys: the usual location is the right kidney-112*48 mm, the contours are clear, even. the left kidney is 101*45 mm, the contours are clear and even. The thickness of the parenchyma of the right kidney -14 mm, the left kidney -16 mm. Corticocentral differentiation is not disturbed. Corticomedullary differentiation is not disturbed. The outflow of urine is not disturbed. The ureters are not dilated. In the projection of the adrenal glands, no mass formations were detected. Bladder: empty. The abdominal aorta is not dilated. Retroperitoneal lymph nodes are not located. In the pleural cavities, free fluid is not located. There is no free fluid in the abdominal cavity. Conclusion: Biliary hypertension syndrome, low level of block. Ultrasound signs of choledocholithiasis. Enlargement of the right lobe of the liver. Diffuse-heterogeneous changes in the structure of the liver. Deformation of the gallbladder. Thickening, diffuse changes in the structure of the walls of the gallbladder. Sludge in the gallbladder. Diffuse-heterogeneous changes in the structure of the pancreas.

The patient is exposed to a preliminary diagnosis: Cholelithiasis: choledocholithiasis. Chronic calculous cholecystitis. Mechanical jaundice.

Upon admission, the patient was urgently performed endoscopic retrograde cholangiopancreatography (ERCP), endoscopic papillosphincterotomy (EPST) in order to eliminate choledocholithiasis and stop the clinic of obstructive jaundice. When performing EPST, a big duodenal papilla (BDP) enlarged to 25 * 15 mm, tense, was revealed. At the mouth, there is villous hypertrophy and portioned bile secretion is visualized. An end knife made a dissection of the "roof" of the BDP from the mouth in a typical place with a length of 15 mm. There was an outflow of bile under pressure. Additionally, the "roof" was dissected with a cannulation papillotome up to 25 mm. Visually, the choledochus is not expanded. 30.0 ml tight filling performed. ultravist contrast. Shadows of concrements were not revealed. A biopsy of the BDP due to severe edema and local hemorrhage after EPST was not performed. The postoperative period proceeded without complications. 5 days after ERCP and EPST, the patient underwent videolaparoscopic cholecystectomy to eliminate chronic calculous cholecystitis. The postoperative period proceeded without complications. 7 days after videolaparoscopic cholecystectomy, in order to monitor the condition of the BDP and take a biopsy of the BDP against the background of the changes identified during the previous endoscopic

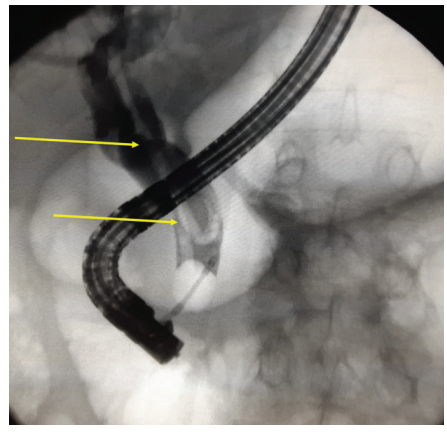

Fig. 1. Endoscopic retrograde cholangiopancreatography. In the lumen of the common bile duct, the shadow of the parasite is visible (showed by yellow figures)

Fig. 2. Macroscopic view of parasite

Fig. 3. Parasite in neutral formalin

operation, the patient underwent fibrogastroduodenoscopy with taking a biopsy of the BDP. Intraoperatively: from the previously dissected BDP into the lumen of the duodenum, the head of a round, worm-shaped parasite of a whitish color sticks out. A biopsy was taken from the edges of the BDP and a smear-imprint for cytology. A Fogarty-type probe was inserted, 15.0 ml of Ultravist was introduced, ERCP was performed, where in the lumen of the enlarged choledochus there is a convoluted shadow 5-6 mm thick of the parasite, there are no calculi (Figure 1). With a Fogarty-type probe, the parasite was brought down into the lumen of the duodenum, captured by an endoscopic loop, and removed. The parasite is pale brown in color, up to 20-22 cm long, 5-6 mm in diameter (Figure 2). The parasite is immersed in neutral formalin for examination (Figure 3). The outflow of bile is restored. No complications were observed in the postoperative period. The patient was consulted by an infectious disease specialist based on the results of a laboratory study of the parasite, where a female Ascaris lumbricoides was identified. The final clinical diagnosis was made: Ascariasis complicated by obstructive jaundice. GSD: Chronic calculous cholecystitis. 6 days after the operation, the patient was discharged for outpatient observation with recommendations for deworming under the supervision of an infectious disease specialist at the place of residence.

