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Address:
677000, Yakutsk, 6/3 Yaroslavsky Str.,
Phone: (4112) 31-9394,
e-mail: yscredactor@mail.ru
ymj-red@mail.ru
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ORIGINAL RESEARCH

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E.R. Veisenborn, E.A. Kazachkova, E.E. Voropaeva,
E.L. Kazachkov, L.S. Ischenko, I.V. Safronova

MEDICAL AND SOCIAL CHARACTERISTICS OF PREGNANT WOMEN WHO UNDERWENT COVID-19 AT THE PREGRAVIDAR STAGE

The pandemic of the new coronavirus infection COVID-19 (COVID-19) has had a significant impact on public health, including the reproductive health of women. There is little information on the impact of COVID-19, carried in the pregravidar period, on the course of pregnancy. The medical and social profile, somatic and reproductive health parameters of pregnant women who underwent COVID-19 at the pregravidar stage 6-12 months before pregnancy have not been studied. However, this information may be of significant importance for a preventive approach to the tactics of patient management at the stage of preparation for pregnancy and during gestation.

Keywords: medical and social profile, somatic pathology, new COVID-19 coronavirus infection, pregravidar stage.

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Introduction. The COVID-19 pandemic has had a significant impact on the reproductive health of women [2, 7]. Direct infection with the SARS-CoV-2 virus, immune-mediated damage to the

vascular endothelium, tissues of the bronchopulmonary system, heart, intestine, brain, liver and other organs leads to multisystem manifestations of COVID-19 and clinical polymorphism [1, 22]. With COVID-19, inflammasomes are activated, there is an increase in the levels of pro- and anti-inflammatory immunoregulatory cytokines [6, 23], and endothelial dysfunction develops. The latter leads to vasoconstriction, increased vascular permeability, impaired microcirculation, microthrombosis, hemorrhagic infarctions, necrosis and multiple organ disorders [16]. In pregnant women who have had COVID-19 during gestation, placental damage is formed, contributing to the development of placenta-associated complications [8, 14]. It is known that this infection leads to long-term consequences (post-COVID complications) in a number of patients, the development mechanisms of which are chronic systemic inflammation with an autoimmune component, endothelial dysfunction, thrombosis and hypoxia. Long-term consequences can be metabolic, cardiovascular, neurological disorders, decreased fertility [10, 11, 12, 17, 19, 21]. Information on the impact of COVID-19 suffered in the pregravid period on the course of pregnancy is scarce. Thus, in the study by N.A. Frankevich [13] it was shown that patients who had recovered from the disease at the pregravid stage had worse obstetric and perinatal outcomes, in particular, if pregnancy occurred less than two months after COVID-19, a decrease in the frequency of live births was

observed, which is possibly due to a large proportion of low-quality embryos. In patients with a severe form of the disease, the risk of pregnancy loss before 12 weeks increased by 5 times, and the risk of late preeclampsia - by 7.7 times, which can affect perinatal outcomes. In this regard, patients are advised to postpone pregnancy planning for 2-6 months in order to minimize the risk of obstetric complications. At the same time, the medical and social profile, the features of the somatic and reproductive health of patients who have had COVID-19, planning pregnancy within 6-12 months after COVID-19 have not been studied. At the same time, knowledge and analysis of the data of the medical and social profile, somatic and reproductive health of patients will substantiate the approach to the tactics of patient management at the stage of preparation for pregnancy and during gestation.

Aim: to determine the medical and social portrait, parameters of somatic and reproductive health of pregnant women who had COVID-19 at the pre-pregnancy stage 6-12 months before pregnancy.

Materials and methods. A retrospective cohort study of 265 pregnant women observed in 2021-2024 at the State Autonomous Healthcare Institution "Regional Clinical Hospital No. 3" in Chelyabinsk was conducted. An analysis of medical documentation was carried out: individual medical records of pregnant women and women in labor, birth histories, medical records of patients receiving medical care on an outpatient basis. Medical

FSBEI HE South Ural State Medical University of the Ministry of Health RF: **VEISENBORN Elena Romanovna** – postgraduate student of the Department of Obstetrics and Gynecology, ORCID: 0009-0004-8375-9991, okb3gk2@mail.ru; **KAZACHKOVA Ella Alekseevna** – MD, Professor of the Department of Obstetrics and Gynecology, ORCID: 0000-0002-1672-7058, Doctorkel@narod.ru; **KAZACHKOV Evgeny Leonidovich** – MD, Professor, Head of the Department of Obstetrics and Gynecology, Department of Pathological Anatomy and Main Medicine, ORCID: 0000-0002-4512-3421, Doctorkel@narod.ru; **SAFRONOVA Irina Vladimirovna** – PhD, Associate Professor of the Department of Mathematics, Medical Informatics, Informatics and Statistics, Physics, ORCID: 0000-0003-3604-9319, safronova94@gmail.com; **VOROPAIEVA Ekaterina Evgenievna** – MD, PhD, Professor of the Department of Pathological Anatomy and Forensic Medicine, FSBEI HE South Ural State Medical University of the Ministry of Health RF, Deputy Chief Physician for Obstetrics and Gynecology of the State Budgetary Healthcare Institution Regional Clinical Hospital No. 2, ORCID: 0000-0002-9055-102X, katya_voropaeva@mail.ru; **ISHCHENKO Lyudmila Stanislavovna** – MD, PhD, Associate Professor of the Department of Obstetrics and Gynecology FSBEI HE South Ural State Medical University of the Ministry of Health RF, obstetrician-gynecologist SBHI Regional Clinical Hospital No. 2, ORCID: 0000-0002-9405-0134, lyudalyn@mail.ru.

and social characteristics, the state of somatic and reproductive health were studied. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "South Ural State Medical University" of the Ministry of Health of the Russian Federation. The main group consisted of 152 patients who had COVID-19 in the pregravid period 6 to 12 months before pregnancy; the comparison group included 113 women who did not have COVID-19 during the pandemic and were not vaccinated against COVID-19. Inclusion criteria for the main group: documented fact of COVID-19 (U07.1) 6 to 12 months before pregnancy, availability and accessibility of medical records, observation at a antenatal clinic, reproductive age. Exclusion criteria: probable / suspected case of COVID-19 (U07.2/Z03.8), lack or inaccessibility of medical records, multiple pregnancy, HIV infection, psychiatric diseases, somatic pathology in the decompensation stage, malignant tumors. Inclusion criteria for the comparison group: no history of confirmed, probable, or suspicious COVID-19, observation at a women's clinic, reproductive age, availability and accessibility of medical documentation. Exclusion criteria: severe extragenital pathology in the decompensation stage, oncopathology, HIV infection, psychiatric illness, multiple pregnancy.

The severity of COVID-19 suffered by the patient was assessed based on the document of the Ministry of Health of the Russian Federation - "Temporary guidelines "Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19). Version 18 (26.10.2023)".

Statistical analysis of the study results was carried out using Microsoft Excel 2016 spreadsheets. The characteristics of qualitative indicators are presented as absolute numbers and relative values in percent. Statistically significant differences in proportions were determined using the z-test. The normality of the distribution was assessed based on the Pearson test. Quantitative features of the estimated values that obey the normal distribution law are presented as the mean value (M) and standard deviation (m). Statistically significant differences were assessed using the Student t-test. The critical level of significance was taken as $p=0.05$.

Results and discussion. Patients of the main group had acute COVID-19 6-12 months before pregnancy: mild form – 98 / 152 (64.5%), moderate form – 42 / 152 (27.6%), severe form – 12 / 152 (7.9%). At the same time, COVID-asso-

ciated pneumonia was observed in 21 / 152 (13.8%) women, of which 18 (85.7%) received in-hospital treatment according to temporary guidelines that were relevant at the time of supervision.

The age of patients in both groups corresponded to early reproductive age: in the main group, the average age was 32.2 ± 0.63 , in the comparison group – 31.5 ± 0.71 , which did not have statistically significant differences. In both groups, women belonged predominantly to the East Slavic ethnic group, which prevailed in the main group: 135 / 152 (88.8%) and 86 / 113 (76.1%) ($p=0.01$). Most patients in both groups lived in the Chelyabinsk region: in the main group – 105 / 152 (69.1%), in the comparison group – 87 / 113 (77.0%) ($p=0.15$), in the city of Chelyabinsk – 47 / 152 (30.9%) and 26 / 113 (23.0%) ($p=0.15$), respectively. A total of 74 / 152 (48.7%) patients in group 1 and 42 / 113 (37.2%) patients in group 2 had higher education ($p=0.06$), incomplete higher education – 4 / 152 (2.6%) and 2 / 113 (1.8%) – respectively in the groups ($p=0.64$), secondary general education – 28 / 152 (18.4%) and 49 / 113 (43.4%) ($p=0.001$), secondary specialized education – 46 / 152 (30.3%) and 20 / 113 (43.4%) ($p=0.02$). In the main group, the employed made up 110 / 152 (72.4%), in the 2nd group – 75 / 113 (66.4%) ($p=0.29$), housewives 41 / 152 (27.0%) and 37 / 113 (32.7%) ($p=0.31$), students – 1 / 152 (0.7%) and 1 / 113 (0.9%) ($p=0.83$), respectively. 122 / 152 (80.3%) and 97 / 113 (85.8%) pregnant women were in registered marriage, respectively ($p=0.24$). Thus, the patients of both groups did not have statistically significant differences in place of residence, education, social status and family relationships. Among the bad habits, only smoking was noted in patients of both groups: in the main group – 13 / 152 (8.6%), in the comparison group – 3 / 113 (2.7%) ($p=0.05$).

All patients in the main group had an aggravated somatic history, while in the comparison group, chronic somatic pathology was not detected in 46 / 113 (40.7%). Hypertension was observed with almost equal frequency in both groups – 20 / 152 (13.6%) and 12 / 113 (10.6%) ($p=0.53$), diseases of the genitourinary system – 14 / 152 (9.2%) and 9 / 113 (7.9%) ($p=0.72$), chronic anemia – 6 / 152 (3.9%) and 2 / 113 (1.8%) ($p=0.31$), diseases of the respiratory system – 20 / 152 (13.2%) and 8 / 113 (7.1%) ($p=0.11$). Despite the absence of a statistically significant difference, it should be noted that respiratory diseases were registered twice as often after COVID-19. It is note-

worthy that lipid metabolism disorders of varying degrees were present in 38.2% of women in the main group and 37.2% of patients in the comparison group. At the same time, obesity of varying degrees was statistically significantly more common in the main group: 47 / 152 (30.9%) and 19 / 113 (16.8%) ($p=0.01$). Moreover, 40 / 47 (85.1%) obese patients in the main group noted a progressive increase in body weight after COVID-19. This may be due to a stressful situation, forced social isolation, and physical inactivity during the quarantine and anti-epidemic measures. According to literary data, a change in body weight as a manifestation of post-COVID syndrome can occur in 10.6 – 20% of patients [20].

In 8 / 152 (5.3%) patients, type 2 diabetes mellitus was diagnosed for the first time in the post-COVID period; diabetes mellitus was not registered in the comparison group ($p=0.01$). It is known that the risk of developing diabetes mellitus in the post-COVID period is 59% higher [15]. Impaired carbohydrate metabolism in the post-COVID period may be due to the direct damaging effect of SARS-CoV-2 on pancreatic β -cells, increased insulin resistance against the background of acute COVID-19, and the influence of pathogenetically justified glucocorticosteroid therapy [5].

With COVID-19 and Long-COVID infection, the state of the intestinal microbiome is disrupted, diarrhea, abdominal pain, constipation, nausea, heartburn, belching may occur [4]. In our study, gastrointestinal diseases were statistically significantly more often detected in patients in the main group – 46 / 152 (30.3%) versus 18 / 113 (15.9%) in the comparison group ($p = 0.01$). Moreover, irritable bowel syndrome, functional dyspepsia, intestinal dysbiosis were registered in the post-COVID period in 27 / 46 (58.7%).

It is currently known that the SARS-CoV-2 virus provokes the development of thyroid pathologies (subacute thyroiditis, diffuse toxic goiter, euthyroid sick syndrome, chronic thyroiditis with thyroid dysfunction) [3]. Our studies have shown that thyroid diseases (hypothyroidism, hyperthyroidism, autoimmune thyroiditis, non-toxic diffuse goiter) were statistically significantly more often detected in patients of the main group: 25 / 152 (16.5%) versus 7 / 113 (6.2%) ($p=0.01$). At the same time, during pre-pregnancy preparation, thyroid diseases were detected in 19 / 25 (76.0%) in the post-COVID period.

Ophthalmological manifestations of COVID-19 have been described both in

the acute stage of infection and in the post-COVID period. Such lesions as conjunctivitis, uveitis, retinal microangiopathy, central retinal vein thrombosis, and others are encountered [9]. In our material, eye diseases were statistically significantly more common in patients in the main group than in the comparison group: 64 / 152 (42.1%) and 30 / 113 (26.6%), respectively ($p=0.01$). In addition to refractive and accommodation disorders, which prevailed in the comparison group, conjunctivitis, scleritis, episcleritis, and uveitis were detected in patients in the post-COVID period.

According to the obstetric history indicators, the patients did not have statistically significant differences, in particular, 52 / 152 (34.2%) and 32 / 113 (28.3%) were primiparous ($p=0.31$); 23 / 152 (15.1%) and 20 / 113 (17.7%) were multiparous primiparous ($p=0.58$), and 77 / 152 (50.7%) and 61 / 113 (53.9%) were multiparous ($p=0.59$). Abortion at the woman's request (surgical or medical) was in the history of 29 / 152 (19.1%) patients in the main group and 27 / 113 (23.9%) patients in the comparison group ($p=0.34$). The frequency of spontaneous abortion (including non-viable pregnancy) was 21 / 152 (13.8%) and 17 / 113 (15.0%) ($p=0.09$) respectively in the groups.

Gynecological diseases in the anamnesis were diagnosed in women of both groups almost identically, except for the violation of the vaginal microbiocenosis. Thus, uterine fibroids were registered in 19 / 152 (12.5%) patients of the main group and 7 / 113 (6.2%) of the comparison group ($p=0.09$); inflammatory diseases of the female pelvic organs in 27 / 152 (17.8%) and 14 / 113 (12.4%) ($p=0.31$); polycystic ovary syndrome in 6 / 152 (3.9%) and 3 / 113 (2.7%) ($p=0.57$); menstrual cycle disorders - in 3 / 152 (1.9%) and 2 / 113 (1.8%) ($p=0.90$); endometriosis - in 3 / 152 (1.9%) and 0 / 113 (0.0%) ($p=0.13$); respectively, in the groups. Bacterial vaginosis was detected in 28 / 152 (18.4%) patients in the main group and 11 / 113 (9.7%) in the comparison group ($p=0.05$). The latter circumstance is expected in the post-COVID period, including in connection with the disruption of the intestinal microbiota, which was recorded in our material and is consistent with literary data [18, 24].

Conclusion. Thus, pregnant women who had COVID-19 at the pre-gravid stage 6-12 months before pregnancy have a number of features of the medical and social portrait, somatic and reproductive health, in particular, there is a higher frequency of smoking, comor-

bid somatic pathology (obesity, diabetes mellitus, diseases of the gastrointestinal tract, thyroid gland and organs of vision) and bacterial vaginosis. Moreover, the above-described pathology often occurs for the first time, as a consequence of COVID-19, and can be a significant predictor of complicated pregnancy. It is advisable to take into account the data obtained by us when conducting pre-gravid preparation in patients who have had COVID-19.

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

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Yu.R. Kostyuchenko, L.S. Evert, O.V. Smirnova, A.A. Sinyakov LIPID PEROXIDATION AND ANTIOXIDANT DEFENSE SYSTEM INDICATORS IN ADOLESCENTS WITH TENSION HEADACHE

The aim of the study was to investigate the characteristics of changes in the indicators of the lipid peroxidation (LPO) system and antioxidant defense (AOP) in blood plasma and erythrocytes in adolescents with tension-type headache (TH). Materials and methods: 104 individuals (boys and girls) aged 12-17 years were examined, including 64 adolescents with TH (main group) and 40 without TH (comparison group). The content of LPO-AOP system parameters was determined using spectrophotometric detection methods. The obtained data were processed in the Statistica 12 program. Results: adolescents with TH had higher plasma MDA levels and lower plasma and erythrocyte SOD activity. A large number of individuals with high plasma MDA concentrations and low plasma and erythrocyte SOD activity were found in adolescents with a history of TH episodes. Statistically significant intragroup differences were revealed for most parameters of the LPO-AOP between their gradations: "normal level" and the level "above normal" and/or "below normal". Discussion: considering the significant role of the imbalance of the LPO-AOP system parameters in the development of oxidative stress, the increase in MDA and decrease in SOD activity that we have identified are ambiguous in terms of their interpretation: on the one hand, they can be regarded as metabolic markers of the presence of TH, on the other hand, their role as predictors of the development of this pathology is highly probable. This assumption can be confirmed or rejected by the results of further studies. Conclusions: Adolescents with TH are characterized by a higher MDA content and lower SOD activity, which indicates that they have a greater severity of oxidative stress. In the group with TH, the number of adolescents with the above shifts in the LPO-AOP system is higher than in the group without TH.

Keywords: adolescents; tension headache; lipid peroxidation; antioxidant protection

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Introduction. Tension headache (TH) and migraine are common neurological disorders among adolescents and young

adults, significantly affecting their quality of life. The problem of headache occupies a special place in pediatric practice, its frequency in adolescent populations is 18-25%, reaching a peak in adolescence [7]. One of the most common forms of primary cephalgia among adolescents is tension headache. Its prevalence varies depending on the geographic region, ethnicity, age, gender and socioeconomic conditions.

In recent decades, the role of oxidative stress (OS) in the pathogenesis of headaches has attracted the attention of researchers [4]. A number of relevant studies have been conducted on changes in the lipid peroxidation (LPO) and antioxidant defense (AOD) system parameters in adolescents and young adults with TH and migraine [1]. Changes in the LPO-AOP system parameters confirm the hypothesis of its role in the pathogenesis of TH and migraine. The LPO-AOP system reflects the balance between prooxidant and antioxidant processes. Disruption of this balance can contribute to the development and pro-

gression of pain syndromes, including TH [12].

The focus of research has shifted to the study of the molecular mechanisms underlying these conditions, among which the imbalance of the LPO and AOP system plays a key role [13]. A number of researchers have analyzed changes in LPO-AOP indices in blood plasma and erythrocytes, characteristic of TH and migraine, and assessed their potential as biomarkers of cephalgia [5, 11, 13]. The problem of comorbidity of pain in internal organs and headache is discussed [9]. However, the role of changes in LPO-AOP indices as risk factors or chronicity of headaches, especially in adolescents, remains controversial.

Numerous recent studies have been devoted to the study of various aspects of migraine [8], while very little attention has been paid to the study of similar problems in tension-type headaches [10, 11, 12], especially in adolescents and young adults. To date, the pathophysiology of headache has not been clearly established. A study by S. Vurucu et al. (2013)

Research Institute of Medical Problems of the North, Federal Research Center Krasnoyarsk Scientific Center SB RAS: **KOSTYUCHENKO Yulia Rinatovna** – junior researcher. Clinical Unit of Somatic and Mental Health of Children, ORCID: 0000-0001-6233-6472; axmeldinova@mail.ru; **SMIRNOVA Olga Valentina** – MD, prof., head of the laboratory of clinical pathophysiology, ORCID: 0000-0003-3992-9207, ovsmirnova71@mail.ru; **SINYAKOV Alexander Alexandrovich** – PhD in Biology, senior researcher of the laboratory of clinical pathophysiology, ORCID: 0000-0002-4474-1893, sinyakov.alekzandr@mail.ru; **EVERT Lidia Semenovna** – MD, chief researcher of the clinical department of somatic and mental health of children of the Research Institute for Medical Problems of the North of the FSBSE Federal Research Institute Krasnoyarsk Scientific Center of SD RAS, prof. Department of general professional disciplines of the Medical Institute FSBEI HE N.F. Katanov Khakass State University, ORCID: 0000-0003-0665-7428; lidiya_evert@mail.ru.

found that the average activity of erythrocyte superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPO), as well as malondialdehyde (MDA) levels were significantly higher in adolescents with chronic daily headache (CDH) than in the control group without headache ($p < 0.001$). The results of this work indicate that oxidative stress may play a causal or indirect role in children with CDH [11].

The small number and inconsistency of the results of studies of the parameters of the oxidant-antioxidant system in children and adolescents with tension-type headache, the need to clarify their role in the pathogenesis of this pathology, served as the basis for our study, **the purpose** of which was to study the features of changes in the parameters of the lipid peroxidation system and antioxidant protection in blood plasma and erythrocytes in adolescents with tension-type headache.

Materials and methods of the study.

The object of the study were 104 adolescents (boys and girls) with TH (the main group, $n=64$, including 39 boys and 25 girls) and without TH (the comparison group, $n=40$, including 24 boys

and 16 girls). The criterion for inclusion in the main group was the presence of such a clinical form of primary cephalgia as episodic frequent TH in adolescents. The presence of episodic rare TH in adolescents was not a reason for their hospitalization, and was regarded by us as a criterion for non-inclusion in the study. The parameters of the LPO-AOP system were considered as the subject of the study. The presence of tension headache was assessed using a questionnaire that included the criteria of the International Classification of Headache Disorders (ICHD) for this type of cephalgia [6].

LPO-AOP indicators were assessed in venous blood samples from pediatric patients, collected from their cubital vein in the morning on an empty stomach in Vacutainer tubes with sodium heparin solution (5 U/ml), using spectrophotometric detection methods [3].

The set of laboratory parameters included determination of the parameter of secondary products of free radical oxidation (FRO) of lipids and proteins – malondialdehyde (MDA, $\mu\text{mol/l}$ g protein). Evaluation of the non-enzymatic link of the activity of the endogenous antioxidant defense system included de-

termination of reduced glutathione (GSH, $\mu\text{mol/l}$ g Hb). The enzymatic link of the endogenous AOP system was assessed by the activity of superoxide dismutase (SOD, U/min/1 g protein), glutathione peroxidase (GPO, $\mu\text{mol/l}$ g Hb), catalase (CAT, $\mu\text{mol/s/1}$ g protein), glutathione-S-transferase (GST, mmol/min per 1 g Hb) and determination of ferroxidase activity of ceruloplasmin (CP, mg/l). The complex of laboratory studies also included determination of hemoglobin content (Hb, g/l) and total blood protein.

All procedures performed in this study complied with the ethical standards of the Biomedical Ethics Committee and the principles of the World Medical Association Declaration of Helsinki (as amended in 2013). The study design was reviewed and approved at a meeting of the Ethics Committee of the Federal State Budgetary Scientific Institution, the Scientific Center of the Siberian Branch of the Russian Academy of Sciences (protocol No. 3 dated March 16, 2020). Before inclusion in the study, all patients aged 15 years and older, as well as parents (or legal representatives) of patients under 15 years of age, were informed about the goals and methods of the work and

Table 1

Quantitative indicators of the LPO-AOZ system in adolescents with and without tension headaches

Indicators	Groups	M	N	Me	Mo	25%	75%	p1-2 (no MU)
<i>In blood plasma</i>								
Protein (norm 65-85)	1.without HT 2. with HT	70.32 63.41	34 58	68.50 61.50	85.00 53.00	60.00 54.00	84.00 71.00	0.0140
Malondialdehyde (MDA, $\mu\text{mol/l}$ g protein)	1.without HT 2. with HT	0.38 1.35	34 58	0.35 1.14	multiple multiple	0.18 0.78	0.52 1.53	<0.0001
Superoxide dismutase (SOD, units/min/1g protein)	1.without HT 2. with HT	190.59 132.17	34 57	190.08 136.24	197.14 no mode	152.73 94.43	245.32 169.41	<0.0001
Catalase (CAT, $\mu\text{mol/s/1}$ g protein)	1.without HT 2. with HT	0.04 0.06	34 58	0.03 0.04	0.01 0.03	0.01 0.02	0.08 0.07	0.1048
Ceruloplasmin (CP, mg/l)	1.without HT 2. with HT	278.76 268.16	34 58	253.00 254.50	multiple 187.00	209.00 200.00	311.00 332.00	0.9195
<i>In erythrocytes</i>								
Hemoglobin (Hb, g/l)	1.without HT 2. with HT	93.16 93.03	40 64	96.94 93.91	no mode 61.23	81.12 81.27	110.04 104.97	0.6836
Malondialdehyde (MDA, nmol/1g Hb)	1.without HT 2. with HT	0.24 0.25	37 62	0.16 0.19	0.17 0.14	0.10 0.12	0.29 0.27	0.5773
Catalase (CAT, mmol/s/1g Hb)	1.without HT 2. with HT	14.68 14.55	40 64	13.16 13.06	no mode 12.28	10.84 11.55	16.09 15.89	0.8779
Glutathione peroxidase (GPO, $\mu\text{mol/l}$ g Hb)	1.without HT 2. with HT	0.26 0.25	40 64	0.19 0.21	0.06 0.18	0.11 0.15	0.30 0.32	0.3997
Reduced Glutathione (GSH, $\mu\text{mol/l}$ g Hb)	1.without HT 2. with HT	6.87 7.48	35 61	6.06 6.80	4.67 no mode	4.58 4.41	8.32 9.97	0.3731
Superoxide dismutase (SOD, units/min/1g Hb)	1.without HT 2. with HT	206.58 103.80	40 64	231.65 95.64	no mode multiple	129.29 78.02	274.60 125.62	<0.0001
Glutathione S-transferase (GST, mmol/min/1g Hb)	1.without HT 2. with HT	10.91 10.51	40 64	9.54 10.02	5.47 7.08	6.73 5.68	13.28 14.47	0.6665

signed a written voluntary informed consent to participate.

The obtained material was processed using the nonparametric statistics module of the program "Statistica 12" [2]. The normality of the distribution of quantitative indicators was assessed using the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test. The results of the analysis of quantitative features are presented as median (Me) values and its interquartile range (Q25–Q75). The form of presentation of qualitative (binary) features were the values of % share and the boundaries of the confidence interval (CI) determined by the Wilson method. The significance of differences (p) for quantitative features was assessed by the Mann-Whitney U-test, for binary features – by the Pearson χ^2 criterion. Values of $p \leq 0.05$ allowed us to consider the differences in indicators obtained between the groups statistically significant.

Results and discussion. According to the International Classification of Headache Disorders (ICHD) criteria for frequent episodic tension-type headache [6], adolescents with a frequency of cephalgic episodes from 1 to 15 per month were considered to be persons with this clinical form of cephalgia. Evaluation of the frequency of headache attacks showed that episodes of cephalgia 2 days per week (d/wk) were observed in 13.8% of our patients, 34.5% had headaches 3 days/wk, 20.7% had headaches 4 days/wk, 17.2% had headaches 5 days/wk, and 6.9% each accounted for the number of adolescents with a frequency of cephalgia 6 and 7 days per week. Pain intensity was assessed using a visual analogue scale (VAS) and expressed as points. The average score on this scale in adolescents of the main group (with TH) was 5.7 (CI 4.9-6.6) points. The average duration of the presence of cephalgic episodes in the anamnesis was 3.9 (CI 3.3-4.8) years in adolescents of the main group.

To correctly assess the level of indicators of the LPO-AOP system in the blood plasma and erythrocytes of the examined patients, we preliminarily determined internal standards for each quantitative indicator by verifying their percentile values in adolescents of the control group - without TH. The norm was considered to be the values of each of the indicators in adolescents without TH, which were in the range of $\geq 25\%$ and $\leq 75\%$. The level above the norm was considered to be the value of the indicator $> 75\%$, below the norm - the value $< 25\%$.

The quantitative values of the LPO-AOP system indicators in adolescents

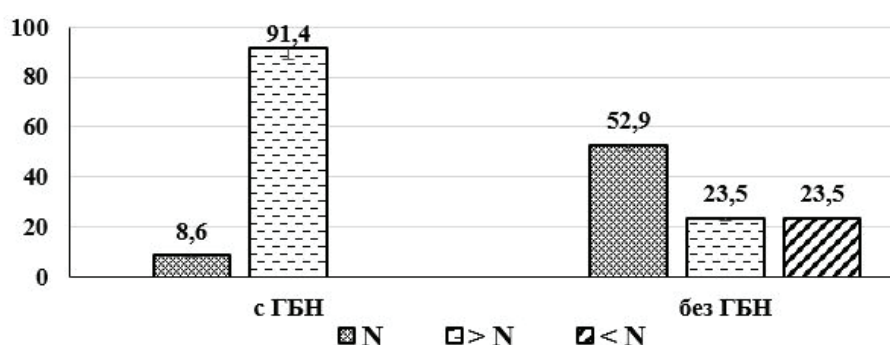


Fig. 1. Distribution of adolescents in the compared groups by the level of malondialdehyde (MDA) in blood plasma, in %. Note: Statistical significance of differences (p) in the comparison groups for the indicator "MDA Level N" $p_{1-2} < 0.001$, $\chi^2 = 22.46$; for the indicator "MDA Level $> N$ " $p_{1-2} < 0.001$, $\chi^2 = 44.17$; for the indicator "MDA Level $< N$ " $p_{1-2} < 0.001$, $\chi^2 = 14.95$

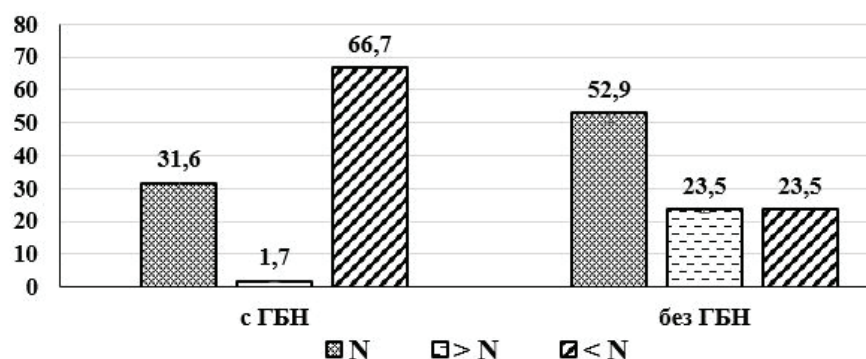


Fig. 2. Distribution of adolescents in the compared groups by the level of superoxide dismutase (SOD) in blood plasma, in %/ Note: Statistical significance of differences (p) in the comparison groups for the indicator "SOD Level N" $p_{1-2} = 0.044$, $\chi^2 = 4.06$; for the indicator "SOD Level $> N$ " $p_{1-2} < 0.001$, $\chi^2 = 11.33$; for the indicator "SOD Level $< N$ " $p_{1-2} < 0.001$, $\chi^2 = 15.85$

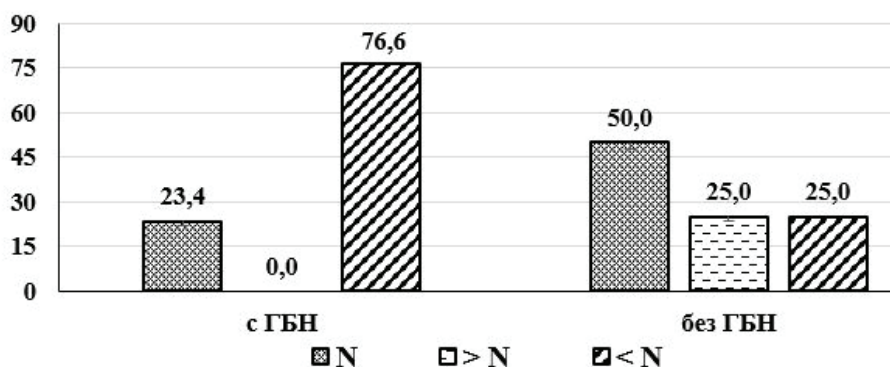


Fig. 3. Distribution of adolescents in the compared groups by the level of superoxide dismutase (SOD) in erythrocytes, in % Note: Statistical significance of differences (p) in the comparison groups for the indicator "SOD Level N" $p_{1-2} = 0.006$, $\chi^2 = 7.78$ for the indicator "SOD Level $> N$ " $p_{1-2} < 0.001$, $\chi^2 = 17.7$; for the indicator "SOD Level $< N$ " $p_{1-2} < 0.001$, $\chi^2 = 26.66$

with and without tension-type headache (TH) are reflected in Table 1.

As follows from the above table 1, adolescents with TH had significantly higher levels of malonic dialdehyde in their blood plasma and lower plasma concentrations of the enzyme super-

oxide dismutase ($p_{1-2} < 0.0001$). The content of this enzyme was also lower in the erythrocytes of those examined with TH ($p_{1-2} < 0.0001$). The metabolic shifts detected in adolescents with TH indicate that they have manifestations of oxidative stress.

The distribution of the examined adolescents with and without TH depending on the level of malondialdehyde in the blood plasma is presented in Fig. 1.

According to statistical analysis, it was established that among those examined with TH, there were significantly more adolescents with a high content of malondialdehyde ($p1-2 < 0.001$), significantly fewer with a level of the indicator within the normal range ($p1-2 < 0.001$), and there were no individuals with a dialdehyde level below the norm among those examined in this group ($p1-2 < 0.001$) (Fig. 1).

Figure 2 illustrates the distribution of adolescents in the compared groups by the level of superoxide dismutase (SOD) in blood plasma.

In the group with TH, there were significantly fewer adolescents with normal and elevated levels of plasma superoxide dismutase, and the proportion of individuals with low values of this indicator was higher. While the comparison group (without TH) had a larger number of individuals with normal and above-normal levels of superoxide dismutase, this group had significantly fewer adolescents with low levels of this enzyme.

Figure 3 shows the results of a comparative analysis of the distribution of adolescents by the level of superoxide dismutase in erythrocytes in groups with and without TH.

As follows from the data presented in Fig. 3, the trend in the distribution of those examined by the level of SOD in erythrocytes was similar to that noted for this indicator, but determined in blood plasma.

In addition to the analysis of intergroup differences, we analyzed intragroup differences in the indicators in each of the compared groups. The results obtained are included in Tables 2 and 3.

In the overwhelming majority of cases, statistically significant intragroup differences were observed between such gradations of the analyzed characteristics as "normal level" and "level above normal", as well as between the gradation "normal level" and "level below normal". Only in isolated cases were the differences between the gradation "level above normal" and "level below normal" statistically significant; such a pattern was characteristic of almost all indicators and all compared groups (Tables 2 and 3).

The percentage ratio of the number of adolescents with normal, elevated and reduced levels of the LPO-AOP system indicators both in plasma and in erythrocytes did not have statistically significant differences. The exception was a smaller

number of individuals with high plasma protein concentration in blood plasma and a larger proportion of individuals with high plasma protein content among adolescents with TH (Table 2).

It seemed interesting to us to analyze the features of the quantitative values of the indicators of the POL-AOP system among the examined adolescents de-

pending on their gender. The results of the comparative analysis of these indicators are presented in Table 4.

As the analysis showed, statistically significant gender differences were revealed only in relation to the content of the enzymatic component of the AOP – erythrocyte glutathione peroxidase: girls with TH had a higher content of this en-

Table 2

Intergroup and intragroup differences in the indicators of the LPO-AOP system in adolescents with and without TH

Groups of those surveyed	Indicators of the LPO-AOP system						P (Pearson's χ^2)
	(a) norm		(b) above normal		(c) below normal		
	abs.	% (DI)	abs.	% (DI)	abs.	% (DI)	
<i>Plasma protein (g/l)</i>							
1 gr. without TH (n=34)	19	55.9 (39.5-71.1)	7	20.6 (10.3-36.8)	8	23.5 (12.4-40.0)	ab=0.003 ac=0.007 bc=0.770
2 gr. with TH (n=58)	28	48.3 (35.9-60.8)	4	6.9 (2.7-16.4)	26	44.8 (32.7-57.5)	ab<0.001 ac=0.710 bc<0.001
Total (n= 92)	47	51.1 (41.0-61.6)	11	12.0 (6.8-20.2)	34	37.0 (27.8-47.2)	ab<0.001 ac=0.054 bc<0.001
p1-2; χ^2	0.482; 0.50		0.051; 3.82		0.042; 4.17		
<i>Catalase (CAT) of blood plasma ($\mu\text{mol/s/l g protein}$)</i>							
1 gr. without TH (n=34)	20	58.8 (42.2-73.6)	7	20.6 (10.3-36.8)	7	20.6 (10.3-36.8)	ab=0.002 ac=0.002 bc=1.000
2 gr. with TH (n=58)	40	69.0 (56.2-79.4)	13	22.4 (13.6-34.7)	5	8.6 (3.7-18.6)	ab<0.001 ac<0.001 bc=0.041
Total (n= 92)	60	65.2 (55.1-74.2)	20	21.7 (14.5-31.2)	12	13.0 (7.6-21.4)	ab<0.001 ac<0.001 bc=0.120
p1-2; χ^2	0.325; 0.97		0.838; 0.04		0.100; 2.71		
<i>Ceruloplasmin (CP) in blood plasma (mg/l)</i>							
1 gr. without TH (n=34)	18	52.9 (36.7-68.5)	8	23.5 (12.4-40.0)	8	23.5 (12.4-40.0)	ab=0.013 ac=0.013 bc=1.000
2 gr. with TH (n=58)	27	46.5 (34.3-59.2)	16	27.6 (17.8-40.2)	15	25.9 (16.3-38.4)	ab=0.035 ac=0.021 bc=0.834
Total (n= 92)	45	48.9 (38.9-59.0)	24	26.1 (18.2-35.9)	23	25.0 (17.3-34.7)	ab=0.002 ac<0.001 bc=0.866
p1-2; χ^2	0.555; 0.35		0.669; 0.18		0.804; 0.06		
<i>Malondialdehyde (MDA) (nmol/1g Hb)</i>							
1 gr. without TH (n=37)	20	54.1 (38.4-69.0)	9	24.3 (13.4-40.1)	8	21.6 (11.4-37.2)	ab=0.009 ac=0.005 bc=0.783
2 gr. with TH (n=62)	41	66.1 (53.7-76.7)	11	17.7 (10.2-29.0)	10	16.1 (9.0-27.2)	ab<0.001 ac<0.001 bc=0.811
Total (n= 99)	61	61.6 (51.8-70.6)	20	20.2 (13.5-29.2)	18	18.2 (11.8-26.9)	ab<0.001 ac<0.001 bc=0.719
p1-2; χ^2	0.233; 1.43		0.431; 0.62		0.494; 0.47		

Table 3

Intergroup and intragroup differences in the indicators of the LPO-AOP system in adolescents with and without TH (continued)

Groups of those surveyed	Indicators of the LPO-AOP system						P (Pearson's χ^2)
	(a) norm		(b) above normal		(c) below normal		
	abs.	% (DI)	abs.	% (DI)	abs.	% (DI)	
<i>Catalase (CAT) of erythrocytes (mmol/s/1g Hb)</i>							
1 gr. without TH (n=40)	20	50.0 (35.2-64.8)	10	25.0 (14.2-40.2)	10	25.0 (14.2-40.2)	ab=0.021 ac=0.021 bc=1.000
2 gr. with TH (n=64)	38	59.4 (47.1-70.5)	16	25.0 (16.0-36.8)	10	15.6 (8.7-26.4)	ab<0.001 ac<0.001 bc=0.188
Total (n= 104)	58	55.8 (46.2-64.9)	26	25.0 (17.7-34.1)	20	19.2 (12.8-27.8)	ab<0.001 ac<0.001 bc=0.317
p1-2; χ^2	0.350; 0.88		1.000; 0.00		0.238; 1.39		
<i>Glutathione peroxidase (GPO) of erythrocytes (μmol/1 g Hb)</i>							
1 gr. without TH (n=40)	20	50.0 (35.2-64.8)	10	25.0 (14.2-40.2)	10	25.0 (14.2-40.2)	ab=0.021 ac=0.021 bc=1.000
2 gr. with TH (n=64)	37	57.8 (45.6-69.1)	18	28.1 (18.6-40.1)	9	14.1 (7.6-24.6)	ab<0.001 ac<0.001 bc=0.052
Total (n= 104)	57	54.8 (45.2-64.0)	28	26.9 (19.3-36.2)	19	18.3 (12.0-26.8)	ab<0.001 ac<0.001 bc=0.136
p1-2; χ^2	0.437; 0.61		0.727; 0.12		0.161; 1.97		
<i>Reduced glutathione (GSH) of erythrocytes (μmol/1g Hb)</i>							
1 gr. without TH (n=35)	19	54.3 (38.2-69.5)	8	22.9 (12.1-39.0)	8	22.9 (12.1-39.0)	ab=0.007 ac=0.007 bc=1.000
2 gr. with TH (n=61)	24	39.3 (28.1-51.9)	21	34.4 (23.7-47.0)	16	26.2 (16.8-38.4)	ab=0.274 ac=0.123 bc=0.325
Total (n= 96)	43	44.8 (35.2-54.7)	29	30.2 (21.9-40.0)	24	25.0 (17.4-34.5)	ab=0.037 ac=0.005 bc=0.420
p1-2; χ^2	0.157; 2.01		0.235; 1.41		0.714; 0.13		
<i>Glutathione-S-transferase (GST) of erythrocytes (mmol/min/1g Hb)</i>							
1 gr. without TH (n=40)	20	50.0 (35.2-64.8)	10	25.0 (14.2-40.2)	10	25.0 (14.2-40.2)	ab=0.021 ac=0.021 bc=1.000
2 gr. with TH (n=64)	23	35.9 (25.3-48.2)	19	29.7 (19.9-41.8)	22	34.4 (23.9-46.6)	ab=0.454 ac=0.854 bc=0.570
Total (n= 104)	43	41.3 (32.4-51.0)	29	27.9 (20.2-37.2)	32	30.8 (22.7-40.2)	ab=0.042 ac=0.113 bc=0.648
p1-2; χ^2	0.157; 2.01		0.605; 0.27		0.314; 1.02		

zyme than a similar group of boys (0.30 and 0.22 μ mol/1 g Hb, respectively) (Table 4). As illustrated by the data presented in Table 4, significant differences in the content of both plasma and erythrocyte concentrations of the LPO-AOP system indicators depended mainly on the presence or absence of TH, and not on gender. Both boys and girls with TH were characterized by a higher content of MDA in both plasma and erythrocytes, in contrast to their peers without TH. In contrast, adolescents without TH, regardless of gender, had a higher content of the SOD enzyme (Table 4). No significant differences were found in the comparison groups for other indicators of the LPO-AOP system - catalase (CAT), ceruloplasmin (CP), reduced glutathione (GSH), and glutathione-S-transferase (GST) (Table 4).

Thus, our study has established the presence of activation of LPO-AOP processes in patients with TH, confirmed by a higher content of malondialdehyde and manifestations of imbalance in antioxidant protection indicators in the form of significantly lower activity of plasma and erythrocyte SOD. We attempted to analyze the features of changes in oxidant-antioxidant status indicators and assess the significance of its imbalance in the genesis of TH in adolescents. The importance of studying these aspects is due to the need to determine the role of these disorders as one of the probable pathogenetic mechanisms for the transformation of this type of cephalgia into chronic forms of psychosomatic pathology, the importance of their early diagnosis and the feasibility of pathogenetically substantiated correction.

The antioxidant defense system plays a critical role in maintaining the balance between the formation of reactive oxygen species and protecting the body from oxidative stress. Components of the antioxidant defense system (SOD, GPx, CAT, GST, GSH, CP) are crucial in protecting the body from oxidative stress, playing an important role in the pathogenesis of TH and migraine in adolescents. Studying changes in the levels of these indicators allows developing prevention and treatment strategies aimed at restoring the antioxidant balance and improving the quality of life of adolescents with TH and migraine.

Over the past decade, the key role of LPO-AOP imbalance in the pathogenesis of migraine and TH in young people has been proven. For a deeper understanding of these aspects, multicenter studies with unified protocols are needed. In our opinion, a promising direction for further

research is the identification of highly informative predictors and diagnostic markers of LPO-AOP system disorders for the purpose of early diagnosis of oxidative stress in adolescents and young adults with recurrent cephalgia for effective prevention, personalized antioxidant therapy and improved prognosis for these types of pathology.

Conclusions:

1. Adolescents with headaches have higher plasma malondialdehyde concentrations and lower plasma and erythrocyte superoxide dismutase activity.

2. The group with TH has a higher proportion of adolescents with high plasma MDA levels and low plasma and erythrocyte SOD activity.

Table 4

Content of POL-AOZ components in adolescents of different sexes with and without TH

Indicators	Groups of those surveyed		M	N	Me	Mo	25%	75%	Std. Dev.	P по MU
In blood plasma										
Protein (norm 65-85)	1rp	without TH (m)	69.90	20	68.50	60.00	82.50	12.58	1-2	0.9581
	2rp	without TH (d)	70.93	14	73.50	60.00	84.00	14.89	3-4	0.1653
	3rp	with TH (m)	61.17	36	60.50	54.50	67.00	10.35	1-3	0.0105
	4rp	with TH (d)	67.09	22	65.50	54.00	79.00	13.41	2-4	0.5156
Malondialdehyde (MDA, μmol/1g protein)	1rp	without TH (m)	0.34	20	0.26	0.13	0.61	0.27	1-2	0.1666
	2rp	without TH (d)	0.44	14	0.39	0.29	0.48	0.25	3-4	0.1492
	3rp	with TH (m)	1.52	36	1.27	0.80	1.60	1.52	1-3	<0.0001
	4rp	with TH (d)	1.06	22	1.08	0.68	1.33	0.40	2-4	<0.0001
Superoxide dismutase (SOD, units/min/1g protein)	1rp	without TH (m)	192.42	20	184.91	137.45	262.77	75.03	1-2	0.9860
	2rp	without TH (d)	187.97	14	197.14	168.57	228.58	67.50	3-4	0.7742
	3rp	with TH (m)	132.93	35	141.51	78.56	175.86	58.05	1-3	0.0050
	4rp	with TH (d)	130.96	22	126.50	96.46	159.25	38.75	2-4	0.0016
Catalase (CAT, μmol/s/1g protein)	1rp	without TH (m)	0.05	20	0.03	0.02	0.08	0.04	1-2	0.3356
	2rp	without TH (d)	0.04	14	0.02	0.01	0.08	0.04	3-4	0.6193
	3rp	with TH (m)	0.06	36	0.04	0.02	0.07	0.07	1-3	0.5324
	4rp	with TH (d)	0.06	22	0.05	0.03	0.07	0.04	2-4	0.0797
Ceruloplasmin (CP, mg/l)	1rp	without TH (m)	257.40	20	238.00	208.00	314.50	67.72	1-2	0.5755
	2rp	without TH (d)	309.29	14	259.50	210.00	311.00	194.98	3-4	0.9744
	3rp	with TH (m)	267.58	36	250.50	214.00	320.50	74.66	1-3	0.6752
	4rp	with TH (d)	269.09	22	256.00	187.00	332.00	94.67	2-4	0.8077
In erythrocytes										
Hemoglobin (Hb, g/l)	1rp	without TH (m)	90.63	24	95.29	76.14	108.31	25.25	1-2	0.4814
	2rp	without TH (d)	96.95	16	98.89	86.41	111.17	20.12	3-4	0.2893
	3rp	with TH (m)	94.20	39	98.21	85.11	106.15	24.51	1-3	0.7023
	4rp	with TH (d)	91.20	25	90.31	80.36	102.77	16.46	2-4	0.2450
Malondialdehyde (MDA, nmol/1g Hb)	1rp	without TH (m)	0.28	22	0.17	0.11	0.37	0.31	1-2	0.2585
	2rp	without TH (d)	0.17	15	0.16	0.08	0.23	0.10	3-4	0.7035
	3rp	with TH (m)	0.28	37	0.18	0.12	0.27	0.37	1-3	0.9937
	4rp	with TH (d)	0.22	25	0.19	0.11	0.24	0.17	2-4	0.3559
Catalase (CAT, mmol/s/1g Hb)	1rp	without TH (m)	14.85	24	13.09	10.61	16.27	6.20	1-2	0.7719
	2rp	without TH (d)	14.42	16	13.35	11.50	15.61	5.04	3-4	0.0622
	3rp	with TH (m)	14.42	39	12.06	10.91	15.15	6.84	1-3	0.7129
	4rp	with TH (d)	14.76	25	14.53	12.28	16.92	3.45	2-4	0.3427
Glutathione peroxidase (GPO, μmol/1g Hb)	1rp	without TH (m)	0.27	24	0.16	0.10	0.31	0.31	1-2	0.5526
	2rp	without TH (d)	0.23	16	0.23	0.14	0.30	0.14	3-4	0.0019
	3rp	with TH (m)	0.22	39	0.17	0.11	0.24	0.20	1-3	0.8874
	4rp	with TH (d)	0.30	25	0.28	0.21	0.36	0.13	2-4	0.1177
Reduced Glutathione (GSH, μmol/1g Hb)	1rp	without TH (m)	7.14	20	6.23	4.28	8.79	4.49	1-2	0.8285
	2rp	without TH (d)	6.52	15	5.81	4.67	8.10	2.81	3-4	0.9706
	3rp	with TH (m)	7.45	37	6.80	4.36	10.05	3.92	1-3	0.5811
	4rp	with TH (d)	7.52	24	6.95	4.59	9.68	3.96	2-4	0.5348
Superoxide dismutase (SOD, units/min/1g Hb)	1rp	without TH (m)	195.89	24	207.33	119.54	274.60	76.46	1-2	0.3136
	2rp	without TH (d)	222.62	16	258.95	180.82	273.82	68.67	3-4	0.1044
	3rp	with TH (m)	108.86	39	106.18	83.87	135.78	32.43	1-3	0.0001
	4rp	with TH (d)	95.91	25	87.41	68.87	117.81	34.71	2-4	<0.0001
Glutathione S-transferase (GST, mmol/min/1g Hb)	1rp	without TH (m)	11.08	24	9.49	6.73	13.08	5.68	1-2	0.8038
	2rp	without TH (d)	10.67	16	9.54	6.78	13.28	5.99	3-4	0.9835
	3rp	with TH (m)	10.41	39	9.99	5.67	14.66	5.70	1-3	0.5475
	4rp	with TH (d)	10.68	25	10.04	7.08	14.16	6.57	2-4	0.9255

3. There are statistically significant intragroup differences for most parameters of the LPO-AOP between their gradations: "normal level" and the level "above normal" and/or "below normal".

4. The level of plasma and erythrocyte concentration of the LPO-AOP system indicators is associated to a greater extent with the presence or absence of TH than with the gender of adolescents.

5. Evaluation of the significance of altered levels of LPO-AOP system indicators as metabolic markers of the presence and/or risk of developing TH in adolescents is relevant and requires further study.

The authors declare no conflict of interest.

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A.V. Krylov, N.I. Pavlova, A.A. Bochurov

COMPARATIVE ANALYSIS OF THE 5-HTTLPR POLYMORPHISM OF THE SLC6A4 GENE IN RUSSIAN AND YAKUT POPULATIONS

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The 5-HTTLPR polymorphism of the *SLC6A4* gene plays a key role in the regulation of serotonergic transmission and may influence susceptibility to anxiety and depressive disorders. This study presents a comparative analysis of the distribution of genotypes and alleles of this polymorphism in representatives of the Russian ($n = 250$) and Yakut ($n = 260$) ethnic groups. A significantly higher prevalence of the S allele (77.7%) and the homozygous SS genotype (63.8%) was observed in the Yakut population compared to the Russian group (44.8% and 20.8%, respectively; $p < 0.001$). The Russian sample was characterized by a higher frequency of the L allele and the SL genotype. The identified differences reflect the high frequency of the S allele characteristic of the Indigenous peoples of Siberia and underscore the ethnic specificity of genetic factors involved in psycho-emotional regulation.

Keywords: 5-HTTLPR polymorphism, *SLC6A4* gene, genetic diversity, ethnic populations, serotonergic system.

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FSBSI Yakut Science Center of Complex Medical Problems, Laboratory of Hereditary Pathology of the Department of Molecular Genetics: **KRYLOV Aleksey Vasilyevich** – researcher, ORCID: 0009-0005-5977-5518, alexkrulovwork@gmail.com; **PAVLOVA Nadejda Ivanova** – PhD in Biology, visiting research fellow, head of the laboratory, ORCID: 0000-0001-7862-1876, solnishko_84@inbox.ru; **BOCHUROV Alexey Alekseyevich** – junior researcher, ORCID: 0009-0008-5414-4102, binbaher@mail.ru

Introduction. Depressive and anxiety disorders constitute a significant burden of disease in global populations, affecting not only individuals but also their families and society as a whole, making them one of the key socio-economic challenges of the 21st century [11, 14]. In the context of this problem, modern genomics has laid the foundation for the transition from syndromic diagnoses to biologically based approaches in psychiatry, opening

the way for personalized treatment strategies [12]. It is predicted that in the next decade, research into the genetic basis of behavioral patterns will take a central place in psychiatry: in-depth analysis of the relationships between genomic variations and neurobiological mechanisms will transform approaches to the study of mental health and optimize therapeutic strategies for anxiety and depressive disorders [5].

Modern genomic studies actively contribute to the identification of genetic factors associated with the pathophysiology of anxiety and depressive disorders. As an example, we can consider the 5-HTTLPR polymorphism of the *SLC6A4* gene encoding the serotonin transporter. Despite the polygenic nature of mental disorders, the study of this gene demonstrates how individual genetic variations can affect neurobiological mechanisms associated with the regulation of emotions and stress resistance [3, 5]. Serotonin plays a key role in the regulation of mood, emotions and cognitive functions. The serotonin transporter (SERT), encoded by the *SLC6A4* gene, regulates the reuptake of the neurotransmitter into the synaptic cleft, affecting the duration and intensity of serotonergic transmission [7]. The 5-HTTLPR polymorphism, associated with variation in the length of the gene promoter region, modulates SERT activity: the short allele (S) is associated with reduced expression of the transporter, which may increase vulnerability to stress and increase the risk of depressive and anxiety disorders [13].

Meta-analyses demonstrate ethnic variability in the distribution of 5-HTTLPR alleles. It is known that the L allele is more common in Caucasian populations, while the S allele predominates in East Asian groups [15]. These differences may explain ethnic-specific patterns of response to antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [9]. However, data on indigenous peoples of Siberia, including the Yakuts, remain limited, making it difficult to develop personalized approaches in the region. The study of genetic characteristics of populations is an important aspect in the field of medicine and biology, since it allows us to identify ethnic specificity of predisposition to various diseases [6].

