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CONTENTS

ORIGINAL RESEARCH

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P.I. Aliyeva

CLINICAL AND LABORATORY EVALUATION OF MULTIPAROUS WOMEN WITH IRON DEFICIENCY ANEMIA

The aim of study is to evaluate the vitamin -mineral complex and the clinical course of pregnancy in all three trimesters of pregnancy among multiparous women suffering from iron deficiency anemia among the population of Azerbaijan. The study was conducted on 110 pregnant women between 18-44 years old during 2014-2022. The I group (control group) consisted of 21 healthy women. The II group (the comparison group) included 30 women without anemia, and the III group (the main group) included 80 multiparous women with anemia. Hemogram, vitamin and mineral content in the blood of pregnant women was studied using clinical and laboratory examination methods. The obtained results were analyzed by discriminant and variance analysis methods. The risk of pregnancy loss was noted in 6 (20,0%) cases in the comparison group and 36 (45,0%) cases in the main group (pH = 0,017). Premature rupture of membranes during childbirth was in 2 (6,7%) cases in the comparison group and in 41(51,2%) (pH <0.001) in the main group. Primary weakness of labor activity during childbirth was found to be in 5 (16,7%) cases in the comparison group, and in 19 (23,8%) cases in the main group (pH=0,132). Due to increased demand for vitamins and minerals during pregnancy, significant changes occured in multiparous women with iron deficiency anemia who were not treated (in the main group). For example, vitamin D in the third trimester was 30,1±1,6 Me=32,7(28,1-33,4) in the comparison group, while in the main group, it was 14,2±0,4 Me=13,5 (12,9-15,6) (pH<0,001), compared to the control group p<0,001. Clinical signs, hemogram, and vitamin-mineral complex deficiency have been determined in pregnant women. Compared to the control group, pregnant women with IDA had a significant deficit of micronutrients. This is more pronounced in the last trimester of pregnancy. These facts are also reflected in the laboratory tests. The reason is that the vitamin-mineral complex undergoes serious changes near the end of pregnancy due to the intensive growth of the fetus.

Keywords: multiparous women, anemia, vitamins, minerals

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Introduction. Iron deficiency is the most common condition in the world, affecting more than 2 billion people. Although widespread in underdeveloped countries, it remains a significant problem even where other forms of malnutrition have been actually eliminated [15]. Anemia develops during pregnancy and affects more than half of women in the world. This is a condition in which the number of red blood cells is not enough to meet the physiological needs of the body to provide a sufficient amount of oxygen [10].

A physiological pregnancy and proper fetal development are impossible in the absence of vitamins, microelements, and minerals. Nutritional deficit in the pregnant woman's body causes issues throughout the gestational phase, and deterioration of the health of the newborn, as well as the development of a wide range of chronic diseases of the offspring [3].

Until now, women of reproductive age in our republic have a high rate of multiple births, and hystory of anemia plays a key role in this group of patients. The large number of pregnancies, the short intervals between births, long-term lactation, and the number of abortions create unfavorable conditions for the development of iron deficiency anemia in this group of women. Despite on the multiple investigations dedicated to anemia and vitamin-mineral status in pregnancy this problem hasn't been studied during all the three trimesters in multiparous women. Taking into account the above, iron deficiency anemia and changes in vitamin-mineral status occur frequently among women with multiple births, so it was decided to conduct scientific research on this group of women.

Aim. The study of clinical parameters, hemogram findings, and changes in the level f vitamins and minerals in multiparous women with iron deficiency anemia in all three trimesters of pregnancy. Since multiparous women are common in Azerbaijan, we decided to conduct the research on this group of women.

Materials and methods. The study was conducted on pregnant multiparous women at the II Department of Obstetrics and Gynecology of the Azerbaijan Medical University, based at Maternity hospital No.5 named after Shamama Alasgarova during the period from 2014 to 2022. Group I (control) included 21 healthy non-pregnant women without anemia. There were 30 pregnant women with normal pregnancy (without anemia) in group II, and 80 pregnant women with anemia in group III. Anemiya was diagnosed during pregnancy. In the present article, iron status and vitamin mineral complex were studied in untreated women. Only the iron deficiency type of anemia has been studied. According to the classification given by WHO (2011) experts, grade 1 anemia was defined as a hemoglobin concentration of 100-110 g/l, grade 2 as 70-99 g/l, and grade 3 as <70 g/l. The study included multiparous pregnant women with anemia, but some participants didn't receive treatment due to refusal of therapy. The study was conducted in accordance with the international ethical standards of the Declaration of Helsinki (WMA, 2013). The study protocol was previously reviewed and approved by the Biomedical Ethics Commitee of Azerbaijan Medical University on July 22, 2022, protocol No.24. During the study, the hemogram test was performed using the "Mythic 18" (Switzerland) hematological analyzer, the serum iron was measured using biochemical chromazurol B (CAB) method with the reagent kit of the company "Human" (Germany) and the serum ferritin was measured by solid-phase enzyme immunoassay (ELISA) method with the reagent kit of the "Pishtaz Teb" (Islamic Republic of Iran) company (Fe-6.6- 26.0 mmol/l, ferritin 20.0-150.0 ng/ml). Folic acid, vitamin B12, and vitamin D were studied according to the solid-phase

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immunoenzyme method (ELISA), (Folic acid-5.0-27.2ng/ml; vitamin B12-197-771pg/ml, vitamin D 30-100 ng/ml). The principle of the method of studying potassium is based on forming a finely dispersed suspension of potassium ions in a protein-free medium with the sodium salt of tetraphenylboron and the potassium salt of tetraphenylboron. For calcium, the principle of the method is based on the formation of a purple complex by calcium ions (Ca^{2+}) with ortho-cresolphthalein in an alkaline medium (8.1-10.4 mg%). The amount of potassium in the blood is directly proportional to the intensity of the color (3.5-5.5 mmol/l). For magnesium, the principle of the method is based on the presence of ethylenediaminetetraacetate in an alkaline environment. Thus, magnesium forms a purple complex compound with xylidyl blue dye (0.8-1.0 mmol/l). The obtained results were processed in the SPSS-26 statistical package with discriminant (chi-square Pearson) and variance (t-Student-Bonferroni) analysis methods and were specified with the non-parametric H-Krskal-Wallis test. In the tables, qualitative data are described in the form of numbers and frequencies, quantitative data in the form of the mean (M, ±m, min, max) and mean structural (Me, Q1, Q3) indicators.

Results. In the conducted study, women were divided into two age groups (18-29 and 30-40 years old) , and women between 30 and 40 years of age were prevalent in all three groups. Thus, 66,7% of the women were in the control group, 56,7% in the comparison group, and 70,0% in the main group, p_H = 0,419. The risk of pregnancy loss was noted in 6 (20,0%) cases in the comparison group and in 36 (45,0%) cases in the main group, p_H = 0,017. Preeclamsia was diagnosed in 6,7 % cases in the comparison group and 23,8 % in the main group, p_H=0,043.

Premature ruptures of membranes was diagnosed in 2 (6,7%) cases in the comparison group and in 41(51,2%) cases in the main group, p_H <0,001. Primary weakness of labor activity was detected in 5 (16,7%) cases in the comparison group, and in 19 (23,8%) cases in the main group, p_H=0,132.

The characteristics of the clinical course of pregnancy are given in table 1.

The evaluation of newborns with the Apgar scale in the first 5 minutes showed 7,9±0,0, Me=8,0 (8,0-8,0) in the comparison group, and 7,7±0,1 Me= 8,0(7,0-8,0) pH = 0,016 in the main group. The birth weight was 3420,0±70,4 Me=3400,0 (3100,0-3600) in the comparison group and 3147,5±64,2 Me =3200,0 (2800,0-3500,0) in the main group p_H =0,029. It can also be noted that although the height indicator differed according to the Student-Bonferroni criterion (p_t=0,036), it was not confirmed by the Kruskal-Wallis criterion (p_H=0,080).

Hemogram indicators were studied in all women included in the study. The results are presented in table 2.

The level of the minerals was also determined. Thus, in the I trimester, the amount of Ca in the control group was 8.7±0.1 Me=8.7(8.5-8.9), in the comparison group - 9.6±0.2 Me=9.7(8.9-10.1), and in the main group 7.6±0.1 Me=7.3(7.1-8.0) P_H<0.001, compared to the control group p<0.001. In the II trimester, this parameter was 9.6±0.3 Me=10.1(9.0-10.2), 7.1±0.1 Me=6.9(6.7-7.3) P_H<0.001, respectively, in the comparison and main groups, compared to the control group p<0.001. In the III trimester, the amount of Ca was 10.0±0.1 Me=10.2(9.8-10.3) and 5.8±0.2 Me=5.4(5.1-6.1) p_H<0.001, respectively, in the comparison and main group, compared to the control group p<0.001.

In the I trimester, the amount of K (potassium) was 4.4±0.1 Me=4.3(4.0-5.0), 4.73±0.19 Me=5.10(3.80-5.20), 3.20±0.06 Me=3.15(3.00-3.30) p_H<0.001, respectively, in the control, comparison, and main groups, compared to the control group p<0.001. In the II trimester, this parameter was 4.50±0.019 Me=4.75(4.35-4.80) and 2.90±0.03 Me=2.90(2.80-3.10), p_H<0.001 in the comparison and main groups, respectively, compared to the control group p<0.001. In the III trimester, the amount of K was 4.32±0.22 Me=4.60(4.00-4.80) and 2.39±0.07 M=2.20(2.10-2.60) p_H<0.001, in the comparison and main groups, respectively, compared to the control group p<0.001.

In the I trimester, the amount of Mg (magnesium) was 0.900±0.012 Me=0.890(0.860-0.940), 0.896±0.014 Me=0.900(0.880-0.930), and 0.755±0.006 Me=0.750(0.730-0.780) p_H<0.001, respectively, in the control, comparison, and in the main groups, compared to the control group p<0.001. In the II trimester, this amount was 0.909±0.032 Me=0.945(0.860-0.970) in the comparison group and 0.683±0.011 Me=0.670(0.630-0.740) in the main group, p_H<0.001, compared to the control group p<0.001. In the III trimester, the amount of Mg was 0.894±0.010 Me=0.880(0.870-0.910) in the comparison group, and

Table 1

Characteristics of the clinical course of pregnancy of the examined women

Indicators	Gradation	Group				$p_{\chi 2}$	p_H
		Comparison		Main			
		N	%	N	%		
Social status	Non-working	24	80.0	61	76.3	0.676	0.677
	Employed women	6	20.0	19	23.8		
Complicated gynecological history	No	28	93.3	75	93.8	0.936	0.937
	There is	2	6.7	5	6.3		
Chronic fetal hypoxia	-	28	93.3	41	51.2	<0.001	<0.001
	+	2	6.7	39	48.8		
Preeclampsia	-	28	93.3	61	76.3	0.042	0.043
	+	2	6.7	19	23.8		
Complicated obstetrics history	-	21	70.0	41	51.2	0.077	0.079
	+	9	30.0	39	48.8		
Delivery	Term	25	83.3	62	77.5	0.503	0.505
	Preterm	5	16.7	18	22.5		
Fetus presentation	Vertex	29	96.7	75	93.8	0.549	0.550
	Breech	1	3.3	5	6.3		
Birth	Physiological	22	73.3	52	65.0	0.407	0.409
	C-section	8	26.7	28	35.0		
Sex	Male	19	63.3	44	55.0	0.431	0.433
	Female	11	36.7	36	45.0		
Rh	Rh (+)	28	93.3	70	87.5	0.382	0.384
	Rh (-)	2	6.7	10	12.5		
Complications of puerperium	-	30	100.0	76	95.0	0.212	0.214
	+	0	0.0	4	5.0		

Note: the statistical reliability of the difference between the indicators of the groups:
pχ2 –based on the Chi-square Pearson criterion; PH – based on the Kruskal-Wallis criterion

Table 2

Analysis of hemogram parameters

		Semigroup											
		Control	Comp. – I trim	Comp. - II trim	Comp. - III trim	Main - I trim – I deg. anemia	Main - I trim - II deg. anemia.	Main - II trim - I deg. anem.	Main - II trim – II deg. anemia	Main - III trim - I deg. anem.	Main - III trim - II deg. anem.	Main - III trim - III deg anem.	P_H
Number		21	11	8	11	12	14	7	20	4	20	3	
	M	4.54	4.51	4.71	4.92	3.98	3.58	3.77	3.65	3.85	3.72	2.80	
RBC	Me	4.50	4.70	4.80	4.90	3.95	3.60	3.80	3.70	3.95	3.75	2.80	<0.001
x10^{12}/L	Q1	4.20	4.10	4.50	4.80	3.90	3.40	3.70	3.60	3.65	3.60	2.40	
	Q3	4.80	4.80	5.10	5.10	4.05	3.70	3.80	3.80	4.05	3.90	3.20	
	M	43.0	37.2	37.4	38.5	32.5	29.8	33.0	31.0	32.3	30.1	24.5	
HCT	Me	42.0	37.2	37.5	38.2	32.7	29.4	32.6	31.0	32.2	29.7	24.2	<0.001
%	Q1	39.0	36.4	36.6	38.0	32.3	29.1	32.5	30.1	32.0	29.3	24.2	
	Q3	46.0	39.0	39.0	39.0	33.4	30.2	33.6	32.2	32.7	30.3	25.2	
	M	11.8	12.0	12.1	12.3	10.5	9.3	10.1	8.4	10.3	8.9	6.7	
HCB	Me	11.8	11.9	12.2	12.5	10.5	9.4	10.0	8.4	10.4	8.9	6.9	<0.001
g/dl	Q1	11.3	11.9	11.8	11.7	10.4	9.1	10.0	7.8	10.2	8.7	6.3	
	Q3	12.1	12.3	12.4	12.8	10.6	9.7	10.3	8.8	10.4	9.3	6.9	
	M	94.6	83.1	79.9	78.4	81.8	83.5	87.6	85.1	84.4	81.3	89.0	
MCV	Me	95.2	81.3	80.2	77.6	82.1	83.0	88.4	84.6	82.6	79.9	86.4	<0.001
µm^3	Q1	91.1	79.2	74.4	74.5	80.4	81.1	85.5	82.5	80.1	75.4	75.6	
	Q3	97.9	85.9	85.0	81.3	85.2	85.6	90.8	88.1	88.8	85.7	105.0	
	M	26.3	27.0	25.9	25.0	26.4	26.1	26.8	23.0	26.8	24.2	24.2	
MCH	Me	26.3	25.6	25.6	24.9	26.6	26.0	27.0	22.7	26.3	24.7	24.6	0.157
Pg	Q1	24.7	24.6	24.2	23.9	25.4	25.3	26.3	21.4	25.6	22.1	21.6	
	Q3	28.1	29.0	26.9	26.1	27.2	27.4	27.4	23.7	28.1	25.9	26.3	
	M	27.8	32.4	32.4	31.9	32.2	31.2	30.7	27.0	31.8	29.7	27.3	
MCHC	Me	28.5	32.3	31.8	32.8	32.0	31.4	30.7	26.8	31.8	29.8	28.5	<0.001
g/dl	Q1	26.3	31.3	31.4	31.6	31.3	30.2	29.8	24.7	31.1	28.4	25.0	
	Q3	30.0	33.8	33.2	33.3	32.8	32.5	31.6	29.2	32.5	30.4	28.5	
	M	16.5	16.8	16.0	16.5	9.4	8.0	7.7	6.1	8.9	6.8	4.9	
Fe	Me	16.9	16.8	16.0	16.5	9.3	7.9	7.9	6.2	8.8	7.0	5.3	<0.001
mkmol/l	Q1	15.6	16.2	14.7	16.0	9.0	7.7	7.0	5.9	8.4	6.1	3.5	
	Q3	18.7	17.6	17.2	17.0	9.8	8.4	8.0	6.5	9.4	7.2	5.8	
	M	54.4	61.4	62.1	59.3	60.7	66.8	70.4	71.7	65.2	74.7	82.0	
TIBC Q	Me	54.1	61.4	60.7	59.7	59.8	69.7	71.0	72.7	65.7	75.0	82.1	<0.001
mkmol/l	Q1	46.7	53.2	57.7	54.8	54.4	62.5	69.1	69.6	62.9	70.5	79.9	
	Q3	61.2	68.6	67.9	62.8	69.3	70.1	71.9	74.2	67.6	79.8	83.9	
	M	38.0	44.6	46.1	42.8	51.3	58.8	62.7	65.6	56.4	67.9	77.1	
LIBC Q	Me	35.1	44.3	45.2	44.0	49.9	61.6	62.6	66.3	56.9	68.0	76.4	<0.001
mkmol/l	Q1	27.5	37.6	41.7	38.3	44.5	54.2	61.3	63.8	54.3	64.2	76.3	
	Q3	45.9	51.5	50.7	46.6	60.0	62.1	63.9	67.9	58.4	72.6	78.6	
	M	31.4	27.7	25.9	28.1	15.9	12.0	11.0	8.5	13.6	9.1	5.9	
	Me	29.5	28.0	25.4	27.6	15.7	12.1	11.0	8.6	13.6	9.2	6.3	<0.001
TDD	Q1	25.3	24.9	24.2	26.3	13.4	11.3	10.1	8.1	13.2	8.0	4.4	
%	Q3	37.9	30.0	28.0	30.1	17.4	12.4	11.6	8.8	13.9	9.9	7.1	
	M	56.5	19.4	19.8	20.9	27.1	16.9	18.3	10.2	6.7	8.5	4.3	
Ferritin	Me	60.0	19.3	20.8	19.9	24.5	15.2	20.9	10.2	5.9	9.4	3.0	<0.001
ng/ml	Q1	53.0	16.6	17.0	18.5	17.5	10.7	14.2	9.3	4.0	5.8	2.0	

Note: the statistical reliability of the difference between the indicators of the groups: pH – based on the Kruskal-Wallis criterion between 3 groups

0.522±0.025 Me=0.430(0.410-0.670) in the main group, p_H<0.001, compared to the control group p<0.001.

In the I trimester, the amount of FA (folic acid) in the control group was 9.9±0.9 Me=9.9 (5.5-12.6), in the comparison group 8.6±0.5 Me=8.9(7.9-9.8), and in the main group 7.2±0.6 Me=6.4(5.8-7.5) pH=0.025, compared to the control group p<0.001. In the II trimester, the amount of FA was 8.5±0.9 Me=9.4(7.6-10.0) in the comparison group and 5.4±0.2 Me=5.7(5.1-6.0) in the main group, p_H<0.001, compared to the control group p<0.001. In the third trimester, the amount of FA was 11.2±1.3 Me=8.9(8.7-13.4) in the comparison group, and 3.4±0.2 Me=3.2(2.7-4.1) in the main group, pH<0.001, compared to the control group p<0.001.

The amount of vitamin B_{12} in the control group was 486.9±34.9 Me=478.0(367.0-602.0), in the comparison group 388.1±19.6 Me=408.0(296.0-437.0), and in the main group 263.2±23.5 Me=235.0(180.0-325.0) p_H<0.001, compared to the control group p<0.001. In the II trimester, the amount of B_{12} in the comparison group was 365.1±19.9 Me=393.5(339.0-398.0) and in the main group 208.0±7.1 Me=198.0(173.0-233.0), p_H<0.001, compared to the control group p=0.020. In the third trimester, the B12 amount in the comparison group was 351.5±9.6 Me=367.0(330.0-372.0), and in the main group 199.0±5.6

Me=195.0(183.0-207.0) pH<0.001, compared to the control group p<0.001.

In the first trimester, the amount of vitamin D in the control group was 37.7±2.0 Me=34.0(31.0-43.0), 38.3±2.9 Me=40.6(32.6-44, 7) and in the main group, it was 26.3±0.8 Me=26.4(24.3-29.0) p_H<0.001, compared to the control group p<0.001. In the II trimester, vitamin D level was 32.7±2.4 Me=35.6(29.6-36.6) in the comparison group and 22.7±1.0 Me=21.3(18.9-25.2) in the main group, p_H<0.001, compared to the control group p<0.001. In the III trimester, the vitamin D amount was 30.1±1.6 Me=32.7(28.1-33.4) in the comparison group and 14.2±0.4 Me=13.5(12.9-15.6) p_H<0.001 in the control group, compared to the control group p<0.001.

Discussion. During pregnancy, a serious change in iron metabolism occurs in iron deficiency anemia. In this regard, the study of the vitamin and mineral complex and their correlation with clinical indicators was of great importance in our research.

Bakhareva's study noted a high percentage of the risk of pregnancy loss, in 15 (50%) cases[2]. In our study, the risk of miscarriage was observed in 36 (45,0%) cases. During pegnancy, a woman's body consumes significantly more macro- and microelements; thus, the micronutrients required to ensure the normal life activity of a pregnant woman's body are the most important factor in ensuring the physiological course of pregnancy and the normal growth of the fetus, Due to the deficiency state, the progress of pregnancy and childbirth becomes complicated, so the risk of placenta formation disorders and perinatal pathology increases, leading to premature birth, birth defects, early neonatal adaptation disorders, deviations in the formation of the infant's mental and physical development in the postnatal ontogeny stage. The most common problem among this group of patients is a lack of iron supply, which leads to iron deficiency anemia. Chronic fetal hypoxia occurred in 43 (0,8%), and fetal growth restriction occurred in 183 (3,4%) cases [1]. In our study, chronic fetal hypoxia occurred in 39 (48,8%) p<0,001 cases, and fetal growth restriction occurred in 6 (7,5%) cases.

According to the global assessment, anemia was found in 42% of pregnant women and 30% of non-pregnant women [17].

Controversial claims that folic acid intake prevents fetal neural tube defects are well known and play an important role in reproductive health [13]. During our research, no fetal neural tube diseases were found. Vitamin B12 and folate are involved in the carbon metabolism cycle and govern fetal growth [5].

According to WHO recommendations, daily intake of folic acid and iron as part of prenatal care reduces the risk of low birth weight, anemia, and iron deficiency in the mother [12]. Micronutrient, vitamin, and mineral deficiencies are critical for health and can be caused by a poor diet or disease [14]. During the study, the existence of a pathological condition in the first trimester of pregnancy, as well as an aversion to meals, resulted in vitamin and mineral deficiencies. Magnesium is one of the ten essential metals in humans, it is the fourth most abundant cation after calcium, potassium, and sodium, and it dominates being the second most abundant intracellular cation in human tissues [7]. In the course of the study, multiparous women with iron-deficiency anemia were found to be seriously deficient in magnesium. Pregnancy is a risk factor for leg cramps. About 30% to 50% of pregnant women experience leg cramps twice a week during the third trimester [11]. Among the pregnant women, signs of calcium deficiency were assessed in the main group, including general weakness, leg cramps and other related symptoms.

Vitamin D is a fat-soluble vitamin, a steroid hormone, synthesized primarily in the skin under the influence of ultraviolet sunlight [4]. Vitamin D is globally associated with maternal, fetal, and infant health in relation to pregnancy-related complications (preeclampsia and gestational diabetes), preterm birth, and infant-related outcomes. A meta-analysis of observational data and trials of vitamin D supplementation, in particular, provided evidence of beneficial effects of vitamin D on fetal weight and size and reduced risk of small-for-gestational-age birth [9]. Vitamin D is primarily involved in bone metabolism, and its deficiency is known to cause osteoporosis [16]. Despitie the fact that Azerbaijan due to its geographical location is characterized by high levels of solar activity neverhteless, the surveyed women suffer from vitamin D deviciency which adversely affects their quality of life.

Conclusion. Thus, the research revealed that multiparous women constitute a high-risk group in our republic. İn our study clinical characteristics and laboratory findings were reflected. İn the course of our study, clinical signs and laboratory data indicated a significant deficiency in hematological parameters and vitamin-mineral complex levels. These changes were statistically significant and became more pronounced as gestational age increased wtih the most marked alterations observed in third trimesteer. The study of vitamins and microelements allows to prescribe appropriate drug treatments for anemia. It is appropriate to prescribe vitamin and mineral complex drugs containing vitamin B12, vitamin C, folic acid, Ca, and vitamin D along with iron preparations.

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

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A.A. Musaev

THE EFFECT OF GESTATIONAL AGE ON THE DEVELOPMENT OF NECROTIZING ENTEROCOLITIS

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Over the past 10 years, 208 children with necrotizing enterocolitis (NEC) have received our treatment. The control group consisted of 50 children whose gestational age was approximately similar to the main group. A case-control study was conducted to determine the role of the influence of gestational age on the development of NEC. 89 (42.8%) children with NEC and gestational age from 30 to 36 weeks had significantly lower percentiles of birth weight, umbilical cord pH, and a 1-minute Apgar score compared with 22 children from the control group of the same gestational age. On the contrary, there were no significant differences between 98 (47.1%) children with NEC and the control group (n= 24) aged 25-29 weeks, except that a small number of children with NEC received breast milk. 21 full-term infants in the main group and 5 infants in the control group appeared to have an obvious predisposing factor. The study proved that the predisposition to NEC depends on the gestational age. In the range of 25-29 weeks, all babies are at risk due to extreme prematurity. In the range of 30-36 weeks, asphyxia and children with stunted growth are at increased risk, while at full term, serious predisposing factors are apparently required.

Keywords: necrotizing enterocolitis, risk factors, gestational age.

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Introduction. Necrotizing enterocolitis (NEC) remains a severe and life-threatening disease that occurs in the neonatal period. In the USA in 2017, 9.9% of newborns were born before 37 weeks of gestational age, which are classified as premature [1]. Necrotizing enterocolitis is usually manifested by bloody stools, food intolerance, and a swollen, painful stomach. Necrotizing enterocolitis is the most common indication for urgent surgical intervention in premature infants. Complications of necrotizing enterocolitis of newborns include intestinal perforation with pneumoperitoneum, abdominal abscess, strictures, short bowel syndrome, septicemia, and death. Despite widespread numerous scientific and practical investigations, the etiology of the disease has not yet been definitively clarified. Some research groups believe that prematurity is almost the only perinatal factor in the development of NEC [2]. At the same time, in other studies that identify other risk factors for NEC, the risk of prematurity is not considered as the main factor of this disease. Hyaline membrane diseases are more common among NEC patients, but it is quite common among the control group of the examined patients [3]. Some authors point out that asphyxia is more common in patients with NEC [4] and usually umbilical vein catheterization is often performed in this category of patients [5]. The presence of such differences seems to underlie the differences among the surveyed population. Back in the 80s of the 20th century, a group of researchers did not detect NEC among the examined premature infants (body weight <1500-1750 gy); however, when analyzing the results of the examination of all newborns, the frequency of NEC detection increased[6].

Warner B.B., et all. in their studies indicate that risk factors for the development of necrotizing enterocolitis vary with birth weight [7]. The risk factors with the greatest prognostic significance are birth weight less than 1500 g, gestational age from 28 to 32 weeks, Apgar scores less than 3 points at birth [8].

An analysis of the literature data suggests that birth weight and gestational age are, to varying degrees, risk factors for the development of NEC [9]. In these case-control studies (retrospective comparison of two groups), comparison of birth weight was most often significant [10]. In one study that controlled for gestational age, only 23 patients had "late onset" NEC. Another group of researchers in their recent reports have provided new information on the etiology of NEC, demonstrating a very significant relationship between the absence or inverse end-diastolic flow velocity (AREDF) curves in the umbilical artery or fetal aorta and the subsequent development of NEC [11].

For the first time, a subgroup of preterm infants has been identified that

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appears to significantly increase the risk of developing NEC. Although these infants were very stunted on average, Malcolm et al., in their case-control studies in which infants were matched for gestational age and birth weight, concluded that the risk of NEC was associated with AREDF keeping up in growth [12]. However, in stunted children, an increased incidence of NEC can be expected; it is surprising that such an association has not been noted in many previous studies involving the identification of risk factors for NEC. Based on this, we decided to conduct a case-control study including indicators of gestational age with NEC.

The aim of the study was to determine the factor of gestational age in the development of necrotizing enterocolitis in newborns.

Material and methods. All 208 neonates who developed NEC were included in this retrospective (case-control) study. The control group consisted of 50 children whose gestational age was approximately similar to the main group.

Among the main group, in 89 (42.8%) children with NEC, in 21 (42%) newborns of the control group, the gestational age was from 30 to 36 weeks; with a gestational age of 25-29 weeks in the main group there were 98 (47.1%) infants with NEC and 24 (48%) infants in the control group. 21 (10.1%) term infants with NEC were in the main group and 5 (10%) in the control group.

The diagnosis of NEC was made on the basis of clinical signs such as the presence of biliary aspirates or vomit, bloating, lethargy of the newborn, detected by x-ray examination of intestinal pneumatosis with or without gas in the portal vein, and/or pathological signs detected during laparotomy or autopsy materials of deceased patients.

Pneumoperiteunum without intestinal pneumatosis, without obvious signs of perforation of the wall of a hollow organ, was not considered a strong symptom indicating HEC [13]. These diagnostic criteria served as the basis for establishing the diagnosis in the examined 133 newborns.

The control group consisted of newborns selected from the ICU register, born at the closest time and with the same gestational age as the infant with NEC. Infants who died earlier compared to NEC infants were excluded from the control group.

The results of ultrasound confirming the duration of pregnancy for the antenatal period were analyzed. Based on such indicators as height, weight, head and chest circumference, a centile table was compiled. We calculated the centile of the body mass of a newborn, taking into account gestational age, using standard methods [14]. The required data for the study is taken from the computerized database of the neonatal intensive care unit. UNC 84%.

Statistical analysis. Statistical processing was carried out using Microsoft Excel 2010, Statsoft Statistica 10.0. Certain indicators were taken into account as the arithmetic mean and standard deviation (M ± σ) for indicators with a normal distribution and as a median Me (25%; 75%) for signs with a distribution that deviated from normal.

In the studied groups with a normal distribution of the trait, the difference in the variation series was assessed by Student's t test; with a distribution that does not correspond to the normal difference between the samples - using the nonparametric U test (Wilcoxon-Mann-Whitney).

During the comparison and probabilistic assessment of differences between groups with a small (<30) number of options, White's W-test was used. In groups and subgroups, the significance of differences in frequencies was assessed using Pearson's $\chi 2$ test with Yates' correction. The odds ratio, 95% confidence interval, the degree of influence of factors, Pearson's and Fisher's coefficients were calculated. When evaluating the effectiveness of each method of therapy, the McNemar criterion was used. In all cases, the differences were considered statistically significant at $p < 0.05$.

The study was performed in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

The study was approved by the Regional Ethics Committee of the Scientific Research Institute of Pediatrics named after K. Farajova, Protocol No. 11 dated 06/25/2018. All parents of patients received full information about the study and signed an informed consent to voluntarily participate in it.

Results and Discussion. 208 cases of NEC were identified. These newborns had a mean birth weight of 1418 g (mean birth weight centile 37%) and a mean gestational age of 30.4 weeks. 30 (14.4%) neonates with NEC died.

The median gestational age of the deceased infants was 28 weeks, the oldest was 34 weeks, while the median for surviving infants was 31 weeks. A total of 85 children (40.9%) were operated on, of which 46 (54.2%) survived. During the diagnosis of NEC, blood cultures performed in 50 (24%) cases gave an increase in microflora: Klebsiella spp. was detected in 24 newborns, Staphylococcus epidermicus - in 8, Eschericha coli - in 8, Clostridium spp. in 5, Enterobacter spp. - in 3 and streptococcus haemolyticus - in 2 newborns.

Before the onset of symptoms of NEC, in all cases, the child was fed. The median age at onset of NEC was 11 days (mod-5 and median 9). A significant negative correlation was found between gestational age and day of onset of NEC (r=-0-35, p=0.002).

Of the 208 newborns, 187 were preterm and 13 were 21 term infants; because term infants had predisposing factors, they were analyzed separately from preterm infants.

Premature newborns. Overall, children with NEC had significantly lower birth weights than control children (p<0-001). They were significantly more stunted, as evidenced by a lower mean centile birth weight (p<0-001), or a higher proportion of infants below the 10th percentile (p = 0-01, odds ratio (OR) 3.6 (95%), confidence interval (CI) ranged from 1.3 to 9.7.

Infants until 30 weeks of pregnancy. Differences in birth weight centile between children with NEC and control group were most noticeable in children of 30-36 weeks of gestation, while among children of 25-29 weeks of gestation, this difference was less significant.

An interesting result was the absence of identifiable risk factors in this age group among infants with NEC, other than increased mortality. However, in the NEC group, factors that were indeed significant were common among infants receiving only infant formula (p=004, OR=4-0, CI=-11 to 14-1), and were found to be less common among infants. with NEC who received only expressed breast milk (p = 003, OR = 0.29, CI = 0.09 to 0.87).

Birth weight and birth weight percentiles in infants with NEC were significantly lower than in controls (p<0.001), and there was a marked increase in the proportion of NEC infants with significant growth retardation (<10 percentile: p=0.02, OR=6.0, CI=1.3 to 26.8, <3rd centile: p=0.03, OR=9.0, CI=1.1-71.0).

Children with NEC born at 25-29 weeks of gestation compared with the control group had significantly lower pH in the arterial blood of the umbilical cord (p=0.05) and Apgar levels in 1 minute (p=004, OR=500, CI = -1.1 to 22.8), but there was no significant difference in feed composition.

Term infants. The 21 full-term infants in the main group who developed NEC had a mean (SD) birth weight of 3121

(469) g, a median birth weight percentile of 46 (33) and a gestational age of 38 (1) weeks.

In 11 cases, the onset of NEC coincided with exchange transfusion (9 through the umbilical venous catheter and 2 through the peripheral vein). In 6 and the newborn was a deep asphyxia at birth (pH of the umbilical cord reached 6.96 and 6.97). UNC 62%

Group with spontaneous perforation. There were 14 infants with NEC who developed pneumoperitoneum but did not show pneumotosis on x-ray. Their mean gestational age was 26 weeks. Five out of 14 did not feed at all and only one had birth asphyxia. The proposed mechanism in these cases is perforation in the area of focal ischemia, possibly due to embolism [15].

This study includes a fairly large number of children with NEC who were subjected to a matched case-control survey design. Comparison by gestational age allowed us to get an idea of its impact on the development of NEC.

The obtained results proved a certain nature of the change in risk factors depending on the duration of pregnancy. It turned out that the main risk factor for the development of NEC is prematurity itself, where the incidence was 10% during 25 weeks of infants, falling to 0-03% at normal gestation. The group with a gestational age of 25-29 weeks was distinguished by the absence of an identifiable risk factor.

The occurrence of NEC in this group Clarko and Miller [16] suggest the interaction of such pathological factors as the composition of the diet and the nature of the bacteria in the distal intestinal mucosa and does not depend on perinatal risk.

The only perinatal factor with the incidence of NEC was largely associated with the feeding of the child with expressed breast milk, that is, whether the child received expressed milk or not. This opinion was confirmed in studies by Eibl et al., in which they found that a mixture of immunoglobulin A/G present in expressed breast milk contributes to a significant reduction in the incidence of NEC [17]. The protective effect against the development of NEC induced by expressed breast milk is supported by other prospective studies. UNC 87%.

As can be seen from Table 2, children with NEC with a gestational age of 30-36 weeks were significantly more stunted than the control group and had a higher incidence of asphyxia, as evidenced by a decrease in pH in the umbilical cord arterial blood (p = 0.05) on the Apgar scale in 1 minute.

Fazilova A.Sh.,et all. their studies proved that there was no significant association between NEC and growth retardation, since only 46% of children with NEC had low gestational ages [18].

At the same time, in this study, 38% of infants in the control group, comparable in birth weight, also had a low gestational age, as a result of which the comparison of these groups did not give stunting as a significant difference.

Kleigman et al. [19] found no association between gestational age and NEC incidence despite the fact that 27% of their NEC cases were below the 3rd centile; at the same time, among the control group of infants weighing <1500 g, there is a higher gestation and among 22% of infants out of 553 children, NEC was detected below the 3rd centile. As a result, a comparison of the results obtained in these two populations did not give a clear confirmation that neither gestational age is a risk factor.

Among full-term infants, NEC is rare (0-03%). Among our examined infants among full-term children, NEC developed in 21 cases; they had mean birth weight, mean birth weight percentile and gestational age of 38 weeks. In these newborns, an association was found between NEC and exchange transfusion and asphyxia at birth.

Our study confirms that gestational age is one of the risk factors for the development of NEC, in which susceptibility to NEC is inversely proportional to gestational age.

In full-term infants, NEC requires significant disruption of the gastrointestinal tract and immune system to develop, while in infants <30 weeks of gestation, NEC most often occurs in the absence of well-defined ischemia. In infants at 30 weeks' gestational age and full term, factors such as growth retardation and asphyxia become increasingly important in the development of HEC.

Conclusion. 1. Newborns at risk of NEC include all infants <30 weeks of gestational age, and term infants with severe asphyxia, shock, exchange transfusion, or polycythemia.

2. Breast milk helps reduce the risk of NEC, especially in children 25-29 weeks of gestational age.

The authors declare no conflict of interest in the submitted article

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Z.V. Gasimova, V.A. Veliyeva, O.F. Gasimov, I.A. Gafarov

LOWER THIRD MOLAR IMPACTION FORECAST BASED ON ANGULATION OF THEIR AXIS ON PANORAMIC X-RAYS

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The aim of the study was to evaluate the diagnostic value (sensitivity and specificity) of lower third molar bud impaction in 121 patients aged 7 to 23 years who presented to an orthodontic clinic with complaints of different malocclusions. All patients underwent multiple panoramic radiographs during orthodontic treatment, specifically: before treatment initiation, after completion of phase 1 therapy, after fixed appliance therapy, and during the retention period.

A retrospective analysis was conducted on a total of 1,085 lower third molar buds across 551 panoramic radiographs obtained from patients with maloclusions before, during, and after orthodontic treatment, as well as during the retention phase.

The study revealed that starting from the age of 14, the inclination angle of lower third molar buds allow prediction of their impaction rate with a sensitivity of 64.8±6.5% and a specificity of 71.4±6.0%. As age increases, higher sensitivity and specificity enable impaction rate prediction even with smaller angles (less than 40°).

The application of these diagnostic methods can enhance the effectiveness of preventive measures for pathological conditions associated with delayed tooth eruption.

Keywords: lower third molars, impaction, eruption dynamics on panoramic radiographs

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Introduction. It is well known that the lower third molars impaction (LTM) is one of the most common pathologies in patients with maloclusions [2,4,18,27]. Studies show that as age increases, the angulation of LTM germs changes, and often, after orthodontic treatment, their pressure on the lower dental arch leads to relapses and crowding in the anterior region of the mandible [1,17,24]. At the same time, a group of authors believes that the eruption of LTM does not affect crowding and does not lead to relapses of maloclusions [13,28].

Classical diagnostics for detecting LTM germs and their angulation was based on radiographic examination—orthopantomography (Panoramic X-ray) [3,8,16]. For a more detailed study of the germ position and their relationships, computed tomography (CT) is subsequently performed [14]. However, due to the high radiation dose associated with CT, repeated dynamic examinations are not feasible. Therefore, orthopantomography remains a relevant diagnostic method, allowing for a comprehensive assessment of this anatomical region over time and tracking changes in the angulation of LTM germs, their subsequent eruption, or impacted position [5,19,21].

The aim of this study was to assess the diagnostic significance (sensitivity and specificity) of retained lower third molar germs in patients presenting to an orthodontic clinic with complaints of malocclusion.

Materials and Methods. Our study included 121 patients with various maloclusions (MO). Among them, 54 were male (44.6%) and 67 were female (55.4%). Pearson's Chi-Square test revealed no significant gender-based differences (p=0.589). In total, 550 orthopantomograms of these 121 patients were analyzed, and the dynamic changes in the angulation of 1,085 LTM were examined in relation to age.

Statistical Processing. The statistical analysis of the results was carried out using variation methods (Mann-Whitney U-test), dispersion analysis (F-Fisher and FS-Fisher-Snedecor), and ROC analysis (calculation of cut off points, sensitivity, and specificity of the test) in the IBM SPSS Statistics 26 software package. The null hypothesis was rejected at $p < 0.050$ [20].

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Results. For the analysis, two data groups were organized. The first group included the results of orthopantomograms of teeth 38 or 48 that had fully erupted over time (n = 626), while the second group included orthopantomograms of retained (unerupted) or extracted teeth during observation (n = 459).

In the analysis of orthopantomograms of 7-year-old patients, the average angulation of erupted teeth in 10 cases was 59.2±3.6°, while in 3 cases where the teeth were later retained, the average angulation was 49.2±0.9° (p = 0.318).

At the ages of 8 and 9, the angulation of third molars that later failed to erupt was higher (61.4±7.4° and 61.4±8.9°) compared to those that were retained (63.7±8.4° and 55.3±3.6°), respectively. However, at this stage, it is still premature to decide on the extraction of third molars (p = 0.631 and 0.136).

At the age of 10, the angulations of both erupted and unerupted third molars were nearly identical. As seen in the table, in this age subgroup, teeth erupted in 17 cases, while in 23 cases they remained retained, despite the fact that the germ positions were nearly the same - 59.4±2.2° for erupted teeth and 60.6±1.6° for retained teeth (p = 0.827).

This trend was observed up to the age of 13, after which the average angulation values in the eruption group and the retention group began to statistically differ.

An important statistical indicator representing the probability of a correct prediction is the ROC analysis (Receiver Operating Characteristic), which can assess prediction accuracy by constructing a graph and calculating the area under the ROC curve. Cutoff points were determined based on the coordinates of the ROC table, and sensitivity and specificity for predicting retention in the subsequent periods of the study were calculated based on these points.

According to the ROC analysis, at 10

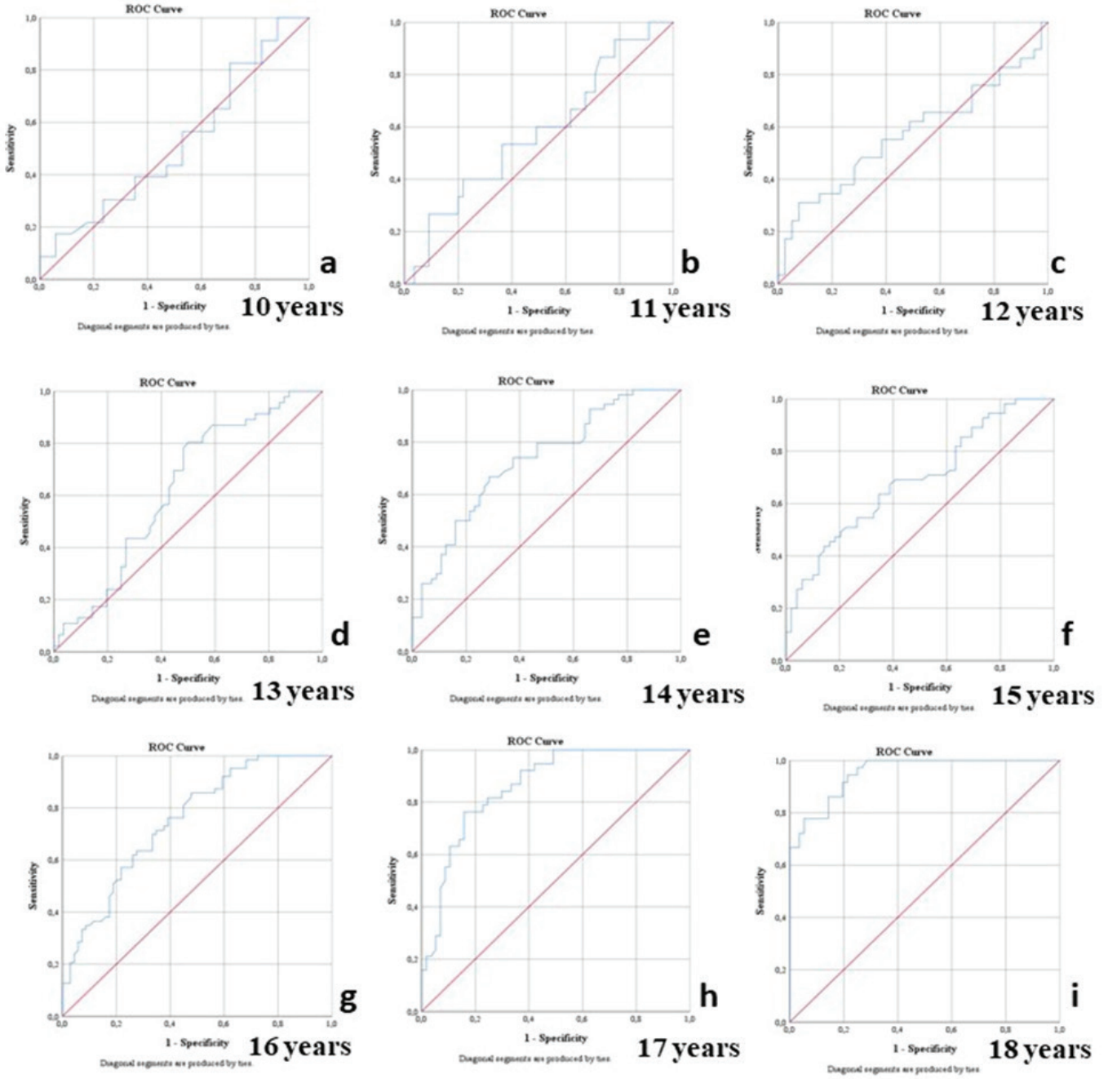

Fig. 1. Results of ROC analysis in different age periods

years old, the informativeness of the angulation values was unreliable (p=0.827), at 11 years old (p=0.376), and at 12 years old (p=0.313) - i.e., it was impossible to predict retention in these age groups (Fig. 1a, b, c). Starting from 11 years old, signs of impaction appeared, but no statistically significant results were found. For instance, at 11 years old, 15 third molar germs were impacted, with an angulation of 57.3±2.8°, while 55 erupted teeth had an angulation of 54.0±1.6°.

At the age of 12, the cutoff angle was 62.75°, meaning that as this angle increases, the probability of tooth retention also increases. At this age, there are good specificity indicators, but they are not sensitive in relation to retention (Table 1).

We studied the angulation results of 28 impacted and 38 unerupted teeth and found that in 28 patients with impacted third molars, the angulation was >62.8°, meaning the sensitivity of this indicator was 31.0±8.6%. Of the 38 unerupted teeth, 36 had an angulation less than 62.8°, meaning the specificity of this indicator in predicting impaction was quite high (92.3±4.3%).

Significant correlations between erupted and impacted third molars in terms of angulation were found starting from the age of 13 (Table 2).

The angulation was found to be a relatively specific and sensitive indicator for further prediction of impaction (p = 0.029) at the age of 13 (Fig. 1d). In this age group, the angulation of 46 impacted and 56 unerupted teeth was studied, revealing that for further impaction of third molars, the angulation was >47.1°, meaning the sensitivity of this indicator was 78.3±6.1%. Of the 56 unerupted teeth, 29 had an angulation less than 47.1°, meaning the specificity of this indicator in predicting impaction was 51.8±6.7%. The area under the ROC curve, which is an integrated parameter of sensitivity and specificity, was 0.626±0.055 (95% CI: 0.517-0.734), p = 0.029, and can be considered statistically significant. Therefore, starting from 13 years old, the impaction of third molars can be predicted.

At the age of 14, according to the ROC analysis, the area under the ROC curve was 0.730 ± 0.047 (95% CI: 0.637-0.823), p < 0.001. These data were obtained from the study of angulations of 54 retained and 56 unerupted teeth, and it was found that when a tooth was subsequently retained, its angulation was greater than 51.8°, meaning the sensitivity of this indicator was 64.8±6.5%. When studying the angulations of the 56 erupted teeth, 40 of them had an angulation less than 51.8°, meaning the specificity of this indicator in prediction was 71.4±6.0% (Fig. 1e).

A similar trend is observed with increasing age. At the age of 15, when studying 55 retained and 49 erupted teeth, it was found that the cutoff point was 54.7°, meaning that if the angle was greater than this value, the tooth was retained, and if it was smaller, the tooth erupted. This is confirmed by the area

Table 1

Indicators of the Angulation of L3M Germs in Different Age Periods

Age (y.o.)	Area Under the Curve				
	Area	Standart error deviation	Asymptotic significance (p)	95% Confidence Interval	
				Lower bound	Upper bound
10	0.520	0.094	0.827	0.336	0.705
11	0.576	0.084	0.367	0.412	0.740
12	0.572	0.074	0.315	0.427	0.717
13	0.626	0.055	0.029*	0.517	0.734
14	0.730	0.047	<0.001*	0.637	0.823
15	0.689	0.051	0.001*	0.588	0.789
16	0.753	0.041	<0.001*	0.672	0.834
17	0.861	0.037	<0.001*	0.789	0.934
18	0.952	0.019	<0.001*	0.914	0.989
19	0.973	0.017	<0.001*	0.940	1.000
20	0.971	0.022	<0.001*	0.928	1.000
21	1.000	0.000	<0.001*	1.000	1.000
22	1.000	0.000	<0.001*	1.000	1.000
23	1.000	0.000	<0.001*	1.000	1.000

Table 2

Informative Value of Indicators by Age Group at Cut off Points

Statistical parameters	12 years	13 years	14 years	15 years	16 years	17 years	18 years	19 years	20 years
Cut off Point	≥ 62.8	≥ 47.1	≥ 51.8	≥ 54.7	≥ 42.3	≥ 46.3	≥ 36.9	≥ 37.6	≥ 39.7
Sensitivity Sn%	31.0±8.6	78.3±6.1	64.8±6.5	43.6±6.7	85.7±4.4	76.3±6.9	94.4±3.8	100.0±0	100.0±0
Specificity Sp%	92.3±4.3	51.8±6.7	71.4±6.0	85.7±5.0	52.2±6.0	84.2±4.8	78.6±5.5	92.0±3.8	88.5±6.3
GDV %	66.2±5.7	63.7±4.8	68.2±4.4	63.5±4.7	68.2±4.1	81.1±4.0	84.8±3.7	95.1±2.4	93.0±3.9
pPV%	75.0±12.5	57.1±6.2	68.6±6.5	77.4±7.5	62.1±5.2	76.3±6.9	73.9±6.5	88.6±5.4	85.0±8.0
nPV%	64.3±6.4	74.4±7.0	68.7±6.1	57.5±5.8	80.0±6.0	84.2±4.8	95.7±3.0	100.0±0	100.0±0
LR+	moderate	not suitable	moderate	moderate	not suitable	moderate	moderate	excellent	good
LR-	not suitable	moderate	moderate	not suitable	moderate	moderate	excellent	excellent	excellent

Note: Cut off point; Sn (Sensitivity); Sp (Specificity); ODV (Total Diagnostic Value); pPV (Positive Predictive Value); nPVт- (Negative Predictive Value); LR+ (Positive Likelihood Ratio); LR- (Negative Likelihood Ratio)

under the ROC curve, which was 0.689 ± 0.051 (95% CI: 0.588-0.789), p < 0.001. In the case of retention of 24 teeth out of 55, the sensitivity of this indicator was 43.6±6.7%. When erupting 42 teeth out of 49, the specificity was 85.7±5.0% (Fig. 1f).

With increasing age, the area under the ROC curve continuously increases: at 16 years old, it was 0.753±0.041 (p <0.001); at 17 years old, it was 0.861±0.037 (p <0.001); at 18 years old, it was 0.952±0.019 (p <0.001); at 19 years old, it was 0.973±0.017 (p <0.001); at 20 years old, it was 0.971±0.022 (p <0.001); from 21 to 23 years old, it was 1.000±0.000, respectively (p <0.001) (Figs. 1g, h, i).

According to Table 2, starting at 17 years old, cut of point reliably decreased: 46.3° at 17, 36.9° at 18, 37.6° at 19, and 39.7° at 20 (Fig. 2).

At 16 years old, the results of 63 retained and 69 erupted teeth were studied, with the cutoff point being 42.3°. Of the 63 retained teeth, 54 had a sensitivity of 85.7±4.4%. When 36 teeth out of 69 erupted, the sensitivity was 52.2±6.0%.

When studying 38 retained and 57 erupted teeth in patients aged 17, the cutoff point was 46.3°. In these patients, the sensitivity for retention was 76.3±6.9%, and for eruption, it was 84.4±4.8%.

The sensitivity indicator in patients with retained third molars (L3M) increases starting from the age of 18: at 18 years old, it is 94.4±3.8%; at 19 years old and 20 years old, it is 100.0±0.000%. For erupted teeth, this indicator changes as follows: at 18 years old – 78.6±5.5%; at 19 years old – 92.0±3.8%; at 20 years old – 88.5±6.3%.

This demonstrates the high prognostic significance of the angulation of third molars with the patient's age. That is, the older the patient, the easier it is to predict retention and create an accurate orthodontic treatment plan, whether involving the removal of wisdom teeth or not (Table 3).

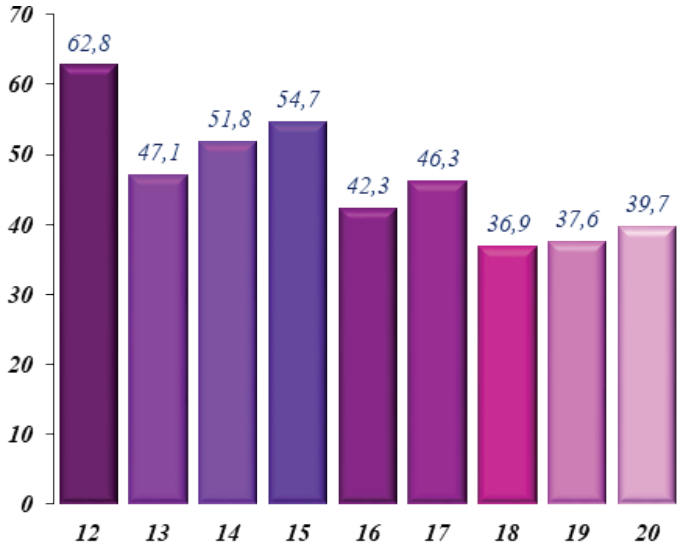

Fig. 2. Cut off Angles for Predicting Retention of Third Molars in Different Age Groups

Table 3

Factor Effectiveness Influence (EIF) of Angulation of Third Molar Germs on the Prediction of Further Eruption by Age Group

Age (y.o.)	Cut off point	Factor EIF (95% ДИ)	P_{FS}
12	>62.8	10.1 (4.7-15.5)	0.008*
13	≥ 47.1	10.5 (6.9-14.0)	0.001*
14	≥ 51.8	15.2 (12.1-18.3)	<0.001*
15	≥ 54.7	11.4 (8.0-14.8)	<0.001*
16	≥ *42.3*	19.0 (16.5-21.4)	<0.001*
17	≥ *46.3*	57.8 (56.0-59.6)	<0.001*
18	≥ *36.9*	103.2 (103.1-103.4)	<0.001*
19	≥ *37.6*	343.6 (331.7-355.5)	<0.001*
20	≥ *39.7*	217.1 (206.0-228.1)	<0.001*

statistical significance by Fisher Snedecor

Discussion. Problems related to the eruption of third molars (ETM) remain a central concern for patients, orthodontists, and maxillofacial surgeons [5,27]. Since the angulation of TM changes during eruption and root formation occurs near the alveolar nerve, this later poses challenges for maxillofacial surgeons during their extraction. The impact of TM on various anomalies, such as anterior crowding, lingual inclination of premolars, caries development on second molars, and potential damage to the inferior alveolar nerve, remains a subject of debate [1,14,17].

Many authors have attempted to predict TM retention based on different parameters using orthopantomograms [9,12,19,21,25,26]. For instance, in a study conducted in 1993 involving 56 unerupted molars in 20-year-old patients, angular inclinations, root development, depth within the bone, and the relationship with the mandibular angle and second molar were measured over six years. Using logistic regression, univariate and bivariate analysis, and clustering methods, the authors developed a predictive model based on the type of impaction and designed a device to forecast TM impaction in 20-year-old patients [25,26].

A graphic-metric method (panorametry) has also been proposed, allowing linear and angular measurements of the mandible. This method enables bilateral comparisons and assesses the contribution of skeletal and dental structures. It includes Dental Panorametry (measurement of posterior mandibular teeth), Mandibular Panorametry (mandible evaluation), and Total Panorametry (combined analysis of the maxilla and mandible) [19].

Retromolar space measurement was conducted to determine linear and angular differences between erupted and retained TMs on panoramic radiographs of 140 patients aged 18–30 years. The authors analyzed retromolar space from the center of the ramus (Xi-7) and the anterior edge of the ramus (AER-7), mesiodistal tooth bud width, and inclination angles of TMs. They concluded that TM eruption likelihood increases when retromolar space measured from AER-7 and Xi-7 is 13 mm and 25 mm, respectively, while mesiodistal tooth width plays a minor role [21].

A study of 264 TMs in 132 patients (71 males and 61 females) aged 15–20 years found that more mature teeth at age 15 had a higher eruption probability (odds ratio: 3.89, P < 0.001). The rate of

root formation was statistically linked to eruption likelihood (odds ratio: 10.50, P = 0.041) [12].

Early prediction of TM eruption or impaction using nine linear and angular measurements on digital panoramic radiographs revealed significant differences in mean values for retromolar space, α-angle (angle between the long axis of the third molar and the gonial-symphysis plane), and β-angle (angle between the long axis of the mandibular second and third molars) (P < 0.05) [11].

A four-year study measuring TM angulation and impaction degree relative to the adjacent second molar and the occlusal plane in 43 students concluded that post-19-year changes in TM position and inclination remain unpredictable [22].

A study of 240 individuals aged 18 determined that specific Hans relationships and changes in TM bud inclination relative to the mandibular base and the second molar could predict impaction or eruption, impacting anterior mandibular crowding [24].

For improved predictive parameters, some authors recommend using computed tomography and lateral cephalograms to analyze retromolar space, angles, and proportions [6,10,14,23].

A study of 53 orthodontic patients measured and compared the mandibular angle with sagittal distance from the anterior mandibular ramus to the alveolar edge between incisors and mesiodistal second molar width. Correlations between profile and panoramic radiograph measurements led to a formula for TM eruption probability calculation [6].

Significant statistical effects of β-angle and gonion-gnathion (Go-Gn) distance on TM eruption level (P < .001 and P < .015, respectively) were found using lateral cephalograms [10]. TM impaction was significantly higher in Class II patients (62.3%) compared to Class III (31.7%; P < .013).

A clinical, biometric, and radiographic study over two years involving 78 patients concluded that retromolar space increased by 1.2–2.2 mm without extractions, 2–2.7 mm with premolar extractions, and 4.5–6.8 mm with first molar extractions. Thus, premolar extractions had minimal impact on retromolar space, whereas first molar extractions significantly increased space, which is crucial for treatment planning [23].

A survey among oral surgeons and orthodontists concluded that TM impaction cannot be reliably predicted using orthopantomograms alone [5,8,29].

A retrospective longitudinal study of TM eruption using artificial intelligence analyzed 771 patients with two panoramic radiographs: the first at 8–15 years (T1) and the second at 16–23 years. Results showed that eruption occurred if adequate retromolar space was present and the initial angle was <32° [7].

Various AI models, including EfficientNet, EfficientNetV2, MobileNet Large, MobileNet Small, ResNet18, and ShuffleNet, analyzed 6,624 TMs on 3,422 orthopantomograms. EfficientNet achieved the highest classification accuracy of 83.7% [15].

Despite extensive literature, there is still no consensus on whether to preserve or extract TM buds before or after orthodontic treatment to prevent relapse and lower incisor crowding.

Conclusion. Since TM eruption remains unpredictable, the best approach is dynamic monitoring of TM angulation over regular intervals. Our statistical data on cut-off points for TM bud inclination at different ages allow orthodontists to predict further tooth impaction. Future studies comparing cephalometric data with orthopantomograms are recommended to identify more precise early-age predictive criteria.

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

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THE RELATIONSHIP BETWEEN GENE EXPRESSION OF CYTOSKELETAL PROTEIN GENES AND THE EPITHELIAL-MESENCHYMAL VIMENTIN MARKER IN LARYNGEAL SQUAMOUS CELL CARCINOMA

Aggressive laryngeal squamous cell carcinoma (LSCC) is characterized by a high metastatic potential, which is closely associated with epithelial-mesenchymal transition (EMT). Initiation of EMT is manifested by changes in the expression of some genes, including those associated with cytoskeleton reorganization. Currently, there are no effective methods for predicting metastasis in LSCC patients. In this regard, the study of SCC molecular characteristics remains relevant. In our study we assessed the relationship between the mRNA level of vimentin (VIM) and mRNA of cytoskeleton proteins: fascin-1 (FSCN1), ezrin (EZR), cofilin-1 (CFL1), profilin-1 (PFN1) and adenylyl cyclase-associated protein 1 (CAP1) in LSCC tumor tissue. The analysis was carried out using RT-PCR in paired samples from LSCC patients with and without lymph node metastases. The PFN1 mRNA level was found to be 6.3 times higher in LSCC patients with lymph node metastases than in patients without metastases. The EZR mRNA level was 17 times lower in patients with stage T3-4N0-2M0 LSCC than in patients with stage T1-2N0-1M0 LSCC. High VIM mRNA levels were associated with high FSCN1 and CAP1 mRNA levels and contributed to a stronger association between CFL1 and PFN1 mRNA levels. Thus, no direct relationship between the level of VIM as a marker of EMP and metastasis in a sample of LSCC patients was found. However, the detected relationships between the levels of cytoskeleton protein mRNA and vimentin mRNA may indicate an active reorganization of the cytoskeleton, which ensures high migration and proliferative activity of malignant cells of LSCC.

Keywords: epithelial-mesenchymal transition, actin-binding proteins, laryngeal squamous cell carcinoma, vimentin, intermediate filament proteins, metastasis

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Introduction. The aggressiveness of laryngeal squamous cell carcinoma (LSCC) is associated with its high metastatic potential, which is closely related to the processes of epithelial-mesenchymal transition (EMT) [17]. Initiation of EMT during tumor growth leads to changes in the expression of various genes, including those associated with cytoskeleton reorganization. For tumor cells of epithelial origin, the activation of molecular biological processes associated with EMT is known to promote malignant transformation [11; 13]. The EMT process is accompanied by a cascade of various changes in molecular genetic events, in particular, the activation of transcription factors, increased production of tissue metalloproteinases, loss of intercellular contacts, changes in the content of actin-binding proteins (ABP) and other intracellular events [5;7; 9; 11; 13; 15]. All these processes ultimately lead to the reorganization of the actin cytoskeleton, which is the final step before the onset of tumor cell invasion [7; 8].

Much attention is paid to vimentin, which as an intermediate filament cytoskeleton protein. It is believed that vimentin is mainly expressed in fibroblasts, endothelial cells and lymphocytes. Sufficient evidence has accumulated for the participation of vimentin not only in the regulation of EMT, but also in the regulation of Wnt / β-catenin and GSK-3 / Snail signaling pathways, which allows this protein to be used as a marker of EMT and metastasis [12]. Cytoskeleton remodeling is known to be mediated by multiple ABP, including cofilin-1 (CFL1), profilin-1 (PFN1), ezrin (EZR), fascin-1 (FSCN1) and adenylyl-associated protein-1 (CAP1), which have different functional roles in the cell [6; 9; 19]. In response to extracellular and intracellular signals, ABP and vimentin regulate cytoskeleton reorganization, thereby participating in cancer cell invasion and metastasis [5; 12]. There is virtually no data on the combined effect of vimentin and the cytoskeleton proteins listed above on metastasis in LSCC. In addition, given that laboratory-specific methods for predicting LSCC metastasis have not yet

been introduced into practice, this area of research remains relevant.

The assessment of the relationship between the expression of genes encoding vimentin and the expression activity of genes encoding cytoskeleton proteins in the LSCC tissue, as well as the assessment of their relationship with lymph node metastasis will be useful as new approaches in diagnostics or search for new therapeutic targets. Therefore, **the aim** of the study was to assess the relationship between the levels of vimentin and cytoskeleton proteins: CFL1, PFN1, EZR, fascin-1 FSCN1 and CAP1 in tumor tissue, as well as the association of the expression of these genes with metastasis in patients with LSCC

Material and methods. The study included 43 LSCC patients who were treated at the Cancer Research Institute of Tomsk National Research Medical Center from 2017 to 2021. Tumor (stage T1-4N0-1M0) and normal tissue samples obtained during videolaryngoscopy were the study material. All patients with histologically verified LSCC were divided into the group with regional metastases (n=25) and the group without metastases (n=18). The obtained tissue samples were placed and stored in RNAlater solution (Ambion, USA). The study was conducted in accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" with the amendments of 2000 and the "Rules of Clinical Practice in the Russian Federation" approved by Order of the Ministry of Health of the RF No. 266 (06/19/2003). Informed consent was obtained from each patient and permission from the Ethics Committee of the Oncology Research Institute of the TNRMC (extract from protocol No. 7 dated 06/24/2019).

Extraction of mRNA and preparation of cDNA. The CCR-50 kit (Biosilica, Novosibirsk) was used to extract the total mRNA pool from paired tissue samples according to the manufacturer's instructions. The concentration and purity of mRNA were assessed using a NanoDrop-2000 spectrophotometer (Thermo Scientific, USA). cDNA synthesis on the RNA matrix was performed using the OT-1 reverse transcription reagent kit (Synthol, Moscow) according to the manufacturer's instructions, and the resulting mixture was then used to perform quantitative real-time polymerase chain reaction (RT-PCR).

Real-time PCR. The level of gene mRNA expression was assessed by RT-PCR using Sybr Green technology and iCycler amplifier (Bio-Rad, USA). Primers were selected using the Vector NTI Advance 11.5 program (Thermo Fisher Scientific, USA) and the NCBI database (http://www.ncbi.nlm.nih.gov/nuccore) [9]. Melting curve analysis (Melt) was used to assess the final PCR product for the presence of primer-dimers or non-specific products. The housekeeping gene of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) enzyme was used as a reference gene to normalize the expression of the studied genes. mRNA (cDNA) isolated from morphologically altered laryngeal epithelium was used as a calibrator. Expression analysis was performed using the 2-ΔΔCT method [14].

Statistical analysis of the results was performed using the Statistica 6.0 and IBM SPSS Statistics 22.0 software packages. The normality of the distribution was checked using the Shapiro–Wilk test. The results are presented as Me (Q1; Q3), where Me is the median and Q1; Q3 is the interquartile range, n is the number of patients in the group and P (U-test) is the nonparametric Mann-Whitney U-test. Spearman correlation analysis was used to analyze the relationships. Differences were considered statistically significant at $p<0.05$.

Results and discussion. A 6.3-fold increase in the level of profilin-1 mRNA was observed in tumor tissue of LSCC patients with lymph node metastases compared to that observed in LSCC patients without metastases. The level of cofilin-1 mRNA in tumor tissue of LSCC patients tended to increase in comparison with that observed in patients without metastases (table 1). No significant differences in the level of vimentin mRNA between patients with lymph node metastases and patients without metastases were found. The extent of the tumor involvement influenced the level of mRNA ezrin, which was almost 17 times lower in patients with stage T3-4N0-2M0 compared to that observed in patients with stage T1-2N0-1M0 (Table 1).

The correlation analysis revealed that metastasis affected the strength and number of correlations between expressed genes encoding cytoskeletal proteins. Thus, in LSCC patients without lymph node metastasis (N0), one strong correlation between the mRNA level of profilin 1 and cofilin 1 was found ($r=0.8$; $p<0.05$) (Fig. 1A).

In the group of LSCC patients with metastases (Fig. 1B), moderate-strength relationships were found between the expression levels of almost all the genes studied ($r=0.5$-0.6; $p<0.05$), with the VIM mRNA level positively associated with the expression activity of the FSCN1, EZR, PFN1 and CAP1 genes ($r=0.6$; $p<0.05$). A positive relationship was also found between the expression activity of the genes encoding PFN1, CAP1 and CFL1 ($r=0.6$; $p=0.04$), with the mRNA levels of PFN1 and CFL1 being less strongly associated ($r=0.5$; $p<0.5$). Thus, the presence of lymph node metastasis increased the number of co-expressed genes, with a positive correlation observed.

The total sample of patients with LSCC was divided into the groups with respect to the median level of vimentin mRNA: patients with a low VIM expression level (below 0.65 U) in the tumor tissue, and patients with a high VIM expression level (above 0.65 U) (Table 2).

Table 1

The relative mRNA level of actin-binding proteins and vimentin in tumor tissue of LSCC patients with and without lymph node metastasis

мРНК	T1-2N0-1M0	T3-4N0-2M0	N0	N1-2	P1	P2
VIM	0.31 (0.01;41.93)	1.27 (0.22;7.31)	0.39(0.01;41.93)	1.44(0.22;18.00)	0.58	0.28
FSCN1	1.31 (0.03;7.15)	0.94 (0.12;8.00)	0.32(0.04;6.60)	1.73(0.21;14.40)	0.70	0.11
EZR	12.50 (0.57;34.32)	0.72 (0.05;4.67)	3.46(0.06;21.99)	1.53(0.07;8.17)	**0.03**	0.50
PFN1	1.19 (0.01;7.30)	2.09 (0.18;18.82)	0.40(0.00;4.69)	2.51(0.76;25.99)	0.22	**0.01**
CFL1	1.53 (0.08;13.77)	1.15 (0.19;6.60)	0.38(0.04;7.75)	3.10(0.19;27.00)	0.94	*0.06*
CAP1	5.46 (1.07;26.93)	3.30 (0.10;29.25)	3.52(0.22;29.33)	4.55(1.07;28.62)	0.87	0.38

Note: a p-value is a level of statistically significant difference between the groups (Mann–Whitney U test)

The group of LSCC patients with a high level of VIM mRNA consisted of 9 patients with lymph node metastasis and 13 patients without metastasis. A similar distribution was observed for the group of patients with a low level of VIM mRNA (Table 2). Although lymph node metastases in the presented patient sample were not associated with VIM mRNA levels, their increase resulted in a significant increase in CAP1 and FSCN-1 expression (Fig. 2).

In addition, the VIM mRNA level affected the relationships between gene expression activities in cancer tissue. Thus, at a low VIM mRNA level, one correlation was observed between PFN1 and CFL1 mRNA (r=0.4; p<0.05) (Fig. 1C), while at a high VIM gene expression, the number of relationships between the ABP mRNA levels increased, and the strength of the relationship between CFL1 and PFN1 mRNA also increased (r=0.8; p=0.04).

The study found that neither lymph node metastasis nor the extent of laryngeal cancer involvement correlated with the expression of the gene encoding type III intermediate filament protein VIM. This fact is partly supported by information obtained from the GEPIA2 database (http://gepia2.cancer-pku.cn/), a resource for gene expression analysis based on tumor and normal samples from TCGA and GTEx data. Expression of the vimentin gene is not associated with the extent of squamous cell carcinoma of the head and neck (Fig. 3A), is not expressed at a sufficiently high level (Fig. 3B) in comparison with conditionally normal tissue and other genes studied (Fig. 3C). Although the high level of vimentin mRNA, did not demonstrate a significant difference in the groups of patients with and without metastases, its increase was combined with a significant increase in the mRNA level of the actin-associated protein PFN1 (Table 2).

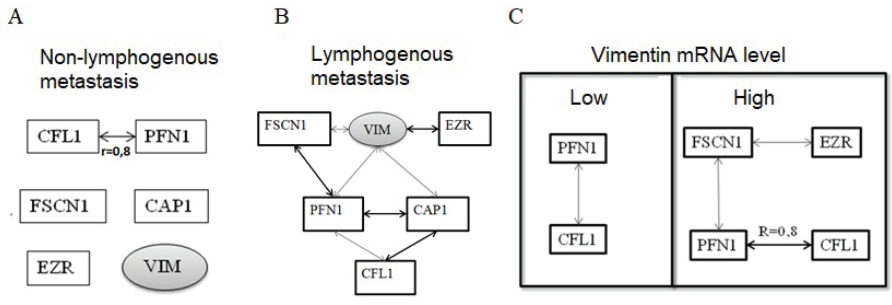

Fig. 1. Expression of genes encoding cytoskeleton proteins in tumor tissue of patients with laryngeal cancer: Spearman correlation coefficients.
Note: bold arrows show coefficient r=0.8, thin arrows show r=0.5-0.6

Table 2

Expression of the gene encoding vimentin in tumor tissue of patients with laryngeal cancer

Groups of patients with LSCC		Level of VIM mRNA		Total number of patients
		low	high	
Lymph node metastasis	no	12	13	25
	yes	9	9	18
Total number of patients		21	22	43

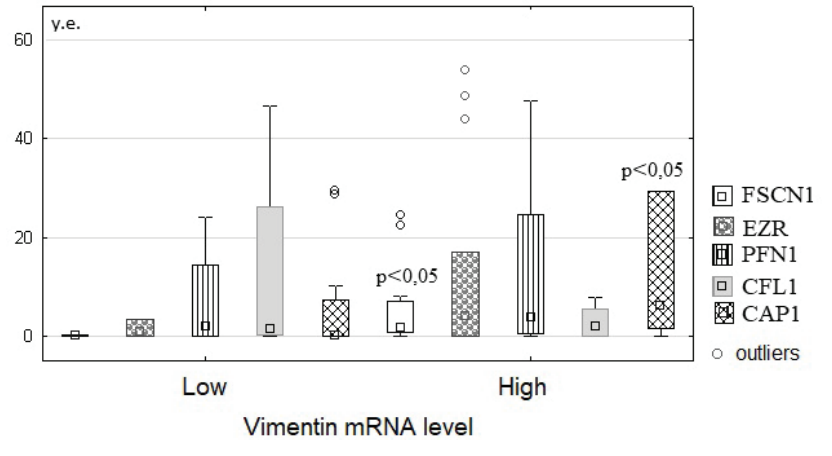

Fig. 2. The expression levels of actin-binding protein genes in tumor tissue of patients with laryngeal cancer depending on the different expression activity of the gene encoding vimentin. (U-test)

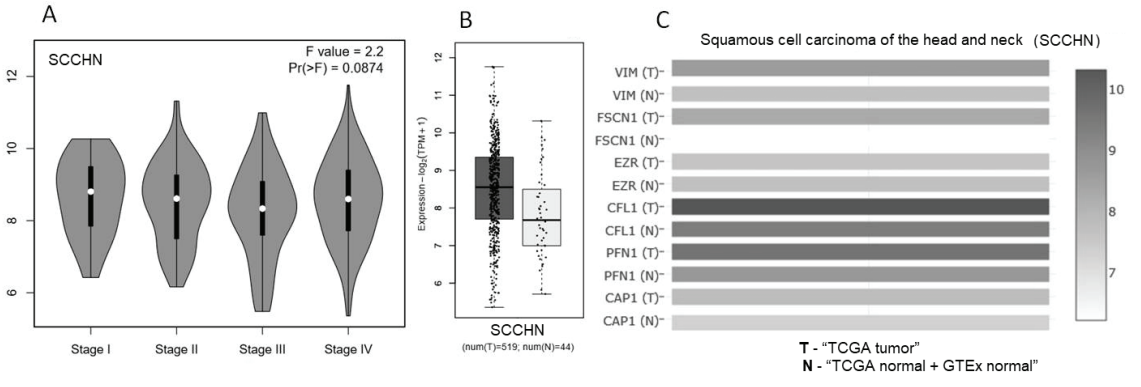

Fig. 3. Vimentin gene expression depending on the extent of head and neck squamous cell carcinoma (A), in normal and tumor tissue of head and neck squamous cell carcinoma (B), and in comparison with the expression of the genes fascin-1, ezrin, cofilin 1, profilin-1 and adenylyl-associated protein 1 in tumor and normal tissue of head and neck squamous cell carcinoma (C)

Correlation analysis revealed that the high expression of EMT marker vimentin enhanced the positive relationships between the mRNA levels of CFL1 and PFN1 and contributed to the development of multiple relationships between the mRNA levels of other proteins. Considering the fact that during cancer metastasis, the establishment of multiple positive relationships between the mRNA expression levels of the studied proteins was also observed, it can be concluded that vimentin has an indirect effect on metastasis. There is evidence that ABP (cytoskeletal proteins) not only regulate the locomotor activity of cells, but also participate in the transcription, since actin and ABPs are present not only in the cytoplasm, but also in the cell nucleus. The cell nucleus contains the monomeric actin, the amount of which depends on the key ABPs – PFN1 and CFL1 [1; 2]. It is possible that the coactivation of the studied genes is related not only to the mobility of tumor cells during metastasis, but also to the processes of transcription, and further to the proliferative activity of the tumor itself.