Conclusion. Despite the typical localization in the intestinal lumen, Ascaris lumbricoides nematodes can migrate into the lumen of the bile ducts, causing obstructive jaundice that is difficult to diagnose, especially in combination with other pathologies of the biliary system.

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A CASE OF CONGENITAL MEASLES

Measles is a highly contagious acute viral infectious disease with an airborne and transplacental transmission mechanism caused by an RNA-containing measles virus (genus morbilliviruses, family paramyxoviruses). Vaccination against measles is included in the National Calendar of Preventive Vaccinations of the Russian Federation and is carried out at the age of 12 months, followed by revaccination at 6 years. Immunity after measles is usually lifelong. Post-vaccination immunity is less prolonged: after 10 years, protective antibody titers remain only in 36% of vaccinated. In this regard, in the conditions of an epidemiological outbreak, there is a shift in morbidity to older age groups. Several cases of measles in pregnant women have been described. However, congenital measles is an extremely rare diagnosis. Our article describes a case of congenital measles in a newborn from a 34-year-old woman. At 28 weeks gestation, the woman was diagnosed with pneumonia, then a typical rash appeared. The diagnosis was confirmed by serological method. Thus, the birth occurred in the acute period of the disease. The baby was born prematurely at 28 weeks gestation by Caesarean section. The child's condition at birth was extremely severe. Apgar score is 5/7. The condition of the newborn was extremely severe due to prematurity and multiple pathology. The child was diagnosed with Respiratory distress syndrome of a newborn with respiratory insufficiency of the III degree. On the ninth day of life, a rash appeared. The diagnosis of measles was confirmed by the determination of antibodies to Measilis virus IgM. The course of measles in the exanthemic period was atypical (spotty rash elements on the first day, not characteristic dynamics of rash appearance). However, the presence of perinatal contact, the appearance of rashes made it possible to suspect such a rare diagnosis as congenital measles, and serological diagnostics confirmed this diagnosis. Against the background of the therapy, the patient's condition stabilized on the 7th day of the exanthemic period, the rash regressed. At the age of 1 month and 23 days, the child was discharged home in a satisfactory condition.

Keywords: measles, newborn, pregnancy, congenital pathology, exanthemic infection, prematurity, congenital malformations.

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Methods and materials: the medical history of a newborn with a diagnosis of severe respiratory distress syndrome of a newborn has been analyzed. Respiratory failure of the II degree. Extreme immaturity. Prematurity is 28 weeks. Measles, the period of rashes. Congenital heart defect: aneurysm of the secondary part of the MPP with a defect. FAP. Perinatal CNS lesion of hypoxic-ischemic genesis.

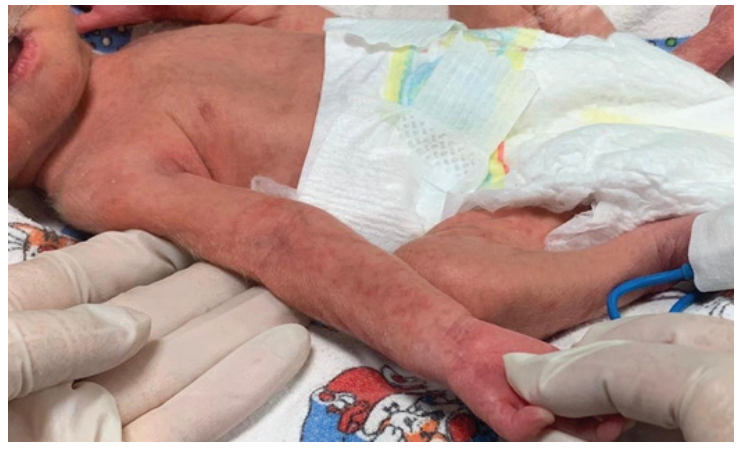
Introduction. The introduction in 1967 of routine vaccination of children against measles with live measles vaccine led to a widespread decrease in the incidence in all age groups. This allowed the world community to set the task of eliminating measles on the planet. In 1998 The WHO Regional Committee for Europe has officially set the goal of eliminating local measles transmission by achieving and maintaining a very high level of coverage (≥95%) with two doses of measles vaccine [1]. Currently, in countries conducting total vaccination against measles, the disease occurs in the form of individual outbreaks and epidemics, involving sev-