The present study focuses on the comparison of Russian (Caucasoid) and Yakut (indigenous peoples of Siberia) populations. Yakuts, with a unique gene pool formed in conditions of extreme climate and isolation, are of particular interest for the study of genetic adaptation and its relationship with mental health [4]. The work fills the gap in data on Siberian ethnic groups and expands the understanding of the role of 5-HTTLPR in the context of global genetic diversity. It is assumed that the Yakut population will demonstrate allele frequencies similar to East Asian groups, in contrast to Russians, which reflects their phylogenetic proximity to Asian ancestors. This may have practical significance for predicting the effectiveness of pharmacotherapy

and developing ethnospecific guidelines in psychiatry.

The aim of this study was to investigate the differences in the distribution of genotypes (SS, SL, LL) and alleles (S, L) of the 5-HTTLPR polymorphism of the *SLC6A4* gene between the ethnic groups of Russians and Yakuts.

Materials and methods of the study. The work was carried out with the written informed consent of all participants. The survey program covered socio-demographic parameters (including health status, bad habits, marital status and hereditary diseases) together with anthropometric measurements. Participants independently filled out questionnaires individually during scientific expeditions to the regions of the Republic of Sakha (Yakutia). FSBIS «Yakut Scientific Center for Complex Medical Problems» (YSC CMP) using the Yakutia Genome Scientific Research Institute (registration number USU_507512). Genomic studies and bioinformatics analysis were performed by the staff of the Laboratory of Hereditary Pathology of the YSC CMP. The study sample included 510 people (250 representatives of the Russian and 260 Yakut ethnic groups) with confirmed ethnicity in three generations. The analysis included data from patients who gave consent for genetic studies in the period 2018–2024.

For molecular genetic analysis, DNA was extracted from whole blood using a commercial Newtaryx DNA extraction kit (Russia, Yakutsk) according to the manufacturer's instructions. DNA concentration in each sample was determined on an Implen Nano Photometer spectropho-

tometer (Germany). Analysis of the 5-HTTLPR (44-BP INS / DEL) polymorphism of the *SLC6A4* gene was performed by polymerase chain reaction (PCR). Amplification of the gene region containing the polymorphic variant was carried out using primers manufactured by Lumiprob RUS LLC, Moscow. Reaction mixture: forward and reverse primer, 1 µl each; buffer - 2.5 µl; betaine - 5 µl; dNTPs - 4 µl; Taq polymerase - 0.25 µl; deionized water - 10.25 µl and DNA - 1 µl. The conditions for carrying out the amplification are presented in Table 1.

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

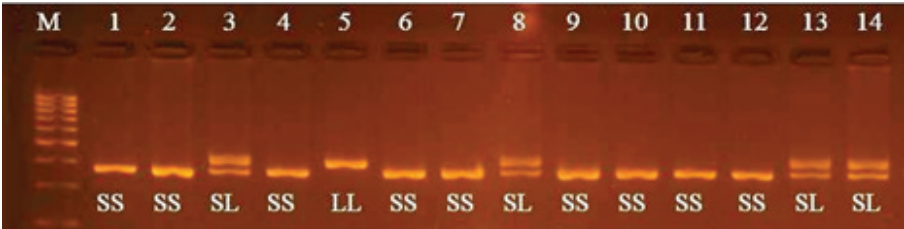
Statistical analysis of the obtained research results was performed using the program «Office Microsoft Excel 2010». Correspondence of genotype distribution to expected values of Hardy-Weinberg equilibrium and comparison of frequencies of allelic variants/genotypes were performed using the criterion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

Results and discussion. Analysis of the distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene showed significant differences in the distribution of genotypes and alleles between the groups (Table 2). In the sample of Russians, a significant difference ($p < 0.05$) in the frequen-

Table 1

Conditions for conducting PCR analysis

Gene	Primer sequence	Length of amplicon (b.p.)	Annealing temperature
<i>SLC6A4</i>	F: 5'-GGACCGCAAGGTGGGCGGGA-3' R: 5'-ATGCCAGCACCTAACCCTAATGT-3'	SS – 376 b.p.; SL – 420 b.p., 376 b.p.; LL – 420 b.p.	62°C



Electropherogram of the amplification product of the *SLC6A4* gene region in 4% agarose gel: lanes No. 1, 2, 4, 6, 7, 9, 10, 11, 12 – SS genotype; 3, 8, 13 and 14 – SL genotype; 5 – LL genotype; M – Step100 marker

Table 2

Distribution of the frequency of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene

Genotypes and alleles	Russians (n = 250)				p	Yakuts (n = 260)				p
	Women (n = 146)		Men (n = 104)			Women (n = 69)		Men (n = 191)		
	n	%	n	%		n	%	n	%	
SS	25	17.1	27	26.0	0.124	39	56.5	127	66.5	0.184
SL	69	47.3	51	49.0	0.882	18	26.1	54	28.3	0.849
LL	52	35.6	26	25.0	0.100	12	17.4	10	5.2	0.005
S	119	40.8	105	50.5	0.039	96	69.6	308	80.6	0.011
L	173	59.2	103	49.5		42	30.4	74	19.4	
X ²	0.066		0.038		-	10.17		1.722		-
p*	0.797		0.845		-	0.001		0.190		-

Note. p is the significance with the Yates correction, X² is the Chi square according to Hardy Weinberg, p* is the significance according to Hardy Weinberg.

cy of alleles was revealed. In both samples, women had a higher frequency of the homozygous genotype LL than men (36% versus 25% and 17% versus 5%). But it is possible that the significant differences ($p < 0.05$) in the frequencies of genotypes and alleles between men and women in the Yakuts are associated with a smaller number (three times) of women studied.

When comparing the distribution of alleles and genotypes of women with women and men with men, significant differences ($p < 0.05$) were found between the samples. The Yakuts more often have the SS genotype (56–66% versus 17–26%) and the S allele (70–80% versus 41–50.5%), while among Russians, both women and men are dominated by carriers of the heterozygous SL genotype (47–49% versus 26–28%).

The analysis of the distribution of alleles and genotypes, as well as the calculation of the odds ratio between the samples of Russians and Yakuts, is presented in Table 3. These differences indicate a significant population diversity in the distribution of this polymorphism. The SS genotype is more common among Yakuts (64% vs. 21%, OR=6.72; $p < 0.001$) and the S allele (78% vs. 45%; OR=4.29), while the SL genotype (48% vs. 28%, OR=0.41; $p < 0.001$) and the allele prevail among Russians. L (55% vs. 22%; OR=0.23; $p < 0.001$). The data obtained highlight the ethnic heterogeneity in the structure of the 5-HTTLPR polymorphism, which may influence differences in the neuropsychiatric profiles of populations.

According to the data in Table 2, the distribution of genotypes in Russians (as a whole, as well as separately in men and women) does not deviate from the Hardy–Weinberg equilibrium ($p^* > 0.05$). At the same time, Yakuts, espe-

cially in the subgroup of women, show a significant deviation, which is also confirmed in Table 3. At the same time, the Yakut balance is shifted towards homozygosity for the short S allele (SS genotype). Especially in women, this bias may be due to a smaller sample size, which increases sensitivity to statistical fluctuations.

Environmental and historical factors have played a key role in shaping population differences. Scientific research shows that the centuries-old habitation of populations in specific environmental conditions has determined not only their appearance and cultural characteristics, but also their morphofunctional characteristics, including metabolic adaptations.

Table 3

Frequency distribution of alleles and genotypes of the 5-HTTLPR polymorphism of the *SLC6A4* gene with odds ratio (OR)

Genotypes and alleles	Russians		Yakuts		OR (CI 95%)	p
	n	%	n	%		
SS	52	20.8	166	63.8	6.724 (4.523-9.997)	<0.001
SL	120	48	72	27.7	0.415 (0.287-0.599)	<0.001
LL	78	31.2	22	8.5	0.204 (0.122-0.340)	<0.001
S	224	44.8	404	77.7	4.291 (3.271-5.630)	<0.001
L	276	55.2	116	22.3	0.233 (0.178-0.306)	<0.001
X ²	0.218		10.514		-	-
p*	0.641		0.001		-	-

Note. OR (95% CI) is the odds ratio with a 95% confidence interval, p is the Yates-adjusted significance, Chi is the Hardy Weinberg square, and p* is the Hardy Weinberg significance.

Table 4

Frequency of the S allele among Russian populations in various regions of Russia

Population (region)	Sample size (n)	The frequency of the S allele	A source
Russians (Vologda)	47	0,36	[7]
Russians (Moscow and Krasnodar)	127	0,38	[1]
Russians (Saint Petersburg)	908	0,38	[3]
Russians (Moscow and the Moscow region)	120	0,39	[2]
Russians (Arkhangelsk)	33	0,41	[10]
The Russians (Novosibirsk)	121	0,43	[13]
Russians (Yakutia)	250	0,45	This work

A.S. Gureev et al. (2014) found that the frequency of the S allele in African populations is lower than in other regions of the world [3]. An interesting fact is that the frequency of the S allele increases as populations move to the east of Asia, both in the northern and southern regions, reaching maximum values among the Japanese and Yakuts. These data emphasize the role of long-term adaptation to environmental conditions, including climate, nutrition, and photoperiodism, in the formation of population-specific traits. Thus, the predominance of the S-allele in Yakuts may be associated with evolutionary adaptation to extreme climatic conditions [13]. Decreased expression of the serotonin transporter (SERT) in S-allele carriers theoretically increases the level of serotonin in the synaptic cleft, which may contribute to resistance to chronic stress typical of the conditions of the Far North [4, 13].

Given the wide area of Russian settlement, from the European part to the northeast of Eurasia, significant regional genetic variability can be expected. In this regard, a comparative analysis of the frequency of the S-allele in the sample of Russians studied by us was carried out with data published in the literature from other regions of Russia (Table 4).

As can be seen from Table 4, the frequency of the S allele increases from west to east: from 0.36 in Vologda to 0.45 in Yakutia, which may be due to adaptation to different climatic and environmental conditions.

The revealed differences in the distribution of genotypes of the 5-HTTLPR SLC6A4 gene between Russians and Yakuts are consistent with the population distribution features previously described in the literature. The Yakuts revealed the dominance of the SS genotype (63.8%) and the S-allele (77.7%), which corresponds to the high-frequency profiles observed in East Asian populations such as the Japanese (up to 80-85%) [3, 15]. At the same time, the data obtained reflect the unique features of the genetic structure of the indigenous population of Siberia, formed under the influence of factors of isolation, adaptation to extreme climate and demographic history of the region. The lowest S-allele frequencies (<25%) were found in African and African-American populations [3], which highlights the pronounced ethnic variability of this polymorphism. [3, 10]. These findings highlight the role of geography and ethnicity in shaping genetic patterns. The results obtained in this study are consistent with previously obtained data from A.N. Savostyanov et al. (2021),

which also demonstrated a high frequency of the S-allele in the indigenous peoples of Siberia [13].

The revealed differences emphasize the need for an ethnospecific approach in psychiatry. Recent studies on the relationship of the 5-HTTLPR polymorphism with the effectiveness of therapy emphasize the ethnic conditionality of pharmacogenetic reactions. So, in a study by Y.J. Jang. and co-authors. (2021) found that carriage of the SS genotype, common among Asian populations, is associated with reduced efficacy of selective serotonin reuptake inhibitors (SSRIs), while the L-allele is considered prognostically significant in Caucasians [8]. These conclusions are consistent with the results of D. Jarčuškova et al. (2024), which showed that in patients of the Slovak population, carriers of the short allele (S) demonstrated a statistically significantly lower therapeutic response to SSRI treatment in major depressive disorder (OR = 0.42; 95% CI: 0.20–0.85; p = 0.015) [9].

Conclusion. These data are of key importance for understanding the ethnospecific risks of developing pathologies associated with the serotonergic system, such as depressive and anxiety disorders. The results of the study can be used to optimize the diagnosis and treatment of mental disorders in multiethnic regions such as the Republic of Sakha (Yakutia). Taking into account the genetic characteristics of populations helps to reduce the risk of ineffective therapy and side effects, which corresponds to the principles of personalized medicine. Further work in this area will expand the understanding of the interaction of genetic and environmental factors in shaping human health.

The authors declare that there is no conflict of interest.

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E.D. Okhlopko, A.A. Grigorieva, S.D. Efremova,
L.I. Borisova, S.I. Sofronova, A.N. Romanova

LEVEL OF TUMOR MARKERS IN THE POPULATION OF SOUTHERN YAKUTIA CONSUMING UNTREATED AND FILTERED WATER

The level of tumor markers was assessed in working-age residents of the Aldan district who consume untreated and filtered water. The average level of tumor markers varied within the normal range. Residents of the city of Aldan who consume unpurified water have shown an increase in the average level of cancer embryonic antigen and carbohydrate antigen Ca19-9 compared to other groups. This group also has a high proportion of individuals with elevated levels of carbohydrate antigen Ca15-3, cancer embryonic antigen, and among women, carbohydrate antigen CA-125. Among individuals who consume filtered water, there is a high proportion of individuals with elevated levels of alpha-fetoprotein, which is more commonly found among residents of the city of Tommot, indicating a need for more in-depth study.

Keywords: tumor markers, filtered water, untreated water, South Yakutia

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Introduction. Cancer incidence is of social significance worldwide. Mortality from cancer in Russia ranks second, in Yakutia in 20 districts the mortality rate from neoplasms for 2022 exceeded the average for the republic, while the Aldan district was one of the districts with the highest cancer mortality rate, the rate per 100,000 population was (217,7), exceeding the average republican rate was 72,3% [3]. In the modern world, screening of tumor markers (oncomarkers - biological substances that are produced by the cancer tissue itself or the body in response to cancer growth) is one of the methods for detecting cancer, determining the stage of the disease and the prognosis of the treatment. However, a temporary increase in the level of tumor markers can also be provoked by other factors, such as a relapse of chronic diseases, as well as environmental pollution

with toxic, chemical substances [11, 5, 8]. Among residents of Primorsky Krai, a dependence of the prevalence of oncological diseases on the quality of the external environment has been identified; in areas of environmental stress, a high incidence of lung, stomach, intestinal and skin cancer is observed [13].

The Aldan district belongs to the industrial regions of the Republic of Sakha (Yakutia), where open-pit mining is carried out, which contributes to the deterioration of the environmental situation, mainly water sources [7]. As a result of the activities of gold mining organizations, 9-12 million cubic meters are returned to water bodies. In 2021 and 2022, the water quality of the Aldan River was characterized as "very polluted", 3rd class of category "b", where out of 14 hydrochemical indicators examined, 9 were polluting, which can contribute to the development of various diseases, including cancer, therefore, medical and environmental monitoring, screening to determine the level of tumor markers in residents of the Aldan district is relevant [1, 2, 10, 15].

The aim of the study was to assess the level of tumor markers in residents of the Aldan region who consume filtered and unpurified water.

Materials and methods of the study: A survey of 170 people of working age from the Aldan district was conducted: 115 people from the city of Aldan (58 men, average age 44 (33; 52) and women 57 and 39 (32; 45) respectively) and 55 people from the city of Tommot (7 men and 48 women), average age of men 62

(41; 64), women 48 (37; 59) years (Table 1). The study was approved by the decision of the Local Ethics Committee at the Federal State Budgetary Scientific Institution "Yakutia Scientific Center for Clinical and Medical Research". The study participants were informed in advance about the goals and nature of the study, and all of them provided written voluntary consent for it to be conducted.

The main source of centralized drinking water supply in the settlements of the Aldan district is underground water, which enters the water supply system from special water intake wells. To determine the type of water consumed for food, all participants completed a survey: "What kind of water do you most often drink?" and selected an answer (1 - water from harvested ice; 2 - packaged, 3 - filtered (household filters), 4 - unpurified (tap). Persons who answered that they drink packaged (bottled water in a polycarbonate container) and filtered water were combined into 1 group, as those who drink purified filtered water.

Blood sampling was performed in the morning before 11 a.m., on an empty stomach. The enzyme immunoassay method was used to determine the level of tumor markers alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigens CA 15-3, CA 19-9 and CA-125 in women only, using test kits from Vector-Best (Novosibirsk, Russia) on the Uniplan enzyme immunoassay analyzer (Russia).

Statistical data processing was performed using the IBM SPSS Statistics

Yakutsk Science Center of Complex Medical Problems: **OKHLOPKOVA Elena Dmitrievna** – candidate of biological sciences, senior researcher, FSBSI YSC CMP, elena_ohlopko@mail.ru; **GRIGORIEVA Anastasia Anatoliievna** – junior researcher of FSBSI YSC CMP, nastiagrigoryeva@gmail.com; **EFREMOVA Svetlana Dmitrievna** – junior researcher of FSBSI YSC CMP, esd64@mail.ru; **KONSTANTINOVA Lena Ivanovna** – candidate of biological sciences, researcher of FGBNU "YSC CMP", konstanta.l@mail.ru; **SOFRONOVA Sargylana Ivanovna** – candidate of medical sciences, chief researcher of FSBSI YSC CMP, sara2208@mail.ru; **ROMANOVA Anna Nikolaevna** – MD, director of FSBSI YSC CMP, ranik@mail.ru

23 software package. The data are presented as median (Me) and interquartile range [Q25; Q75]. The nonparametric Mann-Whitney U-test was used to compare two independent samples. The normality of distribution was tested using the Kolmogorov-Smirnov method. Differences were considered statistically significant if the level of significance was $p < 0.05$. Correlation analysis was performed using the Spearman method.

Results and discussion. Analysis of the content of tumor markers in the blood serum showed that the average levels of CEA, AFP, CA-19-9, CA-15-3, CA-125 in residents of Aldan and Tommot were within normal values in all groups (Tables 1, 2, 3).

Analysis of the level of tumor markers by place of residence and gender revealed that men and women in Aldan had an increase in the level of CEA by 36 and 21%, compared with men and women in Tommot, respectively, while the level of CEA in men in Aldan was 25% higher than in women in Aldan. Men in Aldan also showed an increase in CA15-3 by 35%, compared with women in Aldan (Table 1). The level of other tumor markers did not statistically change depending on place of residence and gender.

Analysis of the level of tumor markers depending on the type of water consumed showed that the average concentration of CEA in Aldan residents consuming untreated water was increased by 22,3% ($p=0.033$) compared to those consuming filtered water from Aldan, and by 46,6% ($p=0.002$) compared to Tommot residents consuming untreated water and by 44,7% ($p=0.000$) filtered water. In Aldan residents consuming filtered water, the level of CEA was also higher by 28,8% ($p=0.041$) compared to Tommot residents consuming untreated water and by 26,9% ($p=0.000$) consuming filtered water (Table 1).

Carcinoembryonic antigen is a glycoprotein protein that is produced in small quantities in the cells of healthy people (0-5 ng/ml), an increase of 7-10 ng/ml is noted in people suffering from alcoholism and from 5 to 10 ng/ml in smokers, a slight increase in the level of CEA can be associated with various inflammatory processes (with liver cirrhosis, chronic hepatitis, pancreatitis, ulcerative colitis, Crohn's disease, pneumonia, bronchitis, tuberculosis, emphysema, cystic fibrosis), autoimmune, benign diseases of internal organs, with oncological diseases it can reach very high values. The CEA test is most sensitive for colon and rectal cancer, so it is used in primary diagnostics, but an increase is also noted in cancer

of the stomach, pancreas, breast, lung, prostate, ovaries, metastases of cancer of various origins to the liver and bones, but in these diseases the sensitivity of the method is significantly lower [14].

The average concentration of AFP in the groups did not statistically change significantly depending on the quality of the water consumed, but among residents of Tommot who consumed filtered water, it tended to increase (Table 2).

Alpha-fetoprotein (AFP) is a glycoprotein produced by the yolk sac of the embryo. It has high diagnostic sensitivity in hepatocellular carcinoma. It increases in teratocarcinoma containing elements of the yolk sac. Indications for AFP testing: diagnostics of primary hepatocellular carcinoma; liver cancer screening in patients with liver cirrhosis and chronic hepatitis once every 6 months; monitoring treatment of primary liver cancer (with successful treatment, normalization within 1 month); early detection of liver cancer recurrence; prenatal diagnostics of fetal neural tube lesions and Down syndrome. AFP level in some pathologies (in IU/ml): - hepatocellular carcinoma > 800 , - hepatoblastoma (children) > 400 , - testicular teratoblastoma > 500 , - ovarian dysgerminoma > 1000 , - liver metastases > 10 , - hepatitis B and C $> 10-50$, - acute poisoning up to 100 [14].

The average level of CA-15-3 in all residents (men and women) and CA-125 in women of Aldan and Tommot did not differ from the type of water consumed (Tables 2, 3). The tumor marker CA-15-3 is often used in diagnosing tumors in the mammary gland, but at the initial stages

of cancer its level may not exceed the norm, and therefore it is recommended to carry out it in combination with CEA. This analysis is prescribed to people with benign or malignant neoplasms in the mammary glands, lungs, ovaries, pancreas, cervix, liver cirrhosis and endometrial carcinoma.

CA-125 is a glycoprotein, a highly sensitive test for detecting ovarian cancer in women, its values vary from 35 IU/L to several thousand and depend on the stage of the disease and the histological structure of the cell type, but an increase in CA-125 from 35 to 150 IU/L in women of reproductive age may be associated with other conditions (pregnancy, tuberculosis, pneumonia, pancreatitis, endometriosis, uterine fibroids, during menstruation, etc.), which in some cases requires additional research, therefore, the determination of tumor-associated antigen CA-125 is not a strictly specific screening marker for the early diagnosis of ovarian cancer [6].

The average content of CA-19-9 in all residents did not exceed the norm, but in Aldan residents drinking untreated water it was slightly higher ($p=0,039$) than in those drinking filtered water in Aldan. Correlation analysis showed the presence of a direct connection with REA ($r=0.427$, $p<0,000$).

The cancer antigen CA 19-9 is a glycoprotein normally produced by epithelial cells of the gastrointestinal tract. Its level increases in almost all patients with tumors of the gastrointestinal tract, especially the pancreas. An increase in the concentration of CA 19-9 is also noted

Table 1

Level of tumor markers in men and women of the Aldan region depending on the place of residence, Me (25-75% percentiles)

Indicators	Aldan		Tommot	
	Men n=58	Women n=57	Men n=7	Women n=48
	1	2	3	4
Age, years	44 (33; 52)	39 (32; 45)	62 (41; 64)	48 (37; 59)
CEA up to 5 ng/ml	3.41 (2.47; 4.36) $p=0.000$ ¹⁻² $p=0.002$ ¹⁻³	2.55 (2.99; 3.04) $p=0.000$ ²⁻⁴	2.17 (1.84; 2.38)	2.01 (1.15; 2.89)
AFP up to 12 IU/L	2.98 (1.87; 4.70)	2.68 (1.74; 4.34)	3.69 (3.47; 8.52) $p=0.087$ ¹⁻³	3.32 (1.73; 7.25)
CA 15-3 3-30 U/ml	15.80 (6.68; 26.45) $p=0.014$ ¹⁻²	10.22 (3.49; 17.79)	15.22 (10.77; 23.57)	10.49 (5.37; 15.02)
CA 19-9 up to 30 U/ml	0.00 (0.00; 1.29)	0.09 (0.00; 3.00)	0.37 (0.00; 2.96)	0.00 (0.00; 1.92)
Ca 125 0-35 U/ml		7.35 (4.83; 10.81)		8.38 (4.53; 11.29)

Table 2

Level of tumor markers in residents of the Aldan region depending on the type of water consumed, Me (25-75% percentiles)

Indicators	Aldan		Tommot	
	Unpurified water n=24	Filtered water n=91	Unpurified water n=10	Filtered water n=45
	1	2	3	4
CEA up to 5 ng/ml	3.67 (2.38; 4.74) p=0.033 ¹⁻² p=0.002 ¹⁻³ p=0.000 ¹⁻⁴	2.78 (2.17; 3.43) p=0.041 ²⁻³ p=0.000 ²⁻⁴	1.96 (1.47; 3.13)	2.03 (1.22; 2.38)
AFP up to 12 IU/L	2.51 (1.79; 4.51)	2.85 (1.84; 4.78)	2.89 (1.15; 4.05)	3.47 (1.73; 7.34) p=0.081 ³⁻⁴
CA 15-3 3-30 U/ml	13.20 (8.11; 21.16)	11.57 (4.55; 22.28)	13.14 (5.69; 21.71)	11.49 (5.53; 16.07)
CA 19-9 up to 30 U/ml	1.77 (0.00; 2.99) p=0.039 ¹⁻²	0.00 (0.00; 1.48)	0.00 (0.00; 0.37)	0.00 (0.00; 1.15)

Table 3

The level of the tumor marker CA-125 in women of the Aldan region depending on the type of water consumed, Me (25-75% percentiles)

Indicators	Aldan		Tommot	
	Women			
	Unpurified water n=12	Filtered water n=45	Unpurified water n=8	Filtered water n=40
Ca 125 0-35 Ед/мл	8.17 (4.95; 14.06)	6.96 (4.88; 10.98)	5.76 (3.86; 9.83)	8.38 (4.51; 11.82)

with the localization of other oncological processes (colorectal cancer, liver cancer, stomach, gallbladder or bile ducts, ovaries), liver diseases (hepatitis, cirrhosis), cholelithiasis, pancreatitis, cystic fibrosis. The CA 19-9 test is of great importance for the early detection of pancreatic tumor metastases, but some people (7-10%) do not have the gene encoding the CA 19-9 antigen and CA 19-9 is not synthesized and is not detected even in malignant tumors, so it is necessary to simultaneously conduct the test with CEA [9].

The proportion of people with elevated tumor marker levels (above the norm) was higher in Aldan than in Tommot. A slight increase in the CEA level was noted in 8 people (4,7%) from Aldan, in 3 (12,5%) consuming untreated water and 5 (5,5%) filtered water. CA -125 was above the norm in 4 people (3,8%), in 3 women (5,5%) from Aldan, one consuming untreated water and two consuming filtered waters, in Tommot in one woman (2,5%) consuming filtered water. CA 15-3 above the norm was noted only in Aldan residents, in 6 people (3,5%) - two (1,2%) consuming untreated and four (2,4%) filtered water. The concentration of AFP above the norm was noted in people consuming filtered water in the city of Aldan in 4 people (2,4%), in the city of Tommot in 7 (4,1%).

Moderate increase in AFP is not always a characteristic sign of cancer; according to literature data, residents of the village of Tommot showed a tendency for AFP levels to increase with age, compared to the control group in the village of Modut, Namsky district, with a satisfactory environmental situation [12]. Increased levels of tumor markers can be caused by drinking water with increased hardness; direct strong correlations between water hardness and tumor marker levels were found in residents of Yakutia: AFP ($r=0,134$; $p=0,000$), CEA ($r=0,211$; $p=0,000$), PSA ($r=0,360$; $p=0,000$) in men and CA-125 ($r=0,290$; $p=0,000$) in women [4].

Thus, the average level of tumor markers CEA, AFP, CA-19-9, CA-15-3, CA-125 among residents of the Aldan district did not exceed normal values for both residents of Aldan and residents of Tommot. However, among residents of Aldan who drink untreated water, the average values of CEA and CA-19-9 were significantly higher compared to other groups. An analysis of the proportion of people with elevated tumor marker levels showed that higher levels (above normal) of CA-125, Ca15-3 and CEA are more common among residents of Aldan who drink untreated water.

Among residents of Aldan and Tommot who drink filtered water, the proportion of people with elevated AFP levels (above normal) is more common than among those who drink untreated water. This fact requires further study, since other negative factors may be superimposed in this city.

The authors declare no conflict of interest.

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M.Y. Grafskaya, E.V. Verenikina, A.Y. Maksimov,
A.A. Demidova, E.V. Bova, M.I. Nazheva, I.V. Dubatova

PROSPECTS FOR THE DETECTION OF OVARIAN CANCER BY GENETIC TESTING OF ASPIRATE FROM THE UTERINE CAVITY

In the article, a genetic study of biological samples from uterine cavity aspirate was performed in patients with serous ovarian carcinoma in order to identify gene mutations characteristic of ovarian tumor lesions. It has been proven that the aspiration from the uterine cavity contains diagnostically significant numbers of cells or fragments of ovarian cancer cells necessary for molecular genetic analysis and detection of mutations in the *TP53*, *FAT3*, *CSMD3*, *BRAF*, and *KRAS* genes. Mutations of the *BRCA1/2* genes are rare. The detection of *TP53*, *FAT3*, *CSMD3*, *BRAF*, and *KRAS* gene mutations in uterine aspirate cells requires an active diagnostic search for the detection of ovarian serous carcinoma.

Keywords: ovarian cancer, serous carcinoma, morbid obesity, oncogenic mutations, aspiration biopsy.

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GRAFSKAYA Maria Yurievna – PhD, doc- torant, Federal State Budgetary Institution National Medical Research Center of On- cology MH RF, ORCID: 0009-0005-8204- 705X, e-mail: mariagrafskaja@ya.ru@ya.ru; **VERENIKINA Ekaterina Vladimirovna** – MD, Head of the Department, Federal State Budgetary Institution National Medical Re- search Center of Oncology MH RF; ORCID: 0000-0002-1084-5176, e-mail: ekat.veren@ yandex.ru; **MAKSIMOV Alexey Yuryevich** – MD, Professor, Deputy General Director, Federal State Budgetary Institution National Medical Research Center of Oncology MH RF. ORCID: 0000-0002-1397-837X, e-mail: rnioi@list.ru; **DEMIDOVA Alexandra Alex- androvna** – MD, Associate Professor, Head of the Department, Rostov State Medical Uni- versity MH RF, ORCID: 0000-0003-3545- 9359, e-mail: alald@inbox.ru@inbox.ru; **BOVA Elena Viktorovna** – PhD, Associate Professor, Rostov State Medical Universi- ty MH RF, ORCID: 0009-0008-3611-6749, e-mail: bova_ev@rostgmu.ru; **NAZHEVA Marina Ibragimovna** – PhD, Associate Pro- fessor, Rostov State Medical University MH RF. ORCID: 0000-0002-7613-5337, e-mail: nazheva@mail.ru; **DUBATOVA Irina Vlad- imirovna** – PhD, Associate Professor, Ros- tov State Medical University MH RF. ORCID: 0000-0002-9374-6009, e-mail: dubatova_ iv@mail.ru

Introduction. Ovarian cancer is the ninth most common type of cancer in women in Russia, accounting for approx- imately 3,7% of all cancers and 4,7% of deaths among patients with oncological pathology [2]. Malignant ovarian tumors occupy the first place among the caus- es of death of women with oncogynec- ological pathology [16]. Most cases of ovarian cancer are first diagnosed at late stages, which is due to the lack of effec- tive methods of early diagnosis and the almost asymptomatic course of the dis- ease [11]. It is extremely difficult to iden- tify clear clinical signs of ovarian tumors, which explains the interest of oncologists in the risk factors for the development of this pathology and the development of ef- fective methodological approaches for its early detection [14].

The use of ultrasound, tomographic (X-ray and magnetic resonance) diag- nostic methods helps to identify malig- nant ovarian pathology in many ways, but these approaches cannot be considered as generally available to a wide range of women, especially at the screening stage [8]. Unfortunately, the determination of the concentration of adenogenic cancer antigen CA-125, the secretory protein of human epididymis 4 (HE4) in the blood, is of little informative value for detecting ovarian cancer at the initial stages [13]. In clinical practice, multiple determination of markers in the blood is used primarily to monitor treatment results and timely detect relapses [15].

Recently, there has been a growing number of proponents that screening should be performed only for primary

epithelial serous ovarian tumors, as they are the main cause of mortality from this disease [16]. Currently, it has been established that the majority of highly differentiated serous ovarian carcinomas occur in the fimbriae of the fallopian tube funnels [12]. It has been proven that circulating tumor cells in ovarian cancer, and especially when the tumor process spreads to the fallopian tubes, enter the uterine cavity through the fallopian tubes and concentrate in the uterine cavity [10]. For this reason, aspirate from the uterine cavity obtained by Pipel biopsy, which is regularly performed in women of pre- and postmenopausal age, especially in the presence of risk factors for oncogynecological diseases, becomes a valuable biological medium for the detection of ovarian cancer. Biological samples taken near the tumor process are always more informative for detecting diseases than venous blood.

Scientific papers have proved that DNA of ovarian cancer cells is detected in the biological medium obtained for the detection of cervical cancer during liquid cytology and uterine body cancer during aspiration biopsy [1,6]. The use of uterine

aspirate, which contains the contents of the fallopian tubes and peritoneal fluid in contact with the ovaries, as well as circulating tumor cells, can be considered as an alternative medium to blood serum. Consideration of the risk stratification of ovarian cancer is also aimed at improving the effectiveness of screening by identifying those most at risk of the disease [8]. In this regard, the aim of the work was to evaluate the frequency of mutations of genes characteristic of ovarian tumor lesions in uterine aspirate cells in patients with serous ovarian carcinoma, taking into account the degree of malignancy of tumor cells and comorbid pathology.

Materials and methods. Two groups were formed for the study: the main group and the control group. The main group included 274 patients with newly diagnosed ovarian cancer. The control group consisted of 226 women of the same age as the main group, but without oncogynecological pathology, who attended preventive gynecological examinations with a Pipel aspiration biopsy. Depending on the presence or absence of morbid obesity in the main and control groups, 1 and 2 subgroups were distinguished. The cri-

terion for morbid obesity was an increase in BMI of more than 40 kg/m². Morbid obesity is a known risk factor for oncogynecological pathology [7]. In the patients of the main group, morbid obesity was found in 67 people (1 main subgroup), and in 207 women it was absent (2 main subgroup). In the control group, morbid obesity was detected in 47 (1 control subgroup), and in 179 women it was absent (2 control subgroup).

When including patients in the main group, the following criteria were followed: primary diagnosis of ovarian cancer; serous ovarian carcinoma by histological type; absence of cancer of the body and cervix; collection of a biological sample before the start of antitumor treatment.

The exclusion criteria were as follows: oncological diseases of other localization; decompensation of somatic diseases with the development of functional insufficiency of the main life-supporting systems (cardiac, respiratory, renal, liver failure).

The study was approved by the Ethics Committee of the Federal State Budgetary Institution "NMIC of Oncology" of the

Table 1

Initial general characteristics of patients in clinical groups

Indicator	The main group (n=274)		Control group (n=226)		p
	1 subgroup (n=67)	2 subgroup (n=207)	1 subgroup (n=47)	2 subgroup (n=179)	
Age, years (M±m)	55.3±1.54	58.4±1.49	58.6±0.66	59.4±1.12	p1=0.81 p2=0.92 p3=0.84 p4=0.95
BMI, kg/m ² (M±m) (M±m)	44.9±1.92	23.1±1.54	40.9 ±1.67	22.3±1.38	p1<0.001 p2<0.001 p3=0.67 p4=0.85
Insulin resistance, abs. (%)	67 (100)	4 (1.9)	47 (100)	2 (1.1)	p1<0.001 p2<0.001 p3=1.0 p4=0.98
Diabetes mellitus, abs. (%)	31 (46.3)	3 (1.4)	16 (34)	1 (0.6)	p1<0.001 p2<0.001 p3=0.19 p4=0.98
Grade of malignancy, abs.(%): low grade high grade	9 (13.4) 58 (86.6)	44 (21.3) 163 (78.7)	-	-	p1=0.16
Stage, abs.(%): IIA IIB IIIA1 IIIA2 IIIB IV	8 (11.9) 13 (19.4) 19 (28.4) 15 (22.4) 11 (16.4) 1 (1.5)	24 (11.6) 39 (18.8) 63 (30.4) 48 (23.2) 31 (15) 2 (1)	-	-	p1=0.99

Note: p1 is the p-value when comparing 1 and 2 main subgroups, p2 is the p-value when comparing 1 main and 1 control subgroups, p3 is the p-value when comparing 2 main and 2 control subgroups, p4 is the p-value when comparing the indicators of 2 main and 2 control subgroups.

Ministry of Health of the Russian Federation. All patients reviewed and gave written informed consent to be included in the study.

The patients of the corresponding main and control subgroups did not differ in terms of age, BMI, or the frequency of concomitant diseases. In the case of morbid obesity, the frequency of insulin resistance and diabetes mellitus was higher in both the main and control groups. All women with morbid obesity had insulin resistance syndrome.

In the main group, the frequency of high-grade malignancy (low differentiation of cancer cells) was higher than the frequency of low-grade malignancy (high and moderate differentiation), regardless of the presence or absence of morbid obesity. Advanced stages of ovarian cancer (III-IV) were more common than early stages (I-II) in both the 1st (88.1% vs. 11.9%) and 2nd (88.4% vs. 11.6%) main subgroups.

The study was to determine in cells from the uterine cavity aspirate somatic mutations specific for ovarian cancer.

From the uterine cavity aspirate obtained by the Pyle biopsy, DNA was isolated using the AllPrep kit (Qiagen) according to the manufacturer's instructions. Five volumes of RLTM buffer (Qiagen) were added to the uterine aspirate samples when the amount of liquid was ≤ 3 ml. When the volume of liquid exceeded 3 ml, cells and cell fragments were precipitated by centrifugation at 1000 rpm for 5 min, and the precipitate was dissolved in 3 ml of RLTM buffer (Qiagen).

Purified DNA was amplified in three multiplex PCR reactions using primers for the amplification of 110- to 142-nucleotide segments of the genes studied: BRAF, KRAS, TP53, CSMD3, FAT3, BRCA1, and BRCA2. Three multiplex reactions were performed for each sample from a single patient, each containing non-overlapping amplicons. Each sample was evaluated in two duplicate wells. To improve the detection of low-frequency mutations, we used the Safe-SeqS (Safe-Sequencing System) technology, which assigns a unique identifier to each template molecule. PCR fragments with the same unique identifier were considered mutant only if they contained an identical mutation in 95% or more of the cases. To characterize each gene mutation, we calculated the minor allele frequency (MAF).

The statistical analysis of the study results was performed using the STATISTICAL 12.0 program (StatSoft, USA).

Results and discussion. A complex of genes with recurrent somatic mutations

characteristic of serous ovarian adenocarcinomas was identified according to a meta-analysis of the results of genetic studies of tumor cells in 489 patients within the Cancer Genome Atlas project [9]. According to the summarized results, in serous ovarian cancer, especially in cases with a high degree of malignancy, mutations in the TP53 gene are detected in 100% of cases, and mutations in the BRCA1/BRCA2, BRAF, KRAS, CSMD3, and FAT3 genes are also detected with a certain frequency [9].

All patients in the main group did not have cervical or uterine body cancer,

and the diagnosis of ovarian serous adenocarcinoma was verified by ultrasound and tomography. All patients in the main group underwent surgery. The histological examination of tumor samples revealed the histotype of the tumor (serous carcinoma) and the grade of malignancy of the tumor cells. Before starting specific antitumor treatment, the patients of the main group underwent a standard liquid cervical cytology examination and a Pyle aspiration biopsy. The women of the control group underwent a Pyle aspiration biopsy as part of their preventive gynecological examinations.

Table 2

Frequency of gene mutations in uterine cavity aspirate samples in patients with ovarian cancer and in the control group

The gene	The main group (n=274)				The control group (n=226)				p
	1 subgroup (n=67)		2 subgroup (n=207)		1 subgroup (n=47)		2 subgroup (n=179)		
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
<i>TP53</i>	63	94.0	202	97.6	1	2.1	2	1.1	p1=0.16 p2<0.001 p3<0.001 p4=0.95
<i>KRAS</i>	7	10.4	18	8.7	-	-	1	0.6	p1=0.67 p3<0.001
<i>BRAF</i>	7	10.4	20	9.7	-	-	-	-	p1=0.85
<i>CSMD3</i>	11	16.4	31	15.0	-	-	-	-	p1=0.78
<i>FAT3</i>	28	41.2	37	17.9	5	10.6	-	-	p1=0.49 p2=0.0001 p4<0.001
<i>BRCA1</i>	5	7.5	9	4.3	1	2.1	-	-	p1=0.32 p2=0.89
<i>BRCA2</i>	3	4.5	5	2.4	-	-	-	-	p1=0.38

Note. p1 – the value of p when comparing the 1st and 2nd main subgroups, p2 – the value of p when comparing the 1st main and 1st control subgroups, p3 – the value of p when comparing the 2nd main and 2nd control subgroups, p4 – the value of p when comparing the indicators of the 2nd main and 2nd control subgroups.

Table 3

The frequency of gene mutations in aspirate samples from the uterine cavity in patients in the main group, depending on the degree of malignancy

The gene	The degree of malignancy				p
	low (n=55)		high (n=219)		
	Abs.	%	Abs.	%	
<i>TP53</i>	46	83.6	219	100.0	<0.001
<i>KRAS</i>	21	38.2	4	1.8	<0.001
<i>BRAF</i>	24	43.6	3	1.4	<0.001
<i>CSMD3</i>	-	-	42	19.2	0.002
<i>FAT3</i>	1	1.8	64	29.2	<0.001
<i>BRCA1</i>	1	1.8	13	5.9	0.33
<i>BRCA2</i>	-	-	8	3.7	0.15

In the uterine cavity aspirate of patients with ovarian cancer, mutations of the TP53 gene were found in the majority of cases (265/274, 96.7%). In one-fifth of the cases (65/274, 23.7%), patients in the main group had mutations in the FAT3 gene, in 15.3% (42/274), in the CSMD3 gene, in one-tenth of the cases of the BRAF genes (27/274, 9.9%) and KRAS (25/274, 9.1%). Mutations of the BRCA1/2 genes were rare (22/274, 8%).

Morbid obesity did not affect the frequency of gene mutations in patients with ovarian cancer, except for the FAT3 gene (Table 2). Mutations of the FAT3 gene were more common in patients with morbid obesity in the main group. In the control group, there were only a few cases of mutations in the studied genes. In the 1st control subgroup with morbid obesity, mutations of the FAT3 gene were found in one-tenth of the cases (10.6%). Consequently, mutations in the FAT3 gene were associated with both ovarian cancer and morbid obesity.

Among the patients of the main group, a low degree of malignancy of tumor cells (low grade) occurred in 55 (20.1%), and a high degree of malignancy of cancer cells prevailed in frequency (n=219, 79.9%). The characteristics of the effect of the degree of malignancy on the distribution of patients with gene mutations are presented in Table 3.

In patients with low-grade serous ovarian carcinoma, mutations were found in the TP53 (83.6%), BRAF (43.6%), and KRAS (38.2%) genes in uterine aspiration cells. In patients with high-grade serous ovarian carcinoma, the number of genes and the frequency of their mutations were higher: TP53 gene mutations were detected in all patients, FAT3 in 29.2%, CSMD3 in 19.2% and BRCA1/2 in 9.6%.

According to literature data, mutations in the BRAF, KRAS, and CSMD3 genes activate uncontrolled growth of tumor cells, which leads to an increase in tumor size and rapid metastasis [5]. Point mutations of the FAT3 gene are simultaneously associated with both the development of ovarian cancer and impaired carbohydrate metabolism [4]. The TP53 gene acts as an oncosuppressor. The mutant P53 protein can activate genes that stimulate tumor growth, metastasis, and resistance to chemotherapy of cancer cells [5]. Mutations in the BRCA1 and BRCA2 genes lead to an increased risk of certain malignancies. The main function of the proteins encoded by these genes is to maintain DNA integrity. With mutations of the BRCA1 and BRCA2 genes, the cell's

ability to repair DNA decreases, which leads to the accumulation of genetic errors [3].

Thus, we performed targeted sequencing of certain genes that are often mutated in ovarian cancer. The most important fact of the study was the proof that in the early and late stages of ovarian cancer, diagnostically significant numbers of cells or fragments of tumor cells necessary for molecular genetic analysis are present in the aspirate from the uterine cavity. This circumstance indicates the effectiveness of a genetic test in the examination of uterine cavity aspirate for early detection of ovarian tumor lesions. If ovarian tumors are detected at a late stage with a positive genetic test for mutations in the BRAF, KRAS, TP53, CSMD3, FAT3, BRCA1, and BRCA2 genes, then this circumstance may also be beneficial. One of the most important prognostic indicators for ovarian cancer is the size of the residual tumor after surgical removal. The earlier ovarian cancer is diagnosed at a late stage, the smaller the total tumor volume and the higher the probability of optimal tumor removal. In addition, it is possible that a small volume of the tumor will be more sensitive to cytotoxic chemotherapy than a large, voluminous tumor characteristic of symptomatic serous carcinoma of high malignancy.

Conclusions

1. In biological samples, aspiration biopsy by Pipel in patients with ovarian serous carcinoma revealed mutations in 96.7% of the TP53 gene, 23.7% of the FAT3 gene, 15.3% of the CSMD3 gene, 9.9% of the BRAF gene and 9.1% of the KRAS gene. BRCA1/2 gene mutations are rare (8%).

2. In patients with high-grade serous ovarian carcinoma, the frequency of mutations in the TP53, FAT3, CSMD3, and BRCA1/2 genes is higher than in low-grade tumors.

3. In patients with serous ovarian carcinoma with morbid obesity, the frequency of FAT3 gene mutations increases.

4. The detection of mutations of TP53, FAT3, CSMD3, BRAF, and KRAS genes in uterine aspirate cells requires further active diagnostic search for the detection of ovarian serous carcinoma.

The authors declare no conflict of interest.

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R.J. Kerimova, Sh.M. Polukhova, M.B. Zulfugarova,
F.E. Gulieva, A.F. Rustamova, E.M. Musayeva, Z.G. Aliyeva,
A.V. Aslanova, N.A. Panakhova

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DETERMINATION OF BIOCHEMICAL MARKERS OF ALTERED HEPATIC METABOLISM IN WHITE RATS EXPOSED TO X-RAYS

The article presents information on a research study conducted to investigate changes in the levels of enzymes and free lipid peroxidation products during metabolic disorders in the liver of experimental animals exposed to X-rays. The study was carried out on 42 intact white rats, which were divided into three groups. The first group (control group) included 6 white rats. The second group consisted of 18 intact white rats that were irradiated with X-rays. In the third group, the levels of liver enzymes in the blood were measured 10 days after the cessation of X-ray exposure (18 animals). The levels of lipid peroxidation (LPO), malondialdehyde (MDA), diene conjugates (DC), hydrogen peroxide (H₂O₂), creatine phosphokinase (CPK), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were determined in the blood (in serum) of the experimental animals.

Keywords: X-rays, liver, biochemical markers

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Introduction. The liver is one of the largest and most vital organs in the human body, serving as the primary site

for drug metabolism and detoxification. In addition to these roles, the liver is responsible for maintaining nutritional homeostasis, regulating cholesterol and glucose metabolism, and synthesizing clotting factors [8]. These essential functions make the liver particularly susceptible to the toxic effects of drugs and chemicals introduced through ingestion or other routes of exposure. Such toxic agents can impair the liver's detoxifying capacity by damaging functional macromolecules—such as lipids, proteins, and nucleic acids—via mechanisms that include free radical generation, antioxidant depletion, inflammation, and apoptosis. Structural damage in liver tissue may involve disruption of hepatocyte membranes and organelles, leading to cellular swelling, injury, and necrosis [5,11].

The liver is a highly active metabolic organ that is sensitive to various environmental factors. One such factor is ionizing radiation, which can cause severe damage or even death in living organisms when exposure occurs at relatively high doses due to its acute effects [7,11]. Moderately high doses of radiation may result in varying outcomes depending on factors such as the type of tissue exposed and the age at the time of exposure. In cancer radiotherapy, although the radiation is typically localized, surrounding healthy tissues including the liver may still receive high-dose exposure, potentially leading to acute damage such

as fibrosis. In everyday life, humans are frequently exposed to radiation through medical procedures, including radiotherapy and diagnostic imaging. The effects of radiation are influenced by several biological variables such as species, age, and sex [6]. Animal studies have consistently shown that these variables including strain play a significant role in determining the severity of radiation-induced effects. Furthermore, lifestyle factors are critically important in human health and are believed to contribute to approximately 70% of cancer cases [9].

The aim of the study was to study changes in the level of enzymes and free products of lipid peroxidation in metabolic disorders in the liver of experimental animals exposed to X-rays.

Materials and methods. The experiments were conducted on white rats weighing 200-250 g, kept in a vivarium under normal conditions at the Scientific Research Center of Azerbaijan Medical University. During the study, we adhered to the guidelines set by the "European Bioethics Commission" (Strasbourg, 1986) and the local bioethics commission of "Azerbaijan Medical University". The rats were exposed to natural light, received a standard diet, and had free access to food and water.

The study was conducted on 42 intact white rats, which were divided into three groups. The first group (control group) consisted of 6 white rats. The second

Azerbaijan Medical University, Baku, Azerbaijan: **KERIMOVA R.J.** – Scientific Research Center, Doctor Neonatologist, Senior Researcher, Candidate of Medical Sciences, statya2021@mail.ru, ORCID: <https://orcid.org/0009-0004-4323-9625>; **POLUKHOVA Shakhzade M.** – Department of Pharmacology, Candidate of Pharmaceutical Sciences, Asst. Senior Lecturer, ORCID: <https://orcid.org/0009-0009-4705-6363>; **ZULFUGAROVA Mehriban B.** – Department of Pharmacognosy, Candidate of Biological Sciences, Senior Lecturer, ORCID: <https://orcid.org/0000-0003-1106-378X>; **GULIEVA Firangiz E.** – Department of Biochemistry, Candidate of Biological Sciences, Associate Professor, ORCID: <https://orcid.org/0000-0002-2206-1803>; **RUSTAMOVA Afag A.** – Department of Normal Physiology, Candidate of Medical Sciences, Associate Professor, ORCID: <https://orcid.org/0009-0003-9953-2276>; **MUSAYEVA Einura M.** – Department of Pharmacology, Candidate of Biological Sciences, Assistant, ORCID: <https://orcid.org/0000-0002-5513-6717>; **ALIYEVA Zinyat G.** – Department of Physiotherapy and Medical Rehabilitation, Assistant, ORCID: <https://orcid.org/0009-0007-3130-6044>; **PANAKHOVA Nurangiz A.** – 1st Department of Internal Medicine, Doctor Cardiologist, Chief Laboratory Assistant, ORCID: <https://orcid.org/0009-0000-0346-7325>

group included 18 intact white rats that were irradiated with X-rays. In the third group, the amount of liver enzymes in the blood of the experimental animals was determined 10 days after the cessation of X-ray irradiation (18 animals).

The irradiation of the experimental animals with X-rays was performed using the "RUM-17" device. According to the recommendation of Eminov (2014), the radiation dose was 4 Gy, and the irradiation of animals was 1 Gy per day for 4 days [2].

- Intensity–180 kV;
- Current intensity–15 m;
- Filters–0.5 mm Cu+1.0 mm Al;
- Focal length factor–3
- Tubeless dose rate–0.86 Gy/sec

The experiments were conducted in all cases under pain-free conditions, and during the experiment, anesthesia was created by injecting 0.3 ml (50 mg/ml) of Calypsol solution into their abdominal cavity. As soon as the mentioned situation arose, the experimental animals were decapitated. After the irradiation was completed, biochemical examinations were conducted on the blood (in serum) samples taken from the experimental animals.

The levels of lipid peroxidation (LPO), malondialdehyde (MDA), diene conjugates (DC), hydrogen peroxide (H_2O_2), creatine phosphokinase (CPK), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were determined in the blood (in serum) of the experimental animals. [1,3].

The blood levels of the indicated markers were measured using reagent kits manufactured by Human on a fully automated BioScreen MS-2000 analyzer, made in the USA.

The concentration of hydrogen peroxide (H_2O_2), a product of free lipid peroxidation, was determined using the method of Askava T. and Matusushita S. (1980). The concentration of diene conjugates (DC), the intermediate product, was determined by the method developed by I.D. Stalnaya (1977). The concentration of malondialdehyde (MDA), the final product, was determined using the method proposed by Uchiyama and Michara (1978).

The determination of MDA (malondialdehyde), DK (diene conjugates) and H_2O_2 (hydrogen peroxide) analyses was performed using a BOECO S-300 (Boeckel & Co, Germany) spectrophotometer using reagent kits and methods. Malondialdehyde - TBA (thiobarbituric acid), diene conjugates - at a wavelength of

232-234nm, and hydrogen peroxide was measured using peroxide reagent kits.

The quantitative indicators of the obtained results were statistically analyzed based on modern recommendations (Lakin Q.F., 1990; Dodj M.S., 1997). For each group of animals under study, the following were calculated:

- mean value (M),
- standard error (m),
- minimum and maximum values;

Based on the obtained distributions, the following were used:

- for distributions close to normal (with ranking and symmetry of values),
- Wilcoxon-Mann-Whitney U-test — in cases where the data do not correspond to normal distribution. The choice of criteria was determined by the nature of the sample distribution, which meets the requirements of modern biomedical statistics. All calculations were performed in EXCEL tables at the Department of Medical Physics and Informatics of AMU.

A critical level of significance was considered at $p \leq 0.05$.

The effect of X-rays (XR) leads not only to an increase in the concentration of enzymes in the blood, but also to enhanced free radical reactions of lipids in the liver tissue. In addition, lipid peroxidation (LPO) products such as hydrogen peroxide (H_2O_2), diene conjugates (DC), and malondialdehyde (MDA) were identified in the liver tissue. For example, while a sharp increase in DC concentration in the liver was observed in 100% of the experimental animals, the level of free LPO products in the liver remained unchanged. Hydrogen peroxide (H_2O_2) is not considered a direct product of lipid peroxidation. It participates in the initiation of free radical reactions by promoting the formation of hydroxyl radicals ($\bullet OH$) through Fenton or Haber-Weiss reactions, which in turn lead to lipid peroxidation.

Results and discussion. The concentration of liver enzymes in the blood of white rats irradiated with X-rays differed from normal levels. The concentra-

tion of aspartate aminotransferase (AST) increased by 27% ($P < 0.05$), alanine aminotransferase (ALT) increased by 30% ($P < 0.05$), gamma-glutamyl transferase (GGT) increased by 17%, and lactate dehydrogenase (LDH) increased by 31% ($P < 0.05$) compared to the intact state.

The concentration of the AST enzyme in the blood of white rats exposed to X-rays ranged from 28 to 50 U/l, with an average concentration of 37.4 ± 3.78 U/l. The concentration of the ALT enzyme ranged from 33 to 57 U/l, with an average concentration of 45.8 ± 4.53 U/l, which was higher than the intact state.

The concentration of gamma-glutamyl transferase in the blood of the experimental animals ranged from 33 to 60 U/l, with an average concentration of 50.6 ± 5.18 U/l. The concentration of the LDH enzyme varied between 320 and 390 U/l, with an average concentration of 482 ± 45.54 U/l.