In our study we also found that the mRNA expression levels of CAP1 and FSCN1 significantly increased with the evidence of high vimentin expression, however, a positive correlation was shown only between the expression of FSCN1, EZR, PFN1 genes, and a strong positive correlation was established between PFN1 and CFL1. Our results are consistent with other recent studies, in which co-expression of actin-binding proteins CAP1, PFN1 and CFL1 and the participation of these proteins in the metastatic cascade were revealed [6; 9; 18]. In our study, the ezrin mRNA level decreased by 16 times with increasing stage from T1-2N0-1M0 to T3-4N0-2M0, but the level of significance was low (p=0.5). Ezrin, a protein which links the cell cytoskeleton, membrane, and extracellular matrix, is involved not only in cell locomotion, but also in adhesion, differentiation, proliferation, signaling, blebbing, and entosis [3; 4; 16], including metastasis [4; 10]. To analyze the relationship between EZR and tumor progression, it is likely necessary to take into account the presence of mutations in its gene, as well as the expression activity of genes of the ERM (ezrin-radixin-moesin) family [19]. In addition, the decrease in ezrin expression may be associated with a disruption of the adhesive properties of tumor cells, which is important for invasion and metastasis. The role of ezrin in tumor invasion, metastasis, progression, and drug resistance is still under investigation [4; 10].

Conclusion. Our data supplement the knowledge about the molecular genetic mechanisms of metastasis in LSCC and their relationship with the EMT processes Considering our data and the fact that the reorganization of the cytoskeleton during the EMT process is controlled by various molecules, we can conclude that almost all the proteins studied, as well as other proteins, participate in molecular biological changes in lymph node metastasis from LSCC. For a more complete analysis of possible mechanisms and confirmation of the results obtained, further in vitro studies, which will expand the knowledge about the regulation of ABP, are required. Nevertheless, the discovered relationships can supplement the knowledge about cancer development and progression, which will be useful in the development of new diagnostic techniques or therapeutic targets.

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

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THE ANTIBIOTIC RESISTANCE OF *KLEBSIELLA PNEUMONIA* AND *ESCHERICHIA COLI* ISOLATES AND THE SPREAD OF CARBAPENEMASES IN A MULTIDISCIPLINARY IMPATIENT FACILITY

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Aim of the Research. A study of antimicrobial resistance of *Klebsiella pneumonia* and *Escherichia coli* isolates and the spread of carbapenemase genes in a multidisciplinary emergency inpatient facility in the Sakha Republic (Yakutia).

Materials and Methods. There was conducted a retrospective observational study of the results of microbiological tests of patients treated in the period 2021–2023 in a multidisciplinary emergency inpatient facility with surgical and therapeutic departments in the Sakha Republic (Yakutia). The spread and identification of carbapenemase genes was performed in *K. pneumonia* and *E. coli* isolates isolated in biological media from 254 patients.

Results and Discussion. The structure of the isolated microorganisms was dominated by pathogens of the *Enterobacterales* genus: *K. pneumonia* was isolated in 29.9% (n=3,314) and *E. coli* – in 20.8% (n=2,306) of the samples. The proportion of meropenem-resistant *K. pneumonia* strains was 47.5% of the isolates, *E. coli* – 13%. As a result of the study, a total of eight carbapenemase genes were isolated. The most common genes for the *K. pneumonia* and *E. coli* isolates by detection frequency were *OXA48* (24.9%), *ctxM-1* (24.0%), *SHV* (21.8%), *TEM* (12.9%), and *NDM* (10.8%). As a rule, there were combinations of three to five gene types: three types were isolated in 86 (33.9%) strains, four types – in 56 (22.0%), and five types – in 54 (21.3%). The presence of one gene type was detected in 33 (13.0%) strains, two types – in 16 (6.3%), six types in 3 (1.2%), and seven types in 6 (2.4%).

Conclusion. Microbiological monitoring, control of local resistance to antibiotics in inpatient facilities and the study of resistance mechanisms can improve the effectiveness of antimicrobial therapy and also serve as an effective method of combating the spread of antibiotic-resistant strains of microorganisms.

Keywords*:* nosocomial infection, *Klebsiella pneumonia, Escherichia coli*, antimicrobial resistance, carbapenemases, carbapenemase genes.

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Introduction. The rapid spread of bacteria with multiple or total resistance to antimicrobial drugs worldwide is a global health problem. According to the World Health Organization (WHO), high rates of microbial resistance to antibiotics and a decrease in the effectiveness of antimicrobial drugs are observed worldwide. The past decade witnessed an extremely negative trend: an increased number of nosocomial strains resistant to carbapenems, which had been considered a reliable and backup class of antibiotics. [9]

Studies on antibiotic resistance indicate that the most common pathogens of nosocomial infections are representatives of enterobacteria, and an increased level of resistance to carbapenems is due to the production of carbapenemases. [2,3,12,13] Thus, the Russian long-term multicenter epidemiological study "MARATHON", conducted since 2011, has revealed that enterobacteria make up 48.2% of all isolated nosocomial bacterial pathogens, with *K. pneumonia* (47.2%) and *E. coli* (30.0%) being the most frequent species. At the same time, there is a clear trend towards increasing resistance to carbapenems – Imipenem, Meropenem and Ertapenem: 6.9%, 6.5% and 23.6% of enterobacteria isolates are resistant to them, respectively. [3] The next stage of this study confirmed that clinical isolates of *K. pneumoniae* are becoming increasingly resistant to carbapenems due to the spread of carbapenemases, which are characterized by diversity and the simultaneous existence

of several genes for their production. The most common carbapenemases are of three main groups: *OXA-48*, *NDM* and *KPC*. [2]

Recent studies abroad also indicate the relevance of the problem with *K. pneumoniae* and *E. coli* and their resistance to antimicrobial drugs. The prospective multicenter cohort study CRACKLE-2, having covered 49 hospitals in the USA to study the molecular and clinical epidemiology of carbapenem-resistant enterobacteria, showed that they accounted for 59%, with *K. pneumoniae* being the most common carbapenemase-producing pathogen. [13] Another large-scale study, INVIFAR (INnvestigación y VIigilancia de la FArmacorResistencia), aimed at analyzing carbapenemase genotypes of clinical isolates collected from 41 medical centers in Mexico, revealed high carbapenem resistance in *E. coli* in the group of patients aged 0–17 years, and in *K. pneumoniae* in the group of 18–59 years of age. The highest resistance to carbapenems was observed in clinical isolates from patients in intensive care units ($p < 0.035$). [12]

The strategy for combating antimicrobial resistance includes the monitoring of antibiotic resistance and collecting information on resistance mechanisms. Here, recording, analysis and systematization of information should be carried out at all levels: globally, within individual countries and regions, as well as in each individual medical organization. [4] Therefore, phenotypic detection of carbapenemase genes (*OXA*, *TEM*, *SHV*, *KPC*, *VIM*, *ctxM-1*, *NDM*, etc.) should be considered one of the conditions for monitoring and combating antibiotic resistance. From this perspective, the analysis of the spread of carbapenem-resistant isolates of *K. pneumonia* and *E. Coli*, as well as the genes responsible for producing carbapenemases in a multidisciplinary inpatient facility, is relevant, has scientific interest and practical significance.

The aim of the study was to examine the resistance of *K. pneumonia* and *E. coli* isolates to antibiotics and the spread of carbapenemase genes in a multidisciplinary emergency inpatient facility in the Sakha Republic (Yakutia).

Materials and Methods. We conducted a retrospective observational study of the results of microbiological tests of patients treated in the period 2021–2023 in a multidisciplinary emergency inpatient facility with surgical and therapeutic departments in the Sakha Republic (Yakutia).

For the period 2021–2023, there was studied the etiological structure of the pathogens isolated in biological media of the patients (tracheobronchial aspirate (TBA), blood, urine, wound drainage, peritoneal and pleural exudate, bile), and the resistance of *K. pneumonia* and *E. coli* isolates to screening antibiotics was determined. The microbiological studies in the patients were performed every 7–10 days. A repeated isolation of the pathogen during the study in a patient was considered as one agent.

The spread and detection of carbapenemase genes were performed in *K. pneumonia* and *E. coli* isolates obtained in the bio-media of 254 patients from the surgical and therapeutic profiles (127 (50%) patients of each profile). The patients' age ranged from 18 to 97 years (median age 66 [50–75] years), including 141 (55.5%) men and 113 (44.5%) women. The length of staying in the intensive care unit was 8 [2–16] days; the total number of patient days in the hospital was 25.5 [17–40.7] days. The mortality rate of the patients was 30.3% (77 patients).

All the patients gave informed consent for the processing and use of personal data upon admission to the hospital.

Data processing and antibiotic resistance analysis were performed on the AMRcloud online platform (version: Beta, 30.01.2023). [10]

Species identification and determination of susceptibility to antibacterial drugs were performed on an automatic analyzer VITEK-2 Compact (bioMerieux, France), as well as by the disk diffusion method on Mueller-Hinton agar using antimicrobial disks (BioRad, USA).

Determination of susceptibility to antibiotics was carried out in accordance with the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the guidelines of the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC) for determining the susceptibility of microorganisms to antimicrobial drugs. [5]

The genes of acquired carbapenemases of the main groups were identified using NG-Test CARBA5 (NG Biotech Z.A., France) and the molecular genetic method (real-time PCR) using the BakRezista GLA kits (DNA-Technology).

The collection, storage and systematization of the database, construction of diagrams were carried out in Microsoft Office Excel 2016 spreadsheets. The statistical processing of quantitative data (age, duration of treatment) was performed using the Jamovi-2.6.44 statistical software and included an assessment of the normality of the sample distribution using the asymmetry and kurtosis testing method, which revealed an abnormal distribution; due to that, the median (Me),

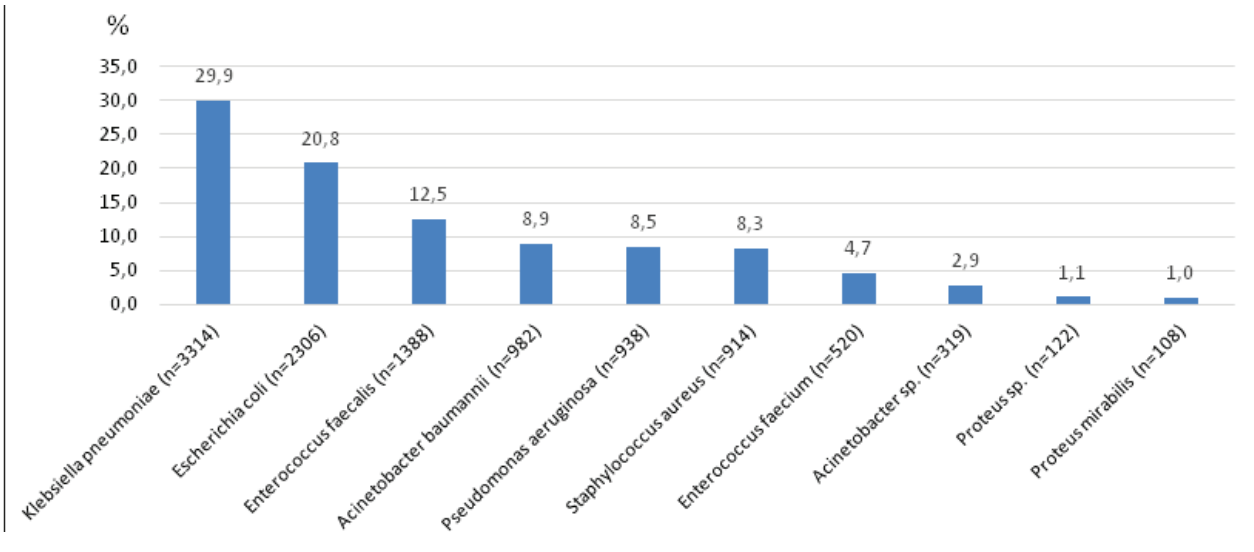

Fig. 1. The structure of the isolated pathogens in the inpatient facility in 2021–2023

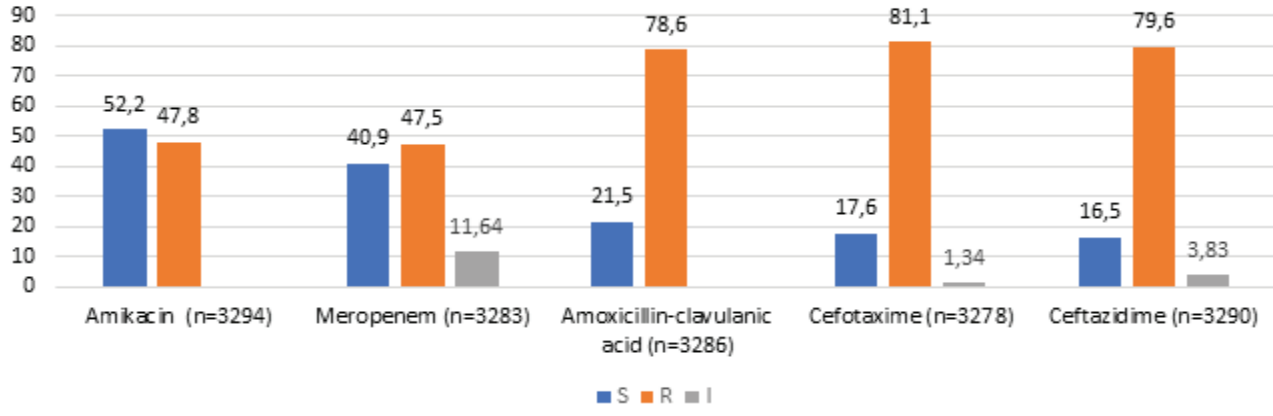

Fig. 2. *Klebsiella pneumonia* resistance to antibacterial drugs

lower and upper quartiles [Q1–Q3] were determined.

Results and Discussion. At the initial stage of our study, we carried out an analysis of the general structure of microorganisms isolated in the inpatient facility in the period 2021–2023, showing the dominance the genus *Enterobacterales* pathogens: *K. pneumonia* and *E. coli*, which were detected in 29.9% (n=3,314) and 20.8% (n=2,306) of the samples, respectively. The proportion of other clinically significant pathogens was as follows: *Enterococcus faecalis* – 12.5% (n=1,388), *Acinetobacter baumannii* – 8.9% (n=982), *Pseudomonas aeruginosa* – 8.5% (n=938), *Staphylococcus aureus* – 8.3% (n=914). Other representatives of the microbial flora were isolated in less than 5% of the tests (Figure 1).

The study of the susceptibility of *K. pneumonia* to antibacterial drugs indicated its susceptibility to aminoglycosides (Amikacin) in 52.2% and to carbapenems (Meropenem) in 40.9% of the isolates. At the same time, they demonstrated low susceptibility to penicillinase-resistant penicillins (Amoxiclav) and third-generation cephalosporins (Cefotaxime, Ceftazidime) (Figure 2).

The susceptibility of *E.coli* to the used antibacterial drugs was significantly higher and was at the level of 92% to Nitrofurantoin, 81.7% to Meropenem, 71.4% to Amikacin, and 65.5% to Amoxiclav. The exception was low susceptibility to Ceftazidime: 35.4% of the isolated strains were sensitive and 10.8% were moderately sensitive (Figure 3).

The next stage of the study was to investigate the prevalence of carbapenemase production genes. For this purpose, microbiological studies of bio-media were conducted in 254 patients of surgical and therapeutic profiles. Among the patients of the surgical profile, the majority were patients of surgical departments No. 1 (17.7%), No. 2 (11.4%) and the proctology department (6.3%). The patients of the therapeutic profile were mainly represented by patients from the neurological department for patients with acute cerebrovascular accident (ACVA) – 66 patients (25.9%) and the emergency department – 38 (15.0%). The anesthesiology, resuscitation and intensive care department (ICU) treated 98 (77.2%) surgical patients and 66 (51.9%) therapeutic patients.

In the studied patients, *K. pneumonia* was isolated in 238 (84.7%) and *E. coli* – in 43 (15.3%) tests. Figure 4 demonstrates the distribution of carbapenemase genes in these isolates.

As a result of the study, a total of eight carbapenemase genes were isolated. The most common genes by detection frequency for *K. pneumonia* and *E. coli* isolates were *OXA48* (24.9%), *ctxM-1* (24.0%), *SHV* (21.8%), *TEM* (12.9%) and *NDM* (10.8%). In most cases, there were combinations of three to five gene types: three types were isolated in 86 (33.9%) strains, four types – in 56 (22.0%) and five types – in 54 (21.3%). The presence of one gene type was found in 33 (13.0%) strains, two types – in 16 (6.3%), six types – in 3 (1.2%) and seven types – in 6 (2.4%).

Thus, as our study showed, the structure of isolated microorganisms in a multidisciplinary inpatient facility in the period 2021–2023 was dominated by *K. pneumonia* and *E. coli*. The share of meropen-

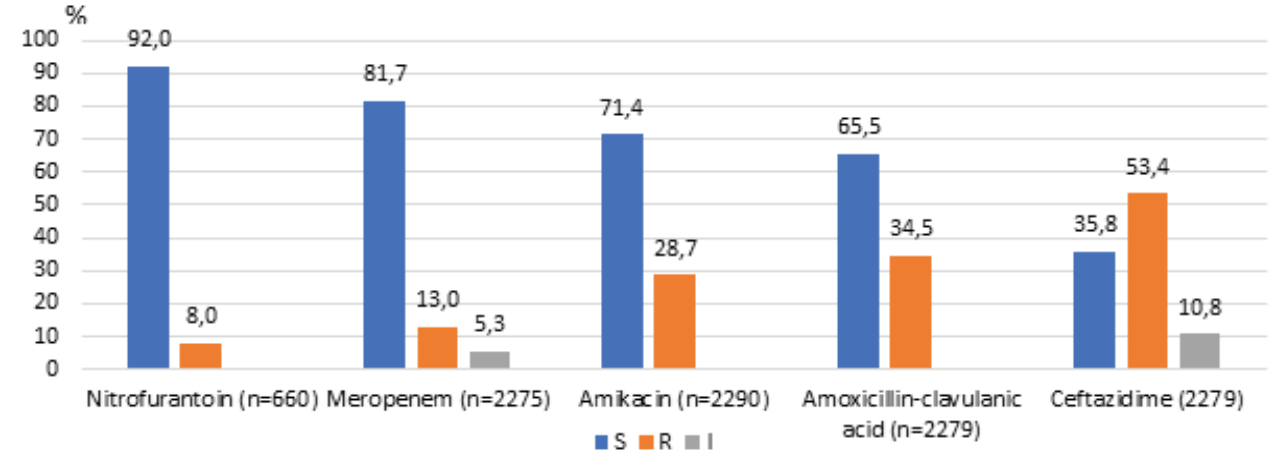

Fig. 3. *Escherichia coli* resistance to antibacterial drugs

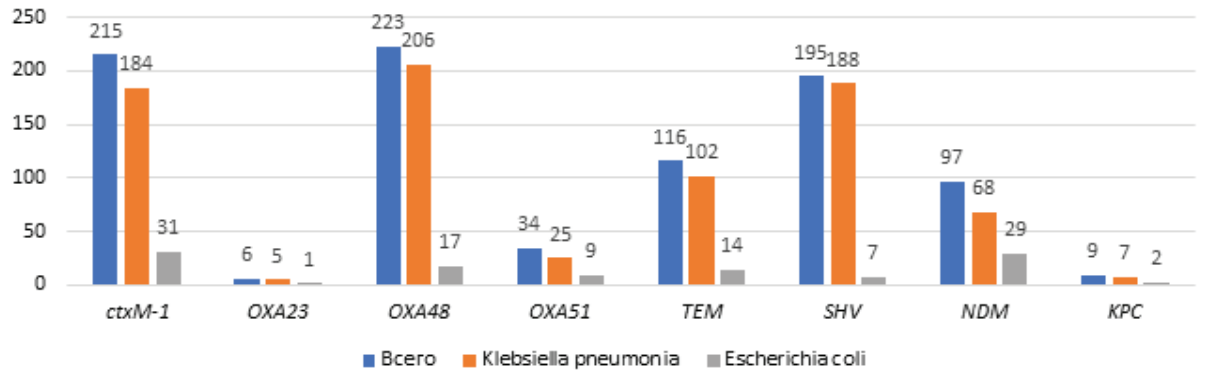

Fig. 4. *Klebsiella pneumonia* and *Escherichia coli* carbapenemase genes

em-resistant *K. pneumonia* strains was 47.5% of the isolates, *E. coli* – 13%. The presented results confirm our previously obtained data on the increased share of meropenem-resistant *K. pneumonia* strains in this inpatient facility, which grew over the period 2016–2022 from 26.7% (95% CI: 16.47–25.61) to 44.1% (95% CI: 40.56–47.8); *E. coli* strains – from 9.5% (95% CI: 6.87–13.21) to 18% (95% CI: 14.98–21.54). [9]

The predominance of *K. pneumonia* and *E. coli* with multiple resistance to antimicrobial drugs in the microbial spectrum is typical of many inpatient facilities and intensive care units in Russia and worldwide [1,2,3,8,12,13,14]. For instance, according to Belotserkovsky et al., the leading pathogens of infection in surgical intensive care units were *K. pneumoniae* (18.5%), whose resistance to meropenem was 83.0%. [1] Jeong et al. (2022) indicate that *K. pneumoniae* account for 81.8% in the group of carbapenem-resistant enterobacteria. [11]

Our results on carbapenemase genes do not contradict, in general, the data of other studies, as well. As in other studies, gene diversity is common; isolates often contain various combinations of them, the number of which can reach seven. In our study, *OXA48* (24.9%), *ctxM-1* (24.0%), *SHV* (21.8%), *TEM* (12.9%) and *NDM* (10.8%) were most frequently observed in *K. pneumonia* and *E. coli* strains. A similar high resistance of *K. pneumoniae* to carbapenems mainly due to the spread of *OXA-48* and *NDM* carbapenemases is presented in the studies by the Kommunarka Moscow Multidisciplinary Clinical Center [6] and in the Russian multicenter study "MARATHON". [3] However, it should be noted that in the above-mentioned works, among the genes encoding carbapenemase, the *KPC* gene was often observed, which was not detected in our study. In the INVIFAR study, the carriage of the *KPC* gene was also observed quite often – in 40% of *K. pneumoniae* strains, and the resistance of *E. coli* to Meronem was represented by the *NDM* gene in 59.2%. [12]

The similarity of carbapenemase phenotypes indicates the resistance of microorganisms to the same carbapenems; conversely, their differences indicate local features of resistance, which should be taken into account when choosing an antibiotic.

Conclusion. The results of this study indicate the relevance of the problem of resistance to carbapenems in the conditions of a multidisciplinary emergency inpatient facility in the Sakha Republic (Yakutia). A crucial and clinically significant factor is the high level of carbapenemase producers in *K. pneumonia* strains, which should be taken into account when choosing antimicrobial therapy.

The need for further study of the mechanisms of resistance to antimicrobial drugs is beyond doubt. Microbiological monitoring, control of local resistance to antibiotics in an inpatient facility and the study of resistance mechanisms can increase the effectiveness of antimicrobial therapy, and also serve as an effective method of combating the spread of resistant strains of microorganisms.

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

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ATYPICAL CASES OF HEARING LOSS IN PATIENTS WITH A MITOCHONDRIAL VARIANT m.1555A>G OF THE *MT-RNR1* GENE IN THE REPUBLIC OF BURYATIA

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In a previous study, we found a high prevalence of the m.1555A>G variant of the *MT-RNR1* gene, which causes mitochondrial hearing loss (OMIM 561000) among deaf patients living in the Baikal Lake region. In this regard, in the present study, a genotype-phenotypic analysis of the hearing function in individuals with the m.1555A>G variant was carried out in the discovered Siberian region. Clinical and audiological analysis was performed in 48 people with this mitochondrial variant, whose average age was 51.3±15.5 years. The obtained genotype-phenotypic data are consistent with previously conducted studies of the features of the auditory function in individuals with m.1555A>G, which note incomplete penetrance of the manifestation of the pathological phenotype. Of particular interest in our cohort are three cases of mixed hearing loss, including both sensorineural (inner ear defect) and conductive (middle ear defect) components. The detected conductive component, which is atypical for this mitochondrial form of the disease, may be associated with idiopathic non-infectious foci of the pathological process in the middle ear. We do not exclude the possibility that the detected clinical signs may be a consequence of systemic damage to the hearing organ in this mitochondrial variant. On the other hand, the detected cases may be related to a cross-pathological effect caused by another form of a less common or rare disease. The obtained results require further genotype-phenotypic studies.

Keywords: mitochondrial hearing loss, m.1555A>G variant, *MT-RNR1* gene, genotype-phenotypic analysis, Buryatia

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Introduction. Mitochondria are intracellular organelles responsible for the production of adenosine triphosphate (ATP) through a process called oxidative phosphorylation [20]. In this process, energy is released by breaking down glucose and fatty acids via the mitochondrial respiratory chain [31]. Mutations in mitochondrial DNA have been described primarily in various rare syndromes, but are also found in more common diseases such as sensorineural hearing loss. One such mitochondrial mutation leading to isolated hearing loss is m.1555A>G in the *MT-RNR1* gene (OMIM 561000). There are several hypotheses regarding the pathogenetic mechanism of m.1555A>G in the *MT-RNR1* gene. In general, researchers believe that the m.1555A>G variant of the *MT-RNR1* gene is one of the “mild” ones compared to other pathogenic variants in mitochondrial DNA, since it does not lead to systemic disorders and does not always lead to hearing loss, and the manifestation of the pathogenic effect of

this mutation requires the participation of modulating factors [12, 22, 24]. Some of these modulators are probably aminoglycoside antibiotics, the principle of action of which is based on their ability to bind to the A-site of the 16S subunit of the bacterial ribosome and thus selectively disrupt the synthesis of prokaryotic proteins without affecting the ribosomes of eukaryotes, due to structural differences [12, 25]. The A>G substitution at position 1555 of human 12S rRNA results in a new C-G pairing, resulting in similarity with the A-site of bacterial 16S rRNA, which is a target for aminoglycoside antibiotics [13]. However, another hypothesis suggests that the m.1555A>G variant of the *MT-RNR1* gene can exhibit a pathogenic effect without the influence of external modulators [10, 12, 13, 16, 23, 25, 30]. Since the substitution of adenine for guanine at position 1555 of the *MT-RNR1* gene results in a change in the conserved A-site (aminoacyl-tRNA acceptor site) of 12S rRNA, this may lead to reading errors during the synthesis of oxidative phosphorylation proteins [23]. In a previous study, we found a high prevalence of the m.1555A>G variant of the *MT-RNR1* gene among patients with hearing impairments living in the Lake Baikal region [15]. With an average worldwide prevalence of the m.1555A>G variant of 1.8% (863/47328), the overall contribution among patients with hearing impairments in the Republic of Buryatia was 12.7% (21/165), and among Buryat patients 20.2% (15/74) [15]. The obtained results indicate that Eastern Siberia is the second largest region of accumulation of the mitochondrial form of hearing loss in the world, after the southern European territory of the Iberian Peninsula, where the overall contribution of this form of hearing loss varies from 17% to 41% [6, 34]. Analysis of the complete mitochondrial genome in 14 unrelated Buryat families carrying the m.1555A>G variant revealed a mitochondrial lineage common to the vast majority of examined individuals, associated with subhaplogroup A5b (92.9%). Considering that more than 90% of Buryat families with the m.1555A>G variant belonged to the same maternal line, it was suggested that the high prevalence of this pathogenic variant in the Lake Baikal region is due to the founder effect [Borisova et al., 2024]. In this regard, in the present work, a genotype-phenotypic analysis of the state of auditory function in patients with the m.1555A>G variant in the *MT-RNR1* gene was carried out in the discovered Siberian focus of accumulation of this mitochondrial disease.

Materials and methods. Study sample. In the Republic of Buryatia, 48 people with the pathogenic variant m.1555A>G of the *MT-RNR1* gene were studied, the average age at the time of the study was 51.3±15.5 years. By nationality, the study sample consisted of: Buryats - 97.9% (47/48), Russians - 2.1% (1/48).

Clinical and audiological analysis. Audiological examination of the hearing state was carried out using pure tone threshold audiometry using an "AA222" audiometer (Interacoustics, Denmark). The degree of hearing loss was assessed by the hearing thresholds of the better hearing ear in the speech frequency range of 0.5, 1.0, 2.0, 4.0 kHz according to the international classification, according to which the first degree of hearing loss corresponds to 26-40 dB, the second degree - 41-55 dB, the third degree - 56-70 dB, the fourth degree - 71-90 dB, deafness >90 dB. For a detailed audiological analysis, we used the clinically important speech frequency range ($PTA_{0.5,1,0.2,0,4.0kHz}$). Audiograms with breaks were normalized by introducing the maximum values (120.0 dB) at frequencies to which the patient did not respond. Sensorineural hearing loss was diagnosed in cases of increased bone and air conduction thresholds on audiograms, mixed - with an increase in bone and air conduction thresholds with an interval exceeding 20.0 dB in total in the $PTA_{0.5,1,0.2,0,4.0kHz.}$ Hearing loss was considered asymmetric if the interaural difference in hearing thresholds at the PTA frequencies of 0.5, 1, 0.2, 0.4.0 kHz was more than 15.0 dB.

Detection of the m.1555A>G variant in the *MT-RNR1* gene. Genomic DNA was extracted from venous blood using the phenol-chloroform method. Detection of the m.1555A>G variant in the *MT-RNR1* gene was performed by PCR-RFLP analysis using the previously described sequence of oligonucleotide primers, with a modified reverse primer, which allows the creation of an artificial recognition site for the restriction endonuclease *Hae*III [10]. As a result, after 12-hour treatment of the amplification product at 37°C with the *Hae*III enzyme: normally (1555A) two restriction fragments are formed (216 and 123 bp), with the substitution (1555G) three restriction fragments (216, 93 and 30 bp). Verification of the presence of m.1555A>G in the *MT-RNR1* gene was carried out by Sanger sequencing using the original sequence of oligonucleotide primers: F - AAACGCTTAGCCTAGCCACA, R - GCTACACTCTGGTTCGTCCA, selected using the Primer-BLAST program [29].

Ethical approval. The studies provided for in this work were carried out after informed written consent of the participants. The research work was approved by the local committee on biomedical ethics at the Yakut Scientific Center of Complex Medical Problems in 2019 (Yakutsk, protocol No. 7 dated August 27, 2019).

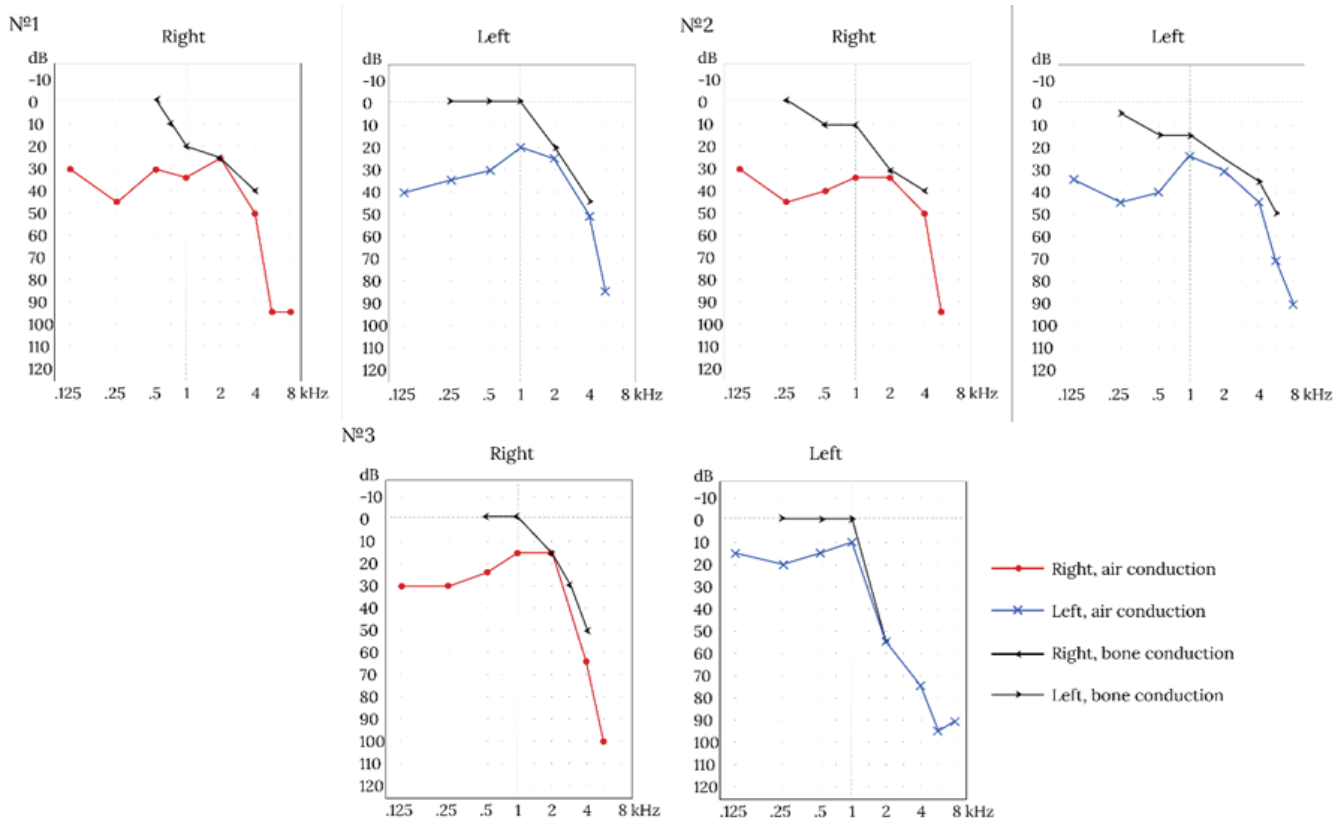
Results and discussion. In this work, a clinical and audiological analysis of the hearing function was performed in 48 individuals with the mitochondrial variant m.1555A>G in the *MT-RNR1* gene (mean age 51.3 years) living in the Republic of Buryatia. As a result, audiological profiles of the state of the hearing function were obtained for all study participants. The characteristics of individuals with m.1555A>G in the *MT-RNR1* gene are presented in Table.

In 27.1% of individuals with the m.1555A>G variant of the *MT-RNR1* gene, hearing in the $PTA_{0.5,1,0.2,0,4.0kHz}$ frequency range was within normal values. In 64.6% of the examined subjects, the type of hearing loss was sensorineural, of varying severity from I–II degree of hearing loss to profound (Table). In 8.4% of patients with the m.1555A>G variant of the *MT-RNR1* gene, a mixed form of hearing loss was detected, including both sensorineural (inner ear pathology) and conductive components (middle ear pathology) (Table). One patient with a mixed type of hearing loss was found to have

The auditory function in individuals with m.1555A>G in the *MT-RNR1* gene

Type and degree of the hearing loss	n	%
Normal hearing	13	27.1
Sensorineural hearing loss (n=31. 64.6%)		
- I-II degree	2	4.1
- III-IV degree	9	18.7
- Profound	20	41.6
Mixed hearing loss (n=4. 48.4%)		
- I-II degree	4	8.4
Total	48	100

Note: n - is the number of individuals with m. 1555A>G in the *MT-RNR1* gene.



Audiograms of patients with mixed hearing loss with the mitochondrial variant m.1555A>G in the *MT-RNR1* gene

a perforation of the eardrum, indicating inflammatory processes caused by otitis media. In three of the four patients, signs associated with developmental abnormalities or otitis media were not detected. The age at the time of the examination of these three patients was 54, 68 and 69 years, respectively. All three patients - one man and two women - came from unrelated Buryat families and lived in the same region of the Republic of Buryatia. It should be noted that before the examination, these patients did not complain about their hearing, but according to the clinical and audiological examination, hearing loss in the speech frequency range ($PTA_{0.5,1,0.2,0,4.0kHz}$) corresponded to the first degree of mixed hearing loss. Audiograms of patients with a mixed form of hearing loss with the m.1555A> G variant in the *MT-RNR1* gene are shown in Figure.

The genotype-phenotypic data obtained by us are consistent with previously conducted studies of the characteristics of the hearing function in patients with the m.1555A>G variant in the *MT-RNR1* gene, which note incomplete penetrance of the manifestation of the pathological phenotype in affected families [10, 12, 13, 16, 23, 25, 30, 32]. In other words, not all carriers of m.1555A>G may have clinically significant hearing loss. It is believed that the age of onset, as well as the degree of hearing loss in individuals with m.1555A>G in the *MT-RNR1* gene, can vary widely - from normal hearing to deafness. The manifestation of signs of hearing loss in carriers of the m.1555A>G variant in some families positively correlated with treatment with aminoglycoside antibiotics [10, 12, 13, 16, 23, 25, 30], as well as with the age of patients [42]. However, not all registered cases of mitochondrial hearing loss can be explained by the ototoxic effect of drugs and progression with age. In this regard, many researchers believe that there are other factors, including genetic ones (mitochondrial environment and/or variants in the nuclear genome), modulating the pathological "manifestation" of the m.1555A>G variant [7, 10, 12, 13, 14, 18, 23, 25, 27, 32]. Since we did not find any references in the literature about conductive or mixed type of hearing loss in patients with m.1555A>G in the *MT-RNR1* gene, and the pathogenetic mechanism of mitochondrial hearing loss is associated with damage to cochlear cells, the type of hearing loss should be exclusively sensorineural. In this regard, three cases of mixed type of hearing loss in patients with m.1555A>G in the *MT-RNR1* gene are of particular interest in our cohort of examined individuals. We do not exclude the possibility that the detected clinical signs may be a consequence of previously undescribed systemic damage to the hearing organ in the mitochondrial variant m.1555A>G. Since, despite the fact that the m.1555A>G variant of the *MT-RNR1* gene is generally considered to be a non-syndromic sensorineural type of hearing loss, there is an alternative opinion that this pathogenic variant is capable of having not only local, but even multi-organ damage potential, which requires a broader clinical study of this form of the disease, since multi-system manifestations can be barely noticeable or even subclinical (short stature, osteoporosis, arterial hypertension and recurrent headache) [11].

On the other hand, our three cases of mixed hearing loss in patients with m.1555A>G in the *MT-RNR1* gene in the Republic of Buryatia may be associated with a cross-over pathological effect caused by another form of a less common or rare disease. Due to the absence of other clinical manifestations in the patients examined by us, as well as their age (54, 68, and 69 years) and gender (one man and two women), it is unlikely that the identified cases are associated with a cross-over effect of an

X-linked recessive form of hearing loss (DFNX2, OMIM 304400). In addition, we cannot completely exclude the version of an atypical manifestation (incomplete penetrance of clinical signs) of one of the rare syndromes in which a mixed type of hearing loss can be observed: branchio-oto-renal syndrome (OMIM 113650), Stickler syndrome (OMIM 108300), Marfan syndrome (OMIM 154700), Treacher Collins syndrome (OMIM 154500), Axenfeld-Rieger syndrome (OMIM 602482) and many others. However, in our opinion, the most likely cause may be an idiopathic non-infectious focus of the pathological process in the middle ear, caused by otosclerosis. The otosclerotic process is based on focal lesions of the bony capsule of the otic labyrinth, with healthy bone being replaced by newly formed porous, spongy, vascular-rich bone tissue during growth, which is why the early stages of otosclerosis are sometimes called otospongiosis. The prevalence of otosclerosis worldwide varies from 1 in 330 in Europe, 1 in 3,300 in Africa, to 1 in 33,000 in Asia [35]. Patients typically have conductive hearing loss, primarily affecting low and mid frequencies, which often progresses to mixed hearing loss. The disease typically manifests in the second, third, or fourth decade and is generally successfully corrected with a combination of surgery and hearing aids [28]. Although both environmental and genetic risk factors have now been identified, the etiology of sporadic cases of otosclerosis remains unknown [5]. An exception are rare familial forms of otosclerosis, segregating according to the autosomal dominant type of inheritance, for some of which genetic loci linked to this disease have been mapped [1, 2, 4, 8, 17, 19, 36, 37]. Despite some success in mapping loci linked to otosclerosis, pathogenic variants in any genes have not been identified to date. However, in 2022, a 15-nucleotide heterozygous deletion in the coding region of the *FOXL1* gene was identified in families with otosclerosis from the Canadian province of Newfoundland and Labrador [3], the product of which is presumably involved in bone remodeling processes in the auditory capsule [26], which was described as casuative for the autosomal dominant form of otosclerosis type 11 (OMIM 620576) [3].

Conclusions. Taking into account the atypical for the mitochondrial form of hearing loss - a mixed type of hearing loss in three Buryat patients with m.1555A>G in the *MT-RNR1* gene, which was not associated with otitis media, the detected clinical signs may be a consequence of a previously undescribed systemic lesion in this mitochondrial variant. On the other hand, the detected clinical signs may be caused by a cross-pathological effect due to another unspecified form of the disease. In our opinion, the most likely cause of the atypical picture of hearing loss in patients with m.1555A>G may be a cross-pathological effect caused by otosclerosis or another rare disease in which a mixed type of hearing loss can be observed (branchio-oto-renal syndrome, Stickler syndrome, Marfan syndrome, Treacher Collins syndrome, Axenfeld-Rieger syndrome and many other syndromes). Given the wide range of nosological forms associated with mixed type of hearing loss, the obtained results require further molecular genetic studies using high-throughput sequencing methods.

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

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DIAGNOSTIC AND TREATMENT METHODS

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SACRUM WITH FIVE PAIRS OF SACRAL OPENINGS, AS A PATHOGNOMONIC SYMPTOM OF LUMBOSACRAL TRANSITIONAL VERTEBRAE

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Introduction. Clinical experience shows that during radiological examination of the pelvis, patients are often diagnosed with a sacrum with five pairs of sacral openings, while normally there should be four. Purpose: To which form of dysplasia should cases of diagnosis of the sacrum with five pairs of sacral openings be attributed. Material and methods. The clinical material for the study was the results of computed tomography of the lower lumbar spine and pelvic bones in 78 patients who were diagnosed with a sacrum with five pairs of sacral openings. The CT examination of the patients was carried out on a 128-slice «General Electric» device. Results. The study established that the analyzed group of 78 patients was heterogeneous and consisted of two subgroups. Patients of the first subgroup (52 (66.7%) patients) had fused upper sacral vertebrae by transverse processes to the left and right of the sacral crest. Patients of the second subgroup (26 (33.3%) patients) had similar bone fusion of two upper sacral vertebrae on one side, there was no such concrescence on the contralateral side, and synchondrosis was clearly defined. Discussion. The sacrum with five pairs of sacral openings should be attributed to such a congenital pathology of the lumbosacral junction as lumbosacral vertebrae. It is known that this disease is divided, according to the classification of A.E. Castellvi et al. (1984), into 7 different types. Those clinical observations that were diagnosed in patients of the studied cohort should be attributed to types IIIb (first subgroup, 52 patients) and IV (second subgroup, 26 patients) of the disease. In the clinical picture of each of the types of pathology, vertebrogenic pain syndrome of lumbosacral localization prevails. Conclusion. The presence of such a bright radial symptom of sacral pathology as five pairs of sacral openings allows for timely diagnosis of cases of transitional lumbosacral vertebrae, informing patients about the nature of the disease, and, if necessary, prescribing therapy adequate to the severity of the condition.

Keywords: sacrum, cranial sacral vertebrae, sacral openings, lumbosacral transitional vertebrae.

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Introduction. In clinical practice, there are often situations when, during a radiological examination of the pelvis, patients are diagnosed with a sacrum with five pairs of sacral openings [9]. In these cases, the question arises: is this radiological picture normal or is it a variant of pathology [11]. There is no direct answer to this question in modern literary sources [3].

Purpose: To establish which form of dysplasia should be attributed to cases of diagnosis of a sacrum with five pairs of sacral openings.

Material and methods. The clinical material for the study was the results of computed tomography (CT) of 252 patients aged 12 to 86 years with injuries and diseases of the lower lumbar spine and pelvis, in whom images of the sacrum were "obtained" during the radiological diagnostics. In total, out of 252 patients

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studied, 78 (30.9±5.2%) people were found to have a sacrum with five pairs of sacral openings. Of the 78 patients in this cohort, 35 were girls and women (44.9±8.4%), and 43 (55.1±7.6%) were boys and men.

The patients underwent CT examination on a 128-slice General Electric machine. When analyzing CT images, the sacrum was specifically studied, including determining the number of sacral vertebrae and the number of sacral openings.

Statistical processing of the clinical material consisted of determining the relative value of the indicator in percent (P) and the representativeness error of the obtained relative value (±m).

The study was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education «Tyumen State Medical University» of the Ministry of Health of the Russian Federation (protocol No. 125/06.1. dated 03/20/2025).

Results. The study cohort of patients with five pairs of sacral foramina consisted of 78 individuals. The radiographic picture of the sacrum was generally typical in all clinical observations, regardless of the age of the patient under study (Fig. 1).

The differences in the radiographic picture of the patients under study concerned only the degree of expression of degenerative-dystrophic changes in the lower lumbar vertebral-motor segments and in the sacroiliac joints. The older the patients, the more pronounced the changes were, and this is a natural involutional process [4].

When analyzing the results of computed tomography of patients in the study cohort, not only the result of the sacrum reconstruction (3D images) but also its scans (sections) were assessed (Fig. 2).

The presented tomograms clearly show that the cranial sacral vertebra has a complete bone fusion with the underlying vertebra on both the left and right sides. Such a radiation picture, with complete bilateral bone fusion, among 78 patients was diagnosed in 52 (66.7±6.5%) clinical observations. In the remaining 26 (33.3±9.2%) patients, the radiation picture from the sacrum side was different, while they also had a sacrum with 5 pairs of openings (Fig. 3).

In Fig. 3 it is evident that the shape of the sacrum differs from those shown in Fig. 1 and 2. Thus, if on the right side the upper sacral vertebra has a full bone fusion with the caudally located vertebra, forming the wing of the sacrum, then on the left side, at the same level, instead of bone fusion, a synchondrosis is clearly visible. In the remaining patients of this subgroup, the radiographic picture on the sacrum sections was similar. Thus, the group of 78 patients with five pairs of sacral openings was represented by two subgroups of patients: one - with a full bilateral bone fusion between two cranial sacral vertebrae (52 (66.7±6.5%) people) and the second - with unilateral bone fusion, combined with contralateral synchondrosis in the cranial parts of the sacrum (26 (33.3±9.2%) people).

Discussion. Five sacral vertebrae, finally merging with each other by the age of 22-24 years in modern humans, form the sacrum, which has four pairs of sacral openings, which is the norm [13]. In cases where patients are diagnosed with a sacrum with five pairs of openings by means of radiographic imaging, these situations should be regarded as a variant of dysplasia, different from the well-known ones, such as agenesis, caudal regression, dysraphism, dysmorphism, posterior wall defect, spina bifida posterior and some others.

Establishing the specific nature of pathological changes in the sacrum is possible only with the use of modern methods of radiographic imaging - magnetic resonance imaging and CT [8]. In the clinical cases discussed (Fig. 1, Fig. 2, Fig. 3, Fig. 4), it was the CT results that made it possible to establish the presence of bone fusion and synchondrosis between two cranial sacral vertebrae in the presence of five pairs of sacral openings.

It was the CT results that allowed us to classify the revealed radiation symptoms of dysplasia in all 78 patients of the study cohort as a pathology such as transitional lumbosacral vertebrae [12]. Transitional vertebrae are differentiated according to the classification of A.E. Castellvi et al. [6]. According to the criteria of this classification, four types of transitional vertebrae are distinguished (I, II, III, IV), with the first three types being divided into subtypes "a" and "b". Thus, in general, the structure of transitional vertebrae includes 7 forms of the disease: Ia, Ib, IIa, IIb, IIIa, IIIb, IV. Those clinical observations that were diagnosed in patients of the study cohort, according to the Castellvi classification, should be classified as types IIIb and IV of the disease. It is with these two forms of transitional lum-

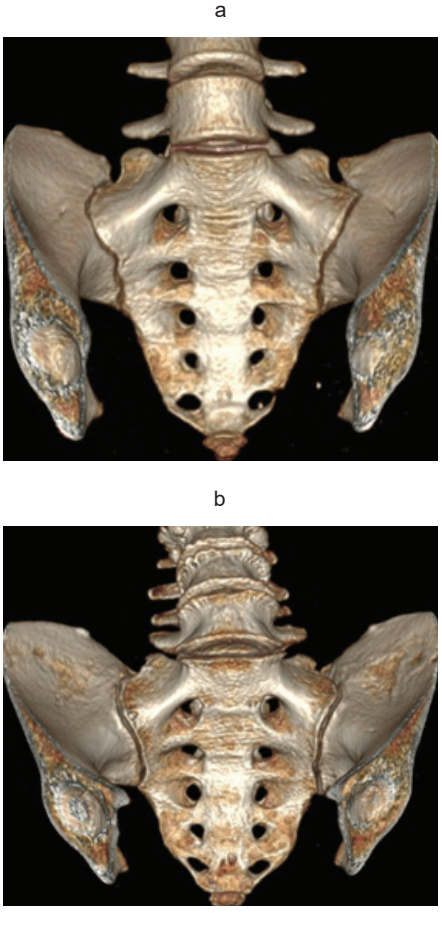


Fig. 1. Computer tomograms of the sacrum of patients 16 years old (a) and 60 years old (b). Five pairs of sacral openings

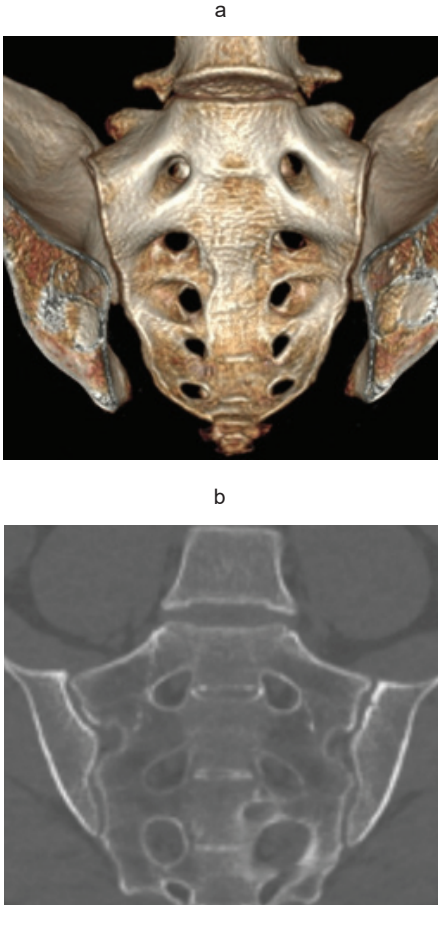
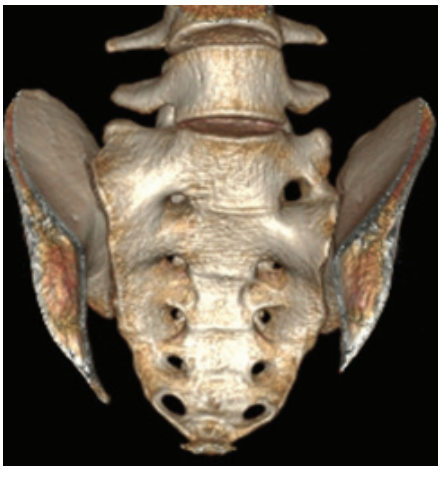


Fig. 2. Computer tomograms of the sacrum of a 32-year-old patient. Volumetric (a) and layered (b) images

a



b

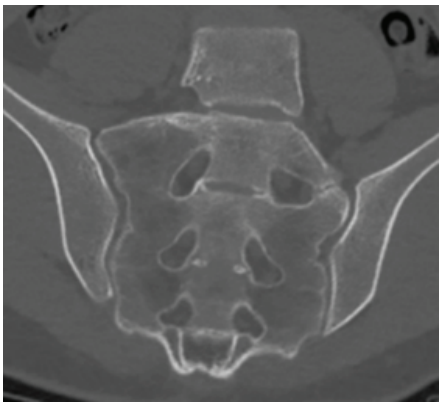


Fig. 3. CT scans of the sacrum of a 29-year-old patient. Right-sided bone block (a), left-sided synchondrosis (b) between two cranial vertebrae

bosacral vertebrae that the sacrum in the patients under study has five pairs of sacral openings [6].

It is known that the average frequency of diagnosis of transitional vertebrae in the modern population is 17% of clinical observations [5]. In the structure of transitional vertebrae, the share of IIIb and IV types of the disease accounts for 4.8±0.3% and 6.7±0.4% of cases. The first rank places in the structure of transitional vertebrae are occupied by IIa and IIb types - 26.9±0.6% and 25.9±0.6% of clinical observations. These indicators were obtained during the analysis of 17 scientific articles by various groups of authors from Europe, Asia and America [3].

The problem of transitional lumbosacral vertebrae is relevant due to the fact that this pathology is one of the most common causes of vertebrogenic pain syndrome of lumbosacral localization [9]. With this anomaly, over time, patients develop extraforaminal stenosis, which is a high-risk factor for impingement of the L5, S1 roots [7]. In addition, according to A. García López et al., transitional vertebrae impart abnormal rigidity (the article uses the expression "abnormal rigidity") to the lumbosacral junction, which negatively affects the shock-absorbing function of the spine as a whole [10]. In cases where the radiographic picture of the transitional vertebrae is accompanied by clinical symptoms, primarily pain syndrome, patients may be diagnosed with “Bertolotti syndrome” [2], and the algic syndrome is assessed as neuropathic, caused by compression of the nerve roots [1].

That is why early diagnostics of transitional lumbosacral vertebrae is an extremely important task, which can lead to an increase in the quality of life of such patients with this disease. The presence of such a bright radial symptom of sacral pathology as five pairs of sacral openings will allow timely diagnosis of the disease, inform patients about its essence, and, if necessary, prescribe adequate therapy.

Conclusions. 1. In a group of 252 patients, 78 (30.9%) were diagnosed with a sacrum with five pairs of sacral openings, which should be regarded as a symptom of transitional lumbosacral vertebrae;

2. Among 78 patients with five pairs of sacral openings, 52 (66.7%) had complete bone fusion of two cranial vertebrae, which should be classified as type IIIb of the disease. In 26 (33.3%) patients, bone fusion of the cranial vertebrae on one side and synchondrosis at the same level on the contralateral side were detected, which corresponds to type IV of pathology according to the classification of A.E. Castellvi et al. (1984);

3. The main clinical symptom of transitional lumbosacral vertebrae is vertebrogenic pain syndrome, caused primarily by impingement of the L5, S1 roots and a decrease in the shock-absorbing function of the spine.

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

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N.A. Shevkunova, E.A.Bulycheva, I.E. Kolushova, I.S. Naidanova

ANALYSIS OF THE RESULTS OF DENTAL IMPLANTATION AGAINST THE BACKGROUND OF SOMATIC PATHOLOGY (USING THE EXAMPLE OF DIABETES MELLITUS)

long-term treatment results. The follow-up groups consisted of patients with DM (n=13), with HD (n=11), with GIT (n=12) and persons who have retained their health (n=24).

Results: the number of missing teeth in patients with somatic pathology was 1.7 times higher than in the control group. The production of single crowns on dental implants was carried out with the same frequency in patients with DM and HD, exceeding the rates of individuals with GIT, but significantly less often than in the control group. A similar pattern was observed in the orthopedic treatment with dental implant bridging prostheses, which were used 3 times less frequently in DM patients than in HD individuals, 2 times less frequently than in GIT patients, and 1.8 times less frequently in controls ($p<0.01$). Bone grafting was performed in patients with DM in 46.2% of cases, with HD – 36.4%, with GIT – 33.3%, compared to 41.7% in the group of individuals without somatic pathology ($p<0.01$). Complications were observed in half of the DM patients 46.2%, which is 2.3 times higher than the comparator group 20.0%.

Conclusion: performing bone grafting on patients young and middle-aged with aggravated somatic status were accompanied by early complications, late – occurred only in patients with DM (15.4%) and HD (9.1%). The period of osseointegration in patients with somatic pathology increases to 5-6 months compared to the indicators of the control group – 4.3± 0.3 months ($p<0.001$). All subjects had a favorable outcome of dental implantation at long-term follow-up.

Keywords: diabetes mellitus, hypertension, gastrointestinal diseases, dental implantation.

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Introduction. The current stage of development of dental implantology allows for full-fledged dental rehabilitation even in difficult clinical situations. In some general somatic pathologies, it is not always possible to achieve a successful result of implantological treatment [1].

Numerous studies have substantiated the safety of dental implantation in patients with diabetes mellitus (DM). The main points of preparation for it are monitoring blood sugar levels, interacting with the attending physician – endocrinologist and maintaining a high level of oral hygiene [2,15]. It is believed that with good compensation for diabetes, dental status is not much different from the status of patients who have maintained health, and the cause of damage to the oral mucosa and jaw bone tissue is not DM, but its complications from the kidneys and cardiovascular system [3,4].

However, most foreign and domestic researchers believe that DM contributes to the development of bone tissue pathology of the alveolar bone with more deep destructive processes, especially in the decompensated form of DM [10,12].

In patients with poorly controlled glycemia, the results of implantation are affected by a decrease in the regenerative abilities of jaw bone tissue, pronounced inflammatory processes, and a decrease in the effectiveness of wound healing [8,16]. Often, implantation is not even considered in the treatment of diabetic patients due to increased risks of rejection, with the subsequent development of peri-implants [5,17], the possibility of developing which increases with an increase in glycosylated hemoglobin values of 7% or more [9]. Some authors considered DM an absolute contraindication to implantation 7-8 years ago [10,13].

Difficulties when working with diabetics arise due to manifestations of osteopenic syndrome, as a consequence of developed metabolic disorders [11]. If the osseointegration process – survival rate of a dental implant is disrupted, researchers recommend conical implants to patients with DM as more stable [6], simultaneous implantation to reduce rehabilitation time and prevent tissue loss [2,7].

In recent years, the dental implant method has led many scientists to apply this treatment in patients with DM. Wagner J., Spille JH, Wiltfang J., Naujokat H. (2022), when implanted against the background of DM2, received positive results in 92.7% of cases [15]. The use of modern orthopedic treatment methods has an impact on quality of life and dietary adherence, which is necessary for patients with diabetes to compensate for the disease [8].

Purpose: evaluate the effectiveness of dental implantation in patients with somatic pathology.

Material and research methods. A population prospective study was conducted in private dental clinics in Izhevsk

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from 2023-2025. Using the random sampling method, 25 women and 35 men aged 28 to 61 years were examined from patients who sought dental implantation. Depending on the presence of chronic disease, groups were formed. The first of 13 patients with a verified diagnosis of type 1 and type 2 diabetes mellitus, a glycemic level of 7 to 15 mmol/l (mean 8.7±0.6 mmol/l) aged 39.9±3.5 years. The second of 11 hypertensive patients (HD) whose mean age was – 47.5± 2.0 years. The third consisted of 12 patients with gastrointestinal pathology (GIT) aged 42.8±3.5 years. Control group formed from 24 patients who remained healthy, middle-aged – 36.8± 2.0 years. The gender composition in the formed groups was balanced.

All respondents underwent a traditional clinical examination, assessment of bone density according to the classification of Lekholm and Zarb (1985), and two-stage intraosseous implantation. The degree of osseointegration was monitored by X-ray examination methods at each stage of treatment. Bone grafting was performed according to the indications. When measuring the tork, as an indicator of implant retention, 20 to 45 N/cm was considered the norm. All participants received informed voluntary consent to conduct the study. Dynamic follow-up was performed for 6 months with regular monthly check-ups.

Statistical analysis of the obtained data was carried out using a software package «IBM SPSS Statistics 23». The nature of the distribution was checked using the Kolmogorov-Smirnov and Shapiro-Wilk criteria. Analysis of quantitative indicators according to Student-Bonferroni. The statistical significance of relative indicators was assessed using criterion χ2. Correlation analysis by Pearson's method. Differences were assumed to be statistically significant at p<0.05.

Results and discussion. When analyzing the age of patients in private clinics who sought prosthetics using dental implants, it was revealed that the majority of them were young people 58.3% (32.9±1.2 years) and middle-aged patients 40.0% (51.1± 0.9 years). It was found that in 60.0% of cases, patients with aggravated somatic status – every 4-6 patients came, most often these were patients with HD and gastrointestinal pathology, less often they came with DM. Only every 2-3 patients had no chronic diseases (χ2=12.296, p<0.01).

Quantitative analysis in observation groups showed that the average number of missing teeth in patients with chronic diseases exceeded 1.7 times the indicators of persons who retained health – 3.2± 1.3 (p<0.001). A high positive correlation was found between age and number of missing teeth (r=0.594, p<0.01). When determining the severity of bone tissue atrophy, the indicators of patients with somatic pathology exceeded 1.5 times the indicators of the control group – 3.0 mm (p<0.001).

In determining bone density in DM patients, the most frequent type of bone was D3, when a thin layer of cortical plate surrounds the less dense cancellous bone. D4 bone tissue type (thin layer of cortical plate surrounding low density cancellous bone) was determined in 25.0% of DM patients, which was 2.8 times higher than the control group (Table 1). D2 thick layer bone tissue type the cortical plate surrounding the dense cancellous bone was 3.3 times less common than in the comparison group. D1 type, when almost all jaw bone consists of cortical bone in DM patients was not diagnosed, occurring in 27.3% in the control group.

The majority of patients with HD – 66.7% had D3 bone tissue type, exceeding 7 times the indicators of the group with equal. The remaining patients with HD were diagnosed with – D2 bone tissue type, in the absence of patients with D1 and D4 bone tissue type. Patients with GIT were most often diagnosed with bone tissue type D2 – 88.9%, 8 times less often the first type in the absence of patients with D3 and D4. Thus, considering that with high bone density the necessary implant stability is more easily achieved, patients with HD and GIT were more prosperous than with DM.

Bone grafting, aimed at strengthening the volume of bone tissue when the own volume is insufficient to fix the implant, was most often used in the treat-

Table 1

Indicators of bone density in patients with somatic pathology

№P/p	Surveillance teams	Bone density (number of patients in %)				p
		First type	Second type	Third type	Fourth type	
1	DM (n=13)	-	16.7	58.3	25	P_{1-4}<0.01
2	HD (n=11)	-	33.3	66.7	-	P_{2-4}<0.01
3	GIT (n=12)	11.1	88.9	-	-	P_{3-4}<0.01
4	Control (n=24)	27.3	54.5	9.1	9.1	

Table 2

Frequency of use of materials for bone grafting in patients with somatic pathology

№p/p	Surveillance teams	Autobone shavings	Xenoplastic material	Total
1	DM (n=13)	2 (15.4)	4 (30.8)	6 (46.2)
2	HD (n=11)	–	4 (36.4)	4 (36.4)
3	GIT (n=12)	2 (16.6)	2 (16.7)	4 (33.3)
4	Control (n=24)	6 (25.0)	4 (16.7)	10 (41.7)

Note: Statistical significance of differences P_{1-4}<0.01; P_{2-4}<0.01; P_{3-4}<0.05.

Table 3

Показатели частоты использования костной пластики на верхней и нижней челюсти у пациентов с соматической патологией

№p/p	Surveillance teams	Maxilla	Lower jaw
1	SD (n=13)	4 (30.8)	2 (15.4)
2	GB (n=11)	3 (27.3)	1 (9.1)
3	GIT (n=12)	3 (25.0)	1 (8.3)
4	Control (n=24)	6 (25.0)	4 (16.7)

Note: Statistical significance of differences P1-4<0.01; P2-4<0.05; P3-4<0.05.

ment of patients with DM (46.2%), using xenoplastic material, 2 times more often than autobone shavings (Table 2.). When treating HD patients in 36.4% of cases, using xenoplastic material alone. In GIT, a third of patients underwent bone grafting using autobone shavings, without the use of xenoplastic material. Patients without somatic pathology 41.7% were 3 times more likely to use xenoplastic material than autobone shavings.

Bone grafting in the upper jaw was performed in patients with somatic pathology (83.1%) 2.5 times more often than in the control group (Table 3.). Mainly with DM than somatic patients of other groups.

In the comparative analysis, it was found that bone grafting in the lower jaw was used in patients with somatic pathology (32.8%) 2 times more often than in patients who remained healthy. In patients with diabetes, it was performed 1.6 times more often than in patients with HD and 1.9 times more often than with GIT.

With the optimal choice of implant length, the lowest values of 10.5±0.9 mm were recorded in patients with DM, the highest 11.9±0.6 in individuals with HD, did not differ significantly in the group of patients with GIT and in the control of 10.8±0.5 mm and 10.7±0.2 mm, respectively ($p<0.001$).

Early postoperative complications (swelling and hyperemia of soft tissues) were observed with approximately the same frequency in the groups of subjects with somatic pathology: in 30.8% with DM, in 45.5% with HD, in 33.3% with gastrointestinal diseases and in 50.0% in the group without concomitant somatic pathology ($\chi2=21.976$; $p<0.01$). Relative to late complications (long-term healing of the postoperative wound due to impaired regeneration processes), they were observed most often in patients with DM – 15.4% and in HD – 9.1%. In the absence of patients with GIT and in the control group ($\chi2=12.687$; $p<0.01$). Treatment of complications was carried out according to standard postoperative antibiotic therapy regimens.

The time frame for achieving secondary stability – fusion of the implant with bone was 5.8±0.5 months in patients with diabetes, with HD – 4.7±0.4 months, with gastrointestinal pathology – 5.2±0.5 months, in the control group 4,3±0.3 months ($p<0.001$), which fell within the regulatory limits from 3 to 6 months [14]. A high positive association was defined between secondary stability and load ($r=0.616$) significant at 0.01. In patients with DM, the insertion torque scores were 25.7±2.2 N/cm and did not differ from the controls –25.7±1.2 N/cm ($p<0.01$). Minor differences observed from indicators of patients with HD – 25.0± 2.6 N/cm ($p<0.05$). Patients with GIT presented the lowest values of tork – 24.4± 3.3 N/cm. The indicators of all observation groups were within normal limits.

According to Pearson's correlation analysis, the relationship between installation torque and osseointegration time was $r=0.858$ and was characterized as very high, positive with a significance of 0.01. The correlation of torque and load was $r=0.497$, as the mean positive relationship, significant at 0.01. Immediate loading with the placement of a temporary crown on the implant was carried out immediately after its insertion into the bone in 7.7% of DM, 33.3% of RVCT and 37.5% of the control group. Patients with HD were not given such a load. For the rest of those examined, the load was delayed, after 6.2-6.5 months.

In the orthopedic treatment, 29 single crowns were made on dental implants to 12 patients with DM, 25 crowns to 9 patients with RVCT, 30 crowns to 9 patients with HD and 42 crowns to 24 patients in the control group ($p<0.001$).

Bridge prostheses were fabricated significantly less frequently for patients with diabetes mellitus (DM) (7.7%) compared to those with hypertension (HD) (27.2%) and gastrointestinal (GI) tract disorders (8.3%), but more often than for somatically healthy individuals (4.2%; $\chi^2 = 11.438$, $p<0.01$). One implant-supported removable prosthesis was placed on the upper jaw of a DM patient and two 4 implant-supported removable prostheses on the upper and lower jaws of one control patient ($\chi2=11.528$; $p<0.01$). No complications were observed with dynamic follow-up for 6 months, and a positive treatment outcome was recorded in all respondents.

Conclusion. When going to private dental clinics for dental implantation, every 4–6 young and middle-aged patients with somatic pathology, for whom single crowns were most often made. It is important to note that the rate of bone grafting among patients with diabetes mellitus (46.2%) was higher than in those with hypertension (36.4%), gastrointestinal disorders (33.3%), and the control group (41.7%). Early postoperative complications were observed in all respondents, late only in patients with DM and HD. The period of osseointegration in patients with somatic pathology increased to 5-6 months. All subjects had a favorable outcome of dental implantation at long-term follow-up.

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

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ACUTE THROMBOSIS OF HEMORRHOIDS: CONSERVATIVE VERSUS SURGICAL TREATMENT

Purpose of the study: to conduct a comparative analysis of the effectiveness of conservative and surgical treatment of acute thrombosis of hemorrhoids. Material and methods: a single-center prospective analysis of the treatment results of 203 patients with acute hemorrhoidal thrombosis was performed: 125 (61.6%) patients who received conservative treatment and 78 (38.4%) operated patients. The conservative treatment program contained recommendations on nutrition, formation of a bowel movement regime, use of thermal baths, and taking systemic and topical medications. Patients of the second group underwent surgical intervention in the amount of thrombectomy or excision of a thrombosed hemorrhoid node under local infiltration anesthesia. Results of the study: patients who received conservative therapy and patients who underwent surgery were comparable in gender, age, and stage of acute hemorrhoidal thrombosis. Statistically significant differences were found between the patients of the two groups in pain assessment on the 1st and 7th days of treatment (p=0.043 and p=0.037, respectively) and the duration of temporary disability (p=0.032). Conclusion: surgical intervention in hemorrhoids complicated by acute thrombosis of hemorrhoids is a method of choice with many advantages. The key ones are to reduce pain on the 1st day after treatment to 3 points on the visual-analog scale (VAS), on the 7th day – to 1 point according to VAS. Compared with the group of patients receiving conservative therapy, after surgical treatment of acute hemorrhoidal thrombosis, a lower incidence of disease recurrence was noted. During the study period, a recurrent course was observed in 1 (2.0%) patient after surgery versus 5 (10.2%) cases in the conservative treatment group. Surgical treatment provides faster labor rehabilitation and reduces the period of temporary disability to 6.3 ± 0.3 days.

Keywords: acute hemorrhoidal thrombosis, surgical treatment of acute hemorrhoidal thrombosis, conservative treatment of acute hemorrhoidal thrombosis

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Introduction. Acute thrombosis of hemorrhoids (ATH) is one of the most painful pathologies of "minor" proctology. The main factor contributing to the development of ATH is venous congestion. Microtraumas of the endothelium of venous vessels contribute to the activation of hemostasis and thrombus formation, which leads to tissue edema and necrosis [3,8]. The choice of the optimal treatment method is based on the analysis of the patient's complaints, medical history and the results of the clinical examination [4, 10].

There are two main treatment methods: conservative and surgical. Conservative treatment is recommended for ATH without pronounced symptoms of the disease, the patient's refusal of surgery, as well as in patients with severe concomitant diseases. At the same time, a number of authors claim that conservative treatment is the optimal choice for most patients with ATH [12, 16]. In turn, surgical treatment is recommended in cases of pronounced symptoms of the disease, with ATH with necrosis and with the ineffectiveness of conservative treatment methods. Surgical treatment, in comparison with the conservative method, ensures the fastest recovery and reduces the risk of relapse of the disease. In this regard, in patients with frequent recurrences of ATGU, surgical intervention can be considered as a method of preventing thrombosis [2, 6]. Most researchers emphasize the importance of an individual approach to treatment. The choice between conservative and surgical treatment is based on the severity and course of the disease, taking into account the patient's preferences [15]. A combined tactic is also possible: the use of conservative treatment to relieve the symptoms of ATH in preparation for subsequent surgical intervention [17].

The choice of optimal treatment tactics for patients with ATH is a subject of debate, and studies assessing the advantages and disadvantages of conservative and surgical treatment are still relevant.

The aim of the study: comparative analysis of the effectiveness of conservative and surgical treatment of acute thrombosis of hemorrhoids.

Materials and methods: a retrospective single-centre cohort study was conducted, which included 203 patients treated for ATH at the regional proctology center of the Surgut regional clinical hospital in the period 2020–2024. 125 (61.5%) patients received conservative treatment,

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78 (38.5%) patients underwent surgery. The average age of patients was 41.4 ± 11.9 years. Examination and treatment of patients was carried out in accordance with the clinical recommendations of the Association of Proctologists of Russia [8].

Inclusion criteria: patients over 18 years of age; acute thrombosis of hemorrhoids. Exclusion criteria: patients with concomitant proctological pathology: anal fissure, anal fistula; pregnancy and breastfeeding; individual intolerance to the components of the drugs used; patients with concomitant diseases: liver cirrhosis or after pelvic radiotherapy. This study was approved by the Ethics Committee.