eral tens or hundreds of people [2]. Currently, vaccination against measles is included in the National Calendar of Preventive Vaccinations of the Russian Federation and is carried out at the age of 12 months, followed by revaccination at 6 years. Measles is usually considered a benign viral disease of childhood, people can get sick regardless of age, and severe lesions of the respiratory and nervous systems occur more often before the age of 5 and after 20 years. Thus, women of childbearing age are at risk. In the situation of an epidemic outbreak, monitoring of pregnant women is necessary. Measles during pregnancy can be severe, mainly due to pneumonia. Measles in a pregnant woman is associated with the risk of miscarriage and prematurity [3,4]. Cases of congenital measles are extremely rare. Several cases are described in the literature, including subclinical forms, established only on the basis of serological diagnostic methods [5,6]. The case of manifest form of congenital measles is undoubtedly of interest.

A clinical example. We present a case of congenital measles. A boy born on 07.12.2019 at the gestation period of 28 weeks by caesarean section. The child's mother is a 34–year-old woman suffering from bronchial asthma, atopic variant, persistent course, moderate severity, in incomplete remission. At the age of 5, she was operated on for congenital heart disease (DMJP), currently her condition is stable, there is no circulatory insufficiency. It is known from the obstetric history that this pregnancy is the fourth, the first birth occurred naturally, the second birth by caesarean section, the third pregnancy was ectopic, for which a tubectomy was performed. The real pregnancy in the first half proceeded with moderate toxicosis and the threat of termination of pregnancy, the woman was observed by a gynecologist on an outpatient basis. In the 2nd half of pregnancy, at the age of 27 weeks, the woman sought medical help for a rise in temperature to 38.1 ° C and a paroxysmal cough. Treatment with berodual (1 ml) and symbicort (2 inhalations) was prescribed, treatment was carried out on an outpatient basis. After some improvement in the condition, on the seventh day of the illness, the patient's condition began to deteriorate – the body temperature rose again to 38.5 ° C, there was a sore throat, nasal congestion. The cough intensified, and after another 2 days shortness of breath appeared. With suspected bronchopneumonia, the woman was hospitalized in the pulmonology department of the city clinical hospital with a directional diagnosis: community-acquired pneumonia with respiratory insufficiency (DN) of the 1st degree. On the 2nd day of hospitalization, the patient had a spotty papular rash, on an unchanged skin background, with a tendency to merge. Based on clinical data, measles was suspected. The woman denied contact with the measles patient. According to her, she was fully vaccinated as a child, but there was no documentary confirmation of the vaccination. For diagnostic purposes, a serological examination by the ELISA method was prescribed. According to the results of the examination, IgM to Measilisvirus were detected in the woman, IgG to Measilisvirus were not detected. Based on clinical and laboratory data, the diagnosis was established: Measles, rash period, typical course, severe course. Complication: measles pneumonia. The patient was transferred to the infectious diseases department, where symptomatic treatment was initiated. After 2 days, due to premature discharge of amniotic fluid, it was decided to deliver by caesarean section in a perinatal center.

A boy was born with a weight of 1540 grams, 45 cm long. The condition at birth is extremely severe, due to respiratory insufficiency, physiological immaturity, prematurity (gestation period of 28 weeks). Apgar score 5/7: in the first minute, the heartbeat was estimated at 2 points, breathing -0, skin color – 1, muscle tone – 1 reflexes -1; in the fifth minute, the heartbeat was estimated at 2 points, breathing - 1, skin color – 2, muscle tone - 1 reflexes -1. Resuscitation measures were carried out in the operating room: sanitation of the upper respiratory tract, tracheal intubation, endotracheal administration of surfactant 240 mg, the newborn was connected to an artificial lung ventilation (ventilator). A diagnosis was made at birth: Respiratory distress syndrome of the newborn (RDSN). DN of the III degree. Prematurity is 28 weeks.