It was found that X-rays, at the indicated dose, disrupted the physiological course of metabolism in the liver of white rats, significantly increasing the concentration of enzymes in the blood. Among these enzymes, the main indicator of the reparative process, creatine phosphokinase (CPK), increased the most. Its concentration in the blood was 52% higher than the level in the intact state ($P < 0.001$), ranging between 315 and 463 U/l, with an average concentration of 394.8 ± 24.25 U/l. As a result of the examinations conducted, we determined that the effects of X-rays (XR) not only increased the concentration of enzymes in the blood but also intensified the free radicalization of lipids in the liver tissue. The concentration of hydrogen peroxide (H_2O_2) varied between 3.25 and 4.25 ppm, with an average concentration of 3.75 ± 0.18 ppm. This represented an 87.5% increase compared to the intact state ($p < 0.001$). This increase was observed in 100% of the animals tested.

The concentration of diene conjugates (DC), an intermediate product of

Table 1

The amount of free lipid peroxidation products in the liver

Group	H_2O_2 (ppm)	DC (D232/ml)	MDA (nmol/mg)
Intact	2.00 ± 0.13	1.42 ± 0.12	1.14 ± 0.09
Group 2	$2.75 \pm 0.18^*$	$2.30 \pm 0.18^{**}$	$2.94 \pm 0.16^{***}$
Group 3	$3.75 \pm 0.18^{***}$	$2.37 \pm 0.16^{**}$	$3.00 \pm 0.14^{***}$

Note : * $P < 0.05$ – significant difference from intact group, ** $P < 0.01$ – highly significant difference, *** $P < 0.001$ – very highly significant difference

Table 2

Changes in the enzyme synthesizing function of the liver 10 days after stopping X-ray irradiation of experimental white rats

Group	AST (U/L)	ALT (U/L)	GGT (U/L)	LDH (U/L)	CPK (U/L)	ALP (U/L)
Group 1 (Control)	29.3 ± 2.0	35.2 ± 3.0	43.0 ± 3.5	367.0 ± 25.0	260.0 ± 15.0	234.0 ± 10.0
Group 2 (Post-X-ray)	37.4 ± 3.78 **	45.8 ± 4.53 **	50.6 ± 5.18 *	482.0 ± 45.54 **	394.8 ± 24.25 ****	302.0 ± 8.6 **
Group 3 (10 days later)	35.8 ± 3.38 *	43.2 ± 4.76 *	49.0 ± 4.55 *	467.0 ± 43.09 **	366.5 ± 21.80 ***	286.0 ± 12.08 *

Note : * P = 0.05, ** P < 0.05, *** P < 0.01, **** P < 0.001

free lipid peroxidation (LPO), ranged from 1.9 to 2.8 D232/ml, with an average concentration of 2.3 ± 0.16 D232/ml. This was 61.5% higher than the level in the intact state ($p < 0.01$). A sharp increase in the concentration of DC was observed in 100% of the animals tested. The concentration of malondialdehyde (MDA) increased significantly (158%) compared to the intact state ($p < 0.001$), ranging between 2.5 and 3.4 nmol/mg in the experimental animals. The average value was 2.94 ± 0.16 nmol/mg. The duration of free lipid peroxidation in the liver of white rats irradiated with X-rays is provided in Table 1.

Examinations were performed on white rats in group 3, 10 days after stopping irradiation. It was found that after the cessation of irradiation, the concentration of liver enzymes in the blood decreased moderately. The concentration of the AST enzyme varied between 28 and 46 U/L, with an average of 35.8 ± 3.38 U/L. Although the concentration of AST was 22% higher than the level in the intact state, it decreased by 4% compared to the irradiated animals ($P = 0.05$ in both cases). The concentration of the ALT enzyme in the blood taken from the white rats ranged from 30 to 56 U/L. The average concentration was 43.2 ± 4.75 U/L, which was 23% higher than the level in the intact state and 6% lower than the level in group 2 animals ($P = 0.05$ in both cases).

The concentration of gamma-glutamyl transferase (GGT) enzyme increased from 33 U/L to 58 U/L among the experimental animals. Its average concentration ($M \pm m = 49 \pm 4.55$ U/L) increased by 13% compared to the intact state. After stopping the irradiation, the concentration of LDH enzyme in the blood of white rats increased from 315 U/L to 575 U/L. Accordingly, the average concentration of LDH enzyme in the blood was 27% ($P < 0.05$) higher than the normal level, with a value of 467 ± 43.09 U/L. Compared to the animals in group 2, the concentration of LDH enzyme in the blood decreased by 3% ($P = 0.05$). The concen-

tration of CPK enzyme in the blood of the white rats in the experiment ranged from 286 U/L to 415 U/L, with an average concentration of 366.6 ± 21.80 U/L. Compared to the intact state and group 2, the concentration of CPK in the blood of the experimental animals in group 3 was 41% higher than normal ($P < 0.01$). Compared to the level in the blood of the white rats in group 2, it decreased by 7% ($P = 0.05$).

The concentration of the alkaline phosphatase (ALP) enzyme ranged from 260 to 330 U/L, with an average concentration of 286 ± 12.08 U/L. It was 22% higher than the level in the intact state and 5% lower than the level in the blood of irradiated experimental animals (group 2) ($P = 0.05$ in both cases). The restoration of the enzyme-synthesizing function of the liver after exposure to X-rays is presented in Table 2.

Despite removing the subject from the radiation field, the liver function, which was disrupted by the effects of X-rays, cannot be fully restored [10,12]. The results indicate that even after removing the experimental animals from the X-ray zone, the high intensity of free lipid peroxidation in the liver continues. As a result, 100% of the experimental animals in groups 2 and 3 exhibited higher-than-normal levels of free lipid peroxidation products in their livers [4].

Conclusion. X-ray radiation has a significant negative effect on the enzyme-synthesizing function of the liver. Even after cessation of irradiation, the liver function, impaired by X-ray exposure, is not fully restored. Thus, at a dose of 4 Gy (1 Gy per day for 4 days), animals experience symptoms of acute radiation sickness, such as weight loss, loss of appetite, diarrhea, lethargy, and general weakness. This dose is considered high enough to damage the hematopoietic system, which leads to a decrease in the number of leukocytes and platelets, as well as an increased risk of infections and bleeding.

The authors declare no conflict of interest.

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E.A. Krasavina, E.I. Choinzonov, D.E. Kulbakin, I.K. Fedorova, V.O. Tskhai, D.I. Novokhrestova, E.Yu. Kostyuchenko, S.D. Tomilina

CRITERIA OF QUALITY OF LIFE FOR ASSESSING THE EFFECTIVENESS OF SPEECH REHABILITATION OF PATIENTS AFTER HEMIGLOSSECTOMY

KRASAVINA Elena Aleksandrovna – Candidate of Biological Sciences; speech therapist of the Department of Head and Neck Tumors; Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, e-mail: krasavinaea@mail2000.ru, ORCID 0000-0002-8553-7039; **CHOINZONOV Evgeny Lhamatsyrenovich** – academician of the Russian Academy of Sciences, MD, Professor; head of the Department of Head and Neck Tumors; Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, e-mail: info@tnimc.ru, ORCID: 0000-0002-3651-0665; **KULBAKIN Denis Evgenievich** – MD, senior researcher of the Department of Head and Neck Tumors; Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, e-mail: kulbakin_d@mail.ru, ORCID 0000-0003-3089-5047; **FEDOROVA Irina Kazanovna** – junior researcher, head of the Department of Head and Neck Tumors; Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, e-mail: irina_fedorova96@mail.ru, ORCID: 0000-0002-7540-8532; **TSKHAJ Vladislav Olegovich** – PhD student of the Department of Head and Neck Tumors; Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences; e-mail: tskhaivlad@mail.ru; ORCID: 0009-0003-3257-9002; **NOVOKHRESTOVA Daria Igorevna** – Ph.D. of Engineering Sciences, research associate, Laboratory of medical and biological research, Tomsk State University of Control Systems and Radioelectronics.(Tomsk, Russia); e-mail: ndi@fb.tusur.ru; **KOSTYUCHENKO Evgeniy Yuryevich** – Ph.D. of Engineering Sciences, associate professor, Head of Laboratory, Laboratory for the collection, analysis and management of biological signals, Tomsk State University of Control Systems and Radioelectronics.(Tomsk, Russia); email: key@fb.tusur.ru; **TOMILINA Svetlana Dmitrievna** – engineer, Department of Complex Information Security of Computer Systems. Tomsk State University of Control Systems and Radioelectronics.(Tomsk, Russia); email: tsd@fb.tusur.ru

The quality of life (QOL) of patients after radical surgery for oral cavity and oropharyngeal cancer is an important factor in determining the treatment effectiveness. Restoring functional and social capabilities, particularly speech and nutrition, is a crucial aspect of rehabilitation. **The purpose of the study** was to assess QOL of patients as one of the criteria for evaluating the effectiveness of speech rehabilitation technique using the OnkoSpeech v4.0 computer software. **Materials and methods.** The study included 140 patients with stage II–IV oral cavity and oropharyngeal cancer, who underwent hemiglossectomy (resection of ½ of the tongue). The median age of the patients was 54 years (range, 34 to 70 years, IQR-26). All patients were divided into two groups. Group I consisted of 70 patients who underwent speech restoration using the computer-software complex (OnkoSpeech v4.0 computer software). Group II comprised 70 patients who used the standard technique for speech restoration. To assess QOL, the EORTC QLQ-30 (version 3.0) and QLQ-H&N35 questionnaires were used. The assessment was carried before starting combination treatment, before starting rehabilitation, after completing rehabilitation, and 6 and 12 months after competing rehabilitation. **Results.** The analysis of data revealed significant differences in the parameters of speech restoration and quality of life between the groups. Group I (OnkoSpeech v4.0) patients demonstrated a statistically significant improvement in these parameters compared to group II patients ($p < 0.05$). The EORTC QLQ-C30 scales did not show a statistically significant difference in the values of the functional scales (physical, role and social functioning) between the groups. According to the QLQ-H&N35 data, group I patients experienced less severe symptoms associated with speech, swallowing and social communication compared to group II patients. The standard technique (Group II) showed a slower recovery and less severity of positive dynamics. **Conclusion.** The use of OnkoSpeech v4.0 demonstrated higher efficiency of speech rehabilitation and improvement of patients' quality of life compared to the standard technique. The data obtained highlight the potential of integrating digital technologies into speech rehabilitation of cancer patients, which can be recommended for further implementation in clinical practice.

Key words: surgical treatment; functional disorders; speech rehabilitation; quality of life; computer software complex "OnkoSpeech v4.0".

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Introduction. Rehabilitation of patients after combination treatment for cancer is essential and growing trend in cancer care [1,6]. Evaluation of the effectiveness of rehabilitation techniques using the QOL criterion provides a deeper and more comprehensive understanding of their significance for patients [2,3,5]. The QOL assessment incorporates subjective patient-reported psychological, social, and functional aspects alongside objective clinical data to evaluate a re-

habilitation technique's overall impact [4,7]. Comparison of QOL before and after using a new rehabilitation technology provides objective evidence of its effectiveness, allowing for a comparison with current methods. This approach helps ensure that patients receive the most suitable and effective treatments by evaluating how a new technology impacts their well-being [6,8].

The purpose of the study was to assess patients' QOL as one of the criteria

for evaluating the effectiveness of speech rehabilitation technique using the computer-software complex (OnkoSpeech v4.0 computer software).

Materials and methods. The prospective study included 140 patients with stage T1–T4N0–N2M0 oral cavity and oropharyngeal cancer, who were treated at the Department of Head and Neck Tumors of the Cancer Research Institute from 2004 to 2022. The median age of the patients was 54 years (range, 34 to 70 years, IQR-26). The patients underwent hemiglossectomy (resection of ½ of the tongue) without capturing the root and excision of the floor of the mouth muscles on the affected side. Lymph node dissection of the neck (right/left, on both sides) was performed if indicated. In the postoperative period, all patients had a speech disorder characterized by difficulty with pronunciation and speech prosody, along with swallowing problems. All patients were divided into two groups. Group I consisted of 70 patients who underwent speech rehabilitation using the computer-software complex (OnkoSpeech v4.0 computer software) for acoustic analysis of speech signals. Group II included 70 patients who used the standard technique for speech restoration (fig.1).

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-30 questionnaire (version 3.0) was used to assess patients' QOL, which was found to be reliable and valid for cancer patients. This allowed for a detailed assessment using 5 functional scales, 3 symptom scales, general health status, and 6 individual questions.

Special tools can identify changes typical for patients diagnosed with oral cavity and oropharyngeal cancer. In our opinion, the QLQ-H&N35 questionnaire, specially designed for patients with head and neck tumors, is the most effective for this category of patients. It assesses the severity of problems and symptoms that most often occur in these patients. The questionnaire contains 7 scales assessing pain, swallowing, sensations (taste and smell), language, diet, social contacts, sexuality and 11 separate questions.

The characteristics influencing patients' QOL were compared during speech therapy and 6 and 12 months after speech therapy. The QOL assessment scale has a range from 0 to 100 points. According to the EORTC QLQ-30 protocol (version 3.0), a higher score means a higher (improved) functional level and QOL (general health status). According to the EORTC QLQ-H&N35

protocol for symptomatic scales and individual questions, a higher score indicates a high (worse) level of symptoms. The QOL study was conducted at five control points: before starting combination treatment, after diagnosis confirmation, after surgical treatment at the beginning of speech therapy, after completion of

speech therapy, and 6 and 12 months following speech therapy.

Statistical analysis was performed according to the EORTC protocols, with data entered into the Statistica 9.0 and SPSS 25 software to calculate results as medians and interquartile ranges. Interquartile range (IQR) defined as the dif-

Table 1

The EORTC QLQ-30 questionnaire (version 3.0). Dynamics of patients' quality of life indicators according to functional scales (from 0 to 100 point scale)

Functional scales of EORTC QLQ-30 (version 3.0) questionnaire		Group I (n – 70) Speech rehabilitation using OnkoSpeech v4.0 computer software	Group II (n – 70) Speech rehabilitation using the standard technique
Study phases			
Physical functioning PF2	Before starting combination treatment	78.3 (63-100)	81.1(66 -100)
	Before starting speech rehabilitation	55.6 (43-66)	57.9(40-66)
	After completing speech rehabilitation	61.2 (46-76)	64.2(46-83)
	6 months after speech rehabilitation	69.6 (56-100)	72.1(60-100)
	12 months after speech rehabilitation	74.6 (56-100)	72.6(60-100)
Role functioning RF2	Before starting combination treatment	44.2 (0-64)	76.4(67-100)
	Before starting speech rehabilitation	61.5 (50-67)	41.5(17-67)
	After completing speech rehabilitation	63.6 (34-87)*	48.1(33-67)
	6 months after speech rehabilitation	65.2 (50-100)	58.3(50-83)
	12 months after speech rehabilitation	70.1 (50-100)	62.2 (50-83)#
Emotional functioning EF	Before starting combination treatment	44.2 (0-64)	36.2 (23-50)
	Before starting speech rehabilitation	61.5 (50-67)	66.1(50-83)
	After completing speech rehabilitation	63.6 (34-87)*	71.2 (34-100)*
	6 months after speech rehabilitation	65.2 (50-100)	69.8 (50-100)
	12 months after speech rehabilitation	70.1 (50-100)	71.9 (50-100)
Social Functioning SF	Before starting combination treatment	81.4 (50-100)	72.6(67-100)
	Before starting speech rehabilitation	36.1 (17-50)	38.5 (17-50)
	After completing speech rehabilitation	45.6 (17-67)	49.3 (17-67)
	6 months after speech rehabilitation	69.6 (50-83)	64.6 (50-83)
	12 months after speech rehabilitation	71.1 (50-100)#	67.6 (50-87)#

Note. In table 1-3: M – arithmetic mean; n – number of subjects; the sample range, minimum and maximum, respectively, are indicated in parentheses; * - values have statistically significant differences between groups ($p < 0.05$); # – statistically significant difference in indicators at the third (after RR) and fifth (12 months after RR) stages of the study.

Table 2

The EORTC QLQ-30 questionnaire (version 3.0). Dynamics of QOL (general health status) indicators of patients on a 0 -to -100 scale

Study phases	Group I (n – 70) Speech rehabilitation using OnkoSpeech v4.0 computer software	Group II (n – 70) Speech rehabilitation using the standard technique
Before starting combination treatment	64.1 (33-100)	62.6 (33-100)
Before starting speech rehabilitation	39.4 (25-50)	38.5 (16-50)
After completing speech rehabilitation	52.2 (41.5-75)	55.1 (41.5-75)
6 months after speech rehabilitation	59.4 (41.5-75)	61.3 (41.5-75)
12 months after speech rehabilitation	67.5(50-83) #	60.6 (50-83) *#

ference between the third (Q3) and first (Q1) quartiles, was used to assess the data variability. Differences were considered statistically significant at a p value less than 0.05.

Results. Almost all functional scales (PF2, RF2, SF) and the general health status (QOL) were found to show similar changes over time, except for the emotional functioning scale (EF) (Table 1, 2). In the postoperative period, the mean score and median statistically decreased, indicating a significant deterioration in physical, role and social functioning. After completing speech rehabilitation, as well as 6 and 12 months after speech rehabilitation completion, the indicators were improved. These results highlight that physical rehabilitation depends primarily on the patient's general health status rather than on the speech rehabilitation technique. The decrease in the standard deviation indicates a decrease in variability in the results, which indicates a homogeneous improvement dynamics in both study groups. In our study, there were patients who showed complete recovery according to the scales (PF2, RF2, SF) (100 points) 6 and 12 months after speech rehabilitation. Group I patients had better results in restoring social contacts. This may also indicate that speech rehabilitation using OnkoSpeech v4.0 contributes to better patient involvement in social life. Group I showed an improvement in the overall health status (QOL), especially 12 months after speech rehabilitation (Table 2). The difference between the groups was 6.9 points, which was statistically significant ($p < 0.05$).

The scores on the emotional functioning (EF) scale in both study groups at the first control point were the lowest over the entire observation period, subsequently tended to increase. The decrease in the standard deviation indicates a decrease in variability in the results (Table 2).

Statistically significant differences in symptom scales for problems with speech (HNSP), social contacts (HNSC), social eating/nutrition (HNSO), and swallowing (HNSW) were found between the study groups. Group I patients had better outcomes in reducing these problems compared to group II patients, thus confirming the high efficacy of OnkoSpeech v4.0 computer-software (Table 3).

Discussion. Postoperative speech rehabilitation for oral and oropharyngeal cancer patients was shown to lead to statistically significant improvements in functional and symptomatic indicators. Functional scales, such as PF2 (physical functioning), RF2 (role functioning), SF (social functioning), as well as the gener-

al health status (QOL), showed positive outcomes after the completion of speech rehabilitation in both patient groups.

However, an important point is that the dynamics of the emotional functioning scale (EF) indicators differs from other functional scale indicators. The lowest scores were recorded at the phase before starting combination treatment. Receiving a cancer diagnosis and expecting surgery significantly worsens patients' emotional state in both patient groups. At the phase of speech rehabilitation, a tendency towards improvement was observed, which was confirmed by a decrease in the standard deviation and an increase in the average values on this scale. This may indicate that emotional recovery is closely related to physical and social well-being, and successful speech rehabilitation contributes to the improvement of psycho-emotional state of the patient. A decrease in variability in the results of the emotional functioning scale may also indicate the effectiveness of speech rehabilitation techniques in both groups.

In both patient groups, gradual functional improvements in physical, role, and social areas were observed immediately after speech rehabilitation completion and continued to improve over the following 6 and 12 months. Both patient groups showed a gradual recovery in physical, role, and social functioning from the completion of speech rehabilitation until 6 and 12 months following therapy. The decrease in the standard deviation in both groups indicated a more homogeneous improvement over time, which confirmed the stabilization of recovery outcomes among patients who underwent speech rehabilitation.

Particular attention should be paid to the improvement of social functioning in Group I, where OnkoSpeech v4.0 computer software was used for speech rehabilitation. This indicates the prospect of using digital technologies in speech rehabilitation, which actively involve patients in social life, which is especially important for improving their QOL in the postoperative period.

Computer-based speech rehabilitation technique (OnkoSpeech v4.0) demonstrated its effectiveness, showing clear advantages in various symptomatic scales. The indicators obtained on scales related to speech (HNSP), social contacts (HNSC), nutrition (HNSO) and swallowing (HNSW) confirmed that the use of this digital technique provided better results in reducing these problems compared to speech rehabilitation techniques without the use of digital technologies. This emphasizes the high efficiency of innovative technologies that can significantly accelerate the restoration of patients' speech, improving their quality of life and reducing postoperative symptoms, such as speech and swallowing problems.

Conclusion. Speech rehabilitation following oral and oropharyngeal cancer surgery has a significant impact on the restoration of functional indicators, including physical, role and social functioning, as well as general health status.

It is important to consider that emotional functioning requires special attention. It can be significantly improved during speech rehabilitation, which is confirmed by changes in scores on the EF scale.

Digital technologies, such as the OnkoSpeech v4.0 computer software, play an important role in successful speech rehabilitation, providing a better effect in

Table 3

The QLQ-H&N35 questionnaire. Dynamics of patients' quality of life indicators using a 0-to-100 scale

Symptom scales of the QLQ-H&N35 questionnaire		Study phases	Group I (n – 70) Speech rehabilitation using OnkoSpeech v4.0 computer software	Group II (n – 70) Speech rehabilitation using the standard technique
Problems related to eating (HNSO)	Before starting combination treatment		12.1(0-22)	8.9(0-27)
	Before starting speech rehabilitation		54.9(17-100)	63.9(13-100)
	After completing speech rehabilitation		33.4(0-46) #	41.2(0-50)*#
	6 months after speech rehabilitation		21.9 (0-27)	27.4(0-25)*
	12 months after speech rehabilitation		15.7(0-22) #	17.9 (0-22)#
Problems related to speech (HNSP)	Before starting combination treatment		10.1 (0-33)	7.9(0-33)
	Before starting speech rehabilitation		54.2 (33-100)	55.1 (33-100)
	After completing speech rehabilitation		31.6 (17-50)#	34.5(17-66)#
	6 months after speech rehabilitation		20.4 (0-50)	24.1 (0-50)*
	12 months after speech rehabilitation		16.4(0-43)#	18.0(0-50)*#
Problems related to social contacts (HNSC)	Before starting combination treatment		6.8(0-33)	6.5(0-33)
	Before starting speech rehabilitation		68.9(50-100)	65.9(50-100)
	After completing speech rehabilitation		31.4(33-50)#	33.7(33-50)#
	6 months after speech rehabilitation		23.5 (0-50)	26.8(0-50)*
	12 months after speech rehabilitation		19.8 (0-50)#	22.1 (0-50) #
Swallowing problems (HNSW)	Before starting combination treatment		14.3 (0-23.5)	19.3(0-25)
	Before starting speech rehabilitation		64.8(10-83)	63.1 (9-87)
	After completing speech rehabilitation		23.2(0-46)	21.6(0-46)#
	6 months after speech rehabilitation		12.6 (0-25)	10.5 (0-25)
	12 months after speech rehabilitation		9.6 (0-22)	8.9 (0-22)

eliminating problems related to speech, social contacts, nutrition and swallowing. The use of these technologies opens up

new prospects for improving patients' long-term QOL. Thus, the integration of digital tech-

nologies into the speech rehabilitation of patients who have undergone surgery for oral cavity and oropharyngeal cancer holds significant potential to improve functional and symptomatic outcomes, and may become a key component of successful speech restoration.

The authors declare no conflict of interest.

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M.F. Heybatova

INVESTIGATION OF THE ONSET OF PREGNANCY AND CHANGES DURING SUBSEQUENT OUTCOMES AFTER ADMINISTRATION OF CYCLOPHOSPHAMIDE AND DOXORUBICIN TO FEMALE WHITE RATS

The article presents a study conducted to study changes during pregnancy and its outcomes after administration of cyclophosphamide and doxorubicin to female white rats for therapeutic purposes. Women taking antitumor drugs from the cytostatic group may become pregnant during treatment. Given the conflicting opinions about the effects of these drugs on pregnant women and the fetus, the therapeutic use of cyclophosphamide and doxorubicin has been determined. These drugs are representatives of the cytostatic group, individually and in combination, depending on the dose, affect the onset, course of pregnancy and fetal development in the prenatal and early postnatal periods. Since cytostatics, when used together, cause a sharp decrease in the amount of sex hormones, no pregnancies have been observed against their background. The results of our studies show that compared with the use of a dose of 2.5 mg/kg of doxorubicin and a dose of 10 mg/kg of cyclophosphamide, cyclophosphamide has a stronger teratogenic and effective effect.

Keywords: reproductive hormones, pregnancy, cyclophosphamide, doxorubicin

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Introduction. Pregnancy and childbirth are a serious challenge for women's health, they play an important role in procreation and increasing the number of offspring [2]. During pregnancy, a woman's body not only experiences additional stress, but also provides itself and the fetus with nutrients. Hormonal changes in the body of a pregnant woman are inevitable, and begin from the moment the egg is fertilized. The corpus luteum, which is formed during egg fertilization, begins to synthesize progesterone [5]. The fetus and placenta gradually join this process. A single fetoplacental system develops between the fetus, placenta and mother. Hormones synthesized by the ovaries, corpus luteum, and fetoplacental complex contribute to ensuring the normal course of pregnancy. During this period, the hypothalamus is inactivated, reducing the secretion of antidiuretic hormone, vasopressin and oxytocin. At the same time, the pituitary gland mass in pregnant women increases 2-3 times. The pituitary gland regulates the activity of the thyroid gland and adrenal glands by increasing the secretion of adrenocorticotrophic hormones and triiodothyronine [8]. The syn-

thesis of FSH and LH, which cause egg maturation and ovulation, also weakens. In the early stages of pregnancy, the corpus luteum synthesizes progesterone, the pregnancy hormone. Further development of the placenta leads to the fulfillment of the main endocrine function – the synthesis of progesterone, placental gonadotropin, placental lactogen, corticoliberin and estrogens. In the future, the amount of hormones in the blood varies depending on the duration of pregnancy. Sometimes pregnancy doesn't go so smoothly. In particular, a number of diseases, including cancer, may be detected in pregnant women as a result of sample examinations. In this case, there are certain problems in the treatment of patients. How to treat a woman so that she can become pregnant; how to ensure the normal course and completion of pregnancy? Unfortunately, given the rather negative effects of chemotherapy used in the treatment of cancer, and conflicting opinions about the effect of these drugs on the fetus. We conducted a study to study the effect of widely used representatives of the cytostatic group, cyclophosphamide and doxorubicin, individually and in combination for dose-dependent treatment on the onset of pregnancy, its course, and fetal development in the prenatal and early postnatal periods in female white rats.

Objective: to study changes during pregnancy and its outcomes after admin-

istration of cyclophosphamide and doxorubicin to female white rats for therapeutic purposes.

Materials and methods. The study was conducted on 66 female white rats of unknown lineage, weighing 180-200 g, raised in the vivarium of the Scientific Research Center of the Azerbaijan Medical University. The animals are divided into 7 groups. Six female rats were used in the control group, and 10 female rats were used in each experimental group. During 1 week, the first experimental group of females received intraperitoneal injections of 10 mg/kg, the second group received 20 mg/kg of cyclophosphamide (Russian Federation), the third group received 2.5 mg/kg of doxorubicin (Germany), the fourth group received 5 mg/kg, the fifth group received 10 mg/kg of cyclophosphamide and 2.5 mg/kg of doxorubicin, and the sixth group received 20 mg/kg of cyclophosphamide and 5 mg/kg of doxorubicin [10]. After 1 week of cytostatic treatment, each female rat of each group was placed in one cage with two intact males in a ratio of 1:2, respectively. The animals were kept together until fertilization, after which the males were separated from the females. Pregnancy was assessed by the detection of spermatozoa in a smear of the vaginal contents of female rats and by weight gain of animals after 1 week. Pregnant females were monitored. The course of pregnancy and the condition of the born offspring were

HEYBATOVA Milana Faig gizi – Assistant Professor of the Department of Pharmacology, Azerbaijan Medical University; ORCID: <https://orcid.org/0009-0000-9837-9570>, statya2021@mail.ru.

assessed by visual observation. When conducting scientific research, the provisions of the European Parliament and the European Union on the protection of animals were observed. The parametric Student's criterion and the nonparametric Wilcoxon-Mann-Whitney U criterion were used to calculate the experimental data. The results were processed using the Microsoft Excel statistical program.

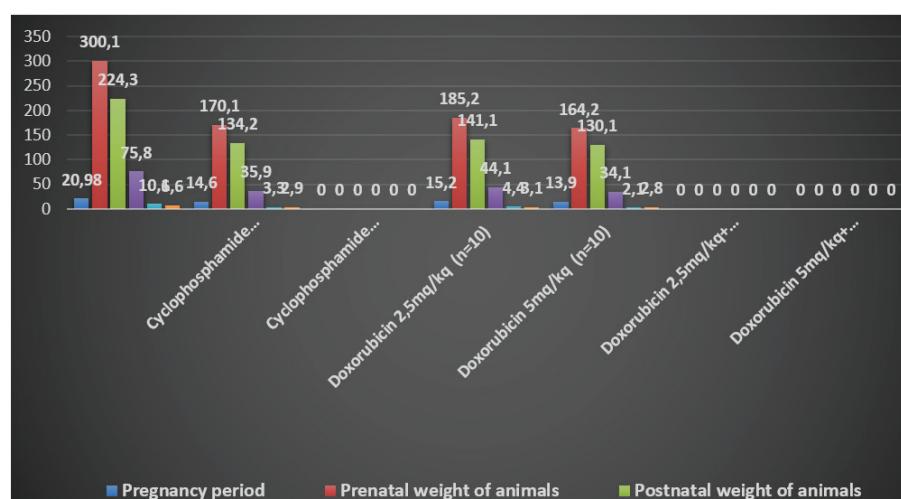
Results and discussion. In a study on the effect of repeated administration of cyclophosphamide and doxorubicin on reproductive function [4], the goal was to consistently study the following stages: 1) pregnancy 2) the course of pregnancy 3) duration 4) the process of childbirth 5) postpartum condition 6) the quantitative composition of the offspring born 7) the weight of the cubs. The study of the development and onset of pregnancy and childbirth provides detailed scientific information on the effect of the drugs we studied, both individually and in combination, on reproductive function, depending on the dose and on the background of repeated use [1, 9]. Taking into account the exceptional role of the concentration of hormones of the reproductive system in ensuring fertilization, the onset of pregnancy and its successful completion, the results of long-term use of cyclophosphamide and doxorubicin, administered separately and in combination in various doses, for the specified periods of pregnancy were studied. The noted cytostatic and chemotherapeutic properties of both drugs were studied both before pregnancy and continuously throughout pregnancy and regularly after childbirth. As can be seen in Figure, an analysis of the re-

sults of the study showed that the onset and duration of pregnancy in animals of the control group, differences in pre- and postnatal weight of animals, the number of cubs and the weight of cubs at birth were within the normal range.

When cyclophosphamide was administered at a dose of 10 mg / kg to female rats during mating with males for 1 week, the following pattern was observed. In females treated with cyclophosphamide at a dose of 10 mg/ kg, the duration of pregnancy decreased by 69.5% compared with the control group. The prenatal weight of the animals decreased by 56.6% and the postnatal weight by 59.8% compared to the control group. The difference between prenatal and postpartum weight was 47.3%. The number of

cubs decreased by 67.4% compared to the number of cubs in the control group. There was also a decrease in the birth weight of the cubs. So, if in the control group the birth weight was 6.6 ± 0.1 g, then in the group receiving cyclophosphamide at a dose of 10 mg/kg, this indicator significantly decreased by 56.1% and amounted to 2.9 ± 0.01 . Interestingly, when female rats were given a dose of cyclophosphamide 20 mg/kg for 5 days and then placed in the same cage with males in a 1:2 ratio, there was no fertilization, pregnancy and, consequently, no offspring. The results of the study are presented in Table.

The study found that when female rats who received 2.5 mg/kg of doxorubicin twice a week were placed in the same



Changes occurring in female white rats before pregnancy, during pregnancy and in offspring on the background of cyclophosphamide and doxorubicin administered separately and together for a long time ($M \pm m$) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared to with the control group

Changes in the mother and offspring before and during pregnancy with prolonged administration of cyclophosphamide and doxorubicin separately and in combination to female white rats ($M \pm m$)

Groups	Duration of pregnancy	Prenatal body weight of animals	Postnatal body weight of animals	Differences	Number of pups	Birth weight of pups
Control (n=6)	20.98±0.1	300.1±1.5	224.3±1.3	75.8±1.2	10.1±0.9	6.6±0.1
Cyclophosphamide 10 mg/kg (n=10)	14.6±0.01 *** (-30.5%)	170.1±0.08 *** (-43.3%)	134.2±1.2 *** (-40.2%)	35.9±1.1 *** (-52.7%)	3.3±0.1 *** (-67.4%)	2.9±0.01 *** (-56.1%)
Cyclophosphamide 20 mg/kg (n=10)	-	-	-	-	-	-
Doxorubicin 2.5 mg/kg (n=10)	15.2±0.01 *** (-27.6%)	185.2±1.1 *** (-38.3%)	141.1±0.95 *** (-47.1%)	44.1±1.0 ** (-58.2%)	4.4±0.2 * (-56.5%)	3.1±0.01 ** (-53.1%)
Doxorubicin 5 mg/kg (n=10)	13.9±0.01 ** (-32.8%)	164.2±1.01 *** (-54.7%)	130.1±0.9 *** (-58%)	34.1±0.8 * (-44.9%)	2.1±0.01 * (-79.3%)	2.8±0.01 ** (-57.6%)
Doxorubicin 2.5 mg/kg + Cyclophosphamide 10 mg/kg (n=10)	-	-	-	-	-	-
Doxorubicin 5 mg/kg + Cyclophosphamide 20 mg/kg (n=10)	-	-	-	-	-	-

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared to the control group

cage with males, they became pregnant, but the duration of pregnancy was reduced by 27.6% compared with the females in the control group. The prenatal weight of the animals was 38.3% lower than in the control group, and the postnatal weight was 37.1% lower. The difference between prenatal and postpartum weight decreased by 58.2% compared to the control group. As for the number of cubs, a serious decrease in the number of cubs was detected. So, if the number of pups in the control group was 10.1 ± 0.9 , then after administration of doxorubicin at a dose of 2.5 mg/kg, this indicator decreased by 56.5% and amounted to 4.4 ± 0.2 . The birth weight of the cubs also decreased by 53.1% compared to the control group. Against the background of the administration of doxorubicin at a dose of 5 mg/kg, the duration of pregnancy decreased by 32.8% and amounted to 13.9 ± 0.01 days. The prenatal weight of pregnant rats decreased by 54.7% to 164.2 ± 1.01 g. In the study of body weight after childbirth, it was found that compared with the control group, this indicator decreased by 42% and amounted to 130.1 ± 0.9 g. The difference between prenatal and postpartum weight decreased by 44.9%. The number of cubs also decreased by 79.3% compared to the control group, and the birth weight of cubs significantly decreased by 57.6%. Currently, monotherapy in cancer chemotherapy is a rare phenomenon. Two or more drugs are used to increase the effectiveness of treatment [4]. In this regard, studies have been conducted to determine the course and final outcome of pregnancy in women of reproductive age suffering from cancer, receiving combined chemotherapy and wishing to become pregnant, in order to form an opinion on the onset and course of pregnancy, the number and health of offspring born against the background of combined administration of cyclophosphamide and doxorubicin to female white rats, depending on doses. Initially, female rats were placed in cages with males in a 1:2 ratio, received cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg for 1 week and were monitored. As a result of long-term observations, despite the detection of spermatozoa in the uterus of some female rats, pregnancy did not occur [3]. At the next stage of experiments with animals, which we administered cyclophosphamide at a dose of 20 mg/kg in combination with doxorubicin at a dose of 5 mg/kg, pregnancy was also not observed. Visual observations show that administration of both drugs to female rats before preg-

nancy, depending on the dose, revealed significant deviations in the behavior of pregnant rats during the onset and during pregnancy, differing from those in the control group. It was noted that the mucous membranes of pregnant rats are clean, and the outer hair is smooth and thick. It was noted that pregnant females in all the studied groups did not build nests made of straw to house their cubs 2-3 days before giving birth. On the other hand, it was found that there is a significant difference in the course and nature of the birth process in pregnant rats of the corresponding experimental groups compared with similar indicators of the control group females. In addition, our study determined the postpartum body weight of pregnant rats: differences and changes between body weight in the last days of pregnancy and postpartum weight were evaluated. Visual observation of lactating female rats showed a tendency for them to ignore newborn cubs. Compared with the rats of the control group, the females in the corresponding experimental group did not protect or shelter their young from the environment, and were indifferent to them. Even with individual use, the cytostatics we studied prevent pregnancy, reduce the levels of reproductive hormones such as FSH, LH, ER, and ED, and inhibit egg maturation in the follicles of female rats. Pregnancy was not observed with the combined administration of cytostatics as a result of a sharp decrease in the amount of sex hormones. The main hormones regulating egg maturation, reaching the uterus after fertilization, implantation and further development of the embryo are progesterone and estradiol. Similarly, given that estradiol is closely related to the synthesis of progesterone, the synthesis of both of these hormones decreases dramatically when we prescribe cytostatics. The results of our research have clarified the controversial notion that cytostatics have a negative effect on the reproductive system. The idea has been confirmed that even optimal antitumor doses of the studied cytostatics have a negative effect on the amount of sex hormones and reproductive ability. The administration of the studied drugs to female white rats for a certain period of time before pregnancy caused serious violations of the reproductive ability of the animals. Therefore, first of all, proper pharmacological correction of side effects developing during treatment with these drugs should be carried out in order to prevent serious negative complications of treatment [6, 7]. From all of the above, it can be concluded that the reason for the lack of pregnancy in female rats, despite

the detection of spermatozoa in the uterine tract and preimplantation fetal death, is a sharp decrease in the concentration of the hormone estradiol in blood plasma.

Conclusion. The research results show that compared with the use of doxorubicin at a dose of 2.5 mg/kg and cyclophosphamide at a dose of 10 mg/kg separately, cyclophosphamide has both a negative effect on the onset of pregnancy and a pronounced teratogenic effect. The combination of these drugs, regardless of the dose, has the strongest negative effect on both hormonal balance and the onset and course of pregnancy. Also, the combined use of these medications prevents the onset of pregnancy.

The authors declare that there is no conflict of interest.

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A.V. Alexandrova, O.N. Ivanova, E.N. Sivtseva, L.A. Nikolaeva

IRON DEFICIENCY IN ADOLESCENTS OF THE SAKHA REPUBLIC (YAKUTIA)

The article is devoted to an urgent problem – iron deficiency conditions in children in the Far North. The aim of the study was to study the prevalence and risk factors for the development of iron deficiency anemia in children of the Republic of Sakha (Yakutia). Among the 200 adolescents aged 12 to 17 years examined, iron deficiency anemia was detected in 28% and latent iron deficiency in 30%. The group of examined 56 adolescents with iron deficiency anemia was divided into two groups: 32 girls and 24 boys. The presence of anemia was confirmed by laboratory indicators. Risk factors for the development of iron deficiency anemia in girls were heavy and prolonged menstruation, fasting, refusal to eat meat, intense physical activity, gastritis and colitis, and in boys - pubertal growth spurt, intense physical activity, refusal to eat meat.

Keywords: anemia, iron, hemoglobin, transferrin, adolescents.

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Introduction. Iron deficiency anemia (IDA) and latent iron deficiency are a pressing problem in modern pediatrics. IDA is observed in 6-40% of the child population depending on the region of residence. Over the past fifteen years, the incidence of anemia in children has increased 3.7 times. The highest prevalence of iron deficiency is observed in the Northern territories, where latent iron deficiency is detected in 50-60% of children [1, 2]. Of all anemias, 80% is IDA. Regional statistics on the frequency of anemia in children and adolescents in Russia vary greatly, reaching maximum figures in the republics of the North Caucasus and the northern territories of Russia. According to statistics for 2023, the incidence of anemia in adolescents aged 15 to 17 in the Republic of Sakha (Yakutia) was 4161 cases per 100 thousand adolescent population, which is a high figure

for the Russian Federation (1694 per 100 thousand adolescent population) [5]. The prevalence of IDA in children changes with age and depends on the child's gender. During the period of rapid growth, iron deficiency reaches 50% and prevails in girls, they grow faster and experience menstrual blood loss. Literature data on the prevalence of IDA in children indicate not only the socio-medical significance of iron deficiency conditions, but also the importance of the influence of micro- and macroecological regional elements. Over the past two decades, the incidence of IDA in children of the Republic of Sakha (Yakutia) has changed, which requires further study.

Objective of the study: to study the prevalence and risk factors for the development of IDA in adolescents of the Republic of Sakha (Yakutia).

Materials and methods. We analyzed the data of 200 patients who visited the outpatient clinic of the Republican Hospital No. 1 - National Center of Medicine, using the free sampling method. The inclusion criteria in the study group were: the child's age from 12 to 17 years and complaints of weakness, fatigue, frequent acute respiratory viral infections. The exclusion criteria from the group were congenital pathology of the hematopoietic system (megaloblastic anemia, thrombocytopenic purpura, hemolytic anemia, etc.). Girls predominated in the study group (60%), by age, children were most often aged 12 to 15 years - 65%,

the remaining children (35%) were aged 15 to 17 years.

The adolescents underwent an in-depth study of venous blood from the cubital vein on an empty stomach. Blood was tested to determine the general extended blood test, iron-binding capacity of serum, blood iron level, ferritin and transferrin saturation coefficient. When comparing statistical differences in groups, a nonparametric evaluation criterion, the Mann-Whitney method, was used. The critical value of the significance level (p) was taken to be 0.05.

Results and discussion. According to the results of the analysis of 200 adolescents who visited the clinic for various diseases, half of them were found to have iron deficiency conditions: IDA was found in 56 (28%) and latent iron deficiency in 60 (30%) adolescents.

All children with identified IDA complained of weakness - 80% (160 children), fatigue 100% (200 children), dizziness in 50% (100 patients), taste perversion in 20% of those examined - children had a desire to eat chalk, earth, etc., pale skin and mucous membranes were noted in 100% of those examined, headaches were noted in 80% of those examined (160 children).

Table 1 shows the distribution of latent iron deficiency and IDA by gender in adolescents from 12 to 17 years old.

Thus, as can be seen from Table 1, latent iron deficiency and IDA were more often observed in adolescent girls.

SAI RS (Y) "Republican Hospital No. 1 - M.E. Nikolaev National Center of Medicine: **ALEXANDROVA Anna Vasilyevna** – head, Children's Clinic, kp_rbnm@mail.ru; **NIKOLAIEVA Lyudmila Alekseevna** – director of the Pediatric Center, detstbo@mail.ru; **IVANOVA Olga Nikolaevna** – Doctor of Medical Sciences, Professor, M.K. Ammosov North-Eastern Federal University, ORCID: 0000-0001-5210-0220, olgadoctor@list.ru; **SIVTSEVA Elena Nikolaevna** – Candidate of Medical Sciences, Senior Researcher, FSBSI "Yakut Science Center of Complex Medical Problems", ORCID: 0000-0001-6907-9800, sivelya@mail.ru.

According to the World Health Organization (WHO, 2021), the global prevalence of anemia among adolescents (15–19 years) remains significant, with IDA accounting for about 50% of all cases of anemia in children and adolescents. The exact rates vary by region, but on average, IDA is detected in 10–20% of adolescents in developed countries and up to 30–40% in developing countries [13].

The Global Burden of Disease (GBD) 2019 study found that the global age-standardized prevalence of anemia in 2019 was 23,176.2 per 100,000 population, with higher rates among adolescent girls (especially 15–19 years) due to menstrual blood loss [8].

In developing countries such as South Asia and sub-Saharan Africa, the prevalence of IDA among adolescents can reach 35–50%, which is associated with malnutrition, infections (e.g. malaria), and low availability of iron-rich foods [8, 10].

Data for circumpolar regions are limited, but studies indicate an increased prevalence of IDA among indigenous peoples. For example, among Inuit and other indigenous children in Canada, IDA is found in 20–30% of adolescents; in Scandinavia, the prevalence of IDA is lower (about 10–15%) among the Sami, due to better access to health care and iron fortification programs, but is still higher among adolescent girls [9].

The prevalence of IDA in Russia varies greatly by region: from 6% in large cities with good medical infrastructure to 40% in rural and northern regions [2, 3]. This is higher than the European average, but lower than in South Asia or Africa.

An analysis of laboratory parameters of IDA blood in adolescents was conducted. Table 2 shows the data on the content of hemoglobin and erythrocytes in the general blood test.

As can be seen from Table 2, adolescents had low red blood cell counts per unit volume of blood and hemoglobin, while the decrease in hemoglobin in adolescent girls was statistically significantly lower than in boys.

Table 1
Distribution of iron deficiency conditions in adolescents depending on gender

Iron deficiency conditions	Girls	Boys
Latent iron deficiency, n=60	36 (60%)	24 (40%)*
Iron deficiency anemia, n=56	32 (57%)	24 (43%)

Note. In table 1-3 *p<0.05.

Table 2
Comparison of general blood test parameters in adolescents with iron deficiency anemia by gender (girls n=32, boys n=24)

Standards of indicators	Hemoglobin		Erythrocytes	
	120-150 g/l		4.0-5.2 · 10 ⁹ /l	
Groups	girls	boys	girls	boys
Values	90.0±0.05 г/л	115.2±0.03 г/л*	3.3±0.08·10 ⁹ /л	3.9±0.06·10 ⁹ /л

International standards for diagnosing IDA in adolescents include hemoglobin levels below 12 g/dl for girls and 13 g/dl for boys (WHO). According to literature, adolescents with IDA often have average hemoglobin values of 9–11 g/dl [7, 10], which correlates with the results of this study.

All children with IDA (56 people) had their blood tested to determine serum iron-binding capacity, blood iron levels, ferritin, and transferrin saturation coefficient. The data obtained were compared among girls and boys. Table 3 also provides international standards for diagnosing IDA in adolescents.

As can be seen from the table, the average values of all the studied parameters of the blood ferrum complex were below the generally accepted norms. In this study, statistically significantly lower ferritin levels (10 µg/l), serum iron levels (4.3 µmol/l) and an increase in the iron-binding capacity of the serum (81.8 µmol/l) were found in adolescent girls than in adolescent boys, which corresponds to international data on a more severe course of IDA in girls due to physiological iron losses [11].

Analysis of laboratory parameters indicates a decrease in iron per unit volume of blood (serum iron), as well as transport forms of blood proteins containing iron (ferritin), a decrease in the blood iron saturation coefficient (transferrin saturation coefficient), an increase in the level of the parameter reflecting the amount of iron that can be transported by the blood throughout the body (total iron-binding capacity of the blood serum) [7].

When ascertaining the data of the anamnesis of the disease, the following factors contributing to the development of iron deficiency anemia were identified: refusal to eat meat (beef, horse meat, venison), spurt growth, intense physical activity, heavy menstruation in girls (Table 4).

Risk factors for the development of IDA in girls include fasting, abstinence from meat, weight-loss diets, gastritis, and colitis. The main predisposing factor for IDA in girls was found to be heavy and prolonged menstruation.

Risk factors for the development of iron deficiency in boys include a pubertal growth spurt, intense physical activity, and abstinence from meat.

Table 3
Comparison of ferrum complex levels in blood serum in adolescents with IDA by gender (girls n=32, boys n=24)

Standards of indicators	TIBC		Serum iron blood		Transferrin saturation coefficient		Ferritin	
	45.3-77.1 µmol/l		8.95-30.43 µmol/l		15-45%		15-150 mcg/l	
Groups	girls	boys	girls	boys	girls	boys	girls	boys
Values	81.8±0.05 µmol/l	77.2±0.03 µmol/l	4.3±0.08 µmol/l	7.09±0.06* µmol/l	10±0.0%	11±0.03%	10± 0.07 mcg/l	15±0.03* mcg/l

TIBC – total iron-binding capacity of serum

Table 4

Risk factors for the development of iron deficiency conditions in adolescents

Risk factors	Girls, n=32	Boys, n=24
Abstinence from red meat (beef, horse meat, venison)	13 (41%)	6 (25%)
Weight loss diets	5 (16%)	-
Pubertal growth spurts	-	12 (50%)
Intense physical activity	3 (9%)	9 (38%)
Heavy and prolonged menstruation	22 (69%)	-
Gastritis and colitis	7 (22%)	4 (17%)

In developing countries, the high prevalence of IDA is associated with nutritional deficiencies (low intake of heme iron), parasitic infections (malaria, helminthiasis), and chronic diseases. For example, in India, 52–63% of adolescents have anemia, with IDA prevalent due to vegetarian diets and low socioeconomic status. [12] In developed countries such as the United States and Europe, IDA is less common (5–10% among adolescents), but remains a problem among risk groups (vegetarians, girls with heavy menstruation). Iron screening and food fortification programs reduce the prevalence of anemia [11].

According to the literature, in circum-polar regions, the main risk factors include: limited access to iron-rich foods due to geographic isolation; a shift from traditional diets to diets low in red meat (e.g. replacing beef with chicken or canned meats with lower iron bioavailability); environmental factors such as cold climates, which increase energy requirements and the burden on iron metabolism [6].

Conclusion. Among adolescent patients living in Yakutia and seeking medical attention with various diseases, half were found to have iron deficiency conditions: IDA was found in 28%, latent iron deficiency in 30% of adolescents. This study indicates a high prevalence of pathology in the region and correlates with data from a number of regions of the Russian Federation [2, 4].

The work on the study of the presence of IDA in adolescents is confirmed by the results of laboratory tests: reduced levels of ferritin (10–15 µg / l), serum iron (4.3–7.1 µmol / l), transferrin saturation coefficient (10–11%), erythrocytes (3.3–3.9 · 10⁹ / l), hemoglobin (90–115 µmol / l) and a high level of iron-binding capacity

of blood serum (77.2–81.8 µmol / l). The main factor contributing to the development of IDA in adolescents is the discrepancy between the body's iron stores and needs. The main risk factors for IDA in adolescent girls include heavy and prolonged menstruation, as well as refusal to eat meat and fasting. In adolescent boys, the risk factors for IDA are: pubertal growth spurt, intense physical activity and refusal to eat meat.

During examination of adolescents from 12 to 17 years old, a thorough anamnesis is collected (to identify risk factors), a complete blood count and the level of serum iron, transferrin, ferritin and total iron-binding capacity of the blood serum are required. Children with IDA and latent iron deficiency are recommended to eat foods rich in iron (meat, liver, etc.), treat gastrointestinal diseases, limit intense physical activity, and take iron supplements. Girls should be examined by an obstetrician-gynecologist.

Adolescence is a period of increased iron demand, which not only affects the iron level in the blood, but also the general condition of the adolescent child.

The authors declare no conflict of interest.

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L.D. Olesova, N.T. Borisova, E.D. Okhlopkova, S.D. Efremova

EVALUATION OF THE EFFECT OF SOME BIOLOGICAL PROPERTIES OF SPROUT JUICE OF YAKUT WHEAT VARIETIES ON WOMEN'S BODIES

The article presents a study on the effectiveness of the immunomodulatory and anti-inflammatory properties of juice from wheat sprouts growing in the extreme climatic conditions of the Far North. Based on clinical and immunological analyses of 27 volunteers from Sakha women aged 40 to 60 years who took vitgrass for 24 days in a volume of 20 ml, positive changes were obtained: there is a significant increase in lymphocytes and monocytes, which indicates the activation of immune mechanisms while maintaining homeostasis. In 29,6% of the participants, elevated ESR levels returned to normal after taking the juice, which shows the anti-inflammatory effect of vitgrass. Restoration of leukocyte and granulocyte levels in 14.8% of participants with reduced levels indicates support for hematopoiesis and immunological balance. A moderate increase in IgA, IgM, and IgG antibodies after juice intake causes a strengthening of humoral immunity and the interaction of various parts of the defense system.

The results obtained are consistent with the literature data and open up opportunities for further study of the biological properties of juice from the sprouts of local wheat varieties growing in the extreme climatic conditions of Yakutia, its potential for use in complex therapy of immune disorders and for the development of effective natural remedies for the treatment and prevention of many diseases in the North.

Keywords: whitegrass, green shoots, wheat, chlorophyll, immunity, inflammation.

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Introduction. Ensuring the health of the population in the North, especially in Arctic and rural areas, becomes particularly important against the backdrop of a deteriorating environmental situation, poor nutrition, and a rise in disease incidence. It necessitates the search for effective natural methods and means to strengthen and restore the health of northerners. One such natural product that can replenish the body with vitamins, minerals, essential amino acids, and enzymes is young wheat sprouts, 10–12 cm long, grown using the hydroponic method [5]. The therapeutic effect of wheatgrass juice is due to its high content of chlorophyll (70%), carotene, vitamins (A, C, E, K, B vitamins), bioflavonoids, iron, mineral substances (calcium, potassium, sodium, zinc, copper, aluminum, and magnesium), sulfur, phosphorus, and 17 amino

acids, 8 of which are essential (lysine, isoleucine, tryptophan, phenylalanine, and others). Its composition includes proteins - 7.5 g, fats - 1.3 g, carbohydrates - 41.4 g. [4].

The vitamin-mineral composition of juice from wheat sprouts is richer than that of whole grain, as during the sprouting of wheat, the content of vitamin E (tocopherol) increases by 50 times, vitamin B6 (pyridoxine) by 10 times, vitamins F and P by 3-4 times, protein compounds by 2-3 times, and fats by 4-5 times. The energy value is 198 kilocalories [9, 12].

Numerous studies of the therapeutic properties of this product have proven its immunomodulatory, antioxidant, anti-hypoxic, nephroprotective, anti-inflammatory, and anti-tumor effects [1].

In Yakutia, under conditions of extremely cold climate, the production of wheatgrass has started relatively recently, and the main feature of local production is the use of zoned wheat varieties «Tuymaada», «Prilenskaya-9», grown in the ecologically clean territory of the largest agricultural region of the republic.

The aim of the study is to assess the immunomodulatory and anti-inflammatory properties of juice from the sprouts of Yakut varieties of wheat.