For an objective assessment of the treatment results, a comparative analysis of groups of patients who received conservative and surgical treatment was conducted based on the main anthropometric and clinical features. For a comparative description by age, the World Health Organization (WHO) classification was used [13]. Clinical manifestations were assessed according to the classification of the Association of Proctologists of Russia. By localization: external thrombosis and internal thrombosis. By the degree of spread of the inflammatory process: I degree - thrombosis of external or internal hemorrhoids without an inflammatory process. II degree - thrombosis with inflammation of the hemorrhoids. III degree - thrombosis of hemorrhoids, aggravated by inflammation of the subcutaneous tissue, edema of the perianal area and/or necrosis of the mucosa [8].

The intensity of pain syndrome was assessed at the time of initial medical treatment, 1, 7 and 14 days after the start of treatment. In the comparison groups, the structure, frequency of complications and relapses of the disease were analyzed. Relapse was considered to be the appearance of symptoms (pain and bleeding) or new thrombosis within 3 months after completion of treatment. Also, a comparative analysis of the duration of disability was carried out.

Indications for conservative therapy were refusal of surgical intervention and stage III of ATH. The conservative therapy program included recommendations on nutrition, formation of a defecation regimen, use of heat baths, systemic and topical drugs, the action of which is aimed at improving regional blood flow and reducing inflammation. All patients received conservative treatment with drugs registered and approved for use in the Russian Federation. Therapy was carried out within the framework of indications and in accordance with the approved instructions for medical use. The choice of topical drug depended on the clinical manifestations of ATH: bleeding, pain syndrome, itching, etc.

Indications for surgical intervention were the patient's consent to surgical intervention and the absence of severe concomitant somatic and individual proctological diseases.

Surgical interventions were performed under local infiltration anesthesia in the lithotomy position. Two types of surgical interventions were performed: thrombectomy in 53 (67.9%) and excision of the thrombosed hemorrhoidal node in 25 (32.1%) patients.

The surgical intervention began with the treatment of the surgical field with an antiseptic solution. After local infiltration anesthesia, anoscopy, revision of the anal canal, perianal area and lower third of the rectum were performed. For thrombectomy, an incision no longer than 1.0 cm was made over the thrombosed hemorrhoidal node to evacuate the thrombus. When performing excision of a thrombosed hemorrhoidal node, two converging semi-oval incisions were made, followed by removal of the node. No sutures were applied to the wound. After achieving hemostasis by electrocoagulation, a sling-like bandage with a chlorhexidine solution was applied.

During the perioperative period, patients received painkillers and anti-inflammatory drugs, venotonic drugs, heat baths, topical drugs and drugs that affect effective defecation.

Statistical analysis was performed using the StatTech v. 4.7.0 program (developer – StatTech LLC, Russia). Quantitative indicators were assessed for compliance with the normal distribution using the Kolmogorov-Smirnov criterion. In the absence of normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3). Categorical data were described using absolute values and percentages. Comparison of two groups by a quantitative indicator whose distribution differed from normal was performed using the Mann-Whitney U-test. Comparison of percentages in the analysis of four-field contingency tables was performed using the Pearson chi-square test (for expected event values greater than 10), and the Fisher exact test (for expected event values less than 10). Comparison of percentages in the analysis of multi-field contingency tables was performed using the Pearson chi-square test.

Results and discussion. In the analyzed groups there were 106 (52.2%) men and 97 (47.8%) women. There were 77 (37.9%) young people, 83 (40.9%) middle-aged people and 43 (21.2%) elderly patients. Comparative assessment in the analyzed groups was performed using Pearson's chi-square. The number of young people did not differ statistically (ptotal = 0.393, pmale = 0.451, pfemale = 0.334). Similar values were obtained among patients of middle (ptotal = 0.595, pmale = 0.621, pfemale = 0.569) and elderly age (ptotal = 0.231, pmale = 0.163, pfemale = 0.299) (Table 1).

When assessing the gender and age composition of patients in the conservative therapy and surgical treatment groups, we did not find statistically significant differences; therefore, conducting a comparative analysis of their effectiveness is not appropriate.

In addition, a comparative evaluation was performed of the proportion of males and females and the stage of OTH in the analyzed groups using Pearson's chi-square test and Fisher's exact test. The number of males and females in the conservative and surgical treatment groups with Stage I OTH did not differ statistically (ptotal = 0.176, pmale = 0.118, pfemale =

Table 1

Distribution of patients by gender and age

Age	Conservative therapy (n = 125)		Surgical treatment (n = 78)		P-value*
	Men abs. (%)	Women abs. (%)	Men abs. (%)	Women abs. (%)	
Young	26 (20.8)	21 (16.8)	16 (20.5)	14 (17.9)	$p_{tot} = 0.393$ $p_{men} = 0.451$ $p_{wom} = 0.334$
Middle-aged	25 (20)	24 (19.2)	18 (23)	16 (20.5)	$p_{tot} = 0.595$ $p_{men} = 0.621$ $p_{wom} = 0.569$
Elderly	15 (12)	14 (11.2)	6 (7.9)	8 (10.2)	$p_{tot} = 0.231$ $p_{men} = 0.163$ $p_{wom} = 0.299$

0.234). Similar values were obtained for patients with Stage II (p_total = 0.495, p_male = 0.476, p_female = 0.513) and Stage III (ptotal = 0.90, pmale = 0.859, pfemale = 0.941) (Table 2).

When assessing the stage of acute thrombosis of hemorrhoidal nodes, no statistically significant differences were found between patients in the conservative therapy and surgical treatment groups.

Pain syndrome is one of the leading symptoms of OTH; therefore, evaluating the intensity of pain at various stages of treatment is an important criterion for assessing the effectiveness of conservative therapy or surgical intervention.

When assessing the severity of pain syndrome before treatment in patients receiving conservative therapy and those undergoing surgery, no statistically significant differences were found (p = 0.839). Significant differences were observed on the 1st and 7th days of treatment (p = 0.043 and p = 0.037, respectively). It is worth noting that the intensity of pain was significantly lower after surgical intervention compared to conservative therapy. However, by the 14th day of treatment, the pain intensity approached zero and was similar in both groups (p = 0.856) (Table 3).

Postoperative bleeding was observed in 1 patient (1.3%). No other complications were noted during the postoperative period.

The time to return to normal activity averaged 6.3 ± 0.3 days in the surgical group and 11.6 ± 1.8 days in the conservative therapy group (p = 0.032).

Disease recurrence within three months after treatment occurred in 6 patients (12.2%): 5 patients (10.2%) after conservative therapy and 1 patient (2.0%) after surgery (p = 0.267).

According to studies conducted within the Russian Federation, the prevalence of OTH accounts for 10-20% of all hemorrhoid cases [8]. Data from various sources indicate that the incidence of OTH among the adult population in Russia ranges from 4% to 25%. Men are affected by OTH 1.5-2 times more often than women [7,8]. The average age of patients ranges from 30 to 50 years, with the highest number of cases observed in the age group of 40-49 years.

In Europe, the incidence of OTH varies from 5% to 15% [4,5]. Studies confirm that men are more susceptible to this condition, with a male-to-female ratio of approximately 2:1.

In the United States, OTH occurs in about 4-5% of adults, with men accounting for about 60% of all cases. The average age of patients ranges from 45 to 55 years [2].

In Asia, particularly China, the prevalence is estimated at 8-12%. Similar to other regions, men are more frequently affected than women, with a male-to-female ratio of approximately 1.5:1 [10].

The first step in conservative treatment is alleviating pain syndrome. For this purpose, non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce inflammation and pain [4,8]. Local anesthetics such as creams or ointments containing lidocaine are applied to the anal area to decrease discomfort [15]. The second line of treatment focuses on relieving constipation, which can worsen the condition and promote further thrombosis. Increasing fiber intake is recommended; including fruits, vegetables, and whole grains helps normalize bowel movements [16]. Sitting baths with warm water can help reduce discomfort and swelling; such procedures are advised for 15-20 minutes several times a day, especially after defecation [11]. Additionally, venotonic drugs that strengthen venous walls and improve venous outflow are prescribed. Treatment of hemorrhoidal thrombosis involves a comprehensive approach aimed at symptom relief and improving patient quality of life.

Surgical intervention is recommended for thrombosed hemorrhoids, especially when complications such as bleeding or severe pain occur. Currently, there is no conclusive evidence indicating significant risks associated with surgical treatment for OTH.

Our study demonstrates that surgical intervention for OTH provides rapid reduction in pain intensity, shortens disability duration, decreases recurrence risk, and increases patient satisfaction. Mild postoperative pain and absence of serious complications facilitate quick recovery to normal activities. Therefore, surgical treatment is an effective alternative to conservative therapy. Careful patient selection based on clinical severity can lead to optimal individualized treatment plans. Some patients opted for conservative management due to fear of postoperative pain and complications.

The results suggest that conservative treatment prolongs disease duration and increases recurrence likelihood in patients with OTH. Most patients prefer starting with conservative therapy due to fear of surgery; however, those who underwent surgery experienced fewer postoperative complications.

Our study has limitations: it was retrospective with a limited number of patients and data were obtained from a single center, which may introduce selection bias. Additionally, three coloproctologists participated in treatment decisions; their

Table 2

Distribution of patients by degree of thrombosis

Возраст	Conservative therapy (n = 125)		Surgical treatment (n = 78)		P-value*
	Men abs. (%)	Women abs. (%)	Men abs. (%)	Women abs. (%)	
I Degree	10 (8)	8 (6.4)	5 (6.4)	4 (5.1)	$p_{tot} = 0.176$ $p_{men} = 0.118$ $p_{wom} = 0.234$
II Degree	55 (43.2)	50 (40)	34 (43.6)	34 (43.6)	$p_{общ} = 0.495$ $p_{муж} = 0.476$ $p_{жен} = 0.513$
III Degree	2 (1.6)	1 (0.8)	1 (1.3)	0 (0)	$p_{общ} = 0.90$ $p_{муж} = 0.859$ $p_{жен} = 0.941$

Table 3

Assessment of Pain Intensity at Different Stages of Treatment

VAS Score	Conservative treatment n=125	Surgical treatment n=78	P-value
Before treatment	7 (6–8)	7 (6–8)	0. 839
Day 1 after treatment	7 (5–8)	3 (2–5)	0.043
Day 7 after treatment	3 (2–4)	1 (0–2)	0.037
Day 14 after treatment	1 (0–1)	0 (0–0)	0. 856

individual approaches could have influenced outcomes. Further randomized studies are needed.

Conclusions. Surgical treatment for hemorrhoidal disease complicated by OTH is an effective method offering several advantages: a significant reduction in pain severity from an average VAS score of around 3 points on day one post-treatment to about 1 point by day seven; a decrease in disease recurrence from approximately 10.2% to 2%; and shortening disability duration to about 6.3 ± 0.3 days.

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

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CLINICAL FEATURES OF DENTAL RECONSTRUCTION WITH SEVERE JAW ATROPHIES IN PARTIAL AND COMPLETE ADENTIUM

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Currently, dental implantation is widely used in practical dentistry to restore defects in dental arches with fixed orthopedic structures. At the same time, complex anatomical and topographic conditions of the bone tissue of the alveolar process of the upper and lower jaws cause a number of clinical difficulties that require bone grafting before installing dental implants, which requires an individual approach. In case of severe atrophy of the alveolar process of the jaws in the frontal and lateral sections, the choice of surgical correction method is bone augmentation by distraction osteogenesis, splitting of the alveolar ridge, grafting of autogenous, allogeneic and xenogeneic bone blocks, as well as the method of tissue regeneration. In general, restoration of dental arch defects and the function of the dental system requires the necessary placement of dental implants in the most correct position for their subsequent osseointegration and fixation of fixed orthopedic structures, which ensures the achievement of the expected clinical result with full restoration of the patients' aesthetic requirements and an improvement in the patient's quality of life.

Keywords: atrophy of the alveolar process, anatomical and topographic features, maxillofacial region, dental implantation, bone grafting, sinus lifting, splitting and reconstruction of the alveolar process, restoration of dentition, fixed orthopedic structures, medical and social rehabilitation.

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Introduction. Nowadays, dental implantation is actively used in practical dentistry, which allows expanding the scientific, theoretical and practical aspects of the restoration of dentition defects with fixed orthopedic structures [7, 8, 12, 16, 17, 32, 34]. A fixed prosthesis on artificial supports has a number of advantages associated with solving physiological problems of functioning and biomechanics of the dentoalveolar system, aesthetic requirements of patients with improvement of their psychological, professional and social status [3, 4, 8, 13, 15, 35]. In this regard, there are studies solving the main problems of dental implantation in the restoration of dental defects with pronounced uneven atrophies of the alveolar process, which is an urgent general medical problem.

There is the research evidence that the predominant part (71.4%) are people of working age 25-40 years old, where women consult 2 times more than men [4, 16, 18, 21, 24, 50] in the structure of patients who require orthopedic rehabilitation, with the use of intraosseous artificial supports. At the same time, recently there has been an increase in a negative trend, where persons with complete adentia are found not only among the elderly and senile age, but also among younger patients. Meanwhile, the clinical possibilities of dental implantation cover a wide range, including the restoration of single defects, as well as the complete restoration of dentitions on toothless jaws [1, 4, 5, 6, 8, 14, 20, 24, 26, 35, 41, 46, 51]. In our opinion, this trend in the North is especially acute, since the high prevalence of dental diseases in the population determines the frequency of detection of dental defects and the need of residents for dental implantation.

The section of basic dental implantation mainly provides for the installation of implants under standard anatomical conditions, where the sufficient height and thickness of the alveolar process are determined, which in 30% of cases due to pronounced uneven atrophies of the alveolar process can be used only with certain modified methods [7, 8, 9, 10]. In such cases, the use of rod-type implants of optimal length and diameter becomes difficult, which require additional osteoplastic surgical measures to prepare the alveolar crest [4, 24, 38]. Meanwhile, with uneven vertical and horizontal atrophic processes leading to a pronounced decrease in the size of the alveolar processes, the installation of intraosseous structures in the jaws must be carried out with preliminary reconstructive surgery [11, 16, 18, 19, 23]. Nevertheless, the development of modern medical science leads to minimally invasive interventions through the use of digital technologies and the features of micro- and macro-design of implantation systems.

It should be emphasized that the above determines the presence of complex anatomical and topographic conditions of the bone tissue of the alveolar process of the upper and lower jaws, where dental implantation acquires the use of different variations that require an individual approach [1, 4, 11, 16, 18, 24, 31]. The variability of the tactical management of the patient with pronounced atrophy of the alveolar process includes the optimal choice of dental implants, taking into account the micro- and macrodesign of the intraosseous parts of the implants, depending on the specific clinical and anatomical proposal, intended for use in case of a lack of height and width of bone tissue with additional bone augmentation in order to reconstruct and create optimal

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conditions, if necessary, the use of lateral subperiosteal implants [18, 24, 31]. As practice shows, the use of micro- and macrodesign of various types of implants allows expanding the range of indications for their use, which in some clinical cases allows avoiding volumetric reconstructive interventions.

It should be noted that there are air cavities on the upper jaw, as well as low bone density with the presence of gravity phenomena on orthopedic structures, which have a negative effect on longer osteointegrative processes, which can reach 6 or more months. In this case, the percentage of complications and unsatisfactory results of dental implantation can reach up to 24% [10, 18]. In addition, with severe atrophy of the bone tissue of the alveolar process, the possibility of using intraosseous implantation of standard sizes is reduced due to the likely perforation of the bottom of the maxillary sinus with the subsequent development of acute and exacerbation of chronic sinusitis [1, 11, 21, 25, 27, 43, 47, 49]. Meanwhile, there is a problem even after reconstructive surgical interventions in the alveolar process, where the installation of full-size implants can be difficult and complications associated with rupture or perforation of the Schneider membrane, maxillary sinusitis, focal acute osteomyelitis of the jaw and augmentate rejection can occur [21, 25, 27, 43]. Meanwhile, augmented bone tissue does not have sufficient density, which leads to the formation of low primary stabilization of a standard titanium implant in the newly formed "young" bone tissue of the jaws in reconstructive surgery [2, 11, 16, 37]. At the same time, multi-stage treatment creates the prerequisites for the rehabilitation increase in case of upper and lower jaws dentition defects, where orthopedic rehabilitation can last up to one and a half years. Moreover, it is associated with the presence of physical and psychological trauma, as well as the high cost of medical manipulations, where in some cases there may be a need for inpatient treatment of patients, which ultimately reduces the availability of medical care [4, 5, 6, 7, 8]. Studies have established alternative implantation options of the alveolar process reconstruction of the upper jaw depending on the clinical situation, aimed at bypassing the lower borders of the maxillary sinus and nasal cavity, which are associated with the installation of implants in the tubercles, in the palatine process, as well as in the zygomatic process [11, 16, 21]. The listed surgical interventions are technically complex, with more serious complications, both during and after the operation [25, 26, 36]. In clinical practice, there is a reconstruction technique by basal implantation which is used in cases of bone deficiency of the alveolar process, where there is a possibility of developing a significant number of complications associated with injury to soft and bone tissue during implantation, osteolysis during aseptic rejection of the established intraosseous part of the structure [38, 40]. Practical experience, as well as the development of additive technologies in dentistry, suggest that the installation of implants can be made bypassing the subantral space using the anatomical features of the canine buttress and the wing-jaw space of the upper jaw.

It is important to note that today there is a way to prepare the conditions for the dental implant on the lower jaw, which is associated with lateralization of the mandibular nerve, where such a complication as persistent paraesthesia in the innervation zone may increase, which determines the limitation of its use in clinical practice [3, 11, 16, 19, 23]. In the last period, the preferred methods for pronounced atrophic processes of the alveolar process of the jaws are directed regeneration of bone tissue using resorbable and non-resorbable membranes, as well as bone materials, autotransplantation of bone blocks, distraction osteogenesis, splitting of the narrow alveolar crest, bone plastic using individual titanium scaffolds, subperiosteal and endo-subperiosteal implants [2, 3, 4, 11, 13, 22]. The disadvantage of subperiosteal reconstruction implantation is two invasive surgical interventions, which are associated with large skeletonization of jaw bone tissue.

It should be noted that in modern surgical dentistry, the method of distraction osteogenesis is mainly used to restore a sufficient volume of bone tissue. However, according to a number of researchers, the method has certain disadvantages that are associated with invasiveness, possible formation of fistula passages in the distractor area, accompanied by the inflammatory process of the surrounding soft tissues, which, accordingly, causes certain discomfort and aesthetic shortcomings in the patient, a longer course of treatment, as well as the probable risk of mandibular fracture during retraction [3, 11, 19]. Moreover, in some clinical cases, a significant part of specialists prefer to carry out the reconstruction of a significantly atrophied alveolar process of the jaws using autogenic bone, which has a number of contraindications and is determined by the occurrence of complications [2, 3, 4, 16, 23, 27, 30, 39]. Currently, the method of directed bone regeneration is widely applied using bone implants of xenogenic and allogeneic origin with resorbable and non-resorbable membranes, the use of which significantly increases the treatment period, where optimal osteointegration of the implanted material is not achieved in all cases. Moreover, the use of materials of non-autogenic origin in reconstructive interventions is associated with a higher risk of augmentate infection, and some patients may also develop intolerance to "foreign" material [2, 6, 25, 42, 45]. According to a number of scientists, the most optimal method of dental implantation for patients with severe atrophy of the alveolar process, is the use of short implants without bone expansion, where a change in the ratio of crown length to implant length is a risk factor for the development of areas of overvoltage in bone tissue that contribute to the formation of a recession of bone tissue around the implant [4, 11, 16, 21, 26, 31, 40, 43]. In our opinion, although there is a wide range of materials and methods of augmentation using bone substitutes and barrier membranes, the most predictable is bone augmentation using autogenic tissues.

In general, despite the extensive study of the main problems of dental implantation in the restoration of dental defects with pronounced uneven atrophies of the alveolar process, they remain completely unresolved, which requires additional study of effective methods that will focus on improving the quality of dental care and rehabilitation measures, as well as improving the quality of life of patients [5, 6, 7, 12, 31]. There are various approaches to reconstructive surgery that are used when there is insufficient bone volume in the area of the alveolar process of the jaws. These techniques include the use of bone grafts, which allows to restore the missing volume of bone tissue and create adequate conditions for the installation of implants, which require additional operational preparation for dental implantation [1, 2, 3, 4, 8, 11, 34]. As our dental implantation experience shows, the problems of improving the reconstruction of the alveolar process of the upper and lower jaws with secondary partial and complete adentia have not been fully resolved, which characterizes its significance and relevance in clinical dentistry and requires further research.

It should be noted that certain difficulties in clinical practice cause the elimination of pronounced defects in the alveolar processes of the jaws [1, 2, 4, 8, 11, 19, 23, 27]. At the same time, special attention is paid to preserving the volume of

bone tissue of the alveolar process after tooth removal, which prevents further atrophy of the well. For this purpose, in practical dentistry, the method of condoning the socket of a removed tooth and bone plastic material is used. Studies have established a significant decrease in the amount of bone plastic to increase the volume of bone tissue of the alveolar process after tooth removal, there are a number of methods preserving the volume of the surrounding bone and soft tissues, where the key aspect is to minimize bone loss and prevent resorption that may occur as a result of tooth removal [1, 5, 8, 20]. These atrophic processes require a more comprehensive approach, which may include the use of bioresorbable membranes in combination with bone grafts and various tissue regeneration technologies [28, 29, 30]. In general, bioresorbable membranes are typically made of materials that are able to integrate with patient tissues and resorb over time without having to remove them surgically, making them particularly relevant in dental practice before installing dental implants, augmentation of the upper and lower jaws is mandatory.

It should be noted that the standard surgical protocol for reconstruction involves the installation of a dental implant with a diameter of 3.5-4.0 mm into bone tissue with a width of at least 6-7 mm [31, 34]. Moreover, according to the generally accepted clinical standard for successful implantation in conditions of bone deficiency of the alveolar process, bone augmentation is up to 5-7 mm wide and up to 8-10 mm high [11, 24, 40]. In this regard, preparatory surgical reconstructive interventions before the dental implants installation should be carried out according to the results of clinical and radiological studies, which are important in a favorable outcome of treatment [20, 24, 45]. The frequency of patients who required bone plastics before implantation was 87%, which determines the prevalence of categories of patients with significant atrophies of the jaw bones [2, 3, 4, 8, 11, 20, 24]. According to some researchers, when performing reconstructive sinus lifting from both sides simultaneously with the installation of a dental implant, it is preferable to use xenogenic and autogenic bone-plastic material [2, 3, 11, 19, 21, 22, 23, 24, 47]. Sinus lifting surgery requires specialists to maintain the integrity of the Schneider membrane of the maxillary sinus, where perforations are likely to occur during its detachment [2, 21, 27]. Our practical experience confirms that anatomical and topographic features detected on the upper jaw, as a rule, require reconstructive augmentation many times more compared to the lower jaw.

In case of vertical atrophy of the alveolar part of the lower jaw, the sandwich plastic method is used, as a result of which a predictable result of treatment can be obtained [3, 11, 19]. When using the directed bone regeneration method to close a bone defect using an insulating membrane, the regeneration of connective tissue strands is achieved, which ensures the creation of optimal conditions for the migration and differentiation of osteogenesis stem cells [1, 2, 3]. Moreover, a prerequisite for this method is the presence of autogenic viable bone cells in the area of augmentation, which are the main source of bone formation and development [3, 39, 44]. An important point for reconstructive surgical interventions of the alveolar process of the upper and lower jaws is not only the type and characteristics of the drug used that play an important role in the recovery process, but also the individual characteristics of the patient's body. These include age, the presence of concomitant diseases, as well as the volume and location of the bone defect in the implantation area. All these factors can significantly affect the result of treatment and the effectiveness of implantation, including possible postoperative complications [6, 8, 11]. Thus, the pathogenetic mechanisms of the inflammatory response of the tissue bed and the regenerative processes of the surrounding tissues are widely studied when using various bone-plastic materials, where the optimal choice of bone-plastic types is of great practical importance for the successful implementation of reconstructive-plastic interventions on the upper and lower jaws [2, 11, 22]. Optimal augmentation by the splitting method is achieved with a deficiency of the bone tissue of the alveolar process in the horizontal direction, where cuts of the cortical plate in the sagittal plane are carried out without significant violation of the integrity of the bone fragment [19, 23]. The main purpose of bone augmentation by splitting when installing dental implants is the practical application of the ability to regenerate periosteum and alveolar bone tissue. The essence of the technique consists in intercortical osteotomy, where in its space, due to the preservation of the spongy substance, favorable conditions are created for feeding the surrounding tissues and the process of osteogenesis, which in turn allows installing dental implants in the correct position for the subsequent manufacture of orthopedic structures, where a high level of 10-year "survival" of implants is determined with achievement of clinical effectiveness up to 95.7% [31, 39]. According to our data, the 10-year "survival" of implants reaches values from 94 to 97%.

It is important to note that when preparing bone before dental implantation, the use of avascular bone autografts is considered the most optimal option for performing reconstructive bone grafting on the jaws [3, 19, 23, 27]. The positive clinical properties of these grafts are their osteoplastic, osteoconductive and osteoinductive properties, which significantly improve the conditions for bone regeneration and remodeling. The peculiarities of bone block sampling include the exclusion of bone tissue overheating to reduce its injury and preserve viable cells, which is of great practical importance that determines the successful outcome of the operation [3, 23, 27, 38]. In addition, it is necessary to pay special attention to the condition of the recipient bed, where correct incisions, delamination of the mucoperiosteal flap of the correct shape, as well as rigid immobilization of bone blocks to the receiving area and hermetic suturing of the surgical wound make it possible to significantly reduce the percentage of complications [11, 23, 27]. Depending on different anatomical zones, as well as the extent and severity of the atrophic process of the alveolar process of the upper and lower jaws, various bone autografts can be used [3, 23, 27]. So, when restoring deformities of bone tissue of alveolar process within 4 teeth, bone blocks are taken in the area of external oblique line, mental symphysis, anterior edge of mandibular branch, as well as maxillary tubercle and coronary process. In case of extensive defects, autogenic grafts from extrauterine zones can be used, including areas of the bone of the cranial vault and the anterior surface of the tibia in the form of bone chips, bone blocks, or a combination thereof [23, 27, 43]. When obtaining autobody in the area of the external oblique line for reconstruction, it gives the clinician the opportunity to obtain a larger volume of bone compared to other areas of the oral cavity. However, when taking a large block, there are risks of a number of complications, such as damage to the mandibular nerve when the lower border of the transplant is close to its canal, as well as a fracture of the lower jaw [3, 6, 24, 38]. When working with the donor zone in the area of the tubercle of the upper jaw, there is a possibility of perforation of the bottom of the maxillary sinus with the appearance of oral-antral communication. Sampling of autogenous bone tissue from intraoral anatomical for-

mations is characterized by the possible development of complications, including cicatricial changes in the vestibule of the oral cavity, the formation of keloid scars in the retromolar region and insufficient volume of autografts for augmentation [3, 27]. According to research resources, extrauterine donor zones make it possible to obtain a bone autogenic graft of a larger volume, the hallmark of which is the presence of several operational zones, which at the postoperative stage cause the appearance of great discomfort [23, 27, 38]. Taking into account the above, the authors developed a soft tissue protector-retractor device for a surgical angular tip for taking an autogenous bone block from the external oblique line, which allows for minimally invasive interventions that increase the quality of dental care and the quality of life of patients (utility model patent No. 233201 dated 11.04.2025. Published by 11.04.2025 Buhl. № 11).

Today, there are various methods of surgical restorative operations that solve the important clinical problem of soft tissue deficiency of the keratinized gum and vestibule depth in the area planned for the restoration of dental defects by various orthopedic structures during dental implantation. This tactic ensures minimization of postoperative complications, which determine the success of the treatment measures [2, 3, 11, 19]. Technically, the operation to enlarge the attached keratinized gingiva is closely related to the use of a free-gingival autograft from the donor zone. In this regard, this method at the present stage of surgical dentistry is the "gold standard" of mucogingival surgery. At the same time, the area of the mucous membrane of the hard palate remains preferable in choosing the donor zone, since the area of the hard palate has a multilayer morphological structure, including adipose and glandular tissues, a connective tissue base, as well as its own epithelium [24, 26, 30, 31, 37]. Meanwhile, in the postoperative period, an extensive area requiring soft tissue correction appears after bone plastic, which in turn is limited by the mucous membrane of the hard palate, which creates certain difficulties for the recipient area to be completely covered with an autograft [6, 8, 11, 48]. Meanwhile, there are some disadvantages in mucogingival surgery, associated with large autografts, which are likely to develop necrosis in the flap due to thermal ischemia and existing reperfusion injuries that can develop when the microvasculature in the surgical area normalizes [22, 25, 30, 33]. This surgical approach to dental implantation does not completely solve the problem of lack of soft tissues at the site of their installation [30, 36].

Thus, clinical dentitions reconstructions with pronounced uneven atrophies of the alveolar process of the upper and lower jaws with secondary partial and complete adentia have their own differences associated with individual anatomical and topographic features. Such a tactic requires the installation of the intraosseous part of the implant in an optimal orthopedic position for the subsequent fixation of non-removable structures on them, which ensures the achievement of the clinical expected result with a full restoration of the aesthetic requirements of patients and an increase in the quality of life of the patient.

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HEALTHY LIFESTYLE. PREVENTION

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ORGANIZING MANDATORY VACCINATION AGAINST TICK-BORNE ENCEPHALITIS IN RUSSIA: HISTORY AND MODERNITY

The study presents the results of the analysis of regulatory legal acts and the practice of applying the rules related to mandatory vaccination against tick-borne encephalitis. The purpose of the study: analysis of the procedure for mandatory preventive vaccinations against tick-borne encephalitis and the implementation of the right to vaccination. Materials and methods: analysis of regulatory and legal acts in the field of immunoprophylaxis of tick-borne encephalitis by the method of expert assessments, comparative legal, analytical, statistical methods. Medical and epidemiological analysis of the content of the Calendars of preventive vaccinations regarding vaccination against tick-borne encephalitis from 1980 to 2021. Results: In 2023, most of the territories of the constituent entities of the Russian Federation were endemic for tick-borne encephalitis. In 2024, 4 million citizens of the Russian Federation were vaccinated against tick-borne encephalitis. Historical retrospective has shown that vaccination against tick-borne encephalitis was started for the purpose of disease prevention in endemic territories in relation to certain professional categories of the population. At the same time, immunoprophylaxis was mainly carried out according to epidemiological indications, with the exception of 1980-1997, when it was included in the routine vaccination. When establishing the mandatory vaccination, 4 acts are taken into account: Federal Law "On Immunoprophylaxis of Infectious Diseases"; Calendar of Preventive Vaccinations; SanPiN 3.3686-21; List of works, the performance of which is associated with a high risk of infectious diseases and requires mandatory preventive vaccinations. SanPiN 3.3686-21 expands the contingent that receives preventive vaccinations against tick-borne encephalitis. Conclusions and discussion: mandatory vaccination is defined by the list of professional risk groups and requires a decree of the chief state sanitary doctor or an order from the head of the organization. To increase the effectiveness of immunoprophylaxis and prevent abuse, it is necessary to systematize regulatory and legal acts.

Keywords: vaccination, immunoprophylaxis, tick-borne encephalitis, vaccinations, vaccination calendar, legal regulation, categories of the population

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Introduction. In the Far Eastern Federal District, as a territory with a large number of forests and a high number of virus carriers, one of the main medical and epidemiological problems [6] is tick-borne viral encephalitis (hereinafter referred to as the «TBE»).

It is known that the incidence of tick-borne encephalitis increases in countries endemic for tick-borne encephalitis in both Europe and Asia [25, 26]. This problem is undoubtedly relevant and requires a solution in accordance with modern legal acts to preserve the health and well-being of the population [22, 23]. In Russia, in 2023, numerous entities were registered as territories endemic for tick-borne encephalitis [7, 21] (see Fig. 1). In the Far Eastern Federal District (hereinafter referred to as the «FEFD»), only 3 entities do not have registration of tick-borne encephalitis: Kamchatka Krai, Magadan Oblast, and Chukotka Autonomous Okrug. Of the thirty-five territories of the Sakha Republic (Yakutia), four are endemic for tick-borne encephalitis, including the Aldan, Neryungri, Lensky, and Olekminsky Districts. In the remaining entities of the FEFD, all or most of the administrative territories are endemic.

In 2023, more than 503 thousand people in the country suffered from ticks, which is 6.5% more than the long-term average (472,491), and also 12.6% more than in 2021 [22]. According to Rospotrebnadzor, 4 million people in Russia were vaccinated against tick-borne encephalitis in 2024.

The medical significance of tick-borne encephalitis is determined by the high mortality rate, disability and severity of the disease [3, 5, 7, 22, 23]. The legal significance is determined by the relationship between the principle of voluntary vaccination and the mandatory nature of immunoprophylaxis, due to the need to mitigate the consequences of complications of the central nervous system disease and reduce the risk of contracting a zoonotic infection [11, 12].

The aim of the study is to analyze the procedure for mandatory vaccination against tick-borne viral encephalitis, categories of citizens subject to vaccination and the implementation of the right to vaccination.

Materials and methods. Regulatory and legal acts in the field of immunoprophylaxis against tick-borne encephalitis in Russia were studied. The following methods were used: comparative legal, analytical, medical-epidemiological, statistical, content analysis, expert assessments.

The article provides an analysis of data from authors devoted to immunoprophylaxis against tick-borne encephalitis, in particular A.S. Kilyachina, E.A. Leushina, Yu.A. Zubova, A.G. Sergeev, and others. The works of foreign research in this area are studied, in particular O.N. Khanenko, U. Kunze, M. Müller, A. Pilz, J. Shedrawy and others [24, 25, 26].

Results and discussion. The constitutional right to health protection includes

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the sanitary and epidemiological well-being of the population [12].

Prevention of infectious diseases by medical and epidemiological methods, including immunoprophylaxis, is carried out through the use of vaccines against tick-borne encephalitis, which is a specific prevention of the infectious transmissible disease viral tick-borne encephalitis. Despite the diverse range of entities that carry out such activities – from government bodies to public associations – specific preventive measures are limited to the national calendar (hereinafter referred to as the «Calendar») of preventive vaccinations (part 1) and the calendar of preventive vaccinations for epidemiological indications (part 2). The Calendar was approved by order of the Ministry of Health of Russia dated 06.12.2021 N 1122n [14] and is a normative legal document that establishes the names of diseases, a list of preventive vaccinations and categories of citizens subject to mandatory vaccination. Clause 7 in Part 2 refers to vaccination against tick-borne encephalitis [11, 14].

According to the International Statistical Classification of Diseases and Related Health Problems, Eleventh Revision (ICD-11) [8], TBE is included in viral infections of the central nervous system in 1C8G "Tick-borne encephalitis", and is subdivided into 1C8G.0 "Far Eastern tick-borne encephalitis", 1C8G.1 Central European tick-borne encephalitis, 1C8G.2 Siberian tick-borne encephalitis, 1C8G.Z Tick-borne encephalitis, unspecified. As of January 2025, ICD 10 has effectively ceased to be effective, and the implementation of ICD 11 was suspended in january 2024.

The neurotropic tick-borne encephalitis virus was first described as the etiologic factor of tick-borne encephalitis by Lev Aleksandrovich Zilber more than 85 years ago [4]. The area of tick-borne encephalitis virus coincides with the area of the main carriers of the pathogen – ixodid ticks of the species: *Ixodes persulcatus* and *Ixodes ricinus*, in some areas *Ixodes pavlovskyi*, additionally representatives of ticks of the genera *Haemaphysalis* and *Dermacentor* [17].

The TBE virus belongs to the *Flaviviridae* family, *Flavivirus* genus, *TBEV* species. TBE is caused by TBEV virus subtypes, such as the European subtype (*TBEV-Eur*), Siberian subtype (*TBEV-Sib*) and Far Eastern subtype. The Far Eastern subtype of the TBE virus affects the severity and outcome of the disease [17, 18].

The unknown disease diagnosed in 1922 as "toxic flu" in the taiga regions

Fig. 1. Subjects of the Russian Federation endemic for tick-borne viral encephalitis in 2023 (Figure created by V.I. Ratnikova using the website https://www.supervisited.ru)

of the Far East was investigated by the People's Commissariat of Health expedition in 1937 [20, p. 32-33], the etiological factor of the disease was determined - a virus. In 1938, the first inactivated vaccine based on the Far Eastern strain Sofjin was created [5]. In 1941, for emergency prevention of TBE, it was proposed to use serums obtained from convalescents and hyperimmunized animals [18, p. 1]. During this period, vaccination against TBE was experimental and tested on the territory of the Oborsky forestry enterprise in the Khabarovsk Territory [5]. In 1954, production of a vaccine against TBE began at the Tomsk Research Institute of Vaccines and Serums of the USSR Ministry of Health based on inactivated TBE virus obtained on the brain tissue of white mice, and then on chicken embryos.

In 1964, Academician of the USSR Academy of Medical Sciences M.P. Chumakov and his colleagues registered a new technology for processing the TE virus and an inactivated vaccine [2], which was used until 1984, when a new production strain of the TE virus No. 205, isolated in Khabarovsk Krai in 1973 by Professor L.A. Vereta and co-authors, was proposed [3]. The new vaccine had immunogenic activity against taiga encephalitis [1]. In 1966, vaccination against TBE was established as a preventive measure by the order of the USSR Ministry of Health dated 28.12.1966 N 990 "On the timing of preventive vaccinations for children and adolescents." In 1973, a new order was issued on the timing of preventive vaccinations, which divided them into planned vaccinations and vaccinations for epidemiological indications by decision of the Ministry of Health of the Union Republic. Vaccination against TBE was included in the group - for epidemiological indications. In 1980, a vaccination calendar was introduced, and from 14.01.1980, vaccination against TBE became routine, the vaccination start date was from 4 years, and a line appeared on revaccination - annually for 3-4 years. Routine vaccination against TBE was carried out for the population and individual professional groups living in endemic or enzootic territories (see Fig. 2). In 1990, NPO Virion (Tomsk) produced an sorbed inactivated vaccine against tick-borne encephalitis. In 1997, the order "On the calendar of preventive vaccinations" dated 18.12.1997 N 375 was approved. Vaccination against tick-borne encephalitis was included in the Calendar of Preventive Vaccinations for Epidemiological Indications from the age of 4 and with annual revaccination for 3 years. Subsequently, the Calendar was repeatedly changed - in 2001, 2011, 2014 and 2021 [14]. The genesis of changes concerning vaccination against tick-borne encephalitis in Russia is shown in Fig. 2.

The genesis of changes to the vaccination calendar regarding vaccination against tick-borne encephalitis shows that the indications of exact dates of vaccination and revaccination were removed in 2011, possibly due to the significant diversity of vaccines. As for the contingent, since 2001 the list of jobs associated with the risk of tick-borne encephalitis has been clarified, and has remained virtually unchanged since 2001.

In SanPiN 3.3686-21, the contingent of people who must undergo preventive vaccinations against tick-borne encephalitis is expanded (see Fig. 3).

The list is open. It specifies that the adult population is vaccinated taking into account the risk of disease, occupation or type of activity. If in the Calendar vaccination is required for persons working with live cultures of the tick-borne encephalitis pathogen, then in SanPiN 3.3686-21 - the activity is associated with the use of the TBE. In addition to these two acts, there is a list of works, the performance of which is associated with a high risk of contracting infectious diseases and requires mandatory preventive vaccinations [15] (hereinafter referred to as the «List»). This List is approved by the Gov-

ernment resolution and includes, among other things, the works established by the Calendar regarding construction, logging, work with live crops, etc. Thus, the question arises of who exactly is subject to mandatory vaccination and whether there is a legal possibility of refusal. In addition, the state guarantees free preventive vaccinations included in the Calendar within the framework of the compulsory medical insurance program. Regarding TBE, there is no regulation on the indications for its implementation, for example, poliomyelitis.

The provisions of Article 10 of the Federal Law "On Immunoprophylaxis of Infectious Diseases" (hereinafter referred to as Federal Law No. 157) [11] establish the mandatory decision-making on vaccinations by the chief state sanitary doctors of the Russian Federation and/or constituent entities of the Russian Federation in the event of a threat of infectious diseases that pose a danger to others [16]. Additionally, this norm is reflected in subparagraph 6 of paragraph 1 of Article 51 of the Federal Law "On the Sanitary and Epidemiological Welfare of the Population" [9] (hereinafter referred to as Federal Law No. 52).

Despite the above provisions of the laws, in practice there are several options for implementing mandatory vaccination. One of them is based on the fact that the provisions of the List and Article 5 of Federal Law N 157 are the norms on the basis of which the obligation to be vaccinated arises for those specified in it, regardless of the epidemiological situation under the threat of suspension or refusal to hire (Article 5 of Federal Law N 157). The employer issues an order on vaccination with a local definition of the list of employees subject to vaccination. In the absence of a complicated epidemiological situation, a category of persons not provided for in the List has the right to refuse preventive vaccinations [13].

The conditions for mandatory vaccination are:

1) the work is included in the List;

2) the employer requires vaccination specified in the Calendar for the required categories of employees, since he is obliged to carry out sanitary and anti-epidemic (preventive) measures (Articles 11, 25, 29, 35 of Federal Law N 52, SanPiN 3.3686-21);

3) the Calendar contains an indication of such categories of citizens. For example, item 9: work with patients with infectious diseases; item 10: work with live cultures of pathogens of infectious diseases; item 11: work with human blood and biological fluids. Employees of

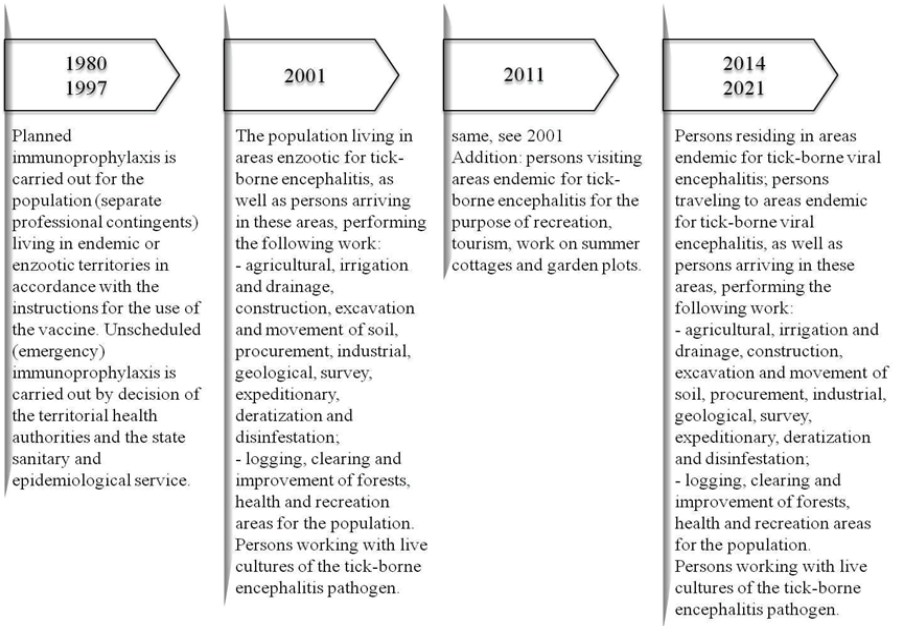

Fig. 2. Comparison of the contents of the Calendars of Preventive Vaccinations for Vaccination against Tick-Borne Encephalitis from 1980 to 2021

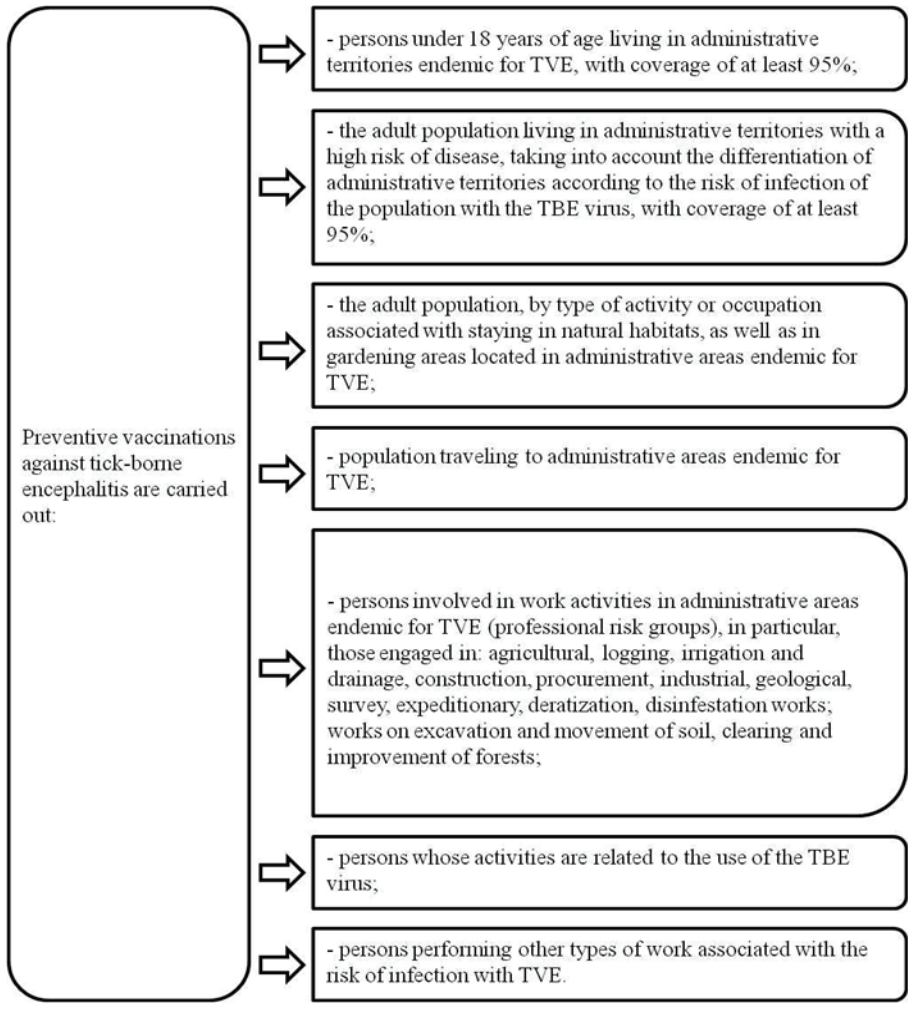

Fig. 3. List of persons who are given preventive vaccinations against tick-borne encephalitis (TBE), according to SanPiN 3.3686-21 "Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases"

medical organizations are required to be vaccinated against hepatitis B; diphtheria and tetanus; measles (36-55 years); flu (adults); hepatitis A, etc.

Analyzing these acts, we can identify the following: the employer is obliged to develop and implement sanitary and anti-epidemic (preventive) measures, which include preventive vaccinations. Which ones exactly are not specified, since the norm refers to Federal Law No. 157. At the same time, there are two emphases: the type of activity of the organization and the cases of paragraph 2 of Article 50 of Federal Law No. 52 [10, 17].

Based on this chain of legal norms, it turns out that much depends on the presence of a threat of occurrence/spread of diseases. Vaccination against TBE becomes mandatory if the subject has issued a corresponding decree of the chief sanitary doctor on vaccination of certain categories of citizens.

The conditions for the commencement of such vaccination are:

1) a resolution/act of the chief sanitary doctor on the vaccination of individual citizens or categories of citizens;

2) the employer requires vaccination specified in the Vaccination Calendar for Epidemiological Indications. If the employee does not have confirmed contraindications to vaccination and refuses the procedure, the employer is obliged to suspend him from work (Article 76 of the Labor Code of the Russian Federation).

Despite the above, according to the act of the chief sanitary doctor, immunoprophylaxis against any disease from the Calendars may be recommended.

Conclusion. The threat of epidemic diseases creates the need to maintain public health at the proper level, for which purpose the employer is obliged to comply with sanitary regulations, and citizens are obliged to take care of their health. Taken together, this leads to a restriction of the right of citizens to refuse vaccination, which will not be a violation of human rights and freedoms under paragraph 3 of Article 55 of the Constitution of the Russian Federation.

The above legal aspects create a medical and social problem, since the lack of vaccination in some cases may entail the violation of the rights of other persons entering into industrial contact with a potentially unprotected subject. A decrease in the number of vaccinated persons may entail a threat of an increase in the incidence of the disease in an area endemic for TBE. A legal problem arises - the inability of workers to exercise the right to refuse vaccination. The lack of vaccinations among workers, if their mandatory implementation is provided for by law, entails administrative liability of the employer under Art. 6.3 of the Code of Administrative Offenses of the Russian Federation, paragraph 1 - a fine of up to 10-20 thousand rubles, suspension of the activities of legal entities for up to 90 days.

Discussion requires clarification of the legal norms regarding the list of persons from professional risk groups and the method of implementing their right to free vaccination, indicating the operational epidemiological situation for tick-borne encephalitis and determining the degree of risk of infection with tick-borne encephalitis in each subject of the Russian Federation. Regarding mandatory vaccination against viral tick-borne encephalitis, the start date of vaccination and the list of contraindications require clarification.

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

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AWARENESS OF HEALTHCARE PROFESSIONALS ABOUT THE RISKS OF OCCUPATIONAL INFECTION WITH HEMOCONTACT INFECTIONS: QUESTIONNAIRE RESULTS

Cases of the introduction of pathogens of hemocontact viral hepatitis and HIV infection into medical organizations pose a potential threat of infection of medical workers in the course of their professional activities. The purpose of the study is to study the awareness of medical professionals about the dangers of occupational infection. Within the framework of this study, a survey of medical professionals was conducted according to the author's questionnaire. The results of a survey of 1,046 respondents on the issues of awareness of medical professionals in ensuring safety in the provision of medical care are presented. Cases of workplace emergencies were identified among 14.2 % of the surveyed medical workers. At the same time, 28.1 % do not register emergency cases in the "Emergency Register for medical procedures", and 10.7 % of doctors do not have vaccination against viral hepatitis B. This requires the development of measures to prevent and raise awareness of occupational infection among medical professionals.

Keywords: safety of medical workers; questionnaire; awareness; hemocontact infections; HIV; hepatitis B; hepatitis C

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Introduction. The relative indicator of the number of newly detected cases of HIV infection, as well as the incidence rate per 100 thousand population of the Altai Territory (80.7 and 65.5, respectively), according to the federal statistical observation form No. 2, "Information on Infectious and Parasitic Diseases," exceeded the average Russian value. In the Altai Territory, there was an increase in the proportion of viral hepatitis C in both the structure of the incidence of acute (48.57%) and chronic viral hepatitis (57.54%) [1]. The incidence of CHB and CHC in AK tended to increase by 2.2 times and 7.2 times, respectively (from 2000 to 2023) [1]. From 2013 to 2023, there was a 1.2-fold decrease in the incidence of HIV infection among medical workers in the Altai Territory (from 22.6 ± 0.2 0/0000 to 26.0 ± 0.2 0/0000, $p \leq 0.00001$) [2].

In the Krasnoyarsk Territory in 2023, 2295 cases of HIV infections were de-

tected, the incidence rate was 84.84 cases per 100 thousand population [3].

The incidence of chronic viral hepatitis B and C in the Krasnoyarsk Territory in 2023 increased by 35.4% and 24.8% compared to 2022 and exceeded the indicators in the Russian Federation by 62.5% and 73.2%, respectively [3].

Health care workers (HCPs) are at increased risk of contracting viral hepatitis. According to studies, the frequency of detection of these diseases among health workers is 7-10 times higher than among the general population [4, 5, 6, 7]. Viral hepatitis in healthcare personnel is of important epidemiological importance, especially in the context of healthcare-associated infections. In advanced stages, such as cirrhosis and liver cancer, these diseases become a serious clinical and socio-economic problem [6].

Analysis of information on professional infection of medical workers (hemocontact hepatitis B, C, HIV) at the present stage shows that it is impossible to completely exclude the risk of infections in any medical organization [8].

A component of the system for preventing occupational infection with hemocontact infections is monitoring the level of competence, increasing knowledge, skills and abilities in this area.

Diagnosis of the level of awareness is the first stage of increasing the competence of medical workers as the basis for their self-preserving behavior in the implementation of professional activities.

The purpose of the study is to study the level of awareness of medical workers about the risks of occupational infection with hemocontact infections.

Research materials and methods. The methods used in this article can be divided into theoretical and cognitive (analysis of the literature on the corresponding problem, comparison, generalization, synthesis of the obtained data); empirical methods (the basis is a questionnaire survey in online format using the Google form, which includes nominal scales); frequency distribution method, which allows you to fix the relative values (%) associated with the prevalence of representations and installations. Data processed using Excel.

In the period from May 1 to May 20, 2024 in the semi-structured author's Internet questionnaire "Hemocontact infections. The risk of professional infection "was attended by 1,046 employees of various medical organizations in the Altai Territory and Krasnoyarsk Territory.

As a result, the sample population is represented by the following socio-demographic characteristics:

• age categories: 20-30 years old - 18.5%, 31-40 - 24.3%, 41-50 - 26.2%, 51 and older - 31%;

• gender: men - 9.9%, women - 90.1%.

• education level: doctors - 33.3%, with secondary medical - 64.3%, junior medical staff - 2.4%;

• working students - 5.1%: 5th course - 44.2%, residents - 19.2%, 6th course - 17.3%, 3rd course - 5.8%, 3.8% each - 1 and 4 courses and open source software, 2nd course - 1.9%).

The main content blocks of the questionnaire were aimed at identifying such issues as awareness of the dangers of transmitting hemocontact infections during various manipulations, on the rules for preventing occupational infection with hemocontact infections, actions in emergency situations (including registration at the workplace), and post-exposure prophylaxis measures.

The study was conducted in compliance with ethical standards and taking into account measures to protect the privacy of research subjects and the confidentiality of their personal data.

Category questions of particular practical and theoretical importance to the study and answer options are presented in Table.

Results and discussion. The study revealed a high level of self-esteem (99.8%) of medical workers regarding their awareness of the risks of contracting hemocontact infections (viral hepatitis B, C, HIV infection) while performing professional duties. In particular, 99.6% are sure that they know about the rules for the prevention of occupational infection with hemocontact infections; 99.2% of doctors say that they know which situations at the workplace are emergency: the ingress of biomaterials on the mucous membranes of the mouth/eyes - 94.5%, an injection with sharp instruments - 94.3%, a cut - 87.1% and the ingress of biomaterial on overalls - 63.7%. Since the questionnaire question suggested the possibility of multiple choices, the sum of the answers received exceeds 100%.

Despite the high percentage of subjective assessment of risk awareness (99.8%), 14.2% of medical workers note the occurrence of emergency situations (ES) at the workplace. Of these, isolated cases for the entire period of work occur in 86.3% of respondents, once a year - in 4.1%, 3.4% each noted the occurrence of situations once a month and once every six months. Approximately 2.1% respondents celebrate AS once a quarter and 0.7% - 1 times a week.

The most frequently noted by respondents causes of emergencies at the workplace, creating the risk of infection with hemocontact infections, are as follows: "hurried when performing manipulation" - 38.4%; "performed manipulations in" extreme "conditions (at home, unstable furniture, etc.) - 24.0%; 15.0% put the cap on the used needle, when performing operations/invasive procedures, the tool broke or was incorrectly applied - 7.5%; 6.2% reported feeling unwell during the working day, 5.5% encountered a restless patient; other reasons were indicated by 3.4% of respondents.

According to the results of the study, violations of the rules for registering emergency situations were revealed. So, only 71.9% were registered in the "Log of emergency situations during medical manipulations" (hereinafter - the Log). Almost every third event (28.1%) is not recorded. As reasons justifying these indicators, the respondents note: lack of awareness of the presence of the Journal, lack of access to the Journal, confidence in the absence of further actions on the part of the management, the employee's negligence towards his own health ("maybe it will pass"), were not considered necessary.

In the event of an emergency at the workplace, post-exposure prophylaxis was carried out only by 81.3% of medical workers. Despite the fact that in 4 out of 5 cases of ES, post-exposure prophylaxis was carried out, 18.8% of respondents used an incorrect algorithm of actions (for example, 10.3% of them performed the algorithm with "squeezing out a drop of blood").

As a justification for a passive reaction to ES at the workplace, the majority of respondents indicate "no need" ("negative" for hemocontact infections, the minimum risk of infection (according to a medical worker) - 51.8%, silence of the AS that occurred and lack of therapy - 18.5%).

An important aspect in overcoming the negative scenario in ES is specific prevention (a full course of vaccination against viral hepatitis B). According to the data obtained, only 89.3% of medical practitioners are vaccinated (of the total number in each category of workers, 17.1% of doctors, 7.3% of nurses and 12.5% of junior medical workers are not vaccinated).

Indicative situation: 4 respondents have a history of established diagnosis (OVG/HVG/cirrhosis/HIV infection). Of these, 50% (doctor, paramedical worker) note a connection with infection with professional activities (emergencies at the workplace and the need for emergency manipulation of a patient without a known history). Both employees were

Questions of the Internet questionnaire «Hemocontact infections. Occupational infection risk. »

1	2	3
Question №	**Question Text**	**Answer Options**
General questions		
1.	Your Gender	Male
		Women's
2.	Your age (full years, number)	Free answer
3.	Name of settlement where you live	Free answer
4.	Are you currently an employee of a medical organization?	Yes
		No
For healthcare professionals		
5.	Please indicate your position in the medical organization	Junior Medical Staff
		Nursing staff
		Doctor
6.	Department of the medical organization in which you work	Free answer
7.	Are you aware of the dangers of transmitting hemocontact infections (viral hepatitis B, C, HIV infection) during work operations?	Yes
		No
8.	Are you aware of the rules for the prevention of occupational infection with hemocontact infections?	Yes
		No
9.	Do you know what workplace situations relate to emergencies?	Yes
		No
10.	In your opinion, what situations can occur at the workplace?	Injection with sharp instruments
		Cut
		Ingress of biomaterial on overalls
		Ingress of biomaterial on mucous membranes of eyes/mouth
11.	Have you ever had a workplace emergency?	Yes
		No
Accounting for emergency situations		
12.	How often do you experience workplace emergencies?	1 times a week
		1 monthly
		1 quarterly
		1 every half year
		1 times a year
		Single cases for the entire period of work
13.	Indicate what the emergencies were related to	Free answer
14.	Were these emergencies recorded in the "Emergency Accounting" Log?	Yes
		No
Post-exposure prophylaxis		
15.	Has post-exposure prophylaxis been carried out following a workplace emergency?	Yes
		No
16.	What exactly was done (what kind of prevention)?	Free answer
17.	For what reason was post-exposure prophylaxis not carried out?	Free answer
18.	Describe the reasons why emergency situations are not recorded in the logbook	Free answer
Vaccination		
19.	Are you vaccinated against viral hepatitis B?	Yes
		No
20.	Specify the number of vaccinations according to your vaccination calendar	Vaccination 1
		Vaccination 2
		Vaccination 3
		Vaccination 4
		Revaccination

End of table

1	2	3
21.	Why did you refuse to be vaccinated against hepatitis B?	Free answer
22.	Do you have an established diagnosis (OVG/HVG/cirrhosis/HIV infection) (if yes, write the date of diagnosis in the line "other")	No
		Other
Link to occupational infection		
23.	Is there a connection between the established diagnosis and your professional activity, in your opinion?	Yes
		No
24.	The cause of infection, in your opinion	Free answer
For students		
25.	Are you currently students of a medical university?	Yes
		No
26.	What is your course?	1
		2
		3
		4
		5
		6
		Internship
		Postgraduate study
		Secondary vocational education

not vaccinated against hepatitis B, while, based on subjective data, post-exposure prophylaxis was carried out (use of a first aid kit).

Conclusion. The performance of health professionals in their professional duties is inevitably associated with contact with sources of infection, which poses a potential threat to their health in terms of the risk of infection in the working environment.

The presented results of the survey allow us to conclude that despite the high self-assessment of knowledge of hemocontact infections and the risks of ES at the workplace, in fact, there is a low awareness of medical workers in the Altai and Krasnoyarsk Territories on issues of occupational infection, ES and the rules for their registration.

The percentage of the questionnaire response options such as "ingress of biomaterials on the mucous membranes of the mouth/eye," "injection with sharp instruments" and "cut" is in the satisfactory range from 87% to 95%. The exception is the option of the answer "getting biomaterial on overalls," which may, in the future, be the basis for the development of a vocational training program.

Violations of the rules for registering ES at the workplace determine the direction of organizational actions that can reduce the overall level of threats to the health of a medical worker and the epidemiological situation in a medical institution.

The incorrect algorithm of actions in the event of ES is probably associated with the low awareness of medical workers about the content of new regulatory documents, which is an important aspect in professional activities to preserve their own health and well-being.

Preventive immunization of personnel of medical organizations against HBV is carried out in accordance with the national and regional calendars of preventive vaccinations, the vaccination calendar for epidemiological indications, as well as in accordance with the decisions of the chief state sanitary doctor for the constituent entity of the Russian Federation. The survey revealed a deviation from these points (10.7% of medical workers are not vaccinated against hepatitis B), which indicates insufficient informing of medical personnel (including the management structure of medical organizations) about the problems of occupational infection.

Thus, the key tasks of practical health care are the study of factors contributing to the infection of employees of medical institutions, the development of preventive measures, as well as raising awareness through educational programs. It is necessary to minimize the risk of infections associated with the provision of medical care among medical personnel.

As a solution to key tasks, it is proposed to create and introduce into practical healthcare a training program for medical workers of various specialties on professional infection with hemocontact infections.

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

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ATTITUDES OF PEDIATRIC GASTROENTEROLOGISTS, RHEUMATOLOGISTS, AND PARENTS TOWARD VACCINATION BASED ON AN ANONYMOUS ONLINE SURVEY

Differences in vaccination coverage among patients with IBD, JIA, and healthy children, as well as to identify differences in vaccination attitudes between parents and physicians, including barriers and facilitators of immunization were assessed. Vaccination coverage, reasons for refusal, trust in vaccines, and physician involvement in immunization were assessed. Statistical analysis was performed using Pearson's χ^2 test and the Mann-Whitney test. Insufficient vaccination coverage among patients with IBD and JIA is influenced by both parental concerns and the cautious approach of specialists. The main barriers include medical exemptions, concerns about disease exacerbation, and inadequate coordination between primary care physicians and specialists. Improving vaccination coverage requires the development of personalized immunization strategies, interdisciplinary collaboration, and educational programs for both physicians and parents. To increase vaccination coverage, personalized immunization strategies, interdisciplinary collaboration, and educational programs for doctors and parents are needed.

Keywords: vaccination, juvenile idiopathic arthritis, inflammatory bowel disease, vaccination coverage, immune-mediated diseases

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Introduction. Vaccination remains the cornerstone of preventing vaccine-preventable infections in paediatric populations, yet it is critically important and often more complex for children who receive long-term immunosuppressive therapy for juvenile idiopathic arthritis (JIA) or inflammatory bowel disease (IBD) [4, 7, 14]. Immunosuppression amplifies susceptibility to common pathogens and increases the likelihood of severe disease courses and complications. Consequently, both ECCO [7] and EULAR [5] recommend that these patients follow an accelerated and, where possible, complete schedule of inactivated and live vaccines prior to or, when necessary, during treatment.

Adherence to immunization schedules can vary markedly across patient groups and is influenced by awareness, health literacy, and personal attitudes. Individuals with IBD and JIA belong to a high-risk cohort for infectious complications, making vaccination a cornerstone preventive strategy [1]. Their increased susceptibili-

ty stems not only from the autoinflammatory disease itself but also from the use of immunosuppressive agents [3, 6, 13]. In this population, immunization serves both a preventive and therapeutic purpose, lowering the incidence of severe infections and improving the overall prognosis of the underlying disease [2, 15].

Ensuring robust vaccination coverage in children with immune-mediated inflammatory diseases, including JIA and IBD, therefore remains a pressing challenge in pediatrics [10]. These patients are more prone to severe infections and often undergo prolonged immunosuppressive therapy, which can compromise their ability to mount a full vaccine-induced immune response [5, 6, 14, 16].

Although vaccination records are routinely documented, they do not always guarantee effective protection some patients exhibit so-called immunological gaps, meaning sub-protective antibody levels despite completed immunization [4, 14]. This hidden vulnerability mandates the systematic incorporation of post-vaccination immunity monitoring into the routine management of children with IBD and JIA.

Immunization is a shared responsibility of the treating specialist (gastroenterologist or rheumatologist), the primary-care pediatrician, and the child's parents [9]. Clear communication pathways must ensure that each stakeholder understands their role, thereby providing the child with timely protection [12]. Such coordination not only improves vaccine adherence but also prevents the transfer of responsibility between healthcare professionals and the family.

Objectives To analyze the attitudes and practices of parents and physicians (gastroenterologists and rheumatologists) toward vaccinating children with inflammatory bowel disease and juvenile idiopathic arthritis.

Materials and Methods. Study design. This was a single-centre, cross-sectional comparative study based on an anonymous online survey conducted from January to April 2022.

Participants. Two main respondent groups were enrolled:

1. **Parents** of children with juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and of healthy children.
2. **Physicians** paediatric gastroenterologists, paediatricians, and rheumatologists who voluntarily completed the questionnaire.

Data collection. Information was gathered with a purpose-designed questionnaire that covered:

- Demographic characteristics of respondents;
- Vaccination coverage and reasons for refusal or delay;
- Sources of information on vaccination;
- Trust in vaccines;
- Parent–physician interaction regarding immunisation.
- The survey was administered online via professional medical networks and parent community groups.

Statistical analysis. Continuous variables are presented as mean ± standard deviation (mean ± SD) or, when non-normally distributed, as median with interquartile range (median [IQR]). Categorical variables are expressed as absolute numbers and percentages.

Between-group comparisons were performed with one-way analysis of variance (ANOVA) for continuous data and the Pearson χ^2 test for categorical data. The Mann–Whitney U test was applied for non-parametric comparisons. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Cases with missing values were excluded from the analyses. Statistical calculations were carried out with Statistica, version 10.0 (StatSoft Inc., USA).

Ethics approval. The study was approved by the Ethics Committee of Saint Petersburg State Pediatric Medical University (Protocol No. 09/02, 11 February 2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

Results. Demographic characteristics of respondents. A total of 287 respondents were enrolled in the study and were stratified into two overarching categories.

- **Parents** of children with inflammatory bowel disease (PIBD, n = 51), juvenile idiopathic arthritis (PJIA, n = 81) and healthy children (HC,n = 58).
- **Physicians**, comprising paediatric gastroenterologists (n = 51) and rheumatologists (n = 46), whose median years of professional experience were 13.6 years (2.7–17.0) and 7.8 years (2.0–18.0), respectively (Table 1).

Across all study cohorts, respondents were predominantly female; their proportion was slightly lower among parents of children with juvenile idiopathic arthritis (JIA) 87.7 % (71/81). All physicians surveyed (gastroenterologists, n = 51; rheumatologists, n = 46) had higher professional education (100 %). By contrast,

Table 1

Demographic characteristics of respondents

Parameter	Gastroenterologists. (n=51)	Rheumatologists. (n=46)	Parents of children with IBD. (n=51)	Parents of children with PJIA. (n=81)	Healthy Controls. (n=58)	p-value
Gender. female. n (%)	48 (94.1)	43 (93.5)	49 (96.1)	71 (88.7)	57 (98.3)	0.123
Education. higher. n (%)	51 (100.0)	46 (100.0)	33 (64.7)	66 (81.5)	45 (77.6)	<0.001
Employment rate. employed. n (%)	51 (100.0)	46 (100.0)	32 (62.7)	48 (59.3)	37 (63.8)	<0.001

Table 2

Analysis of antibody levels to vaccine-preventable infections

Parametr	Parents of children with IBD, (n=51)	Gastroenterologists, (n=51)	Parents of children with JIA, (n=81)	Rheumatologists, (n=46)	p-value
Antibody monitoring prior to immunosup-pressive therapy, n (%)	22 (43.1)	18 (35.3)	24 (29.6)	26 (56.5)	0.043

the prevalence of higher education was markedly lower among parents, reaching its minimum in the group of parents of children with inflammatory bowel disease (IBD) 64.7% (33/51). The highest proportion of unemployed respondents was observed in the JIA parent group 40.7% (33/81).

Among gastroenterologists, 23.5% (n=12) had more than 10 years of practice, and 56.8% (n=29) also practised general paediatrics. In the rheumatology cohort, 54.0% (n=25) had > 10 years of experience, and 78.3% (n=36) likewise worked in paediatrics, underscoring the interdisciplinary nature of their clinical activity.

Practice setting also differed between the specialties: 61% of gastroenterologists and 52% of rheumatologists were employed in outpatient care, highlighting the substantial share of specialists operating at the primary-care level and emphasising their pivotal role in vaccination strategies.

Vaccination coverage and reasons for refusal. According to parental reports, age-appropriate immunisation in line with the National Immunisation Schedule had been completed in 79.9% of children with juvenile idiopathic arthritis (JIA) and 82.3% of those with inflammatory bowel disease (IBD). Following diagnosis, routine immunisation was continued in merely 14.3% of children with IBD, underscoring substantial shortcomings in catch-up vaccination and the need for early review of vaccination status and personalised schedules in both immune-mediated disease groups.

The most frequently cited reason for deferring vaccination in both IBD and JIA was the child's unsatisfactory health status; refusal was less common among parents of IBD patients than among parents of JIA patients or healthy controls.

Physician responses revealed divergent perceptions of immunisation. While most clinicians 88% of paediatric gastroenterologists and 69.6% of rheumatologists did not associate vaccination with the development of immune-mediated inflammatory diseases, 18% of gastroenterologists and 47.8% of rheumatologists explicitly advised against vaccinating patients during ongoing treatment (p=0.009). This indicates a more conservative stance among rheumatologists, which may contribute to lower vaccine uptake in the JIA population.

Post-vaccination reactions. Parents reported the following reactions after immunisation:

- No adverse events: 38 children with inflammatory bowel disease (IBD) – 74.5%; 41 children with juvenile idiopathic arthritis (JIA) – 50.6%; and 31 healthy controls – 53.5% (p = 0.02).
- Fever: 11 children with IBD – 21.6%; 27 with JIA – 33.3%; and 14 controls – 24.1%.
- Local reaction (erythema or oedema at the injection site): 2 children with IBD – 3.9%; 13 with JIA – 16.1%; and 13 controls – 22.4%.

According to the physician survey, 13.7% of paediatric gastroenterologists and 21.7% of rheumatologists believed that vaccination could trigger a disease flare; an additional 21.6% and 34.8%, respectively, answered "rather yes than no" (p = 0.083). Such concerns may contribute to the lower rate of immunisation recommendations issued by rheumatologists and, consequently, to reduced vaccine adherence among parents of children with JIA.

Role of healthcare personnel in vaccination decisions. Parental engagement in vaccine decision-making was strongly influenced by the treating physician's opinion and the quality of communication. Nevertheless, discussions of immunisation with medical specialists were far from universal: only 32% of parents of children with IBD and 28.4% of parents of children with JIA reported having such conversations. Preparation for immunosuppressive therapy also differed: antibody titres were checked more often in the IBD group (43.2%) than in the JIA group (29.6%).

Overall, 84% of parents of children with IBD stated that their physicians encouraged vaccination, whereas the corresponding figure among parents of children with JIA was 69.1%.

Among clinicians, 32 % of gastroenterologists and 21.7% of rheumatologists did not involve themselves in the vaccination process, considering it the responsibility of primary-care physicians (p=0.009). This division of duties and fragmented approach indicate insufficient coordination among subspecialists, paediatricians and families, which can lead to inconsistent recommendations and hinder parental decision-making on immunisation (Table 2).

Principal reasons for parental refusal of vaccination. Temporary medical contraindications: reported for 9 of 51 children with inflammatory bowel disease (IBD, 17.6%), 14 of 81 with juvenile idiopathic arthritis (JIA, 17.3%), and 2 of 58 healthy controls (3.4%; p < 0.0001). Complete rejection of immunisation: 0 of 51 children with IBD (0%), 2 of 81 with JIA (2.5%), and 3 of 58 controls (5.2%; p = 0.00001).

Barriers identified by clinicians. Among physicians, the leading impediment to vaccination was parental fear of disease flare-ups, cited by 82.4% of paediatric gastroenterologists and 100% of rheumatologists (p=0.003). Additional obstacles included dissemination of inaccurate media reports on vaccine adverse effects (51.0% vs. 80.4%; p = 0.003), concerns expressed by primary-care physicians (37.2% vs. 56.5%; p = 0.058), and insufficient awareness among parents and physicians of the need for immunisation (58.8% vs. 76.1%; p = 0.071) (table 3).

These findings underscore the necessity of an integrated strategy enhanced

Table 3

Adherence to vaccination: parents' and specialists' opinions

Parametr	Parents of children with IBD, (n=51)	Gastroenterologists, (n=51)	Parents of children with JIA, (n=81)	Rheumatologists, (n=46)	p-value
Vaccination was discussed with a doctor, n(%)	16 (31.4)	35 (68.0)	23 (28.4)	36 (78.3)	<0.001
Physician's advice as an incentive for vaccination, n (%)	42 (82.4)	-	56 (69.1)	-	0.137
Do not participate in vaccination, n (%)	-	16 (31.4)	-	10 (21.7)	0.360
Discouraged from vaccination during treatment, n (%)	-	9 (17.6)	-	22 (47.8)	0.002

educational initiatives for both clinicians and parents, clear clinical guidelines on immunisation, and improved coordination between paediatricians and subspecialists to increase vaccine coverage in children with IBD and JIA.

Discussion. The study revealed substantial differences in vaccination coverage among patients with IBD, JIA, and healthy children, as well as divergent views on immunisation held by parents and physicians. These findings highlight barriers related to awareness, clinical guidance, and perceived vaccine safety patterns previously described by Lester R. (2015) [9].

One key determinant of coverage is the cautious approach to immunisation adopted by rheumatologists, which shapes the advice given to parents of children with JIA. In the present survey, 47.8% of rheumatologists actively discouraged vaccination during treatment, compared with 18% of paediatric gastroenterologists (p=0.009). This discrepancy may reflect stronger concerns among rheumatologists about provoking disease flares and is consistent with their greater scepticism regarding the safety of live vaccines [11].