a



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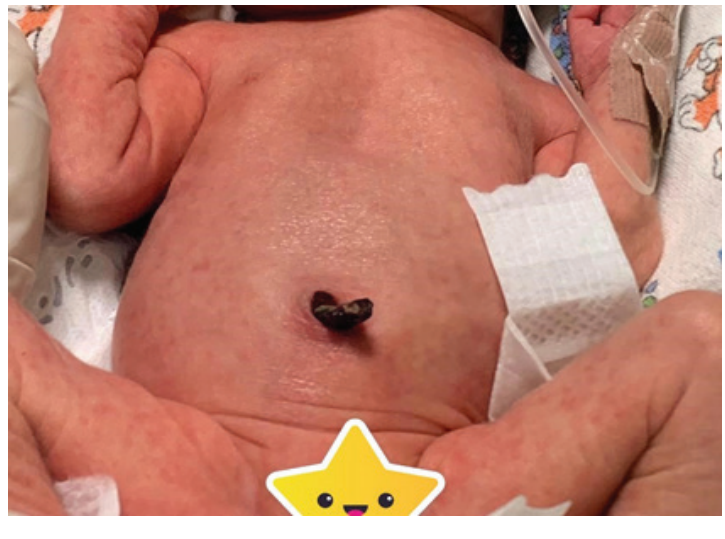

Small-spotted rash on the 9th (a) and 10th (b) days of life

There is a high risk of intrauterine infection (perinatal contact with measles). The newborn was transferred to the box of the Department of Anesthesiology, Intensive Care and Neonatal Intensive care (OARITN), placed in an incubator in the department. During the examination in the OARITN, depression of consciousness was noted, he reacted to the examination with weak motor activity and a pained grimace. The body temperature was 36.5 °C. The sutures of the skull are closed, a large fontanel 1x1 cm, calm. The pose is weakly flexor, muscle tone is reduced. The skin is pink, clean. There was a general pasty of soft tissues. Visible mucous membranes are clean, moist. Microcirculation is satisfactory, the symptom of a pale spot is up to 2 seconds. Oxygenation –$SatO_2$ 97%. For the purpose of infusion therapy and sampling of assays in aseptic conditions, catheterization of the umbilical vein was performed. Considering the severity of the RDSN, the ventilator was continued by the Hamilton C2 device in PSIMV mode with the parameters: Frequencies 50 per minute, FiO2 40%, PIP 16 cm H_2O, PEEP 5 cm H_2O. Breathing is synchronized with the ventilator, there is a moderate retraction of pliable places, auscultative breathing is carried out evenly across all fields, weakened, scattered crepitating wheezes are noted. The heart tones are clear, rhythmic. The pulse in the peripheral arteries is satisfactory. The heart rate is 140 beats per minute, blood pressure is 52/40/27 mmHg. The abdomen is soft, podzdut. The liver protrudes from under the costal arch by 1.5 cm, the edge is smooth and elastic. Intestinal peristalsis is sluggish. According to laboratory studies, leukopenia was noted in the newborn in the general blood test (UAC), the number of leukocytes was 7 × 10^9, with a norm from 10×10^9 to 30×10^9. No antibodies to Measilisvirus were detected at birth. The newborn was prescribed empirical antibacterial therapy with Ampicillin sulbactam 75 mg / kg / day in two doses. Based on the clinical protocol for antibacterial therapy for newborns on mechanical ventilation" On the second day of life, the condition remained severe, he did not assimilate enteral nutrition. At the same time, normalization of the number of leukocytes was noted in the UAC (15.31 *10^9), the lecocyte formula was not changed, the number of erythrocytes was 4.12* 10^{12}, hemoglobin – 154 g/ l, the number of platelets - 163*10^9. Ultrasound revealed the presence of free fluid in the abdominal cavity in a small amount. Taking into account the changes in the hemogram, the drug Gentamicin 5 mg / kg / day was connected in two doses. On the fourth day of life, normalization of the number of leukocytes was noted in the UAC (9.02*10^9). For the purpose of passive immunization, human normal immunoglobulin was injected at a dose of 1.5 ml. On the fifth day of the disease, the newborn's condition is regarded as severe, but stable. The child was extubated and transferred to NCPAP auxiliary ventilation (nasa lconstant positive airpressue)flow 6-6.5 l/min. According to neurosonography, the child had hyperechogenicity of the periventricular zone. Ultrasound of the abdominal organs – left calicopyelectasia. EchoCG – Atrial septal aneurysm (MPP) with a defect (0.21 cm). the functioning arterial duct (FAP) is 0.18 cm.