Materials and Methods. The study voluntarily involved 27 women of Yakut nationality aged from 40 to 61 years, living in the city of Yakutsk. All participants in the study signed informed consent for the research after being briefly informed

about the purpose and objectives of the study, approved by the Local Committee on Biomedical Ethics at the Federal State Budgetary Institution 'Yakutsk Scientific Center for Complex Medical Problems', Yakutsk (protocol No. 60 of April 10, 2024).

The work was conducted at the base of the YNC KMP. The study program included a survey on general health status; anthropometric examination - measuring height, body weight, waist and hip circumference, chest using scales and a tape measure; functional studies of the cardio-respiratory system: heart rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), performing a general analysis of blood, determining IgA, IgG, IgM, and IL-6. Venous blood was taken in vacuum containers in the morning on an empty stomach before taking wheatgrass and after 24 days of taking wheatgrass (the course recommended by the manufacturer).

Statistical processing was carried out using the IBM SPSS Statistics 27 software package. The normality of the distribution of quantitative indicators was determined by the Kolmogorov-Smirnov test. Values are presented as median (Me) and quartiles (Q1; Q3). The significance of differences was assessed using the Mann-Whitney test. The probability of the null hypothesis being true was accepted at $p < 0.05$. Correlation analysis was conducted using the Spearman method,

FSBSI "Yakutsk Science Center for Complex Medical Problems": **OLESOVA Lyubov Dyginovna** – PhD, Senior Researcher, ORCID: 0000-0002-2381-7895, oles59@mail.ru; **OKHLOPKOVA Elena Dmitrievna** – PhD, Researcher, ORCID: 0000-0002-7061-4214, elena_ohlopkova@mail.ru; **EFREMOVA Svetlana Dmitrievna** – junior researcher, ORCID: 0000-0002-5225-5940, esd64@mail.ru; **BORISOVA Natalya Tarasovna** – intern at FSBEI of HE "Arctic State Agrarian University", individual entrepreneur of the city farm "Ykt.botanic", Biotech Laboratory of Technopark "Yakutia", ORCID: 0009-0008-1445-9265, ipborisova@yandex.ru.

where r is the correlation coefficient, and p is the significance of the result.

Results and discussion. The dynamics of the complete blood count indicators in the subjects before and after taking wheatgrass shows that the increase in lymphocytes by 17% ($p=0.036$), MID (monocytes, eosinophils, basophils) by 40% ($p<0.001$), as well as the decrease in ESR by 46% ($p<0.002$), indicate positive changes in immune status and a reduction in inflammation. All indicators remained within reference a value, which suggests the maintenance of homeostasis and the absence of negative effects [14].

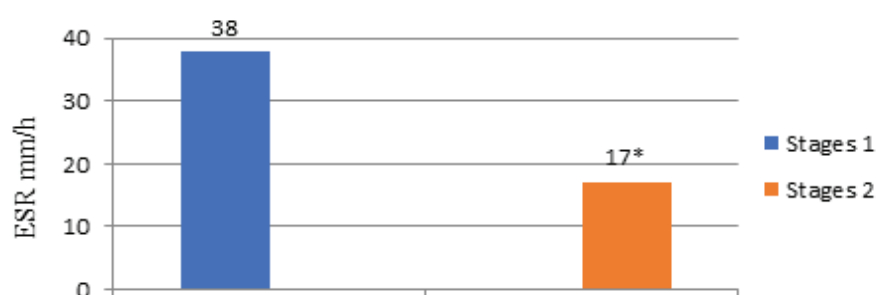
Positive changes in lymphocyte ($p=0.036$) and monocyte ($p=0.001$) counts upon juice consumption indicate activation of the cellular component of the immune system (Table 1). Furthermore, the activation of monocytic and eosinophilic lines in the second stage may suggest the activation of the body's adaptive defense mechanisms [2], which is consistent with the known immunomodulatory and anti-inflammatory effects of plant components rich in isoflavones, polysaccharides, and phytochemical compounds that promote the harmonization of the immune response [4,15,17].

ESR is a nonspecific marker of inflammation, and the observed twofold decrease in the median ESR value in our participants after taking vitgrass ($p<0.002$) also indicates the anti-inflammatory and immunostimulating properties of whitegrass [13,18]. Importantly, the initial inflammatory reactions are not exacerbated; on the contrary, they decrease, confirming the safety and potential effectiveness of using vitgrass in the treatment of inflammatory processes.

In 8 participants (29.6%), elevated ESR levels (23 - 54 mm/h) were identified prior to the intake of the juice while leukocyte levels remained stable, indicating the presence of hidden inflammatory processes or reactions in the body that are not accompanied by obvious signs of infection (Fig. 1).

After consuming the juice, the ESR values in the participants significantly improved and returned to normal, which once again demonstrates the anti-inflammatory and immunomodulatory effects of this herbal adaptogen. Such a separate analysis underscores the importance of a comprehensive assessment of the body's condition when using biologically active substances.

In 4 participants (14.8%), the median levels of leukocytes ($3.45 \times 10^9/L$) and granulocytes ($1.65 \times 10^9/L$) were below



Improvement of ESR indicators in eight participants after consuming wheatgrass juice. 1- stage before the reception, 2- stage after taking.

normal; however, after taking whitegrass, these levels significantly increased and returned to normal values ($4.5 \times 10^9/L$ and $2.2 \times 10^9/L$, respectively). At the same time, the levels of lymphocytes and ESR remained within the normal range. Indeed, the decrease in leukocytes and granulocytes may indicate temporary immune system disruptions possibly due to stress, nutrient deficiencies, and quality of life [16]. The absence of bright inflammatory signs or an acute infectious

process with normal ESR aligns with the concept of 'hidden' or chronic infections or conditions related to a deficiency in the immune system's resources [11]. The recovery of leukocytes and granulocytes after taking whitegrass further indicates its potential role in supporting and restoring immune functions and highlights the possibility of integrating natural remedies into modern approaches to strengthening immunity, which is a promising and relevant area of science.

Table 1

Indicators of peripheral blood, antibodies, and IL-6 before and after taking wheatgrass

Показатель	Me (25%;75%)		p
	1 этап	2 этап	
WBC, $10^9/L$	5.60 (4.60; 6.10)	5.60 (4.60; 6.50)	
Lymph#, $10^9/L$	1.70 (1.40; 2.10)	2.00 (1.60; 2.30)	0.036
Mid#, $10^9/L$	0.50 (0.30; 0.50)	0.70 (0.50; 0.90)	<0.001
Gran#, $10^9/L$	3.30 (2.50; 3.60)	3.00 (2.10; 3.80)	
Lymph#, %	32.80 (29.80; 29.40)	35.70 (30.90; 49.00)	
Mid, %	8.40 (6.70; 9.70)	12.40 (10.50;13.10)	<0.001
Gran, %	57.80 (52.50;61.80)	51.10 (46.30; 55.60)	0.003
RBC, $10^{12}/L$	4.07 (3.66;4.21)	3.90 (3.60; 4.11)	
HGB, g/L	113.00 (105; 120)	108.00 (99; 117)	
HCT, %	35.40 (33.00; 38.00)	35.60 (32.30; 37.50)	
MCV, fL	92.10 (86.00;94.10)	92 (86.90; 94.80)	
MCH, pg	29.30 (27.60; 30.60)	28.20 (27.30; 29.70)	
MCHC, g/L	322.00 (320; 327)	311.00 (305; 314)	<0.001
RDW-CV, %	13.90 (13.60; 14.60)	14.60 (14.00; 15.20)	0.04
PLT, $10^9/L$	212.00 (180; 254)	213 (181; 257)	
MPV, fL	9.10 (8.60; 10.40)	9.70 (8.90; 10.40)	
PDW	15.80 (15.50;16.00)	15.90 (15.60; 16.20)	
PCT, %	0.19 (0.18; 0.23)	0.19 (0.17; 0.23)	
P-LCC, $10^9/L$	66.00 (51.00; 74.00)	69.00 (54.00; 81.00)	
P-LCR, %	31.10 (26.00; 39.00)	33.90 (27.20; 38.80)	
ESR, mm/h	15.00 (10.00; 27.00)	7.00 (4.00; 11.00)	0.002
IgA, 0,8-4,0 mg/ml	4.60 (3.17; 6.32)	4.90 (2.80; 7.09)	
IgM, 0,48-2,16 mg/ml	2.66 (2.07; 4.32)	2.41 (1.64; 3.79)	
IgG, 4,8-16 mg/ml	8.30 (5.99; 13.22)	7.54 (5.40; 10.48)	
Il-6, 6-10 pg/ml	4.10 (3.86; 5.00)	4.12 (3.84; 6.03)	

Table 2

Correlations of IgA, IgM, IgG, IL-6 with peripheral blood parameters. Spearman's Correlations

		IgA 0,8-4,0 mg/ml	IgM 0,48-2,16 mg/ml	IgG 4,8-16,0 mg/ml	Il-6 up to 10 pg/ ml	WBC, 10 ⁹ /L	Mid#, 10 ⁹ /L	Gran#, 10 ⁹ /L	RDW-CV, %	RDW-SD, fL	P-LCR, %	MCV, fL	HGB, g/L
IgA 0,8-4,0 mg/ml	Correlation coefficient	1.000	.269*	.181	.542**	.352**	.332*	.332*	-.091	-.210	.355**	-.045	.187
	Significance (bilateral)	.	.049	.191	-.001	.009	.014	.014	.514	.127	.008	.743	.176
	N	54	54	54	54	54	54	54	54	54	54	54	54
IgM 0,48-2,16 mg/ml	Correlation coefficient	.269*	1.000	-.071	.036	.081	.012	.052	-.089	-.367**	-.029	-.281*	-.183
	Significance (bilateral)	.049	.	.612	.795	.561	.934	.710	.520	.007	.834	.039	.185
	N	54	54	54	54	54	54	54	54	54	54	54	54
IgG 4,8-16,0 mg/ml	Correlation coefficient	.181	-.071	1.000	.040	.116	.062	.127	.138	.185	-.207	-.134	-.090
	Significance (bilateral)	.191	.612	.	.775	.403	.656	.359	.328	.181	.133	.335	.516
	N	54	54	54	54	54	54	54	54	54	54	54	54
Il-6 up to 10 pg/ml	Correlation coefficient	.542**	.036	.040	1.000	.340*	.260	.370**	-.134	-.111	.230	.932	.387**
	Significance (bilateral)	-.001	.795	.775	.	.012	.058	.006	.335	.424	.094	.818	.004
	N	54	54	54	54	54	54	54	54	54	54	54	54
WBC, 10 ⁹ /L	Correlation coefficient	.352**	.081	.116	.340*	1.000	.656**	.927**	-.207	-.217	.108	-.106	.151
	Significance (bilateral)	.009	.561	.403	.012	.	-.001	-.001	.134	.115	.438	.445	.277
	N	54	54	54	54	54	54	54	54	54	54	54	54
Mid#, 10 ⁹ /L	Correlation coefficient	.332	.012	.082	.260	.656**	1.000	.466**	.111	.128	.171	.043	.094
	Significance (bilateral)	.014	.934	.656	.058	-.001	.	-.001	.425	.358	.217	.760	.501
	N	54	54	54	54	54	54	54	54	54	54	54	54
Gran#, 10 ⁹ /L	Correlation coefficient	.332*	.052	.127	.370**	.927**	.466**	1.000	-.231	-.271*	.083	-.111	.152
	Significance (bilateral)	.014	.710	.359	.006	-.001	-.001	.	.094	.047	.549	.423	.272
	N	54	54	54	54	54	54	54	54	54	54	54	54
RDW-CV, %	Correlation coefficient	-.091	-.088	.136	-.134	-.207	.111	-.231	1.000	.491**	-.011	-.388**	-.482**
	Significance (bilateral)	.514	.520	.326	.335	.134	.425	.094	.	-.001	.0934	.004	-.001
	N	54	54	54	54	54	54	54	54	54	54	54	54
RDW-SD, fL	Correlation coefficient	-.218	-.364**	.185	-.111	-.217	.128	-.271*	.491**	1.000	-.087	.327*	-.001
	Significance (bilateral)	.127	.007	.101	.424	.115	.358	.047	-.001	.	.530	.016	.993
	N	54	54	54	54	54	54	54	54	54	54	54	54
P-LCR, %	Correlation coefficient	.355**	-.029	-.207	.230	.106	.171	.083	-.011	-.087	1.000	-.141	.076
	Significance (bilateral)	.008	.834	.133	.094	.438	.217	.549	.934	.530	.	.308	.585
	N	54	54	54	54	54	54	54	54	54	54	54	54
MCV, fL	Correlation coefficient	-.046	-.281*	-.134	.032	-.106	.043	-.111	-.388**	.327*	-.141	1.000	.401**
	Significance (bilateral)	.743	.039	.335	.818	.445	.760	.423	.004	.016	.308	.	.003
	N	54	54	54	54	54	54	54	54	54	54	54	54
HGB, g/L	Correlation coefficient	.187	-.183	-.090	.387**	.151	.094	.152	-.482**	-.001	.076	.401**	1.000
	Significance (bilateral)	.176	.185	.516	.004	.277	.501	.272	-.001	.993	.585	.003	.
	N	54	54	54	54	54	54	54	54	54	54	54	54

* The correlation is significant at the 0.05 level (two –tailed). ** The correlation is significant at the 0.01 level (two-tailed)

Despite a slight decrease in the level of red blood cells (RBC) within the normal range and the maintenance of a low hematocrit (HCT) value, one can say that the function of erythropoiesis is preserved and there are no severely expressed anemias (Table 1). However, the decreased concentration of hemoglobin (Hb) and MCHC (hemoglobin in red blood cells) ($p=0.035$) indicates pathological features that are characteristic of hypochromic anemias, where the decrease in MCHC is mainly related to iron deficiency or disruptions in hemoglobin synthesis. At the same time, it is important to consider that a reduction in MCHC may also be due to a deficiency of nutrients necessary for hemoglobin synthesis, such as vitamin B12, folic acid, and trace elements, such as copper or zinc, whose deficiency disrupts the normal metabolism of erythrocytes [10]. Therefore, an extensive study with an assessment of nutritional status will be appropriate for accurately determining the cause of the changes.

Antibodies IgA, IgM, and IgG are different types of immune proteins and vary in structure, function, and timing of appearance during the immune response. The main function of IgA is to prevent the entry of pathogens through mucous membranes. IgM is the first immunoglobulin that appears in response to infection and indicates a recent infection. IgG are the main antibodies in the blood and tissues, providing long-term protection.

Our research showed that the levels of IgA and IgM antibodies in the subjects slightly exceeded the reference values both before and after the intake of wheatgrass (Table 1). At the same time, the content of IgA in the second phase increased slightly compared to IgM and IgG. According to some authors, in individuals living in Arctic conditions, elevated concentrations of IgM and IgA, 1.4–2.6 times higher, and the frequency of elevated concentrations, 2.4–8.8 times higher, are associated with an increase in the content of neutrophilic granulocytes and the cytokine interferon-gamma (IFN- γ), which in turn is aimed at ensuring the effectiveness of clearance of metabolic products under hypoxic conditions [7]. In other studies, this fact is associated with a decrease in adaptive potential, an increase in morbidity [8], or the peculiarities of the immunological reactivity of the indigenous Arctic population under harsh climatic conditions [6]. A slight excess of the upper limit of the norm of IgM may also be a response of the immune system to a recent infection that occurred in the spring. At the same time, the average IL-6 level in our study participants

is slightly lowered and has not changed since the stage of the study (Table 1), which indicates the absence of obvious inflammatory reactions in the body, since Interleukin-6 is a cytokine, that is, a signaling molecule that plays an important role in regulating immune and inflammatory responses in the body. This aspect is important for understanding the features of the immune response in people living in harsh conditions, and requires further research to fully uncover the mechanisms of this phenomenon.

The correlation analysis showed a direct link between IL-6 and IgA as well as the content of HGB (Table 2), which further confirms the role of IL-6 as an important modulator of the immune response, especially in the regulation of IgA production - the main antibody of mucous membranes and its key role in the production of erythropoietin (EPO) - a hormone that stimulates the formation of red blood cells in the bone marrow.

Correlations of IgA, IgM, IgG, IL-6 with peripheral blood parameters.

Thus, the application of wheat grass from local varieties of wheat contributes to positive changes in the immune status of Sakha women. There is a significant increase in lymphocytes and monocytes, as well as a decrease in ESR, which indicates activation of immune mechanisms and reduction of inflammatory processes while maintaining homeostasis. An important aspect is the restoration of leukocyte levels among participants in the study with reduced levels, which indicates support for hematopoiesis and immunological balance. The analysis of IgA, IgM, and IgG antibodies shows a tendency for their moderate increase, indicating a strengthening of humoral immunity and the interaction of various components of the defense system. Despite the stable level of IL-6, its correlation with IgA confirms the significance of cytokines in regulating the immune response of mucous membranes. Overall, the results confirm the immunomodulatory and anti-inflammatory properties of wheatgrass from local wheat varieties on the female body, which is consistent with the literature.

Conclusion. The obtained results open up the possibility for further extensive study of the biological properties of wheatgrass juice, which grows in the extreme climatic conditions of Yakutia, with the aim of developing effective local natural remedies for the comprehensive therapy of immune disorders, prevention, and treatment of various diseases in the North.

The authors declare that there are no conflicts of interest.

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DIAGNOSTIC AND TREATMENT METHODS

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ZHARNIKOVA Tatyana Nikolaevna – PhD, Associate Professor of the Basic Department of Oncology, Medical Institute of M.K. Ammosov North-Eastern Federal University, Deputy Chief Physician for Clinical Expert Work, Surgeon, Mammologist, State Budgetary Institution of the Republic of Sakha YAROD, zharnikova_tn@mail.ru, <https://orcid.org/0000-0002-7967-3704>;

OKONESHNIKOVA Alena Konstantinovna – PhD, Associate Professor of the Department of Surgery and Dentistry, the Medical Institute of M.K. Ammosov North-Eastern Federal University, neurosurgeon, surgeon ORCHMDiL SBI RS (Y) YAROD, alena-okoneshnikova@mail.ru, <http://orcid.org/0000-0003-1556-3095>;

SOLOVYOVA Aitalina Eremeevna – surgeon, mammologist SBI RS (Y) YAROD, ayyta@yandex.ru, <https://orcid.org/0009-0005-5094-7918>;

NIKIFOROV Pyotr Vladimirovich – Director of the State Budgetary Institution of the Republic of Sakha (Yakutia) "YARMIAC", Associate Professor of the Basic Department of Oncology, the Medical Institute of M.K. Ammosov North-Eastern Federal University, niciforof@mail.ru, <https://orcid.org/0000-0002-2758-155X>;

NIKOLAEVA Tatyana Ivanovna – PhD, Associate Professor of the Basic Department of Oncology, Medical Institute of M.K. Ammosov North-Eastern Federal University, Head of the State Budgetary Institution of the Republic of Sakha (YAROD), NTI_Nika@mail.ru, <https://orcid.org/0000-0002-1099-573X>;

AFANASYEVA Lena Nikolaevna – MD, Associate Professor, Head of the Basic Department of Oncology, the Medical Institute of M.K. Ammosov North-Eastern Federal University, Minister of Health, the Republic of Sakha (Yakutia), lenanik2007@mail.ru, <https://orcid.org/0000-0003-2592-5125>;

IVANOVA Feodosia Gavrilievna – PhD, head of the department of drug treatment, SBI RS(Y) "YaROD", leading oncologist of the Ministry of Health of the Republic of Sakha (Yakutia), Associate Professor of the basic department "Oncology" of the Medical Institute of the FSAEI HE M.K. Ammosov North-Eastern Federal University, e-mail: feodossiaiv@inbox.ru, <https://orcid.org/0000-0001-7661-1279>

T.N. Zharnikova, A.E. Solovyova, A.K. Okoneshnikova, P.V. Nikiforov, T.I. Nikolaeva, L.N. Afanasyeva, F.G. Ivanova

EXPERIENCE OF USING SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER USING ICG FLUORESCENCE IN THE REPUBLIC OF SAKHA (YAKUTIA)

Breast cancer is the leading cause of malignant neoplasms among women worldwide. Today, lymph node biopsy is one of the main diagnostic methods to assess the extent of the oncological process. The aim of the study has been to investigate the possibilities of conducting and evaluating the performance of diagnostic statistical methods of ICG fluorescence for sentinel lymph node biopsy in breast cancer in the Republic of Sakha (Yakutia). The study included 223 patients diagnosed with cT1-3N0M0, occurring in the period from 2022 to 2023. Surgical treatment for the mammary gland with sentinel lymph node biopsy using the ICG fluorescence method was performed in the Department of Breast Oncology and Skin Oncology of the State Autonomous Institution of the Republic of Sakha (Yakutia) in the OOMZhIOK (Department of Breast Oncology and Skin Oncology) of the Yakut Republican Oncology Dispensary. As a result of the study, metastases in the lymph nodes were detected in 44 (19.73%) cases out of 223. It has been established that the use of the method of sentinel lymph node biopsy in breast cancer using ICG fluorescence of the gland allows for large-scale surgical treatment of the initial form of mammary gland cancer.

Keywords: sentinel lymph node biopsy, fluorescence lymphography, breast cancer, lymph node dissection, indocyanine green.

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Introduction. Currently, one of the leading sites of cancer among oncological diseases in women is the mammary gland (BC). According to GLOBOCAN, in recent years, the propensity index for the incidence of BC cancer has increased; in 2020, 2.3 million cases of BC cancer were registered worldwide, which is 11.7% of all cancer cases [11]. In Russia, BC in the female population ranks 1st among all malignant neoplasms, and its incidence is 22.1% [3]. This problem is relevant in the oncology service in the Republic of Sakha (Yakutia). It was reg-

istered that in the period from 2013 to 2022, high rates of BC indicators were observed in the population of Yakutia at the early stages (I-II) of the disease in 72.7% of cases.

It has been proven that timely diagnosis of regional lymph node involvement is essential for determining the prognosis and selecting the optimal treatment strategy [1]. Today, the standard principle of surgical treatment of malignant neoplasms of various organs is the mandatory removal of all lymphatic collectors. Extended lymph node dissection in breast

cancer often leads to a decrease in the patient's quality of life up to disability. Some of the most common complications may be: prolonged lymphorrhea, lymphostasis of the upper limb, severe chronic pain syndrome with a neuropathic component due to plexitis, ligature fistulas, postoperative serums, and granulomas of the postoperative scar [4]. Today, one of the urgent tasks in oncology is the development of minimally invasive interventions in regional zones in patients with unaffected lymph nodes in the early stages of breast cancer [1,4,7].

In 1923, the British scientist L.R. Braithwaite first introduced the term "sentinel" lymph node (SLN), by which he meant the very first lymph node in the regional lymphatic basin from the transitional organ [1,6,10,15]. SLN biopsy determines the volume of lymph node dissection depending on the country or the state of metastases in it. According to many authors, the absence of metastases in the SLN in 95% of cases allows us to predict the presence of altered lymph nodes in the axillary and connective tissue. [6,8].

To date, two main methods of early detection of SLNs have been presented, using a radiopharmaceutical and a fluorescent dye with intraoperative histological examination of sentinel lymph nodes [6,9]. The first method is based on a solution of sodium pertechnetate, ^{99m}Tc from a technetium- 99m generator and lyophilisate. The result of this method is high radioactivity at the site of the first injection, which requires additional radiation protection measures [9,12,14].

The ICG fluorescence method is based on a fluorescent drug – indocyanine green (indocyanine green (ICG)). Indocyanine green (ICG) is a water-soluble green dye with fluorescent properties. This method is based on molecular fluorescence due to the binding of ICG to proteins of lymphovascular system cells. The absolute advantage of this method is the absence of radiation and simplification of the procedures [2,9,11].

The aim of the study: to study the possibilities of conducting and evaluating the diagnostic characteristics of the ICG fluorescence method for performing sentinel lymph node biopsy in breast cancer in the Republic of Sakha (Yakutia).

Materials and methods of the study: in the period from January 2022 to December 2023, 223 surgical interventions for late-stage breast cancer (Tis . T1-3) were performed in the departments of breast oncology and skin tumors (OOMZhIOK) of the State Budgetary Institution of the Republic of Sakha (Ya-

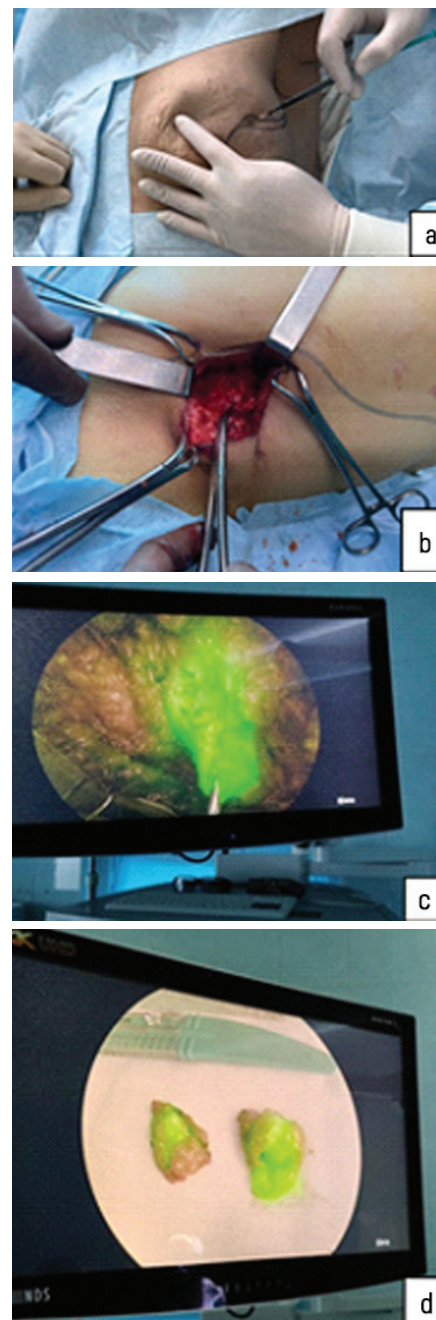
kutia) "Yakutsk Republican Oncology Dispensary". The average age of the patients was 61 years (from 32 to 86 years). At the examination stage, all patients undergo a study of regional lymph nodes and fine-needle aspiration biopsy of the axillary lymph nodes.

Surgical technique. Under the conditions of the procedure, the preparation of 5 mg indocyanine green (ICG) in a room of 1 ml was administered immediately before the operation using a disposable 1 ml syringe subcutaneously into the periareolar zone of the affected mammary gland in the projection of the tumor, followed by massage of the area, carried out for 3-5 minutes (Fig. a). Then, a 2-6 cm long incision was formed in the axillary region. After layer-by-layer excision of the skin and subcutaneous fat and installation of retractors, layer-by-layer excision of tissues in the axillary fossa was performed observing a bloodless surgical technique to prevent bleeding and damage to the lymphatic vessels, which could cause leakage of the preparation into a narrow strip axillary wound (Fig. b). The axillary stage of the operation consisted of a biopsy of the SLN using a fluorescence technique and lymphadenectomy of levels I-II-III, with verification of metastatic lesions of the lymph nodes. Mapping was performed using the Karl Endoscopic Fluorescence Imaging System. Storz SE & Co. KG. Dr /-Karl-Storz-Strasse-37 78532. Tittlingen (Germany) for visualization and image processing with a kitchen stove H3-Z FI TH102. SN ZQ019077-K and optics 26003 BRA Hopkings 30 NIR/ICG at first (Fig. c). Then, after visualization of the SLN with the help of holding instruments, the SLN was captured. The SLN wire was isolated in compliance with the atraumatic surgical technique in order to preserve the lymph node capsule (Fig. d). After removal of the SLN, control visualization of the removed specimen and revision in the axillary region were performed. Then the specimen was sent for histological analysis to the pathological clinic. The time of fixation and formation of fresh frozen sections is on average up to 20 minutes. Further, depending on the presence of metastases, the volume of surgical intervention is defined. In the event of data on metastatic damage, the cavity of the axillary wound was sutured layer by layer after revision and careful hemostasis.

Statistical processing of the research results was carried out using applied data processing programs based on Microsoft Excel and Statistics-8.

Results and discussion. The nature of the material is presented in Table

1. As a result of the study, it was found that the T1 tumor categories accounted for 25 (11.2%) patients, in most cases 111 (49.78%) patients were assigned the T1 category, in a third of patients 74 (33.18%) were assigned the T2 category, and in 13 (5.83%) patients the T3 category was assigned. Most often, in 115



Intraoperative photographs of sentinel lymph node biopsy using ICG fluorescence lymphography using the Karl Storz SE & Co endoscopic fluorescence imaging system. KG. Dr/-Karl-Storz-Strasse-37 78532: a – introduction of a fluorescent drug – indocyanine green, b – removal of the sentinel lymph node, c – visualization of the sentinel lymph node, d – macroscopic specimens with removed sentinel lymph node

(51.57%) patients, the tumor was located in the upper outer quadrant of the mammary gland.

In most cases, organ-preserving surgery was performed in 147 (65.92%) cases, and mastectomy was performed in 76 (34.08%) cases. According to the degree of tumor differentiation, moderately differentiated carcinoma was detected in the vast majority of patients (147 (65.92%)), highly differentiated carcinoma was detected in 56 (25.1%) patients, and poorly differentiated carcinoma was detected in 14 (4.04%) patients.

In the pathomorphological examination, in most cases ductal carcinoma was diagnosed in 116 (52.02%) patients, in a third of patients lobular carcinoma was detected, in isolated cases - 16 (7.17%) long duct carcinoma, carcinoma, 10 (4.48%) mucinous carcinoma, in 24 (10.76%) ductal carcinoma *in situ* (DCIS), in 1 (0.45%) lobular carcinoma *in place* (LCIS). During the immunohistochemical study, molecular biological subtypes of the tumor were established. In the overwhelming majority of cases, Luminal subtype A was detected in 122 (54.71%) cases.

Metastases in sentinel lymph nodes were detected in 44 patients (19.73%). The average number of lymph nodes removed during lymph node dissection was 10.25. According to the planned histological examination, the number of affected lymph nodes ranged from 1 to 5. A false-positive result in intraoperative histological examination was obtained in 1 patient (0.45%). During the study, we did not identify a single case of occurrence and systematic adverse effects with subcutaneous administration of indocyanine.

The effectiveness and safety of using the fluorescent dye indocyanine green to determine metastases in the SLN, according to specialized literature, varies from 80% to 98% [6, 9, 13, 14].

According to the results of a meta-analysis on the effectiveness of using fluorescent visualization of SLNs with indocyanine and methylene blue dyes, it was found out that the indocyanine group had a higher detection rate [OR = 8.64, 95% CI: 5.46–13.66, $p = 0.000$] and a lower rate of false negative results [OR = 0.10, 95% CI 0.02–0.43, $p = 0.002$] [13].

In addition, in a systematic review, the authors conducted a comparative analysis of the effectiveness of using indocyanine green fluorescence with a radioisotope for SLN biopsy in early stages of breast cancer. The analysis included 2301 patients from 19 studies. The authors did not find any indicators between traditional studies (OR = 0.90,

Material characteristics (n=223)

Sign		Number of patients	%
Tumor size	Tis	25	11.21
	T1	111	49.78
	T2	74	33.18
	T3	13	5.83
Localization of the tumor	Upper lateral	115	51.57
	Upper medial	45	20.18
	Center.	23	10.1
	Lower lateral	16	7.17
	Lower medial	15	6.73
	Common	9	4.9
Degree of differentiation	G1	56	25.1
	G2	147	65.92
	G3	14	6.28
	Unknown	6	4.04
Morphological variant	Flowing carcinoma	116	52.02
	Lobular carcinoma	44	19.73
	Lobular ductal carcinoma	16	7.17
	Mucous carcinoma	10	4.48
	Flowing carcinoma <i>in situ</i> (DCIS)	24	10.76
	Lobular carcinoma <i>in situ</i> (LCIS)	1	0.45
	Other	8	3.59
	Unknown	4	1.79
Molecular biology subtype	Luminal type A	122	54.71
	Luminal type B, Her2 negative	22	9.87
	Luminal type B, Her2 positive	17	7.62
	Her2/ neu 2 positive	11	4.93
	Triple type	14	6.28
	Unknown	37	16.59
Volume of operation	Sectoral resection	147	65.92
	Mastectomy	76	34.08
Sentinel lymph node status	Mts -	179	80.27
	Mts +	44	19.73

95% CI 0.66-1.24) and sensitivity (OR = 1.23, 95% CI 0.73-2.05). With the combined use of indocyanine green fluorescence with a radioisotope, the sensitivity was significantly higher compared to single mapping using only the radioisotope method (OR = 3.69 95% CI 1.79-7.62) or indocyanine green fluorescence (OR = 3.32 95% CI 1.52-7.24) [6].

A study of the remote results of fluorescence- and blue-dye-guided SLN biopsy in 237 patients found that after 5 years of follow-up, 0.64% of patients with a negative SLN had ipsilateral regional recurrence [14]. A similar study conducted in 2021, where the authors reported that patients with a negative SLN biopsy result have a 0% five-year probability of regional recurrence [5]. Krivorotko et al. presented 3-year results of treatment of patients who underwent SLN biopsy. The authors reported that the 3-year over-

all survival of the structure was 99.3% (SE 0.4%), recurrence-free survival was 99.2% (SE 0.4%). The survival rate of patients with unaffected sentinel lymph nodes reached 100%, with affected ones – 97.4% (SE 1.8%) [2].

In our series (n = 223), it was found that the frequency of detection of SLNs in the group was 100%. In 80.27% of cases, patients did not require an extended stage of surgery with lymph node dissection, which resulted in metastases in the SLNs.

Conclusion. Biopsy of sentinel lymph nodes is the standard of medical care. Thus, the method allows us to determine the adequate radical volume of the operation and the lowest possible risk of the operation, duration and trauma of the operation.

The authors declare that there are no conflicts of interest.

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USHNITSKY Innokenty Dmitrievich – MD, Professor, Head of the Department of Therapeutic, Surgical, Orthopedic and Pediatric Dentistry, MK Ammosov North-Eastern Federal University, e-mail: incadim@mail.ru, ORCID.org/0000-0002-4044-3004; **UNUSYAN Onik Sarkisovich** – Ph.D., Associate Professor, Department of Surgical Diseases and Dentistry, M.K. Ammosov North-Eastern Federal University, e-mail: onikunusyan@gmail.com, ORCID.org/0000-0002-8839-4205; **SEMENOV Alexander Dmitrievich** – PhD, Associate Professor of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Pediatric Dentistry, M.K. Ammosov North-Eastern Federal University, e-mail: sadstom@mail.ru, ORCID ID: 0009-0008-2937-5232; **IVANOV Andrian Vladimirovich** – PhD, Associate Professor of the Department of Surgical Diseases and Dentistry, M.K. Ammosov North-Eastern Federal University, e-mail: andrian_ivanov@mail.ru, ORCID.org/0009-0003-9352-1111; **UNUSYAN Larisa Sarkisovna** – dentist, dental clinic of M.K. Ammosov North-Eastern Federal University, e-mail: lara.unusyan77@gmail.com, ORCID.org/0009-0002-6506-1077

I.D. Ushnitsky, O.S. Unusyan, A.D. Semenov, A.V. Ivanov, L.S. Unusyan

THE METHOD OF SPLINTING MOBILE TEETH IN COMPLEX TREATMENT OF CHRONIC PERIODONTITIS

Nowadays, the prevalence of inflammatory periodontal diseases in the population remains at a high level. Meanwhile, periodontal diseases are chronic foci of oral infection, which often cause the development of focal-related diseases. In addition, tooth loss due to complications of chronic periodontitis leads to dysfunction of the dental alveolar system and mandibular joint. In this regard, the study of these aspects is an urgent general medical problem, including clinical dentistry. Thus, a comprehensive study of chronic periodontitis was carried out in the population living in the North, and on the basis of the obtained results, a method for splinting teeth in periodontitis was developed. To carry out the developed method in periodontological practice, a double silicone cast of the upper and/or lower jaw is first taken with further personalized planning of the splinter apparatus on a plaster model of the jaws, further, a splinting structure for immobilisation of movable teeth is made from colourless plastic and titanium woven wire, and the ready combined splint is additionally fixed from lingual or palatal sides of teeth with light hardening composite material on upper and/or lower jaw; splinting is performed with duration from 1 to 3 months. Depending on the complexity of the clinical situation, patchwork operations are performed to reduce the size of the periodontal pockets and create conditions for the formation of a new tight attachment of the gum to the teeth, followed by orthopedic treatment. The results of clinical-functional analysis of developed method application in complex treatment of chronic periodontitis of moderate severity confirm its clinical efficiency, connected with fixation of vestibular, oral sides of movable teeth and additionally composite filling material, which contribute to improvement of biomechanics and functional properties of dental alveolar system, and also aesthetic qualities of

splinting apparatus. In this regard, the proposed method of splinting teeth in periodontitis can be successfully applied in periodontal practice as an alternative method.

Keywords: periodontal tissues, periodontal diseases, anatomical and topographic features, gingival hyperemia, gingival bleeding, tooth mobility, temporary dental splinting, treatment, prevention, medical and social rehabilitation.

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Introduction. Today, the prevalence of inflammatory periodontal diseases in the population remains at a high level, which often leads to tooth loss, leading to disorders of the dental alveolar system and the mandibular joint [2, 4, 9, 12]. Inflammatory periodontal diseases contribute to the formation of a periodontal pocket, where there is a microbiota, and as a chronic focus of oral infection, it causes sensitization of the body with the subsequent development of focal-related diseases [3, 6, 7, 8]. One of the main symptoms of the inflammatory-destructive process of periodontal tissues is the mobility of teeth having a periodontal pocket. In this regard, when carrying out complex medical and preventive measures, special attention is paid to eliminating the mobility of teeth located in the foci of the inflammatory process. For this, there are quite a few different methods and means that do not completely solve the problem of tooth mobility and require further research [1, 5, 10].

In general, the study of these aspects is an urgent general medical problem, including clinical dentistry [2, 11, 12]. A comprehensive study of topical issues of chronic periodontitis in the population living in the North was carried out to improve periodontal care.

Purpose of the research is to develop a method for splinting mobile teeth in the complex treatment of chronic periodontitis and practical recommendations.

Material and research methods. The study of the clinical effectiveness of the method of splinting movable teeth in the complex treatment of chronic periodontitis of moderate severity was carried out on the basis of the dental clinic of the "M.K. Ammosov North-Eastern Federal University" as well as in the dental clinics "Form" and "Adenta" (Yakutsk). In carrying out the research work, the prevalence and intensity of periodontal diseases were determined, where the classification of Grudyanov A.I. et al. (2001), CPI indices (WHO), Russell's PI (1956), PMA (1957) and gingival sulcus IC (1986) were used, and tooth mobility and the microcirculation index were also studied. In addition, a method for splinting teeth in case of periodontitis has been developed. (application No.

2024128912 dated 30.09.2024, a positive decision on patent granting for the invention from 20.01.2025). The developed method was used in 101 male and female patients in the age group from 35 to 65 years old (main group) underwent professional hygiene, anti-inflammatory and antimicrobial therapy were carried out, including the introduction of the medicinal paste "Yagel" with the birch bark extract "Betulin" of the following composition into the periodontal pocket, in wt. %: dry residue "Yagel" - 10-11, birch bark extract "Betulin" - 10-11, zinc oxide - 49-50, oil solution of vitamin "A" - 28-31, a course of 10 procedures (patent No. 2751809, published on July 19, 2021). At the beginning, a double silicone cast of the upper and/or lower jaws was taken with further individual planning of the splinting structure on a working plaster model of the jaws. After that splinter apparatus for immobilization of movable teeth of jaws was manufactured from colorless plastic and titanium woven wire, where it was additionally fixed from oral side of teeth with composite material of light hardening on upper and/or lower jaws, splinting is performed with duration from 1 to 3 months. Further, in the presence of clinical indications, flap operations were performed aimed at reducing the size of the periodontal pockets and creating conditions for the formation of a new tight attachment of the gum to the teeth, followed by orthopedic treatment. For comparative analysis, a control group (n = 36) aged 35-65 years old was formed, where similar therapy was carried out using the medicinal paste "Vitadont", a course of 10 procedures, splinting was carried out using a lingual wire stand.

In the practical application of the developed method, its clinical efficacy was evaluated in the main and control groups based on the obtained data on the research of microcirculation of periodontal tissues using laser Doppler flowmetry (LDF) on the apparatus of the LAKK-O2 laser blood flow analyzer (NLP Lazma, Moscow) with two radiators for probing tissue in the infrared region of the radiation spectrum, power 1 mW. In addition, the degree of tooth mobility in chronic periodontitis was determined using the

Periotest-S device (Germany). Periodontal pocket depth (PC), periodontal index (PI), Russell index (Russell A., 1956), papillary marginal alveolar index (PMA) percentage (Parma C., 1960) and bleeding index (IR) (Muehleman H.P., Son S., 1971)

Statistical processing of the obtained research results was carried out using the Microsoft Excel 2020 software package (USA). The results obtained were grouped according to the set of identical study patterns.

Research results. The analysis of the prevalence and intensity of periodontal diseases in the examined population is characterized as an unfavorable clinical situation. Thus, CPI prevalence rates in the age groups of 15 years, 20-34 years, 35-44 years, 45-54 years and 65-74 years range from $68.59 \pm 0.71\%$ to $97.24 \pm 0.11\%$ ($p < 0.05$), where the average value was $89.14 \pm 0.13\%$. At the same time, there is a certain pattern associated with a decrease in показатели распространенности CPI prevalence rates with age in the components "bleeding," "tartar" and "healthy," and in the data of the "periodontal pocket" indicator, on the contrary, an increase in the trend line was detected ($p < 0.05$). In addition, the examined age groups of elderly people have a pronounced decrease in the pathological processes of periodontal tissues $68.59 \pm 0.71\%$ ($p < 0.05$). This clinical and epidemiological situation is associated with the presence of complete secondary adentia on the upper or lower jaw, removed teeth in sextants, which create the prerequisites for an increase in the frequency of severe chronic periodontitis with age. Accordingly, a similar situation is determined in the data on the intensity of periodontal diseases, where the indicators "healthy," "bleeding," "supra- and subgingival stones" ranged from 0.62 ± 0.07 to 0.04 ± 0.01 , from 2.39 ± 0.07 to 0.21 ± 0.09 and from 2.93 ± 0.07 to 0.59 ± 0.09 , determining their decrease with age ($p < 0.05$). Periodontal pocket and unaccounted-for sextants tended to increase with age and ranged from 0.41 ± 0.09 to 3.23 ± 0.08 , 0.04 ± 0.01 to 2.37 ± 0.05 , respectively ($p < 0.05$). Such a clinical situation of the intensity of periodontal tissue damage determines the severity of

the clinical course of chronic periodontitis with age.

One of the main symptoms of the chronic inflammatory process of periodontal tissues is tooth mobility, which determines the severity of the course of the pathological process. In this regard, when conducting complex therapy, an important criterion is the early detection and timely treatment of tooth mobility, which will contribute to the preservation of teeth, as well as a significant improvement in the prognosis of chronic periodontitis and the patient's quality of life. Taking into account the above, a clinical assessment of the use of the developed method of splinting teeth in periodontitis was carried out. Presence of support-retaining components of plastic splint and fixation of titanium woven wire with composite material from oral side of movable teeth makes it possible to restore full-fledged biomechanics of dental alveolar system, where wire ligature is in stressed state, which performs shock-absorbing function at teeth closure. The developed method is atraumatic for movable teeth, since it does not require preparation of hard tooth tissues.

Case report. Patient A., 56 years old, visited dental clinic of the "M.K. Ammosov North-Eastern Federal University" for professional oral hygiene. Complaints: mobility of the front lower teeth, pain when biting when taking hot and cold food, bleeding when eating and brushing teeth. Anamnesis morbi: two years ago, the patient underwent a course of therapy for mild chronic periodontitis, where a pronounced improvement was observed. She calmed down and did not visit dentists over the past years.

External examination: the face configuration is unchanged, the skin is clean. Regional lymph nodes are not palpable. Mouth opening is free. Lip border unchanged. In the oral cavity, the mucosa is unchanged.

Objectively: dental crowns 3.2, 3.1, 4.1 and 4.2 are not destroyed, where grade 2 mobility is determined. The probing is painless. Bleeding of the marginal gingiva is determined when the probe is touched. The reaction to temperature stimuli is positive without aftereffect. Percussion is slightly painful. The mucous membrane of the marginal, interdental and partially alveolar gums in the area of these teeth is slightly hyperemic, palpation is slightly painful. Diastema and tremas are determined between teeth 3.2, 3.1, 4.1 and 4.2. Degree II tooth mobility is determined. In the area of 1.1 and 2.1 teeth, there is a gingival recession by 1/3, there is no mobility. A CT scan dat-



Fig. 1. Double silicone functional impression of the mandible



Fig. 2. Individual layout of splinting structure on mandibular plaster model



Fig. 3. Tire is made of a combination of colorless plastic and titanium woven wire for immobilizing movable teeth



Fig. 4. A view of the combined mandibular splint from the vestibular side



Fig. 5. A combined colorless plastic and titanium woven wire splint for immobilizing movable teeth from the oral side

ed 10.01.2025 showed osteoporosis in the lower incisors and a decrease in the bone tissue of the alveolar process to a 1/2 height with destruction of its cortical plate, and in the 1.1 and 2.1 teeth by 1/3.

Diagnosis: K05.31 - chronic periodontitis. Generalized.

Treatment: based on the analysis of clinical data, it was decided to carry out splinting of mobile teeth from the vestibular and oral surfaces with chronic periodontitis of moderate severity using colorless plastic, titanium woven orthodontic wire and composite filling material. A double silicone functional impression was taken on the lower jaw with chronic generalized periodontitis of moderate severity (Fig. 1). Next, an individual layout of the splinting structure was made on a gypsum model of the lower jaw (Fig. 2). At the same time, a splint made of colorless plastic and titanium woven wire was made to immobilize the movable teeth of the lower jaw with moderate periodontitis (Fig. 3), after which the made combined splint was fixed to the lower jaw from the vestibular and oral sides, where additional fixation was made from the oral side of the teeth with a composite light hardening filling material (Fig. 4 and 5). Splinting is carried out with a duration of up to one and a half months, where after the therapeutic and preventive measures, the patient underwent a flap operation aimed at reducing the size of periodontal pockets and creating conditions for the formation of a new dense attachment of the gum to the teeth. 3 months after surgery, soft tissue volume will be evaluated and a non-removable metal-free prosthesis will be made on the lower jaw with the appropriate volume.

Distinctive features of the developed method is efficiency treatment increase of chronic periodontitis due to fixation of movable teeth from vestibular and oral sides with application of colourless plastic, titanium woven wire and composite filling material. And this, in turn, provides reliable fixation of mobile teeth from the vestibular and oral sides without disrupt-

Clinical and functional characteristics of dental splinting using a combined splint made of colorless plastic and titanium woven wire for moderate periodontitis

Indicators /timelines	Before treatment	Main group			Control group		
		7 день	14 день	28 день	7 день	14 день	28 день
Depth of pockets (mm)	4.81± 0.06	4.75± 0.06	4.39± 0.07**	3.92± 0.08***	4.79± 0.12	4.49± 0.13**	4.38 ± 0.14]***
PI index (point)	3.92± 0.08	1.91± 0.12*	1.43± 0.12**	1.29± 0.13***	2.34± 0.22*	1.54± 0.25**	1.38± 0.26***
PMA (%)	44.91± 1.08	22.64± 1.52*	6.72± 1.83**	4.56± 1.88***	34.23± 2.58*	11.64± 3.47**	9.11± 3.57***
FMBS (point)	2.44± 0.01	1.72± 0.02*	0.63± 0.04**	0.45± 0.05***	2.11± 0.03*	1.34± 0.06**	1.29± 0.06***
Tooth mobility (c.u.)	+22.73± 0.01	+10.25± 0.38*	+8.84± 0.41**	+7.91± 0.43***	+13.24± 0.65*	+12.65± 0.68**	+11.24± 0.73***
Microcirculation indicator (M), (p.u.)	23.22± 0.39	33.54± 0.18*	37.31± 0.11**	41.86± 0.02***	29.24± 0.54*	35.11± 0.31**	40.46± 0.09***

Note: * = significance of differences before and after 7 th day of treatment; ** = significance of differences before and after 14th day of treatment; *** = significance of differences before and after 28th day of treatment.

ing their function, without dissecting hard dental tissues, which contributes to the restoration of full-fledged biomechanics of the dental alveolar system and is characterized by pronounced aesthetics due to colorless plastic, where the wire ligature performs a shock-absorbing function when closing teeth. The above positive clinical properties confirm the prospects of the developed method and can be practically used in medical institutions by dentists.

The results of immobilization of mobile teeth in the complex treatment of chronic periodontitis using the developed method were evaluated by clinical, functional and diagnostic methods of research and were considered over time according to the studied parameters in a group of 35-65 years old (Table 1). Thus, the assessment of periodontal inflammation at the stages of treatment of chronic periodontitis characterizes that before treatment, the intensity of the inflammatory process according to the PMA index was $44.91 \pm 1.08\%$, which is interpreted as average severity. At the end of the first month of complex treatment, the mean rate in the main and control groups was on average $6.83 \pm 2.72\%$ ($p < 0.05$), characterizing a mild degree. The mean pre-treatment Russell periodontal index (PI) score in the core and control groups was 3.92 ± 0.08 points, which decreases to 1.33 ± 0.19 points on day 28 ($p < 0.05$). At the stages of dynamic control, changes in the depth of the periodontal pocket are determined, where before treatment in the groups the average depth was 4.81 ± 0.06 mm, and at the end of the month it was 4.15 ± 0.11 mm ($p < 0.05$). Analysis

of the bleeding index indicators characterizes that before treatment, the average indicator in the studied groups (main and control) was 2.44 ± 0.01 points, and after 28 days - 0.87 ± 0.05 points ($p < 0.05$). The study of dental mobility in chronic periodontitis of moderate severity using the Periotest-S apparatus determines that before treatment in groups, the average dental mobility index is $+22.73 \pm 0.01$ conv. units, and by the end of the first month of medical and preventive measures - $+9.57 \pm 0.58$ conv. units ($p < 0.05$), which determines the positive dynamics of changes in indicators at the stages of complex treatment. The analysis of periodontal tissue microcirculation disorders showed that the average value in the groups was 23.22 ± 0.39 p.u. before treatment, and by the end of dynamic observation amounted to 41.16 ± 0.05 p.u. ($p < 0.05$).

Thus, results of clinical-functional analysis of complex treatment of chronic periodontitis of moderate severity with application of method of teeth splinting confirm its clinical efficiency associated with fixation of vestibular, oral sides of movable teeth and additionally composite filling materials, which contribute to improvement of biomechanics and functional properties of dental alveolar system, and also aesthetic qualities of splinting apparatus. The data obtained to some extent indicate that the proposed method of dental splinting in chronic periodontitis has the prospect of successful application in periodontological practice as an alternative method.

The authors declare that there are no conflicts of interest.

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D.V. Kamlyk, V.E. Kolesnikov, S.V. Gurova, A.V. Galina, I.V. Golovinov, D.V. Khodakova, A.A. Shulga

THE INFLUENCE OF TUMOR SAMPLING TOPOLOGY ON THE EFFECTIVENESS OF THE XENOTRANSPLANTATION PROCEDURE IN THE CREATION OF A PDX MODEL OF GASTRIC CANCER

As indicated in the extant literature, numerous research groups encounter challenges in creating PDX models of gastric cancer, which is associated with a low level of engraftment of tumor samples. Consequently, in the pursuit of enhancing and refining the conventional implantation technique, we have recognized the significance of the tumor sample collection site. It was hypothesized that cells located on the tumor periphery and forming the invasion front may have a more pronounced potential for malignant growth and, consequently, the ability to grow as xenografts. To this end, ten gastric tumor samples were obtained from each patient: five from the tumor edges and five more from areas more than 5 mm from the visible tumor edge. All samples were implanted subcutaneously on the right side of Balb/C Nude mice. A subsequent analysis of the results indicated that, upon the collection of biological material concurrent with the capture of the visible tumor edge, the formation of tumor nodules occurred in three out of five recipient animals. Consequently, the xenotransplantation efficiency in this instance was determined to be 84%. Conversely, when tissue samples were obtained from areas distant from the tumor edge, the formation of tumor nodules in recipient animals was observed in only one procedure out of five. Consequently, the xenotransplantation efficiency was 20%. The histological examination conducted as part of this study revealed that the heterotopic PDXs accurately reproduced the histotype of the corresponding donor tumors, confirming their adenocarcinoma status. We also conducted an IHC study, which demonstrated that the level of Ki-67 expression in the tumor edges forming the invasion front was significantly higher, with an average value of 70 [60; 80]%. Conversely, in samples extracted from non-marginal regions of the same tumor, Ki-67 expression levels were notably lower, with an average of 15% [5; 25%] ($p < 0.05$). The obtained data suggest that the higher proliferative potential characterizing the marginal areas of tumors may contribute to more effective xenotransplantation of such tumor samples compared to samples obtained from areas of the tumor remote from the visible edge and characterized by a lower proliferative potential.