Comparison of parental and physician responses suggests that poor coordination among healthcare providers and limited interaction between primary-care and specialty clinicians contributes to suboptimal coverage. A substantial proportion of specialists refrain from actively managing vaccination: 32% of paediatric gastroenterologists and 21.7% of rheumatologists consider immunisation to be the sole responsibility of primary-care paediatricians, which may leave parents without clear guidance.

For parents, the principal barriers continue to be temporary medical contraindications (17.6% in IBD, 17.3% in JIA, 3.4% in controls; p<0.0001) and fear of post-vaccination disease exacerbation. Such apprehension is reinforced by some clinicians: 13.7% of gastroenterologists and 21.7% of rheumatologists consider vaccination a potential trigger, while a further 21.6% and 34.8%, respectively, answered “rather yes than no” (p=0.083), findings echoed in other studies [8]. Insufficient parental knowledge and the impact of misinformation also play a role, as evidenced by the high proportion citing misleading media reports on adverse events (51.0% of gastroenterologists, 80.4% of rheumatologists; p=0.003) [2, 16].

Influence of medical specialists on vaccination decisions. The influence of medical professionals on vaccination decisions remains significant. Parents of children with IBD more often reported that their attending physicians encouraged vaccination (84%) compared with parents of children with JIA (69.1%). In addition, 43.2% of parents of IBD patients checked antibody titres before starting immunosuppressive therapy, which is also an important element in building trust in vaccination. These data highlight the need for active physician involvement in educating parents and patients.

The results indicate the need to introduce personalised vaccination strategies for patients with immune-inflammatory diseases. Key measures to improve vaccination coverage may include: developing unified tactical recommendations for vaccinating patients with IBD and JIA that contain clear immunisation algorithms depending on disease stage and current therapy; enhancing interdisciplinary cooperation among paediatricians, gastroenterologists and rheumatologists to produce harmonised recommendations; increasing parental awareness of vaccine safety and necessity through educational programmes and physician-led outreach; and creating an individualised vaccination approach that takes into account disease status, antibody levels and risk factors, thereby increasing the confidence of patients and their families in immunisation.

Thus, better coordination among medical specialists, greater awareness among physicians and parents, and the introduction of personalized vaccination strategies may help increase vaccination coverage among patients with IBD and JIA, reduce the risk of infectious complications and improve their quality of life.

Study limitations. This study has several limitations. First, the survey relied on self-reports from parents and physicians, which may lead to subjective data perception and possible information bias. Second, the study included a limited number of respondents, which may restrict the generalisability of the findings to a broader population of patients and medical professionals. Third, the inability to verify vaccination data against medical records prevents assessment of the accuracy of the responses provided. Further research using objective vaccination data will clarify the identified trends and confirm their clinical significance.

Conclusion. Our study demonstrates that, despite the existence of guidelines and a generally high level of physician awareness, both vaccination coverage and post-vaccination immunity remain suboptimal in children with inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA). We identified significant differences in vaccination management between paediatric gastroenterologists and rheumatologists: some specialists do not perceive immunoprophylaxis as part of their remit, leading to blurred responsibility and less effective communication with parents.

The presence of “immune gaps” in children who have already been vaccinated underscores the need not only for documentary verification of immunisation status but also for laboratory assessment of antibody titres before and during immunosuppressive therapy. Effective vaccination in this population requires coordinated involvement of all stakeholders treating specialists, primary-care paediatricians and parents. Implementing a unified immunisation pathway, centred on antibody monitoring and an individualised approach, could enhance protection and reduce the risk of infectious complications.

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

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE PAND EDUCATION

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CURRENT ISSUES OF TRAINING OF DOCTORS-ORGANIZERS OF HEALTH CARE IN MODERN SOCIO-ECONOMIC CONDITIONS

The aim of the study was to identify ways and opportunities to improve the system of special training of health care managers in the specialty "Public Health and Health Care". Currently, graduates of medical universities, in addition to professional competencies, should demonstrate universal or supraprofessional competencies, including those related to the issues of competent management of medical organizations of various forms of ownership. The article presents an opinion on the ways to improve the training of specialists in the field of public health and health care, substantiates the necessity of teaching the discipline (the module) "Management" for students of medical specialties. The goals, objectives and range of issues to be studied within the discipline "Public health and public health care" at the stages of pre- and postgraduate education in medical universities of Russia are outlined. The conclusion is made that management training, including project-based learning, will allow future doctors to form competencies necessary in modern professional activity.

Keywords: medical education, health care organization, management in health care, training of managers of medical organization.

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Introduction. In modern Russia, which is purposefully developing a market economy, the issues of management personnel training are of paramount importance for all spheres of professional activity and industries. This also applies to the training of modern managerial personnel, the category of which includes doctors-organizers of health care. In the training of this category of managers of medical organizations of the industry, a particularly important place is occupied by training in the specialty "Public Health and Health Care".

The purpose of this study was to identify ways and opportunities to improve the system of special training of health care managers in the specialty of "Public Health and Health Care".

Materials and methods of the study. The method of content analysis and monographic method were used in the study. Materials of special publications, orders and legislation in the field of health care were studied, personal experience of the authors of the article was generalized.

Results of the work. Physician-organizer of health care occupies a special position among representatives of other medical specialties, and in this aspect, training at the site of postgraduate and additional professional training is a particularly important direction of his professional development and staff growth.

Speaking about the very first stage of medical education of a future doctor, i.e. his/her training at the student bench of a medical university, it is necessary to understand that this is the very first stage in the special education that the medical profession requires. A medical graduate

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at the beginning of his professional activity is very far from being able to carry out the functions that society imposes on him quite consciously and at the proper level. At this, the very first stage of his activity, the young doctor has an understanding of his place and purpose in the clinical specialty. If a young doctor, for one reason or another, loses interest in the clinical specialty, he has two ways of his further professional life, the first - to leave the field of medical activity altogether, or to keep himself in the industry as a doctor-organizer of health care. The second option of situation development for such a doctor is more attractive, especially from the point of view of his retention and use in the medical industry, because the costs invested in his training should pay off regardless of whether they are budgetary or extra-budgetary funds. Such professional reorientation with retention in the industry is possible through specialization, for example, in public health and health care.

At the stage of postgraduate education there is a need for primary specialization, which allows both to ensure the formation of the necessary knowledge and skills, and to carry out a preliminary selection of persons with abilities for managerial activity. This process simultaneously acts as a filter to assess the potential effectiveness of a doctor as a manager, to determine the vector of his professional growth - from a manager of a medical organization to a specialist of the hardware level.

According to the student survey data obtained by O.A. Bashmakov (2015), 41.9% of the respondents would like to simply complete their studies at the university in a clinical specialty (Fig. 1-2). However, more than half of the surveyed students (52.2%) expressed interest in occupying management positions in medical organizations (hereinafter - MOs), despite the lack of a clear understanding of the functional specifics of these positions. This trend can lead to the formation of a distorted perception of the role of a manager as the easiest and most prestigious trajectory of professional development, which, in turn, negatively affects the quality of management in medical organizations [1].

Ultimately, this situation may have a negative impact on the provision of the treatment and preventive sector of the industry and the market of medical organizations with qualified managers - doctors-organizers of health care.

Based on the results of the study, it can be concluded that the process of identifying and training potential managers should begin already within the framework of basic medical education. The leading role in this process is played by the departments of public health and health care, whose task, in addition to the implementation of standard educational programs, should be the identification of students with high managerial potential and their extended training in the field of management, marketing, economics, law and entrepreneurship. This approach contributes to the formation of competencies necessary for a new type of physician-manager with the orientation on the implementation of his professional activity in the position of not just a medical worker - doctororganizer of health care (doctor-methodologist, medical statistician), but a manager (manager) of one or another level of the health sector.

In the conditions of market economy development, training of specialists in the field of health care organization and public health requires special attention, since the level of competence of these specialists determines the effectiveness and efficiency of the implementation of the State Program "Health Development" both within a particular medical organization and at the level of the entire industry.

However, the educational model of both pre-diploma and post-diploma education implemented in medical universities, which has been preserved until now, is poorly adapted to the new political and economic requirements of the modern Russian state. This leads to the fact that future graduates of medical universities in most cases intuitively choose this or that specialization and the expected place of their professional activity. I.e. their motivation in most cases is not conscious. As a result - errors in the choice of the specialty and the place of future work. The consequence of this is unsatisfactory quality of professional activity. This

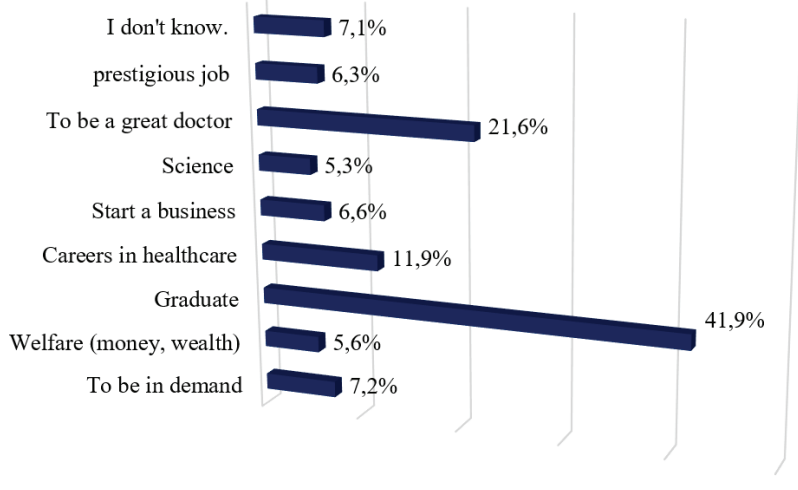

Fig. 1. Goals and objectives of students in future professional activities (%) [1]

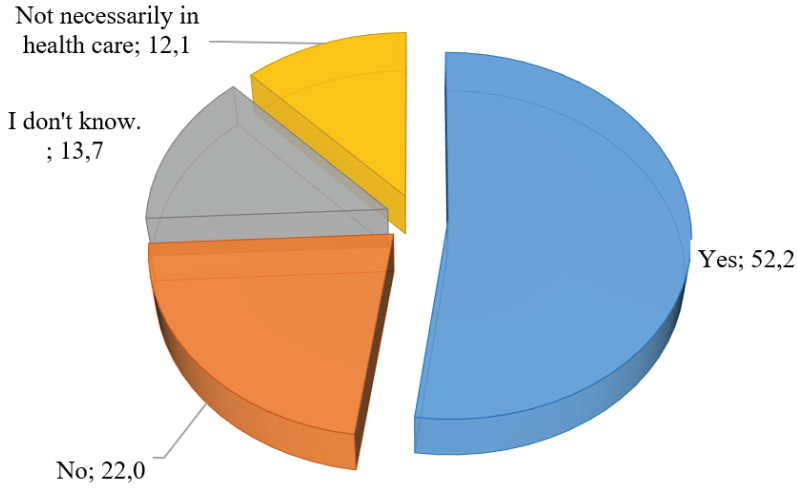

Fig. 2. Distribution of students' responses according to their attitude towards managerial work in healthcare (%) [1]

situation does not contribute both to the career growth of such doctors and their retention in the health care industry as labor resources.

This situation is especially acute in the process of training future doctors-organizers of health care. Students' motivation to obtain the specialty of health care organizer is often associated not with the presence of professionally significant qualities and competencies, but with disappointment in other medical specialties. So-called "successful" by academic performance students are 1.5 times less likely to strive for the implementation of their professional activity as doctors-organizers of health care. Less successful students just give preference in their future professional activity in health care organization.

As follows from the report of the head of the department, Doctor of Medical Sciences, Professor V.A. Reshetnikov (I.M. Sechenov PMSMU) "Modern approaches to the training of specialists in the field of health care organization and public health" [2]. [2], about 40% of all health care organizers are doctors "who by fate got to the positions in the health care industry"

This situation indicates the need for deep transformation of the training system in educational organizations of higher and additional medical education. These transformations involve updating and strengthening the role of technologies that form specialists on the basis of their personal characteristics, psychophysiological features and qualities integrated into professional potential. It is obvious that there is a need to optimize the training of specialists in new conditions using new educational technologies.

The most effective tool for assessing students' professional predisposition to management is psychophysiological testing. It allows not only to identify aptitudes to management work, but also to form individual educational trajectories that increase the effectiveness of training and contribute to the rational use of human resources in health care. In the future, this approach will contribute to the effectiveness of their career guidance and selection for further training in residency and will create prerequisites for a more effective use of human resources.

However, this is only the first step to a systemic solution of the issue concerning the development of the model of training physicians-organizers of health care. From the point of view of the modern economic model, a health care organizer is a potential head of a medical organization, i.e. a manager - manager.

The Strategy for the development of health care of the Russian Federation for the period up to 2025 (in the wording of the Decree of the President of the Russian Federation from

27.03.2023№ 202) noted the need to improve the system of medical education and staffing [3]. In the context of this document, training of managerial personnel is one of the main objectives of the health care sector. However, both in the issues of personnel training and management, both universities and medical organizations remain outdated, mostly they make decisions only at the level of managers (rectors, directors, chief physicians), strictly subordinated to the management vertical of the health sector, where any information comes from the top down. This state of affairs is a consequence of the Taylor administrative model (behavioral model), based on the principle of standardization and rigid subordination. The main disadvantage of this model is the underestimation of the human factor, reliance on optimization and rationalization of the production cycle. And although this administrative model was criticized by apologists of MarxistLeninist philosophy, it became the dominant model throughout the USSR [4].

The head of a sectoral educational or medical organization is fully subordinate to higher apparatchiks who distribute treasury funds. He does not have sufficient power, but is directly dependent on government functionaries, who can remove him from his leadership position at any time.

Modern managers in the field of health care face a high level of administrative burden, the need for prompt decision-making, rapid adaptation to changing conditions of activity, which requires from them a high level of stress resistance. These professional qualities cannot be formed exclusively within the framework of a standard course in the discipline of "Public Health and health care". Many nuances of modern managerial activity inevitably emphasize the importance of obtaining special education beyond the traditional educational programs of medical universities. Therefore, there is a need to revise both the content and methods of training with a focus on the development of universal competencies, including project management, strategic thinking and managerial responsibility.

This state of affairs obliges the teaching staff of the departments of public health and health care to pay special attention to the need to form readiness for labor activity of future graduates of medical universities in the direction of "Management".

The strategic direction of economic and social development of modern Russia at this stage of development requires the organization of training of completely new highly qualified subjects of professional activity. In the conditions of intensive development of the market economy, the foundation of which is private property with the inevitable capitalization of the results of the production of goods and services, the management of MO involves the transformation of the functions of the top administrative level into managerial ones. Simply doctors, even if trained in the residency on health care organization, do not have the necessary knowledge, skills and abilities to effectively manage such a multifaceted subject of economic turnover in the market of medical services as MO. Today, holding a managerial position, a medical worker essentially ceases to be a doctor. The socio-economic situation affecting the organization of the entire economic activity of the MO forces him to transform into a manager in the market of medical services. And this manager acts either as a hired professional manager, namely in the sector of private medicine, or as a founder and owner of his own medical production (business). At the same time, economic and managerial knowledge in his/her activity should be of fundamental importance, because the level of managerial literacy in terms of personnel, financial and economic management will determine the sustainability and performance of the managed medical organization [4].

IO leadership involves two of the most important managerial qualities:

The ability to detach and the ability to assess a situation and take a "bird's eye view" of it;

the ability to take responsibility for the performance of his subordinates.

This is the very quality of a manager that distinguishes management from traditional hardware administration. This is the main thing that distinguishes a health care manager from a functionary of the health care system.

Alas, but this is exactly what is not taught today in the departments of public health and public health care. They teach medical statistics, medical demography, criticism of bourgeois theories of medicine, rules and requirements for drawing up certificates of incapacity for work, organizational bases of medical and social expertise, normative and legislative requirements for the organization of medical care for the population

at different levels of the public sector of the industry, etc. Undoubtedly, all these sections of the discipline are necessary for obtaining basic training, are important for gaining knowledge and forming the necessary competencies in the context of public health and organization of medical care to the population in the state-municipal sector of the industry. However, in the conditions of market economy, they are absolutely insufficient for competent, qualified, competent, effective and rational organization of both medical care of the population and provision of medical care to patients.

From the point of view of the canons of scientific and educational discipline "public health and public health care", it is possible to continue to train future doctors-organizers of public health care at the specialized departments, but the fact is that, firstly, they are unlikely to rise beyond the positions of medical statisticians and medical methodologists in their professional career, and secondly, the cost of their labor in the market of specialists will be negligible or, if more delicately put, budgetary, i.e. profitless. After all, the main thing in the process of their training today comes down to the fact that the content of educational programs in the subject "public health and health care" is fully consistent with the requirements of the professional standard for the same specialty.

Today, the shortage of qualified managers in the healthcare sector is one of the most acute problems of staffing the industry. According to expert estimates, the minimum need for medical administrators and managers is not less than six positions for every 10 thousand population. However, the actual supply of managerial personnel - doctors-organizers of health care (including heads of large MOs of various forms of ownership, heads of specialized departments, managers of entrepreneurial structures), falls far short of this indicator. This deficit is especially acute in the private health care system, where the level of satisfaction of the need for professional management training is only 0.02%, and in the public sector it does not exceed 2% [5].

A paradoxical situation has developed in Russian healthcare. While for clinical and pharmaceutical specialties, higher medical schools have developed scientifically based training programs, including residency and postgraduate education stages, the management of a medical organization is often outside the scope of systematic educational training. Often physicians acquire management skills after they have been appointed to a management position, which is contrary to the principles of professional competence. In most cases, clinicians with a qualification category in one of the therapeutic or surgical specialties, who have, at best, completed short-term professional retraining courses in public health and health care programs, are appointed to managerial positions in state and municipal health care institutions. However, even so, the vast majority of them do not have specialized education in management. And this is despite the fact that the already formed market relations require from the heads of MIs to acquire new knowledge, skills and abilities, which include effective use of the mechanism of multichannel financing, economical use of limited health care resources, redistribution of functions between primary and specialized medical care, prevention, treatment and rehabilitation.

The situation is very difficult with the teaching staff of specialized departments of the specialty "public health and health care". The main staff of these educational units of medical universities are the same doctors! Some of them came to the department by one or another circumstance from clinical medicine, having defended a candidate or doctoral dissertation, someone after residency at this department entered postgraduate studies, again, to write a candidate dissertation, after the defense of which remained at the department in one or another position. But few of them during their entire pedagogical life get a second higher or additional professional education in economics, law, management, marketing and entrepreneurship. At best, such departments of medical universities can employ teachers who do not have higher medical education, but are specialists in the above-mentioned areas. This format is acceptable, but it should be understood that these teachers, who do not have professional knowledge in the field of medical sciences, will try to adjust the specifics of medicine and health care to the economic, organizational and management clichés of the sphere of production, more precisely, industrial. As a result, the process of training students with such teachers will contrast with the established canons of formation of a doctor, his culture, traditions, customs, peculiarities of psychology, the concept of medical skill with its mission and model of professional medical activity.

This state of affairs leads to the fact that in the market of educational services the niche of training modern managers of health protection sphere is filled by commercial offers of various non-medical educational organizations of private form of ownership, providing interested medical workers with an opportunity to become holders of appropriate diplomas of so-called "health managers" for adequate, as a rule, not very big money. The level of professional knowledge of such "managers", of course, leaves much to be desired, but the potential opportunities to fill vacant positions of heads of MOs are significantly increasing.

The solution to this problem, on the one hand, lies in the context of diversification of educational programs in public health and public health care with their orientation to modern market requirements, and on the other hand, requires the creation of conditions for teachers of the same departments to undergo training in programs of additional professional education on the basis of non-medical universities. Also, programs of additional professional education should be available on the platform of medical universities for those who have received higher non-medical education. This approach will allow them to master the appropriate amount of knowledge on the organization and informatization of health care, as well as pedagogy and androgogy. In turn, this will help the management of medical universities in making effective personnel decisions related to the involvement of these specialists in professional pedagogical activities at the relevant specialized departments of medical universities.

Another important aspect is that within the framework of continuing medical education programs it is more rational to stimulate the formation and promotion of short-term cycles of thematic lectures, seminars and practical classes of those representatives of the teaching staff of the departments of public health and public health, whose scientific and methodological materials (developments) have the potential for demand from certain consumers of intellectual products. It is such specialists of the departments can make a real contribution to at least two aspects of professional pedagogical activity. First, they can and should become the main mediators of extrabudgetary activities of the departments. Secondly, being market teachers, i.e. demanded by consumers as suppliers of intellectual product, they can become drivers of marketing offers in the market of educational services to promote not only their own educational programs, but also diversified educational products taking into account modern trends and requirements of departmental programs of pre-diploma, post-diploma and additional professional education.

As international practice shows, nowadays the key role in ensuring the competitiveness of the economy and social sphere belongs to human capital, whose contribution to economic growth is determined by higher labor productivity of qualified and educated workers, but, most importantly, it acts as a source of new ideas and innovations, a factor facilitating their perception and dissemination. This largely determines the requirements to the quality of labor force and the system of personnel training. It is the interface between the sphere of labor and the sphere of professional training that is the cornerstone of the entire system of reproduction of qualified workers in the health care system.

Nowadays, qualification is increasingly associated with competencies that an employee possesses and can use effectively in labor activity.

In the West, the need for extended institutionalization of the process of reproduction of qualified workforce was quickly enough realized, which eventually led to the development and implementation of national qualification systems and professional standards. However, unlike the domestic analogues developed by the Ministry of Labor of Russia, by their functional purpose professional standards of countries with developed market economies reflect not only normative requirements for the qualification of workers, but also the prerequisites and conditions of professional activity formed by the real business environment, which stimulate a high level of qualification of the workforce, corresponding to the innovative way of development of national economies. And what is certainly important is that professional standards should fully correspond with the educational standards for training specialists, and not reconfigure them to their own regulatory and legislative content. It should be taken into account that the basic training of specialists is carried out in accordance with educational standards, but additional (postgraduate) professional education is carried out according to the thematic programs offered by universities, developed and implemented taking into account the qualifications and competencies of the pedagogical staff of the given university.

Taking into account the fact that training in VET programs is associated with the disconnection of employees from their workplaces, at present, medical universities have established a practice that allows for training on thematic courses and professional development cycles in the amount of 72, 100, 144 hours. Educational practice shows that it is more expedient to conduct training within these cycles on a modular basis.

Thus, in the specialty "Health Care Organization and Public Health" it is more logical and rational to offer to the attention of potential students such thematic modules as "Economics of health care and medicine as an element of market economy", "Models of economic entities of economic turnover in the field of health protection", "Organization of medical business (business), types of entrepreneurship in the field of health protection", "Management, marketing and economic analysis of the activities of entities of economic turnover in the field of health protection", "Technologi

Currently, in many departments of public health and public health organization, the issue of teaching such a discipline as "Management" ("Management") is perceived differently. The traditional approach to teaching public health and public health care, based on the principle of "purity of the subject", uncompromisingly defended by teachers of the Soviet school of social hygiene and health care organization, carefully substitutes any mention of the terms "management" or "management" with such concepts as organization and administration. And only in those departments where professional economists, managers and legal scholars work in the teaching staff, the issues of teaching management (management) are given due attention.

It is likely that an effective solution to the issue of teaching this discipline, as well as a number of similar non-medical disciplines, would be properly developed in the conditions of creation in medical universities of specialized departments on management (scientific specialty 5.2.6. "Management"). Dolicensing in this discipline is not a very labor-intensive and economically costly process. This administrative maneuver of the medical school management would allow to get an answer to the burning question whether it is necessary to teach the discipline "Management" to future medical workers.

Modern challenges facing the health care system require not only updating the content of professional training, but also the introduction of innovative educational approaches, among which project-based learning plays a key role. This method, which is widely used in pedagogical and technical universities, is not yet widespread enough in medical education. At the same time, the project approach has a high potential in the formation of universal (supraprofessional) competencies, including the ability to manage a project at all stages of its life cycle - a competency provided by the federal state educational standards for specialty and master's degree programs in health care and medical sciences. [6].

Implementation of project-based learning in the framework of physician training allows to form not only managerial, but also communicative, organizational and analytical skills that are critical for future medical leaders. As a rule, elements of the project approach are introduced into the existing disciplines of the basic part of the curriculum, in which students are offered to work in project groups. Such work includes:

– definition of the actual problem;
– formulating a project assignment;
– Drawing up a step-by-step implementation plan;
– distribution of roles and functions in the team;
– Developing criteria for evaluating the success of the project; - defense of the results in front of an expert audience [7].

These elements of project-based learning should be aimed at building project teamwork skills, as well as building basic skills in project activities and project management.

As a result, students develop not only knowledge of a specific discipline, but also sustainable skills of interdisciplinary interaction, organizational thinking, responsibility for the result and orientation towards achieving specific goals. In medical education, project-based learning can become an effective tool for training managers of a new type, focused on the integration of clinical, organizational and economic tasks in a unified health care management system.

Some educational institutions are already taking steps in this direction by implementing programs such as "Economics and Management in Medical Organizations". These programs are aimed at forming in students a holistic view of the functioning of a medical organization as a subject of market economy. They include disciplines on management, marketing, financial planning, legal support of medical activities and other aspects of key importance for the effective functioning of the health care system.

Conclusion. Thus, the inclusion of the discipline "Management" in the structure of educational programs of medical universities should be considered as an objective necessity and the most important condition for the training of highly qualified medical personnel. Only in the conditions of systematic introduction of

managerial knowledge and skills it is possible to form specialists who are able to function effectively in modern socio-economic conditions and ensure sustainable development of health care industry.

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ORGANIZING MEDICAL CARE FOR CORONAVIRUS INFECTION IN THE YAKUT ARCTIC

The article presents a retrospective analysis of COVID-19 morbidity and mortality in the Arctic zone of the Republic of Sakha (Yakutia), and also considers key aspects of organizing medical care during a pandemic in this territory, which differs significantly in all conditions from most of the region.

In 2020, the incidence of COVID-19 in the Yakut Arctic exceeded the Russian average by 2 times, the republican average - by 1.8 times, by 2023 the share in the Arctic zone of the Republic of Sakha (Yakutia) in the overall morbidity structure decreased. For 2019-2023. In the Arctic zone of the Republic of Sakha (Yakutia), 211 deaths were recorded (6.2% of the total number in the republic), the peak of mortality occurred in 2021 (124 cases) due to the spread of the Delta strain.

The COVID-19 pandemic has clearly demonstrated that in the modern world, the inaccessibility of populated areas does not guarantee their epidemiological safety. The experience gained emphasizes the need for investment in equipping remote medical institutions, digitalization of healthcare and adaptation of anti-epidemic measures taking into account the geographical and social characteristics of the Arctic.

Keywords: coronavirus infection, COVID-19, Yakutia, Arctic zone, extreme climate, organization of medical care.

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Introduction. In the Republic of Sakha (Yakutia), the first case of COVID-19 was recorded on March 17, 2020, and according to data from March 18, 2025, 247,602 cases of the disease were registered in the region with a cumulative number of deaths equal to 2,169 cases (fatality rate 0.88%) [1, 5].

The Yakut Arctic is characterized not only by extreme climatic conditions and a vast territory, but also by poorly developed transport infrastructure. Of the 84 settlements in the Arctic zones of the Republic of Sakha (Yakutia), about half are located more than 100 km (by air) from their district centers, and more than 80% have no land communication with them for six months or more. For example, the village. Kharyyalakh of the Olenek district, located just 2 km from the district center, remains cut off from the Central Regional Hospital in the spring and autumn. Theoretically, these facts should have contained the spread of the infection, but this was not observed. Moreover, the organization of anti-epidemic measures, includ-

ing the deployment of hospitals, provision of medicines, diagnostic tests, etc., in the Yakut Arctic was achieved with significant difficulties and financial costs.

Objective: to analyze the incidence and mortality of the population from coronavirus infection in the Arctic zone of the Republic of Sakha (Yakutia) and the organization of medical care during the pandemic.

Materials and methods: The article presents a retrospective analysis of the incidence and mortality of the population from coronavirus infection in the Arctic zones of the Republic of Sakha (Yakutia) for 2020-2023 based on official statistics of the Territorial Administration of Rospotrebnadzor in the Republic of Sakha (Yakutia) and reporting forms of the Ministry of Health of the Republic of Sakha (Yakutia). To calculate indicators reflecting the intensity of the epidemic process with COVID-19, information on the population of the republic and the Arctic regions provided by the State Statistics Committee of the Republic of Sakha (Yakutia) was used. The real positive experience of organizing medical care for the population in the Arctic zones of the Republic of Sakha (Yakutia) during the coronavirus pandemic is described.

Results. It is well known that the level of social activity of the population directly affects the intensity of the epidemic process. In this regard, immediately after humanity realized the danger of COVID-19, various restrictive measures were introduced around the world [6]. However, in the vast majority of countries, it led to a colossal overload in the field of healthcare and millions of human casualties [8, 11]. In Russia alone, in 2020-2021, COVID-19 claimed the lives of at least 600 thousand people. In addition, such sectors of activity as transport, culture, sports, tourism, education, etc. suffered everywhere [4, 7, 9, 10]. Of course, Yakutia was no exception.

In March 2020, a decree of the head of the region banned mass events (with the exception of settlements that do not have year-round motor transport) and suspended the activities of shopping centers, gyms, computer clubs, etc[1]. On April 2, 2020, when 15 cases of the disease were noted in the Republic of Sakha (Yakutia), restrictive measures were introduced in organizations with round-the-clock presence of people[2]. In May 2020, the above-mentioned decree of the head of the republic was supplemented with a clause on mandatory 14-day quarantine for those arriving in Yakutia from other subjects of the Russian Federation (with the exception of employees of transport and logistics companies, law enforcement agencies and some other categories of citizens).

Table 1

The number of telemedicine consultations on COVID-19 issues conducted with central district hospitals in the Arctic zones of the Republic of Sakha (Yakutia)

District	Years			
	2020	2021	2022	2020-2022
Abyisky	14	29	11	54
Allaikhovsky	5	10	6	21
Anabarsky	7	3	1	11
Bulunsky	8	46	4	58
Eveno-Bytantaysky	17	23	3	43
Momsky	53	39	23	115
Nizhnekolymsky	27	85	13	125
Oleneksky	10	35	12	57
Srednekolymsky	4	22	4	30
Ust-Yansky	18	9	0	27
Verkhnekolymsky	8	17	19	44
Verkhoyansky	19	11	8	38
Zhigansky	3	5	3	11
Total for the arctic zone	193	334	107	634
Total for the Republic of Sakha (Yakutia)	1684	2001	329	4014
Share of telemedicine consultation in the arctic zones of the Republic of Sakha (Yakutia), %	11.5	16.7	32.5	15.8

In order to combat the coronavirus infection, regional authorities purchased personal protective equipment, test systems, medical equipment and medicines, launched the Hotline information service and the Medset application for remote monitoring of the health of self-isolated people, and increased home care as much as possible [2]. Remote prescriptions for basic therapy of chronic diseases were also introduced, and the media increased educational work on the prevention of COVID-19. Anti-epidemic measures were established in shift camps of industrial enterprises, workers underwent preliminary observation, double PCR testing and enzyme immunoassay for the presence of IgM and IgG antibodies. Weekly video conferences with employers were organized, and morbidity in these institutions was constantly monitored.

However, the high contagiousness of the infection, the peculiarities of local logistics, insufficiently effective control over compliance with all necessary safety measures, a large number of so-called shift camps, and most importantly, the underestimation by a significant part of the population of the danger of the new infection and, as a result, an irresponsible attitude to the isolation regime, contributed to the rapid spread of COVID-19 throughout the republic, especially in the Arctic zones of the Republic of Sakha (Yakutia), which at first created significant difficulties in the prompt organization of anti-epidemic measures, the deployment of hospitals and the provision of medicines.

To increase the existing bed capacity in the region, temporary hospitals and outpatient centers were opened on the territory of sports facilities and educational institutions, and a number of medical organizations in the region were repurposed. Of course, these forced measures had a negative impact on the state of healthcare in the region. Thus, in 2020, the hospitalization rate compared to 2019 decreased by 23.7%, the volume of inpatient care - by 24%, the intensity of use of beds in hospitals - by 14.8%. Mainly due to the increase in the number of infectious disease beds for adults (from

[1] Decree of the Head of the Republic of Sakha (Yakutia) «On the introduction of a high alert regime in the Republic of Sakha (Yakutia) and measures to counter the spread of a new coronavirus infection (COVID-19)» dated March 17, 2020 No. 1055.

[2] Resolution of the Chief State Sanitary Doctor of the Republic of Sakha (Yakutia) «On the introduction of restrictive measures (quarantine) for a new coronavirus infection in organizations with round-the-clock presence of people in the Republic of Sakha (Yakutia)» dated April 2, 2020 No.7.

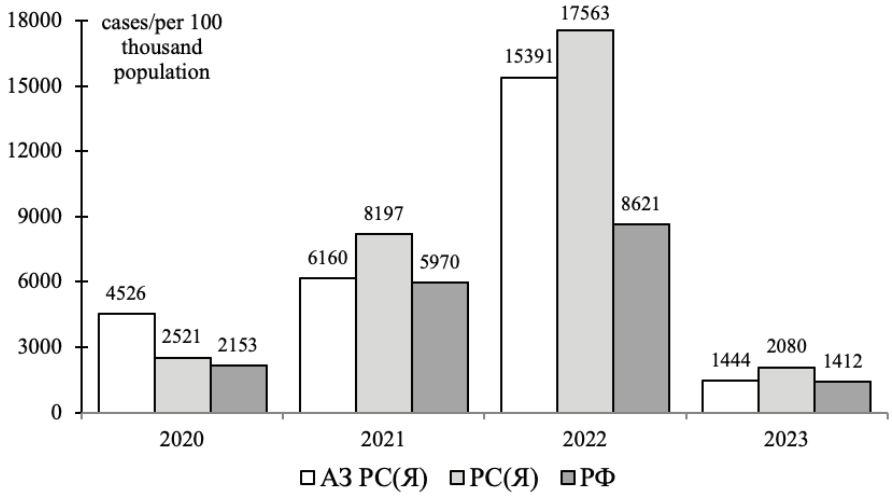
264 to 1691), the number of therapeutic (by 40.9%, or from 1377 to 814 units), tuberculosis (by 29.1%, or from 731 to 518 units), neurological (by 35.8%, or from 386 to 248 units), gynecological (by 35.6%, or from 388 to 250 units), pediatric somatic (by 34.9%, or from 708 to 461 units) decreased. This exacerbated the already complicated situation in healthcare, especially in remote districts [3].

Due to the lack of round-the-clock anesthesia posts in the Arctic zones of the Republic of Sakha (Yakutia) and the overload of the capital's hospitals, the Ministry of Health of the Republic of Sakha (Yakutia) opened inter-district infectious disease centers at large central regional hospitals. Thus, seriously ill patients from the Olenyok district were transported by ambulances to the Bulunsky district, residents of Western Yakutia - to the hospital in the city of Mirny. In a short time, the capacity of laboratories performing PCR diagnostics was significantly increased in the region - up to 4,000 tests were performed per day, which made it possible to identify patients in a timely manner.

In April 2020, a regional telemedicine center for consultations on issues related to coronavirus infection was created on the basis of the Yakut Republican Clinical Hospital by the faculty of the NEFU named after M.K. Ammosov. In the period from 2020 to 2022, specialists conducted more than 4 thousand telemedicine consultations, incl. 639 – for specialists of Arctic central regional hospitals (Table 1).

The first case of coronavirus infection in the Arctic zone of Yakutia was recorded in the Ust-Yansky district on May 5, 2020 (the patient was a demobilized soldier who arrived from the city of Khabarovsk), i.e. 48 days after the first case was recorded in the region. Later, cases of coronavirus infection began to be recorded in other districts of the Arctic zones of the Republic of Sakha (Yakutia). However, despite the relatively late appearance of the infection in the Yakut Arctic, in the first year of the pandemic, the incidence of COVID-19 in the Arctic zones of the Republic of Sakha (Yakutia) was at the level of 4526 cases / 100 thousand inhabitants, i.e. more than 2 times higher than the average in the Russian Federation and 1.8 times higher in the region (Figure). The total number of identified diagnoses of coronavirus infection was 3062 or 12.5% of the total number in Yakutia (Table 2). In subsequent years, namely in 2022 and 2023, the incidence rate continued to grow, but the share of the Arctic zones of the Republic of Sakha (Yakutia) decreased significantly.

According to the results of 2020, the



Incidence of COVID-19 in Yakutia and Russia

Table 2

Absolute number of COVID-19 cases in the Arctic zones of the Republic of Sakha (Yakutia)

District	Years				
	2020	2021	2022	2023	2020-2023
Abyisky	24	66	777	323	1190
Allaikhovsky	88	196	405	1	690
Anabarsky	334	29	262	56	681
Bulunsky	23	426	277	3	729
Eveno-Bytantaysky	408	262	326	17	1013
Momsky	324	640	1027	82	2073
Nizhnekolymsky	398	601	940	107	2046
Oleneksky	411	199	1062	16	1688
Srednekolymsky	274	285	403	14	976
Ust-Yansky	330	558	1065	33	1986
Verkhnekolymsky	161	361	1985	249	2756
Verkhoyansky	286	165	965	26	1442
Zhigansky	1	167	356	1	525
Total for the Arctic zones of Yakutia	3062	3955	9850	928	17795
Share of the total in Yakutia, %	12.5	5.0	5.7	4.5	6.0

share of the child population of the Sakha Republic (Yakutia) among all those infected with COVID-19 was 13.5%, in 2021 the number of infected children increased to 19.6%. The incidence of COVID-19 among children (under 17 years old) by the districts of the Arctic zones of the Sakha Republic (Yakutia) is presented in Table 3. The territorial features of the Yakut Arctic contributed to a gradual increase in the number of infected children in the study area, in 2021, 851 children fell ill, in 2022 - 3761, which amounted to 7.8% of the total number of infected children in Yakutia.

In 2019-2023, only 211 people died from COVID-19 in the Arctic zones, which amounted to 6.2% of the total number of deaths from coronavirus infection in Yakutia for this period (Table 4). The largest number of deaths was observed in the Verkhoyansky (n = 39) and Zhigansky (n = 31) districts. A significant number of deaths in 2021 (124 people) is associated with the circulation of the Delta strain in the population, which is characterized by a more severe course.

The rapid response system should be based on the qualifications of medical workers with a high level of theoretical and practical training in infectious diseases. In order to prevent a significant burden on the healthcare system, it is necessary to strengthen the equipment of even remote medical institutions with modern equipment for early diagnostics, including the ability to conduct PCR diagnostics.

Conclusion: The COVID-19 pandemic has become a serious challenge for

Table 3

Incidence of COVID-19 among children (under 17 years) by regions of the Arctic zones of the Republic of Sakha (Yakutia)

District	Years			
	2021		2022	
	n	per 100 thousand population	n	per 100 thousand population
Abyisky	11	1030.0	336	33038.3
Allaikhovsky	60	7528.2	214	27191.9
Anabarsky	6	476.6	23	1816.7
Bulunsky	69	3046.4	48	2087
Eveno-Bytantaysky	36	3833.9	76	8278.9
Momsky	105	3343.9	366	12461.7
Nizhnekolymsky	164	11365.2	258	17659.1
Oleneksky	53	3386.6	355	22511.1
Srednekolymsky	15	1204.8	199	16583.3
Ust-Yansky	195	12142.0	472	28365.4
Verkhnekolymsky	79	3207.5	855	35389.1
Verkhoyansky	28	1374.6	421	20496.6
Zhigansky	30	3246.8	138	15198.2
Total/on average* for the Arctic zone of Yakutia	851	4245.1*	3761	18544.4*
Share of the Arctic zone of Yakutia, %	5.5	-	7.8	-
total/on average* in Yakutia	15596	5895.4*	48230	18222.8*

Table 4

The number of deaths from COVID-19 and their share of the total number of deaths in the area

District	Years									
	2020		2021		2022		2023		2020-2023	
	n	%	n	%	n	%	n	%	n	%
Abyisky	3	4.9	14	21.9	3	5.0	0	0.0	20	8.5
Allaikhovsky	1	2.9	6	14.3	1	2.6	0	0.0	8	5.3
Anabarsky	3	6.5	3	8.1	1	3.8	0	0.0	7	5.0
Bulunsky	1	1.2	14	15.9	2	3.0	0	0.0	17	5.7
Eveno-Bytantaysky	3	5.6	3	5.8	0	0.0	0	0.0	6	2.8
Momsky	10	6.8	21	16.9	8	7.0	0	0.0	39	8.2
Nizhnekolymsky	9	13.8	21	31.8	1	2.4	0	0.0	31	14.3
Oleneksky	2	3.6	7	12.3	4	10.3	2	5.7	15	8.0
Srednekolymsky	1	1.7	8	12.9	1	2.5	0	0.0	10	4.9
Ust-Yansky	9	18.0	10	20.8	3	7.9	1	3.3	23	13.9
Verkhnekolymsky	1	1.0	14	14.1	7	8.1	0	0.0	22	6.2
Verkhoyansky	6	7.5	0	0.0	2	2.6	0	0.0	8	2.2
Zhigansky	1	3.3	3	8.1	1	3.2	0	0.0	5	4.1
Total	50	5.8	124	13.9	34	4.7	3	0.5	211	6.7

the healthcare system of the Republic of Sakha (Yakutia), especially in the Arctic regions, where extreme climatic conditions, poorly developed transport infrastructure and low population density have complicated the organization of medical care. Despite the prompt introduction of restrictive measures, the expansion of hospital beds, the creation of inter-district infectious disease centers and the active use of telemedicine, the spread of coronavirus infection in the first years of the pandemic in the Arctic zone of the Republic of Sakha (Yakutia) was more intense than the average for Russia and Yakutia.

An analysis of morbidity and mortality showed that the greatest difficulties arose in 2020-2021, which was associated with both the high contagiousness of the virus and objective logistical difficulties, insufficient equipment of remote medical institutions and low adherence of the population to preventive measures. However, by 2022-2023, thanks to the accumulated experience, increased laboratory diagnostics and optimization of patient routing, it was possible to reduce the burden on the healthcare system and reduce the share of Arctic regions in the overall morbidity structure.

The data obtained indicate the need for further development of healthcare infrastructure in hard-to-reach regions, including equipping medical institutions with equipment for early diagnosis, expanding telemedicine capabilities, and increasing the readiness of medical personnel to respond to epidemiological threats. In addition, it is extremely important to carry out more intensive preventive work among the population, especially among risk groups. The lessons of the COVID-19 pandemic should be taken into account when forming strategies for the prevention and control of future infectious diseases.

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

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ASSESSMENT OF THE ROLE OF VARIOUS FACTORS IN THE FORMATION OF ARTERIAL HYPERTENSION IN CHEMICAL WORKERS BY A MACHINE TRAINING METHOD

The article discusses key cardiovascular risk factors hypertension in workers of chemical industries. The study aims to identify the contributing factors using machine learning methods.

Materials and methods. The study involved 643 male workers, including 551 operators from two chemical production facilities (Ethylene-Propylene and Ethylbenzene-Styrene plants) and 92 automation center workers. The evaluation of production and non-production risk factors was conducted through periodic medical exams, consultations with cardiologists, and assessments of stress and depression levels. A gradient boosting method in the CatBoost library was used to analyze the data, considering both work-related and personal factors like age, smoking, anxiety, depression, and lipid profiles.

Results. The analysis showed that age, smoking, high LDL levels, BMI, and years of work in harmful conditions were the most significant factors in predicting the development of AH. For the Ethylbenzene-Styrene (EBS) operators, the major factors influencing AH risk were work experience (23.78%), age (18.06%), and smoking (14.53%). For the Ethylene-Propylene (EP) operators, the key factors were work experience (20.59%), smoking (20.22%), and LDL levels (18.07%). Statistically significant differences in anxiety and stress levels were found between the EP and EBS groups ($p<0.05$).

Conclusion. The study concludes that both production-related and non-production factors contribute significantly to the risk of developing AH among workers in chemical industries. Key factors like smoking, BMI, and LDL levels, along with harmful occupational exposures and high emotional stress, should be addressed in preventive measures to reduce hypertension risks in this workforce.

Keywords: chemical industry, risk factors, machine learning, occupational stress.

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Introduction. Research conducted in recent decades has allowed for the identification of key risk factors for the development of cardiovascular diseases (CVD), the study of their interrelationship, and the formulation of the concept of overall cardiovascular risk [1].

It has been established that the main risk factors include hypertension (HT), dyslipidemia, excess body weight (BMI), obesity, diabetes, hyperuricemia, thrombogenic factors, and inflammatory factors [4]. It is important to note that ecology, the social environment, and lifestyle also have a significant impact on the development of CVD. The interaction of these factors with genetic and gender characteristics can contribute to the progression of cardiovascular diseases [15].

Low educational levels, lack of social support, psychosocial stress, as well as anxiety and depressive disorders in the working-age population also play an important role in the development of CVD, as confirmed by the results of numerous epidemiological studies [11,14,5]. Smoking is one of the most significant clinical risk factors for CVD [3,8].

Lack of physical activity and obesity also lead to a decrease in the adaptive capacity of the cardiovascular system, worsening tolerance to physical exertion, and increasing the risk of developing CVD [9,12]. Disruption of lipid metabolism is recognized as one of the main risk factors for the development of atherosclerosis and coronary artery disease (CAD) [16].

Numerous studies confirm the adverse effects of harmful occupational factors and chronic workplace stress on the onset and progression of CVD [6,2,7,10].

The above justifies the need for special studies among workers in various industries to establish the causal relationship between the prevalence of CVD and cardiovascular risk factors.

Materials and Methods. The study involved 643 male workers, of which 551 were chemical production operators (295 workers in the EBPS and 256 in the EP) and 92 workers from the automation center (AC).

The study evaluated both occupational and non-occupational factors influencing the risk of developing hypertension. The evaluation of occupational risk factors was conducted based on materials from a special assessment of working conditions, industrial control, and self-inspection of workplaces.

The main non-occupational risk factors were studied through periodic medical examinations (PME) (Order of the Ministry of Health of the Russian Federation No. 29n, dated January 28, 2021). Additional studies included cardiologist consultations, lipid profile determination, and the assessment of anxiety and depression levels using the HADS scale, Reader.

To assess the contribution of occupational and non-occupational risk factors to the development of hypertension in workers, the gradient boosting method on decision trees was used, implemented in the CatBoost library.

The model training was conducted on a sample that included both occupational (working years in harmful conditions, factors of the working environment and labor process) and non-occupational (age, levels of anxiety, depression, and stress, body mass index, lipid profile indicators) risk factors. Hypertension presence was considered as the target variable (binary classification). To interpret the results, we used the built-in CatBoost method for assessing factor importance, which allowed for determining the contribution of each factor to the development of hypertension. The visualization of the distribution of factors and their contribution to the probability of the disease is presented in the form of density diagrams (violin plots), showing the direction and strength of their impact. The significance metrics used for the factors were the mean absolute SHAP value (mean abs shap) and the percentage impact of each feature.

Results. The research was conducted at two chemical production facilities: ethylene-propylene production, which is partially automated, and the highly automated ethylbenzene-styrene production. The majority of the staff consisted of operators who remotely controlled technological processes from control rooms. The continuous technological process schemes, automation, and the use of mainly sealed equipment at both facilities do not eliminate the possibility of operators being exposed to a complex of harmful occupational factors.

The final assessment of working conditions for operators at the ethylbenzene-styrene production corresponds to the third class of the first degree of harm (class 3.1), while at the ethylene-propylene production, it corresponds to the third class of the second degree of harm (class 3.2).

The differences in the final assessment of working conditions for the operators at these productions depended on the level of automation and computerization of the production processes, which determined the time the worker spent directly at the equipment, as well as the spectrum and levels of harmful occupational factors (Table).

Self-assessment of psychosocial stress levels using the Reeder scale

Main characteristics of the studied groups

Indicator	EBS Operators (n=295)	EP Operators (n=256)	AC Workers (n=92)	*p*		
				EBSvs.EP	EBSvs.CA	EPvs.CA
Working Conditions						
Harmful Substances	2	3.1	2	-	-	-
Noise	2	3.1	2	-	-	-
Lighting Environment	3.1	2	2	-	-	-
Severity	2	3.1	2	-	-	-
Intensity	3.1	3.1	2	-	-	-
Final Assessment	3.1	3.2	2	-	-	-
Male gender (%)	100	100	100	-	-	-
Age (years)	47.2±7.1	48.3±7.6	49.9±9.7	0.86	0.40	0.73
Years of employment	24.1±8.2	23.9 ± 8.0	26.7±9.5	0.88	0.29	0.11
Smoking (%)	32.9	40.6	34.8	0.07	0.83	0.39
BMI ≥30 (%)	36.9	37.1	39.1	0.96	0.80	0.93
LDL >3.0 mmol/L (%)	50.7	46.1	50.0	0.32	0.99	0.60
TC >5.0 mmol/L (%)	56.9	52.0	50.0	0.28	0.29	0.84
Stress level and psychoemotional state						
HADS-Anxiety. > 7 points (%)	24.7	37.9	21.7	**0.001***	0.65	**0.007***
HADS-Depression. > 7 points (%)	14.9	19.8	15.2	0.162	0.92	0.44
Psychosocial Stress (Reeder). > 1 point (%)	39.0	49.2	34.8	**0.016***	0.20	**0.024***

Notes: * - statistically significant differences ($\chi 2$ test. $p<0.05$)

and psychoemotional state using the HADS scale revealed that the highest prevalence of high levels of anxiety and stress was recorded among operators in the EP production (37.9% and 49.2%, respectively). A statistically significant difference was found in anxiety levels between operators at the EP production and those at the EBS production ($\chi2 = 10.49$; $p = 0.001$), workers in the AC ($\chi2 = 7.20$; $p = 0.007$), as well as in stress levels between operators at the EP production and those at the EBS production ($\chi2 = 5.86$; $p = 0.016$), and workers in the AC ($\chi2 = 5.12$; $p = 0.024$). To develop a model assessing the contribution of various risk factors to the onset of hypertension, the following risk factors were used: data on working conditions, clinical and laboratory tests, and assessments of anxiety and depression levels for 551 operators (Figure 1).

As a result of machine learning using artificial intelligence, factors that have the greatest impact on the prediction of hypertension development in operators were identified: age, smoking, low-density lipoprotein (LDL) levels, excess body weight, and years of work in harmful working conditions.

In the next stage, models were developed to assess the risk of hypertension development separately for operators at the EBS and EP production facilities. In the presented model, factors related to the working environment and labor process were not taken into account, as they were the same for operators in both groups.

Based on the results of the evaluation of the influence of individual risk factors on the development of hypertension in operators at the EBS production, the leading factors were: years of work (impact 23.78%), age (impact 18.06%), smoking (impact 14.53%), LDL levels (impact 13.61%), BMI (impact 7.82%), stress level (impact 7.07%), and total cholesterol level (impact 6.10%) (Figure 2, a).

It was found that in the EP operators group, the factors that had the greatest impact on the accuracy of hypertension development predictions were work experience, smoking (impact 20.59%), age (impact 20.22%), LDL levels (impact 18.07%), body mass index (impact 10.90%), years of work in harmful conditions (impact 9.67%), total cholesterol (impact 6.83%), and psychoemotional factors: anxiety and stress levels (impact 6.34% and 4.93%, respectively) (Figure 2, b).

Furthermore, the results of the statistical analysis revealed the average values

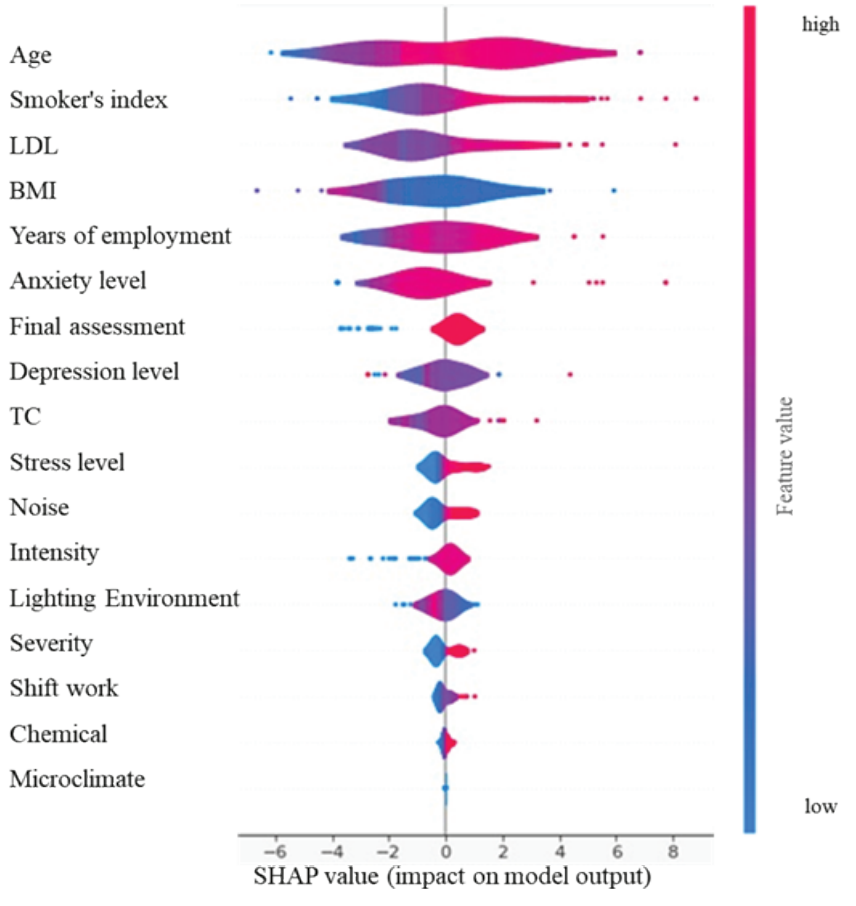

Fig. 1. Contribution of Each Predictor to the Predictive Ability of the Overall Model

of risk factors for hypertension development in operators at the EBS and EP productions (Figure 4).

Discussion. Despite the increasing number of studies examining the impact of harmful occupational and non-occupational risk factors on the cardiovascular health of workers in various industries, the number of studies dedicated to this issue in the chemical industry is limited [6,13]. In line with the stated objective, this study examined the influence of occupational and non-occupational factors on the risk of developing hypertension in workers at specific chemical productions and scientifically justified a set of preventive measures for cardiovascular risk based on the identified priority risk factors.

Based on the constructed mathematical model, it was determined that the risk of developing hypertension in operators of chemical productions is influenced by several factors, the key ones being age, years of work, smoking, increased body mass index, and low-density lipoprotein levels. These factors, in combination with chronic exposure to workplace environmental factors and high emotional stress, contribute to an increased cardiovascular risk due to their cumulative effect on the cardiovascular system.

The complex of harmful occupational factors also contributes to the increase in blood pressure. It should be noted that industrial noise exceeding hygienic standards activates stress reactions in the body, while exposure to chemicals disrupts the functioning of the vessel walls.

Conclusion. Thus, the presented materials clearly demonstrate that the combination of occupational and non-occupational factors contributes to an increased risk of developing hypertension among workers in the chemical industry. Statistically significant differences in the prevalence of hypertension among operators at the EP production are primarily due to the high prevalence of smoking as a risk factor, as well as exposure to a number of harmful occupational factors exceeding standard values.

Operators at the EP production facility have the highest prevalence of high anxiety and stress levels compared to operators at the EBS production and workers in the AC.

Based on the results of the study, a cardiovascular risk prevention program

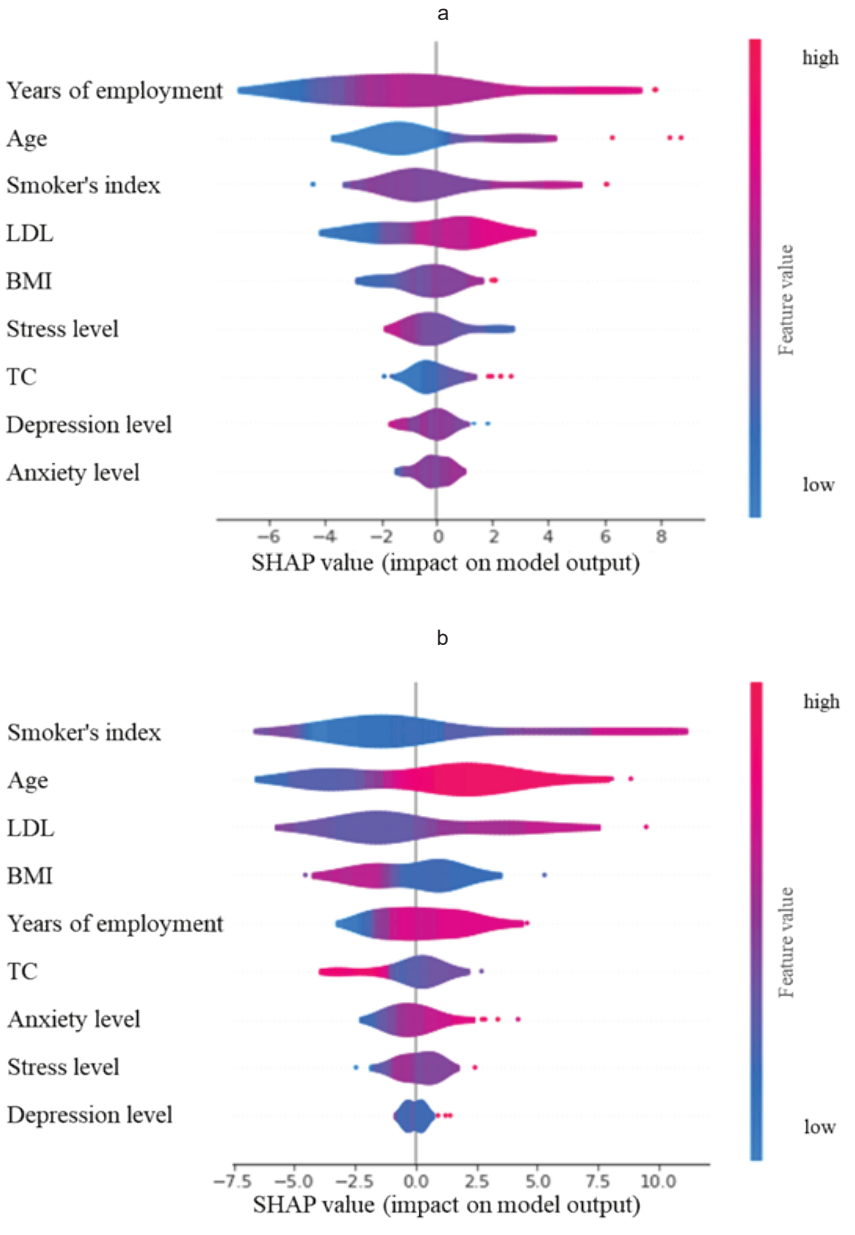

Fig. 2. Model of the influence of risk factors on the development of hypertension in production operators: a-EBS, b-EP

has been developed, aimed at minimizing the negative effects of stress factors, as well as occupational and non-occupational risk factors. Therapeutic and preventive measures include the formation of groups for dispensary observation depending on cardiovascular risk levels, and conducting the necessary volume of therapeutic and health improvement activities in various medical and health institutions.

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

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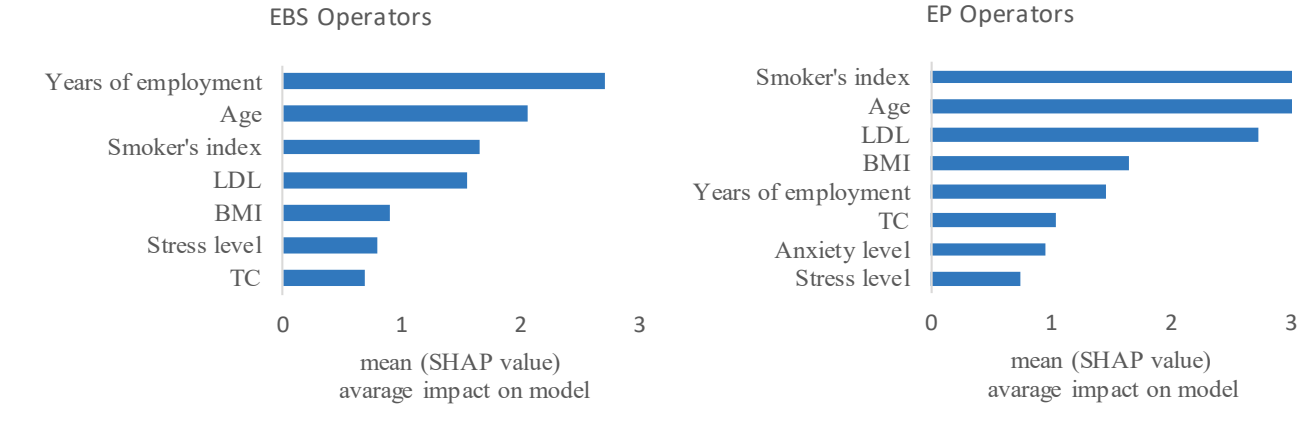

Fig. 3. Average values of risk factors affecting the development of AH in operators

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TOPICAL ISSUE

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A.A. Ivanova, A.F. Potapov, T.E. Burtseva, E.M. Klimova

PREVENTABLE CAUSES IN THE MORTALITY STRUCTURE OF THE POPULATION OF THE SAKHA REPUBLIC (YAKUTIA) AND ITS ARCTIC ZONE

When studying a population mortality, a survey of the factors by influencing which it is possible to minimize losses are of great practical and scientific interest. The aim of the survey was to assess the population mortality from preventable causes in the Sakha Republic (Yakutia) using the Russian classification.

Materials and Methods. Using the methods of comparative and mathematical analyses, the data on the population mortality in the Sakha Republic (Yakutia) and its Arctic zone in 2020-2023 were studied, with grouping of the causes of deaths which could have been avoided either by preventing the risks of developing diseases, by timely diagnosis of a disease, or by adequate treatment.

Results and Discussion. It was found that 37.2% of the total number of deaths in the republic in 2020-2023 could have been avoided, including 71.8% of the cases by primary prevention measures (Group 1 of the causes); 3.2% – by early diagnosis of diseases (Group 2 of the causes); and 25.0% – by adequate treatment (Group 3 of the causes). In the mortality structure in the Arctic zone of the republic, these causes accounted for 75.1%, 2.6%, and 22.3%, respectively. The greatest contribution to preventable mortality of the population in Yakutia is made by lifestyle-related diseases. Losses due to injuries and poisoning account for 35.7% in the preventable mortality in the republic as a whole and for 45.0% in the Arctic zone of the region. 24.9% of fatal cases in the Arctic zone (10.5% in the republic) directly depended on the quality of medical care. To minimize these losses, it remains important to identify diseases at early stages; to address them with adequate treatment; and, for district hospitals, to refer patients to level 3 medical institutions in a timely manner.

Keywords: mortality, preventable causes, Sakha Republic (Yakutia), Arctic zone.

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Introduction. The introduction of the Rutstein concept of preventable mortality in foreign countries in the second half of the 20th century made it possible to adequately assess the performance of healthcare as a social institution and significantly increase the efficiency of investments in maintaining public health. The concept is based on the differentiation of nosological forms of diseases, death from which can be avoided through medical intervention [4,5,6,7]. There are two lists of preventable mortality causes, where the grouping is determined by levels of prevention: "old" ("Avoidable mortality") and new ("Amenable mortality"). The first list includes the efforts of the entire public health system, the second – only healthcare institutions. The index of causes in the lists may change as medical science and practice develop, and diagnostic and therapeutic capabilities expand. The difficulty with applying this methodology as it is in the

Russian Federation is due to the lack of a universally agreed list of preventable causes of mortality. However, attempts to create it have been repeatedly made and, according to experts, the "old" list is more applicable to Russia, since the regions of the country differ significantly in both living conditions and the level of development of the healthcare system. [1,2,3]

The aim of the survey was to assess the population mortality from preventable causes in the Sakha Republic (Yakutia) using the Russian classification.

Materials and Methods. A retrospective analysis of data from the territorial authority of the Federal State Statistics Service for the Sakha Republic (Yakutia) for the period 2020–2023, provided at the request of the authors, was conducted. To group the causes of preventable mortality, the classification of A.E. Ivanova, V.G. Semenova and T.P. Sabgaida was used, based on which three groups of the

Table 1

Dynamics of deaths from preventable causes in the Sakha Republic (Yakutia) in 2020–2023

Causes of death	2020	2021	2022	2023	Всего
Causes leading to losses that can be avoided through primary prevention measures (Group 1)					
Lip, oral cavity and throat cancers	29	37	40	29	135
Esophageal cancer	38	31	42	36	147
Liver and intrahepatic bile duct cancers	120	154	131	156	561
Laryngeal cancer	19	14	14	25	72
Tracheal, bronchial and lung cancers	293	244	250	291	1078
Cancers of other and not-localized respiratory and thoracic cage organs	12	16	6	10	44
Bladder cancer	18	25	19	21	83
Cancers of other and not-identified urinary organs	4	5	2	4	15
Subarachnoid hemorrhage	53	73	64	32	222
Intracerebral and other intracranial hemorrhages	180	210	166	141	697
Cerebral infarction	192	236	179	171	778
Stroke not diagnosed as hemorrhage or infarction	8	12	2	15	37
Other cerebrovascular diseases	15	19	5	5	44
Alcoholic liver disease (alcoholic cirrhosis, hepatitis, fibrosis)	52	49	59	30	190
Liver fibrosis and cirrhosis (not alcohol-related)	147	159	120	122	548
Other liver diseases	49	35	25	28	137
Injuries, poisoning and some other consequences of external impact	1206	1098	1113	1329	4746
Causes leading to losses that can be avoided through timely diagnosis of diseases (Group 2)					
Cutaneous malignant melanoma	5	8	6	9	28
Other skin cancers	5	4	1	4	14
Breast cancer	54	50	56	43	203
Cervical cancer	28	26	45	15	114
Cancers of other and non-specified parts of uterus	12	18	20	14	64
Causes leading to losses that can be avoided through improved treatment and medical aid (Group 3)					
Prostate cancer	35	17	27	35	114
Male genital cancers	1	2	3	3	9
Hodgkin lymphoma	0	0	3	4	7
Non-Hodgkin lymphoma	20	13	16	13	62
Leukemia	22	29	18	24	93
Chronic rheumatic heart diseases	25	13	14	11	63
Arterial hypertension	161	149	132	90	532
Gastric ulcer	23	20	22	13	78
Duodenal ulcer	9	10	17	17	53
Diseases of the appendix	1	2	0	1	4
Hernias	3	3	8	9	23
Cholelithiasis	13	20	29	18	80
Cholecystitis	8	10	6	6	30
Infectious and parasitic diseases *	110	111	109	81	411
Respiratory diseases	400	466	416	475	1757
Pregnancy, delivery and postpartum complications	1	8	5	0	14
Total	**3371**	**3396**	**3190**	**3330**	**13287**

causes were identified depending on the stage of the process: Group 1 combines the causes avoidable by primary prevention; Group 2 – by efficient diagnosis; and Group 3 – by adequate treatment at all stages of aid. The authors used the methods of comparative and mathematical analyses.

Results and Discussion. Following the classification, individual forms of diseases that resulted in deaths in Yakutia in 2020–2023 were divided into three groups (Table 1). Group 1 includes malignant neoplasms (MN) of the digestive and respiratory organs; cerebrovascular accidents and cerebrovascular diseases; alcoholic damage and other diseases of the liver; as well as all accidents, the occurrence and development of which are largely influenced by lifestyle, diet, bad habits (smoking, alcohol abuse), and behavioral factors. In these cases, death can be avoided by primary prevention measures. Group 2 includes MN of the skin, mammary gland, cervix and other parts of the uterus, the outcomes of which depend on timely detection and early diagnosis of the disease. Group 3 of the causes includes MN of the prostate gland and male genital organs, lymphoma, leukemia, chronic rheumatic heart diseases, hypertension, gastric ulcer and duodenal ulcer, appendix diseases, hernias, cholecystitis, infectious and parasitic diseases, respiratory diseases and conditions associated with pregnancy and childbirth, deaths from which can be avoided by high-quality medical care and proper treatment.

According to the analysis, of the total number of deaths from all causes in the republic over the four years (35,697), the share of preventable deaths was 37.2% (13,287 cases). By years, in the period 2021–2023, a decrease in the number of deaths was noted; it is partly explained by tackling the pandemic of the new coronavirus infection COVID-19, which had led to a sharp increase in fatalities at the height of its spread in 2021. The dynamics of the number of deaths that could have been avoided by primary prevention measures, timely detection of diseases and high-quality treatment was relatively stable (Figure 1). The change in their share in the total number of deaths in 2021–2023 is characterized by an upward trend (Figure 2).

A study on the contribution dynamics of the three groups of causes to the total number of deaths in 2020–2023 revealed that the largest share (from 22.9% to 31.3%) was made by Group 1 causes, which can be amended by preventing the risks of developing pathological conditions before the onset of the disease (Table 2).

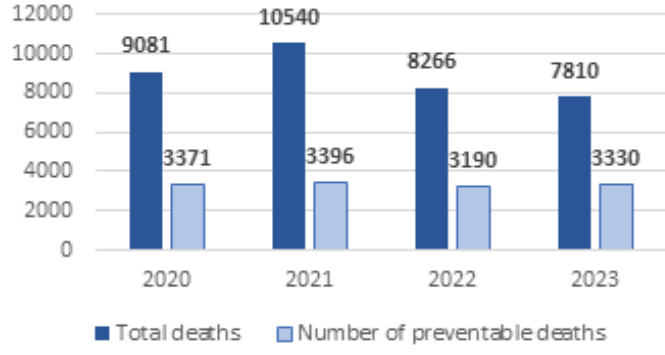

Fig.1. Total number of deaths and the number of preventable deaths in 2020-2023

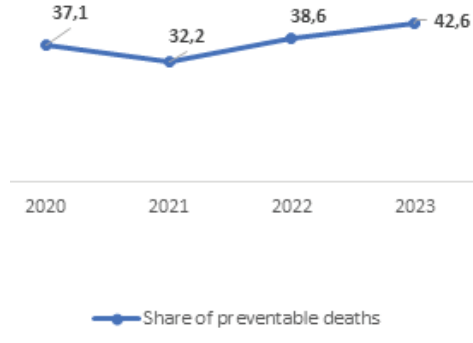

Fig. 2. Dynamics of the share of preventable deaths in 2020–2023

Table 2

Dynamics of the number and share of preventable causes of mortality in 2020-2023

Years	Total number of deaths	Group 1 causes		Group 2 causes		Group 3 causes	
		abs.num	share	abs.num	share	abs.num	share
2020	9 081	2435	26.8	104	1.1	832	9.2
2021	10 540	2417	22.9	106	1.0	873	8.3
2022	8 266	2237	27.0	128	1.5	825	10.0
2023	7 810	2445	31.3	85	1.1	800	10.2

The stable and small share of Group 2 causes indicates an improvement in diagnostic capabilities in healthcare institutions of the region (the material and technical base meeting modern requirements, the level of professional training of personnel). The share of Group 3 causes, losses from which could have been avoided by high-quality treatment, demonstrated an increasing trend, which is worth paying attention.

The bulk of Group 1 was made by losses from external causes. Mortality from injuries and poisoning in 2020–2022 ranked third in the structure of mortality of the population in the republic and was characterized by a decrease during the pandemic in 2021–2022 (from 123.4 to 111.2–111.6 per 100,000 population). The subsequent increase in the indicator to 133.0 per 100,000 people moved this class of causes of death up to second place (Figure 3).

By years, in 2020, 3,371 deaths or 37.1% of the total number of deaths (9,081) could have been avoided, including 2,435 cases (72.2%) through primary prevention measures, 104 cases (3.1%) – through timely detection of the disease, 832 cases (24.7%) – through high-quality appropriate treatment.

In 2021, the total share of preventable mortality was 32.2% (3,396 out of 10,540 deaths from all causes), including effective primary prevention could have prevented 71.2% of deaths (2,417), early detection of the disease – 3.1% (106), high-quality treatment – 25.7% (873).

In 2022, out of 3,190 preventable deaths, 2,237 (70.1%) depended on pri-

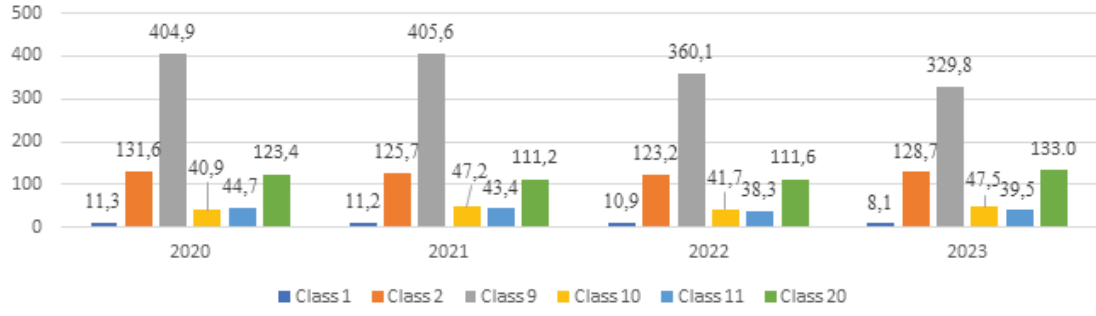

Fig. 3. Dynamics of the indicators of mortality from main classes of causes in the Sakha Republic (Yakutia) in 2020–2023 (per 100,000 population)

Table 3

Dynamics of deaths from preventable causes in the Arctic zone of the Sakha Republic (Yakutia) in 2020-2023

Causes of death	2020	2021	2022	2023	Всего
Causes leading to losses that can be avoided through primary prevention measures (Group 1)					
Lip, oral cavity and throat cancers	1	3	1	2	7
Esophageal cancer	4	1	5	6	16
Liver and intrahepatic bile duct cancers	7	20	13	8	48
Laryngeal cancer	2	0	1	1	4
Tracheal, bronchial and lung cancers	24	19	22	25	90
Cancers of other and not-localized respiratory and thoracic cage organs	2	2	0	1	5
Bladder cancer	4	2	1	3	10
Cancers of other and not-identified urinary organs	0	0	0	0	0
Subarachnoid hemorrhage	3	4	4	1	12
Intracerebral and other intracranial hemorrhages	19	14	8	11	52
Cerebral infarction	15	17	9	8	49
Stroke not diagnosed as hemorrhage or infarction	1	4	2	6	13
Other cerebrovascular diseases	1	2	0	2	5
Alcoholic liver disease (alcoholic cirrhosis, hepatitis, fibrosis)	3	2	3	1	9
Liver fibrosis and cirrhosis (not alcohol-related)	14	4	8	9	35
Other liver diseases	8	2	2	4	16
Injuries, poisoning and some other consequences of external impact	148	138	111	157	554
Causes leading to losses that can be avoided through timely diagnosis of diseases (Group 2)					
Cutaneous malignant melanoma	0	0	0	2	2
Other skin cancers	0	1	0	0	1
Breast cancer	3	3	3	2	11
Cervical cancer	4	1	8	1	14
Cancers of other and non-specified parts of uterus	0	0	2	2	4
Causes leading to losses that can be avoided through improved treatment and medical aid (Group 3)					
Prostate cancer	2	2	1	1	6
Male genital cancers	0	1	0	0	1
Hodgkin lymphoma	0	0	0	0	0
Non-Hodgkin lymphoma	0	1	0	2	3
Leukemia	0	1	0	2	3
Chronic rheumatic heart diseases	1	3	1	2	7
Arterial hypertension	14	16	21	15	66
Gastric ulcer	0	1	1	0	2
Duodenal ulcer	0	0	1	0	1
Diseases of the appendix	0	1	0	0	1
Hernias	0	1	1	0	2
Cholelithiasis	2	0	1	2	5
Cholecystitis	2	3	0	0	5
Infectious and parasitic diseases *	9	6	9	7	31
Respiratory diseases	47	35	28	31	141
Pregnancy, delivery and postpartum complications	0	0	0	0	0
Total	**340**	**310**	**267**	**314**	**1231**

mary prevention, 128 (4.0%) – on early detection of the pathological condition, 825 (25.9%) – on the quality of treatment. The total share of the preventable component in the mortality structure was 38.6% (3,190 out of 8,266).