On the ninth day of life, a small-spotted rash appeared in the newborn's groin area and on his hands (pic. 1). The child's condition was regarded as very serious, but relatively stable. Enteral nutrition through the probe, the infant absorbed the Alfare milk mixture of 16-18 ml. He reacted to the examination with moderate motor activity, crying is weak. The large fontanel is not tense. Weak flexor posture, muscle hypotension, hyporeflexia. The skin is subicteric on a pink background. The oral mucosa is clean. Visible mucous membranes are clean, moistened. Microcirculation is not disturbed. Breath with auxiliary ventilation, the chest excursion is uniform with slight retraction of compliant places. Auscultation breathing is carried out evenly across all fields, the noise of oxygen-air flow was listened to. The heart tones are clear, rhythmic. The hemogram showed leukocytosis 28*10^9 (norm 9-12*$10^{9)}$, the leukocyte formula showed a shift to myelocytes (2%), lymphopenia (18%), monocytosis (15%), the number of erythrocytes was 3.91*10^{12}, the hemoglobin index was 143g/l, the number of platelets was 254*10^9. The procalcitonin index was 10 ng/ml. Taking into account perinatal contact with measles, the material for ELISA for antibodies to Measilis virus was taken. According to the results of the study: IgM - 2.626 IU/ml were detected, IgG - not detected. Diagnosis: Severe respiratory distress syndrome of a newborn. DN II degree. Extreme immaturity. Prematurity is 28 weeks. Measles, a period of rashes. Congenital heart defect: aneurysm of the secondary part of the MPP with a defect. FAP. Perinatal CNS lesion of hypoxic-ischemic genesis, acute period. The antifungal drug Fluconazole 3 mg / kg / 48h intravenous break was added to the treatment in order to prevent fungal infection against the background of prolonged antibacterial therapy. In order to stimulate the respiratory center of the central nervous system, caffeine benzoate 20% is prescribed in a maintenance dose of 5 mg / kg / 24h / 1 r / day.

The next day, the general condition of the child remained unchanged, a rash appeared on the hips, rash elements in the form of small spots (pic. 2). On the third day, the rash on the hands and in the groin folds became less bright. There are new rashes on the skin of the face, neck, trunk and thighs of a spotty-papular nature. At the same time, the mucous membranes of the oral cavity are clean, moistened. The conjunctiva is clean, there is no discharge. The tongue is clean, moist. The lips are bright, drying out a little. There is no discharge from the nose. In the lungs, breathing is harsh, isolated dry crepitating wheezes were heard from both sides. On the 4th day of the exanthemic period, no new rashes were noted. Previously appeared elements of the rash faded away. On the 7th day after the appearance of the rash (day 16 of life), the exanthema regressed. IgM - 1,904 IU/ml and IgG - 0.059 IU/ml were detected by the ELISA method. Against the background of a stable condition, normal procalcitonin levels and normalization of hemogram indicators, antibacterial therapy was canceled. NCPAP auxiliary ventilation has been continued.

On the 28th day of life, against the background of stabilization of the condition, independent breathing, the newborn was transferred to the second stage of nursing. At the time of the transfer (on the 19th day after the rash appeared), there were no rash elements on the skin, there was a slight bran-like peeling. At the age of 1 month and 23 days, the child was discharged home in a satisfactory condition. At the time of discharge , IgM – 0.774 IU/ml and IgG - 1.226 IU/ml were detected by the ELISA method.

Conclusion. Thus, when analyzing this clinical case, it can be assumed that the infection occurred in utero, and not intranatally, since the first rashes appeared already on the ninth day of life. It is not possible to estimate the timing of the development of the prodromal period, since the condition of the newborn was extremely severe due to prematurity and multiple pathology. Taking into account the respiratory distress syndrome with DN III in a newborn, it is impossible to unequivocally assert the measles etiology of lung damage. The course of measles in the exanthemic period was atypical (spotty rash elements on the first day, not characteristic dynamics of rash appearance). However, the presence of perinatal contact, the appearance of rashes and

typical changes in the general analysis of covi made it possible to suspect such a rare diagnosis as congenital measles, and serological diagnosis confirmed this diagnosis.

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