Keywords: gastric cancer, heterotopic model, PDX models, mouse models

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FSBI National Medical Research Centre of Oncology Ministry of Health of Russia, Ros-tov-on-Don: **KAMLYK Dmitry Vyacheslavovich** – postgraduate student; kamlyk01@gmail.com, ORCID:0009-0004-7432-9420; **KOLESNIKOV Vladimir Evgenyevich** – MD, surgeon, Kolaksay@yandex.ru, ORCID: 0000-0002-9979-4095; **GUROVA Sofya Valerievna** – junior researcher, testing laboratory center, gurova.sophie@gmail.com ORCID: 0000-0002-9747-8515; **GALINA Anastasia Vladimirovna** – junior researcher, testing laboratory center, volkovaav58@mail.ru ORCID: 0000-0001-7823-3865; **GOLOVINOV Igor Viktorovich** – junior researcher, testing laboratory center, ivgolovinov@yandex.ru ORCID: 0000-0003-3011-6904; **KHODAKOVA Darya Vladislavovna** – research fellow, testing laboratory center, KhodakovaDV@yandex.ru; ORCID:0000-0003-3753-4463; **SHULGA Anna Aleksandrovna** – junior researcher, testing laboratory center, slip.anka96@mail.ru; ORCID: 0009-0006-1125-2897

Introduction. Gastric cancer (GC) is an oncological disease that ranks fifth in prevalence and is also the fourth cause of cancer death worldwide [7]. The etiology of this disease is multifaceted. Its development is influenced by a multitude of both intrinsic and extrinsic factors, including, but not limited to, genetic susceptibility, infectious diseases, and dietary habits [1,13]. Patients with early-stage gastric cancer undergo surgical resection followed by chemotherapy, and the post-

operative 5-year survival rate can reach 90% [1]. However, the detection rate of gastric cancer at the first stage is low, which is associated with the absence of pronounced clinical signs. Therefore, the majority of patients (>70%) are diagnosed with the disease at late stages [10]. Despite considerable progress in radiation, immune, and chemotherapy treatments, surgical resection remains the only radical method for treating gastric cancer [2,11]. Consequently, there is

an imperative for further research to enhance our comprehension of the underlying pathobiology of gastric cancer and to formulate targeted therapeutic interventions. In such studies, the preliminary selection of therapeutic candidates at the preclinical stage plays a pivotal role. In the context of experimental studies on anticancer therapy, *in vivo* tumor models are instrumental in facilitating the progression of a promising drug candidate to clinical trials [12]. Currently, leading pharmaceutical companies and research organizations increasingly use the practice of using PDX (patient-derived xenograft) models in preclinical trials, which are obtained by implanting tumor fragments obtained from patients into animals. Animal models are extremely important for understanding the biological behavior of tumors and the molecular mechanism of carcinogenesis and evaluating the effectiveness of drugs [5].

However, the variability of the engraftment rate of tumor material obtained from patients and, accordingly, the development of PDX models of gastric cancer in immunodeficient mice ranges from satisfactory to extremely low [8]. This characteristic of PDX models imposes limitations on their broad application in the implementation of individualized approaches to gastric cancer therapy. Consequently, there is a pressing need to prioritize the investigation of methodological approaches that have the potential to enhance the efficacy of xenotransplantation. [9].

In this regard, the aim of our study is to investigate the influence of tumor sample collection topology on the effectiveness of the xenotransplantation procedure when creating a heterotopic PDX model of gastric cancer in Balb/c Nude mice.

Materials and methods. Animals and their maintenance. In the course of the experiment, female Balb/c Nude mice aged 8-10 weeks, with an average weight of 24-27 g, were used. The animals were obtained from the in-house breeding vivarium of the Testing Laboratory Center of the National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation and were kept in individual ventilated cages, food and water were provided without restrictions. All manipulations carried out within the framework of the study were carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETSN 123, Strasbourg, March 18, 1986). The study protocol was approved by the local bioethics commit-

tee of the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation.

Tumor samples. Gastric cancer samples were obtained from 5 patients undergoing treatment at the "National Medical Research Centre for Oncology" of the Ministry of Health of the Russian Federation. Written informed consent for the transfer of biological material was obtained from all patients.

Anesthesia. The surgical manipulations performed on the animals in this experiment were carried out using intramuscular injection anesthesia of the veterinary drugs "Xyla" (20 mg/kg) and "Zolelil-100" (50 mg/kg).

Technique of creating a heterotopic (subcutaneous) model of gastric cancer using tumor samples obtained from patients. Consequently, surgical intervention was undertaken to obtain tumor samples from patients diagnosed with gastric cancer. The tumor material was subsequently transferred to the vivarium for a 15-minute period in a DMEM nutrient medium containing 10% gentamicin. The tumor material obtained from the patients was then implanted heterotopically (subcutaneously) into the right side of the mice. Upon reaching the requisite depth of anesthesia, the skin was dissected on the right side of the animals, followed by the introduction of sterile closed blunt scissors into the subcutaneous space to separate the peritoneum from the skin to create a subcutaneous pocket. The tumor material was then meticulously implanted without causing injury to the abdominal cavity. The surgical wound was then closed using an interrupted suture. All surgical interventions were performed under sterile conditions.

Assessment of tumor node growth. The linear dimensions of tumor nodes were measured using a caliper weekly, starting from the 14th day after implantation of tumor material into immunodeficient mice. The volume of tumor nodes was calculated using the formula:

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

where L, W are the linear dimensions of the tumor.

Euthanasia. The euthanasia procedure entailed the execution of the animal by decapitation, followed by the collection of the tumor nodes at the conclusion of the observation period.

Histological and immunohistochemical (IHC) examination. The material obtained was fixed in 10% formalin for 24 hours, then embedded in paraffin. Sections were made using a rotary microtome,

and were then deparaffinized according to the standard protocol. The hematoxylin and eosin staining was carried out in accordance with the established technique. IHC staining of tumor tissues was performed automatically in a BenchMark ULTRA Ventana immunohistostainer. The following antibodies were used: Ki-67 (clone SP6), Cell Marque, in a dilution of 1:200. To perform expression analysis, the proportion of cells with stained nuclei (percentage of the total number of tumor cells) was calculated in at least 10 fields of view.

Statistical analysis. Statistical data processing was performed using the Statistica 10 software package (StatSoft, USA). The results obtained are presented as a median and 25th and 75th percentiles; the Mann-Whitney test was used for comparison; the significance of differences was considered significant at $p < 0.05$.

Research results and their discussion. According to the literature, many research groups face difficulties in creating PDX models of gastric cancer, which is associated with a low rate of engraftment of tumor samples. In one study, it was demonstrated that the rate of successful engraftment was 28.12% [4], in another study, PDX models of gastric cancer were successfully created in 24.2% [3].

Therefore, in the context of searching for a way to improve and optimize the traditional implantation method, we considered the importance of the tumor sampling zone. We assumed that cells located on the tumor periphery and forming the invasion front may have a more pronounced potential for malignant growth and, therefore, the ability to grow as xenografts.

In this regard, gastric cancer samples from each patient, obtained from the marginal areas of the tumor ($n=5$) and from areas more than 5 mm away from the visible edge of the tumor ($n=5$), were implanted subcutaneously into the right flank of Balb/C Nude mice. Tumor samples from the central areas were not used to create PDX, since these areas usually contained necrotic areas. The tumor was considered to have successfully engrafted if the volume of the tumor node reached at least 60 mm³. Observation was performed for 3 months, if no growth of tumor nodes was observed during this time, the xenotransplantation procedure was considered ineffective.

The results are presented in Table.

Analysis of these results showed that when selecting biological material with the capture of the visible edge of the tumor, 3 out of 5 procedures led to the

Results of heterotopic implantation of gastric cancer samples into Balb/C Nude mice

Code xenograft procedures	Method of obtaining material	Evaluation of implantation results using samples distant from the visible edge (1st generation)	Evaluation of implantation results using samples, capturing the visible edge of the tumor (1st generation)
PDX-GC-01	Дистальная субтотальная резекция	0/5	3/5
PDX-GC-02		3/5	4/5
PDX-GC-03		0/5	0/5
PDX-GC-04		0/5	3/5
PDX-GC-05		0/5	0/5

formation of tumor nodes in recipient animals and the efficiency of xenotransplantation with this approach was 84%, which exceeded the results obtained when using tissue fragments from areas located further from the edge of the tumor, where only 1 out of 5 procedures led to the formation of tumor nodes in recipient animals, respectively, the efficiency of xenotransplantation was 20%.

The importance of the topology of tumor samples was also demonstrated in the work of Bastola S. et al. – in the PDX glioblastoma model it was shown that cells originating from the edges of the tumor demonstrated a higher capacity for infiltrative growth in contrast to cells in the central areas of the tumor sample [6].

The histological examination performed within the framework of this work

showed that heterotopic PDX reproduced the histotype of the corresponding donor tumors and were adenocarcinomas. We also conducted an IHC study of the marginal areas and central samples of patients' tumors. In the course of the work, it was found that the marginal and central samples had differences in the level of Ki-67 expression (Figure).

The results of our study showed that the level of Ki-67 expression in the tumor margins forming the invasion front was significantly higher and amounted to 70 [60; 80] %. At the same time, in samples taken from non-marginal areas of the same tumor, Ki-67 expression was significantly lower and amounted to 15 [5; 25] % ($p < 0.05$). The obtained data allow us to suggest that, probably, the higher proliferative potential characterizing the marginal areas of tumors may contribute to more effective xenotransplantation of such tumor samples, compared to samples obtained from areas of the tumor remote from the visible edge and characterized by a lower proliferative potential. Based on data from scientific papers and the results of our own research, We have gained insight into the importance of tumor sample topography for the effectiveness of xenograft engraftment.

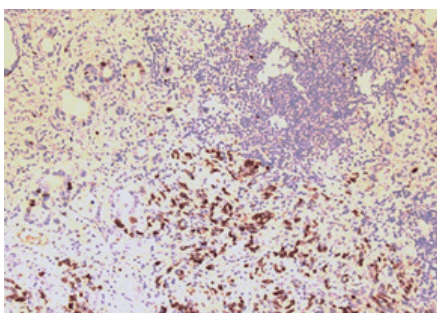
Conclusion. The results of the work provided the foundation for a proposed method to enhance the outcomes of xenotransplantation in the development of a heterotopic PDX model of gastric cancer. This method is predicated on the utilization of samples obtained from the marginal areas of the tumor. This novel method facilitates the augmentation of the efficiency of the conventional method of implantation. The incorporation of this approach into research protocols promises to enhance the precision and adaptability of experimental tumor models. Notably, this methodology fosters conditions conducive to a personalized approach in anti-cancer research, which has the potential to further enhance treatment outcomes for patients with gastric cancer.

The authors declare that they have no conflict of interest.

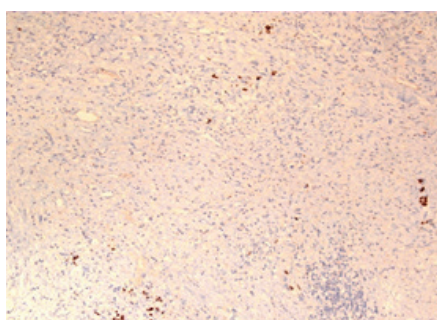
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A



B



Immunohistochemical staining of cancer samples for Ki-67 human stomach, magnification×100. A – marginal central areas of the tumor; B – areas of the tumor, far from the edge

HEALTHY LIFESTYLE. PREVENTION

A.A. Osinskaya, A.B. Guryeva

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**THE STUDY OF VARIATIONS
IN ADHERENCE TO THE PRINCIPLES
OF HEALTHY LIFESTYLE
AND PERCEPTION OF ITS CONCEPT
AMONG MEDICAL AND NON-MEDICAL
STUDENTS OF M.K. AMMOSOV
NORTH-EASTERN FEDERAL UNIVERSITY**

The purpose of the study was to evaluate and compare the observance and understanding of the concept of a healthy lifestyle among students of medical and non-medical specialties of M.K. Ammosov Northeastern Federal University (NEFU). Research hypothesis: We assume that students studying in medical and non-medical specialties have different attitudes towards the concept of a healthy lifestyle and, therefore, adhere to it in different ways. Research materials and methods: Theoretical, verbal-communicative and statistical research methods were used. The survey was conducted using a standardized selective remote survey method developed by the authors on the Google Forms Internet resource. The 434 students (aged 17 to 27) of M.K. Ammosov NEFU took part in the survey. The respondents were divided into two groups: the first group – students of the medical institute (n=216), the second – students of other faculties and institutes of NEFU (n=218). The statistical method was performed in the software application Microsoft Excel and SPSS Statistics version 22.0. Research results: The conducted research has shown that modern students generally adhere to the basic principles of a healthy lifestyle. There was a lower proportion of people with bad habits among medical students and a higher number of students who adhere to the principles of healthy eating. At the same time, students of non-medical specialties are 2.48 times more likely to study in sports sections. It has been established that in the group of students of non-medical specialties, there are those who do not perceive a healthy lifestyle as a success factor in various spheres of human activity and consider compliance with the principles of a healthy lifestyle not mandatory. Conclusion: The hypothesis of the present study has been confirmed. Students studying in medical and non-medical specialties have different attitudes towards the concept of a healthy lifestyle and, therefore, adhere to it in different ways. The results obtained dictate the need to popularize the versatility of a healthy lifestyle as a foundation for the formation of a full-fledged, harmonious personality in all spheres of life.

Keywords: students, healthy lifestyle, questionnaire, learning profile.

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Introduction: Youth, as a social stratum of society, performs many important functions of social development and is a key potential for the progress of modern society. The younger generation is a dynamic organism that subtly reacts to any fluctuations in global trends and transforms them. Due to their susceptibility, young people are easily susceptible to harmful influences, in particular, blind fashion adherence [4, 9]. These fashion trends often run counter to the principles of a healthy lifestyle and can have long-term, irreversible consequences for

health and social life [3]. It is believed that medical students demonstrate a more positive attitude towards a healthy lifestyle than students of other specialties [1, 2]. However, both of them may face obstacles in its observance, which dictates the need to take into account the variety of factors determining the choice of their lifestyle. A multidimensional study of the student youth's attitude to the concept of a healthy lifestyle is essential for developing effective strategies to support students in their pursuit of a healthy lifestyle.

The purpose of the study: To evaluate and compare the observance and understanding of the concept of a healthy lifestyle among students of medical and non-medical specialties of the NEFU named after M.K. Ammosov.

Research hypothesis: We assume that students studying in medical and non-medical specialties have different attitudes towards the concept of a healthy lifestyle and, therefore, adhere to it in different ways.

Research materials and methods:

The following research methods were used in this study: theoretical, verbal-communicative and statistical. The theoretical method included analysis, generalization of scientific literature on the problem and drawing up a questionnaire based on the information received. The verbal and communicative method was implemented using the Internet resource "Google Forms". The questionnaire developed by the authors consisted of 20 dichotomous questions and questions with a choice of answer. The questionnaire included questions aimed at obtaining information about the respondents' social characteristics, attitudes towards a healthy lifestyle, including smoking, proper nutrition, and sports. The survey was conducted in compliance with the principles of anonymity and voluntariness. The survey was conducted using a standardized method of selective remote survey of full-time students of M.K. Ammosov NEFU in 2025. The exclusion criteria were ques-

OSINSKAYA Alena Alexandrovna – Candidate of Medical Sciences, Associate Professor of the Department of Human Anatomy, Medical Institute, North-Eastern Federal University, osin_alen@rambler.ru, ORCID 0000-0003-4926-6232; **GURYEVA Alla Borisovna** – MD, Professor, Department of Human Anatomy, Medical Institute, North-Eastern Federal University, guryevaab@mail.ru, ORCID 0000-0003-2398-0542

tionnaires with a significant number of missing answers (more than 20%) and duplicate questionnaires. The survey involved 434 respondents aged 17 to 27, of whom 398 were students of youth age (17-21 years old - youth; 16-20 years old - girls) and 36 of the first period of adulthood (22-35 years old - men; 21-35 years old - women). The overwhelming majority (85,7%) of the respondents were female. 98.2% of the respondents were residents of the Republic of Sakha (Yakutia). According to the objectives of the study, all respondents were divided into two groups: the first group was students of the Medical Institute (n=216), the second group was students of other faculties and institutes (n=218), such as the Institute of Psychology, Natural Sciences, Engineering, Institute of Mathematics, historical and geological faculties.

The statistical method was performed in the software application Microsoft Excel and SPSS Statistics version 22,0. The χ^2 criterion and the Fischer criterion (F) for small samples were used to determine the intergroup differences. The results were considered reliable at $p < 0,05$.

Results and discussion: Statistical analysis of the obtained material showed that among the surveyed students, there are people with and without bad habits with the same proportion. The intergroup comparison did not reveal significant differences ($p = 0,786$), as 50% of medical students and 52,29% of students from other faculties noted the presence of harmful habits. At the same time, it should be noted that from 47.71% to 50% of modern students indicate the absence of bad habits. According to the All-Russian Center for the Study of Public Opinion, the portrait of a smoker has changed since 2009. At that time, 48-50% of the smoking population was between 18 and 44 years old; today, the proportion of smoking youth aged 18-24 has decreased by 1,7 times from 48% to 29% [10]. This fact shows that there is a tendency to promote a healthy lifestyle among young people. The analysis of the prevalence of smoking among students revealed a significantly lower ($\chi^2 = 4,151$; $p = 0,042$) number of them among medical students (22,22%). At the same time, the proportion of smokers in the second group was 11,72% higher. The result obtained may be due to the fact that students of medical specialties have a more in-depth knowledge of the dangers and consequences of smoking, including its connection with a wide range of diseases, which serves as a motivating factor for prevention and quitting smoking [6,7, 8]. Medical education promotes

the formation of professional self-awareness, within which a healthy lifestyle is perceived as an important component of professional competence and ethics, creating a positive example for the public.

Analyzing attitudes to nutrition, significant differences in eating habits among students of medical and non-medical specialties were established. To the question "Do you follow a proper diet?" The majority of respondents in both groups (57,41% and 59,63%) answered "not always", the answer "yes" was presented in a minimal proportion in both groups (Table 1).

According to the survey, there are 2,4 times more healthy foods in the diet of medical students. Due to the trend of the times, fast food as an affordable way of eating is quite common among young people. According to the survey data, the respondents of the first and second groups indicated that fast food is often present in their diet (several times a week) (29,64% and 43,12%, respectively). It should be noted that medical students consume it significantly less frequently ($\chi^2 = 3,987$; $p = 0,046$) and 3,70% of fast food is not present in the diet.

An interesting fact is that the majority of modern students (57,45% and 64,22%) take complex medications as an additional source of vitamins and minerals. In recent years, vitamin intake has been widely advertised among the population, and many doctors recommend supporting the body with vitamin and mineral complexes, especially during periods of increased stress.

A study of students' physical activity showed that the vast majority of students do morning exercises rarely or not at all, while students of non-medical specialties are significantly more likely to exercise daily (Table 2).

The majority of the students surveyed are not involved in any kind of sport. The prevailing reason for this, according to the answers, is the lack of free time. We assume that the insufficient physical activity of modern students is due to the fact that student life is associated with high academic, psycho-emotional and socio-adaptive loads [5]. It is noteworthy that medical students had the answer "I can't because I don't have time" 1,8 times more often ($p < 0,001$). At the same time, there are 2,48 times more students who regularly attend sports clubs among the respondents of non-medical specialties ($p = 0,003$). It is possible that students of medical schools, faced with a high mental and emotional workload, frequent exams, internships and night shifts in hospitals, are limited in their free time.

When analyzing the duration of use of

mobile and computer devices, non-medical students use it more than 12 hours a day 2,5 times more often (27,52% and 11,11%, respectively; $\chi^2 = 1,719$; $p < 0,001$). We believe that students of non-medical specialties, in particular, technical and mathematical profiles, use mobile and computer devices more hours a day due to the peculiarities of their educational process. This is due to the need to perform time-consuming calculations, visualize and model complex objects and phenomena, develop computer programming languages, algorithms and software, and much more. There were no significant intergroup differences in the duration of mobile and computer devices use "less than 6 hours" and "from 7 to 11 hours per day". The constant use of mobile devices and computers is an integral part of modern people's daily lives, providing communication, information storage, entertainment, and access to various information.

Having studied the sleep duration of the respondents, there were no significant differences between students of medical and non-medical specialties. The vast majority of respondents (70,37% and 71,56%) indicated that they sleep less than 8 hours a day. There is no doubt that student life is accompanied by factors that affect sleep duration, among which the most common are intense academic loads, active social and social life, psychophysiological stress during the session, and much more.

Having considered the issues of students' attitude to a healthy lifestyle, it was found that non-medical students in 4,59% of cases do not believe that a healthy lifestyle contributes to success in other areas of human activity (study, work, etc.). Also in this group of respondents, 5,50% believe that it is possible to do without observing the principles of a healthy lifestyle (Table 3). We believe that it is necessary to popularize the promotion of a healthy lifestyle, not only as the absence of bad habits, but also as a foundation for the formation of a full-fledged, successful personality in all spheres of life.

An interesting fact is that 72,22% of medical students believe that creating an absolutely healthy nation is a reality. At the same time, only 31,19%, which is 2,32 times less ($p < 0,001$), of non-medical students support the same point of view. Such a positive attitude of the younger generation of doctors gives hope that they will become a key potential for the implementation of the concept of a "healthy nation".

Conclusion: The hypothesis of the present study has been confirmed. Stu-

Table 1

Students' attitude to nutrition issues

№	Question	Answer option	Group 1 n (%)	Group 2 n (%)	p
1	Are you following a proper diet?	yes	20 (9.26)	20 (9.17)	p=0.978
		no	72 (33.33)	68 (31.20)	p=0.733
		not always	124 (57.41)	130 (59.63)	p=0.810
2	Are there healthy foods (fruits, vegetables, etc.) in your diet?	always	52 (24.08)	22 (10.09)	$\chi^2 = 10.660$; p=0.002
		often enough	92 (42.59)	110 (50.46)	p=0.321
		rarely	72 (33.33)	80 (36.70)	p=0.611
		no	0 (0)	6 (2.75)	$\chi^2 = 5.866$; p=0.016
3	Do you take additional vitamin complexes?	yes	64 (29.63)	54 (24.77)	p=0.390
		sometimes	60 (27.78)	86 (39.45)	p=0.070
		no	92 (42.59)	78 (35.78)	p=0.337
4	Do you have fast food in your diet?	very often (daily)	8 (3.70)	14 (6.42)	p=0.220
		quite often (several times a week)	64 (29.64)	94 (43.12)	$\chi^2 = 3.987$; p=0.046
		rarely	136 (62.96)	110 (50.46)	p=0.167
		no	8 (3.70)	0 (0)	$\chi^2 = 7.929$ p=0.005

Table 2

Students' attitude to physical activity issues

№	Question	Answer option	Group 1 n (%)	Group 2 n (%)	p
1	How often do you do morning exercises?	daily	0 (0)	10 (4.59)	$\chi^2 = 9.692$; p=0.002
		sometimes	64 (29.63)	82 (37.61)	p=0.215
		never	152 (70.37)	126 (57.80)	p=0.202
2	Do you practice any kind of sports?	yes	64 (29.63)	86 (39.45)	p=0.134
		no	152 (70.37)	132 (60.55)	p=0.326
3	Can you afford to visit various sports sections, gyms, swimming pools, etc.?	I can, I visit regularly	16 (7.41)	40 (18.35)	$\chi^2 = 8.941$; p=0.003
		I can, but I don't see the point	32 (14.81)	38 (17.43)	p=0.529
		I can't because I don't have free time	136 (62.96)	76 (34.86)	$\chi^2 = 11.879$; p<0.001
		I can't because I don't have enough money	28 (12.96)	64 (29.36)	$\chi^2 = 11.410$; p<0.001

Table 3

Students' attitude to a healthy lifestyle

№	Question	Answer option	Group 1 n (%)	Group 2 n (%)	p
1	Do you think a healthy lifestyle contributes to success in other areas of human activity (study, work, etc.)?	yes	196 (90.74)	180 (82.57)	p=0.504
		no	0 (0)	10 (4.59)	$\chi^2 = 9.692$; p=0.002
		I can't answer	20 (9.26)	28 (12.84)	p=0.287
2	Your personal attitude to a healthy lifestyle:	it's great	200 (92.59)	174 (79.82)	p=0.294
		can live without it	0 (0)	12 (5.50)	$\chi^2 = 11.581$; p<0.001
		Sometimes it should be observed	16 (7.41)	24 (11.01)	p=0.237
		I can't answer	0 (0)	8 (3.67)	$\chi^2 = 7.787$; p=0.006
3	What do you think is an absolutely healthy nation:	illusion	60 (27.78)	150 (68.81)	$\chi^2 = 25.968$; p<0.001
		reality	156 (72.22)	68 (31.19)	$\chi^2 = 23.746$; p<0.001

dents studying in medical and non-medical specialties have different attitudes towards the concept of a healthy lifestyle and, therefore, adhere to it in different ways. The conducted research has shown that modern students generally adhere to the basic principles of a healthy lifestyle. However, there are differences between students of medical and non-medical specialties in the observance of its individual components. Thus, there was a lower proportion of people with bad habits among doctors, and a greater number of students who adhere to the principles of healthy eating. At the same time, students of non-medical specialties are 2.48 times more likely to study in sports sections. Unfortunately, the implementation of such components of a healthy lifestyle as sleep duration, regular physical activity among students is difficult due to academic and socio-social stress, and psychophysiological stress.

After analyzing the students' attitude to a healthy lifestyle, it was found that there are students of non-medical specialties who do not perceive a healthy lifestyle as a success factor in various fields of human activity and consider compliance with the principles of a healthy lifestyle optional. This fact is alarming and dictates the need to popularize the versatility of a healthy lifestyle as a foundation for the formation of a full-fledged, harmonious personality in all spheres of life. It should be noted that the overwhelming majority of medical students consider the creation of an absolutely healthy nation to be a reality. The obtained result allows us to make a cautiously optimistic forecast

that the younger generation of doctors will become the driver of the development of a new model of a "healthy nation" in the future.

The authors declare that there is no conflict of interest.

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Federal State Budgetary Scientific Institution "N.A. Semashko National Research Institute of Public Health": **GALIKEEVA Anuzya Shamilovna** – MD, PhD, Associate Professor, Leading Researcher. ORCID: 0000-0001-9396-288X, anuzya.galikeeva@mail.ru; **ZUDIN Aleksandr Borisovich** – MD, PhD, Professor, Director, ORCID: 0000-0002-6966-5559, zudin-ab@yandex.ru; **LARIONOVA Tatyana Kensarinovna** – PhD, Associate Professor, Leading Researcher. Federal Budgetary Scientific Institution "Ufa Research Institute of Occupational Medicine and Human Ecology", ORCID: 0000-0001-9754-4685, larionovatk@yandex.ru; **MISHINA Anna Evgenievna** – dentist, State Budgetary Healthcare Institution of the Republic of Bashkortostan "Salavat City Hospital", ORCID: 0009-0008-1562-025X, anna4913@gmail.com.

A.Sh. Galikeeva, A.B. Zudin, T.K. Larionova, A.E. Mishina

DIET OF PATIENTS WITH PERIODONTAL DISEASES: ANALYTICAL DESCRIPTIVE STUDY

The article presents the results of a study of the nutritional characteristics of patients with chronic generalized periodontitis. According to the World Health Organization, more than one billion people in the world suffer from severe periodontal diseases. Periodontal pathologies are closely associated with a number of major chronic non-communicable diseases, which determine their high medical and social significance.

A cause-and-effect relationship was revealed between the degree of manifestation of periodontitis symptoms and nutritional factors of patients. It was found that the less essential nutrients in the diet, the more pronounced the clinical signs of periodontal damage become. Increased body weight can be considered as one of the signs of metabolic syndrome involved in the development of periodontitis. Thus, with an increase in body weight, the severity of the clinical course of periodontitis steadily increases, and the revealed dependence is statistically highly significant ($p = 0.01$). With an increase in the number of proteins, carbohydrates and dietary fiber in the diet, a decrease in the degree of periodontitis is observed. An increase in the number of vitamins (A, B1, C) and a number of macro- and microelements (Cu, Zn, K) has the same effect.

Healthy nutrition is a key element that has a significant impact on the general condition of the human body and helps maintain its well-being. Normalization of diet, including a balanced intake of essential nutrients, is a key element in the prevention of periodontal diseases and an important aspect of rehabilitation. The results of this study can be used to develop scientifically based methods aimed at improving the preventive activities of health care workers, including general practitioners, dentists and dental hygienists, increasing the motivation of the population to lead a healthy lifestyle and adhere to the principles of a balanced diet.

Keywords: Nutrition, population, dental morbidity, periodontitis, prevention

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Introduction. In modern society, in the context of urbanization and lifestyle transformation, there is a tendency towards an increase in the prevalence of major non-communicable diseases (NCDs) among the population. This problem is in the focus of both domestic and foreign researchers and is recognized as one of the key ones in ensuring health and sustainable development of mankind in the 21st century. Dental diseases, closely associated with major non-communicable diseases, affect almost half of the world's population throughout life, from early to old age. This makes the prevention of pathology of oral organs and tissues especially important in the context of solving the problem of NCDs in general, putting it among the priority health tasks [1]. According to the World Health Organization (WHO) report for 2024, more than three billion people worldwide are susceptible to dental diseases, the prevalence of which among people over 45 years of age is 90%. Among the adult population of the world, about 20% suffer from severe forms of periodontitis, which is equivalent to more than one billion cases. According to researchers, patients with chronic periodontitis are three times more likely to have an increased risk of developing heart attacks and strokes than patients with intact gums [14]. In addition, signs of periodontal damage may be potential risk factors for increased mortality [13]. It is known that periodontitis may be associated with both certain somatic pathologies [3] and with the nutritional characteristics of patients [10, 20].

In recent years, there have been more and more studies on the impact of nutrition on public health. Many authors note that an unbalanced diet in 30–50% of cases is the cause of a number of non-communicable diseases: cardiovascular disease, diabetes, obesity, osteoporosis and other systemic disorders. The popularization of foods and drinks with a high sugar content in modern society, excessive caloric intake, and fat consumption with a simultaneous insufficient intake of essential nutrients are factors in the development of alimentary-dependent diseases [8, 11, 12, 15] and are prerequisites for the

occurrence of inflammatory periodontal diseases [6].

The high prevalence of periodontal diseases, predominantly in people of working age and older, often with a progressive course and insufficient effectiveness of measures taken for prevention and treatment, is acquiring the status of one of the most pressing socially significant medical problems at the present stage of society development [3, 4, 9]. It is known that the main role of nutrition is in trophic, plastic and energetic support of the functional activity of the organism and, in particular, the immune system. Food components can have modifying properties in relation to cellular and humoral, as well as non-specific and native (natural) immunity [16]. Balanced nutrition is necessary both for local stability of tissue cells and for the functioning of the immune system of the oral cavity. Disturbances in the diet can lead to the development of pathological processes in the periodontium [17, 21, 22]. Studies aimed at studying the eating behavior of patients with dental diseases are mainly focused on the analysis of their ability to mechanically process food. In scientific literature, there is a lack of studies devoted to the analysis of the relationships between the qualitative characteristics of the diet of patients with periodontal pathology. An in-depth study of the characteristics of the diet of patients will provide scientifically substantiated data for the development of therapeutic and preventive measures aimed at preventing the development and progression of chronic periodontitis.

The aim of the study: to analyze the diet and identify the relationships between the clinical manifestations of chronic generalized periodontitis and the quality of nutrition in order to improve the effectiveness of treatment and preventive measures within the framework of primary health care.

Materials and methods of the study. The object of the study were 412 people of working age, 171 men and 241 women (mean age 42.6 ± 0.8 years), who had periodontal pathology of varying severity: chronic generalized periodontitis (CGP)

(ICD-10 code: K05.31) or chronic gingivitis (K05.10), which was considered as the initial form of periodontitis. No statistically significant differences by gender and severity of periodontal disease were found ($p > 0.05$), which allowed them to be subsequently analyzed in general groups and cohorts.

An analytical descriptive study of the daily diet of patients with periodontal diseases was conducted and the relationships between the signs of periodontal damage and the quality of nutrition were studied.

During the analysis of dental examination data, all patients from the study group were divided into two subgroups. The first subgroup included patients with initial manifestations of periodontal diseases, such as gingivitis and mild chronic periodontitis, and the second included patients with moderate and severe chronic periodontitis. This division allowed us to exclude intermediate values from mathematical analysis and more clearly identify the differences between the initial signs of periodontal tissue damage and more severe forms of the disease.

For a comprehensive assessment of the dental status of the subjects, the main dental methods were used: patient survey (identification of complaints, collection of anamneses), clinical examination (visual and instrumental examination of the organs and tissues of the mouth). Patients were asked about the first manifestations of the disease, the dynamics of its development, the general well-being of the subject, and somatic status were taken into account. Clarification of this information made it possible to establish cause-and-effect relationships between general pathology and changes in dental health. When assessing the periodontal status, the severity of periodontitis, prevalence and intensity of signs of periodontal damage were determined: bleeding gums during probing, supra- and subgingival tartar, periodontal pocket of 4–5 mm, as well as 6 mm and more, pathological mobility of teeth. During the patient survey, nutrition was assessed taking into account the existing somatic status, including the following

data: a sharp and unexpected increase or decrease in body weight, weakness, nausea, dyspeptic disorders, as well as intolerance to certain foods, poor health after eating, eating habits (including negative ones), adherence to dietary nutrition instructions, deviations in the diet due to changes in the taste or olfactory perception of food, difficulty chewing or swallowing food, refusal to eat for any other reasons.

The study of actual nutrition was carried out using the 24-hour (daily) reproduction method. Based on data on the nature and amount of food consumed per day, the nutritional and energy value of the diet was calculated using the Nutri-prof software package, developed using the reference book of the chemical composition of food products and dishes prepared from them [7]. The degree of rationality of nutrition was assessed in accordance with MR 2.3.1.0253-21. The amount of daily intake of added salt was compared with the volume recommended by WHO [19]. To quantitatively assess the nutritional status of the subjects (the presence of deficiency or excess body weight), the Quetelet index (BMI) was calculated.

Mathematical analysis and statistical processing of the obtained data were carried out using the Matlab program, as well as Microsoft Office Excel 2021 software packages (Microsoft, USA). The variables under study were preliminarily tested for normal distribution using the Shapiro-Wilk (Shapiro S.S., Wilk M.B., 1965) and Epps-Pally (Epps T.W., Pulley, L.B., 1983) criteria. If the distribution of the parameters under study could not be considered normal, the median value was used; in case of normal distribution, the mean value and the error of the mean were used. To compare the medians of the parameters in different groups of patients, a nonparametric method for testing the equality of medians was used – the Mann-Whitney U-test. The moving average method was used to illustrate the nature of the interdependencies of the parameters. In the interpretation of this method, the probability was obtained using a two-sided test for equality of medians, the Wilcoxon rank sum test [2]. At $p < 0.05$, the differences were considered statistically conditioned, at $p < 0.15$, as a manifestation of a tendency.

Results and discussion. As part of a comprehensive examination of patients with chronic catarrhal gingivitis, 55 people were examined. Evaluation of the periodontal condition in patients of this group allowed us to establish bleeding gums in 89% of patients, in 58% of cases

an insignificant amount of soft and hard plaque was detected.

In patients with a mild degree of periodontitis ($n = 138$), supragingival and subgingival dental deposits were found in all cases. Periodontal pockets with a depth of 4 to 5 mm were detected in 57% of patients. Bleeding gum when brushing teeth were noted in 76% of those examined.

In the group of people with chronic generalized periodontitis of moderate severity ($n = 152$), bleeding gums were observed in 62% of patients, in 87% of those examined the depth of periodontal pockets ranged from 4 to 5 mm. Pathological tooth mobility of grades I-II was detected in 33% of the examined patients. All of them had soft dental deposits and supragingival/subgingival tartar.

When examining patients with severe chronic generalized periodontitis ($n=67$), 71% had bleeding gums, 27% had tooth mobility, purulent discharge and swelling of the gums. All patients had abundant supragingival/subgingival dental deposits, soft plaque and bleeding gums upon probing. Tooth mobility reached grades II-III, the depth of periodontal pockets was 6 mm or more with purulent exudate.

Based on the results of the anthropometric parameters assessment of patients with CGP, 11% of respondents were found to be overweight, 18% to be obese grades 1–3, 21% to be underweight, and 50% of respondents had a body mass index within the normal range. Statistically significant differences were found between the observation groups: weight and BMI were 1.2 times higher in the group of patients with the developed form of CGP ($p = 0.01$). The diet of the examined patients is characterized by reduced consumption of such foods as milk, fish, eggs, fruits, vegetables, and increased consumption of bread products and potatoes.

The energy value of the diet in the group of patients with the initial form of periodontal pathology (gingivitis and mild chronic periodontitis), calculated based on the results of the actual diet study, is slightly below the limit of the physiological energy requirement, regulated for both women and men. In the group with the developed form of the disease (moderate and severe), the daily energy requirement is met. Moreover, the differences between the groups are statistically significant ($p \leq 0.001$) (Table 1).

The protein content in the diet of both groups is at the lower limit of the norm, the share of the daily energy requirement in the group with the initial form of CGP is 21% higher than the upper limit

of the range, and in the developed form it is within the reference range. Fats in the daily diet, without significantly different values among the groups of subjects, are insufficient and do not exceed the consumption standards as a percentage of the caloric content of the diet. The content of saturated (SFA) and mono-unsaturated fatty acids (MUFA) in both groups exceed physiological norms, and the amount of essential polyunsaturated fatty acids (PUFA) is 50-60% of the daily requirement. No significant differences were found between the groups either. In the diet of subjects in the first group (mild gingivitis and periodontitis), the carbohydrate content is close to the minimum, both in absolute terms and as a percentage of the total caloric content. Patients with moderate and severe periodontitis are characterized by carbohydrate consumption as a percentage of calories that is 10% higher, the differences between the groups are statistically significant ($p \leq 0.001$). Dietary fiber, which is known to participate in the mechanism of preventing dental diseases, is 1.5 times less than the lower limit of physiological need in the diet of the subjects of the first group, and at a minimum level in the group with the developed form of CGP. The differences between the groups are also significant ($p \leq 0.05$). Cholesterol in the diet, without significantly differing between the groups of subjects, is within the NFP, which is probably due to the low level of consumption of such products as cheeses, processed meat and animal fats.

Table 2 presents the results of the study of the provision of the diet of the subjects with micronutrients and minerals.

In general, the diet of patients with chronic periodontitis is deficient in several micronutrients: B vitamins (B1, B2) contain from 39 to 53% of the NFP, vitamin C 42-45%, vitamin E 40-49%. Vitamin A in the diet of both groups is at the lower limit of the norm. The need for niacin is satisfied in both groups by 111-130%, the differences between the groups are statistically significant ($p \leq 0.05$).

The daily diet of the subjects showed a deficiency of the macronutrient's calcium (51-63% of the NFP), magnesium (47-53%), potassium (72%), an optimal level of phosphorus (101-116%) and a slight excess of sodium (106-18%). The intake of added salt in both groups of subjects does not exceed the recommended norms. No statistically significant differences were found between the groups. The level of microelements (iron, zinc, copper and iodine) in the diet of the subjects is generally insufficient, manganese

Table 1

Daily consumption of energy and nutrients by the surveyed

Indicators (per day)	Norms of physiological requirements (NFPs) for energy and nutrients (MR 2.3.1.0253-21)	The actual diet	
		the initial form of CGP	the developed form of CGP
		M±m	M±m
Energy value (kcal)	M 2150-3800; W 1700-3000	1634±58	2346±121**
of Protein, g	M 75-114; W 60-90	68±2	78±8
of Protein, % of kcal	12-14	17±1	13±1
Fats, g	M 72-127; W 57-100	51±3	54±6
Fats, % of kcal	He > 30	28±2	21±3
NLC, % of kcal	He > 10	16±1	13±2
MNFA, % of kcal	He > 10	15±1	17±2
PUFA, % of kcal	6-10	4±1	3±1
Carbohydrates, g	M 301-551; W 238-435	223±13	375±31**
Carbohydrates, % of kcal	56-58	55±3	64±6
Dietary fiber, g	20-25	13±3	20±3*
Cholesterol, mg	He > 300	182± 35	145±31
Added salt, g	5	3.4±0.5	3.8±0.4

Note: M – men, W – women. The differences between the groups with initial and advanced forms of CGP are statistically significant: * - p<0.05; ** - p<0.001.

Table 2

Daily intake of micronutrients and minerals by the surveyed

Показатели (в сутки)	Standards of physiological requirements SPR (MR 2.3.1.0253-21)	The actual diet			
		the initial form of CGP		the initial form of CGP	
		M±m	% NPN	M±SD	% NPN
Vitamin A, mcg pet. eq	M 900; W 800	736±118	-	809±255	-
Vitamin E, mg current eq.	15	6.1±0.6	40	7.3±0.8	49
Vitamin B1, mg	1,5	0.7±0.1	47	0.8±0.1*	53
Vitamin B2, mg	1,8	0.7±0.1	39	0.7±0.1	39
Vitamin C, mg	100	45±4	45	42±9	42
Niacin (vitamin PP), mg niac. eq	20	22±1	111	26±1*	130
Calcium, mg	1000	513±44	51	632±87	63
Magnesium, mg	420	198±10	47	225±21	53
Phosphorus, mg	700	707±25	101	809±66	116
Potassium, mg	3500	2515±130	72	2511±253	72
Sodium, mg	1300	1374±189	106	1532±245	118
Iron, mg	M 10; W 18	12±1	-	16±1***	-
Zinc, mg	12	9.6±0.5	80	12.6±1.0**	105
Iodine, mcg	150	53.5±5.3	36	60.3±11.5	40
Copper, mg	1	0.74±0.07	74	1.13±0.12**	113
Manganese, mg	2	2.19±0.35	110	3.52±0.50*	176

Note. M – men, W – women. The differences between groups with initial and advanced forms of CGP are statistically significant: * - p<0.05; ** - p<0.01; *** - p<0.001.

content is 110-176% of the NFP, while the indicators, except for iodine, differ significantly between the groups, in patients with an advanced form of CGP their content is higher.

A comparative analysis of the diet of patients with periodontal pathology of varying severity showed statistically significant differences in the groups in the energy value of the diet, the amount of carbohydrates and dietary fiber, as well as in the content of several micronutrients (vitamins) and minerals. However, the use of a methodological approach based on a moving average made it possible to identify statistical relationships between the degree of development of CGP (by signs), weight and BMI of the subjects (Fig. 1). Thus, with an increase in body weight and, accordingly, the BMI value, the severity of the clinical course of periodontitis steadily increases, and the identified dependence is statistically highly significant ($p=0.01$), a decrease in the degree of periodontitis is observed with the normalization of proteins, carbohydrates and dietary fiber in the diet. An increase in the amount of vitamins (A, B1, C) and a number of macro- and microelements (Cu, Zn, K) in the diet has the same effect.

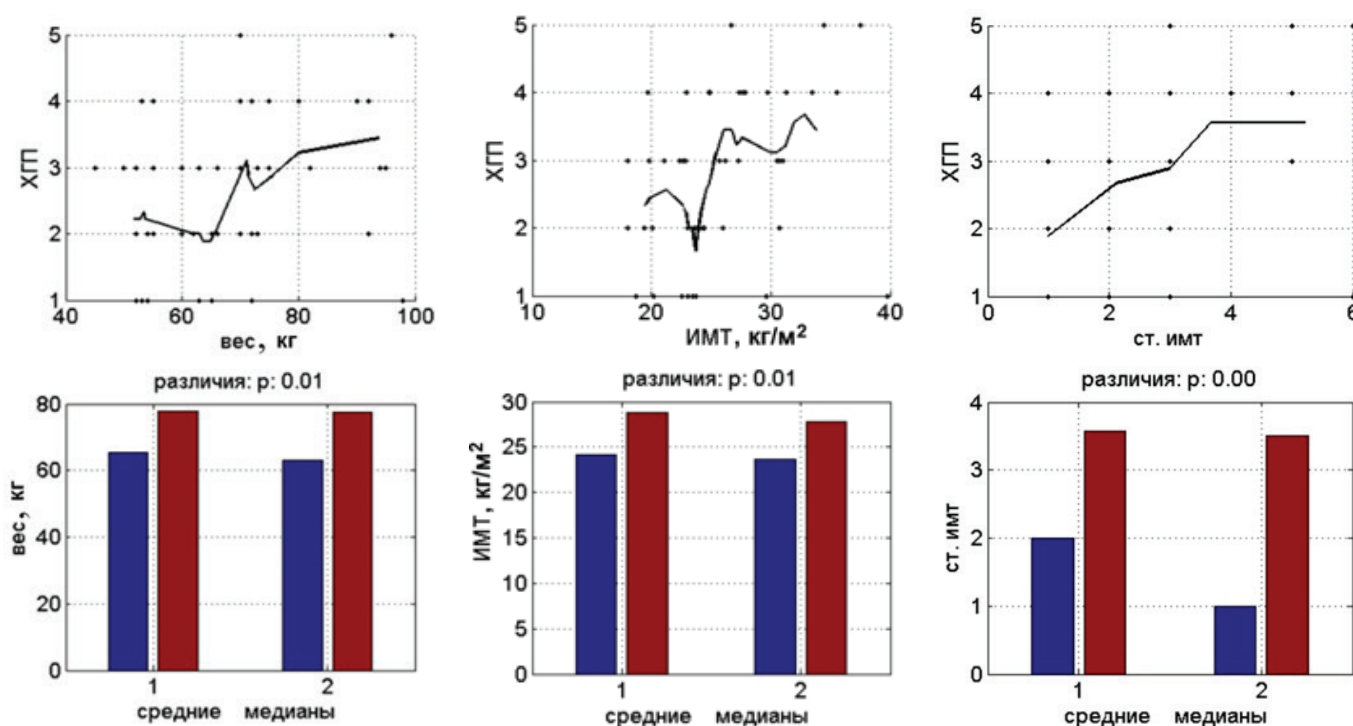
The research conducted established that the most common complaint in the group of subjects was bleeding gums

(87%), which may be associated with a deficiency of potassium and vitamins B1, B2, E in the body (potassium intake is 72% of the NFP, vitamins less than 50%). The identified significant calcium deficiency (51-63% of the NFP) may affect the condition of the enamel and lead to disruption of the bone structure of the periodontium. Deficiency of vitamin A in the daily diet demonstrates a tendency for patients to develop the most pronounced signs of periodontitis, such as a periodontal pocket 6 mm or more deep, pathological mobility of teeth, characteristic of a severe stage of the disease. With a deficiency of vitamin A, the thickness of the dentin layer decreases, the tendency to develop caries increases, yellow pigmentation of the enamel appears, and its hypoplasia develops. Deficiency of ascorbic acid contributes to the disruption of the collagen structure, leads to the development of pathological periodontal pockets and, subsequently, to tooth mobility [5], which is confirmed by our studies - the provision of the diet of patients with chronic periodontal disease with vitamin C is less than half of the daily NFP.

Microelement balance in the body is the most important aspect of homeostatic regulation. The identified deficiency in the diet of such elements as potassium, magnesium, iron, zinc, iodine, copper

can lead to defects in the hard tissues of the teeth, the mucous membrane of the oral cavity, the occurrence and progression of periodontal diseases [18].

It should be noted that patients with initial manifestations of chronic generalized periodontitis (CGP) have an imbalance in the consumption of a number of nutrients, which can contribute to the progression of the disease. At the same time, some patients with an adequately balanced diet were found to have clinical signs of severe periodontitis. These observations may indicate manifestations of malabsorption syndrome. To confirm this assumption and exclude possible pathologies, additional diagnostic measures and consultation with specialized specialists are recommended. The established deficiency in the intake of a number of macro- and micronutrients partially explains the increased susceptibility of periodontal tissues to infection, slowdown in reparative activity. Lack of protein, dietary fiber, vitamins and minerals leads to a weakening of the body's defense mechanisms against external negative influences and can contribute to the development of most chronic non-infectious diseases. The frequency and severity of signs of periodontal damage are associated with impaired intake and absorption of nutrients, which play a key role in many processes of cellular metabolism. Providing



Dependence of the presence of CGP signs (1- bleeding gums, 2 – tartar, 3 – periodontal pocket 4-5 mm, 4- periodontal pocket 6 mm or more, 5- tooth mobility) it depends on the weight of the examined, the BMI value and its degree

the body with the necessary nutrients is one of the key aspects of periodontal disease prevention, since an unbalanced diet contributes to the development of chronic periodontitis [15, 17, 20, 21].

Conclusions. 1. The established cause-and-effect relationship between patients' nutritional factors and the degree of periodontitis confirmed that an unbalanced diet can lead to more severe pathological processes in the periodontium and aggravate the course of the disease. The fewer essential nutrients in the patients' diet, the more pronounced the clinical signs of periodontal damage become. Increased body weight can be considered as one of the signs of metabolic syndrome involved in the formation of periodontitis. Normalization of the diet, including balanced consumption of proteins, fats, carbohydrates, dietary fiber, vitamins (A, B1, B2, C, E) and a number of macro- and microelements (Ca, Mg, K, Fe, Cu, Zn), is a key element in the prevention of periodontal diseases and an important aspect of patient rehabilitation during treatment and observation.

2. The practical significance of this study is determined by the possibility of using its results to develop scientifically based methods for preventing alimentary-dependent diseases in patients with chronic periodontal pathologies. This will provide additional tools for general practitioners, dentists and hygienists in implementing preventive measures and motivating the population to lead a healthy lifestyle, including adherence to the principles of rational nutrition.

3. The implementation of this approach is carried out within the framework of the national project "Long and Active Life", the key event of which is an in-depth study and correction of diets of the population in the constituent entities of the Russian Federation in order to eliminate the deficiency of macro- and micronutrients, taking into account regional characteristics.

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Yu.I. Logvinov, E.A. Berseneva, E.A. Gorbunova, P.A. Drozdov

FEATURES OF EMOTIONAL BURNOUT IN THE CONTEXT OF TRAINING DOCTORS USING SIMULATION TECHNOLOGIES

Relevance: The high prevalence of burnout syndrome among medical professionals has a negative impact on mental and physical health, leading to a decrease in labor productivity and the effectiveness of medical organizations.

The purpose of the study: to determine the formation of phases and severity of symptoms of burnout syndrome among doctors who have been trained in programs using simulation technologies.

Material and methods: The study involved 142 doctors of state medical organizations who are studying advanced training at the Training and Accreditation Center - the Medical Simulation Center of the Moscow Multidisciplinary Scientific and Clinical Center named after S.P. Botkin in 2024. The analytical method, methods of comparative analysis, psychological testing, and statistical methods were used. To study the burnout syndrome, the methodology proposed by V.V. Boyko (1996) was used. Parametric (Student's t-test) and nonparametric (Mann-Whitney U-test) methods were used in statistical processing of the material. The statistical analysis was performed using Microsoft Excel 2016, SPSS Statistics 23.0 programs.

Results: All three phases of burnout syndrome were detected in 71 (50%) respondents. 25 (17.61%) people did not have a single formed phase, but they had some symptoms of PBS. Individual symptoms of burnout syndrome were identified in 140 of the 142 study participants, the most common were "experiencing traumatic circumstances" (83/58.45%), "inadequate selective response" (82/57.74%), "reduction of professional responsibilities" (79/55.63%). Compared with surgeons, anesthesiologists-resuscitators had more often the formation of all three phases, and such a symptom as "emotional and moral disorientation" was more pronounced ($p < 0.05$).

Conclusion. The data obtained on the high incidence of burnout syndrome, the degree of formation of phases and the severity of individual symptoms among doctors studying advanced training cycles using simulation technologies allow us to identify the main areas of preventive work in the future..

Keywords: emotional burnout, phases and symptoms of burnout syndrome, surgeons, anesthesiologists, intensive care physicians, advanced training, simulation technologies.

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LOGVINOV Yuri Ivanovich – PhD, head of the Training and Accreditation Center – Medical Simulation Center, SBHI S.P. Botkin Moscow Multidisciplinary Scientific and Clinical Center of the Moscow Department of Healthcare; Associate Professor of the Department of Public Health Organization with a Course in Healthcare Technology Assessment, Russian Medical Academy of Continuous Professional Education MH RF, ORCID: 0000-0001-8687-526X, LogvinovYI@zdrav.mos.ru; **BERSENEVA Evgeniya Aleksandrovna** – MD, PhD, Prof., head of the Department of Healthcare Organization and Quality Management, Russian Presidential Academy of National Economy and Public Administration; Scientific Director of the National Institute of Quality of the Federal Service for Surveillance in Healthcare; Scientific Director of the All-Russian Research and Testing Institute of Medical Equipment of the Federal Service for Surveillance in Healthcare, ORCID: 0000-0003-3481-6190, eaberseneva@gmail.com; **GORBUNOVA Elizaveta Aleksandrovna** – Psychologist, Training and Accreditation Center – Medical Simulation Center, S.P. Botkin Moscow Multidisciplinary Scientific and Clinical Center, Department of Health of the City of Moscow, ORCID: 0000-0002-4329-9968, Eliza.gorbunova@gmail.com; **DROZDOV Pavel Alekseevich** – MD, PhD, Deputy Director for Research, S.P. Botkin Moscow Multidisciplinary Scientific and Clinical Center, Department of Health of the City of Moscow, Associate Professor, Department of Surgery, Transplantology, and Applied Oncology, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation, ORCID: 0000-0001-8016-1610, dc.drozdov@gmail.com.

Introduction. Studies of burnout syndrome indicate that healthcare professionals are more susceptible to "burnout", and the professional "burnout" of doctors has reached epidemic proportions [19,13]. Manifestations of this condition are more common in representatives of medical specialties related to the provision of emergency and emergency medical care, employees of the district service [10].

Surgeons have a high risk of "burnout", resulting in such consequences as exhaustion, devaluation of personal achievements, depersonalization, depression with suicidal thoughts, decreased quality of life, progressive threat of making medical mistakes [12,17,18,14], 8.9% are worried that they have made a serious medical mistake in the last 3 months, and 70% of surgeons believe that the error is caused not by systemic, but by individual factors [3,4,6]. Among other determinants of burnout, there is an imbalance between working hours and family life, long work shifts, and poor workplace relations [12]. D. Brock Hewitt et al. (2021) in a study conducted among 7,413 surgical residents, 38.5% revealed symptoms of emotion-

al exhaustion and depersonalization; 23.7% of residents found symptoms of emotional exhaustion themselves over the past year; 4.5% of the surveyed had suicidal thoughts [21]. In a study of the causes of death of 324 residents from 2000 to 2014, conducted by Yaghmour N. A. et al. (2017), the prevalence of cancer and suicide among the causes of death was found, while death as a result of suicide was more common among male residents, and girls were more likely to die from malignant neoplasms [16].

A study conducted in 2020 in the USA clearly demonstrates the high risk of burnout among anesthesiologists (59.2%), the proportion of the identified syndrome is 13.8%, to a large extent, the reason for the risk lies in the lack of support from doctors of this specialty, in professional everyday realities [15]. The analysis published by domestic colleagues reinforces the general trend, where 65.9% of anesthesiologists have high scores on the scale of "emotional exhaustion", or on the scale of "depersonalization", or "reduction of professional achievements", and 12.19% have a high value of the systemic burnout index [8]. Using the observations obtained as a starting point, "burnout"

correlates with depression, personal and situational anxiety [8].

The study of the factors contributing to professional distress, the patterns of formation of burnout syndrome in representatives of various medical specialties will determine the main directions of its prevention.

Due to the fact that burnout syndrome has a negative impact on both mental and physical health, as well as on labor productivity and organizational effectiveness, the study of this phenomenon seems relevant and timely.