According to the 2023 data, 2,445 deaths (73.4%) could have been avoided by primary prevention measures, 85 cases (2.6%) – through timely detection, and 800 cases (24.0%) – through adequate medical care. Thus, 42.6% of deaths were preventable (3,330 out of 7,810 deaths from all causes).

Consequently, in total in the period 2020–2023, of those who died from all causes (35,697), 26.7% of deaths depended on primary prevention measures (9,534), 1.2% – on the quality of disease diagnosis (423), 9.3% – on the quality of treating diseases and pathological conditions (3,330); therefore, 10.5% of deaths could have been avoided by the efforts and resources of the healthcare system (3,753).

A similar analysis of the mortality structure of the population in the Arctic group of districts of the republic for 2020–2023 established that in the period, the share of preventable deaths was higher (1,231 cases out of 3,128 deaths) than in the region as a whole: 39.4% versus 37.2%. In the causal profile, 75.1% of the cases depended on primary prevention measures (925 deaths out of 1,231), 2.6% (32 cases out of 1,231) – on the quality of disease diagnosis, 22.3% (274 out of 1,231) – on the quality of treatment (Table 3). The main contribution to Group 1 of preventable causes was made by external causes – 59.9% (554 out of 925), followed by subarachnoid, intracerebral and other intracranial hemorrhages, strokes – 13.6% (126 out of 925), malignant neoplasms of the trachea, bronchi and lungs – 9.7% (90 out of 925).

Group 2 of preventable causes, determined by the quality of diagnosis, consisted mainly of visualized forms of neoplasms: malignant neoplasms of the cervix and mammary gland (43.8% and 34.4%, respectively).

In Group 3 of preventable causes dependent on the quality of treatment, respiratory diseases accounted for the main share (51.5%, or 141 out of 274 cases), hypertension – for 24.1% (66 out of 274), and infectious and parasitic diseases – for 11.3% (31 out of 274). In this group of causes, it is worth noting the zero values for pregnancy, delivery and postpartum complications. This is a result of the centralization of obstetric care in the republic, when women from all districts with any complicated pregnancies and predicted difficult deliveries are transported to the perinatal centers in Yakutsk. Such a system led to a significantly reduced maternal and infant mortality in the region. Thus, the medical component (causes of Groups 2 and 3) of the total array of preventable deaths for the period 2020-2023 amounted to 24.9% (306 deaths out of 1,231).

Conclusion. Naturally, the data present an approximate idea of the number of cases when the death of citizens could have been avoided rather than an exact one. However, the absolute dominance of the number of deaths from injuries and poisonings once again confirms the severity of the problem with mortality from external causes in the region, especially in its Arctic zone. Unlike Groups 2 and 3 of preventable causes, the direct medical component in preventing deaths from Group 1 causes is of little importance, since they are primarily due to the level, quality and way of life, diet, and behavioral habits. Yet in terms of reducing mortality from malignant neoplasms of the lip, oral cavity, pharynx, larynx, respiratory organs, liver, and bladder, the most important role is played by the alertness of primary health care workers, proper and complete examination of the cases of suspected malignant neoplasms, high-quality medical preventive examinations. For districts of the region with less equipped medical institutions, timely referral of patients with suspected malignant neoplasms for diagnosis verification to level 3 institutions in Yakutsk remains relevant. In the preventable mortality of the Arctic zone of the republic, 24.9% of fatal outcomes depended directly on the quality of medical care (in the republic, as a whole – 10.5%).

A more accurate assessment of the effectiveness of the regional healthcare can be made based on mortality rates from causes of Groups 2 and 3, which depend on the quality of diagnosis and treatment. The impact on the causes of these groups can lead to a real reduction in mortality through the efforts of the healthcare system. Of great importance in the early detection of these diseases is the attention of citizens to their health, their awareness and timely seeking of medical help. Among the causes that depend on the adequacy and proper conduct of treatment, attention is drawn to the highest figures for losses from respiratory diseases and hypertension, with their minimization depending on all stages of the process: timely consultation, early diagnosis, adequate treatment, effective medical examination, and patient devotion to treatment.

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

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ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN OF BARNAUL

The results of a survey of 1,118 Barnaul children aged 0 to 17 years to determine the etiological structure of community-acquired pneumonia pathogens from January to October 2024 are presented. Mycoplasma pneumoniae was the predominant pathogen - 36%, less often COVID-19. The clinical picture of mycoplasma pneumonia in children is atypical. Etiotropic therapy brings good results.

Keywords: children, community-acquired pneumonia, mycoplasma

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Introduction. In Russian pediatrics, as in most countries of the world, pneumonia is defined as "an acute infectious disease of the pulmonary parenchyma, diagnosed by the respiratory distress syndrome and/or physical data, as well as infiltrative changes on the radiograph" [3,7,8].

The most important principle from a clinical point of view provides for the division of pneumonia into community-acquired (CA) and nosocomial [11].

The etiological structure of pneumonia in children is very diverse and depends on the age of the child. Data on the etiology of CA in children vary greatly, which can be explained by the different epidemiological conditions in which the studies were conducted, as well as their methodologies. The study of this problem is relevant both for the choice of etiotropic therapy tactics, and for the prognosis of the disease and measures of specific and non-specific prevention [1,5,6].

Materials and methods. In a cross-sectional retrospective study, weekly reporting forms for monitoring community-acquired pneumonia for the Ministry of Health of the Altai Region were analyzed. The period of results evaluation was from January to November 2024. The study included three large medical and preventive healthcare institutions in the city of Barnaul, providing primary care to children. The pathogen was identified by the polymerase chain reaction (PCR) method after collecting biological material (a swab from the throat and nose) from a child during the initial visit to the clinic. An analysis of 30 medical records of patients who were treated in the somatic-pediatric department of the Altai State Budgetary Institution of Health "Children's City Hospital No. 1, Barnaul" was also conducted. All children were diagnosed with community-acquired pneumonia caused by Mycoplasma pneumoniae (J15.7). The complete blood count was determined using the Mindray BC 5150 automatic hematology analyzer. Biochemical studies were performed using the Mindray BS 380 automatic chemistry analyzer. C-reactive protein (CRP) was determined photometrically. The following pathogens were determined: mycoplasma, rhinovirus, RS virus, parainfluenza virus types 1,2,3,4, adenovirus, Ebstein-Barr virus, influenza A, COVID 19 using the polymerase chain reaction (PCR) method on the BioExpert PCR amplifier. The control group included children of health groups 1 and 2.

Statistical processing of the results was performed using the statistical software package "STATISTICA 10.0 (StatSoftInc). The Shapiro-Wilk test was used to test the hypothesis of the normal distribution of empirical data. It evaluates the sample data with the null hypothesis that the data set is normally distributed. The Mann-Whitney U test was used to determine whether there was a significant difference between two independent, non-normally distributed groups of data. Fisher's exact test and Pearson's $\chi 2$ test determined whether there was a statistically significant difference between the qualitative indicators in the study groups.

Results and discussions. 1,118 children aged 1 to 17 years were examined. Girls are 581 (52%), boys are 537 (48%).

Table 1 shows the distribution of children by age, with school-age children predominating ($p<0.01$). The control group for comparison of laboratory parameters consisted of 92 children who were comparable by gender and age: 37 girls (40.2%), 55 boys (59.8%).

As can be seen from Table 2, the largest number of analyses were performed in the largest (in terms of the number of registered children) City Children's Clinic No. 14 – 765, significantly fewer in Children's Clinic No. 9 – 213, and 140 in Children's Clinic No. 3.

The main pathogen in children was Mycoplasma pneumoniae (32.3-33.3%) ($\chi 2=203.7$, $p<0.01$), less frequently isolated were Rhinovirus and Human orthopneumovirus. Parainfluenza viruses and COVID-19 were detected in 1.5%. Undifferentiated pathogens were registered in 58.2-62% of patients ($\chi 2=129.3$, $p<0.01$). The peak incidence was observed from mid-September to October.

Depending on age it was found that children aged 0 to 2 years are the least likely to get sick ($p<0.05$), the pathogen type was mostly undetermined, mycoplasma was isolated less frequently (32.3%). From 3 to 6 years, parainfluenza, pneumometavirus and unknown pathogens are predominantly determined. Most children in the age group of 7-14 years have mycoplasma as the causative agent of pneumonia ($p<0.05$). 15-17 years old children have mainly mycoplasma (32.3%) and less frequently influenza A (1.5%).

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After examination at the pediatric department, the pediatrician diagnosed all children with ARVI (J06.9) and prescribed symptomatic treatment and antiviral drugs. After 3-5 days the condition was without positive dynamics, the high temperature persisted, the children took antipyretic drugs, and a hacking cough appeared. They returned to the pediatrician. An X-ray examination of the chest organs, an overview X-ray and PCR diagnostics were performed.

Infiltrative changes in the lungs were detected and mycoplasma was isolated; the child was sent for hospitalization to the Altai State Budgetary Institution of Health «Children's City Hospital No. 1, Barnaul» with a diagnosis of «Pneumonia».

The analyze of hospital case histories showed that disease began acutely with a rise in temperature to 39.0 ° C -39.6 ° C. A dry cough appeared after 2 days. There were signs of intoxication (headache, weakness, malaise), but not in all patients, only three children from 30 had ones - 10%.

When analyzing the complaints of children in the study group who were hospitalized (Picture 1), it was found that the main ones were: fever (86.7%), unproductive cough (76.7%), productive cough (23.3%), intoxication (16.7%), respiratory failure (10.0%), chest pain (6.7%).

2/3 of patients had complaints about the course of acute respiratory viral infection (ARVI).

During auscultation of 30 children wheezing was not heard in 19 (63.3%) children throughout the disease. 7 (23.3%) had wet fine-bubble wheezing, which stopped on the 4-5th day, but harsh breathing remained, another 5-6 days in 4 (13.3%) children wheezing appeared on the 4-5th day of treatment.

In the clinical blood test, moderate leukocytosis up to 10-12 thousand in 1 μl was detected only in 17 (32.7%) patients, a shift in the leukocyte formula to the left - in 9 (17.3%) children. Of the hematological changes characteristic of mycoplasma infection, eosinophilia was detected in 13 (25%) people, increased ESR (20-40 mm / h) - in 25 (48.1%). The average ESR values \u200b\u200bin children with pneumonia was 7.9 mm / h. Leukocytosis out of 30 patients was observed in 8 (26.6%) children, its average value was 12.1 x 109 / l. Thrombocytosis was observed in 3 (10%) children. Lymphocytopenia was observed in 17 (56.6%) children. Monocytosis was found in 14 people (46.6%), monocytopenia was observed in 4 children (13.3%). Average hemoglobin value in 7 people was 109

Table 1

Распределение обследованных детей по возрасту, абс. (%)

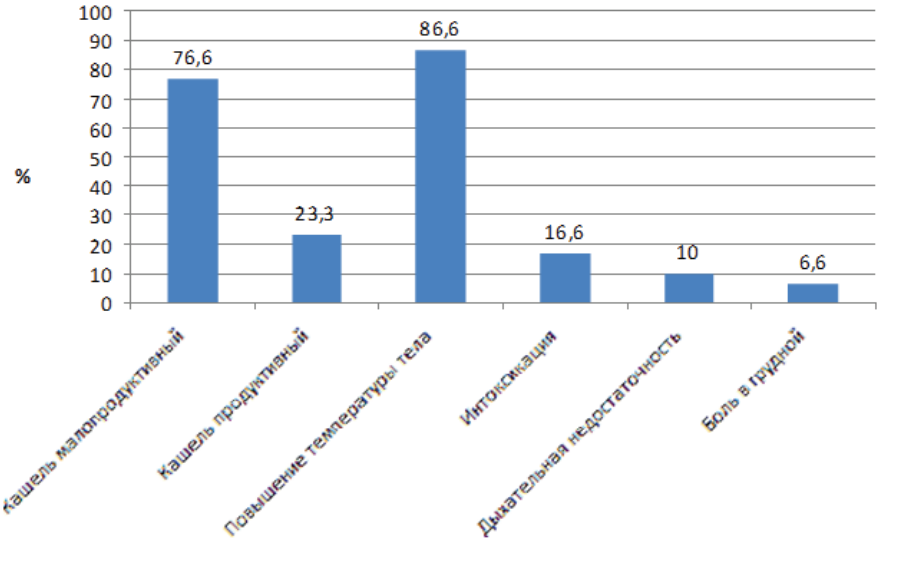
Возраст детей (лет)	0-2 года	3-6 лет	7-14 лет	15-17 лет
Поликлиника № 3	6 (0,54)	26 (3,22)	73 (6,53)	17 (1,52)
Поликлиника № 9	12 (1,07)	45 (4,92)	73 (10,73%)	24 (2,15)
Поликлиника № 14	45 (4,03)	126 (11,4)	423 (37,84)	159 (14,22)
Всего	63	218	569	200

Table 2

Возбудители внебольничной пневмонии у детей по данным детских поликлиник г. Барнаула, абс. (%)

Поликлиника	Возбудитель							
	Микоплазма	Риновирус	РС-вирус	Вирусы парагриппа 1,2,3,4 типа	Другие респираторные вирусы (аденовирус, ВЭБ, грипп А и др.)	Недифференцированные внебольничные пневмонии	COVID 19	Всего
3	83(20,6/ 59,3)	2(18,2/ 1,4)	-	3(60/ 2,1)	3(14,3/ 2,1)	43(6,7/ 30,7)	6(28,6/ 4,3)	140
9	71(17,7/ 33,3)	-	6(35,3/ 2,8)	1(20/ 0,5)	7(33,3/ 3,3)	124(19,3/ 58,2)	4(19/ 1,9)	213
14	248(61,7/ 32,3) *	9(81,8/ 1,1)	11(64,7/ 1,5)	1(20/ 0,1)	11(52,4/ 1,5)	474(73,9/ 62) *	11(52,4/ 1,5)	765
Всего	402	11	17	5	21	641	21	1118

Примечание. ВЭБ – вирус Эпштейна-Барр, * - статистическая значимость рассчитана по χ^2 критерию Пирсона.



Жалобы пациентов с микоплазменной пневмонией (%)

g/l, first-degree anemia [5]. In children of the study group, hemoglobin and leukocyte levels were statistically significantly higher than in children of the comparison group ($p<0.05$). Hypochromic anemia was detected in 7 (23.3%) children of the study group. This may be due to the fact that the causative agent is mycoplasma, which can cause hemolysis and hemagglutination of erythrocytes, which leads to the development of transient hemolytic anemia [2]. An increase in platelets in some children is due to high temperature, which leads to impaired microcirculation and the development of microthrombosis (development of DIC syndrome) [4].

In the absence of changes in the general blood test characteristic of the usual "bacterial" nature, they may prompt the doctor to consider the microplasma nature of pneumonia [10].

Biochemical blood test. Total protein average value 72.64 g/l. - normal, C-reactive protein (CRP) average value is 56.3 mg/l - elevated. Currently, CRP is considered the most sensitive "reference" laboratory marker of systemic inflammation, tissue damage and infectious alteration. An increase in its concentration in the blood of more than 50 mg/l in the presence of respiratory symptoms with a high probability confirms the presence of community-acquired pneumonia.

General sputum analysis. Segmented neutrophils are continuous. They may indicate an acute, severe inflammatory process. Detection of more than 25 neutrophils in the field of view indicates an infection (pneumonia, bronchitis). Flat epithelium has 3-4 (4-5) cells. The presence of more than 25 flat epithelial cells in the sputum indicates the presence of saliva in the sputum. Abundant coccal flora was observed with bacterial pathogens and infectious processes in the respiratory tract. Sputum cultures are ineffective in mycoplasma pneumonia.

Results of chest X-ray in direct projection are showed the following: lobar pneumonia is in 22 children (73.3%). Upper lobe pneumonia is in 5 children (22.7%), middle lobe pneumonia is in 6 children (27.3%), lower lobe pneumonia is in 11 children (50%), polysegmental pneumonia is in 3 children (10%). As a rule this is a bilateral pneumonia. Most often it is in segments S4, S5 and S9. Segmental pneumonia is in 5 children (16.6%). In 3 children the S3 segment is involved in the process (60%). And one S4 and S6 (20%), as a rule, are manifested in segment atelectasis.

In the hospital, Azithromycin tablets and symptomatic treatment were prescribed. A positive result was noted against the background of this treatment. The temperature was stopped on the 2-3 day and did not rise anymore. The child's health improved significantly. Signs of intoxication disappeared along with the temperature. The children felt much better. Children are discharged on the 7-10 day and transferred to outpatient treatment, if necessary.

When prescribing therapy, the characteristics of Mycoplasma pneumoniae should be taken into account. It is characterized by natural resistance to antibiotics that act on the synthesis of the cell wall - b-lactams, glycopeptides, fosfomycin [9]. It is a very small, free-living, gram-negative, facultative anaerobic bacterium lacking a true cell wall. [10]. Macrolides are the first line of treatment for mycoplasma pneumonia. Azithromycin has better in vitro activity, while lincosamides, especially lincomycin, exhibit moderate activity. In addition, it has an immunomodulatory and anti-inflammatory effect. It is considered less toxic and bladeless, which is important when choosing therapy for a child's body [10]. However, it differs from other macrolides in its significantly greater effectiveness against these bacteria. It exceeds other drugs in the group in terms of effectiveness. Its high effectiveness against intracellular mycoplasma pathogens has been proven [10].

When starting antibiotic treatment, the temperature drops on the second day to 37.5°C -37.0°C. On the 3rd day it went to 37.0°C -36.7°C and did not rise again throughout the entire course of the disease.

Conclusion. Thus, community-acquired pneumonia remains a relevant and problematic topic. Clinically, pneumonia caused by Mycoplasma pneumoniae is very difficult to diagnose when a patient first comes to the clinic. Because the first signs are hidden under «masks». In this regard, most doctors miss the onset of the disease, which further complicates treatment.

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DETECTION OF LIVER MALIGNANT TUMORS AND INTRAHEPATIC BALL DUCTS IN THE REPUBLIC OF SAKHA (YAKUTIA)

The article presents a cross-sectional retrospective study of cases of malignant neoplasms of liver and intrahepatic bile ducts (C22) in the Republic of Sakha (Yakutia) (RS (Y)) in 2010–2019 based on statistical registration forms No. 7 and 35. During the study period, significantly increased incidence and mortality rates from malignant neoplasms of the liver and intrahepatic bile ducts were recorded. At the same time, the proportion of detection of the studied pathology at early stages remains low, despite the strengthening of diagnostic measures within the framework of preventive examinations and screening programs. In the dynamics for 2010–2019, an increase in the prevalence of malignant neoplasms of the liver and intrahepatic bile ducts is noted in the RS (Y), but the number of patients under observation for 5 years or more tends to decrease. The obtained data substantiate the need to improve organizational approaches to early diagnosis and treatment, optimize patient routing, and study precancerous factors of liver cancer of population of the Republic of Sakha (Yakutia).

Keywords: malignant neoplasms of liver and intrahepatic bile ducts, cancer, detectability, the Republic of Sakha (Yakutia).

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Introduction. There are enough works in the literature devoted to the study of pre-cancerous genesis of malignant neoplasms of the liver and bile ducts. It is described that the causes of liver cancer have ethnic, territorial, and social heterogeneity. It is well known that viral hepatitis C, alcoholic liver disease, and fatty hepatosis are among the top three factors in the development of liver cancer in developed countries. In developing countries where hepatitis B vaccination is not established, the main cause of liver cancer is hepatitis B. Due to the increasing global incidence of liver cancer and the national, regional, and population specificity of the causes of this cancer, targeted prevention strategies for its various etiologic types are currently needed to reduce the burden of liver cancer [1].

The highest incidence of liver cancer is observed in such regions of the world as East and Southeast Asia, North and West Africa [2]. These differences are due to the prevalence of risk factors, which include chronic hepatitis B and C [3,4], hemochromatosis [5], diabetes mellitus [6], cirrhosis and fatty liver disease [7], obesity [8], alcohol abuse [9], exposure to certain carcinogens, hormones, dyes [10, 11], aflatoxins [12], etc. Of these, more than half of the cases of hepatocellular carcinoma (HCC) are associated with viral hepatitis B (HBV). In regions with a high prevalence of this infection, the proportion of HCC cases reaches 70–80% [3]. According to case-control studies, the relative risk of HCC among HBV-infected people varies from 5 to 49, according to cohort studies - from 7 to 98 [3]. According to the results of multicenter epidemiological studies, it was proven that viral hepatitis B and C were the main cause of liver cancer and death of patients. It is described that viral hepatitis B is most common in the countries of Southeast Asia. Statistics have shown that 85% of the world's cases of liver cancer and deaths from this disease for the period from 1990-2017 occur in these countries. Approximately 15% of the total number of deaths and cases of liver cancer in the world are caused by alcoholism. Alcohol can cause liver cirrhosis and create an environment favorable for viral hepatitis infection. In fact, the risk of developing liver cancer doubles in individuals who have chronically consumed > 80 g of alcohol for > 10 years. According to data from 1990 to 2017, alcoholism was the leading cause of liver cancer in several European countries (Bulgaria, Croatia, Czech Republic, Hungary, Poland, Slovakia, Austria, Denmark, Germany, Luxembourg, Sweden, Canada and Greenland). Hepatitis C and alcohol abuse were the leading risk factors for liver cancer in developed countries (UK, USA, Italy and Canada). More than 30% of the total number of liver cancer-related deaths and cases in Central Europe, Eastern Europe, Australia and Western Europe were caused by alcohol consumption [1].

The Sakha Republic (Yakutia), which is part of the Arctic region, is the subject of the Russian Federation (RF) with the highest incidence rates of malignant neoplasms of the liver and intrahepatic bile ducts in the country. The population of the Republic of Sakha (Yakutia) as of January 2020 reached 972 000 people with a population density of 0.32 people/km^2.

The COVID-19 pandemic has caused significant disruptions in the provision of cancer care worldwide, including delays in the organization of screening, follow-up of patients at high risk for developing HCC, referral to specialists, diagnosis, therapy, and follow-up. Although cancer screening resumed in many countries in the summer of 2020, the long-term impact of missed screenings is not

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well understood. According to studies, skipping recommended cancer screenings and fewer doctor visits during the pandemic lead to an increase in the number of primary diagnoses at late stages, a decrease in the number of malignant neoplasms detected during dispensary observation or incidental detection, as well as a longer-term increase in cancer mortality [13; 14; 15; 16].

To conduct the epidemiological analysis, data from the pre-pandemic period (2010–2019) were used, which made it possible to establish reference values for the subsequent study of the impact of the COVID-19 pandemic on the dynamics of morbidity and the structure of the stages of detected cases. The data obtained are key to the correct interpretation of changes associated with the peculiarities of the organization of the healthcare system during the pandemic (2020–2021) and their long-term consequences, including possible long-term shifts in the epidemiological indicators of liver cancer. The aim of this study is to analyze the detection rates of malignant neoplasms of the liver and intrahepatic bile ducts (C22) in the Republic of Sakha (Yakutia) for the period from 2010 to 2019.

Materials and methods. Open data from the P.A. Herzen Moscow Oncology Research Institute - a branch of the National Medical Research Center of Radiology of the Ministry of Health of the Russian Federation on the localization of "liver and intrahepatic bile ducts" (C22 ICD-10) since 2011 (up to and including 2010, data on liver cancer were not collected separately), data from the State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Oncology Dispensary" (statistical forms No. 7, 35) have been used in the work. Information on patients registered in oncological institutions of the Russian Federation for 5 years or more from the moment of diagnosis of malignant neoplasm of the liver and intrahepatic bile ducts, from the number registered at the end of the reporting year, has been entered into statistical form No. 35 of the federal statistical observation since 2011 (since 2016, form No. 7). Therefore, when calculating the share of the contingent of patients registered in oncological institutions for 5 years or more, data for 2011-2014 were used.

Results. In 2015-2019, the frequency of cases of active detection of malignant neoplasms of the liver and intrahepatic bile ducts during preventive and screening examinations of the population increased from 2.7% in 2011-2014 to 16.8%. (Table). However, the proportion of cases with morphological verification of the diagnosis continues to remain low, and amounts to 49 and 42%, respectively, during these time periods.

Indicators of liver cancer diagnostic activity and five-year survival, in %

Indicator	2011–2014*		2015–2019	
	РС (Я)	РФ	РС (Я)	РФ
Actively detected, %	2,7	3,8	16,8	6,4
Diagnosis confirmed morphologically, %	49,3	50,8	42,3	66,1
detected: stage1	1,2	1,3	1,8	2,7
Stage 2	3,9	6,8	11,4	10,2
Stage3	33,7	22,2	45,1	22,8
Stage3	61,3	57,0	41,1	57,4
Stage not established	0,0	12,8	0,5	5,8
Percentage of those registered for 5 years and more	31,1	26,9	22,2	31,3

Note: *The figures are calculated for 2011–2014, since in 2010, data on liver cancer in Russia were not collected separately.

In the last years of the study period, the detection rate of liver cancer and intrahepatic bile duct cancer at early stages improved and reached the average Russian values, as a result of which the share of advanced cases decreased from 61.3% to 41.1%. If we take into account the indicators of the Russian Federation as a whole, then for the analyzed periods the share of cases with morphological verification of the diagnosis is on average higher than for the RS (Ya). This is due to the instrumental and laboratory methods of diagnosis, and with the introduction of a hepatospecific method of radiation diagnostics. In 2015-2019, the proportion of liver cancer and intrahepatic bile duct cancer cases detected at stages 1 and 2 of the disease in the Republic of Sakha (Yakutia) and the Russian Federation as a whole are generally comparable (13.2 and 12.9%, respectively), and the proportion of advanced cases (at stage 4) is lower in the Republic of Sakha (Yakutia). In 2015-2019, the proportion of patients under the supervision of an oncology institution for 5 years or more in the Republic of Sakha (Yakutia) amounted to 22%, and in the Russian Federation as a whole - 31% of the number of those registered at the end of the year. At the same time, in 2015-2019, compared with the period 2010-2014, the proportion of those registered for 5 years or more in the Republic of Sakha (Yakutia) decreased by 1.4 times, in the Russian Federation as a whole it increased by 16.4%.

In 2011 and 2019, the number of patients with malignant neoplasms of the liver and intrahepatic bile ducts under observation in the oncology dispensary of the Republic of Sakha (Yakutia) for 5 years or more did not change (41 and 40 people, respectively), but during this period until 2014, there was an increase of 1.2 times (49 people) with a subsequent decrease. From 2011 to 2019, there was an increase in the number of all patients registered with a diagnosis of malignant neoplasms of the liver and intrahepatic bile ducts by 1.6 times (2011 - 138, 2019 - 218 people). In the Russian Federation as a whole, there is an increase in both the number of patients diagnosed with cancer of the liver and intrahepatic bile ducts who are under observation in oncological institutions for 5 years or more, and the number of all patients registered with a diagnosis of cancer of the liver and intrahepatic bile ducts, by 1.7 and 1.4 times, respectively (1817 and 6670 people in 2011, 3076 and 9057 in 2019, respectively).

Discussion. The Republic of Sakha (Yakutia) is a subject of the Russian Federation with the highest rates of morbidity and mortality from cancer of the liver and intrahepatic bile ducts. Over the study period from 2015-2019, the activity of detecting cancer of the liver and intrahepatic bile ducts has significantly increased as part of preventive and screening examinations of the population. Morphological verification of the diagnosis lags behind the Russian average, but it is necessary to take into account that, according to the clinical recommendations of the Ministry of Health of the Russian Federation, it is possible to establish a diagnosis of hepatocellular carcinoma based on the results of clinical and radiological data, which accounts for about 80% of the structure of malignant neoplasms of the liver and intrahepatic bile ducts.

Although the level of detection of malignant neoplasms of the liver and intrahepatic bile ducts at early stages has increased with a decrease in the share of diagnosis of this pathology at late stages, the detection rates at stages 1-2 continue

to be low, compared with the indicators of the Russian Federation as a whole, but have a tendency to increase. In 2015-2019, the detection rates of liver cancer and intrahepatic bile ducts at stages 1 and 2 of the disease in the Republic of Sakha (Yakutia) and the Russian Federation as a whole are comparable, while the diagnosis of cancer at stage 4 is lower in the Republic of Sakha (Yakutia) than the Russian average.

In the Republic of Sakha (Yakutia) in 2015-2019, the proportion of patients with this malignant neoplasm who are under observation for 5 years or more is approximately 10% lower compared to the data for the Russian Federation as a whole. There is some significant decrease in the proportion of this category of patients in 2015–2019 compared to 2010–2014. In the Republic of Sakha (Yakutia) for 2011–2019, an increase in the total number of patients registered for dispensary care with a diagnosis of malignant neoplasms of the liver and intrahepatic bile ducts was revealed compared to the all-Russian data.

Conclusion. Thus, the conducted analysis of the epidemiological indicators of malignant neoplasms (MN) of the liver and intrahepatic bile ducts in the Republic of Sakha (Yakutia) for 2010–2019 shows a high incidence rate, improved early detection rates, and a slight tendency to increase of the survival rate of 5 years or more when analyzed by year.

Moreover, our analysis of pre-pandemic data (2010–2019) allowed us to establish important reference values for epidemiological indicators of malignant liver neoplasms. These data are of particular importance in the context of assessing the impact of the COVID-19 pandemic on oncology services, particularly in liver cancer. The results obtained create a scientific basis for an objective analysis of the changes that occurred in the healthcare system in 2020–2021 and their potential long-term consequences, and lay the methodological foundation for a subsequent comprehensive analysis of the impact of the pandemic crisis on oncology care for the population.

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SOCIAL AND ECONOMIC DAMAGE (DALY) FROM MALIGNANT NEOPLASMS OF FEMALE GENITAL ORGANS IN THE TOMSK REGION

The purpose of the study is to assess direct and indirect economic damage from cervical, uterine, and ovarian cancer in the Tomsk region.

Material and methods. Data from Rosstat for the Tomsk region covering the period from 2013 to 2023 were utilized, including population size, life expectancy, gross regional product per capita, and reporting forms C51 "Distribution of deaths by gender, age groups, and causes of death." Additionally, information on the costs of examination and treatment for genital cancer under compulsory medical insurance and high-tech medical care in rubles for 2016-2020 was analyzed. The losses of DALYs (person-years) and economic damage (rubles) were calculated according to WHO guidelines, using the segmented regression method.

Results. The maximum loss of DALY values for cervical cancer was in the range of 35–49 years, for uterine cancer and ovarian cancer in the range of 55–69 years. The highest expenditure was allocated to the treatment of ovarian cancer (325.24 million rubles), followed by lower amounts for uterine cancer (205.5 million rubles) and cervical cancer (189.8 million rubles). The total economic impact (including direct and indirect costs) amounted to 3.9 billion rubles for cervical cancer, 2.8 billion rubles for ovarian cancer, and 2.3 billion rubles for uterine cancer.

Conclusion. The findings of the study, quantified in monetary terms, are recommended for use in optimizing the allocation of budget funds under current conditions.

Keywords: economic burden, DALY, cancer, cervical cancer, uterine cancer, ovarian cancer, Tomsk region

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Introduction. In 2020, out of 9.23 million new cancer cases among women worldwide, more than 1.39 million (15.1%) were related to gynecological malignancies. Among the 4.4 million women who died from cancer that year, 14.8% of deaths were caused by cancers of the female reproductive organs. According to WHO statistics, by 2035, the number of cancer-related deaths is expected to rise to 7 million, with gynecological cancers accounting for 12.0% of these cases [9].

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In the Tomsk region, the age-standardized incidence rate (ASR) of cervical cancer was 16.9 per 100,000 population (compared to 13.7 in the Russian Federation, RF), endometrial cancer-18.9 (RF-16.4), and ovarian cancer-10.1 (RF-10.2). In the structure of cancer incidence among the female population, these malignancies ranked fifth (5.2%), fourth (7.4%), and ninth (3.7%), respectively, collectively accounting for 16.3% of all female reproductive organ tumors. The age-standardized mortality rates for cervical cancer were 5.7 (RF-4.8), endometrial cancer-3.9 (RF-3.8), and ovarian cancer-3.8 (RF-4.8) per 100,000 population. In the structure of cancer mortality, these malignancies ranked eighth (4.6%), ninth (4.1%), and tenth (4.0%), respectively, with gynecological cancers accounting for 12.8% of all cancer-related deaths [1, 3].

According to estimates by researchers from the Heidelberg Institute of Global Health (Germany), the Chinese Academy of Medical Sciences, and the Peking Union Medical College (China), the global economic cost of cancer from 2020 to 2050 will amount to 25.2 trillion US dollars (inconstant 2017 prices) , averaging 0.84 trillion per year. This is equivalent to an annual tax of 0.55% on global GDP. However, cancers of the female reproductive system are not among the top ten most costly malignancies: cervical cancer (CC) ranks 11th (estimated cost: $ 682 billion), ovarian cancer (OC) ranks 15th ($ 519 billion), and endometrial cancer (EC) ranks 24th ($193 billion) [8].

The mortality rate serves as a key indicator for evaluating the effectiveness of cancer control measures, as it directly depends on timely diagnosis and treatment efficacy.

According to WHO data [10], among non-communicable diseases in Russia in 2020, the burden of gynecological diseases across all age groups resulted in 973.7 disability-adjusted life years (DALYs) lost per 100,000 population, ranking fifth in the DALY structure-after ischemic heart disease, stroke, "low back and neck pain," and diabetes. The Global Burden of Disease (GBD) database [11] does not provide region-specific data for Russian federal subjects, including the Tomsk region. Due to frequent methodological changes in DALY calculations (the latest revision was in May 2024) [14] and the lack of standardization in calculation approaches, it is currently difficult to compare previous studies from Siberia and the Russian Far East with GBD data [4, 5].

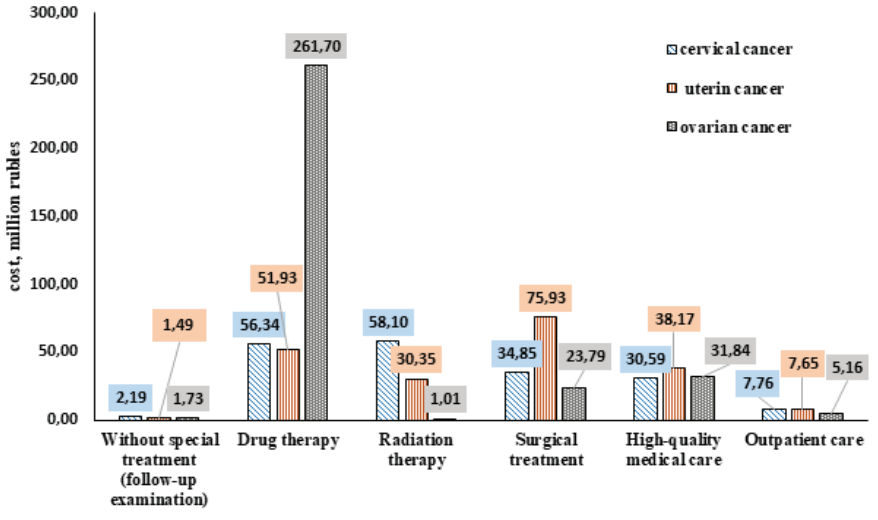
The government allocates substantial funds to provide medical care, including significant expenditures for supporting disabled citizens. Even greater financial losses stem from the premature mortality of cancer patients. All these economic costs can be quantified in monetary terms

to enable rational budget reallocation when planning cancer control measures. Therefore, conducting an analysis of both direct and indirect economic burdens caused by gynecological malignancies in the Tomsk region is particularly relevant.

Research Objective: To assess the direct and indirect economic burden caused by cervical, endometrial, and ovarian cancers in the Tomsk region.

Materials and Methods. The study included data from 2013-2023 for the Tomsk region, provided by the Territorial Office of State Statistics and Rosstat: demographic distribution by sex and age, life expectancy, gross regional product (GRP) per capita, mortality statistics (Form C51: "Distribution of deaths by sex, age groups, and causes of death"). Economic losses from malignancies consist of direct costs (10–20%) and indirect costs (80–90%). Direct costs include: prevention, diagnosis, treatment, rehabilitation, and social support for patients. Data sources included reimbursement records from the Territorial Compulsory Health Insurance Fund (CHI) for 2016–2020 and the hospital registry of the Tomsk Cancer Research Institute for high-tech medical care (HTMC). Additional reference was made to HTMC tariffs listed in the State Guarantees Program for Free Medical Care (Section II).

Indirect costs include: lost national income due to disability (5%) or premature death (75%) [2, 4]. These were calculated using the DALY method (disability-adjusted life years) multiplying DALY values by GRP per capita [7]. DALY losses (person-years) and economic damage (rubles) were computed using the "Onco DALY" software [6], developed by the Epidemiology Laboratory of the Tomsk Cancer Research Institute based on WHO guidelines [14].Trend analysis was performed using segmented regression [12] in JASP software.



Direct costs (million rubles) by types of medical care provided cervical cancer, uterine cancer, ovarian cancer in the Tomsk region, 2016-2020

Results: *Direct costs of female reproductive cancers in the Tomsk Region.* An assessment of the treatment costs for malignant neoplasms (MN) of the reproductive organs in the female population of the Tomsk region was conducted based on the data from payment registers for medical care provided under the territorial and federal compulsory health insurance (CHI) funds. The evaluation took into account the type of medical care provided in hospitals and outpatient clinics, including follow-up examinations, drug therapy, radiation therapy, surgical

Table 1

Indirect economic damage (thousand rubles) and DALY losses (person-years) of cervical cancer, uterine cancer, ovarian cancer in the Tomsk region in 2013-2023

years	GRP per capita, rubles	DALY Losses			Economic damage, rubles		
		cervical cancer	uterine cancer	ovarian cancer	cervical cancer	uterine cancer	ovarian cancer
2013	403 575,20 ₽	1628	819	1075	657 020 426 ₽	330 528 089 ₽	433 843 340 ₽
2014	430 138,20 ₽	1687	541	827	725 643 143 ₽	232 704 766 ₽	355 724 291 ₽
2015	520 296,60 ₽	1751	856	810	911 039 347 ₽	445 373 890 ₽	421 440 246 ₽
2016	484 654,70 ₽	1573	871	683	762 361 843 ₽	422 134 244 ₽	331 019 160 ₽
2017	515 560,30 ₽	1571	558	1072	809 945 231 ₽	287 682 647 ₽	552 680 642 ₽
2018	570 191,30 ₽	1279	882	1047	729 274 673 ₽	502 908 727 ₽	596 990 291 ₽
2019	575 297,10 ₽	1276	759	993	734 079 100 ₽	436 650 499 ₽	571 270 020 ₽
2020	517 023,00 ₽	1227	825	776	634 387 221 ₽	426 543 975 ₽	401 209 848 ₽
2021	679 724,80 ₽	1185	791	1138	805 473 888 ₽	537 662 317 ₽	773 526 822 ₽
2022	769 028,80 ₽	988	668	773	759 800 454 ₽	513 711 238 ₽	594 459 262 ₽
2023	870 868,90 ₽	987	696	730	859 547 604 ₽	606 124 754 ₽	635 734 297 ₽
period, average annual change over the period, level p		2015-2013, -94.60*; p=0.001	2013-2023, -1.75; p=0.888	2013-2023, -7.73; p=0.646	2013-2023, +4.5 млн руб.; p=0.585	2013-2023, +26.7* млн руб.; p=0.004	2013-2023, +28.9* млн руб.; p=0.016

Note: *– statistical significance of the differences ($p < 0.05$) was estimated using segmented regression.

Table 2

Direct and indirect economic damage (million rubles) of cervical cancer, uterine cancer, ovarian cancer in the Tomsk region in 2016-2020

	cervical cancer		uterine cancer		ovarian cancer	
	million rubles	%	million rubles	%	million rubles	%
Indirect economic damage	3 670.05 ₽	95.08	2 075.92 ₽	90.99	2 453.17 ₽	88.29
Direct economic damage	189.83 ₽	4.92	205.52 ₽	9.01	325.24 ₽	11.71
Total	3 859.88 ₽	100	2 281.44 ₽	100	2 778.41 ₽	100

treatment, and outpatient care. (Figure):

The highest costs were associated with antitumor drug therapy for ovarian cancer (OC) (36.3% of all expenses for gynecological cancer care), surgical treatment for uterine cancer (UC) (10.5%), and radiation therapy for cervical cancer (CC) (8.1%). The lowest expenditures were on diagnostic/follow-up examinations for diagnosis establishment and clarification (0.2–0.3% for each cancer type) and outpatient care for women with this pathology (0.7–1.1%). The most funded treatment was for OC (325.24 million RUB), followed by UC (205.5 million RUB) and CC (189.8 million RUB). When assessing annual direct medical costs for gynecological cancer patients, the lowest expenditure level was recorded in 2018 (91.84 million RUB), while the highest was in 2020 (196.71 million RUB). This trend can be explained by increases in compulsory health insurance (CHI) tariffs and high-tech medical care (HTMC) costs. Over the five-year period, no statistically significant cost growth was observed for OC (p=0.079), CC (p=0.059), or UC (p=0.123). However, a clear increase in costs was noted for all studied malignant neoplasms (MN) in the most recent years (2016 and 2020), averaging 80.6%: CC showed a growth rate of 63.9%, UC-26.7%, and OC-121.8%.

Indirect costs of female reproductive organs malignant neoplasms in the Tomsk region. During 2016-2020, DALY losses amounted to: 6,957.71 for cervical cancer; 3,911.66 for uterine cancer; 4,588.89 for ovarian cancer (in person-years). The highest DALY losses for cervical cancer occurred in the working-age groups of 35-39, 40-44, and 45-49 years (821.1, 1,159.0, and 817.4 DALY person-years, respectively). For uterine and ovarian cancers, peak losses were observed in post-working-age cohorts (55-59, 60-64, and 65-69 years): UC: 574.3, 764.5, and 696.5 person-years; OC: 1,060.2, 781.5, and 587.2 person-years. The time trend analysis using segmented regression (Table 1) revealed a statistically significant decrease in DALYs for cervical cancer (CC) during 2013-2015, with an average annual reduction rate of 94.8 person-years (p = 0.001). While the economic burden showed an increasing trend during this period, the change was not statistically significant (p = 0.585). For uterine cancer (UC) and ovarian cancer (OC), no significant changes in DALY losses were observed during the study period. However, the overall economic burden increased significantly for both cancers: for UC at an average annual rate of 26.7 million RUB (p=0.004), and for OC at 28.9 million RUB (p=0.016).

Direct and indirect costs of female reproductive cancers in the Tomsk region. During 2016-2020, the highest total direct and indirect economic burden was associated with cervical cancer treatment (3.9 billion RUB), followed by ovarian cancer (2.8 billion RUB) and uterine cancer (2.3 billion RUB) (Table 2).

Discussion: Currently, for data spanning 2000–2021, the methodology for calculating DALY employs the maximum healthy life expectancy at birth from World Population Prospects 2024 [13], projected to reach 90.6 years by 2050 (previously, the 2013 benchmark of 87.1 years was used). Following the COVID-19 pandemic, global life expectancy at birth has resumed growth, reaching 73.3 years in 2024 an increase of 8.4 years since 1995 [13]. This trend is expected to drive higher cancer incidence and, consequently, increased healthcare expenditures.

The persistently high economic burden of gynecological cancers, further exacerbated by annual growth in GDP per capita, could be mitigated by reducing mortality among the working-age population. Thus, it is critical to prioritize greater funding for preventive and rehabilitative anti-cancer programs. Such initiatives should aim to: promote women's proactive health management; enable early detection and treatment of precancerous conditions, and facilitate the rapid reintegration of radically treated patients into society and the workforce.

Conclusion. In the current era of rising cancer incidence, addressing the multifaceted challenges of reducing cancer mortality as outlined in the federal project "Combating Oncological Diseases" requires a comprehensive analysis of direct and indirect economic losses. This analysis is critical for healthcare policymakers to prioritize interventions, including: primary cancer prevention, patient rehabilitation. To evaluate the efficiency of healthcare expenditures, it is essential to compare the costs of medical care for gynecological cancer patients against the economic losses attributable to female mortality.

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

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ARCTIC MEDICINE

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LEVELS OF GLUCOSE AND ITS METABOLITES, PANCREATIC HORMONES, AND ADIPONECTIN IN THE ARCTIC POPULATION

The search for the causes underlying changes in carbohydrate metabolism remains relevant due to the lifestyle of the Arctic population and its changes in the indigenous population, which leads to a change in the "northern" hormonal and metabolic profile and the development of metabolically related diseases, including diabetes mellitus. The aim of the study was to identify the characteristics of carbohydrate metabolism, pancreatic hormones, and adiponectin in an almost healthy Arctic population, depending on their ethnicity and lifestyle. Materials and methods. A cross-sectional study of the population of the local Caucasian population and the aborigines of the Arctic (Nenets) aged 18 to 74 years was conducted. The levels of proinsulin, insulin, and adiponectin in blood serum were studied by enzyme immunoassay, and glucose, lactate, and pyruvate were studied by spectrophotometric analysis. The HOMA, Caro, lactate/pyruvate, and Proinsulin/Insulin indices were calculated. Results and discussion. The analysis of glucose levels showed that a statistically significantly high glucose content was found in the local Caucasian population relative to nomadic and sedentary aborigines. At the same time, 21.9% of nomadic aborigines, 17.8% of settled Aborigines and 28.9% of the local Caucasian population had excess glucose levels and 7.1%, 8.8% and 10.0% had prediabetic blood levels. Lactate levels, lactate/pyruvate values, and insulin in the groups were highest in sedentary Aborigines ($p=0.001$, $p<0.001$, $p=0.046$), while in nomadic aborigines and the local Caucasian population, insulin levels were minimal ($p=0.046$), and proinsulin levels and proinsulin/insulin values ($p<0.001$), on the contrary, is higher in the absence of significant differences in the level of pyruvate. A significantly low content of adiponectin was observed in sedentary aborigines, both relatively nomadic and the local Caucasian population ($p<0.001$). Conclusion. The lowest levels of glucose and insulin found in nomads against the background of increased proinsulin and adiponectin may indicate a decrease in the secretory activity of pancreatic beta cells and an improvement in insulin resistance; in sedentary aborigines, the predominance of anaerobic processes over aerobic ones is associated with a restriction of proinsulin production and is associated with an increase in insulin resistance with low levels of adiponectin, while in the local Caucasian population, insulin levels increase slightly while maintaining a higher level, which leads to an increased load on beta cells of the pancreas, causing an increase in adiponectin synthesis.

Key words: glucose, lactate, pyruvate, insulin, proinsulin, insulin resistance, adiponectin, Arctic population.

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Introduction. Trends in the spread of diabetes mellitus 2 (DM 2) persist among the indigenous population of the Arctic (about 20% of cases) [3]. In this regard, it is of interest to evaluate the metabolic mechanisms underlying its development in the practically healthy population of the Arctic. At the same time, such rearrangements occur in different directions for each indicator and lead to the formation of a specific "northern" hormonal and metabolic profile of the body, characterized by minimizing the carbohydrate component of metabolism against the background of intensification of lipid (L.E. concept Panina, 1978), resulting in a completely different structure of metabolic relationships [6]. Perhaps one of the reasons for the decrease in glycemia among the indigenous inhabitants of the Arctic of the last century may be the type, intake regime and amount of

carbohydrates that gradually entered the diet, and thus a more pronounced competition between glucose and fatty acids for the oxidation of tissues sensitive to increased insulin [8]. In general, there is no consensus among the Arctic population about the features of the functional activity of the pancreatic insulin apparatus, and the available data still remain very contradictory. It is pointed out that the aborigines of the North, with the condition of preserving the traditional protein–lipid type of nutrition, were characterized by a special, "economical" type of metabolism with a decrease in blood insulin [4]. In addition, residents of the North are characterized by an increase in proinsulin levels against a background of a decrease in insulin and an increase in the proinsulin/insulin ratio. At the same time, other studies show that there are many points of interaction between insulin and adipose tissue [1, 5]. Currently, adipose tissue is considered as a hormonally active system that produces biologically adiponectin, which is involved in the development of insulin resistance [7]. There is little data in the literature on the effect of adiponectin on the level of glycemia in the inhabitants of the North. It has been found that its blood levels vary depending on ethnicity. Thus, the Caucasian population is characterized by a higher content of adiponectin in comparison with African Americans or Asians [14]. Other studies relate to the experimental study in mice of the role of the adiponectin pathway in reducing insulin resistance [10, 14], which, in turn, is a key factor in the development of metabolically related diseases, including diabetes mellitus (DM) [5, 9, 11]. In this regard, the search for the causes underlying the changes in carbohydrate metabolism remains relevant.

The aim of the study was to identify the characteristics of carbohydrate metabolism, pancreatic hormones, and adiponectin in an almost healthy Arctic population, depending on their ethnicity and lifestyle.

Materials and methods. In the course of a single-center observational cross-sectional study, residents of the village of Nelminsky in the North Caucasus Federal District (67°58' s.w.), the municipalities of Sokolskoye (65°17' s.w.), Soyanskoye (65°46' s.w.), and in the village of Dolgoshchelye in the Mezen district of the Arkhangelsk region (66°05' s.s.) – 457 people, as well as the villages of Seyakha (70°10's.s.), Tazovsky (67°21's.s.), Gyda (70°54's.s.), Nyda (66°37's.s.), Nori (6609° n), Antipayuta (69°06'n) – 660 people. The total sample size was 1,117 people (794 women and 323 men), the age of the subjects was 18-74 years. The study examined populations of the local Caucasoid population (ME) of 447 people and the indigenous inhabitants of the Far North (Nenets), who were divided into two groups according to their lifestyle - nomadic (KA, 143 people) and sedentary (OA, 527 people) aborigines. The study was conducted in compliance with the ethical standards set out in the Helsinki Declaration of the World Medical Association of 1964, as amended and supplemented in 2013, and was approved by the Commission on Biomedical Ethics at the Institute of Physiology of Natural Adaptations of the Federal State Budgetary Educational Institution FITSKIA Ural Branch of the Russian Academy of Sciences (protocols

The content (Me – 25%; 75%) of carbohydrate metabolism parameters, pancreatic hormones, and adiponectin in the practically healthy aboriginal and local Caucasian population of the Arctic

Indicators	Nomadic Aborigines (AS) (1)	Settled Aborigines (SA) (2)	The local Caucasian population (LCP) (3)	H - test	The Kraskel-Wallis criterion (H-test) with the Bonferoni correction
Glucose (Glu)	4.70(4.24;5.32)	4.74(4.21;5.35)	5.01(4.49;5.60)	H = 23.812 p < 0.001	1-2 = 2.698 **1-3 = 0.007** **2-3 < 0.001**
Lactate (Lac)	2.88(2.36;3.41)	3.07(2.47;3.73)	2.80(2.22;3.52)	H = 15.817 p = 0.001	1-2 = 0.319 1-3 = 0.860 **2-3 < 0.001**
Pyruvate (Pyr)	0.035 (0.03;0.04)	0.033(0.02;0.04)	0.034(0.02;0.04)	H = 5.258 p = 0.217	*1-2 = 0.087* *1-3 = 0.097* 2-3 = 2.973
Lac/Pyr	89.28(73.2;110.7)	99.58(77.9;125.7)	90.75(68.9;115.3)	H = 19.006 p < 0.001	**1-2 = 0.011** 1-3 = 2.686 **2-3 < 0.001**
Insulin (Ins)	6.36(3.70;13.23)	8.41(4.54;13.75)	6.86(4.42;12.20)	H = 8.373 p = 0.046	1-2 = 0.050 1-3 = 0.901 *2-3 = 0.074*
Proinsulin (ProIns)	2.70(1.55;4.80)	1.76(0.54;2.82)	2.50(1.79;4.05)	H = 53.851 p < 0.001	1-2 < 0.001 1-3 = 2.918 2-3 < 0.001
ProIns/Ins	0.06(0.02;0.15)	0.02(0.01;0.07)	0.06(0.03;0.10)	H = 56.552 p < 0.001	1-2 < 0.001 1-3 = 0.881 2-3 < 0.001
HOMA	1.40(0.72;3.00)	1.82(0.90;2.97)	1.46(0.90;2.67)	H = 4.787 p = 0.274	1-2 = 0.134 1-3 = 0.808 2-3 = 0.507
Caro	0.72(0.37;1.18)	0.57(0.35;0.93)	0.70(0.43;1.07)	H = 13.052 p = 0.004	**1-2 = 0.048** 1-3 =2.116 **2-3 = 0.003**
Adiponectin (Adn)	19.08(13.7; 29.0)	12.44 (8.2; 15.5)	22.40 (11.9; 34.9)	H = 42.797 p < 0.001	**1-2 < 0.001** 1-3 = 1.786 **2-3 < 0.001**

Note. Statistically significant differences are highlighted in bold ($p \leq 0.05$), while trending differences are highlighted in italics ($0.05 < p \leq 0.1$).

dated 2.02.2009, 4.02.2013, 9.11.2016 and 15.02.2022). Exclusion criteria were applied in the survey: people working in shifts), the presence of diabetes, CVD, thyroid diseases, acute pathological conditions and exacerbations of chronic diseases in the subjects.

Venous blood sampling from the examined individuals was carried out in the morning from 8.00 a.m. to 10.00 a.m. on an empty stomach in the Beckton Dickinson BP vacutainers, at the same time questionnaires were conducted with questions regarding chronic diseases and ethnicity. The glucose level (Glu, reference value 3.9–6.1 mmol/L) was determined by the spectrophotometric method using Chronolab AG kits. The content of adiponectin (Adh, norm 10-30 ng/ml), proinsulin (ProIns, norm 0.7-4.3) was determined in blood serum using the enzyme immunoassay kits "DRG Instruments Gmb H" on a tablet analyzer for enzyme immunoassay (ELISA, ELISYS Uno, Human Gmb H, Germany) and a StatFax 303 photometer (USA). pmol/l) and insulin (Ins, the norm is 2.1-22 μed/ml). The indices of the ratio of ProIns to Ins (ProIns/Ins) were calculated. The values specified in the instructions for the kits used were taken as normative. The indices characterizing the presence of insulin resistance (IR) were also calculated: NOMA according to the formula NOMA = (Glu (mmol/l) × Ins (Ume/ml)) / 22.5 and Sago according to the formula Sago = Glu (mmol/L) / Ins (mcME/ml).

Statistical data processing was carried out using the IBM SPSS Statistics 22.0 application software package. The samples obtained were checked for the normality of the distribution based on the results of calculating the Shapiro-Wilk criterion. The median (Me) values were calculated, and the scattering measures included the values of the 25th and 75th percentiles. The statistically significant differences between the independent groups were evaluated using the Kraskel-Wallis test (H-test) with the Bonfferoni correction (to keep the error of the first kind within 5%) [2].

Results and discussion. The indicators of carbohydrate metabolism, pancreatic hormones and adiponectin are presented in Table 1. Thus, the analysis of the level of Glu showed that there are significant differences between the groups under consideration (H=23.812, p<0.001). At the same time, a statistically significantly high content of Glu and ME was detected relative to OA and KA. There were no significant differences in the level of Pir depending on the lifestyle of the surveyed. The Lac level (H=15.817, p=0.001) and the Lac/Pir value (H=19.006, p<0.001) were the highest in the OA population, while the CA and ME were the lowest. In addition, it was shown that in OA, the values of Ins were maximum (H=8.373, p=0.046), in the KA and ME groups they were minimum (H=8.373, p=0.046), and the level of Ins (H=53.851, p<0.001) and the value of Ins/Ins (H=56.552, p<0.001), the opposite is true between the groups under consideration. At the same time, based on the data of Glu and Ins on an empty stomach, the value of the NOME index was calculated, it is informative in detecting IR in people with intolerance to Glu, i.e. those with violations of its level, and the Sago index, which is more sensitive in the absence of changes in the content of Glu. No statistically significant changes were found for the NOME index (H=4.787, p=0.274). Statistically significant changes between the groups were noted for the Sago index (H=13.052, p = 0.004). Our comparative assessment of the blood pressure level showed that there were statistically significant differences between the compared groups (N=42.797, p<0.001). Its significantly low content was observed in OA, both relative to KA and ME (p<0.001).

The socio-economic transformations carried out in recent decades, the influx of migrants and the growth of urbanization have changed the traditional way of life and diet of indigenous peoples, which led to the disruption of adaptive processes with increased intensification of carbohydrate metabolism, which serves as an amendment to Panin's concept [6]. At the same time, the most favorable changes, in our opinion, are represented by nomads who have preserved the traditional way of life with a dietary diet, compared with the settled contingent. At the same time, the lowest level of Glu against the background of a decrease in the level of Ins and an increase in ProIns may indicate a reduced load on the β-cells of the pancreas, and an increase in the level of Adn may improve the IR index, although the risk of developing latent metabolic disorders remains. In turn, sedentary people have multidirectional adaptive mechanisms for regulating glucose homeostasis. Thus, in OA, the predominance of anaerobic processes over aerobic ones is probably due to an increase in the proportion of carbohydrates while maintaining the proportion of lipids in the actual diet, which increases the risk of developing previously unusual somatic diseases, including diabetes. In addition, in OA, a change in the traditional way of life, fixed for centuries, leads to a loss of sensitivity to Ins, which in turn may be a consequence of a decrease in blood pressure [5]. In ME, an increase in the level of glycemia compared with the native population should be accompanied by an increase in the production of Ins for glucose uptake by tissues in order to utilize it, however, we have shown that IU increases the level of Ins more slowly while maintaining a higher level of ProIns and the value of ProIns/Ins compared to OA, which may indicate the entry of immature ProIns into the blood. This, apparently, leads to an increased load on the β-cells of the pancreas and the need for differentiation of adipose tissue, which leads to an increase in Adp synthesis. This may lead to greater oxidation of fats (with a low content of Ann and a high content of Glu). Thus, experiments on mice have shown that an increased level of Adh is a protective property that preserves the function of pancreatic beta cells while limiting the metabolic flow of Glu from beta cells [10, 13], and a decrease in its concentration leads to IR in patients receiving a high-fat diet [12].

Thus, in our opinion, the multidirectional nature of the changes in the studied indicators is related to the peculiarities of nutrition (diet, amount of carbohydrates consumed primarily) and lifestyle among the aboriginal and local Caucasian populations of the North, which themselves vary significantly. Probably, there is competition between Glu and fatty acids at the tissue level to maintain an optimal level of energy exchange in the harsh climate of the North. This issue will be investigated by us in the future.

Conclusion. The results of our study showed that nomads have the lowest Glu levels against the background of a decrease in the level of Ins and an increase in ProIns may indicate a reduced load on the β-cells of the pancreas, and an increase in the level of Adn may improve the IR index.In OA, the predominance of anaerobic processes over aerobic ones against the background of an increase in blood pressure at a lower level of blood pressure may be associated with an increase in the proportion of carbohydrates while maintaining the proportion of lipids in the actual diet due to lifestyle changes, which increases the risk of developing previously uncommon somatic diseases. In MEN, the level of Ins increases slightly while maintaining a higher value of ProIns/Ins, which, apparently, leads, on the one hand, to an increase in the load on the β-cells of the pancreas, and on the other, to the need for differentiation of adipose tissue, which causes an increase in Adp synthesis.

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THE EFFECT OF ELEVATED AND PHYSIOLOGICAL CONCENTRATIONS OF CATECHOLAMINES ON THE FORMATION OF IMMUNOGLOBULINS IN HEALTHYINDIVIDUALS IN THE NORTHERN TERRITORIES OF THE RUSSIAN FEDERATION

An immunological assessment of the health status of 75 Arkhangelsk residents who had no history of acute or chronic diseases at the time of the study was carried out. The aim of the study was to study the effect of elevated and physiological concentrations of catecholamines on the formation of immune responses in residents of the northern territories of the Russian Federation. During a comprehensive immunological examination, a morphological analysis of the blood was performed, including a study of its cellular composition (hemogram). Thus, it has been established for the first time that practically healthy residents of the European North of the Russian Federation experience changes in the content of catecholamines and immunological parameters. An increase in the average dopamine content and a slight increase in the average IdM content was found, which amounted to 33.7±3.56 and 1.83±0.04, respectively. Studies have shown that patients have a tendency to increase the content of IgE immunoglobulin (74.3±8.16). In addition, abnormally high concentrations of IdM (36.84±3.18%) and elevated concentrations of IgG (25.0±2.49%) were detected. There was also a slight increase in the concentrations of cells capable of proliferation (CD10+), which amounted to 1.7±0.22%. Elevated concentrations of catecholamines in practically healthy people have not been established. Concentrations of dopamine were 7.81±0.43%, norepinephrine 4.76±0.08% and adrenaline 3.08±0.27%.The remaining immunological parameters did not exceed the values considered physiologically normal. These changes correlate with the impact of negative climatic factors. Such factors include violation of the light regime and low temperatures, which provoke a chronic state of stress in the body and, as a result, increased stress on the immune system. This phenomenon leads to a malfunction of the immune system and accelerated physiological wear of the body, which can become a predisposing factor for the development of various diseases.

Keywords: catecholamines, dopamine, norepinephrine, adrenaline, immune reactions, northern territories of the Russian Federation, lymphocytes. CD10+, CD95+, immunoglobulins.

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Introduction. The immune system of residents of the northern regions shows increased basic activity in a number of indicators. According to traditional views, the health of the population of the northern territories is subject to the complex effects of a number of adverse factors. These include natural and climatic conditions, including extreme weather conditions, geomagnetic activity, sudden changes in illumination, geochemical features of the area and the unpredictability of atmospheric phenomena. In addition, it is typical to observe sharp fluctuations in temperature, atmospheric pressure, and daylight hours throughout the year. Prolonged exposure to low temperatures combined with strong winds can lead to negative health consequences. Such a meteorological situation contributes to the development of oxygen starvation and an increase in the basic metabolism in the body. High levels of humidity also have a negative impact on health, disrupting cerebral circulation. The interaction of these factors has a complex effect on the functioning of all human body systems. In the context of the topic under discussion, it is also necessary to note the level of social protection of citizens in the field of healthcare, which is carried out at an insufficient level. The influence of extreme conditions on the human body, characteristic of the northern regions, may exceed its ability to adapt [2]. The issue of the scientific justification for setting standards for regional physiological parameters remains important and requires further study.

The state of health of residents of the northern territories of the Russian Federation is the most important indicator of the quality of life and reflects the ability to withstand adverse factors. The formation and functioning of the immune system in the inhabitants of the northern regions has its own characteristics [1]. Undoubtedly, climatic and anthropogenic health risk factors in the subjective assessments of residents of northern cities have a significant impact on the functioning of the immune system [8].

The level of immunity and adaptation to difficult environmental conditions play a key role in maintaining the health of northerners, and the level of resistance to diseases among residents of the northern regions is significantly lower than in other regions. There is a decreased resistance to diseases in the population of the northern regions, in comparison with other regions, as a result, there is a decrease in the immune response [14]. The total effect of exposure to the adverse factors of the North significantly increases the negative impact on the human body in the form of severe stress conditions [15].

In the difficult environment of the North, where living conditions are subject to frequent changes, the process of human adaptation is particularly difficult [3]. It requires significant energy expenditure and uses redundant, and sometimes ineffective, mechanisms to maintain the stability of the human body's homeostasis. The immune system, functioning as the body's defense mechanism, plays a key role in maintaining its stability. Thus, the state of the immune system and its reactivity are important indicators of the overall functional state of the human body and its ability to adapt to adverse conditions. The study of the immune system of representatives of northern populations is an urgent task due to the fact that specific climatic conditions and unfavorable ecology contribute to the modification of its functioning.

The aim is to establish the effect of elevated and physiological concentrations of catecholamines on the formation of immunoglobulins in healthy individuals in the northern territories of the Russian Federation.

Materials and methods. The data of the immunological examination of 75 practically healthy people living in Arkhangelsk, who at the time of the examination had no history of acute and chronic diseases, were studied and analyzed. The average age was 45.4 years. The study participants were in the age group from 18 to 65 years old. The examination was conducted at the Biolam medical company, Arkhangelsk. The study was conducted in accordance with the provisions of the Helsinki Declaration and approved by the Ethics Committee of the Federal State Budgetary Educational Institution FITSKIA Ural Branch of the Russian Academy of Sciences (Protocol No. 001-20/01 dated January 20, 2025). The survey was conducted with the written consent of the respondents.

Blood samples were taken for laboratory examination in the morning (from 8 to 10 o'clock), on an empty stomach. The blood serum was isolated by centrifugation, which made it possible to separate the liquid fraction from blood cells (erythrocytes) in order to prepare biological material for further analysis.

As part of the complex of immunological research, an analysis of the morphological composition of blood was carried out using the Romanovsky-Giemse staining method. The concentrations of catecholamines (dopamine, norepinephrine, epinephrine) in blood serum were studied by enzyme immunoassay on an automatic Evolis enzyme immunoassay analyzer (Bio-RAD, Germany) using diagnostic kits manufactured by IBL Hamburg, Germany. The level of cells capable of proliferation (CD10+) and cells labeled for death (CD95+) was assessed by indirect immunoperoxidase reaction using monoclonal antibodies (Sorbent, Moscow). The content of immunoglobulins A (IdA), M (IdM), G (IgG), and E (IgE) was studied using Biosourse test kits (USA). In the course of statistical analysis of the research data, software packages "Microsoft Excel 2010" and "Statistica 7.0" (StatSoft, USA) were used. The Shapiro-Wilk criterion was used to assess the compliance of the data distribution with the normal law. The results of the analysis showed the similarity of the distributions with the normal one. In this regard, the arithmetic mean (M) and the standard error of the mean (m) were calculated to describe the data. The boundaries of the normal distribution of the studied indicators are also determined. The relationship between the parameters was estimated using the Pearson correlation coefficient (r). The statistical significance of the differences was established at the significance level of the t-test $p < 0.05$.

Results and discussion. The increased content and physiological concentrations of catecholamines, as well as the peculiarities of immune reactions in people living in the North, have been established. According to the results of the study, an increase in the average content of dopamine in the peripheral venous blood was revealed. The reaction from other catecholamines was relatively low. A slight increase in the average IdM content was also found. Studies have shown that patients have a tendency to increase the content of IgE immunoglobulin. The level of other immunological parameters corresponded to the standard values (Table 1).

Dopamine is a monoamine neurotransmitter produced by the synapses of neurons in the brain, which functions

as a chemical mediator and transmits nerve signals between neurons, as well as between the brain and various organs. Dopamine synthesis is also carried out in the adrenal glands, kidneys and intestines. It has been established that approximately 90% of the dopamine circulating in the blood is produced in the intestine [18, 19]. In the context of the functioning of the gastrointestinal tract, dopamine acts as a vasodilator, contributing to the expansion of blood vessels and increased blood flow in the mesenteric region. At the same time, there is a decrease in peristaltic activity. This secretion helps to reduce intestinal motility, as well as modify absorption processes while increasing mucus production. These processes are usually accompanied by an increase in the concentration of specific proteins in the blood serum. Dopamine performs important functions in the body, acting as a hormone. Its effects include: cardiovascular, gastrointestinal and renal. Cardiovascular: increased blood pressure, increased heart rate and strength. Gastrointestinal: relaxation of the smooth muscles of the gastrointestinal tract. Renal: stimulation of fluid filtration in the kidneys, increased blood flow in them, accelerated excretion of sodium in the urine. The effect of dopamine is diverse and depends on its concentration and localization of effects on cells of specific tissues.

Research by scientists shows that residents of the northern regions have elevated levels of the neurotransmitter dopamine [6, 7]. This feature is presumably an adaptive reaction of the body to extreme living conditions at low temperatures. The study examined the effect of catecholamines on the immune status of practically healthy people living in the northern regions. The results showed a statistically significant increase in dopamine levels in a significant part of the examined group [12]. Researchers have established a relationship between the concentration of dopamine and the activity of the thyroid gland in residents of the northern regions. It was found that men have the highest concentration of dopamine. At the same time, women living in the European North are characterized by low levels of this neurotransmitter [13]. This fact deserves close attention and may become a starting point for an in-depth study of the role of dopamine in the functioning of other organs and systems in the inhabitants of the North. Researchers from the laboratories of the Institute of Physiology of Natural Adaptations have also shown that the level of dopamine in the peripheral venous blood of residents of the North is usually elevated. At the same time, there is a seasonal variation: dopamine concentration peaks during the polar day and decreases during the winter months [11].

Class M immunoglobulins (IgM) play a key role in the primary immune response to the appearance of antigens. Their production starts immediately after the antigen enters the body and is identified by the immune system. In blood serum, IgMs have the ability to agglutinate bacteria, neutralize viruses, and activate the complement system. They also ensure the elimination of pathogens from the bloodstream and stimulate the phagocytic activity of cells of the immune system.

Immunoglobulin E (IgE), found in human blood serum, belongs to the class of gamma globulins and is produced by B lymphocytes. Immunoglobulin E (IgE) plays an important role not only in the presentation of antigens, but can also directly affect the maturation of dendritic cells and promote the activation of specific T-lymphocyte proliferation [17]. Their main purpose is to participate in immediate reactions (reagin reactions) and to protect the body from parasitic infections.

Abnormally high concentrations of IdM and elevated concentrations of IgG were detected. Residents of the northern territories demonstrate elevated levels of immunoglobulins [4]. There was also a slight increase in the concentrations of cells capable of proliferation (CD10+). Elevated concentrations of catecholamines in practically healthy people have not

Table 1

Average content of catecholamines and immunological parameters in peripheral venous blood of healthy individuals in the northern territories of the Russian Federation, (M±m)

Investigated parameters	The average content in practically healthy people, n=75, (M±m)	Physiological limits
Dopamine, pg/ml	33.7±3.56	>30 пг/мл
Norepinephrine, pg/ml	391.03±23.82	100-600
Adrenaline, pg/ml	58.94±2.56	<125
Cells capable of proliferation (CD10+), ×109 cells/l	0.47±0.11	0.2-1.5
Cells labeled for death (CD95+), ×109 cells/l	0.52±0.02	0.2-1.5
Immunoglobulin A (IdA), g/l	1.65±0.23	1.2-5.4
Immunoglobulin M (IdM), g/l	1.83±0.04	0.7-1.8
Immunoglobulin G (IgG), g/l	18.35±0.47	7-24
Immunoglobulin E (IgE), units/ml	74.3±8.16	<100

Table 2

Frequency of registration of elevated concentrations of catecholamines and immunological parameters in peripheral venous blood in healthy individuals in the northern territories of the Russian Federation, %

Investigated parameters	Frequency of registration of elevated concentrations in practically healthy people, n=75, %	Physiological limits
Dopamine, pg/ml	7.81±0.43	>30 пг/мл
Norepinephrine, pg/ml	4.76±0.08	100-600
Adrenaline, pg/ml	3.08±0.27	<125
Cells capable of proliferation (CD10+), ×109 cells/l	1.7±0.22	0.2-1.5
Cells labeled for death (CD95+), ×109 cells/l	-	0.2-1.5
Immunoglobulin A (IdA), g/l	2.94±0.5	1.2-5.4
Immunoglobulin M (IdM), g/l	36.84±3.18	0.7-1.8
Immunoglobulin G (IgG), g/l	25.0±2.49	7-24
Immunoglobulin E (IgE), units/ml	28.0±0.7	<100

been established. The remaining immunological parameters did not exceed the values considered physiologically normal (Table 2).

Cells capable of proliferation (CD10+) characterize a population of mature neutrophils capable of suppressing the T-cell immune response. In addition, CD10+ receptor expression is detected on the surface of immature B-lymphocytes during their differentiation. During blast transformation, these immature B lymphocytes are transformed into plasma cells, which are responsible for the synthesis of various immunoglobulins and support T-helper and macrophage activity in triggering and coordinating an adaptive immune response. The presence of an increased level of lymphocytes carrying the CD10+ marker indicates a possible activation of the immune response, characterized by pronounced lymphoproliferation.