The purpose of the study: to determine the formation of phases and severity of symptoms of burnout syndrome among doctors of public medical organizations who have been trained in additional professional development programs using simulation technologies.

Material and methods. The study involved 142 doctors from government medical organizations who are studying advanced training at the Training and Accreditation Center, the Medical Simulation Center of the Botkin Moscow Multidisciplinary Research and Clinical Center in 2024.

The students were trained in the programs "Moscow School of Surgery", "Fundamentals of laparoscopic surgery in a short-term inpatient complex. Basic course", "Basic principles and clinical application of hyperbaric oxygenation", "Cardiopulmonary resuscitation. Basic course", "Modern possibilities of diagnosis and treatment of epilepsy".

Most of them were representatives of specialties related to the provision of emergency and emergency care, surgical specialties: surgeons - 74 (52.11%), anesthesiologists-intensive care specialists - 25 (17.6%), otorhinolaryngologists - 3 (2.11%), oncologists - 2 (1.41%), urologists - 2 (1.41%), endoscopists - 2 (1.41%), obstetricians-gynecologists - 1 (0.7%), emergency physicians - 1 (0.7%), pediatric surgeons - 1 (0.7%). Representatives of the therapeutic and diagnostic profile also participated in the study: neurologists - 11 (7.75%), endocrinologists - 8 (5.63%), ultrasound diagnostics doctors - 2 (1.41%), pediatricians - 2 (1.41%), functional diagnostics doctors - 1 (0.7%), general practitioners (family doctors) - 1 (0.7%), infectious diseases doctors - 1 (0.7%). 5 (3.52%) people have no established specialty.

The analytical method, methods of comparative analysis, psychological testing, and statistical methods were used.

To study the burnout syndrome (PBS), a technique proposed by V.V. Boyko (1996) was used to identify the phase

of emotional burnout, the degree of its formation, and the severity of individual symptoms in each phase [1]. According to the "key", the sum of points was determined separately for each of the 12 symptoms of "burnout", the sum of the indicators of symptoms for each of the 3 phases of the formation of "burnout" was calculated, and the final indicator of "emotional burnout" syndrome was calculated as the sum of the indicators of all 12 symptoms. The severity of each symptom ranges from 0 to 30 points: 9 or less points — a failed symptom, 10-15 points — a developing symptom, 16 or more — a developed one. Symptoms with scores of 20 or more are considered dominant in the phase or in the entire "burnout" syndrome. When evaluating the phase, it was assumed that if the number of points was 36 or less, the phase was not formed; 37-60 points — the phase in the formation stage; 61 or more points — the formed phase.

According to V. V. Boyko's method, the stress phase is characterized by a feeling of fatigue and emotional exhaustion caused by professional activity. The symptoms of the stress phase are experiencing traumatic circumstances, dissatisfaction with oneself, feeling "trapped in a dead end", anxiety and depression. The resistance phase is characterized by excessive loss of emotional resources, manifests itself as inadequate selective emotional response, emotional and moral disorientation, expansion of the sphere of saving emotions, and reduction of professional responsibilities. The exhaustion phase is characterized by psychophysical overwork, depression, devaluation of personal achievements in professional life, discord in professional relationships, increasing cynicism towards others, along with psychosomatic disorders. It is symptomatically manifested by emotional deficit, emotional isolation, personal alienation, and psychosomatic disorders [1].

During the survey, despite the pre-test conversation and guarantees of anonymity of the answers, doctors expressed concerns about disclosing the results of

the survey to the management of medical organizations and did not fully answer questions about the respondent's personality, which significantly narrowed the possibilities of conducting a correlation analysis of factors related to emotional burnout.

Statistical analysis was performed using the Kolmogorov-Smirnov test to test the hypothesis that the data is subject to a normal distribution. Depending on the data obtained on the normality of the distribution, parametric (Student's t-test) and nonparametric (Mann-Whitney U-test) methods were used to identify differences in the severity of burnout phases and their symptoms between surgeons and intensive care anesthesiologists. The statistical analysis was performed using Microsoft Excel 2016, SPSS Statistics 23.0 programs.

Results. Among the doctors who participated in the study, 71 (50%) respondents had all three phases of PBS of varying degrees of formation. 25 (17.61%) people did not have a single formed phase, but they had some symptoms of PBS.

The results of the study on the degree of formation of the PBS phases, presented in Table 1, show that 43 (30.28%) of the listeners who participated in the study have formed the first phase of the PBS, the stress phase, 40 (28.17%) of the respondents are in the formation stage, 59 (41.55%) have not formed. The resistance phase was formed in 73 (51.41%) of the doctors who participated in the study, at the stage of formation – in 41 (28.87%); not formed – in 28 (19.71%) doctors. 44 (30.99%) respondents had a depletion phase, 41 (28.87%) were in the formative stages, and 57 (40.14%) doctors were not.

The analysis of the established and dominant symptoms characteristic of certain phases of PBS is shown in Table 2. As follows from the data presented, in the stress phase, the symptoms of "experiencing traumatic circumstances" are established and dominant in 83 (58.45%) respondents, in the resistance phase - "inadequate selective response" - in

Table 1

The degree of formation of phases of emotional burnout among doctors, abs.% (n=142)

Phases of the Burnout syndrome	The phase has not formed	A phase in the formation stage	The formed phase
Voltage phase	59/41.55%	40/28.17%	43/30.28%
The resistance phase	28/19.71%%	41/28.87%	73/51.41%
The exhaustion phase	57/40.14%	41/28.87%	44/30.99%

82 (57.74%), "expansion of the sphere of saving emotions" - in 62 (43.66%), "reduction of professional duties" - in 79 (55.63%), in the exhaustion phase – "emotional detachment" - in 52 (36.62%) doctors.

Psychosomatic and psychovegetative disorders were not detected in more than half of the respondents (77 people (54.22%), however, 38 (26.76%) have started the formation process, and 27 (19.01%) already have its manifestations that violate the quality of life of the respondents.

The average score of respondents with manifestations of the stress phase was 62.52 ± 1.886 , with manifestations

these, the majority experienced traumatic circumstances, as a result, 22 (15.7%) doctors fully developed the symptom, and 61 (43.6%) The most common symptom of "inadequate selective emotional response" was dominant in 49 (35%) of respondents and in 33 (23.7%) it is a developed symptom ($x = 16.63$; $Me = 19.00$; $Mo = 27$) of the respondents.; $Me = 17.50$; $Mo = 20$). "Reduction of professional responsibilities" is widespread among doctors who have joined the training: 23 (16.4%) have developed a symptom, and 56 (40%) have a dominant resistance phase ($x = 16.97$; $Me = 18.00$; $Mo = 25$).

According to the analysis of the normality of the distribution of samples of

surgeons and anesthesiologists, resuscitators, using the criterion of normality of the Kolmogorov-Smirnov distribution, there was no statistically significant evidence that the data do not obey the normal distribution ($p > 0.05$).

The frequency of occurrence, the degree of formation of phases and individual symptoms were analyzed in a group of surgeons ($n = 74$) and a group of anesthesiologists and intensive care physicians ($n = 25$).

As follows from the data presented in Table 5, the stress and exhaustion phases of surgeons do not significantly differ from those of intensive care anesthesiologists ($p > 0.05$), while the resis-

Table 2

The degree of formation of symptoms of emotional burnout, abs./%, (n=142)

Symptoms of phases of burnout syndrome	An uncomplicated symptom	Emerging symptom	The developed symptom	The dominant symptom in the phase
	Absolute/%	Absolute/%	Absolute/%	Absolute/%
Experiencing traumatic circumstances	38/27.14	19/13.57	22/15.71	61/43.57
Dissatisfaction with oneself	85/60.71	38/27.14	7/5	10/7.14
Being trapped in a cage	86/61.43	29/20.71	15/10.71	10/7.14
Anxiety and depression	61/43.57	39/27.86	13/9.29	27/19.28
Inadequate selective emotional response	20/14.29	38/27.14	33/23.57	49/35
Emotional and moral disorientation	43/30.71	53/37.86	26/18.57	18/12.86
Expanding the sphere of saving emotions	49/35	29/20.71	14/10	48/34.29
Reduction of professional responsibilities	27/19.28	34/24.29	23/16.43	56/40
Emotional deficit	50/35.71	43/30.71	25/17.86	22/15.71
Emotional detachment	41/29.28	47/33.57	32/22.86	20/14.29
Personal detachment (depersonalization)	60/42.86	26/18.57	16/11.43	38/27.14
Psychosomatic and psychovegetative disorders	75/53.57	38/27.14	10/7.14	17/12.14

of the resistance phase - 69.24 ± 1.736 , with manifestations of the exhaustion phase – 65.69 ± 2.011 . It is noteworthy that the majority of respondents had symptoms characteristic of the formed resistance phase. This phase is characterized by the appearance of protective symptoms, continued resistance to the pressure of stressful factors by seeking attempts to avoid the negative influence of external factors for the sake of a sense of mental well-being and peace (Table 3). However, the symptoms can already be noticed by loved ones in situations of "emotional breakdown" at home, while at work the individual tends to minimizing contacts.

The results of the study indicate that symptoms of burnout syndrome were detected in 140 (98.59%) of the 142 doctors who participated in the study (Table 4). Of

Table 3

The values of descriptive statistics on the phases of emotional burnout

-	Voltage phase	The resistance phase	The exhaustion phase
Valid ones, n	83	114	85
Arithmetic mean, $\bar{x}$	62.52	69.24	65.69
Standard error of the average value, $S_{\bar{x}}$	1.886	1.736	2.011
Median, Me	62.00	67.00	62.00
Vogue, Mo	37	61	47
Mean square deviation, σ	17.181	18.534	18.538
Variance, S^2	295.180	343.492	343.667
Range	68	69	68
Minimum	37	37	38
Maximum	105	106	106
Total, Σ	5189	7893	5584

Table 4

The results of descriptive statistics on the symptoms of emotional burnout, (n=140)

	Experiencing traumatic circumstances	Dissatisfaction with oneself	Being trapped in a cage	Anxiety and depression	Inadequately selective emotional response	Emotional and moral disorientation	Expanding the sphere of saving emotions	Reduction of professional responsibilities	Emotional deficit	Emotional detachment	Personal detachment (depersonalization)	Psychosomatic disorders
Arithmetic mean, $\bar{x}$	16.63	8.39	8.04	11.45	17.22	12.94	14.39	16.97	12.53	12.96	13.31	9.74
Standard error of the average value $S_{\bar{x}}$	0.786	0.602	0.633	0.769	0.625	0.554	0.857	0.739	0.703	0.566	0.889	0.689
Median, Me	19.00	8.00	6.00	10.00	17.50	12.00	14.00	18.00	12.00	12.50	13	8.00
Vogue, Mo	27	0	0	0	20	10	0	25	0	10	0	10
Mean square deviation, S	9.300	7.123	7.490	9.096	7.398	6.553	10.137	8.742	8.313	6.695	10.517	8.148
Variance, S^2	86.494	50.744	56.107	82.738	54.735	42.938	102.758	76.431	69.100	44.826	110.606	66.394
Asymmetry	-0.441	0.857	0.819	0.507	-0.344	0.468	0.062	-0.337	0.263	0.072	0.318	0.880
St. excess error	0.205	0.205	0.205	0.205	0.205	0.205	0.205	0.205	0.205	0.205	0.205	0.205
Range	30	30	30	30	30	30	30	30	30	25	33	30
Minimum	0	0	0	0	0	0	0	0	0	0	0	0
Maximum	30	30	30	30	30	30	30	30	30	25	33	30
Total, $\sum$	2328	1175	1125	1603	2411	1811	2015	2376	1754	1815	1864	1364

tance phase of intensive care anesthesiologists is more pronounced than that of surgeons ($p < 0.05$).

A comparative characteristic of the frequency of symptoms of burnout syndrome in the group of surgeons ($n=72$) and intensive care anesthesiologists ($n=25$) is presented in Table 6.

The symptom of "emotional and moral disorientation" was more pronounced among anesthesiologists than that of surgeons ($p < 0.05$).

Among surgeons, 18 (24.32%) people did not develop COMECON phases, while only 2 (8%) people did not develop COMECON phases among anesthesiologists and intensive care physicians. All three phases of PBS were formed in 31 (41.89%) surgeons and 16 (64%) intensive care anesthesiologists.

A comparative characteristic of the formation of phases and symptoms of PBS indicates that anesthesiologists and intensive care physicians were more likely to have the formation of all three phases of PBS, and the symptom of "emotional and moral disorientation" was more pronounced than that of surgeons ($p < 0.05$).

Currently, the Moscow Multidisciplinary Scientific and Clinical Center named after S.P. Botkin of the Moscow Department of Health is implementing an 18-hour professional development program for doctors of all specialties "Prevention of professional burnout in the work of a doctor", accredited in the NMO system. The training is conducted full-time. The main purpose of the program is to train doctors in ways of self-regulation and modern approaches to the prevention of professional burnout (<https://botkinmoscow.ru/specialists/sim-tsentra/o-tsentre/obrazovatelnye-programmy/>

profilaktika-professionalnogo-vygoraniya-v-rabote-vrach/).

Discussion. Researchers' close attention to the problem of emotional burnout among medical professionals is only growing every year. A number of experts tend to equate the concepts of "stress" and "burnout", which is not a misconception, because the causes and symptoms of these phenomena are similar. The sources of distress are diverse, they become disastrous for an individual when the demands are inversely proportional to the available resources, as well as when stressful conditions persist

Table 5

Phases of burnout syndrome in a group of surgeons and intensive care anesthesiologists

No	Phases of emotional burnout	Doctors-surgeons, n= 74, Me	Intensive care anesthesiologists, n=25, Me	U	Z	p-value
1.	Voltage phase	63.00	65.00	326.500	- 0.433	0.665
2.	The resistance phase	66.00	71.00	526.500	- 1.162	0.245
3.	The exhaustion phase	68.50	60.00	316.000	- 0.740	0.459

Table 6

Symptoms of burnout syndrome in the group of surgeons and anesthesiologists- resuscitators

№	Symptoms of emotional burnout	The Mann-Whitney criterion				The t-Student criterion			
		Doctors-surgeons, Me	Intensive care anesthesiologists, Me	U	p-value	Doctors-surgeons, $\bar{x}, S_{\bar{x}}$	Intensive care anesthesiologists, $\bar{x}, S_{\bar{x}}$	t	p-value
1.	Experiencing traumatic circumstances (in the stress phase)	17.0	22.0	740.0	0.186	15.61 1.130	18.72 1.562	1.460	0.147
2.	Dissatisfaction with oneself (in the stress phase)	7.0	10.0	690.0	0.081	7.71 0.837	10.16 1.350	1.505	0.136
3.	Caged (in the stress phase)	5.0	10.0	751.5	0.217	7.47 0.877	9.20 1.324	1.027	0.307
4.	Anxiety and depression (in the stress phase)	10.0	11.0	847.0	0.660	11.03 1.067	11.80 1.826	0.367	0.715
5.	Inadequately selective emotional response (in the resistance phase)	17.0	20.0	707.5	0.111	15.83 0.887	18.80 1.290	1.757	0.082
6.	Emotional and moral disorientation (in the resistance phase)	10.0	15.0	644.0	0.034	12.17 0.739	15.44 1.244	2.255	0.026
7.	Expansion of the sphere of saving emotions (in the phase of resistance)	13.0	13.0	817.0	0.492	13.72 1.193	15.24 2.017	0.646	0.520
8.	Reduction of professional responsibilities (in the phase of resistance)	15.5	20.0	698.0	0.095	15.68 1.082	19.36 1.465	1.812	0.073
9.	Emotional deficit (in the exhaustion phase)	10.0	15.0	668.5	0.056	11.42 0.880	14.88 1.773	1.902	0.060
10.	Emotional withdrawal (in the exhaustion phase)	13.0	15.0	836.0	0.597	13.00 0.776	13.88 1.473	0.558	0.578
11.	Personal detachment (Depersonalization) (in the exhaustion phase)	13.0	15.0	777.0	0.308	12.31 1.236	14.84 2.152	1.034	0.304
12.	Psychosomatic and psychovegetative disorders (in the exhaustion phase)	7.0	10.0	709.5	0.115	8.63 0.900	11.40 1.703	1.520	0.132

for a long time, being a destructive basis for the formation of diseases. During the work process, a person is confronted with several types of stress, divided into three main clusters: stress associated with work, or rather with its conditions; professional stress, as a result of stress related to the type of activity; organizational stress- the product of the impact of the distinctive properties of the institution where a person works.

The American psychoanalyst Herbert J. Smith plays a fundamental role in the study of professional distress. To Freudenberg, who was the first to introduce the concept of "burnout." Despite the growing number of publications devoted to the problem of "burnout", there is currently no single definition. In the works of Vodopyanova N.E., "burnout" is presented as a synthesis of mental experiences and behavior, which affects

not only professional activity, but also well-being, as well as the relationship of a "burned out" employee. Consequently, the syndrome occurs in response to long-term stress in career activities [1]. Without going into specifics, "burnout" refers to emotional exhaustion, which acts as a protective mechanism in response to traumatic stimuli [2]. Burnout affects not only the doctor himself, but also his close circle of associates, his colleagues and, in general, the health care system, the ability to provide high-quality care to patients [3,4].

The combination of symptoms such as emotional exhaustion (indifference, feeling of emptiness, impoverishment of the emotional background); depersonalization; reduction of personal achievements (weakening confidence in one's own competence, reducing the value of personal professional success) and

forms burnout syndrome [6]. The concept formed by the authors (K. Maslach, S. Jackson, N.V. Grishina), allows us to conclude that internal psychological experience, including motivation, as well as individual negative experiences and the boundaries of the "emotional self", integrating, act as determinants of burnout syndrome. As a result, stress affects, to varying degrees, physical and mental health, adversely affecting the quality of work and adaptive potential [1].

N.A. Sirota (2017) in his work cites examples of the development of burnout syndrome not only among doctors, but also among students [17]. The work of A.N. Petri (2017) indicates the influence of professional experience on the level of emotional burnout. Thus, specialists with more than five years of experience are susceptible to professional burnout syndrome in the presence of indirect

aggression and feelings of guilt. The author emphasizes the important role of the doctor's self-acceptance and personal character traits, in particular, he points to a significant degree of involvement in the development of emotional burnout of such a personality quality as pedantry [18]. The results of a domestic study demonstrate revealed professional burnout in a third of district internists (298 out of 1014 internists who participated in the study) [16].

The data obtained in this study are generally consistent with the results of other studies on the prevalence of emotional burnout among doctors, and the greater susceptibility of specialists providing emergency and emergency care to this syndrome. The professional environment of surgeons and anesthesiologists is stressfully saturated, which requires doctors to have a strong adaptive potential, a high level of neuropsychiatric stability, willingness to take risky actions, and the ability to make responsible decisions in emergency situations. At the same time, such factors as impotence in total control over the object of one's professional activity; ambiguous ethical aspects; lack of positive feedback from patients; possible disagreements with fellow surgeons and other circumstances are highly likely to lead to destructive consequences have a negative impact on stress tolerance. The most common are burnout syndrome, addictive behavior, anxiety disorders, depression, and even suicidal tendencies.

To date, there are studies among scientific publications aimed at studying methods of countering burnout, ways to correct emotional stress by medication, which is used by about a third of medical professionals, or by changing professional activities [19].

The current recommendations for the prevention of burnout indicate that if two conditions are met - duration and consistency of use – the effectiveness of preventive measures increases. Preventive measures aimed at the intellectual sphere involve changing the type of activity, expanding the range of activities, communication, new acquaintances, which can be realized through additional professional training and regular professional development. All this has a positive effect on career motivation in the future, increases the chances of rethinking previous unsuccessful experiences, redirects attention to one's own achievements, followed by transformation into a resource experience [8,20].

Compliance with the following recommendations should reduce the likelihood of developing burnout syndrome: mas-

tery of self-regulation skills, meaningful guidance for the future, interest in the very process of life in the current period of time, a positive view of the past, an internal locus of control. Professional development, advanced training, additional education, as well as participation in conferences and other scientific events will increase the level of resistance to emotional burnout.

There are prospects for further study of Burnout by doctors in the direction of assessing the impact of various potentially stressful factors, developing rapid screening of burnout symptoms before and after training, and building predictive models of the risk of Burnout formation depending on the specialty and working conditions of doctors.

Conclusion. Half of the doctors (71 people (50%)) who participated in the study had all three phases of burnout syndrome of varying degrees of development. 25 (17.61%) people did not have a single formed phase, but they had some symptoms of PBS.

Of the three phases of emotional burnout, the stress phase was formed in 43 (30.28%) listeners, half of the respondents (73 (51.41%) people) have a developed resistance phase, the exhaustion phase was detected in a third (44 (30.99%) people) of doctors, while 2/3 of doctors have a combination of two or more three phases of varying degrees of formation.

Symptoms of burnout syndrome were identified in 140 of the 142 study participants. Among them, the most common were "experiencing traumatic circumstances" (83/58.45%), "inadequate selective response" (82/57.74%), "reduction of professional responsibilities" (79/55.63%), "expansion of the sphere of saving emotions" (62/43.66%), "emotional detachment" (52/36.62%).

Psychosomatic and psychovegetative disorders have not been identified in more than half of the respondents, but the process of their formation has been started in 38 (26.76%) of respondents, and 27 (19.01%) of doctors already have its manifestations that violate the quality of life of respondents.

A comparative characteristic of the formation of phases and symptoms of burnout syndrome indicates that anesthesiologists and intensive care physicians were more likely to have all three phases; and the symptom of "emotional and moral disorientation" was more pronounced than that of surgeons ($U=644,000$, $p=0.034$).

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S.M. Tarabukina, S.N. Zhirkov, I.I. Vinokurova, G.I. Fedotova

THE CONCEPT OF A UNIFIED DEPARTMENTAL APPROACH TO THE MANAGEMENT OF QUALITY AND SAFETY OF MEDICAL ACTIVITIES IN THE REPUBLIC OF SAKHA (YAKUTIA)

The article devoted to the development of a concept for a unified departmental approach to quality and safety management of medical activities in the Republic of Sakha (Yakutia), examines issues related to the implementation and dissemination of practical recommendations of the National Institute for Quality of Roszdravnadzor. This can be achieved through the creation of an integrated system for managing the quality and safety of medical activities in subordinate medical organizations, based on the Regional Competence Center in the field of quality and safety management of medical activities.

The Regional Competence Center is a key element in the concept of the approach aimed at improving the management of quality and safety in medical activities. Its creation makes it possible to consolidate knowledge, resources, and efforts for the development and implementation of effective tools in the field of quality and medical care, as well as to disseminate best practices and existing experience.

The concept of a unified departmental approach to managing the quality and safety of medical activities is intended to create conditions for improving approaches to the organization of internal control over the quality and safety of medical activities. Its main idea is to develop measures aimed at the consistent and phased implementation of the practical recommendations of the National Institute for Quality of Roszdravnadzor in the medical organizations of the republic.

Keywords: competence center, quality and safety of medical activities, staff involvement, practical recommendations of Roszdravnadzor, internal quality control in a medical organization.

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TARABUKINA Sardana Makarovna – Doctor of Pharmaceutical Sciences, Professor of the Medical Institute of FSAEI HE 'M.K. Ammosov North-Eastern Federal University', tcmx@mail.ru; Republican Hospital No. 1, National Center of Medicine: **ZHIRKOV Stanislav Nikolaevich** – CEO, rb1ncm@gov14.ru; **VINOKUROVA Inna Ivanovna** – deputy CEO for Organizational, Methodological, and Preventive Work, innavin@mail.ru; **FEDOTOVA Galina Igorevna** – director of the Consultative and Diagnostic Center, FedotovaGI@inbox.ru

Introduction. Ensuring the quality of treatment and patient safety is the most important component of the activities of medical organizations. As many researchers emphasize, treatment quality and patient safety are inseparable and mutually complementary scientific and practical categories, while patient safety itself is a comprehensive concept that integrates advanced educational, clinical, and management technologies aimed at preventing adverse treatment

outcomes, based on their internal interconnections and shared development prospects [4]. This is reflected in many strategic documents dedicated to the development of healthcare, ranging from individual medical organizations to federal subjects and the country as a whole. In the republic, there is a need to establish a holistic departmental system for quality and safety management, taking into account contemporary challenges and aimed at consolidating avail-

able efforts, resources, knowledge, and practices.

Research objective: to develop a concept of a unified departmental approach to managing the quality and safety of medical activities in the Republic of Sakha (Yakutia) through the use of accumulated experience, testing and implementation of best practices in pilot medical organizations, as well as by increasing the overall engagement and involvement of medical personnel in this work.

Research tasks: to develop organizational and functional technologies for creating an integrated comprehensive system for managing the quality of medical activities based on the practical recommendations of the National Institute for Quality of Roszdravnadzor, specifying the stages and measures for implementation; to determine the key indicators of medical activity quality and patient safety for evaluating the effectiveness and efficiency of the system in the future.

The work is based on the authors' own research and an analysis of regulatory legal documents in the field of quality control at the federal, republican, and local levels. The research included summarizing data on the state of quality control in the republic's medical organizations, conducting an audit across 18 key sections of the practical recommendations for ensuring quality control and safety in medical activities, which involved inspections, monitoring, and staff interviews. A comprehensive methodology was applied in the study, including: review and generalization of experience, content analysis, methods of systems analysis, expert assessments, organizational and legal analysis, organizational modeling, and other methods.

Discussion. State healthcare policy clearly defines ensuring the quality and safety of medical activities as a top priority, which is reflected in federal documents and initiatives. Continuous improvement of the quality and safety management system for medical activities is a pressing task for healthcare authorities. One effective solution to this problem is the implementation of a management system based on practical recommendations for organizing internal quality control and safety of medical activities in the medical organization of the National Institute of Quality of the Federal Service for Surveillance in Healthcare [3, 7]. As a result of systematic work in the republic, the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 - National Center of Medicine named after M.E. Nikolaev" received the

National Certificate of Quality and Safety of Medical Activities for the first time. In addition to this institution, two other institutions underwent independent audits by authorized experts in their outpatient departments, subsequently receiving certification: the State Autonomous Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Ophthalmological Clinical Hospital" and the State Autonomous Institution of the Republic of Sakha (Yakutia) "Yakutsk Medical Center." Key elements of the quality management system include internal audits, risk management, documentation, staff training, and advanced training. Staff training should cover not only specific medical skills but also quality and safety principles, risk management methods, and patient safety. Risk management involves identifying, analyzing, and assessing potential risks, and developing and implementing mitigation measures. Effective documentation management ensures transparency and accessibility of information.

As noted by the authors Murashko M.A., Samoylova A.V., and others, the methodology for implementing the Practical Recommendations is based on the most proven effective practices and approaches to ensuring the quality and safety of medical activities [8, 10]. Implementing an effective quality and safety management system in medical organizations is not simply fulfilling formal requirements, but a strategic step that allows for the use of the strengths of the medical organization and the minimization of the impact of weaknesses caused by external factors, such as the characteristics of the regional infrastructure.

Effective management decisions are based on a system of internal control, which is only possible with reliable information covering all aspects of a medical organization's operations. Therefore, the implementation of management mechanisms based on advanced information technology is a pressing issue [1].

The key strategy for regional quality and safety management includes the active involvement of medical organizations, physicians, patients, and public organizations in ensuring appropriate treatment and effective internal control.

To establish unified approaches to improving internal control and implementing quality and safety principles, a roadmap has been approved for the phased implementation of an integrated quality and safety management system for medical activities in medical organizations under the jurisdiction of the Ministry of Health of the Republic of Sakha (Yakutia). To consistently implement the plan's activi-

ties, regional working groups have been formed based on the sections of the Practical Recommendations for Organizing Internal Quality Control and Safety in Medical Activities. Following preliminary discussions and approval by all stakeholders, 11 pilot medical organizations in the Republic have been included in the project to implement the Proposals of the National Institute for Quality of Roszdravnadzor.

The successful functioning of a management system requires not only formal compliance with regulatory documents but also a deep understanding of quality and safety principles by all participants—from nurses and doctors to administrative staff and management. This includes not only knowledge of standard requirements but also the ability to apply them in practice, adapting them to the specific operating conditions of the institution. Moreover, an effective system goes beyond internal organizational processes. It presupposes a well-established system of interaction between medical organizations, ensuring uninterrupted continuity in the provision of medical care and minimizing the risk of errors associated with the transfer of information and inconsistencies in actions.

In this context, the role of centers of excellence in quality and safety in medical activities is crucial. They should provide methodological and advisory support to medical organizations, facilitate the exchange of experience, and implement best practices. Implementation of the system should be based on generally accepted management principles planning, implementation, verification, and adjustment. This cyclical process of continuous improvement involves ongoing monitoring and analysis of quality and safety indicators, identifying problem areas, and developing measures to address them. This requires collecting and analyzing the healthcare organization's performance indicators, including the frequency of violations of standards and procedures, satisfaction levels, and mortality and morbidity rates. Analyzing these indicators allows us to identify trends, predict risks, and take measures to prevent adverse events.

In June 2023, the Regional Competence Center for Quality and Safety Management in Medical Activities of the Republic of Sakha (Yakutia) (hereinafter referred to as the Center) was established at the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 – M.E. Nikolaev National Center of Medicine."

The Center represents an important element of the regional management

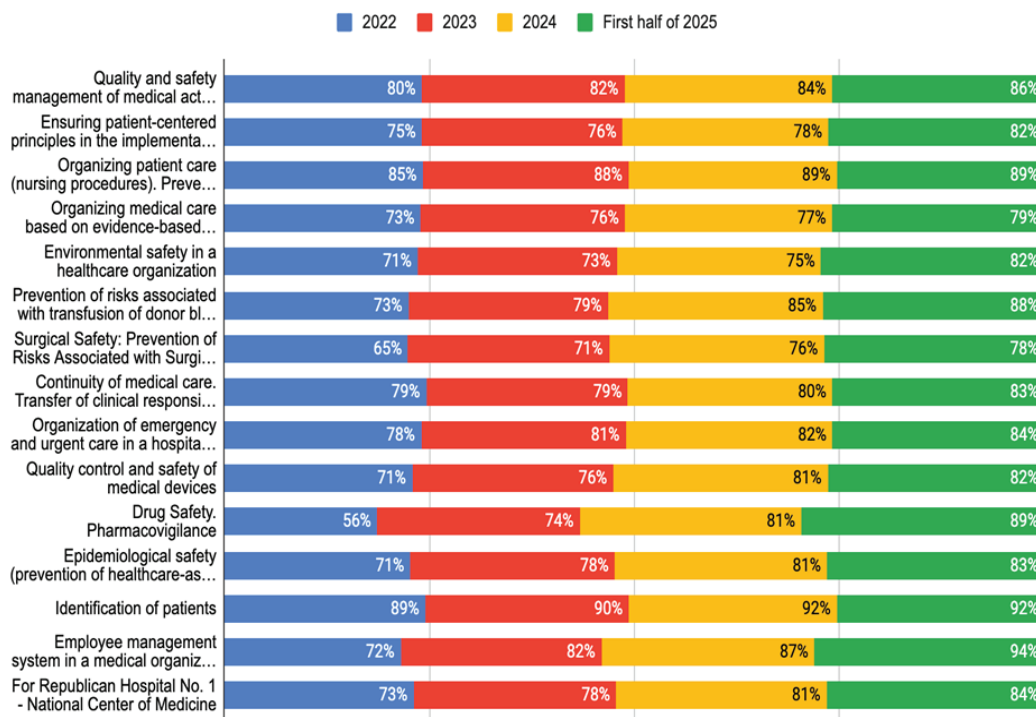


Fig. 1. Audit results for 2022 – first half of 2025

strategy aimed at improving the health-care system. The creation of the Center enables the integration of knowledge and best practices, facilitating the development and implementation of effective standards and tools.

Its activities are aimed at implementing advanced practical methods of quality and safety management in medical organizations of the Republic, covering a wide range of tasks [8]. Particular attention is paid to the development of a safety culture, including the active identification and analysis of adverse events, incidents, and other situations that could have led or have led to harm to a patient. The performance monitoring system developed and maintained by the Center is a tool for objectively assessing the effectiveness of both the institution itself and other medical organizations in the republic. Monitoring data is used to target resource allocation, optimize processes, and improve the overall quality of medical care.

Audit is a key tool for assessing the compliance of medical organizations. In this context, audit is a systematic, independent, and documented process aimed at objectively assessing a medical organization's compliance with standards and procedures [2]. This includes not only document review but also process analysis, staff interviews, and observation of medical personnel. It is important to note that audit is not a goal in itself, but a tool for continuous improvement.

In November 2024, the Yakutsk Republican Oncology Dispensary conducted its first primary audit a cross-assessment of the internal quality control and safety system for medical activities

management, and others. The audit covered 18 key sections of practical recommendations for ensuring quality control and safety in medical activities, dividing the analysis between the institution's

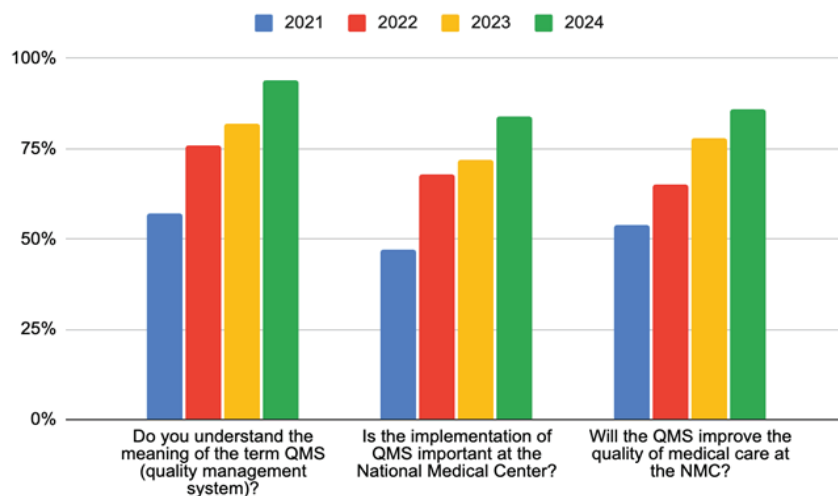


Fig. 2. Results of employee interviews for 2021–2024

for compliance with the requirements of the voluntary certification system for medical organizations by the Center of Excellence in Quality and Safety Management in Medical Activities of the Republic of Sakha (Yakutia). This was the Center's first experience assessing the performance of its colleagues, conducted in key areas of internal control, including epidemiological, surgical, and drug safety, personal identification, personnel

inpatient and outpatient departments. The first phase of the audit focused on a thorough assessment of compliance with established standards in order to comprehensively prepare for the subsequent certification stage, which involved an in-depth study of the content and areas of audits. Audits identify problem areas, and the collected data helps adapt management approaches and make adjustments to decisions. Control is one of the man-

agement functions aimed at establishing the conformity or non-conformity of actual activities with the specified level [5].

To replicate organizational and methodological foundations and organizational technologies, the Center has jointly developed a standard operating procedure, "Procedure for Developing Regional and Local Clinical Treatment Protocols." Standard operating procedures for patient routing by specialty have been developed and are currently being tested.

Furthermore, training in various aspects of medical care quality and safety plays a key role in the quality and safety management system for medical activities. The Center not only organizes training but also plays a leading role in the development and implementation of educational programs. These programs are adapted to constantly changing requirements and take into account the specifics of various medical specialties. Training is based on a multi-level system, including a variety of formats: from seminars and workshops aimed at practical mastery of internal quality and safety control methods to more in-depth educational programs that cover complex aspects of medical law, drug safety, risk management, and ethics. Seminars and training sessions are held regularly for medical organizations, ensuring access to high-quality training, regardless of the employee's location or specialization. These seminars discuss potential risks and current issues. This creates a platform for the exchange of opinions and ideas between doctors and nurses, fostering a deeper understanding of existing challenges and the search for collaborative solutions, ultimately positively impacting the quality of medical services. Continuous education not only promotes the personal and professional growth of specialists but also improves the overall quality and safety of medical services.

As part of enhancing safety culture, a strategic session was held in conjunction with World Patient Safety Day, attended by chief physicians, healthcare administrators, and media representatives. The session, which presented a variety of opinions from medical organization leaders and representatives, confirmed the relevance and importance of the concept of a unified departmental approach to managing the quality and safety of medical activities in the Republic of Sakha (Yakutia). The specifics of organizing and implementing the assessment (audit) of the quality and safety of medical activities at the level of medical organizations are reflected in the practical recommendations for organizing internal quality

control and safety of medical activities in medical organizations of the Federal State Budgetary Institution "National Institute for Quality" of the Federal Service for Surveillance in Healthcare by areas of work. Within each area, the tools are standardized and represented by a specific set of documents. The selection of criteria for assessing quality and safety is carried out by the heads of working groups for each area, based on the requirements of the main regulatory documents, based on those proposed by the Federal State Budgetary Institution "Central Medical and Electronic Expertise" of Roszdravnadzor, as well as those necessary within the context of the organization (their own needs) [6].

Based on the results of audits conducted in the inpatient departments of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 - National Center of Medicine named after M.E. Nikolaev", it was established that the implementation of a quality management system based on Practical Recommendations improves the quality and safety of medical activities. Figure 1 presents the results of audits for 2022-2024 and the first half of 2025. The main goal of such audits is to identify problems, risks and errors for their analysis and prevention in the future, but in no case to punish the perpetrators [9]. Significant improvement in indicators was achieved in the sections of the employee management system in a medical organization, epidemiological safety (prevention of infections associated with the provision of medical care), prevention of risks associated with the transfusion of donor blood and its components, products from donor blood. At the same time, the relatively low result in the "Surgical Safety" section shows that there is a need to take additional measures aimed at preventing risks associated with surgical interventions.

Effective management decisions are based on an internal control system, which is only possible with reliable information covering all aspects of a healthcare organization's operations [1]. In this regard, in 2024, the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 – M.E. Nikolaev National Center of Medicine" implemented the "Internal Quality Control and Safety of Medical Activities" information system, which ensures the implementation of a risk-based approach within the healthcare organization. The system enables prompt monitoring of all

indicators related to quality and safety management, facilitates the timely identification of potentially hazardous situations, and the implementation of preventive measures, which directly impacts the reduction of adverse events.

At the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Hospital No. 1 – M.E. Nikolaev National Center of Medicine," a study was conducted by interviewing employees using a structured questionnaire. The results of employee interviews for 2021–2024 are presented in Figure 2. As can be seen, employee awareness of the importance of implementing and maintaining a quality management system has increased year over year. The 2024 employee survey revealed that 94% understand the importance of a quality management system, 84% believe the system is important, and 86% of respondents are confident that implementing the system will improve the quality of medical care.

The development of a departmental integrated quality and safety management system, including the phased implementation of best practices and institutional expertise, necessitates research projects to assess the quality and safety of medical activities in the republic. Scientific study of these aspects will ensure the reliability of conclusions and confirm the practical value of implemented solutions, facilitating the development of strategically sound approaches to healthcare management. Research on the quality and safety of medical activities will soon begin, involving leading researchers and healthcare administrators in the republic.

Conclusion. Thus, it can be concluded that only a comprehensive approach combining management decisions, corrective measures, methodological support, and the active participation of all stakeholders can ensure the achievement of state healthcare policy goals and improve the quality and safety of medical activities.

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Z.A. Zaikova, D.A. Arkhincheeva, T.A. Bayanova

ANALYSIS OF PRIMARY DISABILITY OF WOMEN DUE TO BREAST CANCER

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Based on the depersonalized database of the State Medical and Social Expertise Bureau of the Irkutsk Region, an analysis of primary disability in women due to breast cancer (BC) was conducted. Among the contingent of primary disabled people, women with the second disability group, living in urban areas and over 55 years of age, currently prevail. For 2009–2023, a statistically significant increase in the overall indicators of primary disability due to BC was noted: "gross" by 1.4 times and standardized - by 1.3 times. The increase in the average age of disabled women from 53.2 to 58.1 years is associated with both improved medical care and patient survival, and with the aging of the population. Despite the improvement of diagnostics [3], the multidirectional dynamics of the proportion of disability groups 1 and 2 (an increase in the share of group 1 from 14.8 to 18.4% and a statistically significant decrease in the share of group 2 from 57.7 to 48.2%) does not correlate with the data on primary breast cancer incidence by stage, which is explained by legislative changes in detailing the classification and criteria for the implementation of primary examination by medical and social expertise institutions. To prevent severe disability due to breast cancer, a set of measures is necessary: active interdepartmental cooperation of all interested specialists, effective diagnostics of breast cancer, accessibility of medical care, and the development of a regional prevention program.

Keywords: breast cancer, primary disability, disability groups, age groups, average age of disabled women.

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ZAikova Zoya Aleksandrovna – PhD, associate professor of the Department of General Hygiene, Irkutsk State Medical University, e-mail: zaikovazoy@mail.ru, Irkutsk State Medical University, Ministry of Health of the Russian Federation; ORCID:0000-0001-8104-4264; **ARKHINCHEEVA Dina Aleksandrovna** – physician-statistician of the organizational and methodological department of the Federal State Institution "State Bureau of Medical and Social Expertise in the Irkutsk Region" of the Ministry of Labor of Russia, e-mail: arkhidina@yandex.ru, ORCID: 0009-0007-6863-7496; **BAYANOVA Tatyana Aleksandrovna** – PhD, associate professor of the Department of Epidemiology of Irkutsk State Medical University, e-mail: bayanova_tanya@mail.ru, FSBEI HE Irkutsk State Medical University; ORCID: 0000-0003-4289-3460

Introduction. Breast cancer (BC) is the main oncological pathology of women in Russia and around the world, leading to disability and death [7, 8, 10, 11]. In the Russian Federation, more than 80 thousand women are diagnosed with BC annually, 20 thousand die from it [4]. Assessing the state of population health is impossible without analyzing primary disability, including taking into account individual nosological forms [1, 6]. In addition, primary disability rates can serve as an indirect criterion for the quality of medical care in the field of diagnostics: a significant proportion of first-group

disabled people indicates that cancer was detected at advanced stages [8]. In 2023, the level of primary disability of the adult population of the Irkutsk region due to malignant neoplasms exceeded the all-Russian level by 19.0%; among the older population - by 29.6% [5].

The aim of the study: analysis of primary disability of women due to breast cancer in the Irkutsk region.

Materials and methods of the study. The study used a depersonalized database of women aged 18 years and older of the Main Bureau of the Medical and Social Expertise, reporting statistical

forms No. 7 for 2009-2011 and 2021-2023, and Irkutskstat data on the number of women in the Irkutsk region. The calculation of "crude" indicators of primary breast cancer incidence and newly diagnosed disability due to breast cancer was carried out for 5-year age groups for the average annual population, taking into account the UPN; standardized indicators - according to the world standard. The work used a graphical method and a statistical method: descriptive statistics, calculation of confidence intervals with a significance level of 95% (95% CI) using standard Windows programs (version 10.0).

Results and discussion. The structure of newly established disability of women in the Irkutsk region due to malignant neoplasms in 2023 is similar to 2009: breast cancer still ranks first (28.5%) [7], all subsequent localizations have changed places (Fig. 1).

The "crude" rates of newly established disability among women in the Irkutsk region due to breast cancer were 4.9 [4.4 ÷ 5.3] in 2009; 6.9 [6.4 ÷ 7.4] per 10,000 women over 18 in 2023; standardized rates were 2.6 [2.3 ÷ 2.9] and 3.4 [3.0 ÷ 3.7] per 10,000, respectively (Table 1). Thus, a statistically significant increase of 1.4 times in "crude" rates and 1.3 times in standardized rates was recorded.

In 2009, high rates of primary disability in women due to breast cancer were observed in the age groups from 50 to 74 years, excluding women aged 60-64 years: 50-54 years – 8.3 [6.5 ÷ 10.0]; 55-59 years – 10.4 [8.3 ÷ 12.4]; 65-69 years – 10.0 [7.2 ÷ 12.8] and 70-74 years – 7.9 [5.7 ÷ 10.2] per 10 thousand (Fig. 2). Since in these age groups the rates were more than 1.5 times statistically significantly higher than the overall rate, they can be considered risk groups in terms of primary disability due to breast cancer – the excess was 1.6-2.1 times. In 2023, the age groups from 55 to 74 years with an excess of the general indicator by 1.6-1.9 times were classified as risk groups for the level of primary disability of women due to breast cancer in the Irkutsk region: 55-59 years – 12.4 [9.8 ÷ 14.9]; 60-64 – 12.2 [9.9 ÷ 14.6]; 65-69 – 13.2 [10.8 ÷ 15.7] and 70-74 years – 10.7 [8.3 ÷ 13.2] per 10 thousand. In 2023, compared to 2009, a statistically significant increase in primary disability of women due to breast cancer by 2.3 times was noted only among women aged 60-64 years from 5.4 [4.0 ÷ 6.8] to 12.2 [9.9 ÷ 14.6] per 10 thousand.

A parallel analysis shows that the risk groups for primary breast cancer incidence are shifted to older age groups compared to the rates of primary disability

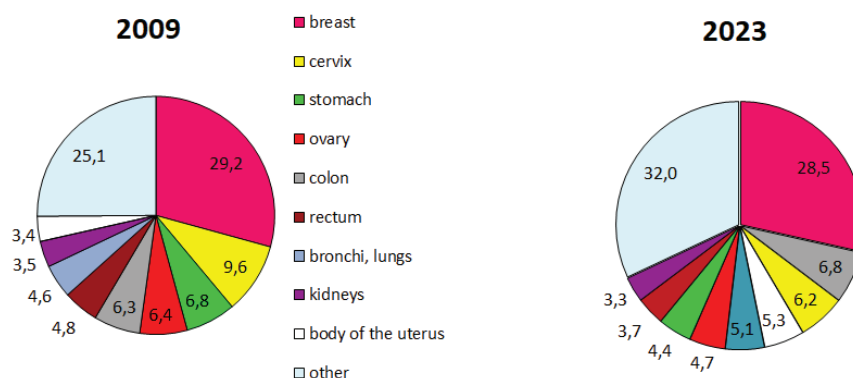


Fig. 1. Structure of primary disability of women in the Irkutsk region due to malignant neoplasms in 2009 and 2023. (%)

Table 1

Primary disability rates of women in the Irkutsk region due to breast cancer in 2009-2011 and 2021-2023 ("crude" and standardized, per 10 thousand. 95% CI)

years	"rough" indicators			standardized indicators		
	the entire population	urban population	rural population	the entire population	urban population	rural population
2009	4.9 [4.4÷5.3]	no data	no data	2.6 [2.3÷2.9]	no data	no data
2010	4.9 [4.5÷5.3]	no data	no data	2.7 [2.4÷3.0]	no data	no data
2011	5.2 [4.7÷5.6]	no data	no data	2.8 [2.5÷3.2]	no data	no data
2021	5.1 [4.7÷5.5]	5.5 [5.0÷6.0]	3.5 [2.7÷4.3]	2.6 [2.3÷3.0]	2.8 [2.47÷3.2]	1.9 [1.3÷2.46]
2022	5.9 [5.4÷6.4]	6.4 [5.8÷6.9]	4.0 [3.1÷4.9]	2.9 [2.6÷3.3]	3.1 [2.75÷3.5]	2.1 [1.4÷2.71]
2023	6.9 [6.4÷7.4]	7.3 [6.7÷7.9]	5.5 [4.4÷6.5]	3.4 [3.0÷3.7]	3.5 [3.1÷4.0]	2.7 [2.0÷3.4]

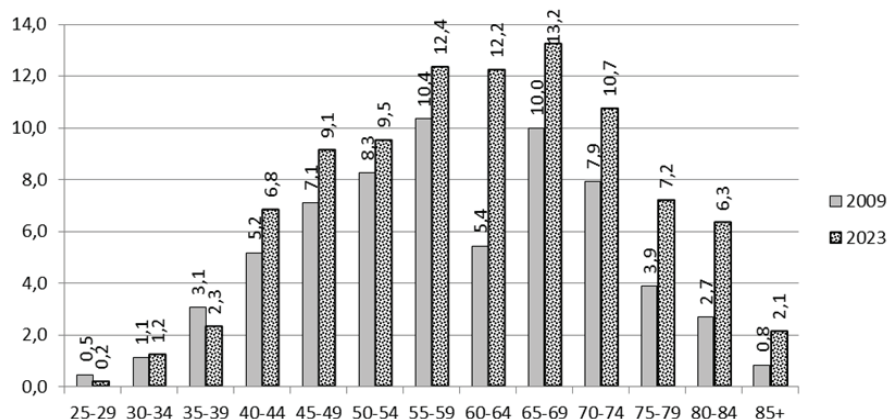


Fig. 2. Primary disability rates for women due to breast cancer in the Irkutsk region by individual age groups in 2009 and 2023 (per 10 thousand)

ty; the maximum rates for primary breast cancer incidence are recorded in the 70-74 year old group (Fig. 3).

Women who were first recognized as disabled due to breast cancer were distributed among disability groups in 2009: first – 14.8%; second – 58.7% and third – 26.5%; 2023 – 18.4; 48.3 and 33.3%, respectively (Table 2). During the study

period, the proportion of women with the second disability group has statistically significantly decreased, and in recent years this group has come to occupy less than 50% of the structure. The increase in primary disability rates due to breast cancer among middle-aged and retired people, the prevalence of the second group were also noted in other studies [7, 8].

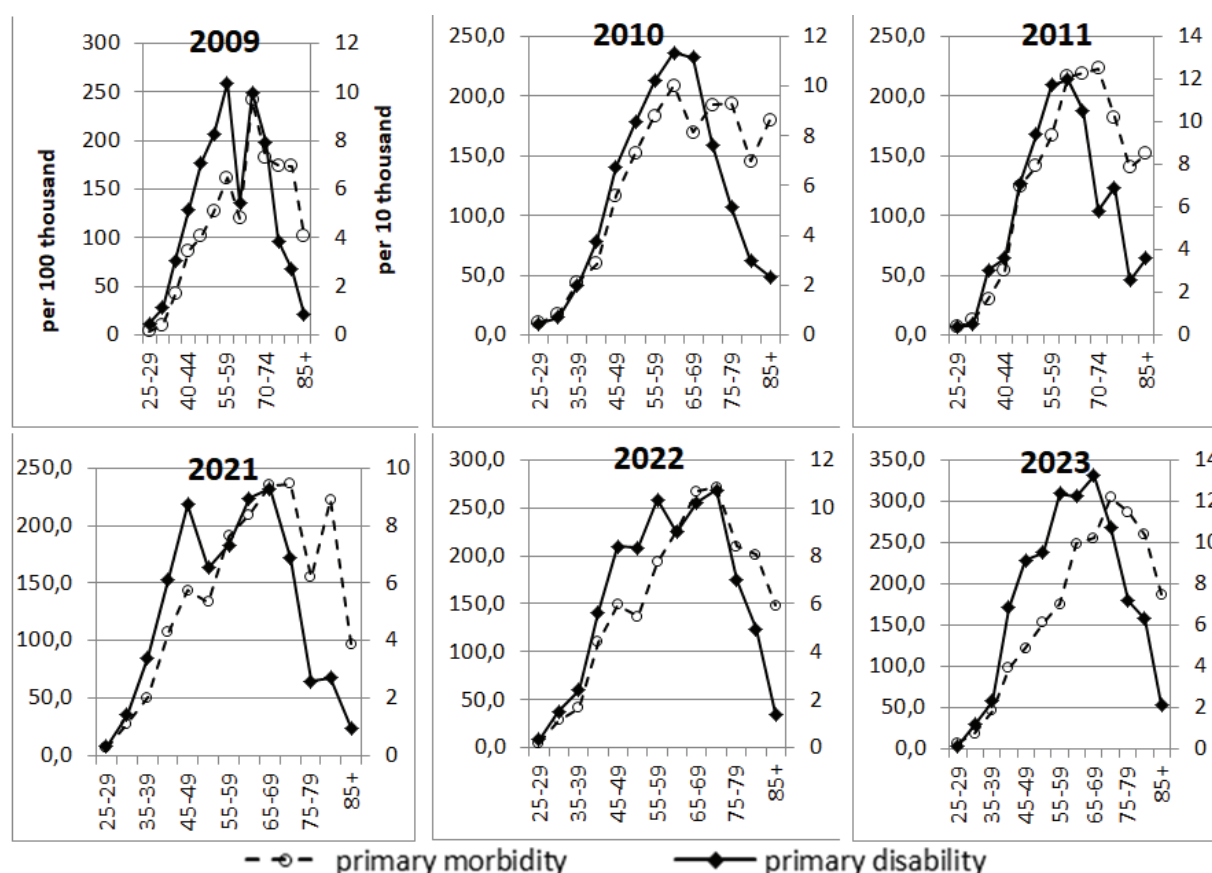


Fig. 3. Rates of primary breast cancer incidence (per 100 thousand) and primary disability due to breast cancer (per 10 thousand) in the Irkutsk region in 2009-2011; 2021-2023

In the Irkutsk region, both in 2009 and in 2023, the first disability group was established for the first time for women at all stages of breast cancer (Table 2), but mainly at stage IV. The increase in the share of this disability group during the study period is associated with an in-

crease in the share of women with stage II of the oncological process. In 2023, the second disability group was established only in the presence of stages I-III of breast cancer, and in 2009, this disability group was also established for 15 women with stage IV and for 22 women without

specifying the stage (the total number of women is 513 people), which in total affected the decrease in the share of the second disability group. The third disability group was established for all stages of breast cancer, except for IV. But in 2023, compared to 2009, the proportion

Table 2

Distribution of women with primary disability due to breast cancer by disability groups and breast cancer stages in the Irkutsk region in 2009 and 2023 (percentages, 95% CI)

2009							
disability groups	stages						total
	0	I	II	III	IV	н/д	
1		0.2 [0.0÷1.6]	1.4 [0.4÷2.4]	2.7 [1.3÷4.1]	9.7 [7.1÷12.3]	0.8 [0.0÷1.6]	14.8 [11.7÷17.9]
2		1.8 [0.6÷3.0]	24.6 [20.9÷28.3]	25.1 [21.3÷28.9]	2.9 [1.4÷4.4]	4.3 [2.5÷6.1]	58.7 [54.4÷63.0]
3	0.2 [0.0÷1.6]	4.1 [2.4÷5.8]	17.3 [14.0÷20.6]	2.5 [1.1÷3.9]		2.3 [1.0÷3.6]	26.5 [22.7÷30.3]
2023							
disability groups	stages						total
	0	I	II	III	IV	н/д	
1		2.2 [1.1÷3.3]	4.5 [2.9÷6.1]	1.9 [0.9÷2.9]	9.7 [7.5÷11.9]	0.1 [0.0÷0.3]	18.4 [15.5÷21.3]
2		2.0 [1.0÷3.0]	21.1 [18.0÷24.2]	25.2 [21.9÷28.5]			48.3 [44.6÷52.0]
3	0.4 [0.0÷0.9]	11.6 [9.2÷14.0]	20.9 [17.9÷23.9]	0.3 [0.0÷0.7]		0.1 [0.0÷0.3]	33.3 [29.8÷36.8]

Note: statistically significant differences in proportions are indicated by shading similar cells in gray

of women with stage I in this disability group became statistically significantly higher, and the proportion of women with stage III and without stage determination decreased.

Thus, when analyzing the intra-group distribution of the proportion of women recognized as disabled for the first time due to breast cancer by the stage of the oncological process, statistically significant changes were identified in establishing disability groups 1 and 3, as well as a decrease in the proportion of group 2 as a whole. Such dynamics do not correlate with improved breast cancer diagnostics and establishing a diagnosis at an earlier stage in the Irkutsk region during the study period [3] and are associated primarily with changes in legislation. Currently, in the Russian Federation, disability caused by diseases, including breast cancer, as well as the consequences of injuries or defects, is established in accordance with the order of the Ministry of Labor and Social Protection of the Russian Federation dated 26.07.2024 N 374N "On approval of classifications and criteria used in the implementation of medical and social examination of citizens by federal institutions of medical and social examination". Previously, in 2009-2023, 4 orders were in force: the Ministry of Health and Social Development dated 23.12.2009 No. 1013n; the Ministry of Labor and Social Protection of the Russian Federation dated September 29, 2014 No. 664n, dated December 17, 2015 No. 1024n and dated 27.08.2019 No. 585n. If in 2009 the order contained only general formulations of persistent disorders of body functions and restrictions of the main categories of human life activities with degrees of severity, then with the introduction of each subsequent order, the classification and criteria for the initial examination of citizens aged 18 and older for malignant neoplasms were clarified and supplemented:

- 2014 – a quantitative system for assessing the severity of persistent functional impairment from 10 to 100%, in 10% increments, was introduced; in particular, a more detailed approach to breast cancer with different types of mastectomy and after tumor removal during the first 5 years;

- 2015 – criteria for establishing disability groups depending on the above-mentioned quantitative assessment system were clarified;

- 2019 – a detailed approach was given to the quantitative assessment of the severity of persistent dysfunctions of the body depending on the clinical and morphological prognostic factors, local-

ization, size, stage, histological structure of the tumor, etc., taking into account the treatment carried out that affects the prognosis and rehabilitation in accordance with the International Classification of Functioning, Disability, and Health.

During the study period, a statistically significant increase in the average age of disabled women by 2.7 years was noted, from 55.6 [54.7÷56.6] in 2009 to 58.3 years [56.8÷59.8] in 2023, which can be explained by the shift of risk groups to older age groups due to the higher survival rate of patients with the current level of medicine and improved medical care for women with breast cancer, as well as the aging of the population.

In the region, statistically significant differences were registered between the "crude" indicators of primary disability from breast cancer among women living in urban and rural areas (Table 1): in 2021-2022 by 1.6 times, in 2023 - by 1.3 times. Since statistically significant differences were noted in 2021-2022 according to standardized indicators, and they are absent in 2023, it is somewhat premature to draw a conclusion about higher levels of primary disability from breast cancer among women in urban areas due to the predominance of these residents in the region and differences in age structures. To identify possible reasons for the existing differences, further research is required taking into account the place of residence of women in terms of primary breast cancer incidence rates, access to medical care and other factors.

Conclusion. Currently, in the Irkutsk region, the highest rates of primary disability of women due to breast cancer are registered in the age groups from 55 to 74 years; the second group of disability predominates and the level of primary disability of women living in urban and rural settlements statistically significantly differs by 1.3-1.6 times. Over the past 15 years, statistically significant changes have occurred in the characteristics of primary disability of women due to breast cancer: "crude" indicators have increased - overall by 1.4 times, among women aged 60-64 - by 2.3 times; the standardized indicator has grown by 1.3 times; the average age of disabled women has increased by 2.7 years. The statistically significant decrease in the proportion of women with the second disability group due to breast cancer from 58.7 to 48.3% is only partially consistent with improved diagnostics [3]. The dynamics of the proportion of this disability group, as well as the growth in the proportion of group 1, is associated with changes in current legislation - an increasing detailing of

the criteria in the orders of the Ministry of Labor and Social Development of the Russian Federation in the quantitative assessment of the severity of persistent disorders of body functions used in the implementation of medical and social expertise during the initial examination of the adult population over 18 years of age due to diseases, including breast cancer. Unfortunately, the published official data on primary disability allow for analysis only by aggregated age groups [5], while detailed analysis and the formation of scientific and practical recommendations for improving the situation require access to detailed data [2]. When developing comprehensive preventive measures aimed at improving the health of the population, a combined study of morbidity, disability and mortality of the population is required, therefore, it is desirable to introduce uniform reporting statistical forms with differentiation by 5-year age and gender groups [9]. To reduce the burden of breast cancer on healthcare and society, comprehensive measures are needed: interdepartmental cooperation between oncology doctors, primary care physicians and other interested specialists; modern and accessible diagnostics of breast cancer, effective and efficient medical care; development of a regional prevention program for further improvement, development and perfection of all types of prevention [7, 11].

The authors declare no conflict of interest.

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S.N. Kiselev

THE DYNAMICS OF INFANT MORTALITY RATES AND FETOINFANTILE LOSSES IN THE TERRITORIES OF THE FAR EASTERN FEDERAL DISTRICT

The aim of the study was to study the features of the dynamics of the infant mortality rate (including early neonatal mortality), as well as the indicators of perinatal mortality, stillbirth and fetoinfantile losses in the territories of the Far Eastern Federal District in comparison with the data for the Russian Federation for 2012–2023. In the Far Eastern Federal District, as in Russia as a whole, for several decades there has been a positive trend in reducing mortality in children up to 1 year. This is considered one of the important achievements of the region in the socio-economic and medical spheres. A detailed analysis and comparison of infant mortality rates in certain regions of the country is an important tool that allows you to quickly identify the most disadvantaged regions of the Russian Federation, and then understand in detail the causes of the current situation and its correction. The article carried out a retrospective analysis of statistical data on infant mortality in the subjects of the Far Eastern Federal District in the period 2012–2023. The emphasis is on the analysis of the following components: stillbirth, early neonatal mortality, perinatal mortality, infant mortality, the ratio of stillbirth to early neonatal mortality, fetoinfantile losses. It is concluded that there are areas with a low level of prevention of fetoinfantile losses and significant differences in the medical and social efficiency of the maternity and childhood service are assessed.

Keywords: infant mortality, stillbirth rate, early neonatal mortality, perinatal mortality, fetoinfantile losses.

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Introduction. The crisis demographic situation in the Russian Federation, accompanied by a low birth rate and high mortality rates of the population, poses many tasks for the health care system, among which the priority are protecting the health of women during pregnancy, protecting the health of children in the antenatal period and preserving the life of

already born children, the quality of their health in small generations that will appear in the coming years. Today it is the main challenge for the system of protection of motherhood and childhood, which requires solving the problem of saving every life that has taken place and the national gene pool, preserving Russia as an evolving state.

In Russia, infant mortality (IM), along with life expectancy and maternal mortality, is one of the key indicators characterizing the social well-being of the population. At the beginning of 2025, the Government of the Russian Federation prepared and published a "Unified Plan for Achieving the National Development

Goals of the Russian Federation until 2030 and for the Future until 2036," indicating specific targets in terms of health care that will be used to assess the effectiveness and efficiency of the work of the heads of regions. One such indicator is infant mortality. The IM indicator allows us to judge how successfully the regional authorities are coping with the problems associated with the birth and survival of children, ensuring the quality and availability of medical care for pregnant women and newborns, and the development of prenatal and neonatal care. Thus, reducing IM is one of the priority areas of activity of our state and medical communities, primarily neonatal and pediatric services.

KISELEV Sergey Nikolaevich – MD, Professor, Head of the Department of Public Health and Healthcare, Vice-Rector for Academic and Educational Work of the Far Eastern State Medical University of the Ministry of Health of the Russian Federation, ORCID 0000-0003-2047-9824, prorec@mail.fesmu.ru.

Table 1

Ranking of territories of the Far Eastern Federal District by infant mortality rate in 2012-2023

	2012		2023	
	IM	rank	IM	rank
Republic of Buryatia	8.3	3	4.4	4
Republic of Sakha (Yakutia)	9.6	5	3.2	1
Trans-Baikal Territory	7.4	2	7.0	8
Kamchatka Territory	11.3	7	5.1	7
Primorsky Krai	10.4	6	5.0	6
Khabarovsk Territory	11.5	8	3.7	2
Amur region	13.8	9	3.8	3
Magadan region	8.4	4	4.5	5
Sakhalin Oblast	6.5	1	3.7	2
Jewish AR	15.5	10	7.4	9
Chukotka AO	21.2	11	19.1	10

Table 2

Ranking of territories of the Far Eastern Federal District by the level of perinatal mortality in 2012-2023

	2012		2023	
	PM	rank	PM	rank
Republic of Buryatia	9.40	3	6.22	5
Republic of Sakha (Yakutia)	12.66	7	4.83	1
Trans-Baikal Territory	8.90	2	10.87	10
Kamchatka Territory	11.89	4	5.75	3
Primorsky Krai	12.22	5	6.70	6
Khabarovsk Territory	12.90	9	7.86	8
Amur region	12.67	8	5.19	2
Magadan region	13.34	10	7.21	7
Sakhalin Oblast	8.87	1	5.89	4
Jewish AR	12.58	6	8.95	9
Chukotka AO	16.69	11	17.17	11

Table 3

Ranking of territories of the Far Eastern Federal District by the level of early neonatal mortality in 2012-2023

	2012		2023	
	ENM	rank	ENM	rank
Republic of Buryatia	2.63	3	0.78	4
Republic of Sakha (Yakutia)	4.55	5	0.72	3
Trans-Baikal Territory	2.24	1	2.02	9
Kamchatka Territory	6.66	11	1.02	6
Primorsky Krai	5.28	8	1.78	7
Khabarovsk Territory	5.00	7	0.69	2
Amur region	4.73	6	1.01	5
Magadan region	3.59	4	1.81	8
Sakhalin Oblast	2.38	2	0.66	1
Jewish AR	6.09	10	2.25	10
Chukotka AO	5.56	9	11.47	11

As part of the implementation of the activities of the national projects "Health" and "Demography", other federal projects not included in national projects, as well as the draft strategy for demographic and family policy for the period up to 2036, it is planned to reduce IM in the Russian Federation to 3.9 ppm by 2030, by 2036 - to 3.7 ppm.

Achieving this level of IM requires a systematic approach that includes strengthening the health care system, improving the quality of care, mass preventive measures, and addressing social and economic problems affecting the health of children and mothers.

Infant mortality has traditionally occupied and occupies an important place in the demographic development of Russia and the Far East, as evidenced by numerous publications on this topic [1-2, 8-9, 11, 13, 16]. In the Far Eastern Federal District (FEFD), as in Russia as a whole, a positive trend in reducing the mortality rate of children up to 1 year has been achieved for several decades, which cannot be said about other age groups. This is considered one of the important achievements of the region in the socio-economic and medical spheres.

Detailed analysis and comparison of IM indicators in certain regions of the country is an important tool that allows you to quickly identify the most disadvantaged regions of the Russian Federation, and then understand in detail the reasons for the current situation.

The aim of this study was to study the features of the dynamics of the IM indicator (including early neonatal mortality), as well as the indicators of perinatal mortality (PM), stillbirth (SB) and fetoinfantile losses in the territories of the Far Eastern Federal District in comparison with the data for the Russian Federation for 2012-2023.

Material and methods. A retrospective analysis of statistical data on infant mortality in the subjects of the Far Eastern Federal District in the period 2012-2023 was carried out. The starting point for the analysis was 2012, when the Russian Federation switched to the international criteria for live birth recommended by WHO. Emphasis is placed on the analysis of the following components: stillbirth (the ratio of the number of stillbirths to 1000 live and dead births), early neonatal mortality (ratio of neonatal deaths in the first 7 days of life to 1,000 live births), perinatal mortality (ratio of the number of stillbirths and deaths of newborns in the first 7 days of life to 1,000 live and dead births), infant mortality (under-year mortality), stillbirth to early neonatal mortality

ratio, fetoinfantile losses (sum of stillbirths and under-year deaths).

Official publications of open data of the Federal State Statistics Service (Rosstat) were used as information sources [10]. The study was carried out using statistical, mathematical methods, as well as methods of comparative analysis. Publications in domestic scientific journals and monographs on this topic also became a source of information.

For the period of preparation of the material, the data of Rosstat of Russia for 2024 on infant, perinatal mortality and stillbirth were not officially available.

Results and discussion. *Infant mortality.* As already noted, today the value of the IM indicator reflects not only the quality of medical care provided by the maternity and childhood service, this is one of the criteria for assessing the work of the heads of the constituent entities of the Russian Federation. Rosstat data show that for several decades, the IM coefficient both in the Russian Federation as a whole and in the Far Eastern Federal District has been steadily decreasing. For 2012-2023, the IM indicator in the Russian Federation decreased by 51.2% (from 8.6 to 4.2 per 1000 live births), in the Far Eastern Federal District - by 56.9% (from 10.9 to 4.7 per 1000 live births).

The greatest success in reducing IM over the specified period was achieved by the Amur Region (by 72.5%), the Khabarovsk Territory (by 67.8%), the Republic of Sakha (Yakutia) (by 66.7%). In the Trans-Baikal Territory, the IM indicator decreased by only 5.4%, in the Chukotka Autonomous Okrug - by 9.9%. In the remaining territories, the IM decreased by about half.

The ranking of the territories of the Far Eastern Federal District shows a change in their position over the studied period. Higher ranking places in 2023 were taken by the Republic of Sakha (Yakutia) - from 5th to 1st place, Khabarovsk Territory - from 8th to 2nd place, Amur Region - from 9th to 3rd. Kamchatka and Primorsky Krai did not change their indicators, and the Jewish Autonomous Region and Chukotka Autonomous Region, as in 2012, close the rating (Table 1).

Perinatal mortality. The study of regional characteristics of perinatal mortality is of great importance for substantiating the main directions for improving assistance to newborns. The analyzed period in the Far Eastern Federal District and the Russian Federation as a whole was characterized by a tendency to reduce perinatal mortality. As a result of the analysis, it was found that in the Far East-

ern Federal District, the perinatal mortality rate in the period from 2012 to 2023. decreased by 43.1% from 12.32 to 7.01 per 1000 children born alive and dead. In the Russian Federation, over the same period of time, there was a decrease in the PM indicator by 35.1%.

PM indicator in 2012-2023. more than halved in the Republic of Sakha (Yakutia), Amur Region, Kamchatka Territory. In two territories of the Far Eastern Federal District, there was an increase in the PM coefficient (Trans-Baikal Territory, Chukotka Autonomous Okrug).

Higher ranking places in terms of PM in 2023 compared to 2012 were taken by the Republic of Sakha (Yakutia) - from 7th to 1st place, Amur Region (from 8th to 2nd), Magadan Region (from 10th to 7th). The Trans-Baikal Territory, the Republic of Buryatia, the Sakhalin and Jewish Autonomous Regions moved to lower positions in the ranking (Table 2).

Early neonatal mortality. Early neonatal mortality, as a component of PM, also showed a persistent downward trend during the time period studied. In the Far Eastern Federal District, the ENM indicator decreased 3.8 times from 4.85 ‰ in 2012 to 1.27 ‰ in 2023. In the Russian Federation, during the same time, the RNS indicator decreased 3 times from 3.64 ‰ to 1.23 ‰.

It can be seen that the decrease in the RNS indicator occurs differently in different territories of the Far Eastern Federal District. The Khabarovsk Territory looks the most successful in terms of ENM dynamics, where it was possible to reduce this indicator by 7.2 times over 12 years (from 5.0 ‰ to 0.69 ‰), Kamchatka Territory - by 6.5 times (from 6.66 ‰ to 1.02 ‰) and the Republic of Sakha (Yakutia) - by 6.3 times (from 4.55 ‰ to 0.72 ‰).

It should be noted that all territories of the Far Eastern Federal District (with the exception of the Chukotka Autonomous Okrug) have significantly improved their ENM indicators. When ranking territories by the value of the ENM indicator, consistently low ENM indicators are observed in the Sakhalin Region (2nd rank in 2012 and 1st in 2023). Khabarovsk Territory moved from 7th position to 2nd, the Republic of Sakha (Yakutia) - from 5th to 3rd, Kamchatka Territory - from 11th to 6th. The Trans-Baikal Territory and the Magadan Region worsened their rating, the Chukotka Autonomous Okrug and the Jewish Autonomous Okrug continue to be among the outsiders (Table 3).

Stillbirth. Numerous works by domestic and foreign researchers emphasize that a decrease in stillbirth is an important indicator of progress in the field of health

care and improving the quality of life of the population [1, 2, 11, 16]. Infant mortality includes cases when a child was born alive and died after birth. Cases when a child dies before birth fall into the statistics of stillbirth. Stillbirth is the second component of perinatal mortality, which is a more stable indicator than infant mortality. If over 12 years (from 2012 to 2023) in the Far Eastern Federal District, infant mortality decreased by 2.3 times, ENM - by 3.8 times, then stillbirth - only by 23.2% (in the Russian Federation by 2 times, 3 times and 17.2%, respectively). At the same time, in the Republic of Sakha (Yakutia), it was possible to reduce the SB by almost half (by 49.3%) from 8.11 ‰ to 4.11 ‰. Significant success in reducing MR was achieved by the Chukotka Autonomous Okrug and the Amur Region (a decrease of 48.8% and 47.4%, respectively), the Magadan Region (by 44.6%). Minimal changes in the SB indicator were noted in the Khabarovsk (9.2%) and Kamchatka (9.6%) regions. In two territories of the Far East, an increase in the SB indicator (Trans-Baikal Territory and Jewish Autonomous Region) was noted.

The rating of the territories of the Far Eastern Federal District in terms of stillbirth for 2012-2023. has undergone major changes (Table 4). Some territories managed to achieve better results, others, despite the improvement in the SB indicator, moved to lower positions. Thus, the lowest values of the SB indicator in 2023 were noted in the Republic of Sakha (Yakutia) (1st rank in 2023, 8th in 2012), the Amur Region moved from 7th place to 2nd, Magadan Region - from 9th to 6th. The Khabarovsk Territory, where the MR indicator for 12 years decreased by only 9.2%, in 2023 began to occupy the penultimate place, second only to the Trans-Baikal Territory, where the stillbirth rate increased. The Jewish Autonomous Region, Sakhalin Oblast, and the Republic of Buryatia worsened their positions.

In the works of many authors, it is noted that when analyzing the regional features of IM, one of the serious problems is its underestimation. One of the signs with a high degree of probability indicating this underestimation is a noticeable excess of the ratio of the number of deaths in the first week of life to the number of stillbirths [4, 14-15].

In most economically developed countries of the world, this ratio does not exceed 1 to 2. In general, in Russia in 2012 this indicator was 1/1.7, in the Far Eastern Federal District - 1/1.5. After the transition of the country in 2012 to the international criteria for registering dead and live births, this ratio significant-

Table 4

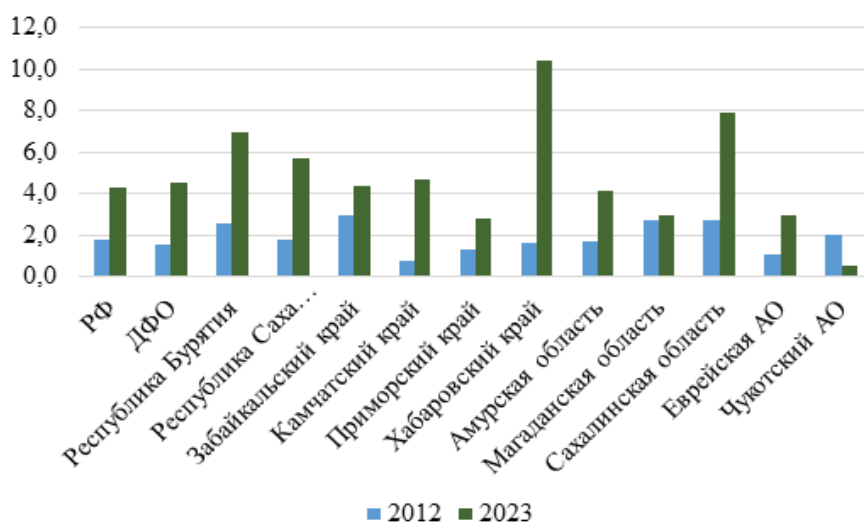
Ranking of territories of the Far Eastern Federal District by stillbirth rate in 2012-2023

	2012		2023	
	SB	rank	SB	rank
Republic of Buryatia	6.77	4	5.44	7
Republic of Sakha (Yakutia)	8.11	8	4.11	1
Trans-Baikal Territory	6.66	3	8.85	11
Kamchatka Territory	5.23	1	4.73	3
Primorsky Krai	6.94	5	4.92	4
Khabarovsk Territory	7.90	6	7.17	10
Amur region	7.94	7	4.18	2
Magadan region	9.75	9	5.40	6
Sakhalin Oblast	6.49	2	5.23	5
Jewish AR	6.49	2	6.70	9
Chukotka AO	11.13	10	5.70	8

Table 5

Ranking of Far Eastern Federal District territories by the level of fetoinfantile losses in 2012-2023

	2012		2023	
	FIL	rank	FIL	rank
Republic of Buryatia	15.07	3	9.84	5
Republic of Sakha (Yakutia)	17.71	6	7.31	1
Trans-Baikal Territory	14.06	2	15.85	10
Kamchatka Territory	16.53	4	9.83	4
Primorsky Krai	17.34	5	9.92	7
Khabarovsk Territory	19.40	8	10.87	8
Amur region	21.74	9	7.98	2
Magadan region	18.15	7	9.90	6
Sakhalin Oblast	12.99	1	8.93	3
Jewish AR	21.99	10	14.10	9
Chukotka AO	32.33	11	24.80	11



Number of stillbirths per 1st deceased in the early neonatal period in 2012 and 2023

ly increased to 4.3 in 2023 in the Russian Federation and 4.5 in the Far Eastern Federal District.

It should be noted that in the Far Eastern Federal District there are a number of territories where the share of stillbirths in perinatal mortality accounts for more than 80% (> 1/4): the maximum indicators were registered in the Khabarovsk Territory (1/10.4), Sakhalin Oblast (1/7.9), Republic of Buryatia (1/7.0). In 2023, the Khabarovsk Territory had one of the highest rates in the Russian Federation of the ratio of the number of deaths in the first week of life to the number of stillbirths after the Republic of Khakassia (28.6), the Chuvash Republic (18.0) and the Lipetsk Region (11.5) (Fig. 1).

Numerous studies conducted by specialists of the Research Institute of Pediatrics and Children's Health, National Research Institute of Public Health named after N.A. Semashko, RNIMU named after N.I. Pirogov, Institute of Demography of the National Research University Higher School of Economics, Peoples' Friendship University of Russia, Russian Medical Academy of Continuing Professional Education [1, 3-5, 8-9, 12, 14-15] show that such a situation can add up due to falsification of data at the regional level. Infant mortality, unlike stillbirth, is an indicator that the authorities pay attention to. Therefore, deaths of children in the early neonatal period can be "transferred" to stillbirth, because this indicator is not a criterion for assessing the work of the subject's administration. The deterioration of indicators is not beneficial to either the medical organization, or the chief specialists, or the regional Ministry of Health, as a result of which the real picture of the level of perinatal mortality and its components in certain territories and in the region as a whole may be distorted. Ultimately, this leads to an inadequate assessment of the organization of medical care in the maternal and child health system.

ENM and SB are influenced by similar factors - the quality of medical care, its availability, a woman's behavior during pregnancy and the quality of child care in the first week of life. If the level of medical care is growing in the territory as a whole, it is logical to expect a simultaneous decrease in both indicators. Moreover, the SB level should not be significantly higher than the level of early neonatal mortality.

Another indicator that allows you to eliminate the influence of possible manipulations with statistics in the territories and reflects the real problems of perinatal medicine is the indicator of fetoinfantile

Table 6

Total ranking of Far Eastern Federal District territories in 2012-2023

	2012 год							2023 год						
	IM	PM	ENM	SB	AIL	Σ	av.rank	IM	PM	ENM	SB	FIL	Σ	av.rank
Republic of Buryatia	3	3	3	4	3	16	3	4	5	4	7	5	25	5
Republic of Sakha (Yakutia)	5	7	5	8	6	31	6	1	1	3	1	1	7	1
Trans-Baikal Territory	2	2	1	3	2	10	2	8	10	9	11	10	48	9
Kamchatka Territory	7	4	11	1	4	27	4	7	3	6	3	4	23	4
Primorsky Krai	6	5	8	5	5	29	5	6	6	7	4	7	30	6
Khabarovsk Territory	8	9	7	6	8	38	8	2	8	2	10	8	30	6
Amur region	9	8	6	7	9	39	9	3	2	5	2	2	14	2
Magadan region	4	10	4	9	7	34	7	5	7	8	6	6	32	7
Sakhalin Oblast	1	1	2	2	1	7	1	2	4	1	5	3	15	3
Jewish AR	10	6	10	2	10	38	10	9	9	10	9	9	46	8
Chukotka AO	11	11	9	10	11	52	11	10	11	11	8	11	51	10

losses. Fetoinfantile losses (FIL) include all cases – stillbirth and death of children in the first year of life and are an integrated indicator, which characterize not only the health of the population and its reproductive potential, but is also used as a criterion for a comprehensive assessment of the activities of various medical organizations of the maternal and child health system, responsible for making management decisions in optimizing activities to prevent infant and perinatal mortality [6-7, 12].

The dynamics of fetoinfantile losses in the Far Eastern Federal District is characterized by positive trends, most of the territories of the Far Eastern Federal District in 2012-2023, managed to achieve significant success in reducing this indicator. Thus, in the Amur Region, the FIL indicator decreased by 63.3%, in the Republic of Sakha (Yakutia) - by 58.7%. The only territory where the FIP indicator increased by 12.7% was the Trans-Baikal Territory.

Thus, the Republic of Sakha (Yakutia) moved from 6th to first place with minimal fetoinfantile losses, the Amur Region moved from 9th position in 2012 to 2nd place in 2023. Among the outsiders in terms of FIL in 2023 are still Chukotka Autonomous Okrug, Jewish Autonomous Okrug and Khabarovsk Territory. The Trans-Baikal Territory significantly worsened its position, moving over 12 years from 2nd place to 10th.

After ranking the territories of the Far Eastern Federal District, a total ranking was carried out separately for each indicator, the results of which are presented in Table 6.

In terms of the sum of all indicators,

the first place in the ranking as of 2023 was occupied by the Republic of Sakha (Yakutia), significantly ahead of other territories over the past 12 years. In 2nd place, the Amur Region, which moved from the outsiders of the rating to the second position, with a minimal margin from it in 3rd place, is the Sakhalin Region. 4th and 5th places in the ranking in the Kamchatka Territory and the Republic of Buryatia. Khabarovsk and Primorsky Territories occupied the middle position among all territories of the Far Eastern Federal District, dividing 6th place. The most unfavorable subjects by rating were the Chukotka Autonomous Okrug, the Trans-Baikal Territory, the Jewish Autonomous Okrug, as well as the Magadan Region.

Conclusion. Thus, the analysis of the regional characteristics of infant and perinatal mortality made it possible to identify the territories of the Far Eastern Federal District with a low level of prevention of fetoinfantile losses and assess significant differences in the medical and social efficiency of the maternity and childhood service. Despite the positive trends in the decline in infant and perinatal mortality rates, fetoinfantile losses in the Far Eastern Federal District, reserves remain in most territories to further reduce reproductive losses and improve the demographic situation in the region.

When analyzing infant mortality rates and their components, it should be remembered that distortion of the true picture of mortality in order to achieve target indicators of the demographic development of territories makes it difficult to analyze the demographic situation, does

not allow forming the right priorities and making the right and effective management decisions to correct it.

The authors declare no conflict of interest.

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A.S. Shastin, V.G. Panov, V.G. Gazimova, T.Yu. Obukhova DISEASES OF THE CIRCULATORY SYSTEM IN THE WORKING-AGE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA) IN 2011–2023

Epidemiological characteristics and patterns of chronic non-communicable diseases in the working-age population (WAP) are often neglected nowadays. Disease rates in the WAP are not the object of statistical observation, which significantly complicates the conduct of targeted studies. Diseases of the circulatory system are the main cause of premature deaths, which determines the relevance of establishing their rates in the WAP, including the analysis of their changes and features during the spread of COVID-19 and in the early post-pandemic period.

Materials and methods. We calculated incidence and prevalence rates of circulatory system diseases (CSD) in the WAP of the Republic of Sakha (Yakutia) and analyzed their dynamics in 2011–2023. We also assessed the statistical significance of differences between the disease rates in Yakutia and the Russian Federation before, during and after the pandemic of the novel coronavirus disease. Direct ranking was used to determine the place of Yakutia among the constituent entities of the Russian Federation in terms of CSD rates.

Results. We established that during the study period, Yakutia belonged to a large group of Russian constituent entities with average CSD rates. We observed a statistical increase in the CSD prevalence in Yakutia in 2022–2023 and in the chronicity rate in 2020–2023. The high rate of increase in the latter indicates a more severe course of chronic CSDs during the COVID-19 pandemic and the early post-pandemic period in the WAP.

Conclusions. The study of trends and regional characteristics of morbidity of the working-age population is an important component of raising effectiveness of government measures taken to increase life expectancy and reduce mortality. The results of such studies should be taken into account when developing local programs of state guarantees for the provision of free medical care.

Keywords: working-age population, diseases of the circulatory system, incidence, prevalence, chronicity rate, COVID-19.

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SHASTIN Aleksandr Sergeevich – PhD in Medicine, senior researcher, Department of Occupational Medicine Organization, Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, <https://doi.org/0000-0001-8363-5498>, e-mail: shastin@ymrc.ru; **PANOV Vladimir Grigorievich** – PhD in Physics and Mathematics, Associate Professor, Leading Researcher, Institute of Industrial Ecology of the Ural Branch of RAS, senior researcher, Department of Toxicology and Biological Prophylaxis, Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, <https://doi.org/0000-0001-6718-3217>, e-mail: vpanov@ecko.uran.ru; **GAZIMOVA Venera Gabdrachmanovna** – PhD in Medicine, head of the Department of Occupational Medicine Organization, Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, <https://orcid.org/0000-0003-3591-3726>, e-mail: venera@ymrc.ru; **OBUKHOVA Tatyana Yurievna** – MD in Medicine, Leading Researcher, Department of Therapy and Medical Rehabilitation, Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, <https://orcid.org/0000-0002-7913-5586>, e-mail: obukhova@ymrc.ru

Introduction. The current demographic and health situation in the Russian Federation and the Republic of Sakha (Yakutia) (hereinafter referred to

as Yakutia) is characterized by downward trends, especially a decrease in the size and proportion of the working-age population (WAP) and an increase in its mean age [4,8,9]. High mortality rates in this group of population both in the country and the republic have been registered for a long time [2,3,13,16]. The causes of WAP mortality and the factors affecting its rates are in the focus of attention of many specialists.

At the same time, despite this unfavorable background, epidemiological characteristics and patterns of chronic non-communicable diseases (CNCDs) in the WAP are often neglected. WAP morbidity is not the object of statistical observation, which significantly complicates the conduct of targeted studies.

Diseases of the circulatory system are the main cause of premature mortality, which determines the relevance of studying their rates in the WAP [6,10,13].

The **purpose** of the study was to analyze the dynamics of the circulatory system disease (CSD) rates in the working-age population of the Republic of Sakha (Yakutia) during the spread of the novel coronavirus disease and in the early post-pandemic period.

Materials and Methods. Using methods of descriptive and applied statistics, we conducted a retrospective study of the rates of circulatory system diseases based on the number of WAP seeking medical attention in Yakutia in 2011–2023. CSD incidence and prevalence rates in the WAP were calculated using data of statistical bulletins followed by estimation of the CSD chronicity rate. The study period was determined by the data available. To assess the statistical significance of differences in the CSD incidence, prevalence, and chronicity rates between the years 2020–2023 and the pre-pandemic period, we constructed confidence intervals (CI) for mean values (M) of 2011–2019. The direct ranking method was used to determine the ranks of all constituent entities of the Russian Federation by the above rates from the highest to lowest. A quintile distribution of the regional rates was used for a comparative evaluation of morbidity. Given the nonlinearity of the dependence of the indicators on the study year, trends were assessed using quadratic regression.

Microsoft Excel and *Wolfram Research Mathematica* v.11.3 were used for statistical data analysis.

Results. Figures 1–3 show the dynamics of the circulatory disease incidence, prevalence and chronicity rates in the WAP of Yakutia.

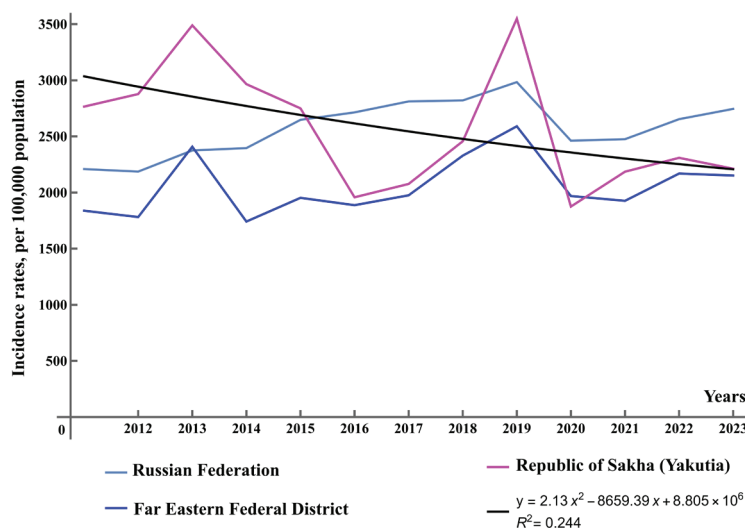


Fig. 1. Circulatory disease incidence rates in the working-age population in 2011–2023 (per 100,000 population).

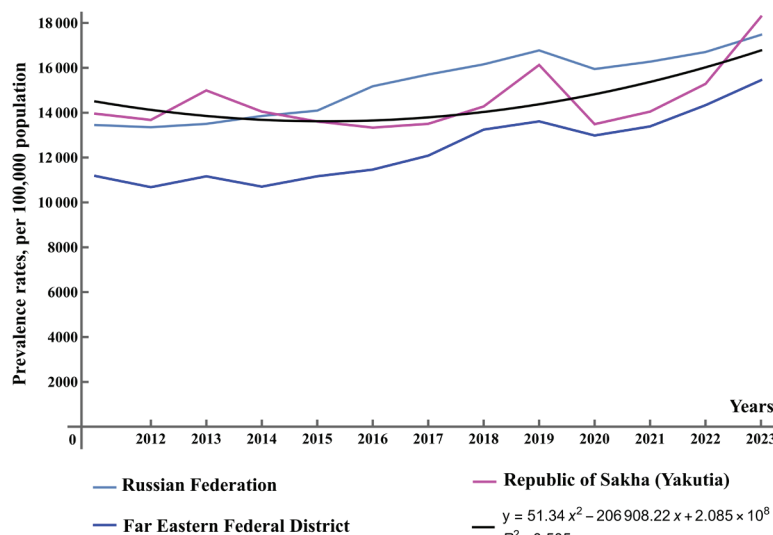


Fig. 2. Circulatory disease prevalence rates in the working-age population in 2011–2023 (per 100,000 population).

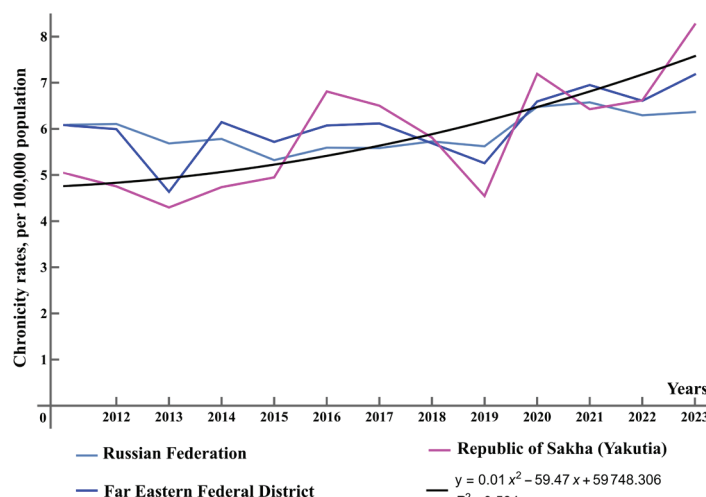


Fig. 3. Circulatory disease chronicity rates in the working-age population in 2011–2023 (per 100,000 population).

Circulatory disease incidence and prevalence rates in the working-age population (per 100,000 population), chronicity and growth rates (%) compared to M.

Territories	M ₂₀₁₁₋₂₀₁₉	2020	2021	2022	2023
Year (rate of increase, %)					
Russian Federation	2571.6 [2350.1;2793.1]	2462.0 (-4.3)	2475.2 (-3.7)	2653.7 (3.2)	2745.1 (6.7)
Far Eastern Federal District	2056.0 [1820.4;2291.5]	1968.9 (-4.2)	1926.1 (-6.3)	2169.1 (5.5)	2151.5 (4.6)
Republic of Sakha (Yakutia)	2765.3 [2343.1;3187.5]	1875.0 (-32.2)	2185.6 (-21.0)	2309.3 (-16.5)	2211.9 (-20.0)
Prevalence rates					
Russian Federation	14673.1 [13672.5;15673.8]	15945.6 (8.7)	16273.8 (10.9)	16705.5 (13.9)	17472.7 (19.1)
Far Eastern Federal District	11699.7 [10878.2;12521.1]	12983.3 (11.0)	13388.3 (14.4)	14334.6 (22.5)	15448.8 (32.0)
Republic of Sakha (Yakutia)	14169.5 [13488.2;14850.8]	13488.0 (-4.8)	14047.1 (-0.9)	15284.9 (7.9)	18279.9 (29.0)
Chronicity rates					
Russian Federation	5.72 [5.53;5.91]	6.48 (13.2)	6.57 (14.9)	6.30 (10.0)	6.37 (11.2)
Far Eastern Federal District	5.75 [5.36;6.14]	6.59 (14.8)	6.95 (21.0)	6.61 (15.0)	7.18 (25.0)
Republic of Sakha (Yakutia)	5.27 [4.59;5.96]	7.19 (36.4)	6.43 (21.9)	6.62 (25.5)	8.26 (56.7)

When described by quadratic regression, the dynamics of CSD incidence rates in Yakutia has an almost linear downward trend, however, due to the high variability of the indicators (i.e. variation coefficient of 21.2%), this model has a small coefficient of determination $R^2 = 0.244$.

In 2011–2019, Yakutia ranked 31st in terms of the mean CSD incidence rate in the fourth quintile of constituent entities of the Russian Federation with the above average level. In 2023, Yakutia moved to the second quintile (rank 63) with the below average level.

Experts also note a decrease in the CSD incidence rate in the general population of Yakutia in 2013–2016 [9].

When described by quadratic regression, the dynamics of CSD prevalence rates in Yakutia has a generally rising trend, which is determined, however, mainly by a noticeable increase in prevalence starting from 2016. In this case, the regression model has a much better quality described by $R^2 = 0.505$.

Changes in Yakutia ranks in terms of CSD prevalence were insignificant: 3rd quintile in the pre-pandemic period (rank 41, average level); rank 58 (below average) in 2020; rank 54 (below average) in 2021; rank 49 (average) in 2022, and rank 37 (average) in 2023.

When described by the same regression model, the dynamics of CSD chronicity rates in Yakutia has a noticeable upward trend with the coefficient of determination $R^2 = 0.584$.

In terms of the chronicity rates, more significant changes in the ranking of Yakutia were established ranging from rank 55 (below average) in 2011–2019 to rank 20 in 2023 (above average), with rank 31

(above average) in 2020; rank 53 (below average) in 2021, and rank 42 (average) in 2022.

In general, Yakutia belonged to a large group of subjects of the Russian Federation with relatively mean indicators in terms of the CSD prevalence in the WAP over the study period.

Table 1 demonstrates CSD rates in the WAP in 2020–2023 against those in the pre-pandemic period of 2011–2019.

Table 1. Circulatory disease incidence and prevalence rates in the working-age population (per 100,000 population), chronicity and growth rates (%) compared to M.

During the pandemic and in the early post-pandemic period, the CSD incidence rates in the WAP of Yakutia, in contrast to the Russian Federation and the Far Eastern Federal District, were significantly lower than those before the pandemic. Only in 2021, the CSD prevalence in Yakutia did not differ significantly from the rates registered in 2011–2019. In 2020–2023, chronicity rates in both the Russian Federation, the Far Eastern Federal District, and Yakutia were significantly higher than in the pre-pandemic period.

Discussion. Experts note a significant impact of COVID-19 on the cardiovascular system and highlight the need to study its consequences [7,12,15]. The decrease in the incidence rates of circulatory system diseases during the pandemic can be partly attributed to the lockdown, poorer access to health care, a lower volume of preventive measures, and self-protective behavior of patients [1,5,6,14]. The statistically significant decrease in the prevalence rate of circulatory system diseases in the Republic of

Sakha (Yakutia) established in 2020 is an atypical phenomenon in the Russian Federation as most regions of the country demonstrate rising trends [11]. At the same time, in 2023, the republican rate of increase in the prevalence already exceeded the Russian one.

We believe that the pronounced regional characteristics include high chronicity rates indicating a more severe course of chronic circulatory system diseases during the COVID-19 pandemic and the early post-pandemic period in the WAP of Yakutia and confirm the forecasts of experts about the long-term adverse effects of the novel coronavirus disease on the cardiovascular system [12,15].

Conclusions. The study of trends and regional characteristics of morbidity of the working-age population is an important component of increasing the effectiveness of government measures taken to increase life expectancy and reduce mortality. The results of such studies should be taken into account when developing local programs of state guarantees for the provision of free medical care.

The authors declare no conflict of interest.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

M.A. Chebargina, O.A. Senkevich, Yu.G. Kovalsky,
S.Yu. Nezhdanova

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IODINE DEFICIENCY IN CHILDREN IN THE FAR EASTERN FEDERAL DISTRICT: PROBLEMS AND SOLUTIONS

An observational, analytical, cross-sectional study was conducted to assess the prevalence of iodine deficiency among children living in the Arctic and southern zones of the Far Eastern Federal District (FEFD). A total of 188 children aged 1 to 18 years, permanently residing in the Arctic zone of the FEFD - Chukotka Autonomous Okrug (ChAO), Anadyr ($n = 120$), and the southern zone - Khabarovsk Krai, Khabarovsk ($n = 68$), were included in the study by simple random sampling. Depending on their age, the study participants were divided into comparison groups: young children (1-3 years old, $n = 38$), preschoolers (4-6 years old, $n = 46$), primary school children (7-11 years old, $n = 46$), and adolescents (12-18 years old, $n = 58$). Iodine status was assessed by determining the concentration of ioduria using the arsenite-cerium method. The study revealed that only 26.1% of children living in the Far North had normal iodine levels in their bodies. Mild, moderate, and severe iodine deficiency was diagnosed in 34.0%, 30.3%, and 9.6% of those examined, respectively. The incidence of low iodine status in children in the Far North was 2.6 times higher than in the southern zone (80.9% and 61.8%, respectively, OR = 2.611, 95% CI 1.339-5.090), with a significant prevalence of moderate iodine deficiency (37.5% and 17.7%, respectively, $p = 0.005$). Interviews with parents of the examined children revealed that only 20.0% of Far East families use iodized salt daily, which is categorically insufficient to eliminate iodine deficiency.

Keywords: iodine, ioduria, iodine deficiency, iodized salt, children, Arctic zone, Far Eastern Federal District

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Introduction. Iodine is an essential microelement required for the synthesis of thyroid hormones and, as a result, plays a key role in maintaining adequate metabolism in the body [20]. Chronic insufficient iodine intake can lead to the development of iodine deficiency diseases (IDD), including endemic goiter, subclinical hypothyroidism, impaired fertility, as well as a decrease in cognitive reserve and the formation of growth and devel-

opmental abnormalities in children [6, 7].

According to the latest global estimates, the incidence of iodine deficiency is 108.3 per 100,000 population, with a higher prevalence among women – 139.8/100,000, for males this figure is 78.1/100,000. The prevalence of iodine deficiency varies depending on the socio-demographic indicator: low-income countries have the highest incidence of iodine deficiency - 205.0/100,000, and, conversely, regions with a high standard of living are characterized by the minimum prevalence of iodine deficiency - 20.5/100,000 [19].

In 2019, the highest iodine deficiency rates at the regional level were recorded in Central Africa (458.95 per 100,000 population), Southern Asia (211.47 per 100,000 population) and Eastern Africa (185.56 per 100,000 population), while the lowest iodine deficiency rate at the regional level was recorded in Oceania (4.31 per 100,000 population) [19].

It is interesting to note that in 1990, the number of people suffering from iodine deficiency worldwide was 146.4 million, in 2021 there was an increase in the global prevalence of iodine deficiency to 180.8 million (an increase of 23.5% compared to 1990) and is projected to reach 194.5 million by 2050 (an increase of 7.6% compared to 2021) [17].

The development of deficiency states in both adults and children may occur due to a number of reasons, namely: un-

balanced nutrition, inadequate nutrient intake, food selectivity, unconventional diets [3, 8, 16], and elemental imbalances in the environment [11]. In nature, iodine is found in the form of chemical compounds, mainly in the form of iodides and iodates [10]. Iodide is mainly found in soil and sea water, and due to its volatility, iodine compounds enter the atmosphere, thus causing its natural biogenic migration with subsequent impact on the iodine content in food products [20]. Historically, high prevalence of iodine deficiency was observed in the population of inland regions (Central Asia and Africa, Central and Eastern Europe, central USA), mountainous areas (Alps, Andes, Atlas, Himalayas) and areas with frequent floods (Southeast Asia) [20]. However, given the current data on the prevalence of iodine deficiency, all population groups require increased attention due to the presence of not only biogeochemical provinces of territories, but also low iodine supply due to inadequate nutritional status.

Over the past decades, a high level of iodine deficiency has persisted among the child population of Russia, regardless of the climatic and geographical zone of residence [1]. Particular attention is required to the regions of the Russian Arctic due to the diversity of elemental status imbalances in children, leading to the development of microelementoses - environmentally dependent diseases of

CHEBARGINA Maria A. – PhD, Associate Professor of the Department of Pediatrics, Neonatology and Perinatology with a course in emergency medicine, Far Eastern State Medical University, Ministry of Health of the Russian Federation, e-mail: marie_work95@mail.ru, <https://orcid.org/0000-0001-8022-3279>; **SENKEVICH Olga A.** – MD, Professor, head of the Department of Pediatrics, Neonatology and Perinatology with a Course in Emergency Medicine, Far Eastern State Medical University of the Ministry of Health of the Russian Federation, e-mail: senkevicholga@ya.ru, <https://orcid.org/0000-0003-4195-2350>; **KOVALSKY Yuri G.** – Doctor of Medical Sciences, Professor, head of the Department of Biological Chemistry and Clinical Laboratory Diagnostics, Far Eastern State Medical University, Ministry of Health of the Russian Federation, e-mail: kovalyura53@mail.ru, <https://orcid.org/0000-0003-1803-9168>; **NEZH DANOVA Svetlana Yu.** – head of the Statistics Department, Statistician, City Polyclinic of Zheleznodorozhny District of the Ministry of Health of Khabarovsk Territory, e-mail: nezhdsveta@ya.ru

biogeochemical nature (IDD) [5], which negatively affects both the health of each individual and the well-being of the population as a whole.

The only territory of the Far Eastern Federal District that is fully related to the Arctic zones of the Russian Federation is the Chukotka Autonomous Okrug. The latest studies of mineral metabolism in the aboriginal inhabitants of the Chukotka Peninsula were conducted in the 1970-1980s [5]. However, it should be taken into account that over a long period of time, global ecological and climatic changes have occurred, as well as a transformation of the demographic structure of the population with a change in lifestyle, including those associated with nutrition [5], which necessitates a revision of the iodine status parameters.

Aim of the study – to assess the prevalence of iodine deficiency among children living in the Arctic and southern zones of the Far Eastern Federal District.

Materials and methods. *Study design:* observational, analytical, cross-sectional study.

Using a simple random sampling method, 188 children aged 1 to 18 years, permanently residing in the Chukotka Autonomous Okrug (ChAO, Anadyr, $n=120$), which is an Arctic territory, and in Khabarovsk Territory (Khabarovsk, $n=68$), which belongs to the southern zone of the Far Eastern Federal District, were included in the study. When analyzing the iodine status depending on the age of children living in the Far Eastern Federal District, study groups were formed according to the main principles of age periodization: young children (1-3 years, $n=38$), preschoolers (4-6 years, $n=46$), primary school children (7-11 years, $n=46$) and adolescents (12-18 years, $n=58$). An analysis of iodine status was also conducted in groups formed by gender, but without taking into account age: a group of boys ($n=103$) and girls ($n=85$).

Biological material was collected to determine iodine status in the period from July to August 2024 in the children's clinic of the State Healthcare Institution Chukotka District Hospital of the Department of Health of the Chukotka Autonomous Okrug, Anadyr, as well as city children's clinics in Khabarovsk. In addition, interviews were conducted with the parents of the examined children to determine the family's commitment to the use of iodized salt and foods with a high iodine content.

Inclusion criteria: children aged 1-18 years, permanently residing in the Chukotka Autonomous Okrug (Anadyr) and

Khabarovsk Territory (Khabarovsk), conditionally healthy (health groups 1-2, established by a pediatrician during a routine preventive examination), who have not taken iodine-containing dietary supplements for at least 3 months prior to the start of the study, written voluntary informed consent to participate in the study from the children's legal representatives.

In 2007, leading international organizations (WHO, UNICEF, ICCIDD) proposed epidemiological criteria for monitoring iodine deficiency states based on ioduria indicators. In this regard, the level of iodine supply to children's bodies was assessed by determining the concentration of the trace element in a single portion of morning urine using the arsenite-cerium method, which is regulated by MU 2.3.7.1064-01. The concentration of iodine in urine of 100-200 $\mu\text{g/l}$ was assessed as a normal level of supply, the range of 50-99 $\mu\text{g/l}$ was defined as mild iodine deficiency, the interval of 20-49 $\mu\text{g/l}$ corresponded to moderate iodine deficiency, and with ioduria less than 20 $\mu\text{g/l}$, severe iodine deficiency was diagnosed [18].

The study was approved by the local ethics committee at the Far Eastern State Medical University of the Ministry of Health of the Russian Federation (protocol No. 2 dated 16.05.2024).

Statistical analysis of the study results was performed using Statistica 12.0 (StatSoft Inc., USA) and IBM SPSS Statistics 20. The study results are presented as the median (Me), interquartile range (Q1; Q3), relative value and its error. Comparison of quantitative indicators in the study groups was performed using the Kruskal-Wallis test with subsequent post hoc analysis and pairwise comparison of groups using the Dunn test. When analyzing multifield tables, the statistical significance of differences in relative indicators was assessed using the Pearson χ^2 test or Fisher's exact test in accordance with the restrictions on the number of observations. For a quantitative assessment of the relationship between a certain outcome and a risk factor when comparing two groups, the statistical indicator odds ratio (OR) was used. When calculating the OR, an estimate of 95% confidence intervals (CI) was used. Differences between groups were considered statistically significant at $p < 0.05$.

Results and discussion. The study showed high prevalence of low iodine status among children in the Far Eastern Federal District, which was observed in 3 out of 4 children. Only $26.1 \pm 3.2\%$ of study participants had normal iodine lev-

els in their bodies. Every third child was diagnosed with mild iodine deficiency ($34.0 \pm 3.5\%$), $30.3 \pm 3.4\%$ and $9.6 \pm 2.2\%$ of children suffered from moderate and severe iodine deficiency, respectively.

When analyzing the age characteristics of the distribution of the level of iodine supply in children, no statistically significant differences were obtained in the study groups (Table 1). The highest median value of iodine concentration in urine was recorded in younger schoolchildren - 70.0 $\mu\text{g/l}$, while it corresponded to a mild deficiency, and the upper quartile slightly exceeded the lower limit of the normal range of supply (104.0 $\mu\text{g/l}$). The medians of ioduria in the groups of early, preschool and adolescent children were lower, but were also within the limits of mild deficiency (59.0 $\mu\text{g/l}$, 54.0 $\mu\text{g/l}$ and 63.0 $\mu\text{g/l}$, respectively).

Table 1. Comparative analysis of the level of iodine supply of children of different age groups living in the Far Eastern Federal District

Comparative analysis of the prevalence of different levels of supply did not reveal reliable differences in children of the comparison groups: in all age groups, mild and moderate iodine deficiency was predominant (Table 1). It should be noted that statistically significant differences in ioduria indicators depending on gender were also not recorded: the median value of iodine concentration in urine in boys was 62.0 $\mu\text{g/l}$, in girls – 65.0 $\mu\text{g/l}$ ($p = 0.488$), the interquartile range was the same 41.0-103.0 $\mu\text{g/l}$.

A study of school-age children from La Pampa, Argentina, yielded results comparable to ours [13]: adequate iodine status was observed in 27.0% of study participants, iodine deficiency was diagnosed in 39.2% of cases. The median iodine value in the urine of the subjects was 145.5 $\mu\text{g/l}$, which is 2 times higher than the value in our study, however, despite its compliance with the optimal level of supply, 28.8% of children had iodine levels below 50 $\mu\text{g/l}$, a fact that the authors of the study attribute to the incomplete coverage of children's daily consumption of iodized salt (85.5%). Also, the concentration of ioduria in boys and girls did not differ statistically significantly and was equal to 139.7 $\mu\text{g/l}$ (29.1–256.9) and 149.3 $\mu\text{g/l}$ (61.5–209.5), respectively [13].