The functioning of immunity in the population of the northern regions is influenced by numerous factors related to the category of climatic, ecological, and socio-economic conditions [5, 16]. In the harsh climatic conditions of the North, there is an increase in the production of antibodies, including autoantibodies. This phenomenon is associated with the effectiveness of the body's adaptation to adverse environmental conditions. In the harsh conditions of the northern climate, the range of antigenic structures of the body expands. Adverse weather conditions contribute to an increase in the concentration of metabolic products of tissues with autoantigenic properties. This, in turn, leads to increased production of autoantibodies. Living in the northern regions leads to significant changes in the functioning of humoral immunity, which, in turn, can contribute to an increase in the level of class M immunoglobulins (IgM) in the body. In the unfavorable conditions of the northern climate, there is an increase in the antigenic load on the body. This leads to a significant increase in the diversity of antigenic structures, including those that are difficult to identify [10]. An increase in the level of IgG immunoglobulin in the population of the northern territories may also be due to the influence of adverse meteorological factors. The increased level of immunoglobulin IgE in the population of the northern regions may be associated with the negative effects of climatic factors, including a cold climate characterized by low temperatures, a lack of sunlight and various diseases of allergic and non-allergic etiology. Cells capable of proliferation (CD10+) have a noticeable tendency to increase in the inhabitants of the northern territories. This correlation is due to the influence of unfavorable climatic and geographical factors, as well as a number of other circumstances that affect the characteristics of the body's immune responses. Disorders of the immune system in the population living in the northern regions may be associated with exposure to ionizing radiation. It can cause increased cell proliferation, which can negatively affect the functioning of the immune system [9].

Conclusion. In the course of a study devoted to the study of the immune system of healthy individuals in the European North of the Russian Federation, characteristic features were identified. Healthy Northerners are characterized by the activation of the humoral link of immunity, manifested by a high concentration of IgM, increased IgE, as well as signs of autosensitization with high levels of autoantibodies. An increase in the average dopamine content and a slight increase in the average IdM content was found, which amounted to 33.7±3.56 and 1.83±0.04, respectively. Studies have shown that healthy people tend to increase the average content of immunoglobulin IgE (74.3±8.16). In addition, abnormally high concentrations of IdM (36.84±3.18%) and elevated concentrations of IgG (25.0±2.49%) were detected. There was also a slight increase in the concentrations of cells capable of proliferation (CD10+), which amounted to 1.7±0.22%. Elevated concentrations of catecholamines in healthy Northerners have not been established. Concentrations of dopamine were 7.81±0.43%, norepinephrine 4.76±0.08% and adrenaline 3.08±0.27%. The remaining immunological parameters did not exceed the values considered physiologically normal. Thus, it was found that healthy individuals in the European North of the Russian Federation experience changes in the content of catecholamines and immunological parameters in peripheral venous blood. These changes correlate with the impact of negative climatic factors. Such factors include violation of the light regime and low temperatures, which provoke a chronic state of stress in the body and, as a result, increased stress on the immune system. This phenomenon leads to a malfunction of the immune system and accelerated physiological wear of the body, which can become a predisposing factor for the development of various diseases.

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SCIENTIFIC REVIEWS

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ANALYSIS OF RISK FACTORS FOR ANASTOMOTIC LEAKAGE IN PATIENTS AFTER SURGICAL TREATMENT OF COLORECTAL CANCER: A SYSTEMATIC LITERATURE REVIEW

This systematic literature review analyzes the risk factors for anastomotic leakage (AL) in the surgical treatment of colorectal cancer. Based on 42 studies, key risk predictors for AL were identified. The incidence of AL in the studies included in this review ranged from 2,8% to 24,7%. The introduction of the RALAR scale significantly improved the objective assessment of AL risk. A comprehensive approach to prevention, based on risk stratification and treatment personalization, can significantly improve the outcomes of surgical treatment for colorectal cancer.

Keywords: colorectal cancer, anastomotic leakage, risk factors, systematic review, PRISMA

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Introduction. Colorectal cancer (CRC) ranks among the leading oncological diseases in terms of both incidence and mortality [18, 36]. According to the World Health Organization, CRC is the third most common malignant neoplasm worldwide [95]. In 2022, more than 1.9 million new cases of CRC were reported, along with approximately 903,000 deaths related to the disease [36]. In the Russian Federation, CRC also holds a leading position in the structure of oncological morbidity, with a rising trend in the number of patients affected by this pathology, potentially reaching 2.2 million cases by 2030 [2, 3].

Surgical intervention remains the primary treatment for CRC, where anastomosis formation is a key stage determining functional outcomes and patients' quality of life [4, 84]. Anastomotic leakage (AL), occurring in 2–19% of cases, continues to be a serious complication [79, 96].

The International Study Group on Rectal Cancer defines AL as a defect in the integrity of the intestinal wall at the anastomotic site [24]. This complication is associated with high morbidity (20–30%), mortality (up to 22%), prolonged hospitalization, increased risk of recurrence, reduced survival rates, and diminished quality of life [59, 89, 90].

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Despite numerous studies on AL in CRC, risk factors for this complication remain a subject of debate. Current literature identifies multiple potential predictors of AL, which can be categorized into several groups: patient-specific (age, sex, comorbidities, nutritional status, harmful habits), tumor-related (location, stage, preoperative therapy), surgical (type of intervention, anastomotic level, operation duration, intraoperative complications), and perioperative factors (use of drains, preventive stoma, antibiotic prophylaxis) [35, 61, 69].

Systematization and analysis of AL risk factors are crucial for developing effective prevention strategies, especially considering emerging data and advancements in surgical techniques in recent years [56, 61]. Risk stratification of patients may help optimize preoperative preparation, intraoperative decision-making, and postoperative management, potentially reducing AL rates and improving CRC treatment outcomes [35, 89].

The aim of this review is to analyze recent literature (within the last five years) to identify and evaluate the significance of risk factors for AL in patients undergoing surgery for CRC.

Materials and Methods. A systematic literature review was conducted following the PRISMA guidelines [92]. The search was performed in electronic databases (PubMed, Google Scholar, and eLibrary) from January 2019 to February 2025 using the following key terms and their combinations in English and Russian:*"colorectal cancer", "колоректальный рак", "anastomotic leak", "несостоятельность анастомоза", "risk factors", "факторы риска".*

Inclusion Criteria

Studies were selected based on the following criteria: Research on risk factors for AL in surgical treatment of CRC; Articles reporting statistically significant risk factors for AL ($p < 0.05$); Publications in English or Russian; Full-text articles in peer-reviewed journals; Original studies, systematic reviews, and meta-analyses.

Study Selection Process

A two-stage screening was applied: 1. Initial screening of titles and abstracts. 2. Full-text review of selected articles. From each publication, the following data were extracted: Authors, study design, sample size; AL incidence rate; Statistically significant risk factors with corresponding metrics.

Out of 1,522 initially identified records, after removing duplicates and applying inclusion criteria, 42 studies were included in the final analysis (Figure 1).

Results and Discussion. *General Characteristics of Included Studies.* This systematic review included 42 studies published between 2019 and 2025. A summary of the included studies is presented in Table.

The incidence of AL across the analyzed studies ranged from 2.8% to 24.7%, reflecting significant heterogeneity in methodological approaches to defining and diagnosing this complication. In most studies (n=31, 73.8%), AL was defined according to the criteria of the International Study Group of Rectal Cancer [24], allowing for a more standardized analysis.

The identified statistically significant risk factors for AL were categorized into four groups (Figure 2). This classification is based on: pathophysiological mechanisms affecting anastomotic healing, chronological sequence of the treatment process, modifiable vs. non-modifiable risk factors. This approach has clinical significance for: preoperative risk stratification, development of predictive models, personalization of surgical treatment. The proposed classification aligns with current scientific approaches, emphasizing the multidisciplinary nature of AL in patients undergoing CRC surgery.

Patient-Specific Risk Factors for Anastomotic Leakage. Male Gender. Multiple studies with high statistical significance have identified male sex as an independent risk factor for AL. Alekseev et al. [42] demonstrated that male patients have nearly a fourfold increased risk of AL (OR 3.8, 95% CI 1.9-7.7, p<0.001). These findings were corroborated by Degiuli et al. [70] (OR 1.55, 95% CI 1.27-1.88, p<0.001) and Dias et al. [64], who reported a relative risk of 1.56 (95% CI 1.40-1.75, p<0.05) for male patients. Further supporting evidence comes from Kryzauskas et al. [74] (OR=2.40, p=0.004) and a comprehensive meta-analysis by He et al. [11] involving 115,462 patients (p<0.0001).

The elevated AL risk in male patients may be attributed to anatomical char-

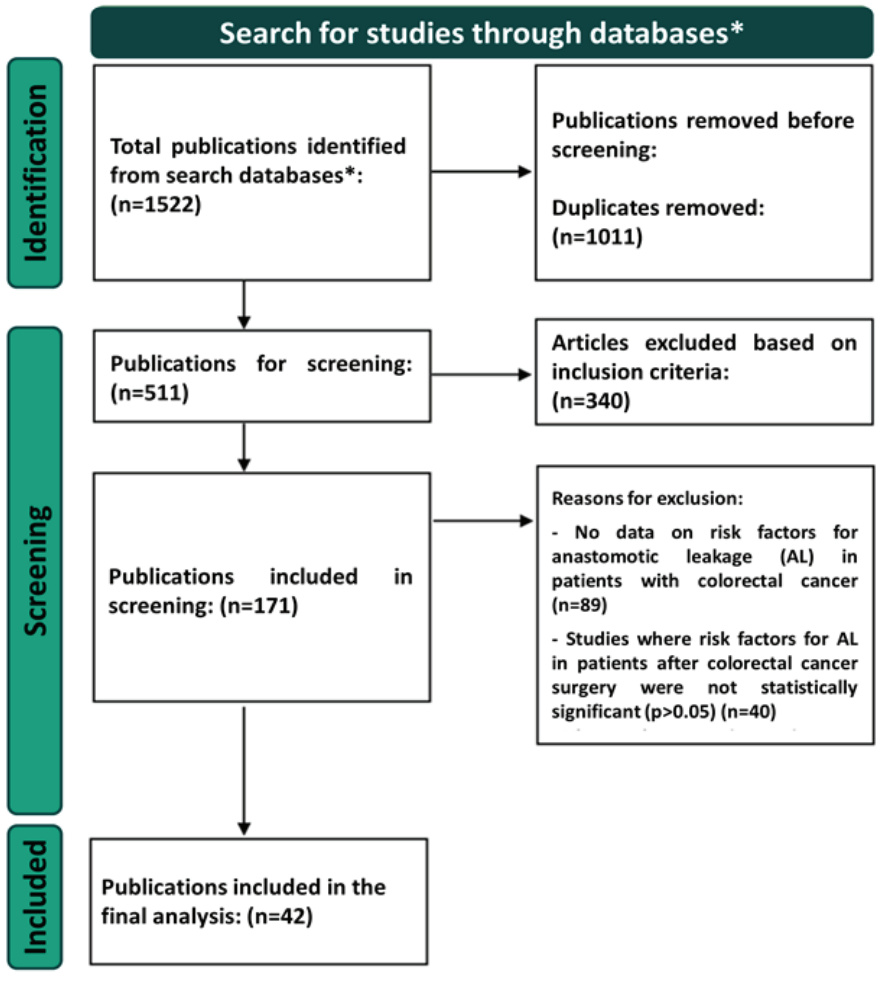

Fig. 1. Flowchart of the systematic literature review conducted according to the PRISMA protocol

Main characteristics of the studies included in the review

Study and year of publication	Study type	Number of patients
Alekseev et al. (2022) [42]	Retrospective cohort study	429
Arron et al. (2021) [93]	Multicenter retrospective study	70229
Artus et al. (2020) [46]	Retrospective cohort study	200
Awad et al. (2021) [87]	Prospective cohort study	315
Brisinda et al. (2022) [12]	Multicenter retrospective study	583
Danardono et al. (2024) [23]	Retrospective cohort study	85
Degiuli et al. (2022) [70]	Multicenter retrospective study	5398
Dias et al. (2022) [64]	Systematic literature review and meta-analysis	184110
Foppa et al. (2023) [80]	Prospective cohort study	643
Harada et al. (2025) [76]	Retrospective cohort study	304
He et al. (2023) [11]	Systematic literature review and meta-analysis	115462
Herrod et al. (2019) [66]	Retrospective cohort study	169
Ito et al. (2024) [13]	Retrospective cohort study	102
Koskenvuo et al. (2024) [48]	Multicenter prospective study	565
Kryzauskas et al. (2020) [74]	Multicenter prospective study	900
Kryzauskas et al. (2020) [43]	Systematic literature review and meta-analysis	7115
Litchinko et al. (2024) [79]	Literature review	Н/Д
Nordholm-Carstensen et al. (2019) [53]	Multicenter retrospective study	1414
Nugent et al. (2021) [54]	Systematic literature review and meta-analysis	32953
Phan et al. (2019) [28]	Systematic literature review and meta-analysis	896
Rodriguez et al. (2024) [77]	Multicenter retrospective study	360
Simillis et al. (2023) [55]	Systematic literature review and meta-analysis	59813
Simpson et al. (2024) [57]	Retrospective cohort study	522
Tan et al. (2021) [91]	Systematic literature review and meta-analysis	666886
Toyoshima et al. (2020) [49]	Retrospective cohort study	117
Tsai et al. (2022) [82]	Retrospective cohort study	1249
Tsalikidis et al. (2023) [61]	Literature review	Н/Д
Wada et al. (2022) [20]	Retrospective cohort study	593
Wallace et al. (2020) [33]	Systematic literature review and meta-analysis	Н/Д
Wang et al. (2022) [10]	Retrospective cohort study	1013
Yang et al. (2019) [65]	Systematic literature review and meta-analysis	8456
You et al. (2020) [37]	Retrospective cohort study	322
Yu et al. (2021) [38]	Retrospective cohort study	1058
Yue et al. (2023) [47]	Systematic literature review and meta-analysis	8852
Zarnescu et al. (2021) [96]	Literature review	Н/Д
Zhang et al. (2023) [9]	Retrospective cohort study	292
Zhou et al. (2020) [32]	Retrospective cohort study	208
Zouari et al. (2022) [34]	Retrospective cohort study	163
Ahmetzyanov et al. (2021) [6]	Literature review	Н/Д
Balkarov et al. (2021) [5]	Prospective cohort study	115
Darbishgadzhiev et al. (2023) [7]	Retrospective cohort study	248
Polishchuk et al. (2021) [1]	Retrospective cohort study	74

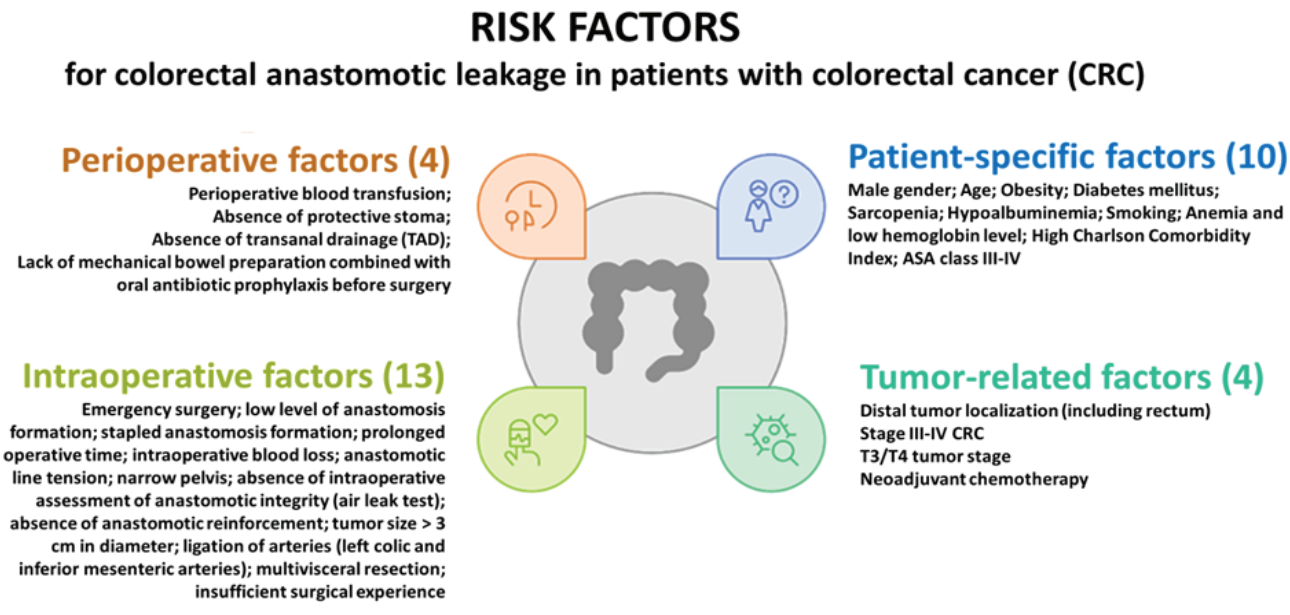

Fig. 2. Summary of risk factors for anastomotic leakage included in the study

acteristics of the male pelvis, which is typically narrower and deeper, creating technical challenges during anastomosis formation, particularly in low rectal resections [74]. Additionally, hormonal factors may influence microcirculation at the anastomotic site, potentially increasing the risk of ischemia and subsequent leakage [26]. These findings underscore the importance of considering male sex as a significant risk factor in surgical planning and postoperative monitoring.

Age. The influence of age on AL risk was confirmed in two studies. Rodriguez et al. [77] showed that age ≥65 years is associated with an increased risk of AL (OR=2.48, 95% CI 1.24-4.97, p=0.003). Similar results were obtained by Danardono et al. [23], where age over 50 years was a statistically significant risk factor (p=0.05).

The increased risk of AL in elderly patients may be associated with age-related changes in microcirculation, reduced tissue regenerative capacity, impaired collagen formation, and a higher incidence of comorbidities [31, 88]. These factors collectively may negatively affect the anastomotic healing process [62].

Obesity. Obesity was identified as a significant risk factor for AL in two studies. Nugent et al. [54] demonstrated that visceral obesity increases the risk of AL by 2.15 times (OR=2.15, 95% CI 1.46–3.15, p<0.05), with this risk being particularly high in patients with colon cancer (OR=2.88) and rectal cancer (OR=2.74). The meta-analysis by He et al. [11] also confirmed a statistically significant association between body mass index (BMI) and the risk of AL (p=0.03).

The negative impact of obesity may be explained by technical difficulties during surgery associated with increased visceral fat, impaired tissue perfusion, and higher intra-abdominal pressure [60, 72]. Additionally, obese patients often present with chronic inflammation, which may adversely affect tissue regeneration and wound healing processes [8].

Diabetes Mellitus. Diabetes mellitus was identified as a risk factor for AL in three studies. A systematic review by Dias et al. [64] established that diabetes nearly doubles the risk of AL (RR=1.97, 95% CI 1.44–2.70, p<0.05). An even stronger association was reported in a meta-analysis by Tan et al. [91], where the OR was 2.407 (95% CI 1.837–3.155, p<0.001). The study by Zouari et al. [34] also confirmed this relationship (p=0.04).

The pathophysiology of the increased risk of AL in diabetic patients involves several mechanisms. Diabetic microangiopathy leads to impaired tissue perfusion at the anastomotic site [81]. Chronic hyperglycemia disrupts neutrophil and macrophage function, potentially delaying the inflammatory phase of wound healing [52]. Moreover, collagen protein glycation reduces the tensile strength of the anastomosis [16]. It is important to note that even short-term episodes of hyperglycemia in the perioperative period can negatively affect healing processes, highlighting the need for strict glycemic control [27].

Nutritional Status. Nutritional status disorders, particularly hypoalbuminemia, were identified as significant risk factors for AL in five studies. Rodriguez et al. [77] established that a preoperative albumin level <3.5 g/dL significantly increases the risk of AL (OR=22.2, 95% CI 11.5–42.9, p<0.001). Zhang et al. [9] also confirmed that low albumin levels (<37.5 g/L) are an independent risk factor (p=0.006). Similar findings were reported by Danardono et al. [23] (p=0.01), Zouari et al. [34] (p=0.01), and Awad et al. [87] (p=0.015).

Sarcopenia, as an indicator of malnutrition, was also identified as an independent risk factor for AL in the study by Herrod et al. [66], where a lumbar muscle density ≤43.5 HU on computed tomography was associated with a 14-fold increased risk of AL (OR=14.37, p=0.026).

Malnutrition negatively affects protein synthesis necessary for tissue repair, weakens the immune response, and impairs regeneration processes [29]. Low albumin levels may reflect both insufficient protein intake and ongoing inflammatory processes, which together worsen the prognosis of anastomotic healing [63].

Smoking. Active smoking was identified as a significant risk factor for AL in four studies. In the systematic review by Dias et al. [64], the relative risk for smokers was 1.48 (95% CI 1.30–1.69, p<0.05). Tsai et al. [82] found that not only active smoking at the time of surgery (p=0.022), but also a history of smoking with cessation less than 10 years prior (p=0.029), significantly increased the risk of AL. This association was also confirmed by Zouari et al. [34] (p=0.01) and Foppa et al. [80] (p=0.03).

The negative impact of smoking on anastomotic healing may be attributed to several mechanisms. Nicotine induc-

es vasoconstriction, leading to tissue ischemia. Carbon monoxide in tobacco smoke reduces oxygen transport to tissues [83]. Additionally, tobacco smoke components impair neutrophil and macrophage function, delaying wound cleansing and granulation tissue formation processes [21].

Anemia. Preoperative anemia was identified as a risk factor for AL in four studies. Harada et al. [76] found that hemoglobin levels ≤10.9 g/dL for men and ≤9.9 g/dL for women were associated with nearly a 10-fold increased risk of AL (OR=9.94, p=0.002). Brisinda et al. [12] showed that hemoglobin levels <10 g/dL significantly increased the risk of AL (11.8% vs. 7.0% with ≥10 g/dL, p=0.02). The association between anemia and AL was also confirmed by Danardono et al. [23] (p=0.007) and Zouari et al. [34] (p<0.01).

Anemia may negatively affect anastomotic healing by reducing oxygen delivery to tissues, which is especially critical in the context of relative ischemia at the anastomotic site [14]. Inadequate tissue oxygenation can impair cellular proliferation, collagen synthesis, and neoangiogenesis processes, which collectively compromise anastomotic strength and integrity [17].

Comorbidity. A high Charlson Comorbidity Index (CCI) was associated with an increased risk of AL in two studies. Artus et al. [46] showed that CCI >5 is an independent risk factor for AL in rectal surgery (p=0.025). Wada et al. [20] found that CCI ≥2 increased the risk of AL by nearly fivefold (hazard ratio=4.91, 95% CI 2.23–10.85, p<0.001).

A high American Society of Anesthesiologists (ASA) physical status classification III-IV was also identified as a risk factor for AL in three studies: Dias et al. [64] (RR=1.70, 95% CI 1.37–2.09, p<0.05), Kryzauskas et al. [74] (OR=3.23, 95% CI 1.10–9.50, p=0.013), and Rodriguez et al. [77] (p=0.032).

A high comorbidity burden reflects the general health status of the patient and may affect anastomotic healing through various mechanisms, including impaired microcirculation, reduced regenerative capacity of tissues, and altered immune response. Moreover, patients with a high comorbidity index often take multiple medications, some of which (e.g., non-steroidal anti-inflammatory drugs, corticosteroids) can negatively influence healing processes [62, 74].

Tumor-Related Risk Factors. Tumor Location. Distal tumor location in the rectum was identified as one of the most significant risk factors for AL in six studies. Rodriguez et al. [77] found a statistically significant association between rectal tumor location and the risk of AL (p=0.001). This association was also confirmed by Zhang et al. [9] (p=0.007) and Brisinda et al. [12] (p=0.006). Kryzauskas et al. [74] showed that the incidence of AL after rectal resection was 10.7% compared to 5.1% after sigmoid resection (p<0.05). Wang et al. [10] established that tumor distance from the anal verge ≤5 cm and 5–10 cm were independent risk factors for AL (p=0.009 and p=0.018, respectively). Polishchuk et al. [1] also confirmed that tumor location 5–10 cm from the anal canal significantly increases the risk of AL (p=0.021).

The increased risk of AL in distal tumor locations may be explained by several factors. Technical difficulties in forming a low anastomosis within the confined space of the pelvis increase the risk of anastomotic failure [72]. Additionally, the blood supply to the distal rectum is less abundant compared to the proximal sections, which may predispose the anastomosis to ischemia [15]. Finally, radiotherapy, commonly used in rectal cancer, may negatively affect tissue healing [45].

Tumor Stage and Size. Stage III–IV CRC was associated with an increased risk of AL in the study by Rodriguez et al. [77] (OR=2.71, 95% CI 1.34–5.48, p=0.005). Kryzauskas et al. [74] also identified tumor stage T3/T4 as an independent risk factor for AL (OR=2.25, p=0.017). Tsalikidis et al. [61] noted in their study that a tumor diameter greater than 3 cm may also increase the risk of AL (p<0.05).

Stages III–IV and larger tumor size may increase the risk of AL through several mechanisms. More extensive resections required to remove large tumors can lead to greater anastomotic tension [71]. Moreover, tumors at more advanced stages are often accompanied by systemic metabolic disturbances, which may negatively affect the healing process [86].

Neoadjuvant Therapy. Preoperative chemoradiotherapy was identified as a risk factor for AL in the systematic review and meta-analysis by Dias et al. [64], where the relative risk was 2.16 (95% CI 1.17–4.02, p<0.05).

Neoadjuvant therapy potentially impairs anastomotic healing through endothelial damage and tissue fibrosis caused by radiotherapy [41], as well as through suppression of cellular proliferation and collagen synthesis during chemotherapy. The combination of these methods may exacerbate negative effects [44]. However, recent studies have not confirmed an increased risk of AL in CRC patients undergoing neoadjuvant treatment [39, 51, 58, 85].

Intraoperative Risk Factors. Type of Surgery. Emergency surgery was identified as a significant risk factor for AL in two studies. Dias et al. [64] demonstrated that emergency CRC surgeries are associated with an increased risk of AL (OR=1.61, 95% CI 1.26–2.07, p<0.05). Awad et al. [87] also confirmed this association in their study (p=0.043).

Emergency surgeries increase the risk of anastomotic leak due to the inability to adequately prepare the bowel, leading to higher bacterial contamination at the anastomotic site [75]. Additionally, unstable hemodynamics in emergency situations negatively affect tissue perfusion. Technical aspects of emergency interventions are often less optimal compared to elective procedures [67].

Anastomotic Level and Type. A low anastomotic level was identified as one of the most significant risk factors for AL in four studies. Litchinko et al. [79] noted that a low anastomotic level significantly increases the risk of AL (p<0.05). Tsalikidis et al. [61] also confirmed this association (p<0.05). Another study [7] demonstrated the relationship between anastomotic height and AL risk: the incidence of AL was 0% at 9 cm and above, 5.2% at 5–8 cm, and 13% at 4 cm or lower from the dentate line (p=0.006). Brisinda et al. [12] also found that the mean distance from the anal verge in patients with AL was 71.0±32.0 mm, compared to 89.0±21.0 mm in patients without AL (p=0.0001).

The type of anastomosis may also influence the risk of AL. Nordholm-Carstensen et al. [53] reported that stapled anastomosis was associated with a higher risk of AL compared to hand-sewn anastomosis (p=0.004).

The higher risk of AL in low anastomoses is due to technical difficulties in forming the anastomosis within the confined pelvic space, which can compromise sealing [73]. Additionally, the distal rectum has a less abundant blood supply, increasing the likelihood of anastomotic ischemia [15]. The stapling technique may traumatize tissues and impair microcirculation along the anastomotic line [40].

Technical Aspects of Surgery. Operation duration was identified as a risk factor for AL in four studies. Zouari et al. [34] found that procedures lasting more than 180 minutes significantly increased the risk of AL (p=0.04). Zhou et al. [32] showed that an operation time ≥140 minutes was an independent risk factor for AL (OR=5.427, 95% CI 1.355–21.727,

p<0.001). Zarnescu et al. [96] and Litchinko et al. [79] also noted in their reviews that surgeries lasting over 3 hours were associated with a higher risk of AL (p<0.05).

Intraoperative blood loss was associated with an increased risk of AL in the study by Simillis et al. [55], which showed that greater blood loss increased AL risk: for losses >250–300 ml, OR=2.06 (p<0.001), and for >400–500 ml, OR=3.15 (p<0.001). Tsalikidis et al. [61] also confirmed this relationship (p<0.05).

Anastomotic tension was identified as a risk factor for AL in the study by Ito et al. [13], where tension at the anastomotic line was associated with an increased AL rate (31.3% in the high-tension group vs. 2.2% in the non-tension group, OR=6.97, 95% CI 1.45–33.6, p=0.016).

A narrow pelvis, particularly in men, was also identified as a risk factor for AL in two studies. Yu et al. [38] demonstrated that pelvic dimensions were independent predictors of AL risk (p<0.05). Toyoshima et al. [49] found that a narrow pelvic inlet area (≤10,074 mm²) was a significant risk factor (p=0.012).

Ligation of arteries (left colic artery and inferior mesenteric artery) [37, 65], as well as multivisceral resections [93], were also reported to affect AL risk.

Surgeon experience may also influence AL risk. Studies by Zarnescu et al. [96] and Wallace et al. [33] confirmed the impact of surgeon experience on AL development risk (p<0.05).

The negative influence of prolonged surgery and blood loss may be attributed to several factors. Lengthy operations are often associated with technical difficulties, increasing the risk of anastomotic failure. Additionally, prolonged anesthesia exposure and hypothermia may negatively impact tissue perfusion. Significant blood loss can lead to hypovolemia and tissue ischemia, which impair anastomotic healing [68, 74].

Anastomotic tension reduces blood supply and increases mechanical stress, while a narrow pelvis complicates anastomosis formation in low resections. Arterial ligation compromises collateral circulation, predisposing the anastomosis to ischemia and subsequent failure [26, 71].

Assessment of Anastomotic Integrity. Lack of intraoperative assessment of anastomotic integrity (air leak test) was identified as a risk factor for AL in the meta-analysis by Kryzauskas et al. [43], which showed that using intraoperative tests significantly reduces the risk of AL (OR=0.52, 95% CI 0.34–0.82, p<0.001).

Lack of anastomotic reinforcement was also associated with an increased risk of AL in two studies. Balkarov et al. [5] found that the AL rate was 8.3% in the group with additional anastomotic reinforcement compared to 25.5% in the control group without reinforcement (p=0.01). Foppa et al. [80] also showed that using a single-layer transanal reinforcement technique was associated with a lower risk of AL compared to the double-layer technique (6.48% vs. 15.28%, p=0.002).

Intraoperative assessment of anastomotic integrity allows for immediate detection and correction of defects during surgery, significantly reducing the risk of postoperative AL [40]. Reinforcing the anastomosis using various methods (additional sutures, biological glues, fibrin sealants) can improve mechanical strength and sealing, thereby reducing the risk of leakage [30].

Perioperative Risk Factors. Blood Transfusion. Perioperative blood transfusion was identified as a risk factor for AL in two studies. Simpson et al. [57] found that blood transfusion significantly increased the risk of AL (p<0.0001). Zouari et al. [34] also confirmed this association (p<0.01).

The negative impact of blood transfusion on anastomotic healing may be due to its immunomodulatory effects, which can disrupt the normal inflammatory response and regenerative processes. Furthermore, the need for blood transfusion often reflects significant blood loss and hemodynamic instability, which themselves can adversely affect anastomotic healing [22, 50].

Preventive Measures. The absence of a protective stoma was identified as a risk factor for clinically significant AL in the meta-analysis by Phan et al. [28]. The study showed that the formation of a diverting stoma significantly reduced the risk of AL (6.3% vs. 18.3%, OR=0.36, 95% CI 0.24–0.54, p<0.00001).

The absence of transanal drainage (TAD) may also increase the risk of AL, as shown in the systematic review by Akhmetzyanova et al. [6] (p<0.05). However, research results on this topic remain controversial.

The lack of mechanical bowel preparation combined with antibiotic prophylaxis was associated with an increased risk of AL in two studies. Yue et al. [47] found that combined preparation (mechanical bowel preparation + oral antibiotics) significantly reduced the risk of AL compared to mechanical preparation alone (p=0.009). Koskenvuo et al. [48] also confirmed this association (p<0.05).

A protective stoma reduces the risk of clinically significant consequences of AL by diverting intestinal contents proximally from the anastomosis, which decreases intraluminal pressure and minimizes bacterial contamination of the anastomotic area [25]. TAD may also reduce intraluminal pressure and promote evacuation of contents, potentially decreasing the risk of AL [94]. Mechanical bowel preparation with antibiotic prophylaxis reduces bacterial load in the intestine, which may positively influence anastomotic healing and reduce the risk of infectious complications [78].

According to the study by Carus et al. [19], intraoperative assessment of anastomotic perfusion using indocyanine green fluorescence angiography reduced the incidence of AL by 48%. Identification of inadequate perfusion, observed in 3.4% of cases, prompted changes in surgical strategy, including the formation of a new anastomosis or creation of a protective stoma.

A significant advancement in AL prevention was the development of the RALAR score, which allows prediction of AL risk based on nine independent variables. Although a protective stoma does not reduce the incidence of AL itself, it significantly decreases the severity of the complication, the need for reoperation, and complication-related mortality. The RALAR score enables surgeons to make informed decisions regarding the formation of a protective stoma in high-risk patients, aligning with the modern concept of a personalized surgical approach [70].

It is important to note that many risk factors are interrelated and may potentiate each other's effects. For example, distal tumor location often necessitates low anastomosis, which, combined with male gender and a narrow pelvis, creates a situation of very high AL risk. Similarly, patients with diabetes mellitus often have obesity, creating an unfavorable background for anastomotic healing.

The findings highlight the necessity of an individualized approach to AL prevention. Stratifying patients into risk groups allows for optimization of preoperative preparation, intraoperative strategy, and postoperative management.

Conclusion. This systematic literature review identified key risk factors for AL following surgical treatment of CRC, with an incidence ranging from 2.8% to 24.7%. The most significant risk factors include male gender, age over 65 years, obesity, diabetes mellitus, impaired nutritional status, distal tumor location, low anastomotic level, prolonged surgery (>180 minutes), and significant intraoperative blood loss.

The implementation of the RALAR score has significantly improved the ob-

jective assessment of AL risk, enabling more evidence-based decisions regarding the formation of a protective stoma during surgery.

A comprehensive approach to AL prevention, based on risk stratification and personalized treatment strategies, can substantially reduce the incidence of this complication. This, in turn, will lead to improved treatment outcomes, shorter hospital stays, reduced healthcare costs, and, most importantly, enhanced quality of life for patients undergoing CRC surgery.

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MODERN ASPECTS OF MORPHOFUNCTIONAL CHANGES IN THE MAXILLOFACIAL AREA IN PARTIAL AND COMPLETE TEETH ABSENCE AT DENTAL IMPLANTATION

Nowadays, there is a high prevalence of major dental diseases among the population, which are associated with carious lesions of teeth and their complications, as well as periodontal diseases leading to tooth loss, which are the main causative factors. The development of secondary deformities of dental rows contributes to the functional activity disorder of the entire dental-mandibular system, where the main etiologic factor is the loss of teeth in various pathological processes. In this case, there is a violation of the functional activity of the dental-mandibular system, which requires timely complex medical and social rehabilitation of patients, which is of great practical importance. One of the restoration types of lost teeth is the installation of dental implants, where in the conditions of pronounced atrophy of the alveolar process of the jaws there are complex clinical situations that are not an easy task for the specialist, as well as for patients. Meanwhile, the restoration of partial secondary and complete adentia with pronounced atrophic changes of the alveolar bone on artificial supports is performed with previous bone grafting, which is a challenging task on the way to improve the quality of life in patients.

In spite of the wide study this problem remains unsolved, which determines its further research aim improving the provision of medical care.

Keywords: complications of dental caries, periodontal diseases, tooth loss, alveolar atrophy, anatomical-topographical features, maxillofacial region, dental implantation, bone grafting, restoration of dental rows, medical and social rehabilitation.

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Introduction. Today, within the framework of the national project “New Technologies for Health Preservation”, special attention is paid to the dental health of the population, which is of great importance in the social-economic development of society. According to the researches A.O. Abdumomunova et al. (2020), V.A. Vakhrusheva (2022), A.A. Britova (2024), the high level of prevalence of the main dental diseases among the population is determined, which are associated with carious lesions of teeth and their complications, as well as periodontal diseases, leading to tooth loss, which are the main causative factors of morphofunctional changes in the alveolar process [1, 2, 3]. In this case, there is a violation of the functional activity of the entire dental alveolar system, which requires timely complex medical and social rehabilitation of patients, which is of great practical importance [4, 5, 6]. One of the types of restoration of lost teeth is the installation of dental implants, where in the conditions of pronounced atrophy of the alveolar process of the jaws there are complex clinical situations that are a difficult task for the specialist as well as for the patients [7, 8, 9].

Restoration of partial secondary and complete adentia with pronounced atrophic changes of the alveolar bone on artificial supports is performed with previous bone grafting, which is a challenging task on the way to improve the quality of life in patients [10, 11, 12]. Meanwhile, despite extensive research, this problem remains unsolved, which determines the need for further studies improving the provision of medical care.

The modern concept of etiological factors and pathogenetic mechanisms of anatomical-topographic changes in the maxillofacial area. The study of the prevalence of partial and complete loss of teeth in the population has an important theoretical and practical significance for the organization and implementation of adequate predictive and preventive measures. According to WHO clinical and epidemiologic data, tooth loss is detected in 75% of the population on a global scale and, accordingly, the restoration of defects in the dental rows and the function of the dental alveolar system is a global problem [13, 14, 15]. In Russia, secondary adentia in the total structure of medical care under state guarantees in therapeutic and preventive dental institutions reaches up to 75%, and in all age groups of the population. There researches say that the frequency of partial tooth loss in young people aged 18-25

years old reaches up to 38.6%, and 70% of the group of people aged 50-60 years old have various prosthetic constructions in the oral cavity, which determines the presence of an urgent medical and social problem of restoring defects of dental rows with the use of artificial supports [16, 17, 18, 19].

Studies by S. Usanova et al. (2021), N. Agbulut (2024), S.K. Akbarjon (2024) established the facts that a person needs at least 20 teeth for biting and chewing food to ensure normal chewing of food and adequate nutrition, as well as the intake of multivitamins, polyminerals and essential nutrients [29, 30, 31]. At the same time, the problems of tooth loss are widely studied, but at the present stage they remain unsolved, which are associated with a high prevalence of major dental diseases that are the main causative factors of secondary partial and complete adentia.

Today, the main causative factors of primary partial adentia have been substantiated and established, which are related to the disruption of embryogenesis of dental tissues, leading to the failure to form the rudiments of permanent teeth [23, 24, 25]. In addition, dysembryogenesis and disturbance of the eruption process often lead to the formation of retained teeth with the formation of primary partial adentia [26, 27, 28].

Dental caries is a common pathology of hard tissues of teeth, which often leads to its complications in the form of pulpitis and periodontitis, causing tooth loss. A wide range of local and general risk factors for the development of dental caries has been substantiated and proved, where qualitative and quantitative changes in the composition and properties of oral fluid and structural resistance of hard tissues of intact teeth can have an impact. In addition, the formation and development of dental caries plays an important role in the presence of general systemic diseases, as well as social-economic and natural-climatic environmental conditions, etc. Dental caries and its complications are chronic foci of infection in the oral cavity, which can cause the development of focal diseases in the body, so the above clinical features are an urgent problem of medicine in general. Changes in the hard tissues of teeth of demineralizing character and its complications cause tooth loss among various population groups, creating varying degrees of severity of disorders of the functions of the dental-alveolar system, gastrointestinal tract, musculoskeletal system, etc. [3, 10, 18].

It is important to emphasize that the severity of the comorbid condition and the number of missing teeth have a direct correlation with age-related aspects. Thus, according to A.A. Vorozhko et al. (2024) the most frequent loss in structure is associated with permanent first molars in the structure of the loss of various groups of teeth, which, as a rule, are most often affected by dental caries during the period of eruption due to a decrease in caries resistance of dental hard tissues [51]. At the same time, extractions of the frontal groups of teeth of the upper and lower jaw are less frequently determined.

It is known that complications of dental caries occur with necrotic processes of dental pulp tissue with subsequent development of granulomas and cystogranulomas in the periapical tissues, and then the formation of cysts, which require therapeutic and preventive measures, including tooth extraction when indicated [32, 33, 34, 35, 36, 37]. At the same time, there are cases of removal of previously treated teeth, which are associated with chipping or splitting of the crown or root of the tooth due to excessive instrumental processing during endodontic treatment, as well as weakened with increased removal of hard tissues of the crown of teeth during their preparation for filling. In addition, traumatic injuries to the teeth, as well as to the bones of the facial skeleton, chemical (acid) necrosis of the hard tissues of the crowns of teeth, and in some cases surgical interventions for inflammatory diseases of the maxillofacial region can lead to tooth loss [38, 39, 40, 41]. In partial secondary adentia, the pathogenetic mechanisms of dental-mandibular system dysfunction are associated with large adaptive and compensatory mechanisms [42, 43, 44].

The prevalence of periodontal diseases among school-age children reaches up to 87%, and in adults this figure is up to 97%. This unfavorable clinical and epidemiological situation has a direct impact on the occurrence of dental defects associated with tooth loss. Thus, by the age of 35 years there are objective facts of losing up to 10 teeth due to complications of inflammatory periodontal diseases [13, 23]. Local and general factors influence the development of inflammatory-destructive processes. Chronic periodontitis is accompanied by a disturbance of microcirculation of periodontal tissues, causing a sharp decrease in the level of oxygen consumption by surrounding tissues, which creates the preconditions for quantitative and qualitative changes in bone density of the alveolar outgrowth of the jaws, which often lead to tooth loss. Such a clinical situation associated with the loss of antagonist teeth from the physiological point of view contributes to a decrease in the functional load of periodontal tissues, leading to deterioration of blood supply and hypoxia with the subsequent development of hemo- and lymphostasis, vascular thrombosis, swelling and destruction of collagen fibers and the formation of osteoporosis and bone tissue resorption [1, 2, 4]. The above determines the need for further research aimed at solving medical and social problems of periodontal diseases.

It is important to note that the presence of various general systemic diseases has an important practical significance in tooth loss. Thus, pronounced changes in metabolic processes in diabetes mellitus have a negative impact on the functional state of the dental-mandibular system, and also contributes to a decrease in immunobiologic reactivity of the organism in patients [8, 16, 21, 29, 30]. At the same time, the main causative factors of tooth loss in patients with diabetes mellitus are the development of microangiopathies, which condition the development of periodontal diseases [4, 5, 46]. In addition, the constant intake of medications, particularly for the treatment of cardiovascular diseases, depressive states, sleep and rest disorders associated with diabetes mellitus, often lead to the appearance of symptoms of xerostomia and other pathological processes of the oral cavity [1, 33, 45]. Meanwhile, in the elderly and seniors, comorbid conditions contribute to an increase in the prevalence of secondary partial and complete adentia, which require restoration of dental defects with various prosthetic structures, including prosthetics supported by dental implants [5, 6, 15, 16, 27, 28, 42].

The analysis of the obtained data showed that there is a high level of prevalence of secondary partial or complete adentia among the population, which determines the timely treatment, prevention and rehabilitation measures, including the restoration of dental defects with prosthetic structures on artificial supports, which necessitates further research aimed at improving dental care for this category of patients.

Etiological factors and pathogenetic mechanisms of morpho-functional changes in the dental alveolar system. Currently, a high prevalence of major dental diseases among the population is determined, where 70% of patients have secondary partial or complete adentia, which are accompanied by significant recession of alveolar bone, which determines the relevance of the problem of complex medical and social rehabili-

tation of patients with marked bone loss [3, 6, 10, 33, 35, 40]. At the same time, pathogenetic mechanisms associated with tooth extraction are known to trigger various interrelated complex restructurings of the dental alveolar system, which are characterized by pronounced anatomical and topographic changes in the tooth rows, as well as in the hard and soft tissues of the upper and lower jaws. Such peculiarities should be taken into account when restoring defects of the dental rows with prosthetic constructions, especially with the support of dental implants [2, 19, 26, 27].

It should be noted that according to A.O. Abdumomunova et al. (2020), G.I. Dzhalilova (2020), Sh. Musaeva (2022) the main anatomical and morphological changes in the alveolar process of the jaws are associated with tooth loss due to complications of dental caries and periodontal diseases, which are common among the population due to clinical and epidemiological features [1, 8, 16]. Thus, during the first year after tooth loss the development of atrophic processes of the external cortical plate is determined up to 25%, and within three years it reaches up to 40%. This clinical situation of the alveolar bone tissue contributes to the displacement of the external compact lamina to the oral side [1, 8, 34, 35, 44]. Studies have shown that pronounced resorption of the bone tissue of the alveolar process, as well as the surrounding soft tissues, is observed within three months after tooth extraction. Thus, six months after tooth extraction there is bone resorption with a decrease in the width of the alveolar ridge by about 4.0 mm, and height - up to 1.5 mm, which is characterized as pronounced anatomical-topographical and morphological changes in the dental arch. Further in 12 months the loss of bone tissue in width reaches up to 50% of the initial volume, and the conducted dynamic control during 2-3 years confirms the loss of bone tissue of the jaw alveolar outgrowth up to 40-60%, which continues in a constant mode from 0.25 to 0.5% per year [1, 8, 34, 35, 44]. Also, it can be noted that atraumatic tooth extraction in clinical practice allows preserving a significant volume of alveolar bone, leading to a decrease in the degree of bone resorption of the dental arches of the upper and lower jaws in the future [1, 19, 33]. Thus, in the presence of a dental row defect, the unified morphofunctional dental-mandibular system, manifests itself as a violation of its biomechanics, where quantitative tooth loss over time leads to impaired mastication function, which largely depend on the topography of dental arch defects and the amount of tooth loss. Compensatory-adaptive reactions in such clinical cases, where antagonist teeth are missing in the areas of the tooth row, condition the chewing or biting of food at the expense of the preserved antagonist groups. The above-mentioned features associated with tooth loss lead to impaired function of periodontal tissues and masticatory muscle groups according to Z. Khabadze (2021) et. all, A.R. Vieira (2021), F. Iaculli et. al (2022), as well as the constituent anatomical components of the temporomandibular joint [45, 46, 47]. The changes in mastication functions begin from the period of partial loss of teeth, which determine the state of the dental alveolar system or its individual links in the work of M.A. Danilova (2021) [48, 49, 50].

From the pathogenetic point of view, A.A. Korobkeeva et al. (2020), Sh. Musaeva et al. (2022), M.B. Fazylova et al. (2023) have established the occurrence of certain disorders in the metabolism of bone tissue of the jaws, which are manifested in the early period after partial tooth extraction, characterized by an increased level of calcium-phosphorus metabolism and a significant decrease in the content of total proteins [14, 16, 27]. With such changes, the compensatory-adaptive response of the jaw bone tissue to the changed conditions of functional load on the periodontium in secondary partial or complete adentia manifests itself as a violation of mineral and protein metabolism. The loss of teeth in the dental arch increases the compression pressure to some extent, where bone tissue atrophy increases with pronounced reduction of the alveolar process [1, 2, 21].

It should be mentioned that patients with tooth loss have an unfixed bite associated with the absence of antagonist teeth, as well as a decrease in the height of the lower face with certain displacements of the lower jaw in relation to the upper jaw [7, 8, 11, 12 , 16]. Also, Also, according to M.A. Danilova et al. (2021), A.Yu. Vasilyeva et al. (2022), in patients with partial and complete adentia, masticatory muscle groups due to disturbances in the biomechanics of the dentoalveolar system create preconditions for the formation of hypertonus with the development of discoordination and asynchrony of mandibular movements, which further leads to the formation of myofascial pain syndrome [7, 11, 49]. At the same time, these clinical situations contribute to the development of pronounced morphofunctional changes in the temporomandibular joint (TMJ) [46, 47, 48,]. There are clinically observed shifts in the position of the remaining teeth along the lines of the Popov-Godon phenomenon with subsequent atrophic processes of the alveolar process in the area of the missing teeth [1].

It is important to emphasize that one of the causes of changes in the anatomical shape and size of the alveolar process is complex tooth extraction, peri-implantitis, odontogenic inflammatory diseases of the maxillofacial region, traumatic injuries of the bones of the facial skeleton, congenital clefts of the upper lip and palate, and postoperative deformations of the upper and lower jaw bones due to various neoplasms [1, 19, 33]. According to the studies conducted, it was found that after tooth extraction on the mandible, the intensity of atrophy of the lingual and vestibular walls of the alveolar process is characterized by the presence of certain features [4, 19]. Thus, pronounced bone loss is determined on the vestibular side of the wall, as its thickness is much thinner than the lingual one, which contributes to a significant reduction in the width of the bone tissue of the alveolar process [1, 2, 4, 16, 19]. In this regard, non-invasive and atraumatic tooth extraction always contributes to the maximum reduction of bone tissue reduction of the alveolar process of the upper and lower jaws. In addition, the severity of atrophic processes of the alveolar process depends on the anatomical localization of extracted teeth within the dental arches, as well as the shape and type of dental defects [1, 19]. For example, in included defects of the jaw rows, bone atrophy is much less, as the remaining teeth act as a natural limiter of further bone resorption, and in terminal defects, bone resorption begins throughout the entire length of the defect. In such clinical cases, crater-shaped deep bone defects are formed in the alveolar process, and resorption is more pronounced in the lateral regions than in the anterior region. Studies have shown that the atrophy of the alveolar process of the dental rows in the mandible is faster compared to the maxilla [21, 33, 35, 44].

Today, the direct influence of a wide range of general and local factors related to the state of organs, tissues of the oral cavity and macroorganism on the loss of jaw bone volume has been proved and substantiated. Recently, correlations between osteoporosis severity indices and hormonal status imbalance in menopausal women have been proved, which are less pronounced in the trabeculae of jaw bones in men [1, 2, 14, 44, 46]. Thus, in individuals over 50 years of age with systemic osteoporosis, a change in the thickness of the cortical layer of the mandible

is determined, which becomes less than 3 mm, creating the need to take these features into account when performing dental implantation [19, 27, 40]. In addition, bad habits, taking various medications have a negative impact on mineral metabolism, contributing to the formation and development of osteoporosis, which worsen the qualitative parameters of bone tissue and increase the rate of its resorption [8, 16].

There are researches that endocrine disorders, hypo- and avitaminosis, disorder of phosphorus-calcium metabolism, as well as infectious diseases, which are risk factors for the development of complications of pathological processes of the organs and tissues of the oral cavity and maxillofacial region, can lead to the development of secondary deformities of the dental rows [6, 16, 34]. In these clinical situations, tooth displacements in various directions with a decrease in interalveolar height are found, which in adults are asymptomatic and last for a long time. After tooth loss in the above systemic diseases and pathologic processes, defects of tooth rows are formed, where the dental alveolar system ceases to function as a single functional unit [11, 18, 22, 29]. In this case, the group of teeth that have no antagonists does not take part in chewing food and forming a food clump, where the entire load of chewing pressure is transferred to the teeth that have antagonists, due to which the primary traumatic syndrome is formed. In the works of A.A. Korobkeev et al. (2020), V.A. Tishchenko (2023) dysocclusion of the upper and lower jaw teeth creates preconditions for the formation of premature occlusal contacts, which significantly aggravate further dysfunction of the dentoalveolar system [51].

It is important to emphasize that traumatic injuries of the bones of the facial skeleton can result in defects of the alveolar process of the maxilla and mandible, which form various acquired pronounced deformities of nonlinear shape, affecting the bone tissue areas adjacent to the dental arch [40, 41, 42]. A.A. Korobkeev et al. (2020) says that from the clinical point of view, defects were formed as a result of radical surgical treatment for various neoplasms pose a particular difficulty for the restoration of the alveolar process [42].

Some studies characterize the features of the mechanisms of bone and soft tissue reorganization after tooth extraction, where the nature of these reorganizations largely depends on the biological type of periodontal tissues [4, 13, 21]. Thus, C. Ochsenbein et al. (1969) introduced the concept of "periodontal biotype", which defined the morphological characteristics of belonging to one or another type of tissue structure [13]. In 2017, the term "biotype" was replaced by "phenotype" at the World Workshop of Periodontology periodontal disease convention, which is categorized into thin and thick [29]. The thin phenotype of periodontal tissues includes a narrow band of keratinized gingiva, thinning mucosa covering the alveolar bone, a shallow oral vestibule, and fenestration of alveolar bone over the roots of teeth [9, 13, 18]. At the same time, Belser U.C., Buser D., Hess D et all. (2000) think that the thick phenotype is characterized by a significant zone of attachment of keratinized gingiva, where it is defined as dense, prone to the formation of coarse-fibrous connective tissue in the form of scar deformities, flattened morphological architectonics of soft and bone tissues of alveolar outgrowths of the jaws [9, 10]. The studies have established their structural features, where thin gingival biotype is detected in 15% of the population, and thick gingival biotype is 85%, respectively.

In general, the development of secondary deformities of the dental rows contributes to the disruption of the functional activity of the entire dental alveolar system, where the main etiologic factor is the loss of teeth in various pathologic processes.

Some features of anatomical and topographic changes in the maxillofacial region during dental implantation. The main functional activity of medical specialists is aimed at preserving the functional state of the dental-mandibular system, which performs vital functions associated with the reception of food, the formation of food clump, the act of swallowing, the correct performance of respiratory movements, speech, as well as psycho-emotional status. In this case, the condition of organs and tissues of the oral cavity, maxillofacial region largely depends on the normal functioning of organs and body systems, which can be negatively affected by multiple local and general factors associated with working conditions, the level of education of the individual, living conditions, bad habits and behavior, the ecological situation of the environment, material security, health care development, social-economic status of the social system, etc. [20, 21, 22].

In a number of cases, defects of the jaw alveolar processes in vertical and horizontal directions may appear, which require additional surgical preparation with increasing the bone tissue of the alveolar process in height and width [11, 19, 24, 26, 28]. When restoring defects of dental rows using dental implants, specialists pay special attention to the qualitative parameters of bone tissue related to its architectonics, as well as the ratio of the cancellous and cortical layer. From the physiological point of view, the bone consists of the cortical lamina consisting of osteons and spongy substance including trabeculae, which are functionally oriented towards the increased occlusal load [18, 46, 51]. At the same time, a decrease in vertical functional load during tooth loss leads to a violation of metabolic processes in bone tissue with the subsequent formation of physiologic resorption of the alveolar outgrowth [11, 19, 24, 26, 28]. According to the research results of A.A. Dolgaleva, V.S. Kadurina, A.E. Mishvelova (2018) and M.A. Danilova, P.V. Ishmurzina (2021), the change in the thickness of the cortical plate of the bone tissue of the dental rows has a negative impact in ensuring the primary stability of dental implants [8, 11].

Defects of the maxillary dentition cause some anatomical-topographical changes, which are associated with the presence of maxillary sinus, nasal cavity, where low bone density is determined [1, 4, 16, 40]. Besides, simultaneously with the decrease in the height of bone tissue after tooth loss there is a decrease in the morphological parameters of the depth of the oral vestibule, where the shallow vestibule formed in this case promotes some mimic muscles to "attach" to the crest of the atrophied alveolar process, which creates certain clinical difficulties in the course of rehabilitation measures when installing dental implants. The reduction of the depth of the oral cavity anterodorsum is the main causative factor of ischemia and chronic secondary trauma of the mobile mucosa, which contribute to the development of the inflammatory process, resorption and accelerated atrophy of bone tissue around implants [16, 19]. In addition, further atrophy of the alveolar process in the maxilla leads to anatomical-topographical changes associated with the displacement of the neurovascular bundle coming out of the incisal aperture to the crest of the alveolar process, and the muscle group lifting the upper lip and the wing of the nose, the corner of the mouth can take an anatomical position closer to the alveolar crest [19, 26]. Meanwhile, the presence of postoperative keloid scars affecting the alveolar processes can cause certain difficulties during dental implantation.

Conclusion. The conducted evaluation and analysis of morphofunctional changes of the maxillofacial region in

partial and complete absence of teeth at dental implantation, characterizes the presence of individual anatomical-topographical features, which require a personalized approach to each patient and require further research to improve the restoration of dental rows with prosthetic constructions on artificial supports at pronounced atrophic changes in the alveolar bone tissue of the jaws.

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COMBINATION OF CHRONIC KIDNEY DISEASE WITH CHRONIC NON-COMMUNICABLE DISEASES

The scientific review examines chronic kidney disease (CKD) in combination with chronic non-communicable diseases. Chronic kidney disease is a serious and growing public health problem worldwide, characterized by a gradual and irreversible decline in kidney function and is one of the leading causes of death worldwide. The priority task of healthcare is the prevention of chronic non-communicable diseases, among which the most significant include cardiovascular diseases, bronchopulmonary diseases, diabetes mellitus, and oncological diseases. The association of CKD with chronic non-communicable diseases, in particular with cardiovascular diseases, makes this pathology especially dangerous, which leads to a deterioration in the quality of life of patients and an increase in mortality. The treatment of patients with comorbid pathology requires a comprehensive and interdisciplinary approach.

Keywords: chronic non-communicable diseases, chronic kidney disease, diabetes mellitus, arterial hypertension, oncological diseases, coronary heart disease, bronchial asthma, chronic obstructive pulmonary disease.

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Introduction. CNID is a long-term ongoing disease caused by prolonged exposure to various causes: environmental factors and genetic characteristics combined with an unhealthy lifestyle (smoking, alcohol abuse, unhealthy diet, low physical activity). The World Health Organization (WHO) estimates that 41 million people die from these diseases every year, accounting for 71% of all deaths; more than 15 million of them are people aged 30 to 69 years. CNID is the main cause of early death and disability of the population [14].

WHO identifies the following categories of NCDs with corresponding mortality rates:

- cardiovascular diseases (CVD): most often – arterial hypertension (AH), coronary heart disease (CHD) and CKD) claiming 17 million lives;
- oncological diseases lead to the death of about 9.3 million people annually;
- diseases of the respiratory system (chronic obstructive pulmonary disease (COPD) and bronchial asthma (BA)) cause 4.1 million deaths per year;
- diabetes mellitus (DM) is the cause of death of 1.5 million people.

Special attention should be paid to CKD, which is a persistent organ lesion for three or more months due to the action of various etiological factors, the anatomical basis of which is the process of replacing normal anatomical structures with fibrosis, leading to its dysfunction by CKD [20]. The causes of CKD include genetic factors and the consequences of concomitant diseases such as hypertension, diabetes, abdominal obesity and lipid metabolism disorders (dyslipidemia). Today, hypertension consistently holds a leading position among all the causes contributing to the progression of CKD, affecting about 10-15% of the world's population [28].

Arterial hypertension and CKD. The basis for the development of hypertension in patients with CKD is the activation of the sympathetic nervous system against the background of deterioration of kidney function. This, in turn, contributes to an even greater increase in blood pressure (BP) in people with CKD. In the process of decreasing glomerular filtra-

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tion rate (GFR), the renin-angiotensin-aldosterone system (RAAS) is activated, resulting in accumulation of Na+ and fluid in the body [2].

The most significant way to detect CKD in patients with hypertension at the outpatient level is to determine the level of creatinine in the blood with the calculation of GFR, which is carried out in conjunction with the determination of daily protein loss. Analysis of both indicators of CKD is especially important, since a decrease in eGFR and an increase in urinary albumin levels, independently of each other and other cardiovascular risk factors, are associated with an increased risk of general and cardiovascular mortality, which increases over time with a decrease in eGFR and an increase in albuminuria [11]. This focuses on the need for timely detection and monitoring of the development of CKD in patients with hypertension.

High blood pressure significantly worsens the prognosis of the disease for patients with pre-existing CKD, as the risk of CKD developing into end-stage renal failure (ESRD) increases. According to the MRFIT (Multiple Risk Factorl ntervention Trial) study, data on 332,544 men over 16 years were collected. After analyzing all the results, it was concluded that people with high and normal blood pressure, unlike patients with optimal blood pressure (less than 120/80 mmHg), are 1.9 times more likely to develop ESRD [5]. The data obtained allow us to conclude that the development of CKD contributes to the aggravation of the course of pre-existing hypertension and is one of the main reasons for the ineffectiveness of antihypertensive therapy.

One of the key aspects contributing to slowing the development of CKD and significantly reducing the risk of cardiovascular diseases is monitoring blood pressure while meeting targets. In addition to blood pressure monitoring, lifestyle modification is necessary to slow the progression of CKD: to give up bad habits, regularly monitor blood glucose levels, avoid taking medications with nephrotoxic effects, and simultaneously carry out effective treatment of the underlying disease, which led to the development of CKD [21].

When hypertension and CKD are combined, antihypertensive therapy should be carefully selected in the patient. It is extremely important to start treatment as early as possible to prevent cardiovascular complications and the progression of CKD. It is recommended to use renin-angiotensin-angiotensin system blockers (RAAS blockers) as the main drugs for the treatment of hypertension combined with CKD, and, if necessary, give preference to HMG-CoA reductase inhibitors, type 2 sodium-glucose cotransporter inhibitors, and glucagon-like peptide 1 agonists [11]. It is important to understand that patients with CKD require special attention and an individual approach. It is necessary to select drugs individually for each patient, taking into account his characteristics and needs [21, 28].

Coronary heart disease and CKD. Coronary artery disease (CHD) is a disease that is caused by insufficient blood flow in the coronary arteries [17]. Modern scientific evidence indicates a close relationship between coronary heart disease and CKD, and coronary heart disease is not only a concomitant disease, but can also provoke the development of kidney complications. The most significant complication of coronary heart disease is the development of chronic heart failure (CHF) [24]. Current epidemiological data confirm a stable relationship between CHF and CKD: CHF is a risk of developing CKD and vice versa [22, 24, 31]. This is the so-called cardiovascular continuum [9].

Among the main mechanisms leading to the formation of CKD on the background of coronary heart disease, one can single out:

1. hemodynamic disorders (due to a decrease in the left ventricular ejection fraction, perfusion decreases, proinflammatory cytokines are activated and, as a result, proliferative processes, in particular fibrosis) [21, 24];

2. Microvascular changes (impaired autoregulation of renal blood flow caused by systemic inflammation in atherosclerosis, worsens the course of ischemic nephropathy) [25];

3. neurohumoral changes (in CHF, a decrease in the shock volume of blood discharged by the left ventricle leads to activation of neurohumoral mechanisms, which is manifested by excessive production of vasoconstrictors (norepinephrine, angiotensin, endothelin, vasopressin and a decrease in secretion or reaction to internal vasodilating factors. Such disorders provoke deterioration of blood supply to the kidneys, progression of oxygen starvation of tissues and structural organ damage) [18].

Dyslipidemia is an important pathogenetic mechanism in coronary heart disease. Endothelial dysfunction, which is the first stage in the development of atherosclerosis, leads to the development of CKD. Vascular cell adhesion molecule 1 (VCAM-1) is a marker of endothelial dysfunction. Its level can be used to judge the onset of inflammatory and atherosclerotic changes in the renal vessels [12]. In 1963, lipoprotein (a) was discovered, which is now used as a marker of increased risk of CVD. It should be noted that this indicator increases at the initial stages of CKD development, however, its study in the blood is currently not widespread [8].

Homocysteine is also an indicator associated with both coronary heart disease and CKD. In the early stages of CKD, homocysteine levels are moderately elevated and continue to rise with the progression of a decrease in GFR [17]. An indicator of CKD in the early stages is also myeloperoxidase, which is one of the main causes of oxidative stress leading to calcification and atherosclerosis of the renal vessels [19].

Thus, coronary artery disease is a significant risk factor for the development and progression of CKD. Understanding the above mechanisms allows us to develop strategies for the early diagnosis and prevention of CKD in patients with coronary heart disease.

Chronic obstructive pulmonary disease, bronchial asthma and CKD. The conducted clinical and epidemiological studies indicate that for many years CKD has been in the shadow of chronic kidney disease, including COPD and asthma. Hypoxia, which develops against the background of chronic bronchopulmonary diseases, can lead to kidney damage. Characteristic kidney cells have a particularly high oxygen demand (especially the cells lining the proximal sinuous tubules), and even subclinical hypoxia can lead to apoptosis of these cells and tissue fibrosis. Hypercapnia in patients with COPD can cause renal afferent arteriolar vasoconstriction, decreased renal blood flow, and activation of the adrenergic pathway. It is obvious from the definition of COPD that harmful gases play a vital role in the pathogenesis of the disease. Nicotine activates the sympathetic autonomic system, causing an increase in blood pressure. This can worsen any nephropathy that the patient already has. The most significant risk factors that worsen kidney function in patients with COPD include lead and hydrocarbons from smoke, systemic inflammation, hypoxemia and hypercapnia, and sympathetic activation [6, 35].

In 2020, a study was conducted with the participation of the Amur State Medical Academy aimed at a comprehensive assessment of the functional state of the kidneys in patients aged 45 to 60 years with documented COPD. The study did not include patients with extremely severe

COPD; patients with hypertension, coronary heart disease, acute cerebrovascular accident, kidney and urinary tract pathology, tuberculosis, and oncological diseases of any localization. The results of the study: in patients with frequent exacerbations of COPD and severe symptoms, the urea level was higher and the GFR value was lower than in the group with mild clinical manifestations and low frequency of exacerbations. Albuminuria (albumin/creatinine ratio in a single portion of urine) of more than 30 mg/g was observed mainly in people with frequent exacerbations of COPD. Thus, the data obtained allow us to consider COPD as a risk factor for the development of impaired renal function. Patients with frequent exacerbations of COPD and severe clinical symptoms require increased monitoring by specialists [4].

The problem of the risk of developing CKD in asthma is also being considered. A number of studies have indicated the relationship between the presence of asthma in a patient and the risk of developing CKD, and risk factors such as gender, age, obesity, diabetes, hypertension, and smoking do not significantly affect this relationship [10]. Huang H.L. et al. In 2014, it was shown that the relative risk (RR) of developing CKD in patients with asthma remains at a high level. However, it is worth noting that in patients who take glucocorticosteroids, the risk of developing CKD (HR=0.56; 95% CI: 0.62-0.61; p <0.001) is more than 2 times lower than in patients with asthma who do not take glucocorticosteroids (HR=1.40; 95% CI: 1.33–1.48; p=0.040). In addition to glucocorticosteroids, expectorant and cholinolytic drugs, leukotriene receptor antagonists, bronchodilators, and muscle relaxants reduce the risk of developing CKD. A 6-year follow-up of patients with ASTHMA to assess the risk of developing CKD showed that in patients with controlled asthma or asthma in remission, proteinuria and a decrease in GFR were observed less frequently than in patients diagnosed with ASTHMA for more than 20 years, uncontrolled or persistent [29].

Oncological diseases and CKD. According to WHO, in 2022, about 20 million new cases of malignant neoplasms (ZNO) and about 9.7 million deaths from them were registered worldwide. Oncological diseases are the second leading cause of death after diseases of the cardiovascular system, not only in the Russian Federation, but throughout the world. CKD and ZNO are quite closely related: Just as cancer can cause direct or indirect damage to the renal tissue, leading to decreased kidney function, CKD is one of the risk factors for kidney cancer [37]. One of the reasons for the development of CKD in CHF is the nephrotoxicity of antitumor drugs [23]. This is largely due to the fact that most drugs are excreted by the kidneys. The components of the drug itself and its mechanism of action can also influence the development of CKD. For example:

- cisplatin contains the heavy metal platinum, which is toxic to the body, and the antitumor effect of the drug is due to the selective suppression of DNA synthesis, the products of its metabolism can damage mitochondria and block the cell cycle [13];

- isophosphamide enhances the expression of cytochrome p450, which metabolizes it into toxic chloroacetaldehyde, which causes acute and chronic damage to the renal tubules [13];

- methotrexate is safe in low doses [34], but in high (1 g/m2) doses, uric acid crystals gradually precipitate under the influence of the acidic environment of urine, which can lead to acute renal failure or CKD [13].

The nephrotoxic effects of cytostatic therapy are dose–dependent (the rate and degree of their realization depend on the dose of the drug) and are most often realized at the level of the proximal tubules, less often the distal tubules and glomeruli [13, 23].

Another reason for the development of CKD on the background of ZNO is paraneoplastic nephropathies. Paraneoplastic nephropathy is damage to the filtering apparatus of the kidneys caused by immunological and metabolic disorders in oncological diseases. In case of HYPERTENSION, excessive production of growth factors, proinflammatory cytokines, and lymphokines causes cell dysfunction and malfunction of the glomerular filter, can lead to the formation of intracapillary blood clots, infiltration of kidney tissue by macrophages and monocytes [37].

The other side of the issue is the development of cancer on the background of CKD. Numerous studies show that patients with CKD have a higher risk of developing cancer than patients without CKD. One of the reasons for this is that due to impaired kidney function, nitrogenous substances and carcinogenic compounds accumulate in the body (for example, 2–amino-6-methyldipyridoimidazole), DNA repair decreases, and oxidative stress constantly occurs [30].

Diabetes mellitus and CKD. Diabetes mellitus (DM) is a group of chronic metabolic diseases characterized by hyperglycemia and/or impaired insulin metabolism. Currently, this chronic non-communicable disease is characterized by a wide prevalence. Constantly elevated glucose levels in diabetes are accompanied by damage to target organs: kidneys, nerves, eyes, and the cardiovascular system [1]. The variety of renal pathology in DM (diabetic glomerulosclerosis proper, chronic glomerulonephritis, urinary tract infection, medicinal nephritis, tubulointerstitial fibrosis, atherosclerotic renal artery stenosis, etc.), having different mechanisms of development, progression dynamics, and treatment methods, is a particular problem for DM patients, since their frequent combination is mutually aggravating [16]. Diabetes is the leading cause of CKD in the world [32]. In patients with impaired carbohydrate metabolism, diabetic nephropathy occupies one of the leading positions among the causes of death, following diseases of the cardiovascular system and hypertension [7].

Along with hereditary predisposition, hyperglycemia is the main mechanism that damages the kidney structure. An increase in glucose levels contributes to the activation of the RAAS, as well as an increase in cell resistance to insulin and, as a result, endothelial dysfunction. These effects are enhanced in the presence of modifiable risk factors.: increased blood pressure, obesity and smoking, which determines the formation of glomerular hyperfiltration and hypertension. As the process progresses, the mechanism of automatic regulation of the tone of the delivering arterioles is disrupted, which is why systemic blood pressure directly affects intraclubular pressure and hypertension becomes constant.

Albuminuria is one of the most important mechanisms of progression of glomerular lesions. At this stage, proteinuria and hypertension develop, which stimulate damage to kidney structures, which leads to a decrease in their functions, up to terminal CKD [3].

It is also known that under the influence of hyperglycemia, end products of glycation (AGE) are formed in the patient's body. The formation of a small amount of AGE is part of the metabolism in a healthy person, but a large amount of glycotoxins produced can have negative consequences [15]. High levels of glycation toxins activate processes (profibrotic and inflammatory changes) that trigger the progression of diabetic nephropathy. One of the mechanisms of action of toxins is the transformation of protein complexes of the extracellular matrix. Glycation of collagen leads to a decrease in its properties, including solubility and

inversion of the charge of monomers, changing the configuration of the basement membrane of nephrons, which destroys the architecture. Glycation of another protein, laminin, also leads to a decrease in its binding to the components of the basement membrane. Glycotoxins affect other matrix proteins, among other things, which worsens the degradation by metalloproteinases, contributing to an increase in the thickness of the basement membrane and the width of the mesangium. These changes lead to a violation of the function of the filtration apparatus of the kidneys, therefore, albuminuria increases and progressive deterioration of kidney function occurs [26].

The diagnosis of diabetic nephropathy is based on the determination of albumin levels in urine and/ or a decrease in GFR. It is typical to have a history of diabetes mellitus, as well as the presence of other complications (for example, retinopathy) [33]. At the same time, CKD in a patient with type 2 diabetes may be the result of diabetes, it may worsen, or it may not be related to diabetes at all [1]. Thus, diabetic nephropathy can be diagnosed mainly on the basis of clinical and laboratory data (general clinical urine tests, eGFR, general blood test, blood creatinine level, determination of glycated hemoglobin, lipid spectrum, blood pressure measurement, ultrasound examination of the kidneys) [27]. It is important to note that kidney biopsy in diabetic nephropathy is performed relatively rarely, only when differential diagnosis with other glomerular lesions, such as glomerulonephritis and amyloidosis, is required [3].

The combination of diabetes and CKD requires an integrated approach to therapy, which boils down to observing the basics of a healthy lifestyle, with a high body mass index (BMI over 26 kg/m2), body weight control and rejection of bad habits are necessary. The main goal of drug treatment is to preserve kidney function and achieve intermediate targets for blood glycemia, lipid spectrum, and blood pressure [1]. In the latest clinical recommendations of KDIGO-2024, it was noted that sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce the risk of renal failure in patients with diabetes mellitus. Thus, both RAAS blockers and SGLT2 inhibitors belong to therapies with proven efficacy that slow the progression of CKD in patients with and without diabetes [36]. In patients with CKD without diabetes, the presence of even mild albuminuria means a potential benefit from the use of RAAS blockers, and in the case of severe albuminuria, significant benefits are expected from the use of SGLT2 inhibitors. It is important that the earlier treatment is started, the higher the chance of slowing down the development of the disease and complications. Prevention of diabetic nephropathy is carried out by monitoring blood pressure, sugar and cholesterol levels and achieving targets. In case of diabetes, it is necessary to screen biochemical parameters every 3 months, in addition, it is necessary to monitor blood pressure levels on a systematic basis, as well as to evaluate GFR in patients with more than 5 years of diabetes experience [26].

Conclusion. The focus of domestic healthcare on the early diagnosis of chronic non-communicable diseases with the aim of timely effective therapy to prevent premature mortality and disability is fixed in the orders on medical examination and dispensary supervision of the adult population of the Russian Federation. Among the most significant chronic non-communicable diseases cardiovascular, chronic bronchopulmonary diseases, diabetes mellitus and malignant neoplasms are considered. The progression of CKD against the background of ineffective treatment of CKD mutually aggravates the prognosis in this category of patients. Monitoring of the functional state of the kidneys by the level of eGFR at the outpatient stage serves as an indicator of the effectiveness of chronic non-communicable diseases therapy. Therefore, an indication of the presence and stage of CKD in the clinical diagnosis is mandatory.

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

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MODERN CONCEPTS OF MUSCULAR DYSTONIA

This study presents a comprehensive analysis of the genetic, clinical, and therapeutic aspects of muscular dystonias — a heterogeneous group of neurological disorders characterized by pathological postures and disabling hyperkinesias. Based on a synthesis of data from recent decades, the authors highlight key advancements: the identification of 25 hereditary forms (DYT1–DYT25), the role of mutations in the TOR1A gene (DYT1) in disrupting intracellular transport, and progress in symptomatic treatments such as botulinum toxin therapy, deep brain stimulation, and MR-guided focused ultrasound (MRgFUS). Special attention is given to the limitations of current approaches, including an incomplete understanding of pathogenesis and therapeutic resistance observed in 30–40% of patients. The necessity of integrating genetic testing, neuroimaging, and emerging biotechnologies (e.g., CRISPR, recombinant toxins) is emphasized as a pathway toward developing targeted treatment strategies. The paper also summarizes epidemiological data (prevalence: 3–60 cases per 100,000), presents the current classification framework, and outlines prospects for personalized medicine – offering a roadmap for future research.

Keywords: dystonia, hyperkinesis, genetics, torsion dystonia, cervical dystonia.

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Introduction. Dystonia is a neurological disorder characterized by impaired motor functions, persistent muscle contractions, and abnormal violent movements that lead to the formation of unnatural postures and disability [1, 2]. The study of dystonia as a nosological entity has a history of more than a century. The first systematic observations were made by A. Schwalbe (1908), who recorded a chronic syndrome combining muscle spasms with psychoneurological symptoms. A significant contribution to the nosological differentiation of the pathology was made by G. Oppenheim (1911), who introduced the terms "deforming muscular dystonia" and detailed the key clinical markers of the disease, including muscle tone disorders and the formation of abnormal postural settings. These works laid the foundation for understanding the pathogenesis and clinical identification of dystonic disorders [3]. Dystonia is the third most common movement disorder after Parkinson's disease and tremor, which emphasizes the need to improve diagnostic algorithms and expand the availability of genetic testing [50]. Different types of dystonia can occur in people of any age, leading to serious disorders and a significant deterioration in the quality of life [10]. In ICD-10 (International Classification of Diseases, 10th revision), dystonia is included under the code G24 [6]. According to estimates, the prevalence of dystonia may be: 3-11 cases per 100,000 population for generalized forms (most often beginning in the 1st or 2nd decade of life and often having a hereditary nature); 30-60 cases per 100,000 population for focal forms, which usually manifest at a later age [7]. There are also statistics on the types of dystonia: Primary dystonia accounts for 60%; of all cases of dystonia. Secondary dystonia - 40% of all cases of dystonia [8].

A variety of heterogeneous movement disorders are grouped under the general term – dystonia. The clinical picture ranges from isolated dystonia to multisystem disorders where dystonia is only an accompanying feature [9]. The pathophysiology of dystonias is still poorly understood. However, over the last two decades, many models have been developed that improve our knowledge of the molecular and cellular basis of this heterogeneous group of movement disorders [10]. Recently, a number of innovative genetic and molecular findings have been obtained. Although these allow for genetic testing and counseling, their translation into new treatments is still limited. Nevertheless, it is worth noting that the road to understanding common pathophysiological and molecular mechanisms has begun [12].

Epidemiology and genetic classification of primary dystonia. The ratio between cases of primary and secondary (degenerative) dystonia is estimated to be approximately 2:1. At the same time, dystonia-plus syndromes are much less common than these two types of dystonia. [37]. Estimates of the prevalence of primary dystonia range from 2 to 50 cases per million for the early form and from 30 to 7320 for the late form, although researchers question the results of statistical analysis. Based on more reliable studies, the following estimates can be distinguished: 111 cases per million for early dystonia in Ashkenazi Jews in New York, 600 for late dystonia in the north of England, and 3000 in Italy among people over 50 years of age [36].

Primary dystonia includes syndromes in which dystonia is the only phenotypic manifestation, except that tremor may also be present. Most cases of primary dystonia have adult onset, and approximately 10% of probands report one or more affected family members [26]. Pathogenic variations in several genes can cause isolated dystonia, and the number of dystonia genes identified is increasing [50]. Hereditary dystonia, denoted by the *DYT* locus symbols, can be divided into three broad phenotypic categories: primary torsion dystonia, where dystonia is the only clinical feature (except tremor) (*DYT1, 2, 4, 6, 7, 13, 17,* and *21*); dystonia plus, where other phenotypes in addition to dystonia are present, including parkinsonism or myoclonism (*DYT3, 5/14, 11, 12, 15,* and *16*); and paroxysmal forms of dystonia/dyskinesia (*DYT8, 9, 10, 18, 19,* and *20*) (Table) [32, 49].

Early-onset dystonia type *DYT1* is the most common form of primary dystonia. In non-Jewish populations, it accounts for about 50% of cases of early-onset generalized dystonia, while in the Ashkenazi Jewish population this figure reaches 80–90% [37]. The *DYT1/TOR1A* gene is located on the long arm of chromosome 9 at locus 9q34.11 (Figure 1). The pathogenesis of *DYT1* also involves autosomal dominant inheritance, but with low pen-

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etrance (about 30%), meaning that not all mutation carriers will exhibit clinical symptoms [39].

Most patients with *DYT1* have a heterozygous mutation representing a deletion of the GAG trinucleotide in the *DYT1/TOR1A* gene, which leads to the formation of an abnormal torsin A protein with the loss of one glutamine residue in its structure [38]. Torsin A is a member of the AAA+ adenosine triphosphatase family and is involved in intracellular transport, vesicular element fusion, formation of tertiary and quaternary protein structure, protein degradation, and organelle biogenesis. Abnormal torsin A promotes the formation of spherical inclusions near neuronal nuclei, which can destabilize the functional form of the protein and lead to its rapid degradation. Dysfunction of torsin A and the widespread distribution of this protein in the extrapyramidal system lead to the characteristic symptoms of primary dystonia type 1, including involuntary muscle contractions and the formation of pathological postures [39].

Therapeutic strategies for dystonia. Treatment of dystonia primarily involves agents targeting dopamine and acetylcholine receptors [8]. Pharmacological agents used include muscle relaxants, benzodiazepines, antiepileptic and certain antipsychotic drugs, as well as antihistamines, the effectiveness of which is supported by evidence at various levels. However, their use is associated with a number of limitations, including side effects, moderate therapeutic efficacy, and the requirement for long-term treatment [16]. Oral medications and botulinum toxin injections are the first-line treatments and play an important role in the initial therapy of patients with dystonia. In cases where the disease is more severe or refractory to treatment, neurosurgical interventions are used to improve the quality of life of patients [51].

Deep brain stimulation (DBS) is the most common surgical approach for the treatment of drug-resistant movement disorders such as tremor and dystonia [40]. It can alleviate the symptoms of genetic and primary dystonia by suppressing abnormal neuronal activity in the motor loop network [41]. Modern DBS systems, adapted from cardiology, included an intracranial electrode, an extension wire, and a pulse generator and have been gradually improved over the past two decades. Improvements in electrode systems and battery cells, the introduction of innovative approaches to neurostimulation, including closed-loop feedback systems and adaptive activation modes, and the development of neuromonitoring methods will significantly improve the therapeutic efficacy and safety profile of DBS methods [42]. In a meta-analysis by *Wang et al. (2021)*, which included data from 71 patients from 31 studies, DBS demonstrated a significant reduction in the severity of myoclonus and dystonia symptoms. The average improvement on the Unified Myoclonus Rating Scale was 79.5% (±18.2), with 94.1% of patients showing a motor function improvement of more than 50% [51]. However, a number of limitations should be taken into account: the risk of postoperative complications, adverse effects during stimulation (dysarthria, paresthesia, cognitive changes), the need for repeated surgical interventions to replace the pulse generator [52].

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive treatment method that uses focused ultrasound waves to heat specific tissue targets in the brain [43]. It is widely recognized as an effective treatment for both essential and parkinsonian tremors [44].

In Russia, this treatment method was approved in 2017. The first experience in Russia using MR-FUS for the treatment of essential tremor demonstrated 96% efficacy with no long-term complications, which confirms the promise of the method [4]. MR-FUS also demonstrated high efficacy in the treatment of refractory cervical dystonia, providing a 70% reduction in symptoms according to the TWSTRS scale, which is comparable to the results of invasive methods [5]. It should be noted that the study by Singh et al. (2020) obtained encouraging preliminary results when studying new indications, including focal dystonia and neurological conditions such as obsessive-compulsive disorder and depression [46]. This innovative technology is characterized by its precision and potential advantages over traditional surgical methods [45]. Importantly, the lesion formation process is closely monitored in real time using both neuroimaging and clinical methods [47]. This technology is characterized by high accuracy and has allowed the development of minimally invasive treatments with results comparable to traditional brain surgery [14]. However, the current level of evidence remains insufficiently high, and limited efficacy, thermal tissue damage, and lack of long-term effect require further study [48].

Botulinum toxin (BT) is used to treat a wide range of muscle hyperactivity syn-

Classification of dystonias

By type of inheritance / By etiology	Autosomal dominant	Autosomal recessive	X-linked
Primary dystonia	*DYT1, DYT4, DYT6, DYT7, DYT13, DYT21*	*DYT2, DYT17*	-
Dystonia-plus	*DYT5/14, DYT11, DYT12, DYT15*	*DYT16*	*DYT3*
Paroxysmal dystonia	*DYT8, DYT9, DYT10, DYT18, DYT19, DYT20, DYT23, DYT24, DYT25*	-	-

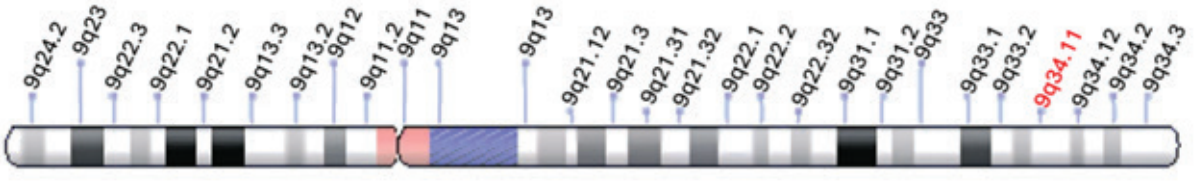

Fig. 1. Schematic representation of chromosome 9 indicating the locus 9q34.11 (highlighted in red), where the *TOR1A* gene associated with the hereditary form of dystonia *DYT1* is located.

dromes. One of the key indications for its use remains dystonia, which is confirmed by numerous studies demonstrating the effectiveness of BT in the symptomatic treatment of this disease [13, 18]. Clinical use of botulinum toxin is highly effective in focal dystonias (improvement in 70-90% of patients with cervical dystonia), low invasiveness (outpatient administration) and rapid action (initial effect - 3-7 days, maximum - 2-4 weeks). Advantages include complete reversibility of the effect, minimal risk of systemic complications due to the local mechanism of action and no need for surgical intervention [36, 44]. However, there are a number of limitations to the method: the transient nature of the therapeutic effect, the need for repeated injections every 3–6 months, the development of secondary resistance in 5–15% of patients, local adverse effects (muscle weakness, dysphagia, xerostomia), high pharmacoeconomic costs and the absence of a significant effect in generalized forms of dystonia [12, 25].

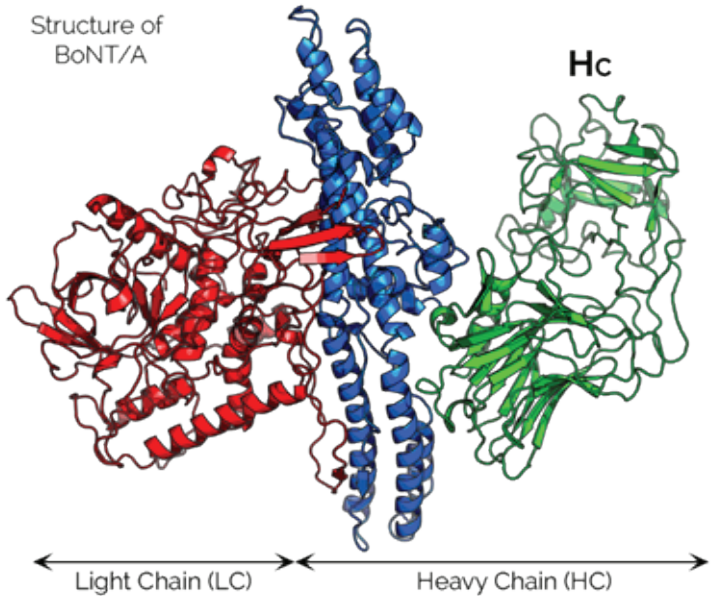

Fig. 2. Crystal structure of botulinum toxin type A (Structure of BoNT/A): binding domain (Heavy Chain (HC) - heavy chain, 100 kDa), translocation domain and catalytic domain (Light Chain (LC) - light chain, 50 kDa) [*Lacy D.B. et al., 1998*].

Botulinum toxin: molecular mechanism. The use of botulinum toxin in medicine demonstrates a paradoxical phenomenon: a substance that causes fatal botulism poisoning has become the basis for innovative therapeutic agents for the correction of neurological pathologies [22]. Botulinum toxins are natural origin toxins produced by the bacteria Clostridium botulinum, Clostridium butyricum and Clostridium baratii. Of the eight (A, B, C1, C2, D, E, F, G) serologically active types of botulinum toxins, only one (C2) does not have tropism for the nervous system [19]. The mechanism of action of all botulinum toxin serotypes, regardless of type, is the presynaptic blockade of SNARE (Soluble N-ethylmaleimide-sensitive factor (NSF Attachment Protein Receptor) transport proteins, which results in the suppression of acetylcholine release into the synaptic cleft and a reversible block of neuromuscular transmission [20, 21].

The chronometry of the therapeutic effect of different botulinum toxin serotypes demonstrates marked heterogeneity due to the molecular features of their protease activity [27]. Clinical observations show that serotype A-based drugs provide neuromuscular blockade lasting 6–9 months, while serotype B exhibits a pharmacodynamic effect for 3–4 months [28, 30]. This dissociation of time parameters correlates with the differential kinetics of SNARE complex regeneration: SNAP-25, a serotype A substrate, undergoes slower intracellular renewal via neuronal protease systems (calpain, cathepsin L), while synaptobrevin, a serotype B target, is resynthesized at an accelerated rate due to the activation of vesicular recycling mechanisms [28, 29]. An additional factor is the structural resistance of proteolytic fragments to degradation: tryptic cleavage of SNAP-25 in the Gln197-Arg198 region creates a more stable product complex compared to the modification of synaptobrevin in the Gln76-Phe77 region [17, 32]. The heavy chain of botulinum toxin has a high affinity for specific receptors on the presynaptic membrane of cholinergic terminals of motor neurons, which facilitates the binding of the toxin to the target cell. The light chain, possessing zinc-dependent protease activity, destroys synaptosomal associated protein 25 (SNAP-25) in the cytoplasm of neurons. This prevents the exocytosis of acetylcholine, which makes it impossible to release it into the synaptic cleft and disrupts neuromuscular transmission [23, 24].

Bacteria produce botulinum neurotoxins in the form of complexes. Their structure contains a non-toxic polypeptide precursor of the neurotoxin, as well as a set of accompanying proteins that do not exhibit a toxic effect. [15, 23]. Endopeptidases break the polypeptide chain, forming a light (50 kDa) and heavy (100 kDa) chains, which are linked by a disulfide bond (Figure 2). Thus, the active toxin is created as a result of changes that occur with the protein after its synthesis (post-translational modifications) [24].

Modern biotechnological modifications have made it possible to create recombinant forms of the toxin with altered properties. Using site-directed mutagenesis, it was possible to obtain variants with a controlled duration of action and an extended temperature range of stability. These achievements have opened up new prospects for the treatment of diseases requiring long-term modulation of neuromuscular activity, such as spasticity in cerebral palsy or post-traumatic muscle contracture [33, 34].

Conclusion. Modern studies of muscular dystonias, despite the identification of 25 genetic loci (*DYT1–DYT25*), have revealed their significant heterogeneity, which limits the effectiveness of therapy. Symptomatic treatment, including botulinum therapy, deep brain stimulation and MRgFUS, demonstrates success mainly in focal forms, but the lack of etiotropic methods and the resistance of some patients require a deeper understanding of the molecular mechanisms (the role of torsin A, SNARE complexes) and the introduction of genetically oriented approaches (CRISPR, AI). The integration of neurology, genetics and biotechnology will be the key to the transition from palliative care to targeted correction of pathogenesis, especially given the high prevalence and disabling nature of the disease.

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

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SURGICAL TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE

Introduction. Gastroesophageal reflux disease (GERD) is a widespread pathology of the digestive tract characterized by the retrograde flow of gastric contents into the esophagus. Since 1990, there has been a significant increase in the incidence and prevalence of GERD, making this condition one of the key challenges in modern gastroenterology. Treatment decisions may vary depending on the type and size of the hiatal hernia, the presence of erosive esophagitis and/or Barrett's esophagus, body mass index, and accompanying physiological abnormalities such as gastroptosis or ineffective motility with a lack of contractile reserve.

Laparoscopic fundoplication is an effective treatment for GERD. This approach is associated with lower postoperative morbidity compared to open surgery and is the preferred option when surgical intervention is indicated.

Robot-assisted surgery in the treatment of GERD represents the next stage in the evolution of anti-reflux procedures. Modern GERD surgery is undergoing a new technological breakthrough the introduction of robot-assisted laparoscopic fundoplication (RALF). This method combines the advantages of traditional laparoscopy (low invasiveness, rapid recovery) with the unique capabilities of robotic systems (Da Vinci Si).

Materials and Methods. A systematic review of available scientific publications on this topic from 2015 to 2025 was conducted. The study analyzed 52 articles, of which 36 were authored by foreign researchers and 16 by Russian specialists. Literature searches were performed on platforms such as PubMed, eLibrary, the Scientific Library of BSMU, CyberLeninka, and others.

Results and Discussion. The surgical treatment of hiatal hernias, including giant paraesophageal hernias, remains a challenging task requiring high precision in anatomical restoration and minimization of intraoperative risks. Currently, the laparoscopic approach is considered the gold standard; however, the introduction of robotic systems (such as Da Vinci) has opened new possibilities due to improved visualization, increased instrument maneuverability, and enhanced ergonomics for the surgeon.

Conclusions. RALF is a promising method for the surgical treatment of GERD, particularly in patients with refractory disease, obesity, and anatomical peculiarities (short esophagus). The technical advantages of the Da Vinci Si robotic system help reduce intraoperative complication risks and improve long-term functional outcomes. However, the high cost and the need for specialized surgeon training limit the widespread adoption of this technique.

Keywords: robot-assisted surgery, systematic data review, surgery, robot-assisted laparoscopic fundoplication, hiatal hernia.

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Introduction. Gastroesophageal reflux disease (GERD) is a widespread pathology of the digestive tract characterized by the retrograde flow of gastric contents into the esophagus. According to the 2006 Montreal Classification of GERD, clinical manifestations are divided into esophageal (typical) and extraesophageal (atypical) syndromes. The most common symptoms include heartburn, regurgitation, chronic cough, and reflux-induced bronchial obstruction (reflux asthma syndrome) [14, 31].

Since 1990, there has been a significant increase in the incidence and prevalence of GERD, making this condition one of the key challenges in modern gastroenterology. Epidemiological studies confirm a steady trend toward rising case numbers, likely due to lifestyle changes, dietary habits, and increasing risk factors such as obesity and physical inactivity.

Recent epidemiological studies indicate that GERD is among the most prevalent gastroenterological diseases. Heartburn the leading symptom of GERD is reported by 20–40% of the population in developed countries. In Russia, the prevalence of GERD ranges from 18% to 46% [27, 17, 31].

Current data suggest that esophagitis affects 5–6% of the population, with 65–90% of cases being mild and 10–35% severe (5 cases per 100,000 people annually). Barrett's esophagus is found in 8% of patients with esophagitis and is associated with a 0.4–0.6% annual risk of esophageal adenocarcinoma. The risk of malignancy progressively increases from 0.1% in cases without dysplasia to 6% in high-grade dysplasia.

The relevance of GERD is further underscored by its significant impact on patients' quality of life, particularly in cases of nocturnal symptoms, extraesophageal manifestations (chest pain, persistent cough), and complications such as bleeding from ulcers and erosions, peptic strictures, and most concerning esophageal adenocarcinoma in Barrett's esophagus [23, 42, 32].

Treatment of GERD requires a multifaceted approach, considering symptoms, endoscopic findings, and potential physiological abnormalities. Treatment decisions may vary depending on the type and size of the hiatal hernia, presence of erosive esophagitis and/or Barrett's esophagus, body mass index, and accompanying physiological abnormalities such as gastroptosis or ineffective motility with a lack of contractile reserve [4, 6, 16].

The cornerstone of medical therapy for GERD involves medications aimed at neutralizing or reducing gastric acid secretion. These include antacids, histamine H2-receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). However, numerous studies demonstrate a high recurrence rate shortly after discontinuation of medical therapy, as well as refractoriness to antisecretory drugs in some patients with esophagitis [3, 21]. Given the high risk of complications in prolonged GERD cases unresponsive to medical therapy, one of the key challenges in managing patients with reflux esophagitis is identifying refractory GERD and determining indications for surgical intervention.

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The enthusiasm for laparoscopic approaches to GERD has renewed interest in the pathophysiology of the disease. Consequently, surgical indications are better defined, techniques are tailored to individual patients based on objective preoperative assessments, and follow-up has improved. Laparoscopic fundoplication is an effective treatment for GERD, offering lower postoperative morbidity than open surgery and serving as the preferred option when surgical intervention is indicated [8, 10, 11, 13, 1, 45, 34].

In the era of minimally invasive surgery, laparoscopic fundoplication (primarily Nissen or Toupet) has emerged as a highly effective alternative to conservative therapy, demonstrating [41, 30, 50]:

- Stable anti-reflux efficacy (85–93% long-term success);
- Minimal intraoperative trauma (blood loss <50 mL);
- Rapid recovery (hospital stay ≤4 days);
- Reduced postoperative complications (4–8% vs. 15–20% with open surgery).

Meta-analyses (GLOBUS, 2022; JAMA Surgeon, 2023) confirm that laparoscopic approaches not only meet safety and efficacy criteria but also surpass open surgery in key parameters, including patient quality of life (GERD-HRQL scores improve by 75–80%). The integration of modern diagnostic algorithms and minimally invasive technologies has transformed fundoplication into the procedure of choice for refractory GERD, balancing radical intervention with physiological preservation [24, 44].

Robot-assisted surgery represents the next evolutionary step in anti-reflux procedures [45, 26, 18, 25, 35, 49]. Modern GERD surgery is undergoing a technological breakthrough with the introduction of robot-assisted laparoscopic fundoplication (RALF). This method combines the benefits of traditional laparoscopy (low invasiveness, rapid recovery) with the unique capabilities of robotic systems (Da Vinci Si), including [38, 39, 22, 29]:

1. Enhanced precision – 3D visualization and tremor filtration enable anatomically superior fundoplication (reducing dysphagia risk).
2. Improved ergonomics – 7 degrees of freedom facilitate maneuvering in the confined hiatal space.
3. Lower conversion rates (<1% vs. 2–3% in standard laparoscopy, per Int J Med Robot. 2023).

Clinical evidence:

- SLEEVEPASS-RCT (2024): RALF shows comparable efficacy to laparoscopy (92% reflux control at 2 years) but 30% fewer intraoperative complications (vagal nerve injury, bleeding).
- Annals of Surgery systematic review (2023): For complex cases (morbid obesity, short esophagus), robotic surgery reduces operative time by 15–20%.

Limitations:

- High cost (additional $3–5K per procedure);
- Steep learning curve (≥50 cases required for proficiency).

Materials and Methods. A systematic review of scientific publications from 2015 to 2025 was conducted, analyzing 52 articles (36 international, 16 Russian) sourced from PubMed, eLibrary, BSMU Scientific Library, CyberLeninka, and others. Keywords included "robot-assisted surgery," "systematic review," "RALF," and "hiatal hernia."

The study aimed to evaluate the efficacy and safety of robot-assisted Nissen fundoplication, assessing postoperative complications, GERD recurrence rates, functional outcomes, and long-term quality of life. Special focus was placed on the Da Vinci Si system's advantages (enhanced visualization, precision, reduced complications) and drawbacks (lack of haptic feedback, high costs).

Results and Discussion

Surgical repair of hiatal hernias, including giant paraesophageal hernias, remains technically demanding, requiring precise anatomical restoration and minimized intraoperative risks [29, 20, 22, 48]. While laparoscopy is the gold standard, robotic systems (e.g., Da Vinci) offer superior visualization, instrument maneuverability, and ergonomics. However, comparative efficacy, safety, and cost-effectiveness remain debated.

Advantages of Robotic Surgery for Hiatal Hernia [33, 19, 37, 47]:

- Technical: 7-degree instrument freedom, tremor filtration, and 3D visualization aid complex steps (gastric mobilization, hernia sac dissection, fundoplication).
- Clinical: Lower conversion rates to open surgery (particularly in obesity or recurrent hernias), shorter hospital stays (1–2 days), and reduced recurrence (<5% vs. 10–15% with laparoscopy).

Limitations:

- Higher complication rates (dysphagia, subphrenic abscesses, thromboembolism) due to prolonged operative times and learning curve challenges [40, 28, 52].
- Economic: Significant costs (equipment, maintenance, disposable instruments) increase expenses by 20–30% versus laparoscopy.
- Evidence gaps: Most data derive from retrospective cohorts, necessitating randomized controlled trials (e.g., ROBuST Trial) and long-term follow-up (5–10 years).

Conclusions. RALF is a promising surgical treatment for GERD, particularly in refractory cases, obesity, and anatomical variants (short esophagus). The Da Vinci Si system reduces intraoperative risks and improves long-term outcomes, but high costs and specialized training requirements limit its widespread adoption [2, 5].

Future directions:

- Cost optimization for RALF;
- Simulation-based training to shorten the learning curve;
- Long-term outcome studies (10+ years) on recurrence and Barrett's esophagus malignancy risk.

In summary, robot-assisted fundoplication marks a significant advancement in anti-reflux surgery, combining high efficacy with minimal invasiveness.

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

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INFLAMMATORY FIBROID POLYP: CLINICAL, MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

In order to study the clinical, morphological and immunohistochemical features of inflammatory fibroid polyp, a literature review was conducted. It was found that inflammatory fibroid polyp is one of the rare benign tumors of the gastrointestinal tract, the clinical picture of which depends on the size, location and complications. The complexity of diagnosis is due to its morphological similarity to malignant tumors of the gastrointestinal tract. Immunohistochemical testing is used to exclude malignancy. It was found that inflammatory fibroid polyp is characterized by pronounced diffuse expression of CD34, reactions to DOG1, CD117, S-100 are negative.

Keywords: inflammatory fibroid polyp; stomach; Vanek's tumor; immunohistochemical study

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Introduction. Inflammatory fibroid polyp (IFP) is a rare benign mesenchymal [17] polypoid lesion [4] arising in the mucosa and submucosa throughout the gastrointestinal tract [8] and characterized by the proliferation of vascular-rich fibrous tissue [14] and an eosinophilic infiltrate [4].

These tumors account for 0.1% [8] to 3.0% of all gastric polypoid lesions and are often discovered incidentally during endoscopic examination [2].

The most common organ affected by VFP is the antrum of the stomach (66%-75%) [2, 17], the second most common organ affected is the small intestine (18%-20%), the third is the colon, which accounts for 8.4%, and the rest of the gastrointestinal tract is affected less frequently (less than 3% in total) [14], the gallbladder (1%) [2, 18], the esophagus (1%), the duodenum (1%), and the appendix (<1%). However, the ileum is the most common site where these polyps cause intussusception [2, 4].

According to the studies by Garmpis et al. [14], when VFP develops in the esophagus, its lower third is most often affected and almost always the lower esophageal sphincter or cardia. In the stomach, after the antral section, the pyloric/prepyloric section (15%), cardia (7%), body of the stomach (4%), then the pylorus and lastly the fundus of the stomach are most often affected [8, 14].

Although a relatively rare disease in clinical practice, VFP has a serious impact on the gastrointestinal function and physical health of patients [19].

The purpose of the study: analysis of publications devoted to the study of clinical, morphological and immunohistochemically features of inflammatory fibroid polyp.

Materials and methods. In this review, we examined the literature devoted to the study of inflammatory fibroid polyp. The search was conducted in the electronic databases PubMed, Web of Science, Google Scholar for 2015-2025. The key words for the search included: inflammatory fibroid polyp, stomach, Vanek's tumor, immunohistochemical study.

A microscopic method was also used, conducted on the basis of the OGBUZ "Belgorod Pathoanatomical Bureau" during our own studies. The material was fixed for 24 hours in 10% neutral buffered formalin, then it underwent histological processing in a closed-type histoprocessor Thermo Scientific Excelsior AS (sequential dehydration, degreasing and impregnation of tissue with paraffin). From the manufactured paraffin blocks, 4-μm-thick sections were made using a semi-automatic rotary microtome Thermo Scientific HM340e. Sections were stained with hematoxylin and eosin, and for immunohistochemical studies, antibodies produced by Cell Marque (USA) were used: CD34 (clone QBEnd/10), CD117 (clone YR145), DOG1 (clone SP31), S-100 (clone 4C4.9). To obtain images, a Hamamatsu nanozoomer s60 scanner was used.

Results and discussion. Inflammatory fibroid polyps are one of the least common benign tumors localized in the submucosa of the gastrointestinal tract [14].

For the first time, VFP was described as "polypoid fibroma" in 1920 by Konjetzny [1]. In 1949, J. Vanek published a description of 6 cases of similar formations in the American Journal of Pathology [5], called them "submucous granuloma of the stomach with eosinophilic infiltration" and interpreted them as a reactive process, probably of inflammatory origin [5, 8, 14, 18]. Later, in 1953, E. Helwig and A. Ranier first introduced the term inflammatory fibroid polyp [8], which became widespread [14]. Also in the literature there are synonyms for the name VFP, such as "Vanek's tumor", granuloblastoma, neurofibroma, hemangiopericytoma, polypoid myoendothelioma, myxoma, submucous fibroma, hemangiopericytoma [12].

The etiology of VFP remains unclear [7, 13, 14], but it may be associated with chemical, physical, metabolic factors and Helicobacter pylori infection [3, 7, 12], as well as allergic reactions, autoimmune processes, genetic/familial predisposition [8, 14], or as an excessive reaction of the body to an unknown irritant [4, 14].

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In turn, it should be noted that the exact pathogenesis of CFP also remains unclear [20]. Yang et al. believe that it can range from reactive lesions with eosinophilic infiltration to tumor lesions [18]. Recent studies in the field of molecular biology [7] have shown that CFPs are often associated with mutations in the platelet-derived growth factor receptor α (*PDGFRA*) gene [3, 7, 8], in exons 12 and 18, and, less commonly, in exon 14 [5]. A number of authors have suggested that CFPs are neoplastic lesions caused by these mutations [7, 20], and not simply inflammatory lesions [20]. Thus, in the fifth edition of the World Health Organization classification of tumors of the digestive system 2019, CFPs are classified as benign tumors of the gastrointestinal tract.

VFP occurs in a wide age range, but most often with a peak incidence from 50 to 70 years of age [4, 5, 8, 12, 14, 18], and is extremely rare in children [4, 5, 15]. This pathology more often affects women (the ratio of women to men is 1.3:1) [8, 14, 16].

Most researchers believe that in most cases, VFP is asymptomatic, but some formations can gradually increase in size and cause complications [5, 7, 12, 14, 20, 21] or be accompanied by vomiting, nausea [14], a feeling of early satiety in the stomach [8], abdominal pain, bleeding from the gastrointestinal tract (large polyps usually collapse and ulcerate superficially) [5], acute abdomen [11, 14, 16, 18]. Severe iron deficiency anemia [3, 4, 14], intussusception or obstruction are also possible if VFP is localized in the small intestine [5, 20].

It should be noted that the clinical picture depends on the size, location and complications [3, 5, 11, 13, 21]. Thus, weight loss [5], epigastric pain and bleeding are the most common symptoms of gastric VFP, while colicky abdominal pain with constipation and bloating are the most common symptoms of intestinal VFP [11]. When localized in the esophagus, it causes dysphagia [5, 6].

Macroscopically, VFPs are small, clearly defined, submucosal formations on a stalk or sessile, arising in the submucosal layer, usually covered by normal mucosa, and protruding into the lumen of the organ; in ¼ of cases, ulceration of the mucosa located above is possible [3, 5, 7, 12]. VFPs can spread to the muscularis propria and even to the serous membrane [7] and be single or multiple [2]. The size of most formations varies from 1 to 12 cm [20], reaching 0.2-20 cm in diameter, but usually have a diameter of 2 to 5 cm [5].

Despite their benign nature, these tumors can mimic other malignancies, so an accurate diagnosis is essential for proper treatment [3]. Histologically, VFPs may resemble gastrointestinal stromal tumors (GISTs), leiomyomas, or other gastrointestinal stromal tumors [7]. GISTs are potentially malignant tumors with varying risks of progression, while VFPs have a favorable prognosis.

According to microscopic examination, the VFP is a submucous formation [17], with a clear border at the level of the muscularis propria [5] and consisting of mononuclear spindle-shaped or stellate stromal cells, edematous stroma with thin-walled blood vessels [3, 12], around which are located the surrounding proliferating fibroblasts [4, 8, 9] with long thin cytoplasmic processes located around the vessels and mucous glands [5], forming a disordered or spiral structure [2]. Mixed inflammatory infiltration is also characteristic, but mainly represented by eosinophils [3, 9, 12, 20] and lymphocytes [7], but plasma cells and histiocytes are also noticeable [5]. Blood vessels are irregularly shaped with muscular walls of varying thickness [8]. Proliferating cells are homogeneous, with abundant cytoplasm and pale rod-shaped nuclei [7]. Spindle-shaped cells proliferate in the submucosa and rarely penetrate the muscularis propria [17]. Mucosal lesions occur in 89% to 93.5% of cases [4]. Thus, some glands may be cystically dilated and inverted into the submucosa, muscularis propria, and tumor stroma. The epithelium of the glands is without atypia, characterized by pronounced hyperplasia and elongation with twisting, expansion, and deformation [18].

Tumor cell nuclei have smooth contours, oval or spindle-shaped, finely granular chromatin, and small nucleoli. The cytoplasm is scanty/elongated and amphiphilic. Mitoses are rare but may occasionally be present in deeper parts of the lesion. Atypical mitoses are never seen [5].

In turn, Righetti et al. [21] believe that, depending on the part of the gastrointestinal tract in which they arise, VFPs look different. Thus, in the stomach, VFPs arise at the base of the proper plate of the mucous membrane, spreading and destroying the muscular layer of the mucous membrane. In turn, Buda et al. [5] believe that the involvement of the proper muscular layer in VFPs of the stomach is rare. They have less pronounced stromal edema and therefore seem denser compared to VFPs in the ileum [21]. According to the authors, in the stomach, as a rule, there is a pronounced perivascular orientation of various cells, and eosinophil infiltration is more pronounced than with VFP localization in the ileum. Intestinal VFPs are intramural growths that press on the muscularis mucosa, eventually destroying it and penetrating the mucosa, often causing ulceration. They destroy the submucosa and the muscularis propria, often penetrating the mesentery [15]. Tumor growth into the mucosa leads to separation of the gastric glands, which leads to disruption of their structure and atrophy [5].

Our study is consistent with the authors' opinion, since the VFP consists of spindle-shaped and stellate stromal cells with a large number of thin-walled blood vessels and pronounced inflammatory infiltration by eosinophils (Fig. 1 a, b).

In the differential diagnosis of VFP, it is necessary to exclude other spindle cell lesions, such as inflammatory fibrosarcoma, spindle cell carcinomas, gastrointestinal stromal tumors (GIST), schwannomas, perineuromas, and inflammatory myofibroblastic tumors. For this purpose, immunohistochemical examination is necessary [2, 17]. Differentiation without immunohistochemistry is difficult, especially between VFP and GIST, because GIST also occurs in the stomach and often appears as polypoid formations. In the intestine, these tumors can manifest as intussusception, like VFP [2].

In turn, Abboud et al. [2] believe that VFP differs from gastrointestinal stromal tumors in its morphology, submucosal origin, and clinical course, although both of these pathologies have common mutational subtypes of the *PDGFRA* gene.

SCFs are very characterized by pronounced eosinophil infiltration and diffuse positivity for CD34 and vimentin [2, 7, 14], while GISTs are positive for CD117 and DOG1, while SCFs are not [2, 3, 8, 14, 17]. Schwannomas are positive for the S100 protein, while almost all GISTs and smooth muscle cell tumors are negative for the S100 protein [10]. Inflammatory myofibroblastic tumors are positive for anaplastic lymphoma kinase (ALK) and negative for CD34 [17], and desmin is present in leiomyomas [3]. It should be noted that the S-100 protein allows us to exclude tumors with neural differentiation. Solitary fibrous tumor also responds to CD34, but it rarely occurs in the gastrointestinal tract (GIT) and is not associated with inflammation [5]. Desmoid tumors consist of spindle-shaped or stellate cells and are negative for DOG1, S-100 protein [10]. Desmoid tumors also have nuclear expression of beta-catenin, which is not observed in HFP.

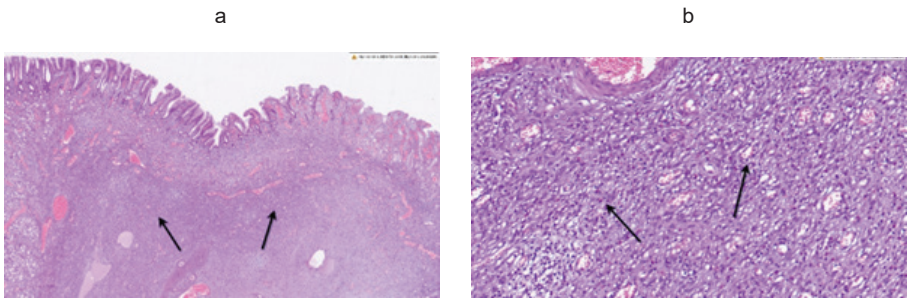

Fig. 1. Inflammatory fibroid polyp of the stomach in a patient born in 1969: a – the specimen shows a tumor-like formation located under the gastric mucosa; b – the tumor-like neoplasm consists of spindle-shaped and stellate stromal cells with a large number of thin-walled blood vessels and pronounced inflammatory infiltration by eosinophils. Magnification a x25, b x200, staining: hematoxylin and eosin

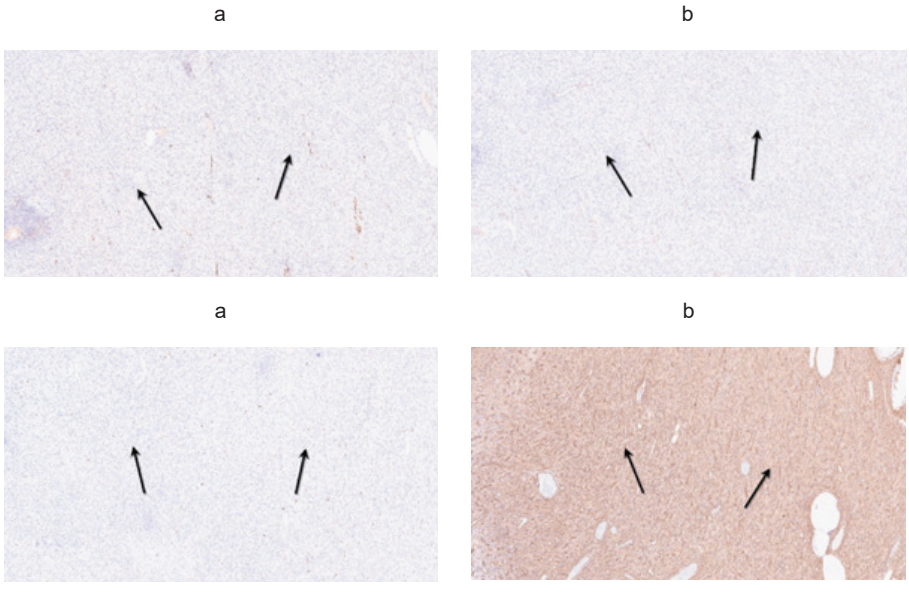

Fig. 2. Inflammatory fibroid polyp of the stomach in a patient born in 1969: a – there is no expression of S-100 in the cells of the neoplasm (staining: S-100), b – there is no expression of DOG1 in the cells of the neoplasm (staining: DOG1), c – there is no expression of CD117 in the cells of the neoplasm (staining: CD117), d – pronounced diffuse cytoplasmic expression of CD34 is determined in the cells of the neoplasm (staining: CD34). Magnification x50

Gastric leiomyomas, both morphologically and immunohistochemically, in some cases can resemble VFP; they are characterized by a diffuse pronounced reaction to α-smooth muscle actin (α-SMA) and desmin [10].

The results of our immunohistochemical study are consistent with the results of other authors, thus, pronounced diffuse expression of CD34 is determined, reactions to DOG1, CD117, S-100 are negative (Fig. 2 a- d).

It should be noted that the results of the studies by Harima et al. [17] indicate that in some cases, VFPs can behave as locally aggressive neoplasms with infiltrative growth and can recur after incomplete resection.

Conclusion. The results of the analysis showed that inflammatory fibroid polyp is one of the rare benign tumors of the gastrointestinal tract, the clinical picture of which depends on the size, location and complications. Despite the benign nature, these tumors can imitate other malignant neoplasms, so for the correct treatment, it is extremely important to make an accurate diagnosis and here immunohistochemistry is of decisive importance, which we confirmed with our study.

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

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ANALYSIS OF THE EPIDEMIOLOGY, TREATMENT METHODS AND OUTCOMES OF METATARSAL FRACTURES IN CHILDREN

Introduction. According to WHO, 75% of the world's population has some kind of problem associated with foot pathology. The arches of the foot, formed by calcaneal bone the tarsal and metatarsal bones, allow the foot to support the weight of the body. Deformity of arches of the foot called flat feet. There are many causes of flat feet: one of them is traumatic. The main cause of post-traumatic flatfoot is fractures of the metatarsal and calcaneal bone. **The aim of the study** of this review is to systematize scientific literature data on the topic of post-traumatic flatfoot. **Methods.** In the systematic literature review conducted, we applied search filters to find literature in the text summarization domain from eLibrary, pubMED, Scopus. **Results and discussion.** The arches of the foot, formed by the calcaneal bone at the back and two heads of the metatarsal bones: I and V. Post-traumatic flat feet occurs after fractures of the calcaneus or metatarsal bones. Fractures of the metatarsal bones associated with post-traumatic flatfoot in the outcome of the disease. The literature review indicates clinically significant correlations between fractures of the foot bones and occurrence of post-traumatic flatfoot. Most of the material presented on the influence of calcaneal fractures on the occurrence of post-traumatic flatfoot with a direct correlation. **Conclusions.** There are sources on the correlation between metatarsal bone fractures and post-traumatic flatfoot. In the studies, the authors link metatarsal fractures and flat feet. They also note a direct correlation between the disease and its complications. The literature review show correlations between fractures of calcaneus or metatarsal bones and occurrence of post-traumatic flatfoot. Research in the field of fractures of the bones of the foot and post-traumatic flat feet, is relevant now and requires further scientific research. There was also a small amount of material on studies of post-traumatic flatfoot in children.

Keywords: post-traumatic flatfoot, metatarsal bones, fracture, foot fracture, osteosynthesis, children

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Introduction. The human foot is a complex structure composed of 28 bones and 33 joints, ensuring transmission of axial load from the whole body. In the foot there are three parts: the posterior (talar and calcaneus), the middle (palatal, three wedge-shaped and cubic bones) and the anterior (five metatarsus and phalanges of the fingers) [30].

Walking are the main functions of the foot, which provided by complex structure of foot. In the foot, there are three support point - the calcaneal bone, I and V heads of the metatarsal bones and two arches - longitudinal and transverse [30].

According to WHO, 75% of the population of the Earth have problems related to foot pathology, disrupting a person's normal life, which allows us to consider this problem not only from the medical side but also from the social side [24]. Out of all deformations, flat foot is 61.3%. According to the etiology, congenital and acquired flat feet are distinguished. Acquired in turn is divided into traumatic, traumatic, paralytic [56].

The main cause of post-traumatic flat foot is fractures. Their frequency distributed as follows: finger phalanxes occupy the leading position (74.3%), metatarsal bones come in second place (21.5%), tarsal bones and calcaneus make up 4.2% and 1.8% respectively of the total number of foot fractures [56].

The current problem is the early diagnosis of impairment of anatomy and function of the foot after injuries, with subsequent rehabilitation measures for effective pathogenic correction of post-traumatic flat foot.

The purpose of this literature review is to analyze and systematize data from the scientific literature in the context of metatarsal fractures, and their correlation with post-traumatic flat foot.

Materials and methods. The search for literary sources was carried out on the following databases: the Russian scientific electronic library eLIBRARY.RU, the information database of the National Library of Medicine (PubMed), the SCOPUS database. The search was conducted by the following key words: post-traumatic flatfoot, metatarsal bone fractures, children. The study includes original and review articles containing information on the topic of post-traumatic flat foot, fracture of foot bones in Russian or English. Articles 5 to 10 years old have been used predominantly.

Results and discussion. The metatarsal bones are a group of five short tubular bones in the anterior section of the foot, located between the tarsal bones and the phalanges of the fingers. The peculiarity of this fractures, especially II, III, IV, is the close attachment of bones to each other, a developed common connective apparatus, which makes displacement of bone rarer in comparison with bone fractures of other localizations [53]. Despite this, displacement fracture occurs and carry the risk of complications if not treated properly. Displacement bone fracture associated with high frequency of unsatisfactory treatment results. In 21.4% of cases, there are multiple fractures of the metatarsals, often leading to impaired foot function [29,32]. There is a high percentage of

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complications associated with bad diagnosis of fractures.

The peculiarities of regional blood supply play a special role in the development of unsatisfactory treatment results, due to slow consolidation. The development of arterial ischemia can adversely affect regeneration processes [32]. It is noted that in displaced fracture there is a direct correlation between the severity of the injury and the disruption of regional blood flow. J. P. Ardashev, V. N. Drobotova with the help of duplex scanning of the foot vessels examined 15 patients with fractures of the metatarsus. The results showed a decrease in the index of peripheral resistance in the artery [32]. These data suggest the importance of local blood supply disruption due to trauma in the development of regional ischemia. Accordingly, treatment measures aimed at improving regional blood flow should be taken.

The treatment tactics depend directly on the type of fracture of the bones. In the classification by localization, fractures of the proximal section, diaphysis, neck and head of the metatarsus are distinguished. There is an international classification of the Association of Osteosynthesis, in which fractures of the proximal and distal end are distinguished: partial and complete joint: simple, complex.

Special attention to fractures of the V metatarsal bone, as it carries a supporting function and is where the ligaments of the large tibia muscles are attached. The typical fracture is a Jones fracture, it is an extrinsic localization of the fracture of the proximal end V of the metatarsus. There is a classification according to Dameron T. B., in which the fractures of proximal section V of the metatarsus are divided into 3 anatomical zones, classification according to Stewart I. M. in which 5 fracture types are distinguished, classification according to Torg J. S., based on radiological features of consolidation [32].

Early diagnosis is an important factor in the success of displaced fracture of metatarsal bone treatment. The predominant symptom of metatarsal bone fractures is impaired walking and support function [5]. In the treatment of this fractures is used both operational and conservative method. The restoration of the original geometry, the structure of the foot arch, is the main problem of fractures of the metatarsals, which can subsequently lead to post-traumatic changes.

Conservative treatment methods are no different from those for other localization fractures, but in the case of metatarsal fractures may be ineffective due to the instability of bone fragments and eventually lead to secondary displacement with the formation of a post-traumatic flat foot [26].

If the fracture is still considered stable and conservative treatment is decided, the immobilization period is normally 4 weeks, with mandatory X-rays control. Further rehabilitation consists in wearing an elastic brace with static and then axial load [15].

In the case of unsatisfactory standing bone deposits, first of all, a closed manual reduction is performed by pulling on the toes and pressing towards the opposite of curvature, also it is possible to apply skeletal traction by Clapp [35]. However, more often in these cases resorted to surgical treatment.

The spectrum of surgical treatment methods is varied. Extracellular (plates), intramedullary (Kirschner's wire) are used. In cases where open osteosynthesis is required [48,31].

Kirsanova V. A., Kovaleva V. A., Mezzinko V. V. examined a sample of 33 patients with fractures of the metatarsal bones. Researchers found the following statistical pattern in fracture distribution: I metatarsus - 4 patients (12.1%), II metatarsus - 7 patients (21.2%), III metatarsus - 6 patients (18.2%), IV metatarsus - 7 patients (21.2%), V metatarsus - 9 patients (27.3%), multiple metatarsus fractures - 2 patients (6.1%). The primary treatment is fixation by Kirschner's wire. The results were evaluated according to the «Functional Scale for the Lower Extremities» by M. Binkley, 1999. It was found that in all cases satisfactory results were achieved with minimal complications [22]. No post-traumatic deformation was detected in these groups.

Metatarsal fractures can occur not only due to a direct traumatic factor. Metabolic disturbances of the carbohydrate exchange are a serious problem, which in some cases is complicated by traumatic fractures. Researchers J. V. Girsh, V. V. Mesheryakov [13] found that adolescents with dysmetabolic carbohydrate exchange disorders had fractures, with the main location of injuries in the projection of the heads of 2-3 metatarsus (31%). Researchers associate this distribution with the fact that localization data are high load areas. In 6.8% of adolescents, a reduction of the angle of the posterior flexion of the foot less than 40° was diagnosed, which in turn leads to an increase in plantar pressure and may complicate pathological fractures with the development of post-traumatic deformation. The most frequent findings were longitudinal flatfoot, valgus deformation of the foot, which required further correction [13].

Often metatarsal fracture studies performed on a cohort of adult patients over the age of 18. Telitsiny P. N., Grodkov S. N., Shirshov S. N. were recruited 52 subjects with lesions of the bones of the anterior section of the foot. As a result, the following distribution of frequencies was obtained for localization of fractures: in the majority of cases there were isolated fractures of the metatarsals - in 18 patients (34.6%), in second place the phalanges of the toes in 11 (21.1%) patients, and finally, combined foot phalange fractures toes with metatarsal bone fractures occurred in 9 (17.3%) patients. In 14 (27%) patients, anterior dislocation of the foot was combined with fracture dislocation of the middle part of the foot, including tarsometatarsal joint in 7 cases [45].

Data on prevalent treatment tactics are consistent with the study presented above. Operative treatment tactics were applied in 43 patients (82.7%), conservative treatment was given to 9 (17.3%) of the subjects [45].

In the postoperative period, complications were observed in 9 (20.9%) cases. The standardized scoring scale was used to analyze the work performed. Predominantly (in 6 - 75% of patients) good results were obtained (84.33 points), these are patients with isolated fractures of the bones of the anterior part of the foot. Satisfactory results (66 17.97 points) were noted in 2 (25%) cases, unsatisfactory results were not observed. In terms of surgical outcomes, 24 (72.8%) had a good score (83.25 1.99) and two (6.1%) had an unsatisfactory score [45]. In patients with unsatisfactory treatment results, further development of post-traumatic deformation of the foot was noted.

Based on this, the authors concluded that the optimal treatment method in which satisfactory results were achieved was open intramedullary osteosynthesis by Kirschner's wire, which prevented rotational, angular and axial displacement, which has significantly improved the treatment results of this pathology [45].

In addition to intramedullary osteosynthesis, other surgical treatment techniques are used for the treatment of metatarsal bones. Babovnikov A. V. developed an extramedullary fixator for osteosynthesis of fractures of the metatarsal bones. It is a plate that is attached to bicortical screws and has a curvature corresponding to the curvature, which ensures stability of fixation [44].

As a result of traumatic damage to the growing area of the bone, there is post-traumatic shortening of the bones in children and adolescents. Skvortsov A.

P., investigated and conducted surgical intervention on 5 patients with shortening of IV metatarsus. The operative treatment methods chosen are an original method and a composition of the Ilizarov apparatus with a dispersion regime of 0.25 (mm) - 2 times a day. As a result, positive treatment results have been achieved in all patients [40]

A serious problem is post-traumatic overload metatarsalgia, which develops due to the damage of the stabilizing structures of the tarsometatarsal joints and overloading of the head of the metatarsal bone, resulting in further degenerative changes, with the development of posttraumatic deformations [8]. L. S. Weil proposes in this case to use osteotomy of the metatarsal bones by the original method [23].

In adolescence, especially in boys, there is a problem of fatigue fractures of the metatarsals (march foot), due to overloading of the anterior section of the foot. Eisunt O. L. reviewed new principles of treatment for fatigue fracture of the base of the metatarsus, in particular the fifth metatarsus, using 12 adolescent patients. In all cases, the treatment method was tunneling the injury zone, with further monitoring using CT scans. As a result, all children treated had satisfactory results [11].

Based on the results of a study conducted by R. M. Tikhelov, it is claimed that post-traumatic flat foot occurs in 10% of cases among all the longitudinal arch plates (48.6% among patients according to the author). The pattern of foot damage and flatness is observed at all levels, with different correlations depending on the section of the foot [40].

Ayoglu, N., Afacan, M. Y., describe the case of multiple metatarsal bone fracture with dislocation in a teenager after a road accident. The authors describe the failure of the closed reposition and the success of the open reposition with highly dislocated fractures of all metatarsal bones in children. After eight weeks, the correct axis of all the metatarsals was marked on the X-ray. This case shows the forced need for open reposition in cases of multiple fractures with significant deformations, despite the fact that in routine practice closed low-invasive osteosynthesis is preferred [3].

When talking about flat foot in general, this term refers to the group of orthopedic disease, which is characterized by a change in the shape of the arches of the foot. They distinguish mobile and rigid flat foot, and on the presence of complaints symptomatic and asymptomatic [2].

Mobile asymptomatic (physiological) flat foot is a reflection of the stages of development of the child's foot. The formation of the arch ends at 7 years, in children's physiological flat feet can be maintained, but by 9 years in normal disappears with the possibility of its complete self-correction. The term "mobile" means that the arch of the foot returns to its normal position when the load is removed [49].

The frequency of detection of flat foot in children and adolescents in different age groups was different. The frequency of detection of flat foot has a tendency to decrease with age. Martin Pfeiffer found that flat foot were detected in 54% of children in the 3-year-old group, while flat foot were detected in only 24% of children in the 6-year-old group. In a cross-sectional study conducted in 2020, Yohannes also found that the younger one is, the more likely it is to detect flat foot. Some studies have also shown that the incidence of flat foot in children and adolescents has a tendency to decrease from 72.6% to 37.9% at age 7-12 [18].

A large-scale study on 882 asymptomatic legs of healthy children shows that mobile flatfoot is common. In most children, flatfoot develops spontaneously during the first decade of life and is within the norm observed in adults. Vanderwilde examined X-rays of the feet of seventy-four normal children aged six months to 10 years and showed a spontaneous improvement of the foot [18,20].

Etiology distinguishes between congenital and acquired forms. Panyyotis showed that the frequency of detection of flat foot was 5.0% in boys and 3.4% in girls; Martin's result showed that the frequency of detection of flat foot was 52% in boys and 36% in girls. [18,20].

The risk of flat foot in men is always higher than in women, and this risk is not significantly related to age. This difference may be due to the fact that girls grow and develop earlier than boys. The development of posture balance and physical development in girls also occurs earlier. The physiological development of the foot arch occurs earlier in girls, the development of the longitudinal arches in boys is slower than in girls, and the fat deposits in boys are thicker than in girls [26].

Mobile symptomatic flat foot is associated with hypermobile syndrome, which in turn is hereditary deterministic, and the analogue of this term in literature is the term «static flat foot» [18,20,26].

The relationship of hypermobility and deformation of the foot was investigated in the work of A. A. Kardanova, A. S. Karandina. The study cohort consisted of 138 patients with deformities at the level of the anterior part of the foot, in the process the type of elasticity of the anterior section was determined and a direct correlation between hyperelasticity and deformation of the foot was established in 11% of cases [1, 20].

The causes of a rigid symptomatic flat foot are defects in the development of the foot - rotation of the bones of the tarsus, congenital deformation of the foot with a vertically located talus bone. The causes of rigid asymptomatic flat foot are not fully understood, they may be developmental anomalies as well as neuromuscular pathology [1].

Talking about the main methods of clinical examination, the most frequently used are objective visual examination, radiography in two projections. These methods are also applicable for the diagnosis of post-traumatic flatfoot [27,28].

The diagnostic value of visual examination is small, it is considered that 30-40% of foot deformities are not diagnosed. Therefore, further diagnostic search of the doctor may be prompted by symptoms such as: deformation of the fingers with growth of the heads I and V of the metatarsals, change in the height of the arches, presence of fractures of metatarsals in the anamnesis [29].

The accurate and available method is the plantography - examination of the arch by the imprint of the floor surface. The essence of the method is to determine the degree of flatfoot in relation to the width of the loaded and unloaded parts [30]. Digital (computer) plantography, with evaluation of dynamic and static load [4], is now firmly established.

R. Z. Salykhov, Y. A. Plakseichuk conducted a of planetary changes on digital plantography in patients with foot injury [32]. The study involved 35 patients with post-traumatic foot changes. The researchers identified the development of post-traumatic flatfoot, which is characterized by an increase in the melting factor, the longitudinal flattening factor, and an increase in the area of contact between the foot and the plane in 23 (65.7%) patients. In 3 patients (8.6%), post-traumatic changes of the bony bone were observed, with a clear trend towards vasodilation of the foot and overload of the external section [38].

Another informative, available method of diagnosis of foot pathology is X-ray, which allows to examine the bone component of the foot. An important indicator is the angle of the arch of the foot, measured in a lateral projection, in norm it is equal to 125-130. When the angle is increased to 140, it is said to be flat foot

I degree, when the angle is increased to 160 II, and more than 160o in case of III degree [33].

The X-ray picture of foot deformities was studied by V. I. Shevtsov and G. V. Dyachkova using the example of 28 patients. In case of flat-foot deformity, they are determined by a change in the architectonics of the bones of the posterior and middle sections, the bases of the metatarsal bones, and there is pronounced osteoporosis with a large-looped pattern of bone trabeculae [39].

The X-ray method has become widespread in the assessment of all parts of the foot. L. N. Solomin and K. A. Ukhanov evaluated radiographs of 64 subjects in order to determine the angle between the articular line of the talus block and the axis of the I metatarsal bone, and to determine the coefficient of lengths by the head of the I metatarsal bone and the posterior edge of the talus block. As a result of this work, a method was developed for evaluating and planning corrections of traumatic deformities of the feet in the middle section. [42]

Also, at the present time, realizing all the advantages of the X-ray method, new diagnostic methods are being developed. Leonova S. N., Usoltsev I. V. developed an X-ray method on a special platform for determining the relative position of the metatarsal heads based on 48 patient studies. As a result, this method has found clinical application for determining the relative position of the heads of the 2nd, 3rd or 4th metatarsal bones, with the establishment of the boundaries pathology, which is necessary to determine treatment tactics for post-traumatic deformities [25].

However, radiography has certain features, since the obtained indicators depend on anthropometric data, individual and functional characteristics of the foot, which must be taken into account. For example, the valgus deviation of the posterior part of the foot in children aged 3 years averages 6.4°, and by the age of 6 it decreases from 4.5° to 4° on average [47].

H. B. Menz conducted research comparing the three indicators, and found a significant correlation between them. The index of the arch of the foot, the index of foot loading and the height of the arch of the foot were compared with the height of the outer edge of the navicular bone, the angle of inclination of the calcaneus (radiological indices). Using the example of data from 100 patients, Saltzman et al. There was a correlation between the height of the arch of the foot and the radiological angles of the foot [19].

There are studies by a number of authors with opposite results, which show that angular indexes are not highly specific and diagnostically reliable. For example, the angle of inclination of the talus varies in the population by 26.5 ± 5.3° and decreases with age. An important role is played by the amount of axial load on the foot during the study in patients with deformed and healthy feet [41]. K. K. Zhokha and V. L. Alexandrovich emphasized the correct technique of foot radiography, otherwise the results were considered unreliable [42]. According to the above data, it can be said that the X-ray method best manifests itself as screening for the analysis of dynamics in large groups, when comparing indicators according to standard criteria, or when clarifying the severity of deformity [41].

Computed tomography (CT) has become widespread in our time [52]. According to the results of CT, specialists have the opportunity to determine the parameters of valgus or varus deformity by constructing multiplanar reconstructions. Additional advantages of CT include the ability to measure bone density [52, 37].

Another modern method of interest is the "F-scan" device, which represents insoles with baroreceptors capable of detecting pressure changes during walking. N. N. Rukina wirh the help of this device examined 14 people with an assessment of the distribution of loads on the foot. The criteria for analysis and evaluation were data on the pressure of the feet in the projection of the II–III metatarsal bones, as a result, it was shown that when wearing "non-physiological" shoes with high heels, the pressure in these locations increases, which increases the risk of flat feet [45].

Subjective assessment of pain before and after injury and treatment in patients with foot deformity [46]. To assess these indicators, standardized questionnaires, patient-reported outcome measures scales (PROMs), are becoming more widespread [9, 17].

Several scales have been developed for the functional assessment of feet, examples are the American Orthopedic Foot and Ankle Society scale – AOFAS, or Foot and Ankle Outcome Score – FAOS [34]. The FAOS consists of 42 questions reflecting the characteristics of pain, stiffness, puffiness, daily activity, athletic activity, and quality of life [35]. This questionnaire was tested and researched by Golubev G. Sh., Khadi R. A. When questioning 68 patients with post-traumatic flat feet, the results revealed that these scales are applicable for subjective self-assessment of the results of treatment of foot pathology [51, 52].

The treatment of flat feet in children is a separate significant issue. Currently, there is no international consensus on the correct treatment of flat foot (both surgical and conservative), and opinions vary from country to country. Thus, asymptotic congenital flat feet in young children does not need treatment. This is confirmed by recent studies, which state that flat feet at an early age are the norm and disappear with the growth of the foot [53]. The influence of shoes on the formation of the arch of the foot is a debatable issue [54].

When talking about acquired symptomatic flat foot, orthopedic insoles and shoes come first in treatment. D. J. Soomekh et al. emphasize that surgery should not be rushed, since acquired symptomatic flat foot usually respond well to conservative treatment [21]. Unfortunately, there are not enough high-quality studies confirming the effectiveness of orthopedic insoles for flat feet. Pfeiffer and his colleagues have suggested that more than 90% of orthopedic treatments are unnecessary. On the other hand, surgical treatment is required in symptomatic cases that do not respond to conservative treatment, and in case of rigid forms. The presence of symptoms is an important factor when deciding on conservative or surgical treatment. Symptoms include pain and fatigue of the foot muscles [32].

The plantar fascia forms a connective tissue framework extending from the calcaneus to the phalanges, encompassing the heads of the metatarsal bone. Thus, the longitudinal arch of the foot is raised, and the toes are unbent. Some orthopedic doctors have suggested that muscle weakness contributes to the development of flat feet, and therefore recommended muscle strengthening exercises to improve the arch of the foot.

The question arises about the treatment of flat feet and prevention through wearing shoes. Rao and Joseph [54] assessed the impact of shoes on the development of the arch of the foot by analyzing the static footprints of 2,300 children aged 4 to 13 years and reported that flat feet are more common in children who wore closed-toed shoes.

Bordelon treated fifty children with custom-made inserts and reported an improvement in the transverse tarsal joint angle [56]. Gould and his colleagues suggested that arch development occurs faster during the first 2 years (up to 3 years) when using arch-supported shoes. In a Boxing study, a custom-made rigid orthosis of the foot proved effective after 24 months in the development of the

longitudinal arch of the foot in children over 6 years of age with flat feet [56]

In patients, especially the older age group, it is often necessary to resort to surgical intervention. P. P. Buravtsev and A. S. Neretin studied 6 patients with grade III transverse flatfoot complicated by a hallux valgus deviation of the first finger. These patients underwent osteotomy of the First metatarsal at the level of the distal metaphysis with simultaneous correction, and osteosynthesis using the Ilizarov apparatus, followed by osteotomy of the proximal metaphysis, and the creation of a transverse arch, with deviation of the First metatarsal bone.

Conclusions. Post-traumatic flat foot can develop with fractures of the foot bones. Fractures of the metatarsal bones associated with post-traumatic flat feet are of the greatest interest. The studied literature indicates clinical correlations between fractures of the foot bones and the development of post-traumatic flat feet. In those studies where the authors associate metatarsal fractures with flat feet, there is a correlation. The problem of tactics for treating metatarsal fractures and tactics for treating post-traumatic flat feet remains as relevant as possible. It can be said that research on the correlation of fractures of the foot bones, and in particular the metatarsal bones, with post-traumatic flat foot is relevant at the moment, and requires further scientific research. Research in the field of development and treatment of post-traumatic flat foot in children is especially important.

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POINT OF VIEW

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THE INFLUENCE OF DIET AND NUTRITIONAL STEREOTYPES ON THE BIOLOGICAL AGE OF THE INDIGENOUS POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA)

The study is devoted to assessing the impact of nutrition on accelerating or slowing down biological age in the indigenous population of Yakutia. The study involved 84 participants aged 18 to 89 years living in the central region of Yakutia. The average age of respondents was 58.0 (21.1) years. To analyze the food composition, the frequency questionnaire containing 30 questions were used. Using K-means method of the cluster analysis, two types of the nutrition were identified among the respondents. We assessed the age acceleration, calculating using three biological clock models: Horvath DNAm, Hannum DNAm, GrimAge in these groups of participants. Binary logistic regression showed that the odds of slowing biological ages increased with a moderate diet for Hannum DNAm by 6.3 times, Horvath DNAm by 21 times, and GrimAge by 15.8 times. The frequent overeating had a negative impact on the biological age of respondents. The frequency of consumption of dairy, fried, canned, salted products, and processed meat statistically significantly affected biological age. Acceleration of epigenetic age was observed in respondents with nutritional errors in the form of overeating and frequent consumption of easily digestible, high-calorie, canned foods.

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

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Introduction. The indigenous population of the Republic of Sakha (Yakutia) is characterized by an evolutionarily developed polar (northern) type of metabolism and a protein-lipid rich diet, which is more physiological in the conditions of the sharply continental subarctic climate of the region [2, 5, 18]. The global transformation from the traditional lifestyles and nutrition, occurring in the last century, has contributed to changes in the structure of prevalent diseases and the increase of chronic non-communicable diseases among the indigenous peoples of the North [1, 3, 5, 6].

Advances in epigenetic research and bioinformatics technologies have led to the creation of "aging clocks" – digital models that allow quantitative assessment of the aging process, health level and adaptive reserve of the body [4, 11, 14]. The most well-known and studied biological clocks are Hannum DNAm [11] Horvath DNAm [12, 13], GrimAge [19], which assess biological age based on the methylation level of the genome CpG sites. Our previous study has revealed differently methylated sites in many areas of the genome when comparing the Yakut population with residents of central Russia. Representatives of the Yakut population have demonstrated a statistically significant acceleration of epigenetic age relative to central Russia for the Horvath DNAm age, Hannum DNAm age, DNAm PhenoAge, GrimAge and their improved models [15].

Studies on model organisms have shown that calorie restriction in nutrition prevents age-related changes in the methylome [8], remodels DNA profiles of genes associated with diabetes mellitus,

inflammation and cardiovascular diseases [16], and significantly improves survival [9]. Intervention studies in humans have confirmed the positive effects of a low-calorie diet, rich in polyphenols (vegetables, fruits, legumes, nuts), as well as limiting the consumption of red meat, sugars and alcohol, on DNA methylation [8-10, 20, 21].

Thus, studying of the relationship between the overall quality and stereotypes of nutrition and epigenetic markers can expand knowledge about the molecular genetic mechanisms of the influence of diet on the quality and duration of people life. The aim of the study was to assess the influence of nutrition on the acceleration or deceleration of biological age in the indigenous population of Yakutia.

Materials and methods. The study was conducted in 2022 among the unorganized indigenous population living in Tattinsky and Churapchinsky districts and in the city of Yakutsk in the Republic of Sakha (Yakutia). The study included data from 84 respondents, including 41 men (48.8%) and 43 women (51.2%). The average age was 58.0 ± 21.1 years (range 18 to 90 years). Participation in the study was voluntary. All participants were representatives of the indigenous population of Yakutia (Yakuts). The study was approved by the local committee on biomedical ethics of the NEFU Medical Institute (protocol No. 34 dated March 30, 2022). Exclusion criteria were acute and chronic diseases in the acute stage, pregnancy.

The survey included an analysis of socio-demographic parameters, a frequency-based assessment of nutrition, and a study of the respondents' lifestyle, including their level of physical activity. Anthropometric parameters, blood pressure and heart rate were also measured and assessed.

DNA methylation analysis was performed using the Illumina Infinium MethylationEPIC BeadChip platform [15]. Methylation data were estimated using the Horvath online calculator (https://dnamage.clockfoundation.org/) [12]. The Hannum DNAm method is based on the analysis of methylation levels of specific CpG sites associated with age-related changes [11]. Horvath DNAm is a multi-tissue age predictor based on 353 CpG sites that allows estimation of DNA methylation age in most tissues and cell types [12, 13]. GrimAge was developed based on 7 CpG sets, 8 plasma proteins and pack-years of smoking [19].

A statistical analysis was performed using IBM SPSS STATISTICS 22 and StatTech v. 4.8.0 packages (StatTech LLC, Russia). The normality of the distributions of quantitative indicators was determined by the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparison of groups by quantitative indicators was performed using Student's t-test, Mann-Whitney U-test, Welch's t-test. Comparison of percentages was performed using Pearson's chi-square test and Fisher's exact test. The values of $p < 0.05$ were considered statistically significant. The K-means clustering method was also used. The logistic regression method was used to develop the prognostic model.

Results and discussion. Age acceleration Hannum Acc, Horvath Acc, GrimAge Acc was estimated by subtracting chronological from epigenetic ages. The sample characteristics are presented in Table 1. Given the small sample size and the weak acceleration of biological ages, we focused on the median value of age acceleration for each epigenetic clock. When age acceleration is higher than the median value of the corresponding epigenetic clock, it was considered that there is a tendency towards age acceleration, when values are lower than the median - a tendency towards deceleration. The use of the median in such analyses allows to minimize the influence of outliers and increase the accuracy of interpretation.

Using K-means clustering, two groups were identified based on nutritional characteristics: Group 1 included 51 respondents with nutritional errors (overeating, frequent consumption of fried, salted, canned, processed foods), and Group 2 included 26 respondents with a moderate diet. This second type of diet can be characterized as conservative. This approach to clustering is consistent with modern research, in which the analysis of dietary patterns allows us to more accurately determine their impact on biological aging.

Using the binary logistic regression method, predictive models were developed to determine the probability of acceleration or deceleration of the biological clock of Hannum DNAm, Horvath DNAm, GrimAge depending on the nutrition cluster. The resulting regression models were statistically significant ($p<0.001$). The number of observations was 77. In the model for Hannum DNAm R^2 Nigelkirk's was 20.6%, and the chanc-

Socio-demographic characteristics of respondents. frequency of some risk factors and indicators of age acceleration

Parameter	Group	n	Value
Age (years)*	both sexes	84	58.0 (21.1)
Sex#	female	43	51.2 (95% CI 40.0 – 62.3)
	male	41	48.8 (95% CI 37.7 – 60.0)
Marital status#	family	51	60.7(95% CI 49.5 – 71.2)
	not family	33	39.3(95% CI 28.8 – 50.5)
Education#	higher	37	44.0 (95% CI 33.2 – 55.3)
	not higher	47	56.0 (95% CI 44.7 – 66.8)
Body mass index. kg/m2*	both sexes	84	24.8 (21.8 – 28.3)
Weight (kg)**	both sexes	84	66.3 (14.4)
SBP (mmHg) **	both sexes	84	132.1 (17.2)
DBP (mmHg) *	both sexes	84	82.0 (75.7 – 90.0)
Obesity#	there is obesity	16	19.0 (95 % CI 11.3 – 29.1)
	norm	68	81.0 (95 % CI 70.9 – 88.7)
Abdominal obesity#	presence	16	19.0 (95% CI 11.3-29.1)
	absence	50	59.5 (95% CI 48.3 – 70.1)
Adaptation potential#	satisfactory	5	23.8 (95% CI 8.2 – 47.2)
	voltage	10	47.6 (95% CI 25.7 – 70.2)
	unsatisfactory	1	4.8 (95% CI 0.1 – 23.8)
	failure of adaptation	5	23.8 (95% CI 8.2 – 47.2)
Hypodynamia#	there is hypodynamia	11	52.4 (95% CI 29.8 – 74.3)
	no	10	47.6 (95% CI 25.7-70.2)
Hannum Acc**	both sexes	84	-10.25 (7.06)
Horvath Acc**	both sexes	84	4.29 (7.21)
GrimAge Acc**	both sexes	84	-10.59 (5.73)

Note: data are presented: * - as median and interquartile range (Me (Q1 - Q3); ** - as mean and standard deviation (M (SD)); # - as proportions and 95% confidence intervals (CI).

es of slowing biological age increased by 6.3 times with moderate nutrition. For Horvath DNAm R^2 Nigelkirk's was 37.8%, with the odds of slowing biological age increasing 21-fold with moderate nutrition. For GrimAge R^2 Nigelkirk's was 33.0%, with the odds of a slowing trend increasing by 15.8 times in the presence of moderate nutrition.

Modern research confirms the importance of moderate nutrition to slow down aging. Thus, numerous studies have shown that a balanced diet, rich in antioxidants, vitamins and minerals can slow down age-related changes at the molecular level, including through epigenetic mechanisms [5, 7, 8, 18 19]. In our study, we also observe that moderate nutrition is associated with slower biological age across all three epigenetic clock models. Thus, in Figure 1 it is clear that respondents with a moderate type of nutrition tend to slow down their biological age, while respondents with nutritional errors tend to speed it up.

To analyze the food composition, the frequency questionnaire containing 30 questions were used. The frequency of food consumption was assessed according to 4 gradations: daily, 1-2 times a week, rarely, never. When analyzing these data, we found a statistically significant ($p< 0.001$) tendency to accelerate all studied epigenetic ages with frequent consumption of fried, salted, canned foods, and processed meat. The acceleration of all epigenetic ages examined in this study in individuals who frequently consume fried and processed foods is consistent with the idea that diets high in trans fats and preservatives increase inflammation and accelerate aging. A statistically significant trend towards acceleration according to the Hannum DNAm biological clock was also observed with frequent consumption of easily digestible foods such as cakes, cookies, and candies ($p<0.029$) and according to GrimAge with frequent consumption of salty and pickled foods ($p<0.04$).

It is interesting that, according to the results of the study, frequent consumption of dairy products was associated with a slowdown in biological age according to Horvath DNAm ($p<0.005$), Hannum DNAm ($p<0.011$), GrimAge ($p<0.029$). The literature on the relationship between dairy consumption and slower aging is somewhat inconsistent. However, there is some research that suggests dairy may have a positive effect on biological age, due to its calcium, vitamins D and B12, and probiotics that support gut health and metabolic processes. For example, a study conducted in the United States found that moderate dairy consumption was associated with improved metabolic health and reduced signs of aging at the cellular level [15].

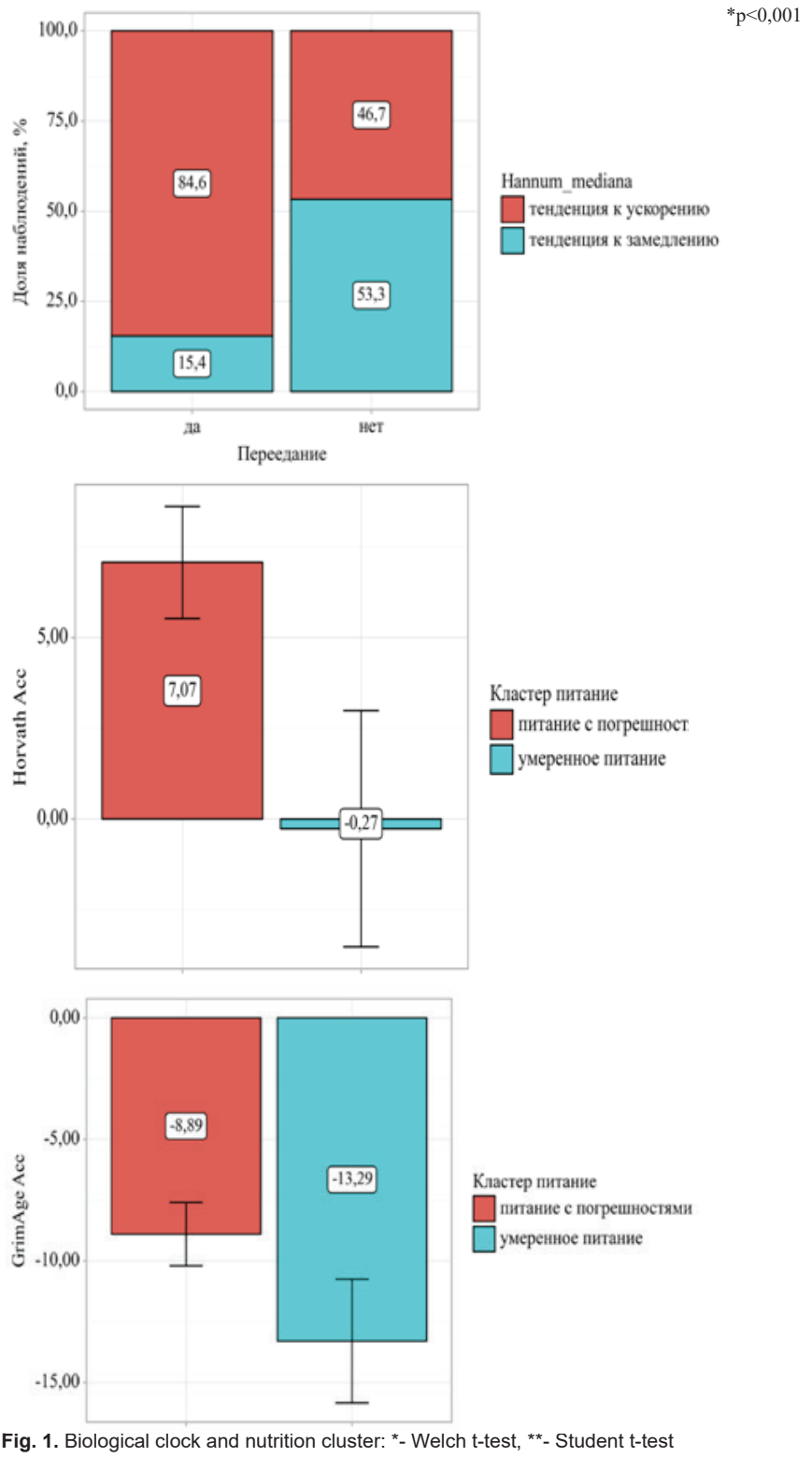

Fig. 1. Biological clock and nutrition cluster: *- Welch t-test, **- Student t-test

The study did not establish statistically significant associations of biological acceleration and the frequency of consumption of fish, vegetables and fruits; this is most likely due to the fact that these products are not consumed very often by observed participants.

A separate analysis of the answers to the question: "Do you think you overeat?" revealed that respondents who had a tendency to overeat had a tendency to accelerate age according to Hannum DNAm in 84.6% versus 46.7% of people who do not overeat, according to Horvath

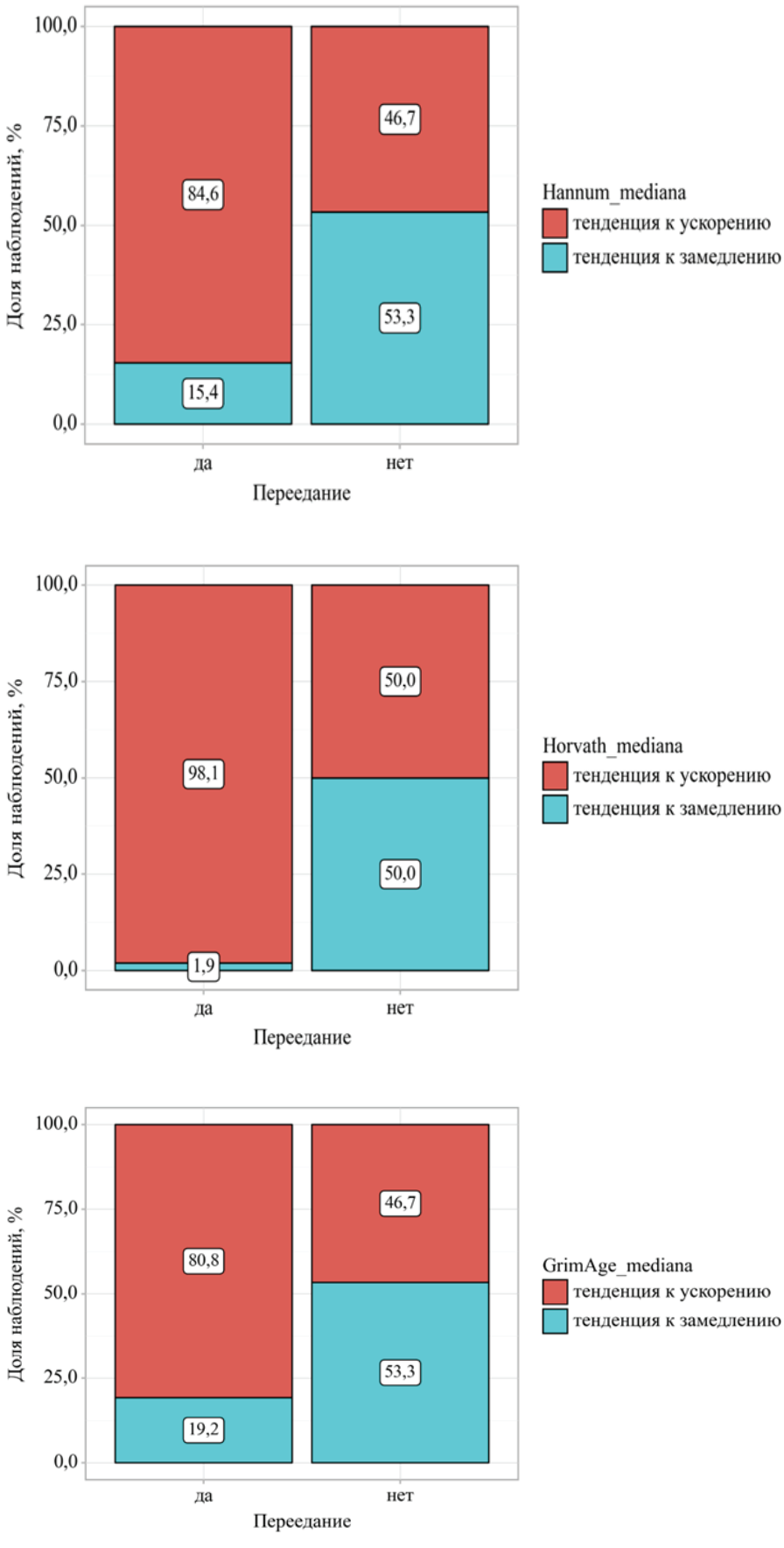

Fig. 2. Age acceleration depending on the answer to the question: “Do you think that you overeat?” (the method used is Fisher's exact test)

DNAm in 98.1% versus 50%, respectively, according to GrimAge in 80.8% versus 46.7%, respectively. This result is consistent with modern studies indicating the negative impact of excessive food consumption on epigenetic aging processes [7, 9, 10, 20, 21].

Conclusion. This study analyzed for the first time the influence of nutrition on age acceleration in the indigenous population of Yakutia. Despite the small size of the study sample, we have established the negative influence of overeating, frequent consumption of fried, canned products, processed meat, and easily digestible products on the epigenetic age. A predictive regression model has been developed to determine the probability of acceleration or deceleration of the epigenetic clock depending on the type of nutrition. Respondents who adhered to a moderate diet had a 6.3-fold chance of slowing down their biological age for Hannum DNAm, 21-fold for Horvath DNAm, and 15.8-fold for GrimAge. Our study confirms that moderate nutrition has a beneficial effect on slowing down biological age, which in the future may form the basis for the development of personalized nutrition programs to prevent aging and increase lifespan.

Further studies with larger sample sizes and more in-depth nutritional studies with the additional clinical parameters will help identify new factors that contribute to accelerated aging.

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

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CLINICAL CASE

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A CLINICAL CASE OF THE COMBINED ACUTE PROMYELOCYTIC LEUKEMIA AND JUVENILE IDIOPATHIC ARTHRITIS

A clinical case of enteritis-associated juvenile arthritis during the therapeutic stage of consolidation of acute promyelocytic leukemia is presented in the article. It describes the clinical case of a 16-year old teenager. Arthritis in a patient with leukemia is commonly associated either with an exacerbation of the underlying disease or with an infectious process in the joint or the adjacent bone. Leukemic arthritis is commonly manifested by monoarthritis, involving large joints and presented with severe night pain, lymphadenopathy, and hepatosplenomegaly. Joint pain reduction is a sign of a clinical response to chemotherapy.

Musculoskeletal system involvement caused by infection is represented by local inflammatory process accompanied with fever, local hyperemia, hyperthermia, inflammatory changes in blood test results and requires a course of intensive antibacterial therapy with the temporary cessation of chemotherapy. The development of juvenile idiopathic arthritis during leukemia therapy caused diagnostic and therapeutic difficulties due to uncommonly rare association of the both diseases, which required the exclusion of leukemia recurrence and an infectious complication. NSAID therapy brought temporary relief, janus kinase blocker (upadacitinib therapy) was ineffective, only subsequent switching to etanercept allowed the remission of arthritis. Leukemia treatment was carried out in conjunction with JIA treatment.

Keywords: acute promyelocytic leukemia (APL), juvenile idiopathic arthritis, leukemia chemotherapy, myelogram, children and adolescents.

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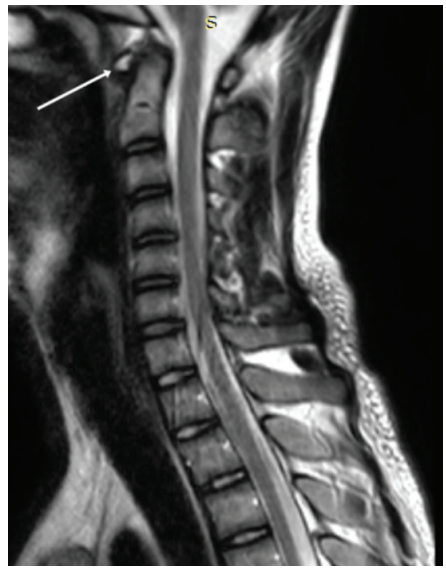
Introduction. Acute promyelocytic leukemia results from the variant of a gene, caused by abnormal overgrowth of promyelocytes. Acute promyelocytic

leukemia occurs in 5-10% of all cases of acute myeloid leukemia [3,8]. It is severe disease characterized by expressed skin and mucosal hemorrhage syndrome [7,18].

In a case of acute promyelocytic leukemia alpha is abnormal, which encodes nuclear hormone transcription factor and is present in the long arm of chromosome 17, participating in APL [9,19,21]. It promotes to expression of the several genes after binding to retinoic acid. In most cases (90%) APL is associated with t translocation (15;17) (q22:q21), which results in fusion of promyelocytic leukemia gene to RAR-alpha to generate 2 genes. These translocations are also clinically significant because of their sensitivity or partial/complete refractoriness to retinoids [4,9,12].

The incidence of APL is increasing with age. It occurs in 3-4% of all cases at the age of 0-17. APL is almost uncommon for children under 10 years of age. Clinically the APL patients develop weakness, fatigue, frequent nose bleed, gum bleeding and high fever. Early manifestations of leukemia are similar to rheumatic signs and symptoms. Moreover, it is known that arthritis is common manifestation of leukemia in children [8,11].

A clinical case. A 16-year patient N., Sakha by origin, was admitted to the department of oncohaemotology of M.E. Nikolaev Republican hospital #1 of the Republic of Sakha (Yakutia) to receive the second course of ATRA supportive therapy. It is evident from the anamnesis, that the child started complaining of dizziness, weakness, in a few days there was a high fever up to 39.0 C; asthenia, flaccidity, dizziness and lack of appetite were new symptoms. The results of full blood count revealed: leukocytes – 2.6x10^{9}/L, lymphocytes – 69.4%, monocytes – 10.0%, granulocytes – 20.6%, erythrocytes – 2.2 x10 ^{12}/L, hemoglobin – 63 g/L, platelets - 28 x10 ^{9}/L, ESR – 69 mm/hr. The patient was admitted to the oncological department of M.E. Nikolaev Republican hospital #1 of the Republic of Sakha (Yakutia). The myelogram revealed hypercellular marrow with total metaplasia of the blast cells reaching up to 93%, with reduced normal immature blood cell production, according to morphological and cytochemical signs these blasts can be referred to the variant of AML M3. Immune phenotype of the blast cells can be morphologically referred to M3 variant. MRI of the brain revealed the signs of small subdural hematoma in the distal part of the right parietal region and small subdural hygroma along the frontal and temporal areas of the both sides. Acute promyelocytic leukemia is diagnosed, classified as M3 variant at the period of progression. Subdural bleeding in the right temporal part is noticed. Subconjunctival hemorrhage in the right side and retinal hemorrhage of the both eyes were determined. Coagulopathy is revealed.



MR imaging of the cervical spine (T2 protocol): synovitis in cholesteatoma (arrow).

The treatment was performed according to APL treatment protocol (by 2008) remission induction (lasted 2.5 months), consolidation (6 days), intensive therapy (3 days).

The consolidation phase was accompanied with pains in the neck, high temperature (up to 38.8 C) and pains in the right knee joint. The local examination of the right knee joint showed that it was bigger in size, swollen and painful there was increased temperature above the joint. The laboratory findings revealed elevated CRP 189 mg/L (norm: 0-5 mg/L). The full blood count showed: erythrocytes – 3.1 x 10^{12}/L, leukocytes – 4.9 x^{10}/L, platelets – 254 x10^{9}/L, hemoglobin – 86 g/L, monocytosis – 18%, blasts – 2%, myelocytes – 12%, metamyelocytes – 4%, polymorphnuclear leukocytes (neutrophils) -33%, elevated ESR up to 70 mm/hr.

The myelogram on a 4-graded score on the 91 day of the disease revealed that bone marrow was characterized by increased cellularity and polymorphism. The blast cells were: 1.6%; 1.6%; 1.0%; 1.6%.

Biochemical blood test results on the 94th day were: elevated ALT – 41.5 Un/L (norm <37 Un/L), AST – 39 Un/L (norm

The indices of the biochemical blood test results and full blood count

	On admission	On the 7th day	On the 15th day	RR (reference range)
Erythrocytes	4.25	4.18	4.34	3.93-5.29x10Un^{12}/L
Leukocytes	2.26	3.03	2.96	3.84-9.84x10Un^{12}/L
Hemoglobin	135.0	132.0	135.0	108-145g/L
Platelets	168.0	167.0	171.0	175.0-345.0x10Un^{9}/L
Polymorphnuclear leukocytes (neutrophils)	44.0	64.0	50.0	47.0-72.0%
Lymphocytes	43.0	22.0	37.0	19.0-37.0%
Monocytes	8.0	7.0	5.0	3.0-11.0%
ESR by Panchenkov	4.00	2.00	2.00	1.0-10.0mm/hr
Albumin	37.30	41.50	42.40	35.00-52.00g/L
Protein total	60.50	60.80	62.90	64.00-80.00g/L
Urea	3.40	2.80	2.50	2.50-6.40mmol/L
ALT	54.60	78.10	247.10	0,00-27,00 ед/л
AST	25.40	23.10	60.70	0,00-29,00 ед/л
Creatinine	57.80	58.40	67.10	62,00-115,00 ммоль/л

<29Un/L), ferritin – 992 mg/L (RI: 15-204 mg/L).

Coagulogram results on the 94th day of the disease were: PT 84% (RR – reference range: 95-105%); PT 12.5 sec. (RR: 11-18 sec); INR (international normalized ratio (MHO)) – 1.1; aPTT (activated partial thromboplastin time) - 35.9 sec (reference range: 25-50 sec.); fibrinogen – 10.2 g/L (reference range: 1.25 – 4 g/L). HLA antigen – B27 is positive.

Digital radiography of the knee joints was carried out in 2 projections and revealed indirect X-ray signs of arthritis in the right knee joint. MRI of the knee joint showed synovitis. MR imaging of the cervical spine showed fluid in the cholesteatoma (figure). MR imaging of the lumbar and sacral spine revealed infiltration of the muscles in L4-L5.

After rheumotologist consultation the data of the radiological methods of investigation were changed, juvenile idiopathic arthritis, B-27 associated HLA, oligoarticular variant of the III-rd degree of activity was diagnosed, grade 2 is established according to radiological findings. Upadacitinib therapy was administered. As the upadacitinib therapy was ineffective it was changed into etanercept which showed positive dynamic.

Both after leukemia intensification and arthritis therapy the patient received supportive therapy of APL.

By the second stage of therapy with all-trans retinoic acid (ATRA) the patient objectively had severe condition caused by the main disease. The patient was active although no significant changes in the general condition were noticed. The skin was pale and clean. The osteoarticular system had no visible defects.

Laboratory findings are represented in the table.

Antibiotics therapy, chemotherapy and etanercept are administered.

The leukemia treatment finished. There were no data of reccurence. The child is discharged from the hospital to be followed up by the local pediatrician.

Discussion. We represented a complicated clinical case of the rare combination of juvenile idiopathic arthritis debut in a teenager which occurred during leukemia treatment. The musculoskeletal manifestations in the patients with oncological and hematologic malignancies can be of various nature, most commonly pains in the bones and the joints can be associated with bone marrow infiltration caused by the blast cells. Transient synovites were associated with the blast cells producing proinflammatory cytokines [11]. The articular syndrome can also be associated with hyperuricemia resulting from massive blast cell breakdown. The musculoskeletal complaints of those patients who are receiving chemotherapy should exclude reccurence of hematological disorders, septic arthritis, hematogenous osteomyelitis, avascularnecrosis, osteoporosis including pathological stress fractures [21]. It is noted that arthritis can be a complication of leukemia [11,16]. Leukemic arthritis is frequent in children. 60% of the pediatric patients with leukemia complain of pains of the musculoskeletal system, arthritis is diagnosed only in 5% of them [11,20]. Joint pain complains can be initial manifestation of leukemia and it should be born in mind when diagnosing. Juvenile idiopathic arthritis (JIA) is most common kind of chronic rheumatic disorders in children under 16 [2]. There are several kinds of manifestations, B27 HLA associated juvenile arthritis is the most common in the Republic of Sakha (Yakutia). It is defined that B27 HLA antigen is present in all subtypes of JIA in children of indigenous population of the Republic of Sakha (Yakutia) [1]. The symptoms of JIA in that case started during the consolidation period, which was carried out according to APL protocol by 2008. It was determined that arthritis did not recur in combination with leukemia, moreover septic arthritis and hematogenous osteomyelitis were excluded as possible infectious complications of chemotherapy.

Chronic arthritis in leukemia patients is commonly rare. Although blood disorders and rheumatic diseases are associated with immune system dysfunction; the course of cancer therapy, as a rule, is stronger and targeted and is unable to control arthritis. Combined therapy is required in such patients which includes the drugs of different class and enables to control both hematological and rheumatic diseases. Immunoinflammatory manifestations are described in patients with APL on ATRA therapy as ATRA-syndrome, which is characterized by high fever without confirmed infection, fluid retention resulting in edematous syndrome with increase of body mass, acute respiratory distress with pulmonary infiltrates, bloody expectoration and development of respiratory failure, pleuritis and pericarditis, arterial hypotension, acute renal failure (acute kidney injury) [13]. The syndrome is based on inflammatory cytokines production and development of capillary leak syndrome. The same changes are noticed in rheumatic patients with syndrome of macrophage activation, multisystemic inflammatory syndrome, DRESS-syndrome [10,14]. Some singular arthritis cases are described in the patients on ATRA therapy [5]. It should be noted that ATRA itself has anti-inflammatory effect against arthritis; it was confirmed clinically in rats by suppressing Th17-related pathway and change of the gut microbiota composition [6].

The cases of sacroiliitis and spondiloarthritis which occur as a result of retinoid (isotretonoin) therapy for dermatological conditions are well known. Thus, 149 articles are found by the key words "Isotretinoin-induced arthritis" searching in the PubMed and almost all of them describe the adult patients [15]. A most profound investigation of 513 adult patients on isotretinoin therapy showed that 24% of them complained of pains in the lower part of the spinal column, 17.1% were diagnosed with arthralgia, Achilles tendon enthesopathy was determined in 2 patients. 42.3% were diagnosed with sacroliitis, which was confirmed by MRI, 10.1% of all the group developed pain in the lower portion of the spinal column. Among PRI-confirmed sarcoliitis 51.9% corresponded to ASAS classification criteria for ankylosing spondiloarthritis. MRI of the sacro-iliac joints showed normalization within 9 months in all the patients after retinoid therapy cessation [17].

Conclusion. Chronic arthritis associated with leukemia is uncommon in children, especially when it occurs during chemotherapy. The musculoskeletal symptoms occurrence requires a wide range of differential diagnosis and choice of therapy taking into account both diseases and safety profile. The case demonstrates not only difficulties in juvenile arthritis diagnosis but also possible development of arthritis induced by retinoid therapy.

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

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POST-COVID ACUTE DISSEMINATED MENINGOENCEPHALITIS IN A 2-YEAR-OLD CHILD: A CLINICAL CASE

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Among all published studies, it has been noted that in COVID-19, in addition to respiratory system dysfunction, one-third of patients (30–35%) exhibit signs of nervous system (NS) involvement. Descriptions of various neurological diseases complicating the course of coronavirus infection (COVID-19) or representing its unique clinical manifestation are available. One of the neurological complications of COVID-19 is meningoencephalitis.

This article examines the clinical presentation, diagnosis, and treatment of acute disseminated meningoencephalitis (ADME) that developed in a child following COVID-19. Special attention is given to the pathogenesis of the disease, which is associated with the body's immune response to the SARS-CoV-2 virus, leading to inflammatory processes in the central nervous system. Data from instrumental and laboratory diagnostics, as well as treatment, are presented. The importance of early detection and comprehensive treatment to prevent severe neurological complications and improve prognosis in young patients is emphasized.

Keywords: COVID-19, meningoencephalitis, central nervous system disease, neurological complications

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Introduction. Acute disseminated meningoencephalitis (ADME) is an inflammatory disease of the central nervous system (CNS) characterized by damage to the brain's soft tissues and meninges, leading to various neurologi-

cal consequences. Despite its rarity, this condition can have serious outcomes, including disability and even death, underscoring the need for deeper study of its diagnostic, therapeutic, and pathogenetic aspects.

The primary cause of ADME is considered to be an autoimmune response triggered by a viral infection. The SARS-CoV-2 virus, which causes COVID-19, can induce inflammation, leading to disseminated *encephalitis* foci. Potential mechanisms include both direct neuronal damage and the body's immune response, resulting in an attack on its own tissues.

The literature describes isolated cases of post-infectious encephalitis and meningitis following acute coronavirus infection (CVI) [1,6]. One of the most studied complications of CVI is multisystem inflammatory syndrome, including involvement of the meninges [3]. It has been reported that nervous system involvement may manifest as encephalitis, although direct evidence of SARS-CoV-2 neurotropism is lacking [1, 2].

Most cases of meningoencephalitis in COVID-19 result from an immune-mediated response to the virus, occurring when the virus enters the CNS through the blood-brain barrier (BBB) [5]. The clinical picture of meningoencephalitis may appear alongside the initial symptoms of COVID-19, including fever, depressed consciousness, neurological deficits, focal neurological signs, meningeal symptoms, and altered mental status. Cerebrospinal fluid (CSF) analysis reveals leukocytosis and cell-protein dissociation. Neuroimaging shows the presence of encephalitic foci. Most patients exhibit sinusitis or pansinusitis [1]. The question of whether meningoencephalitis is a clinical manifestation or a complication of COVID-19 remains debated.

Involvement of the central nervous system (CNS) is a harbinger of poor prognosis. Therefore, clinical assessment should focus not only on viral and infectious manifestations but also on the emergence of focal neurological symptoms.

Objective: To present a clinical case of meningoencephalitis following a coronavirus infection.

Materials and Methods. A retrospective analysis was conducted using the medical records of a patient admitted to Psychoneurological Department No. 2 of the Pediatric Center at the GAU RS(Y) "Republican Hospital No. 1 – National Medical Center named after M.E. Nikolaev". Data included clinical observations, laboratory tests, and instrumental diagnostics.

Clinical Case. A 2-year-old patient was admitted to the intensive care unit of a children's infectious disease hospital in critical condition, presenting with complaints of repeated vomiting, diarrhea, and fever up to 39°C.

According to the history, the child fell acutely ill, with symptoms beginning as repeated vomiting (up to 10 episodes), diarrhea (3-4 times daily), and fever up to 39°C. On the second day, vomiting and diarrhea persisted, and the parents called a doctor, but no medical assistance was provided. By the third day, the child remained febrile (39°C), with persistent vomiting (10 episodes), watery diarrhea, lethargy, and weakness. Emergency medical services were called, and the child was transported to the infectious disease hospital. Upon admission to the Intensive Care Unit, the child was in critical condition with worsening neurological deficits: stupor, seizures, and limited active/passive movements due to spastic tetraparesis. Muscle tone was notably increased in the arms. Tendon reflexes in the limbs were diminished. The skin exhibited pronounced marbling. Meningeal and cerebral symptoms included hyperesthesia and nuchal rigidity (1 fingerbreadth).

At the pediatric infectious disease hospital confirmed: Positive PCR for SARS-CoV-2 RNA. Concurrent rotavirus infection detected.

Treatment included: Antibacterial therapy: meropenem (20 mg/kg). Dexamethasone (20 mg/m² body surface area) for mast cell stabilization and anti-inflammatory effects. Heparin (200 IU/kg) for anticoagulation. Topiramate (2 mg/kg) for seizure control. Symptomatic therapy.

Due to the severity of the condition and clinical/laboratory improvement for COVID-19 and rotavirus infection, the child was transferred to Psychoneurological Department No. 2 of the Pediatric Center.

In the psychoneurological department, neurological symptoms persisted: the child remained stuporous, with oral automatisms, twitching of the right hand, and limited active and passive movements due to spastic tetraparesis.

Laboratory findings included leukocytosis with a left shift, anemia, erythropenia, and thrombocytopenia (77 x 10^9/L). Biochemical blood tests showed elevated C-reactive protein, creatinine (198 µmol/L), transaminases (ALT - 791 U/L, AST - 1474 U/L), and ferritin (1000 ng/mL). Urinalysis revealed proteinuria, leukocyturia, and hematuria.

From the instrumental diagnostic data on MRI of the brain: a series of tomograms obtained images of sub- and supratentorial structures of the brain and the craniovertebral junction. The topographic position of the anatomical structures of the craniovertebral junction is not disturbed. The midline structures of the brain are not displaced. In the white matter of the cerebral hemispheres periventricularly, in the subcortical section of the right frontal lobe, in the structure of the basal ganglia on both sides, multiple pathological foci are detected, hyperintense in T2WI, TIRM, isointense in T1WI, with signs of diffusion restriction, ranging in size from 3 mm to 8 mm. After contrasting, most foci do not accumulate the contrast agent, point accumulation of contrast is noted in the lesion in the right frontal lobe. The corpus callosum is of normal thickness and signal intensity. The brainstem and cerebellum have a normal configuration and signal intensity.

The lateral ventricles are slightly and uniformly dilated (width at the level of the bodies: 34 mm; width of the third ventricle: 5 mm). The fourth ventricle is midline. No periventricular edema is observed. The convexity subarachnoid spaces are moderately and unevenly widened in the frontoparietal regions. The pituitary gland is normal in size, with smooth and clear contours; its structure is unaltered. The pituitary stalk is midline. The optic chiasm and suprasellar cistern are unremarkable. The internal auditory canals are symmetrical and of normal width bilaterally. No pathological formations are detected in the cerebellopontine cisterns.

Conclusion: Multiple pathological foci in the periventricular regions, bilateral basal ganglia, and subcortical area of the right frontal lobe require differentiation between acute ischemic lesions and inflammatory foci (encephalitis). Mild ventriculomegaly. Moderate widening of convexity spaces in the frontoparietal regions.

Follow-up MRI: Regression of pathological FLAIR hyperintensities is noted in the periventricular white matter and subcortical right frontal lobe. Complete resolution of acute ischemic foci is observed.

EEG Findings: On admission to the hospital, the electroencephalogram showed a picture of the soporous stage of coma. No epileptic activity was detected.

In the dynamics of the EEG, a pronounced diffuse slowing of the bioelectrical activity of the brain in both hemispheres was noted with the replacement of the main activity by slow waves of the delta and theta range of high amplitude.

No epileptic activity was detected. EEG picture of encephalitis or diffuse encephalopathy.

Based on clinical and instrumental studies, a final diagnosis was made. Primary diagnosis: Acute disseminated meningoencephalitis (ADME), severe course. Convulsive syndrome with status epilepticus (resolved). Critical illness polyneuropathy (recovery phase). Comorbidities: 1. Mixed infection with systemic inflammatory syndrome (convalescent stage): Laboratory-confirmed COVID-19 (SARS-CoV-2 identified). Acute rotavirus gastroenteritis complicated by severe dehydration (grade 3) and toxemia (grade 2).

Dynamics of the condition and the treatment performed. The patient underwent intensive therapy, including antibacterial therapy with meropenem (20 mg/kg) and bacperazone (40 mg/kg) to treat the infectious process. Also administered: anti-inflammatory therapy, which includes dexamethasone (2 mg) and methylprednisolone (4 mg) with a gradual dose reduction to reduce the inflammatory process in the central nervous system; anticonvulsant therapy, consisting of valproic acid (30 mg/kg/day) to control seizure activity; detoxification therapy. Positive dynamics were noted against the background of treatment, with improvement in clinical and laboratory parameters.

The patient's condition at the time of discharge with clinical improvement. The child's consciousness is clear, adequate response to examination, sufficient motor activity, gaze fixes. Neurological status: diffuse muscle hypotonia, tendon reflexes are reduced in the arms and legs. The range of motion improves dynamically. The patient is able to hold his head up, sits with support. Dysarthria is observed, expressed in the pronunciation of individual syllables and sounds. The patient was discharged in a satisfactory condition with clinical, laboratory and neurological improvements, requiring further rehabilitation and observation.

Discussion. This case highlights ADME development in a child following COVID-19 and rotavirus coinfection. Combined infections exacerbated systemic inflammation and multiorgan dysfunction. ADME pathogenesis involved both immune-mediated mechanisms and indirect hemorheological effects of SARS-CoV-2, compounded by rotavirus.

The clinical picture was characterized by severe neurological deficit, seizures and pronounced systemic manifestations. It is important to note that ADME can develop both in the early stages of infection and against the background of the leveling of general infectious symptoms. Diagnosis of ADME requires a comprehensive approach, including clinical assessment, laboratory tests (CSF analysis, general and biochemical blood tests) and neuroimaging (MRI of the brain). Ischemic foci in the brain could arise due to microthrombosis, endothelial dysfunction and systemic hypoperfusion. The issue of penetration of the SARS-CoV-2 virus through the blood-brain barrier remains controversial. In this clinical case, PCR diagnostics of the virus in the cerebrospinal fluid (CSF) was not carried out, which does not allow this hypothesis to be unambiguously confirmed [4]. However, existing studies and clinical observations provide data supporting the possibility of virus translocation through the blood-brain barrier [3]. Early diagnostics and complex therapy, including anti-inflammatory, anticoagulant and neuroprotective agents, are key to improving the prognosis in such patients. In dynamics, 6 months after the primary disease, neurological symptoms completely regressed, and rehospitalization to the psychoneurological department was not required.

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

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LANGERHANS CELL HISTIOCYTOSIS (A CLINICAL CASE)

Langerhans cell histiocytosis (LCH) is a rare myeloid disorder with a variable clinical presentation, based on the activation of the MEK-ERK signaling pathway in dendritic cell precursors. The localization of pathological lesions varies: the most common sites include the skeleton, skin, posterior pituitary gland, lymph nodes, liver, spleen, bone marrow, lungs, and central nervous system [2].

This article presents a clinical case of Langerhans cell histiocytosis in a newborn delivered at the Perinatal Center of the M.E. Nikolaev Republican Hospital No. 1-NCM. At birth, the child exhibited characteristic skin lesions in the form of a bumpy, dark cherry-colored rash on the scalp, fingers, and toes, with some areas showing light inclusions and a firm texture. Over time, with treatment, the pustules and vesicles ruptured, forming ulcers, crusts, and hemorrhages. The stages of diagnosis, including histological and immunohistochemical studies (CD1a+, Langerin+, S100+), differential diagnosis, and a comprehensive treatment approach, are described in detail. Special attention is given to the challenges of diagnosing newborns and the importance of interdisciplinary collaboration.

Keywords: Langerhans cell histiocytosis, newborns, skin manifestations, diagnosis, treatment, histological examination.

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Introduction. Langerhans cell histiocytosis is a heterogeneous disease characterized by the accumulation of dendritic cells resembling epidermal Langerhans cells in various organs. The disease can affect any organ or system in the human body, but most commonly involves the skeleton (80% of cases), skin (33%), and pituitary gland (25%). Other affected organs include the liver, spleen, hematopoietic system, and lungs (15% each), lymph nodes (5-10%), and the central nervous system, excluding the pituitary gland (2-4%) [3].

Epidemiological data indicate that LCH occurs at a rate of 3-10 cases per 1 million children annually. The male-to-female ratio is 2:1, with the peak incidence occurring in early childhood [4]. Early-onset LCH (before the age of 2) is associated with a high risk of developing multisystem forms, whereas monosystemic and monofocal forms are more commonly identified in children over 5 years old [1].

The causes of Langerhans cell histiocytosis remain unknown. No convincing evidence has been found to support genetic predisposition or infectious etiology. The pathogenesis of LCH is not fully understood. In 50-60% of patients, a somatic V600E mutation in the BRAF gene is detected, leading to activation of the MAPK/ERK signaling pathway [4,9]. In recent years, mutations in the MAP2K1, ARAF, and other components of this pathway have also been described [1, 7].

The clinical course of the disease varies from localized forms with benign progression and spontaneous recovery to disseminated forms with aggressive progression and fatal outcomes. Aggressive forms often present with malaise, weight loss, and developmental delays. Osteolytic bone lesions are observed in 80% of cases, lung involvement in 12-23%, and liver or spleen involvement in 15-50% [2, 5]. Skin lesions occur in 30-45% of cases, ranking second in prevalence after skeletal involvement. Lymph node involvement is the rarest symptom. In newborns and infants, skin lesions may be the only sign of LCH [3,1,8]. The rash can appear on the trunk, scalp, and other areas. Patients with skin, bone, or lymph node involvement classified as "risk-free organs" typically have a good prognosis and require minimal treatment. However, patients with "risk organ" involvement (liver, spleen, lungs, bone marrow) have a poorer overall prognosis. CNS involvement, vertebral or facial bones, or lesions in the anterior or middle cranial fossa also indicate an unfavorable prognosis for recovery. LCH in the orbit, mastoid, or temporal region is classified as a "CNS risk" due to the increased likelihood of diabetes insipidus, other endocrine abnormalities, or brain parenchymal lesions [5,9].

Since Langerhans cell histiocytosis can affect any organ or system, it should be considered in cases of clinical manifestations involving the skin, bones, lungs, liver, or CNS. The diagnosis is clinicopathological and should only be made in an appropriate clinical setting to avoid misdiagnosis due to the presence of normal reactive Langerhans cells, particularly in regional lymph nodes. In addition to clinical and radiological signs, the diagnosis must always be based on histological and immunophenotypic examination of affected tissue, which should be taken from the most accessible but representative lesion [3].

The goal of LCH treatment is to suppress the activity and proliferation of histiocytes, lymphocytes, and macrophages

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causing the disease. Treatment for "risk-free organ" LCH generally yields good results. Aggressive forms require immunosuppressive agents, radiation therapy, and other methods. New insights into LCH mechanisms open prospects for targeted therapy [7].

The prognosis depends primarily on initial "risk organ" involvement (especially bone marrow, liver, and lungs) with impaired function [6]. Timely diagnosis enables effective treatment, significantly improving the prognosis. Current experience shows that LCH with isolated skin involvement in newborns, when treated promptly, has a favorable course [7].

Objective: To describe a clinical case of Langerhans cell histiocytosis in a newborn.

Materials and Methods: A retrospective analysis of the medical records of a patient from the Department of Neonatal and Premature Pathology No. 2 of the Perinatal Center of the M.E. Nikolaev Republican Hospital No. 1-NCM was conducted. Data from clinical observations, laboratory tests, instrumental diagnostics, histological and immunohistochemical studies, and telemedicine consultations were used.

Clinical Case. A newborn boy, from the 6th pregnancy (first half – toxicosis, second half – anemia), 4th delivery. Gestational age: 38.6 weeks. Birth weight: 3750 g, length: 54 cm. Apgar score: 7/8.

At birth, the condition was severe due to grade 2 respiratory failure, signs of intrauterine infection, and pronounced skin syndrome. No resuscitation was required in the delivery room. The cry was loud but short, with groaning. The skin of the scalp, fingers, toes, and palms showed nodular, bumpy, dark cherry-colored rashes with some light inclusions and a firm texture. The face was cyanotic due to hemorrhages. Breathing involved accessory muscles, with retraction of the lower intercostal spaces and lower chest aperture. Auscultation revealed weakened breath sounds and transmitted wet rales. Heart sounds were clear and rhythmic. The abdomen was soft, liver +2 cm, spleen not enlarged. No stool or urination. External genitalia were male. Anus in the typical location.

The child was transferred from the delivery room to the neonatal intensive care unit (NICU) in a transport incubator on spontaneous breathing, connected to a ventilator in NCPAP mode with parameters: T.High – 0.4 sec, FiO2 – 25%, PEEP – 4.6 cm H2O. Conscious, responsive to manipulations with motor activity and crying. Pain score on N-PASS: 2. Head in birth configuration, face symmetrical. Eyelid edema present, photomotor reflex intact. Anterior fontanelle 1.0 x 1.0 cm, level with skull bones, non-bulging, non-pulsating, non-tense. Posterior fontanelle 0.5 x 0.5 cm. Sutures closed. No seizures. Neonatal reflexes present. Muscle tone physiological. No musculoskeletal abnormalities. Visible mucous membranes pink and moist. Nodular cherry-colored lesions present on all skin areas, including the scalp, some with firm-elastic infiltrates, elevated above the skin surface. Eyes clear. Acrocyanosis. Generalized edema. Umbilical vein catheterization was performed for intravenous therapy and blood sampling. Breathing on assisted ventilation, auscultation revealed air-oxygen flow noise transmitted throughout lung fields, weakened, with transmitted rales. Moderate retraction of the lower intercostal spaces. Respiratory failure score on the Silverman scale: 3.

Hemodynamics relatively stable. Heart sounds clear, rhythmic, systolic murmur. Radial and femoral pulses palpable, satisfactory filling. Capillary refill time: 3 sec on the sternum, 4 sec on extremities. Feeding with PreNaN formula and colostrum via gastric tube, bolus every 3 hours starting at 12 hours. Abdomen soft, non-distended, accessible to palpation. Occasional bowel sounds. Liver +1.5-2.0 cm below the costal margin, edge elastic. Spleen not enlarged. Anus in the typical location. No stool at the time of examination. External genitalia male. Urination free into the diaper. Preliminary diagnosis:

Primary diagnosis: P22.0 Neonatal respiratory distress syndrome: NRDS. P39.2 Intra-amniotic fetal infection, not elsewhere classified. Complication: Grade 2 neonatal respiratory failure.

Blood tests showed decreased hemoglobin (148 g/L), lymphocytopenia (16.7%). Biochemical analysis revealed hyperbilirubinemia (46.14 μmol/L). Urinalysis was normal. PCR for intrauterine infections negative. Echocardiography showed a patent ductus arteriosus (0.42 cm), an aneurysm of the secundum atrial septum with shunts (0.25 cm and 0.14 cm), signs of grade 1 pulmonary hypertension. Tricuspid valve regurgitation grade 1-2. Pulmonary artery dilation. Slight right ventricular enlargement. EF 70.1%. Chest and abdominal X-rays revealed hypoventilation and uneven intestinal pneumatization. Given the clinical picture and instrumental findings, ampicillin/sulbactam – 75 mg/kg/day, 0.37 mL twice daily IV, and local treatment of ruptured lesions with 1% potassium permanganate solution were prescribed.

On day 1, the child was transferred to the Department of Neonatal and Premature Pathology No. 2 (DNPP No. 2). Temperature 36.9°C. HR 122 bpm. RR 65 bpm. SaO2 100%. Oxygen support: NCPAP, O2 flow 1 L/min. Condition severe due to grade 1 respiratory failure and infection. Conscious. Loud cry, responsive to manipulations with painful crying and motor activity. Head in birth configuration, face symmetrical. Proportional build. Neonatal reflexes present. Anterior fontanelle 1.0 x 1.0 cm, non-tense. Posterior fontanelle 0.5 x 0.5 cm. Sutures closed. No seizures. Muscle tone in arms and legs physiological. Full hip abduction. Feeding via gastric tube with NaN1 + colostrum. Skin pale pink, face cyanotic, moist, pustules with purulent-hemorrhagic contents present on the scalp, face, behind the ears, fingers, axillae, and groin, some with firm-elastic infiltrates, elevated up to 0.8 cm in diameter, some ruptured with eroded surfaces. Visible mucous membranes clean, pink. Conjunctivae calm. Generalized edema. Peripheral lymph nodes not enlarged. Auscultation: breath sounds weakened, no rales. Percussion: lung sound. Heart sounds rhythmic, clear, systolic murmur at the apex. Femoral pulses palpable bilaterally, satisfactory filling. Abdomen soft, non-tender. Bowel sounds present. Umbilical stump dry, clean. Liver +1.0 cm. Spleen not enlarged. Meconium stool. Urine output monitored. Treatment continued as per orders.

Day 3: Skin pink with jaundice, petechiae on the forehead. Multiple ruptured lesions with crusting on the body and scalp; firm hemorrhagic lesions persist on the index fingers, left axilla, right shoulder, left little toe, and lower lip mucosa with serous-purulent discharge. No new eruptions.

Day 6: A consultation was held with neonatologists, a pulmonologist, and an allergist-immunologist. Further examinations were recommended, including consultations with a dermatovenereologist, geneticist, and tests for Krec, Trec, ANA, anti-denatured DNA, and complement C4.

Additional consultations: Ophthalmologist retinal angiopathy. Head ultrasound moderate periventricular hyperechogenicity. Abdominal and cervical spine ultrasound no abnormalities. Thymus ultrasound enlarged thymus with diffuse parenchymal changes resembling calcifications.

Skin pale, petechiae on the forehead fading. Multiple ruptured lesions with necrosis and hemorrhages on the body, scalp, and shoulders; firm hemorrhagic lesions persist on the left little toe and

lower lip mucosa as an ulcer with serous-purulent discharge. No new eruptions.

Lab results: CRP elevated to 15 mg/L. Staphylococcus saprophyticus and Enterococcus faecalis isolated from umbilical blood; Enterococcus faecalis (10^3 CFU) and E. coli (10^4 CFU) from skin. Coagulogram showed moderate hypocoagulation, prolonged prothrombin time. [Per cardiologist-rheumatologist recommendation, a chest CT was performed: lung volume preserved. Uneven lung aeration. Multiple foci of consolidation in both lungs, some with cavitation. Bronchial lumens narrow. No pleural effusion. No enlarged intrathoracic lymph nodes. Thymus heterogeneous, with hyperdense and hypodense inclusions, enlarged. Transverse thymus size: 6.4 cm, coefficient 0.87. Conclusion: CT findings consistent with bilateral polysegmental destructive pneumonia. Thymomegaly grade 3.] Given CRP elevation to 15 mg/L, ampicillin/sulbactam was increased to 150 mg/kg/day IV in 3 divided doses. Hemostatic therapy: sodium etamsylate 12.5% 10 mg/kg, 0.3 mL IV 4 times; menadione sodium bisulfite 1% 0.3 mL IM once. Immunomodulatory therapy: Viferon-1 150,000 IU twice daily rectally. Local treatment: 1% potassium permanganate solution for ruptured lesions.

Day 9: Second consultation with neonatologists, pulmonologist, and allergist-immunologist. Recommendations: PCR urine for fungi to rule out fungal pneumonia; microscopy for fungi (urine, throat, stool); stool for opportunistic flora; consultations with a surgeon and geneticist; referral for telemedicine consultation to the "Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology, and Immunology" and the "V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology."

Microscopy: isolated fungi in throat swab, none in stool or urine. CRP elevated to 33.54 mg/L. COVID-19 ELISA negative. Consulted by a surgeon, dermatovenereologist, and geneticist. Dermatovenereologist's diagnosis: Pyoderma. Geneticist's diagnosis: Unspecified congenital infectious disease. Pyoderma. Congenital immunodeficiency not excluded.

Gentamicin was added at 7.5 mg/kg/day in 2 divided doses (2.5 mg/kg 3 times daily). Antifungal therapy per clinical guidelines "Invasive Candidiasis in Newborns": fluconazole (Diflucan) 6 mg/kg/72 h IV.

Day 12: Telemedicine consultation with specialists from the "V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology." Given the characteristic skin lesions from birth, their distribution, and clinical progression, Langerhans cell histiocytosis Hashimoto-Pritzker syndrome could not be ruled out. Further differential diagnosis was recommended. Treatment: switch antibiotics to vancomycin + sulperazon; use only aqueous disinfectants for skin lesions; treat erosions with "Sudocrem," "Bepanthen ointment," or zinc ointment.

Following the consultation, a clinical pharmacologist at the M.E. Nikolaev Republican Hospital No. 1-NCM recommended against vancomycin due to severe intrauterine pneumonia, high CRP (33.54 mg/L), and isolation of Staphylococcus saprophyticus and Enterococcus faecalis resistant to clindamycin, cefoxitin, moxifloxacin, and ciprofloxacin. Cefoperazone/sulbactam was prescribed per empirical antibiotic therapy protocol at 40 mg/kg/day in 2 divided doses with IV test dose. Gentamicin continued at 7.5 mg/kg/day in 2 divided doses (2.5 mg/kg 3 times daily). Sodium etamsylate was discontinued due to normalized coagulogram. Antifungal therapy with fluconazole and local skin treatment continued.

Day 14: Skin pale pink. Multiple pale red-pink papules and nodules in regression with crusting on the face, scalp, trunk, and limbs, treated with fucorcin. Single ulcer on the lower lip mucosa in epithealization phase. No new eruptions; significant skin improvement. Healing lesions behind the ears, buttocks, and calves.

Day 16: Condition improved, child more active, pinker, less shortness of breath, no oxygen dependence, skin lesions regressing. Mixed feeding, appetite preserved. Skin pale pink, one vesicle forming on the nose tip; old lesions fading with residual pigmentation, single crusts on the left little toe and hand. Infiltrate on the right shoulder reduced in size, softer. Given clinical improvement and CRP decrease to 29 mg/L, gentamicin was discontinued. After a second telemedicine consultation with the "Dmitry Rogachev National Medical Research Center," viral etiology could not be excluded, so acyclovir was added at 20 mg/kg/day IV in 3 divided doses. Cefoperazone/sulbactam, fluconazole, and local skin treatment continued. Surgery performed to remove the lesion on the right shoulder; specimen sent for histology.

Day 17: Third consultation with the deputy director of neonatology, neonatologists, clinical pharmacologist, pulmonologist, and allergist-immunologist. Decision: continue antibiotics, withhold meropenem + vancomycin given stable clinical picture and declining CRP. Continue fluconazole and acyclovir. Per telemedicine consultation with the "Dmitry Rogachev National Medical Research Center," IV immunoglobulin was added at 1 g/kg over 2 days.

Day 20: Skin pale pink. Lesions resolving with residual pigmentation; crusts shed from the left little toe and hands; crusts persist on the middle finger and scalp, healing. Postoperative wound on the right shoulder, sutures intact. Oral mucosa infiltrate reduced. Day 23: Skin pale pink, residual pigmentation at lesion sites, no new eruptions. Postoperative wound on the right shoulder clean, sutures intact.

At 1 month of age, histology results: Langerhans cell histiocytosis. H&E: 4 IHC: CD1a, Langerin, S100. The report was sent for telemedicine consultation to the "Dmitry Rogachev National Medical Research Center" and the "V.I. Kulakov National Medical Research Center" for further management recommendations.

Conclusion. Based on histology, the diagnosis was confirmed: C96.6 Langerhans cell histiocytosis. The child was transferred from the neonatal pathology department to the oncology unit for specialized treatment. Langerhans cell histiocytosis in newborns presents significant diagnostic challenges due to nonspecific clinical presentation. The gold standard for diagnosis is histological examination with immunohistochemical confirmation. Treatment must be comprehensive, considering the extent of involvement, patient age, and molecular-genetic features. An interdisciplinary approach involving neonatologists, oncologists, immunologists, and other specialists improves prognosis.

Future research should focus on molecular mechanisms of LCH in newborns, developing targeted therapy protocols for this age group, and creating a registry for rare cases.

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STOMACH CANCER AND PREGNANCY

Stomach cancer during pregnancy is extremely rare and accounts for 0.025-0.1% of all pregnancies, while most cases of stomach cancer associated with pregnancy are diagnosed by specialists at a late stage, since its main symptoms (vomiting, nausea, loss of appetite, increased abdominal size) are mistaken for early toxicosis during pregnancy and the likelihood of the development of malignant neoplasms is underestimated. Survival rates for stomach cancer are directly related to its early diagnosis, in such a situation, doctors face two problems: the need to treat stomach cancer in the mother and prolonging pregnancy. Optimal management of this category of patients requires a multidisciplinary approach (including oncologist, obstetrician, surgeon, anesthesiologist, gastroenterologist, radiologist and neonatologist), which establishes the sequence of therapy. Psychological supportive therapy should not be neglected, since the patient's decision is crucial, while the woman's decision is very much connected with the survival of the fetus, sometimes with her victim. In the article, we presented our own experience of treating and monitoring this category of patients in the form of two clinical cases that clearly demonstrate an extremely unfavorable prognosis for a combination of stomach cancer and pregnancy. According to the literature, the five-year survival rate in this category of patients is zero, while in most cases the patient's death occurs within six months after surgery.

Keywords: cancer, stomach, pregnancy, treatment, prognosis

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Stomach cancer (SC) is one of the most common types of cancer with very specific ethnic and socio-economic features in the incidence. According to GLOBACAN, in 2021, about 1 million new cases of stomach cancer were reported worldwide, and almost 70% of them occur in developing countries, most of which are located in East Asia. Known risk factors for stomach cancer include: old age, smoking, ethnicity and geography, a history of gastric ulcers and Helicobacter pylori, immunosuppressive disease, gastroesophageal reflux disease, and obesity. This pathology is more common in men and is diagnosed on average at the age of 70, but in 1% of cases it is registered in people younger than 34 years [1, 2]. Stomach cancer is diagnosed according to the TNM classification system of the American Joint Committee on Cancer / Union of the International Fight against Cancer, depending on the size of the tumor (T), invasion of lymph nodes (N) and metastatic lesion (M). Early SC (at stage I) is limited to the mucous membrane or submucosa (T1), while the tumor is considered clinically localized after invasion of the muscular layer (T2). In stage II, the lymph nodes are affected and (or) the tumor spreads to the subserous or serous membrane. At stage III, the tumor grows into both the (sub)serous membrane and the lymph nodes; at stage IV, it spreads to neighboring organs with damage to the lymph nodes of other areas or distant metastasis occurs. The distribution by stage in the general population of patients with stomach cancer is as follows: 21.6% – stage I, 22.3% – stage II, 44.0% – stage III and 12.1% – stage IV [3]. Stomach cancer during pregnancy is extremely rare and, according to various authors, accounts for 0.025–0.1% of cases. The main inducing factors are: Helicobacter pylori infection, specific susceptibility due to genetic changes in inflammatory mediators to Helicobacter pylori. Most cases of pregnancy-related stomach cancer are diagnosed in the late stages, as its main symptoms (nausea, vomiting, loss of appetite) are mistaken for early toxicosis, and the likelihood of developing SC is underestimated. There are contraindications to instrumental examinations during pregnancy, which can complicate its course, therefore, in most cases, diagnosis and treatment are carried out at a later date. Survival rates in

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SC are directly related to its early diagnosis. In such a situation, doctors face a dilemma: the need to treat SC in a pregnant woman and prolong pregnancy. The most common symptoms of stomach cancer, with the exception of weight loss and melena, are common during pregnancy and do not attract the attention of doctors and patients themselves [4, 5]. Nausea and vomiting often begin a few weeks after the start of the first trimester, then peak simultaneously with the peak of HCG production between the 10th and 16th weeks of pregnancy and subside by the 20th week. However, up to 10% of pregnant women may not have symptoms until the 22nd week. Another hormone associated with this clinical picture is PGE2, which affects the smooth muscles of the stomach. The highest level of PGE2 during pregnancy is observed between the 9th and 12th weeks [2, 6]. Hyperemesis is a severe form of nausea and vomiting associated with the loss of more than 5% of body weight before pregnancy, dehydration and electrolyte imbalance. It begins before the 22nd week of pregnancy, affects 0.3–2.0% of pregnant women and in some cases requires hospitalization [2, 7]. In a Canadian population-based cohort study conducted by D.B. Fell et al. (2006), an increased risk of pregnancy hyperemesis associated with hyperthyroidism, mental illness, previous molar pregnancy, diabetes mellitus, and a history of asthma was identified [3]. Timely diagnosis of SC is often difficult, as up to 80% of patients have an asymptomatic course in the early stages. If nausea and vomiting continue until the 20th week of pregnancy, then doctors should pay special attention to this. Currently, three main causes of vomiting are described in the literature. Firstly, high levels of hCG can have a stimulating effect on the secretory process in the upper gastrointestinal tract. In addition, estrogen stimulation increases the production of thyroid-binding globulin, which leads to a decrease in the level of free thyroxine (T4). A transient decrease in free T4 levels causes thyroid stimulation, and the patient may develop transient gestational thyrotoxicosis, which leads to vomiting. Secondly, HCG is similar in its action to thyroid-stimulating hormone (TSH) and may cause hyperemesis by stimulating the TSH receptor [8, 9]. Thirdly, there is a negative relationship between prolactin levels and nausea/vomiting, while estrogens show a positive relationship. Consequently, higher estrogen levels during pregnancy may increase the risk of hyperemesis [10, 11, 12]. The condition is usually accompanied by hyponatremia, hypokalemia, low serum urea, elevated hematocrit, metabolic hypochloremia, alkalosis, and ketonuria. The level of liver enzymes can be increased by almost 2 times. Such patients are usually diagnosed with exicosis, they suffer from food intolerance and weight loss due to prolonged vomiting [6, 13]. In the study by M.J. Song et al. (2016) revealed that 25% of patients had abdominal pain, 20% had nausea and vomiting, and the rest had bleeding and symptoms of metastasis [7]. T. Cift et al. (2011) recommend an X-ray examination of the stomach of pregnant women complaining of epigastric pain, refractory nausea and vomiting that occur during pregnancy of more than 16 weeks [8]. Bleeding from the upper digestive tract (described in 20% of cases of stomach cancer) may be associated with Mallory–Weiss syndrome, the most common cause of vomiting blood during pregnancy [9, 14]. However, there are no protocols in the literature for optimal endoscopy in pregnant women with nausea and vomiting in the first trimester, when HCG and PGE2 levels reach their maximum values.

In the case of an acute complication of SC (perforation or bleeding), specific clinical signs appear with severe consequences for both the pregnant woman and the fetus. In such situations (vomiting with blood, melena), urgent surgical treatment is required.

Thus, the clinical component of the diagnosis of prostate cancer is quite complex: the initial symptoms are nonspecific, they can develop over a long period of time, and they are often mistakenly attributed to other pathologies. In most patients, the initial forms of prostate cancer are either asymptomatic or have non-specific symptoms of stomach diseases (non-ulcerative dyspepsia, peptic ulcer). The diagnosis of advanced stages of prostate cancer becomes obvious due to complications of the disease [5, 15].

If stomach cancer is suspected in pregnant women, fibroesophagogastroduodenoscopy with biopsy is recommended. CT scans of the abdominal organs in the first trimester are undesirable due to exposure to ionizing radiation. Magnetic resonance imaging is considered a relatively safe method of investigation because it avoids exposure to ionizing radiation on the patient and fetus and often does not require intravenous administration of a contrast agent. Treatment depends on the duration of pregnancy and the stage of stomach cancer. In addition, when choosing a treatment method, the choice of a woman to have a child is an important factor. Surgical intervention during pregnancy should not be postponed if the woman's health and the outcome of the disease depend on it. [10, 12, 13, 16].

Despite its rarity, stomach cancer diagnosed during pregnancy can pose a fatal clinical situation for the pregnant woman and the fetus: patients with stomach cancer diagnosed during pregnancy have an unfavorable prognosis. This may partly be due to the fact that most cases of stomach cancer associated with pregnancy are diagnosed in the late stages, and only 45-56% of patients undergo surgery.

Optimal management of this category of patients requires the work of a multidisciplinary team (including an oncologist, an obstetrician-gynecologist, a surgeon, an anesthesiologist, a gastroenterologist, a radiologist and a neonatologist) who will establish the sequence of therapy. Psychological supportive therapy should not be neglected, since the patient's decision to maintain pregnancy is crucial [17].

One of the largest studies on this problem was published in May 2023 [13]. This review is based on an analysis of the results of relevant studies and articles published over 23 years (from 2000 to 2022), hosted by Embase, PubMed Central, Cochrane Library and MEDLINE Complete. Analyzing the data from this study, we can formulate the main recommendations for the management of this category of patients.

The following tactics of managing patients with stomach cancer during pregnancy have been determined: in the first trimester, with an operable tumor, termination of pregnancy followed by surgical treatment of stomach cancer is indicated. If the patient is in the second trimester of pregnancy, it is recommended to perform a simultaneous gastric resection and a small caesarean section. In the third trimester, if the fetus is viable, a simultaneous gastric resection with cesarean section is performed. If an inoperable tumor is diagnosed, only palliative treatment is possible [18, 19]. The presence of metastases in the ovaries is not a contraindication for gastric surgery. A wait-and-see approach is strongly discouraged in case of operable prostate cancer, as it is difficult to predict the rate of tumor growth and spread. With advanced SC, when the prognosis for a pregnant woman is unfavorable, the life of the unborn child becomes a priority choice. Two studies have found that pregnancy is a "psychological obstacle to the correct diagnosis of stomach cancer." Women suffering from gastric ulcer are recommended to undergo medical or surgical treatment

before conception, otherwise constant endoscopic monitoring with targeted biopsy is necessary throughout pregnancy [20, 21].

As for cytotoxic agent therapy, there is a problem of its effectiveness associated with physiological changes in a woman's body during pregnancy (redistribution of circulating blood volume, changes in hepatic clearance, increased renal elimination due to a decrease in binding protein levels, a decrease in albumin). However, there are currently no dosage recommendations other than those for non-pregnant women. The doses of chemotherapy drugs should be recalculated as body weight and gestation period increase [22, 23]. Teratogenic and mutagenic effects are among the most feared long–term complications. The risk of carcinogenesis over time appears to be critical. The toxic effect on the fetus may result from the penetration of cytostatics through the maternal-fetal barrier. The fetal liver will be metabolized, and the kidneys will remove toxins into the amniotic fluid, from where they can be swallowed by the fetus and reabsorbed into the gastrointestinal tract. The most studied teratogens are anthracyclines found in the placenta, umbilical cord, and fetal tissues [91].

The risk of using cytostatics during pregnancy is classified by the FDA into two categories: C and D [15, 17, 14, 24].

The standard cytostatic treatment for primary prostate cancer consists of a combination of platinum and fluoropyrimidine, such regimens as FOLFOX (folinic acid (FOL), 5-fluorouracil (F) and oxaliplatin (OX)), CAPOX (capecitabine, oxaliplatin), ECF/ECC (epirubicin, cisplatin, 5-fluorouracil/capecitabine) or EOX (epirubicin, oxaliplatin, capecitabine). Trastuzumab combinations can be prescribed for gastric cancer with overexpression of the HER2 gene. Alternatively, it is possible to use taxane-based schemes, for example, FLOT (docetaxel, leucovorin, oxaliplatin, 5-fluorouracil) [16, 17]. The progress of neoplasia is probably enhanced by hyperestrogenism. Estrogen receptors (ER) are detected in 22% of tumor cells, especially in the low-grade type. Estrogen receptors in gastric cancer, unlike in other target organs, such as the breast, seem to be a sign of the tumor's adaptation to treatment.

Neoadjuvant chemotherapy is recommended during pregnancy at 10 to 28 weeks of age for stage II and III tumors. In addition to surgery, adjuvant therapy is recommended, usually after childbirth [17, 25].

As for radiation therapy, this option is not recommended for the treatment of patients with SC associated with pregnancy.

Over time, new descriptions of the combination of stomach cancer and pregnancy have appeared in the literature. In 1962 Molinie summarized 33 observations, in 1974 Verhagen provided 84 descriptions, and in 1978 Querleu reported 127 such cases [14]. The clinical picture most often shows a lack of appetite, nausea, vomiting, a feeling of heaviness and pain in the epigastrium. The pain is similar to that of peptic ulcer. At the same time, almost all the symptoms are unstable, the clinic is lubricated by anemia. The diagnosis is based on fibrogastroscopy with targeted biopsy. In almost 90% of cases, the diagnosis of stomach cancer is established in the second and third trimesters of pregnancy. Late diagnosis, disease progression, and a high risk of termination of pregnancy worsen the prognosis for mother and fetus [23]. In pregnancy-associated SC, only 38% of babies are born alive. In some cases, metastatic lesions were observed in the placenta and in the newborn. The prognosis for the mother remains extremely unfavorable: the five-year survival rate for combined SC and pregnancy is only 2.9% [17].

S. Maggen et al. (2020) conducted an analysis of patients with SC in combination with pregnancy for the period from 2002 to 2018. A total of 13 women were registered. The minimum gestation period of the patients at the time of diagnosis was 6 weeks, the maximum was 30 weeks. 12 out of 13 women were diagnosed with II–

Stage IV of the disease. In total, eight out of 10 live births ended in premature birth due to preeclampsia and deterioration of the mother's condition. Two out of six women who started chemotherapy during pregnancy gave birth on time.

Two newborns who underwent chemotherapy prenatally had growth retardation, and one of them developed a systemic infection with a brain abscess after preterm birth due to preeclampsia 2 weeks after chemotherapy [17]. According to the results of the study, it was also confirmed that the prognosis of the course of prostate cancer during pregnancy is poor, mainly due to the late stage of the disease at the time of diagnosis. Taking into account possible complications such as growth retardation, premature birth and suppression of hematopoiesis at birth, it is advisable to prescribe chemotherapy after delivery.

Thus, stomach cancer during pregnancy is a rare diagnosis. Women usually go to the doctor in the late stages of the disease and have a poor prognosis. Pregnant women with persistent gastrointestinal symptoms that cannot be explained solely by pregnancy should have a low threshold for further diagnostic procedures. When balancing the risks to the patient and the fetus, the possibility of starting chemotherapy may be considered. An interdisciplinary approach is needed to make adequate decisions in this difficult and rare situation.

We present clinical cases of observation and treatment of patients who were conducted on the basis of the Tomsk regional oncological dispensary.

Clinical observation 1

Patient K., 28 years old, turned to an oncologist at the direction of an obstetrician-gynecologist at the Tomsk Regional Perinatal Center . The patient complained of periodic nagging pains in the lower abdomen, periodic nausea and vomiting. At the time of treatment, the woman was found to be 16-17 weeks pregnant. According to ultrasound and MRI of the pelvic organs, bulky ovarian formations of a solid nature were detected, up to 14 cm in size on the right, up to 16 cm on the left, with limited mobility. Tumor markers CA-125 = 35.82 IU, HE-4 = 41.44 pmol/L. Upon further examination according to fibrogastroduodenoscopy: at the level of the border of the upper and middle third of the stomach body, a tumor formation in the form of a flat ulcerative defect with a convergence of folds up to 1.5 cm in diameter and an infiltration zone along the perimeter is determined by a large curvature. A biopsy of 4 fragments was performed: the tissue is dense, the gastric lumen is moderately stenosed at this level. The epithelium of the subcardia and the fundus of the stomach corresponds to the fundus type of structure. The gatekeeper does not close, the lumen of the gatekeeper channel is not changed, oval in shape, freely passable for the device. The bulb of the duodenum (duodenum) is capacious, slimy, and finely fibrous. The post-bulbar section has a smooth angle. The large duodenal papilla is located behind the guard hood of the duodenal mucosa, bile is supplied in portions. Conclusion: Insufficiency of the lower esophageal sphincter. Epithelial formation of the O-Is esophageal transition zone. A tumor of the middle third of the stomach body. Moderate tumor stenosis of the stomach. Chronic duodenogastric reflux.

Histological conclusion based on the results of biopsy of the gastric mucosa: the preparations contain fragments of the gastric mucosa with the presence of a large number of discrete tumor cells and small tubule-like structures, cells with

pronounced polymorphism, and atypical mitoses. The stroma is pronounced, represented by fibrous-muscular layers. An IHC study was conducted using the Leica Bond Max immunostainer (USA) (in sections from the paraffin block: the bright expression of Cytokeratin 7 (clone OV-TL, Dako, Germany) is detected in tumor cells. There is no expression of c-erB-2 (Her2/neu) in tumor cells (Polyclonal Rabbit, Dako, Germany).

Conclusion: Gastric adenocarcinoma, High Grade (ICD-O code 8140/3). c-erB-2 (Her2/neu) tumor status is negative (0).

A consultation was held on the basis of the Tomsk OPC with the participation of oncogynecologists from the Research Institute of Oncology of the Tomsk NIMC and the Tomsk OOD. According to the results of the consultation, the patient was given explanations on the clinical picture, the features of the course, the prognosis and possible treatment methods. The woman agreed with the proposal about the need for surgical treatment with simultaneous termination of pregnancy.

The patient underwent surgical intervention in the following areas: adhesiolysis, extirpation of the uterus with appendages, extirpation of the large omentum, peritoneal biopsy, drainage of the abdominal cavity.

In the postoperative period, on the 8th day, complications arose in the form of small intestinal obstruction, in connection with which a relaparotomy, dissection of adhesions, and drainage were performed.

Histological conclusion based on postoperative material: fragments of the uterine wall with immature placenta structures. The placenta is mostly represented by longitudinal and transverse sections of intermediate mature villi with the presence of vessels. Cell-free fibrinoid deposits are detected in the interstitial space. The basal plate is represented by a layer of Rohr with cytotrophoblast fields, cytotrophoblast cells with their obstruction are detected in the lumen of spiral arteries and veins. Areas of necrosis with focal leukocyte infiltration are noted in a number of visual fields. Fragments of a large omentum with uneven blood filling of blood vessels, small diapedous hemorrhages, focal lymph and leukostasis. There are foci of inflammatory infiltration, represented by lymphocytes and a few segmented leukocytes. No tumor cells were found.

The preparations labeled as "fragments of the peritoneum" revealed signs of subacute inflammation, represented by dilated vessels with erythrostases, diapedous hemorrhages. Fibrin filaments are detected on the surface of the peritoneum. There is diffuse moderate infiltration in the thickness, represented by macrophages, fibroblasts, lymphocytes and single neutrophilic leukocytes. Fragments of the fallopian tube with uneven blood vessels. In the formations of the right and left ovaries Krukenberg's metastases have been identified. The histological pattern in both ovaries is identical. In the stroma of numerous cystic cavities, areas of an invasive tumor are identified, represented by tubular structures of various shapes and sizes lined with multi-row epithelium. Atypical cells are moderately polymorphic with normochromic rounded nuclei and moderate eosinophilic cytoplasm. Between the glandular structures, in the desmoplasmic stroma, small tumor clusters and individual discretely located tumor cells are detected.

An IHC study was performed using a Leica Bond Max immunostainer on sections from paraffin blocks. The tumor cells show diffuse bright expression of Cytokeratin 7 (clone OV-TL, Dako, Germany), CDX2 (clone DAK-CDX2, Dako, Germany), moderate cytoplasmic expression of PAX8 (Poly-clonal, Cell Marque, USA). There is no expression of CA125 (clone Ov185:1, Leica, Germany), Wilms'TUMOR (clone 6F-H2, Dako, Germany), Calretinin (clone CAL6, Leica), Inhibin (clone R1, Dako), CD 56 (clone 123C3, Dako), Progesterone receptor (clone PgR636, Dako), Napsin A (clone of IP64, Leica).

Conclusion: Gastric adenocarcinoma, High Grade (ICD-O code 8140/3). c-erB-2 (Her2/neu) tumor status is negative (0). Krukenberg metastases in both ovaries. No tumor cells were found in the peritoneum and omentum.

After receiving the histological findings, a consultation with a chemotherapist was conducted. It is recommended to carry out polychemotherapy according to the scheme: paclitaxel + carboplatin. The patient underwent three courses of polychemotherapy.

4 months after the surgery, the woman died.

The second clinical case is almost identical to the first, but the tumor process was verified at a later stage of pregnancy.

Clinical observation 2

Patient Yu., 32 years old, turned to an oncologist at the Tomsk OOD in the direction of an obstetrician-gynecologist.

From the medical history: the patient had no previous gynecological diseases, this is the first pregnancy. The family history is burdened by his father's side – stomach cancer. The patient complained of aching, pulling pains in the lower abdomen, which were practically not relieved by antispasmodics and tocolytics. During pregnancy, the woman suffered from frequent nausea and vomiting, but considered it a normal discomfort associated with pregnancy. The patient was under the supervision of a doctor at a women's clinic, and previous examinations did not reveal any pathological abnormalities.

Pain in the lower abdomen, corresponding to premature contractions of the uterus, began at the 29th week of pregnancy, the intensity of pain increased over the last 2 weeks, at the time of treatment, the pain was almost constant, mostly of moderate intensity.

In terms of follow-up, ultrasound and MRI of the pelvic and abdominal organs were performed: moderate ascites and a single homogeneous formation in the left ovary with suspected torsion were detected. Upon additional examination, fibrogastroduodenoscopy revealed a stomach tumor with extensive local spread. Histological conclusion: gastric adenocarcinoma of low degree of differentiation, c-erB-2 (Her2/neu) tumor status is positive.

A consultation was held on the basis of the Tomsk OPC with the participation of oncologists from the Tomsk OOD, as a result of which a decision was made to conduct surgical treatment.

At the 33rd week of pregnancy, surgical treatment was performed in the following volume: cesarean section, adnexectomy on the left (during the revision, a leg twist was revealed), a biopsy of the contralateral ovary, and a biopsy of the peritoneum. A live girl was born, her birth weight was 1620 g, and the Apgar score was 7 and 9 points on the 1st and 5th minutes after birth.

Intraoperatively, the following features were identified: moderate ascites, multiple metastatic formations of various diameters on the large omentum, multiple metastases on the surface of the liver and the peritoneal peritoneum. The left ovary was tightly attached to the uterine wall and fixed to the peritoneum. Histological conclusion: data for Krukenberg's tumor, diffuse infiltration of poorly adhering cells with abundant intracytoplasmic mucin and eccentric nuclei was detected in the tumor of the left ovary.

The course of the postoperative period was smooth, without any special features. Histological conclusion based on the results of biopsy of the peritoneum and large omentum: the presence of multiple metastatic lesions.

The patient was finally diagnosed with stage IV gastric adenocarcinoma.

Due to the inoperable process, a chemotherapist was consulted, and palliative chemotherapy courses were prescribed according to the scheme: oxaliplatin + 5-fluoro-uracil.

The patient died 2 months after giving birth. The child is alive, currently growing and developing according to age.

Thus, both presented cases clearly demonstrate an extremely unfavorable prognosis with a combination of stomach cancer and pregnancy. According to the literature, the five-year survival rate in this category of patients is zero, while in most cases the patient's death occurs within six months after surgery.

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