When assessing ioduria in children living in different climate-geographic zones of the Far Eastern Federal District, a statistically significant difference in iodine status was found in the study groups ($p < 0.001$) (Table 2): the median iodine

Table 1

Comparative analysis of the level of iodine supply of children of different age groups living in the Far Eastern Federal District

Age group	1-3 years (n=38)	4-6 years (n=46)	7-11 years (n=46)	12-18 years (n=58)	p
Me (Q1; Q3), µg/l	59.0 (41.0; 86.0)	54.0 (35.0; 104.0)	70.0 (41.0; 104.0)	63.0 (43.0; 103.0)	0.636
Severe iodine deficiency (abs., P±m)	2 (5.3±3.6)	7 (15.2±5.3)	5 (10.9±4.6)	4 (6.9±3.3)	0.397
Moderate iodine deficiency (abs., P±m)	13 (34.2±7.7)	15 (32.6±6.9)	12 (26.1±6.5)	17 (29.3±6.0)	0.844
Mild iodine deficiency (abs., P±m)	15 (39.5±7.9)	11 (23.9±6.3)	16 (34.7±7.0)	22 (37.9±6.4)	0.380
Normal iodine level (abs., P±m)	8 (21.0±6.6)	13 (28.3±6.6)	13 (28.3±6.6)	15 (25.9±5.8)	0.869

concentration in the urine of children in the Arctic territory was 50.5 µg/l, which is 1.5 times less than in the southern zone (74.5 µg/l). The incidence of low iodine status in children in the Far North was 2.6 times higher than in the southern zone (80.9±3.6% and 61.8±5.9%, respectively, OR = 2.611, 95% CI 1.339-5.090), with a significant predominance of moderate iodine deficiency (37.5±4.4% and 17.7±4.6%, respectively, p = 0.005). Optimal iodine status among northern children was twice as rare (19.1±5.9% and 38.2±5.9%, respectively, p = 0.005; OR = 0.383, 95% CI (0.196-1.747)), which raises concerns.

Table 2. Features of iodine status in children living in different climatic and geographical zones of the Far Eastern Federal District

An analysis of the iodine status of children aged 3-6 years living in different climatic and geographical regions of the Republic of Sakha (Yakutia) showed that the highest prevalence of iodine deficiency was characteristic of the southern territory: in the Central zone, 54.6% of children suffered from iodine deficiency, in the Arctic zone - 57.7%, in the Western zone - 68.5%, in the Eastern zone - 72.8% and in the Southern zone - 77.0% [9], which may be associated with the

peculiarities of the nutritional component of iodine provision, but not the influence of the ecological and climatic component.

Due to the limited number of studies on the iodine status of children living in the Arctic, we decided to study the iodine status of northern children in more detail. In general, when analyzing the absolute values of iodine concentration in the urine, it was determined that in the groups of children of early and primary school age, the median value was in the range of mild deficiency (59.0 µg/l and 62.5 µg/l, respectively), while in preschoolers and adolescents the level of provision corresponded to moderate de-

Table 2

Features of iodine status in children living in different climatic and geographical zones of the Far Eastern Federal District

Territory	Arctic zone (n=120)	Southern zone (n=68)	p	OR (95% CI)
Me (Q1; Q3), µg/l	50.5 (34.0; 87.5)	74.5 (53.5; 114.0)	< 0.001	-
Severe iodine deficiency (abs., P±m)	14 (11.7±2.9)	4 (5.9±2.9)	0.302	2.113 (0.667-6.699)
Moderate iodine deficiency (abs., P±m)	45 (37.5±4.4)	12 (17.7±4.6)	0.005	2.800 (1.356-5.780)
Mild iodine deficiency (abs., P±m)	38 (31.7±4.3)	26 (38.2±5.9)	0.362	0.749 (0.402-1.395)
Normal iodine level (abs., P±m)	23 (19.1±5.9)	26 (38.2±5.9)	0.005	0.383 (0.196-1.747)

Table 3

Level of iodine supply of children living in the Arctic zone of the Far Eastern Federal District

Me (Q1; Q3), µg/l	1-3 years (n=30)	4-6 years (n=30)	7-11 years (n=30)	12-18 years (n=30)	p
Severe iodine deficiency (abs., P±m)	59.0 (41.0; 104.0)	38.5 (23.0; 62.0)	62.5 (32.0; 97.0)	49.0 (34.0; 89.0)	0.045
Moderate iodine deficiency (abs., P±m)	0 (0.0)	7 (23.4±7.7)	3 (10.0±5.5)	4 (13.3±6.2)	0.029
Mild iodine deficiency (abs., P±m)	11 (36.7±8.8)	13 (43.2±9.1)	10 (33.3±8.6)	11 (36.7±8.8)	0.879
Normal iodine level (abs., P±m)	11 (36.7±8.8)	7 (23.4±7.7)	10 (33.3±8.6)	10 (33.3±8.6)	0.720
Нормальный уровень йода (абс., P±m)	8 (26.6±8.1)	3 (10.0±5.5)	7 (23.4±7.7)	5 (16.7±6.8)	0.383

iciency (38.5 µg/l and 49.0 µg/l, respectively) ($p = 0.045$) (Table 3).

Table 3. Level of iodine supply of children living in the Arctic zone of the Far Eastern Federal District

The highest prevalence of moderate iodine deficiency was recorded in preschool children ($43.2 \pm 9.1\%$), slightly less in young children and adolescents ($36.7 \pm 8.8\%$). Severe iodine deficiency was found in preschool children 2 times more often than in school-age children and was not diagnosed at all in children aged 1-3 years ($p = 0.029$). The normal level of provision in children of different ages did not have reliable differences and was found in 1-4 children out of 10 ($p = 0.383$) (Table 3).

Based on the results of interviewing the parents of the examined children, it was found that only $21.6 \pm 5.3\%$ of families in the southern territory of the Far Eastern Federal District use iodized salt in food, while a similar trend is observed in the Arctic zone: $18.3 \pm 3.5\%$ of families are committed to the daily use of iodized salt. Fish and fish products were included in the weekly diet of $26.7 \pm 4.0\%$ of children in the Arctic, which is 2 times less than the consumption among children in the southern zone ($47.1 \pm 6.1\%$, $p = 0.005$). However, the latter prefer river fish, which contains less iodine than sea fish.

Since 1995, China has implemented a policy of universal salt iodization to prevent and treat iodine deficiency diseases, which has gradually solved the problem of iodine deficiency. An analysis of iodine nutrition in Hainan Province found that the main source of iodine was iodized salt, with a coverage rate of 98.6%, while the contributions of kelp, milk, seaweed, fish and seafood were only 8.2%, 7.3%, 6.6% and 2.4%, respectively [15]. Interestingly, the average urinary iodine value of children in the central mountainous zone was 190.8 µg/l, which was significantly higher than that in the western and eastern coastal zones (149.4 µg/l and 161.0 µg/l, respectively) [15].

A similar study of 8- to 10-year-old children conducted in Chongqing Municipality, China, also found statistically significant differences in median urinary iodine concentrations in children from different climatic and geographical regions: the highest mean urinary iodine concentration was observed in children from Southeast Chongqing (252.6 µg/l), slightly lower in those examined in the central city zone (250.0 µg/l), and statistically significantly lower urinary iodine levels were recorded in children from West and Northeast Chongqing (221.0 µg/l and 200.6 µg/l, respectively) [14].

Differences in the level of iodine supply with universal consumption of iodized salt and products with a high iodine content are associated with the characteristics of the content, accumulation and biogenic migration of iodine compounds in soil, water and plant products, which also contribute to the iodine status of residents of these territories and vary depending on the terrain, agrophysical and agrochemical properties of soils, as well as the climate of the territory [10, 15].

Conclusion. The study revealed a high prevalence of low iodine status in children living in the Far Eastern Federal District, which was observed in 73.9% of cases with a higher prevalence of severe and moderate iodine deficiency in children living in the Arctic zone. Statistically significant differences in iodine content in the body of children of different age groups were determined only in northern children, in whom the highest prevalence of iodine deficiency was observed in preschool age, which is probably due to the formation of food selectivity, the lack of iodine supplements in the form of iodized salt, drugs or dietary supplements.

At the present stage, the paradigm of eliminating iodine deficiency with an emphasis on nutritional status comes to the fore, i.e. iodine status largely depends on the level of commitment to the use of iodized salt and iodine-rich foods, which requires health education work by pediatricians in order to increase parents' awareness of ways to eliminate iodine deficiency by correcting children's diets and supplementation to prevent thyroid diseases, physical and cognitive development disorders in the younger generation.

At the national level, it is necessary to develop the production of functional food products, expand the range of snack products and Health & Wellness products for healthy eating, enriched with iodine, which will have a health-saving effect. [2, 4, 12].

The authors declare no conflict of interest.

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N.A. Beigul, L.K. Karimova, E.R. Shaykhlislamova, N.A. Muldasheva, G.G. Gimranova, L.N. Mavrina, L.A. Ilyina HYGIENIC SITUATION AND OCCUPATIONAL MORBIDITY AT COPPER-ZINC ORE MINING ENTERPRISES

The article is devoted to the hygienic assessment of working conditions and their impact on the health of employees of a mining enterprise engaged in the extraction and processing of copper-zinc ore located in the Southern Urals. The relevance of the study is due to the need for a detailed study of the hygienic situation in all divisions of a mining enterprise in order to assess the levels of occupational risk of damage to the health of employees and timely preventive measures aimed at minimizing it. Priority harmful production factors have been identified in the workplaces of various departments: during underground ore mining, noise, vibration, lack of natural light, unfavorable microclimate, severity, and labor intensity; during transportation of extracted ore, vibro-acoustic factors, severity, and labor intensity; during ore processing, noise. The overall assessment of the workers' working conditions corresponded to harmful classes 3.1-3.3. Working environment factors contributed to the formation of chronic somatic diseases among workers engaged in mining and transporting ore, among which dorsopathies and arthropathies prevailed, which is confirmed by the high strength of the association of these diseases with working conditions. In the workers of the processing plant, dorsopathies with an average degree of association were attributed to diseases related to working conditions. The structure of occupational morbidity was dominated by diseases caused by exposure to vibration, aerosols, mainly fibrogenic effects, and physical overloads. Workers engaged in mining and transporting ore have the highest occupational morbidity index (0.32 - 0.50). The highest total assessment of occupational health risk, taking into account all the studied indicators, was established for workers engaged in underground mining. The materials of the conducted research served as the basis for the development of medical and preventive recommendations to minimize the occupational risk to the health of employees of the studied enterprise.

Keywords: mining enterprise, workers, harmful production factors, occupational diseases, diseases related to working conditions

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BEIGUL Natalya Aleksandrovna – Ufa Research Institute of Occupational Health and Human Ecology, senior researcher, PhD in Chemical Science, associate professor, Ufa State Petroleum Technological University, omt_ufnii@mail.ru, ORCID: <https://orcid.org/0000-0002-8006-384X>; **KARIMOVA Liliya Kazymovna** – Ufa Research Institute of Occupational Health and Human Ecology, chief researcher, professor, MD, iao_karimova@rambler.ru, <https://orcid.org/0000-0002-9859-8260>; **SHAYKHLISLAMOVA Elmira Radikovna** – Ufa Research Institute of Occupational Health and Human Ecology, director, PhD in medicine, associate professor, associate professor of the Department Bashkirian State Medical University, shajkh.ehlmira@yandex.ru, ORCID: <https://orcid.org/0000-0002-6127-7703>; **MULDASHEVA Nadezhda Alekseevna** – Ufa Research Institute of Occupational Health and Human Ecology, researcher, muldasheva51@gmail.com; <https://orcid.org/0000-0002-3518-3519>; **GIMRANOVA Galina Ganinovna** – Ufa Research Institute of Occupational Health and Human Ecology, Chief Researcher, MD in Medicine, gala.gim@mail.ru, <https://orcid.org/0000-0002-8476-1223>; **MAVRINA Liana Nikolaevna** – Ufa Research Institute of Occupational Health and Human Ecology, senior researcher, PhD in Biological Science, Liana-1981@mail.ru, <https://orcid.org/0000-0002-0250-2683>; **ILYINA Lusia Askhatovna** – Ufa Research Institute of Occupational Health and Human Ecology, senior researcher, PhD in Economic Sciences, associate professor, list@ufanet.ru; ORCID: <https://orcid.org/0000-0002-6481-0534>

Introduction. Despite the implementation of national programs aimed at preserving the longevity and active life of the working population, a high proportion of workers employed in unfavorable working conditions remains at individual enterprises in various sectors of the economy, and occupational diseases are registered. Such industries include mining, in which more than half of employees work in conditions that negatively affect their health, and the level of occupational mor-

bidity over the past five years, according to Rosstat, has varied from 15.2 to 21.2 cases per 10,000 employees.

There is a high risk of adverse effects of harmful production factors on the health of employees of enterprises in this industry, including companies engaged in the extraction and processing of metal ores [3-5, 7, 8, 10, 13, 15].

According to various authors, vibration sickness, sensorineural hearing loss, diseases of the peripheral nervous

system and musculoskeletal system, as well as pneumoconiosis account for the largest share in the structure of occupational diseases of mining workers. [3, 9, 11, 12, 14].

Mining enterprises in their structure have mines for underground mining, open pits, processing plants, motor transport units that transport ore, as well as auxiliary sites. The largest number of studies are focused on assessing the working conditions and health of workers engaged in underground mining [3, 2, 6, 8-11]; some information is available about the working conditions of workers engaged in ore transportation and processing [1, 2].

The relevance of this study is due to the need for a detailed study of the hygienic situation in all divisions of a mining enterprise in order to rank them according to the levels of occupational risk of damage to the health of employees and timely preventive measures aimed at minimizing it.

Materials and methods of research.

Hygienic studies of working conditions were carried out at the enterprise for the extraction and processing of metal ores located in the Southern Urals. Based on the results of measurements of the factors of the working environment and the labor process, as part of the conducted production control, the working conditions at the workplaces of various departments were assessed in accordance with the requirements of the Manual R 2.2.2006-05¹.

During the periodic medical examination, in accordance with the Order² of the Ministry of Health of the Russian Federation No. 29n, 821 male employees of various production units aged from 23 to 58 years were examined, with an av-

erage age of 45.2 ± 2.4 years and professional experience of 16.4 ± 0.8 years. Occupational morbidity rates among workers have been studied over the past ten years.

Occupational risk and the degree of occupational conditioning are calculated in accordance with the requirements of Guideline P 2.2.3969-23³, taking into account the class of working conditions, indicators of occupational morbidity and diseases related to working conditions (BSUT). The degree of professional conditionality of the identified chronic somatic diseases of employees of production units was carried out based on the calculation of relative risk (RR, units) and etiological proportion (EF, %).

The comparison group included 238 male workers who worked in auxiliary departments in the professions of locksmith of control and measuring devices and automation, electrician, foreman of sites, employees of the central factory laboratory, whose working conditions were not related to underground conditions and corresponded to the permissible class. The compared group was comparable with the main professional groups in terms of age (43.5 ± 3.5 years) and work experience (18.9 ± 1.3 years) by profession.

Statistical processing of the obtained data was carried out using Microsoft Excel programs.

Results and discussion. The functioning of a certain technological stage is associated with the presence of certain harmful production factors and their combinations in the workplace, the intensity of which depended on the power of the equipment used, the type of work performed, raw materials, reagents, the degree of automation and mechanization of production, etc.

The workplaces of workers engaged in the management and maintenance of in-mine equipment for underground ore mining (drilling rig operator (BU), loading and delivery machine operator (PDM), loading and screening machine operator (PSM), fastener) were characterized by harmful working conditions due to a combination of production factors (noise, vibration, illumination (lack of natural lighting), chemical, ACE, microclimate, severity, intensity of the labor process) (Table 1).

Industrial noise generated by in-house

machinery and mechanisms, the levels of which exceeded the maximum permissible level (remote control) by 5-17 dBA, is typical for all workplaces studied (classes 3.1-3.3). Vibration acceleration levels at individual workplaces exceeded hygienic standards by 1-3 dBA. The lack of natural lighting in the mine workings, taking into account the assessment of artificial lighting of the work areas, made it possible to classify the working conditions for lighting as a harmful class of the first degree. On mining equipment operated at the bottom of the mine, which does not provide isolated cabins, the microclimate parameters in the working area did not correspond to the established normalized levels (class 3.1).

The presence of carbon monoxide and nitrogen oxide was recorded in the air of the PDM and PSM machinists' working area, the concentrations of each of them did not exceed the relevant hygienic standards, taking into account the summation coefficient, the class of working conditions corresponded to the harmful class 3.1. When preparing the cement mixture by the fastener for applying it to the arches of the workings, an increased content of silicate dust (cement) in the air was found weakly fibrogenic effect; the frequency of excess reached up to 1.45 times (class 3.1).

The work of the employees of the entire professional group is stressful (class 3.1) due to significant emotional and sensory stresses, which is due to the peculiarities of conducting the technological process of underground ore mining.

The labor process of the fasteners is difficult (class 3.1), as they perform a number of manual auxiliary work related to the movement of cargo up to 35 kg.

The general class of working conditions of workers engaged in underground mining corresponded to the harmful class of the second – third degrees of harmfulness (3.2-3.3).

The extraction, loading and transportation of the extracted ore was carried out using specialized equipment: excavators, bulldozers, tractors, heavy-duty dump trucks of various brands. The professional group in this division is represented by a car driver, a bulldozer driver, an excavator driver and a tractor driver. The combination of harmful production factors affecting the workers of this group was the same and consisted of the vibroacoustic factor, the severity and intensity of the labor process with a general assessment of working conditions corresponding to the harmful class 3.2.

The extracted ore is delivered to the processing plant in order to obtain a com-

¹ Guidelines for the hygienic assessment of the factors of the working environment and the labor process. Criteria and classification of working conditions: Manual R 2.2.2006-05. Bulletin of regulatory and methodological documents of Gossanepidnadzor. 2005; 3(21): 3-144.

² Order of the Ministry of Health of the Russian Federation No. 29n dated January 28, 2021 "On Approval of the Procedure for Mandatory Preliminary and Periodic medical examinations of employees Provided for in Part Four of Article 213 of the Labor Code of the Russian Federation, the list of medical Contraindications to work with Harmful and (or) Dangerous Industrial factors, as well as work performed during which mandatory preliminary and periodic medical examinations are carried out (as amended on February 1, 2022)". Registered with the Ministry of Justice of the Russian Federation on 29.01.2021 N 62277.

³ P 2.2.3969-23 "Guidelines for occupational health risk assessment for employees. Organizational and methodological foundations, principles and evaluation criteria"

Table 1

Working conditions of employees of various divisions of a mining enterprise

The production environment factor	The class of working conditions in the workplace		
	mining of ore by underground method	ore transportation	enrichment plant
Chemical	2 - 3.1	2	2
Aerosols of predominantly fibrogenic action	2 - 3.1	2	2 - 3.1
Noise	3.1 - 3.3	3.1 - 3.2	3.1 - 3.2
Vibration	2 - 3.1	3.1	2 - 3.1
Microclimate	2 - 3.1	2	2 - 3.1
Illumination	3.1	2	2
The severity of the work	2 - 3.1	3.1	2 - 3.1
Labor intensity	3.1	3.1	2
General class of working conditions	3.2 - 3.3	3.2	3.1 - 3.2

mercial concentrate with a higher content of valuable components compared to the initial ore mass. The technological process involves a crusher, a conveyor operator, a mill operator, a flotation device, a reagent solver, a thickener apparatus, a filter and a dryer. The leading harmful production factor in their workplaces was noise, the intensity of which was determined by the type and corresponding capacity of the equipment used (class 3.1-3.2). In addition, there was an increased level of general vibration at the crusher's workplace (class 3.1), an unfavorable microclimate (class 3.1) for workers serving the drying and filtration department, and the presence of silicon dioxide, the content of which exceeded the maximum permissible concentration by 1.5 - 2.8 times (class 3.1), was recorded in the crusher, conveyor machinists, and mills.

The working conditions in terms of the severity of the labor process at most workplaces were acceptable (class 2), with the exception of the workplace of the solvent of reagents, whose work involves manually moving a load weighing 25-30 kg and was characterized by the third class of the first degree of harmfulness (class 3.1). The general class of working conditions of employees of the enrichment plant corresponded to class 3.1-3.2.

According to the results of the medical examination of the employees of the studied enterprise, only 18-24% of the surveyed were recognized as healthy, while 76-82% have chronic diseases.

The main chronic somatic diseases among workers engaged in mining and transporting ores were dorsopathy (53.2%), nervous system disorders (27.5%), diseases characterized by high blood pressure (18.2%), as well as diseases of the digestive system (7.7%).

The processing plant workers were

diagnosed with diseases of the musculoskeletal system and connective tissue (52.5%), mainly dorsopathy, respiratory diseases (45.8%), with a significant proportion being chronic bronchitis (8.6%) and upper respiratory tract diseases in the form of rhinitis, pharyngitis (37.4%), as well as diseases of characterized by high blood pressure (33.3%).

The calculation of the degree of occupational risk of developing BSUT, depending on the specifics of the work performed, demonstrated significant differences. Respiratory diseases (RR = 2.9, EF = 52.0%) have a high degree of association of health disorders with working conditions in workers of the processing plant, diseases characterized by high blood pressure (RR = 1.9, EF = 43.2%), as well as dorsopathy (RR = 1.91, EF = 47.6%) have an average degree.

For workers engaged in mining and transporting ore, dorsopathies (RR = 2.7 - 3.2, EF = 61.0 - 65.2%) and arthropathies (RR = 2.5 - 3.2, EF = 51.0

- 65.3%) have a high degree of association with working conditions, while diseases characterized by high blood pressure have an average degree (RR = 1.8, EF = 42.3%).

Occupational diseases in workers engaged in the extraction and transportation of metal ores were represented by vibration disease, autonomic sensory polyneuropathy of the extremities and radiculopathies, as well as pneumoconiosis. The HP index was 0.32 - 0.50, and the risk was high. At the same time, the age at which occupational diseases were detected ranged from 40.7 to 52.7 years, and professional experience ranged from 14.4 to 20.8 years.

No occupational diseases have been identified in the workers of the enrichment plant.

The frequency of development of signs of noise exposure to the hearing organ in the surveyed differed slightly and amounted to $19.6 \pm 1.2\%$ for workers engaged in underground mining, $15.8 \pm$

Table 2

Assessment of the occupational risk of damage to the health of employees of the main divisions of the enterprise for the extraction and processing of metal ores

Indicator	Division		
	mining of ores by underground method	ore transportation	ore processing
Class of working conditions	3.2 - 3.3	3.2	3.1 - 3.2
Risk category - points	average - 1.5 high - 2.0	average - 1.5	moderate - 1.0 average - 1.5
Clinical signs of occupational diseases and diseases related to working conditions	There is a clinical picture of occupational diseases and diseases related to working conditions		early signs of occupational diseases and diseases related to working conditions have been identified
Scores	7.0	7.0	5.0
Total	8.5 - 9.0	8.5	6.0 - 6.5

1.3% for workers transporting ore, and $14.3 \pm 1.8\%$ for workers at the processing plant.

Based on the studied indicators, an assessment of the occupational health risk of employees of various divisions was carried out (Table 2). When ranking the divisions of a mining enterprise, it was found that workers engaged in underground ore mining have the greatest risk of health problems (the sum of the points is 8.5 - 9.0), followed by workers engaged in ore transportation, having 8.5 points. The lowest risk of health damage in terms of the total score (6.0 – 6.5) is typical for employees of the processing plant.

The unfavorable hygienic situation at this enterprise is similar to the results of research on working conditions at other enterprises in the industry, as evidenced by publications [2].

The clinical examination data confirms the results of hygienic studies. Only 18-24% of the surveyed were recognized as healthy and practically healthy, while the rest had chronic somatic diseases such as dorosopathy, nervous system disorders, diseases characterized by high blood pressure, etc. Our data coincide with the results of other researchers who have studied occupational morbidity and health status of employees of mining and processing enterprises [2,5, 10].

The results of the study substantiate the need to develop and implement comprehensive measures, including technical, organizational, and therapeutic measures aimed at reducing the occupational risk of health problems among employees of various departments of the enterprise.

Conclusions:

1. The working conditions of the employees of the studied enterprise were characterized by the impact of a complex of harmful production factors of varying intensity, which was determined by the stage of the technological process, the equipment used and its capacity, the type of work performed, the degree of automation and mechanization of production, etc., with a general assessment of working conditions 3.1 - 3.3.

2. The unfavorable hygienic situation at work causes the formation of occupational diseases and diseases related to working conditions in employees, the levels of which correspond to high – medium occupational risk categories.

3. The determining role of working conditions (the relative risk of RR is more than two units and the etiological proportion of EF is above 50%) has been identified for chronic diseases of the musculoskeletal system in workers engaged in mining and transporting ore, respiratory organs – in workers of the processing plant.

4. Occupational diseases in workers engaged in the extraction and transportation of metal ores were represented by vibration disease, autonomic sensory polyneuropathy of the extremities and radiculopathies, pneumoconiosis with a high (0.32 – 0.50) HP index.

5. The materials of the conducted research served as the basis for the development of medical and preventive recommendations to minimize the occupational risk to the health of employees.

The authors declare no conflict of interest.

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E.M. Iutinsky, L.M. Zheleznov, S.A. Dvoryansky

CLIMATIC AND ETHNIC MODIFIERS OF FETAL BIOMETRIC PARAMETERS: A COMPARATIVE REGIONAL ANALYSIS

Climatic fluctuations and the ethnic heterogeneity of the population can shift the standards of intrauterine growth; however, their combined effect has been little studied. Air temperature, day length, and pregnancy season, in combination with the mother's ethnicity, modify fetal biometry and newborn weight. A retrospective cohort analysis included 1,812 singleton pregnancies completed between 2018 and 2024. Fetal biometric parameters (BPD, OFD, HC, AC, FL) were measured according to unified ultrasound screening protocols. Climatic data by trimester (mean temperature, number of sunny days, photoperiod duration) were obtained from Roshydromet. Ethnic groups: Russians, Tatars, Mari, Udmurts. Two-way ANOVA and multilevel linear modeling adjusted for gestational age were used. The third trimester of pregnancy, occurring in the spring–summer period (+4°C above annual average), was associated with a 3.1% increase in abdominal circumference ($p < 0.01$) and an increase in newborn weight by 112 g. The ethnic factor manifested from week 24: Finno-Ugric groups showed a significant reduction in femur length (–2.4 mm) with a simultaneous increase in AC (+6.5 mm). In the newborn weight model, climatic predictors explained 18% of the variance, ethnicity 7%, and their interaction 4%. Furthermore, accounting for these factors improved the accuracy of the Estimated Fetal Weight prediction model by 9% compared to the standard Hadlock formula. Climatic conditions and ethnocultural background form independent and interdependent trajectories of intrauterine growth, cumulatively accounting for about one-third of the variance in birth weight. These data substantiate the need for seasonal and ethnic adjustments when assessing fetal biometry.

Keywords: climatic factors, fetal biometry, ethnicity, pregnancy season, birth weight, regional standards, pregnancy

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Introduction. Normative curves of intrauterine growth are a fundamental tool for prenatal management; however, classical tables were constructed on averaged multi-ethnic samples and do not account for either regional climate or the ethnic specifics of the population. Meanwhile, systematic reviews in recent years convincingly show that extreme temperatures, shortened daylight hours, and lack of sunny days are associated with slower fetal growth, increased risk of preterm birth, and lower newborn weight. In the temperate continental climate of the Kirov region, first-trimester temperature and third-trimester insolation explain up to 18% of the variation in birth weight, which is comparable to the contribution of such "classic" factors as smoking or parity.

In parallel, evidence is accumulating

on the influence of ethnicity on various fetal size parameters, including both the length of individual body parts and indicators reflecting overall growth and development. In Russian samples, stable differences in femur length and abdominal circumference have been identified between Finno-Ugric peoples (Mari, Udmurts) and the Slavic population, starting from the 24th week of gestation. Meanwhile, cephalometric parameters remain the most conservative, which is consistent with findings from international anthropological research. Ignoring ethnic characteristics leads to overdiagnosis of growth restriction and an unjustified increase in the number of control ultrasounds.

Climate and ethnicity are rarely considered together, and published works tend to focus either on seasonal fluctuations or on comparisons of large racial-ethnic groups. For the multiethnic Kirov region, where the share of Russians, Tatars, Mari, and Udmurts reaches 90% of the population, such gaps are particularly critical. At the same time, the region exhibits pronounced seasonality, with mean temperatures ranging from –12°C in winter to +23°C in summer, and more than a twofold difference in day length. This creates a unique model for assessing the interaction of "climate × ethnicity" and for developing adjustment coefficients for traditional fetal biometric formulas.

The aim of this study is to quantitatively describe the independent and combined contribution of climatic conditions during pregnancy and maternal ethnicity to the formation of key fetal biometric parameters and birth weight, as well as to propose seasonal and ethnic adjustments to regional standards.

Materials and Methods. This study was conducted as a retrospective cohort analysis and included 1,812 singleton pregnancies completed with live births between 2018 and 2024 at the Kirov Regional Clinical Perinatal Center (Kirov, Russia), stratified by key demographic and population characteristics into several groups for statistical analysis.

For multifactorial analysis, all participants ($n=1,812$) were distributed into overlapping groups based on ethnicity and the climatic-seasonal profile of pregnancy. Each of the four climatic groups (defined by the timing of the third trimester: spring, summer, autumn, winter) included four ethnic subgroups Russians, Tatars, Mari, and Udmurts. Thus, a total of 16 "climate × ethnicity" combinations were analyzed, ensuring representativeness and statistical comparability of the groups (on average, 110–120 observations per subgroup; for example, Russians with the third trimester in spring $n=121$, Tatars $n=114$, Mari $n=98$, Udmurts $n=104$, etc.).

This design made it possible to conduct two-way ANOVA, which assessed

Federal State Budgetary Educational Institution of Higher Education "Kirov State Medical University" of the Ministry of Health of Russia: **IUTINSKY Eduard Mikhailovich** – PhD (Medicine), Associate Professor, Department of Obstetrics and Gynecology, ORCID: 0000-0001-5641-0269, iutinskiy@ya.ru; **ZHELEZNOV Lev Mikhailovich** – DSc (Medicine), Professor, Rector of Kirov SMU, ORCID: 0000-0001-8195-0996, rector@kirovgma.ru; **DVORYANSKY Sergey Afanasyevich** – DSc (Medicine), Professor, Head of the Department of Obstetrics and Gynecology, ORCID: 0000-0002-5632-0447, Kf1@kirovgma.ru

both main effects (climatic season, ethnicity) and their interaction. To enhance the comparability of groups, additional stratification was performed by maternal age (median 28 years, IQR 25–32) and gestational age at delivery (median 39.3 weeks, IQR 38.6–40.1), as well as by other potential covariates (parity, pre-pregnancy BMI, obstetric complications). This approach yielded statistically valid estimates of the effects of climatic and ethnic factors both separately and in combination on fetal biometric parameters and birth weight.

All women were monitored according to a single approved protocol, ensuring comparability of intrauterine growth dynamics data.

Population and Inclusion Criteria. The analysis included patients aged 18–42 years with uncomplicated pregnancies and gestational ages of 11–40 weeks, determined by the date of the last menstrual period and adjusted at the first ultrasound screening based on CRL. Exclusion criteria were multiple pregnancy, severe extragenital pathology, congenital malformations, preterm delivery <37 weeks, and refusal to participate in the study.

Among mild pregnancy complications and maternal somatic diseases in a compensated stage, which did not require substantial adjustment of obstetric tactics, the following were observed: chronic hypertension (4.5%), preeclampsia (3.1%), iron deficiency anemia (8.6%), thyroid disorders (6.3%), diabetes mellitus (any type) (4.1%), compensated forms of fetoplacental insufficiency (1.3%), and threatened preterm labor (10.4%). Other clinical conditions accounted for about 56%. The frequency of these conditions did not differ statistically between the study groups ($p > 0.05$).

Study Variables. Fetal Biometry: Biparietal and occipitofrontal diameters, head and abdominal circumferences, and femur length were measured during scheduled ultrasound screenings on a high-end "Samsung Medison Accuvix A30" device with a 3–7 MHz convex transducer. The imaging technique and slice positioning followed ISUOG recommendations; inter- and intra-operator reproducibility at the center had previously been confirmed with an intraclass correlation coefficient ≥ 0.92 .

Climatic Factors: For each trimester, the mean air temperature ($^{\circ}\text{C}$), number of sunny days, and photoperiod (hours) were individually extracted from the Roshydromet database. Both continuous values and quartile distributions of temperature were used for statistical models; in addition, four seasonal pregnancy

profiles ("Autumn–Winter–Spring", etc.) were formed.

Ethnicity: Determined by the woman's self-identification; the four most represented groups in the region were analyzed—Russians, Tatars, Mari, and Udmurts.

Study Outcome: Newborn weight was recorded in the delivery room using electronic "Baby Scale" scales with an accuracy of ± 10 g and adjusted for gestational age at birth.

Data Processing. Primary verification included checking for missing values, logical inconsistencies, and duplicates. Climatic indicators were "linked" to the individual pregnancy calendar of each participant and then standardized by z-scores to eliminate dimensional effects.

Statistical Analysis. Analysis was performed using IBM SPSS Statistics 25.0. Normality was assessed by the Shapiro–Wilk test, and homogeneity of variances by Levene's test. Two-way ANOVA (4 seasons $\times$ 4 ethnicities) was used for all fetal biometric parameters and birth weight; partial η^2 was calculated to estimate the contribution of each factor and their interaction. Post-hoc comparisons between pairs of groups were performed using Tukey's HSD with Holm–Bonferroni correction for multiple tests, maintaining an overall significance level of $\alpha = 0.05$. To assess the association of continuous climatic variables with fetal size, Pearson correlation analysis was used. Multiple linear regression was constructed with birth weight as the dependent variable; the model sequentially included temperature in the first and third trimesters, number of sunny days in the third trimester, the categorical variable "ethnicity" (dummy-coded), and the interaction term "climate $\times$ ethnicity." Multicollinearity was assessed by the inflation coefficient (VIF), with a critical threshold of <5 . Result validity was additionally checked by sensitivity analysis, excluding cases of gestational diabetes and preterm births <37 weeks; the coefficients obtained did not differ from the main model by more than 5%, confirming the robustness of the conclusions.

Ethical Considerations. The study protocol was approved by the local ethics committee of Kirov State Medical University (protocol No. 25/2024 of October 25, 2024) and complies with the principles of the Helsinki Declaration. All participants provided informed voluntary consent for the use of anonymized medical data. Thanks to unified ultrasound monitoring methodology, standardized meteorological data collection, and strict statistical control, the data obtained reliably reflect

the independent and combined effects of climatic conditions and ethnocultural factors on fetal intrauterine growth.

Results and Discussion. The mean age of the women studied was 28.4 ± 4.9 years, and the median gestational age at delivery was 39.3 weeks (IQR 38.6–40.1). Distribution across ethnic groups and seasonal pregnancy profiles was even; no statistically significant differences were found in smoking, parity, or pre-pregnancy BMI, nor in the incidence of obstetric or extragenital pathology ($p > 0.05$), minimizing the risk of confounding.

Air temperature in the third trimester showed the strongest association with fetal linear measurements. When moving from the lowest to the highest quintile of mean monthly temperature ($+4.2^{\circ}\text{C}$), abdominal circumference increased by 3.1% (95% CI 2.6–3.7; $p < 0.01$), and newborn weight by 112 g (95% CI 86–139; $p < 0.01$). An increase in photoperiod by each additional hour was associated with an increase in femur length by 0.7 mm ($p = 0.018$). Head parameters remained stable, which is consistent with data on the greater conservatism of cephalometric measurements [4]. The dynamics of abdominal circumference by temperature quintiles are presented in Figure 1.

Starting from the 24th week, Mari and Udmurt women exhibited a reduction in femur length by 2.3 mm ($p = 0.004$) and a simultaneous increase in abdominal circumference by 6.4 mm ($p < 0.001$) compared to Russians. Among Tatars, only a minor (~ 1.5 mm) and statistically non-significant ($p = 0.09$) reduction in biparietal diameter was detected. Thus, Finno-Ugric groups demonstrate the so-called "short-legged but massive" phenotype, previously described for northern populations.

Two-way ANOVA showed that the interaction of factors was statistically significant for abdominal circumference ($F = 3.41$; $p = 0.011$; $\eta^2 = 0.042$) and newborn weight ($F = 4.02$; $p = 0.006$; $\eta^2 = 0.047$). The maximum effect was observed in Mari mothers whose third trimester occurred in spring or summer: the mean newborn weight was $3,566 \pm 402$ g versus $3,215 \pm 375$ g in Russians during the cold season ($p < 0.001$). A graphical representation of the interaction effect is shown in Figure 2.

In multiple linear regression, climatic predictors explained 18% of the variance in newborn weight, ethnicity–7%, and the interaction term–4%. The addition of variables increased the model's R^2 compared to the baseline model (gestational age and fetal sex only) from 0.28 to 0.39

($p < 0.001$), confirming the significance of seasonal and ethnic modification.

When recalculating fetal weight using the Hadlock formula with adjustment coefficients obtained in this study, the mean absolute percentage error (MAPE) decreased from 8.7% to 7.9% ($p = 0.032$), and the proportion of deviations $>10\%$ fell from 36% to 27%. A comparison of predictive errors is shown in Figure 3.

The observed increase in birth weight during the summer period supports the concept of a "critical window" in the late gestational period for fat accumulation [1, 4]. Ethnic differences in limb and trunk proportions correlate with the northern "Allen's rule" and are likely an adaptive response to chronic cold [5].

A key new finding was the identification of a statistically significant "climate $\times$ ethnicity" interaction. Judging by the value of η^2 , the synergy of these factors adds another $\sim 4\%$ of the explained variance in newborn weight, which exceeds the range of random fluctuations and confirms the need for seasonal and ethnic adjustments in clinical practice.

The pathophysiological effect may be mediated by vitamin D deficiency and changes in thermoregulatory mechanisms during pregnancy [5]. Therefore, it is advisable not only to expand vitamin and mineral support in the cold season but also to consider the use of ethnically specific fetal biometric standards, especially for long tubular bones.

Limitations and Future Directions. The retrospective nature of the study limits causal inferences, and the lack of precise data on dietary intake and socioeconomic status may result in residual confounding. Nevertheless, rigorous standardization of ultrasound measurements and coverage of births in the region over seven years significantly strengthen the representativeness of the sample. Future research should incorporate a multicenter design with biomarkers of vitamin D, leptin, and IGF-1 growth factor, which will allow for a deeper understanding of the mechanisms underlying climatic and ethnic modification of fetal growth.

Conclusion. Our study demonstrated that climatic conditions during the late gestational period serve as an important independent determinant of birth weight. An increase in the mean temperature during the third trimester by approximately 4°C and a longer photoperiod were associated with a 3% increase in fetal abdominal circumference and an average increase in birth weight of 110 g, confirming the critical role of a "warm" final window of intrauterine development. At the same time, maternal

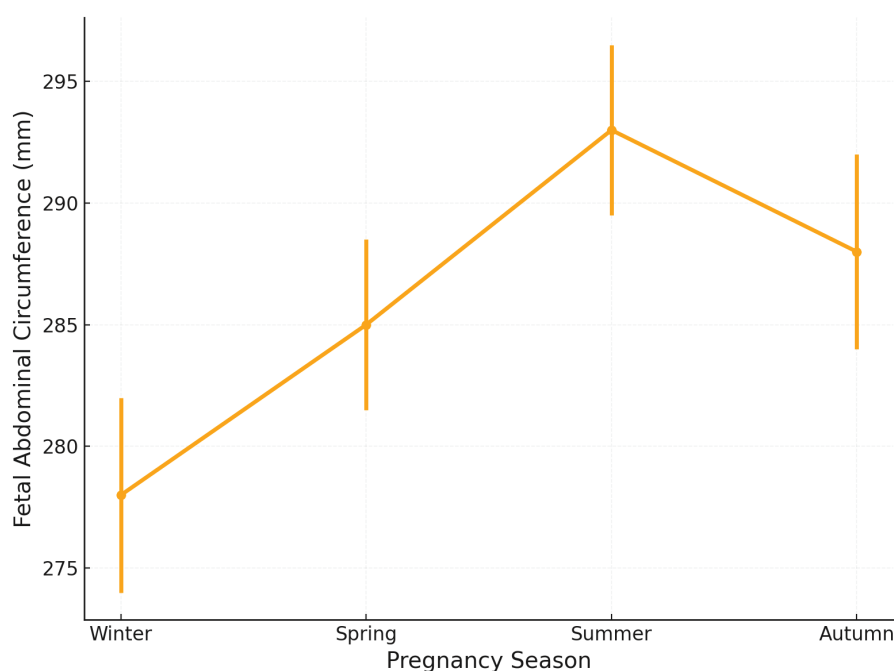


Fig. 1. Temperature-seasonal profile of intrauterine growth

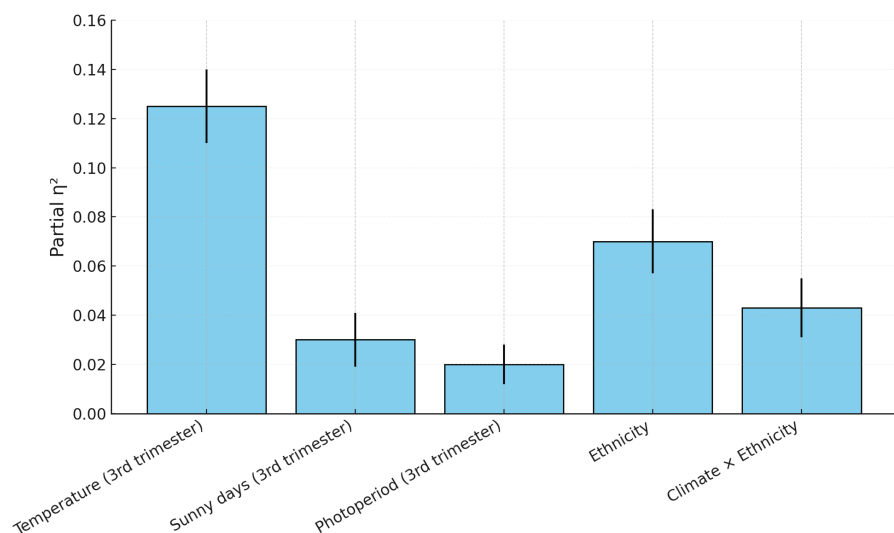


Fig. 2. Contribution of climatic and ethnic factors to the variation of newborn weight

ethnicity determines characteristic fetal proportions as early as week 24. In Mari and Udmurt populations, a "short limb segment – wide trunk" phenotype was identified: femur length was shorter and abdominal circumference larger than in Russians, with Tatars occupying an intermediate position. We also showed that the "climate" and "ethnicity" factors interact synergistically. This interaction was statistically significant for abdominal circumference and birth weight ($\eta^2 \approx 0.04$): the highest birth weights were observed among children of Finno-Ugric mothers whose pregnancies ended in the spring–summer period. In conclusion, taking seasonal and ethnic adjustments into ac-

count improves the accuracy of prenatal prognosis. The modified Hadlock formula, supplemented with adjustment coefficients, reduced the mean absolute error in Estimated Fetal Weight by 9% and lowered the proportion of large errors by more than 10%.

Practical Recommendations. To improve the accuracy of diagnosing fetal growth and development disorders, the use of local ethno- and season-specific regional standards, adapted to the characteristics of a particular population and the climatic-seasonal pregnancy profile, appears promising. The use of universal reference values without considering population-specific features may lead to



Fig. 3. Bland–Altman plot comparing the standard and modified Hadlock formulas

over- or underdiagnosis of intrauterine growth disorders.

Future Directions. A multicenter study including biomarkers of vitamin D and growth factors is needed to verify the identified patterns and to develop unified seasonal and ethnic standards for intrauterine development.

Thus, climatic and ethnic determinants form both independent and interdependent trajectories of intrauterine development. Their consideration in clinical algorithms reduces the risk of overdiagnosis of growth restriction and improves the accuracy of prenatal prediction of birth weight, making pregnancy management more personalized and safer.

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G.F. Adieva, T.K. Larionova, R.A. Daukaev,
E.E. Zelenkovskaya, G.R. Allayarova, E.N. Usmanova,
D.E. Musabirov

HYGIENIC ANALYSIS OF PUBLIC HEALTH RISKS FROM CONSUMPTION OF FOOD PRODUCTS CONTAMINATED WITH HEAVY METALS

Environmental pollution poses a serious threat to public health, being a key factor in the development of many diseases. Of particular danger are substances with carcinogenic properties. For industrial cities such as Ufa with a developed petrochemical industry, this problem is especially relevant. The observed increase in cancer incidence in the region requires a comprehensive risk assessment and the development of effective preventive measures.

In this work, an assessment of the health risk to the population of Ufa associated with chemical contamination of food products with heavy metals was carried out in accordance with the «Guidelines for assessing the risk to public health from exposure to chemicals polluting the environment» (R 2.1.10.3968-23).

The study revealed specific patterns of accumulation of toxic elements in different groups of products: dairy products demonstrate elevated concentrations of Pb, Cd and Ni; meat products – Hg; fruit and vegetable products – As. Analysis of the dietary structure showed the dominant role of dairy (31%), bread (18%), fruit and vegetable (12%) and meat (11%) products in the formation of the daily diet. An excess of the permissible level of non-carcinogenic risk for arsenic ($HQ = 1.143$) was revealed, indicating a potential danger to the nervous and cardiovascular systems. The total carcinogenic risk is at an acceptable level (1.39×10^{-5}), with the main contribution of cadmium (52%) and arsenic (43%). The data obtained emphasize the need for priority control of As and Cd content in food products, development of targeted preventive measures, and optimization of the food monitoring system.

Keywords: heavy metals, carcinogenic and non-carcinogenic risk, food products.

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Introduction. In the context of the growing environmental crisis, environmental pollution remains one of the key global problems. Numerous studies show that most human diseases are caused

by the impact of environmental factors, which are either the direct cause of pathologies or contribute to their development, with the carcinogenic potential of pollutants posing a particular danger [3, 6, 9]. For large cities, in particular for Ufa, the capital of the Republic of Bashkortostan, with its developed petrochemical industry, such studies remain relevant, requiring a comprehensive approach taking into account local environmental characteristics. The region has seen a steady increase in cancer incidence [10], one of the most important tools for preventing it is the assessment of carcinogenic and non-carcinogenic risks, followed by the development of measures to minimize them.

Heavy metals are a group of chemical pollutants present in the biosphere both as a result of natural geochemical processes and as a result of anthropogenic impact on the environment [1, 16].

The main route of human exposure to heavy metals is through the food chain as a result of consuming contaminated foods. Food contamination with heavy metals poses a serious threat to public health. According to WHO, more than 20% of nutrition-related diseases are

caused by exposure to toxic elements, including lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) [12, 15].

Natural concentrations of heavy metals are determined by the geochemical characteristics of the territories, while anthropogenic activity leads to their migration and accumulation in atypical ecological niches [15]. It should be noted that metals play a dual biological role. Despite the participation of heavy metals in key metabolic processes, when they accumulate in excess in the body, they exhibit pronounced toxic properties, leading to the development of pathological conditions [11]. For example, the essential element copper, being an irreplaceable participant in oxidation-reduction processes, exhibits neurotoxic, hepatotoxic and nephrotoxic effects when physiological concentrations are exceeded [5]. Zinc, being one of the essential chemical elements for the body, is involved in the regulation of many enzyme systems, protein and nucleic acid synthesis, but when consumed in excess, it can cause gastrointestinal disorders, weakened immunity, neurological problems, copper deficiency and anemia [14]. At the same time, elements such as mercury, lead, and cad-

Ufa Research Institute of Occupational Health and Human Ecology: **ADIEVA Gyuzeliya F.** – Cand. Sci. (Biol.), senior researcher of Chemical Analysis Department, ufa.lab@yandex.ru, <https://orcid.org/0000-0003-2377-3471>; **LARIONOVA Tatiana K.** – Cand. Sci. (Biol.), Associate Professor, leading researcher, laronovatk@yandex.ru, <https://orcid.org/0000-0001-9754-4685>; **DAUKAEV Rustem A.** – Cand. Sci. (Biol.), head of Chemical Analysis Department, ufa.lab@yandex.ru, <http://orcid.org/0000-0002-0421-4802>; **ZELENKOVSKAYA Evgeniya E.** – junior researcher of Chemical Analysis Department, ufa.lab@yandex.ru, <https://orcid.org/0000-0001-7682-2703>; **ALLAYAROVA Guzel R.** – Cand. Sci. (Biol.), senior researcher of Chemical Analysis Department, guzel-all@mail.ru; <https://orcid.org/0000-0003-0838-3598>, 8-903-3549289; **USMANOVA Elza N.** – junior researcher of Chemical analysis Department, ufa.lab@yandex.ru, <https://orcid.org/0000-0002-5455-6472>; **MUSABIROV Dmitry E.** – junior researcher of Chemical Analysis Department, ufa.lab@yandex.ru, <https://orcid.org/0000-0003-2042-8162>.

mium exhibit pronounced toxicity even at minimal concentrations and do not participate in the physiological processes of the body. Despite the fact that arsenic is a very strong poison in high doses, some studies indicate its potential role in metabolism at minimal concentrations [7].

Purpose of the work: Assessment of the health risk to the population of the city of Ufa associated with chemical contamination of food products with heavy metals.

Materials and methods.

The calculation of the risks to public health due to oral intake of heavy metals from food products was carried out in accordance with the "Guidelines for assessing the risk to public health from exposure to chemicals that pollute the environment" (R 2.1.10.3968-23). The average daily dose was calculated using the formula

$$LADD = [C \times CR \times ED \times EF] / [BW \times AT \times 365], (1)$$

where: LADD – average daily dose, mg/(kg×day); C – concentration of the substance in the polluted environment, mg/

estimated dose of a pollutant to its safe exposure level, has been determined for cadmium, arsenic, mercury, nickel, zinc and copper. For substances with a similar toxicity mechanism, hazard indices (HI) have been calculated, quantitatively characterizing the combined effect on critical target organs.

Food products that form the basis of the diet of the population of the city of Ufa were divided into the following categories: meat and meat products, bread and bakery products, milk and dairy products, vegetables, potatoes, eggs, fish and fish products, fruits, vegetable oil and other fats, sugar and confectionery. Quantitative analysis of the content of elements (Pb, Cd, As, Hg, Ni, Zn, Cu) was performed in the chemical analysis department of the Testing Center of the Federal Budgetary Scientific Institution "Ufa Research Institute of Occupational Medicine and Human Ecology" (unique accreditation record number in the register of accredited persons ROSS RU.0001.510411) using the atomic absorption method with flame and graphite atomization on Varian AA spectrophotom-

eters models 240FS and 240Z (Australia). Sample preparation was carried out using the Speedwave Xpert microwave system (Germany). A total of 3250 food samples were analyzed.

Data on actual food consumption were collected using a food diary method, where respondents recorded their entire diet for 10 days. The research sample (n=286) was formed from among adult urban residents who met the following criteria: satisfactory self-assessment of health, absence of chronic pathology, moderate alcohol consumption, absence of nicotine addiction and professional contact with heavy metals.

The study data were statistically analyzed using Microsoft Excel 2016 and Statistica (version 21.0) software. The study results were processed using standard methods of descriptive statistics, in particular, the calculation of mean values with standard deviations.

Results and discussion. An assessment of the content of elements in the main groups of food products showed a predominant accumulation of nickel in dairy products; arsenic in fruit and vege-

Table 1

Metal content in food products for exposure calculation, mg/kg

Food group	lead	cadmium	arsenic	mercury	copper	zinc	nickel
Meat and meat products	0.124±0.093	0.04±0.03	0.0028±0.0006	0.0029±0.0003	1.34±0.27	18.44±3.96	0.07±0.02
Bread and bakery products	0.066±0.010	0.010±0.001	0.0051±0.0004	0.0004±0.0001	1.91±0.36	14.01±2.11	0.33±0.02
Milk and dairy products	0.072±0.019	0.025±0.013	0.0010±0.0001	0.00004±0.00001	0.19±0.06	3.43±0.74	0.98±0.24
Vegetables	0.013±0.009	0.022±0.002	0.0091±0.0010	0.0006±0.0002	1.13±0.15	4.07±1.49	0.97±0.19
Potato	0.174±0.080	0.012±0.002	0.0089±0.0002	0.0006±0.0001	1.26±0.06	3.53±0.44	0.81±0.26
Eggs	0.091±0.030	0.007±0.002	0.0006±0.0004	0.0010±0.0007	0.38±0.03	8.48±1.36	0.12±0.06
Fish and fish products	0.024±0.009	0.012±0.004	0.0090±0.0023	0.0044±0.0010	0.96±0.19	2.72±0.33	0.89±0.20
Fruits	0.088±0.019	0.016±0.005	0.0069±0.0014	0.0024±0.0008	0.41±0.09	0.38±0.08	0.38±0.04
Vegetable oil and other fats	0.075±0.015	0.014±0.005	0.0001±0.0001	0.0060 ±0.0020	0.07±0.03	0.45±0.12	0.39±0.10
Sugar and confectionery	0.102±0.024	0.007±0.002	0.0041±0.0007	0.0006±0.0001	1.55±0.19	4.09±0.76	0.15±0.06

kg; CR – food intake, kg/day; ED – exposure duration, years (ED=30 years); EF – exposure frequency, days/year (EF=365 days per year); BW – human body weight, kg (BW=70 kg); AT – exposure averaging period (for chronic non-carcinogenic effects AT = 30 years, for carcinogens AT =70 years); 365 – number of days per year.

Individual carcinogenic risk (CR) was estimated for cadmium, arsenic and lead by multiplying the values of the average daily lifetime dose, the slope factor and the malignancy severity coefficient. A hazard quotient (HQ) for non-carcinogenic effects, which is the ratio of the

Table 2

Среднедушевое потребление пищевых продуктов жителями г. Уфы

Food group Products	Food consumption, kg/day
Meat and meat products	0.177
Bread and bakery products	0.280
Milk and dairy products	0.485
Vegetables	0.175
Potato	0.126
Eggs	0.017
Fish and fish products	0.035
Fruits	0.155
Vegetable oil and other fats	0.050
Sugar and confectionery	0.077

table products; lead in potatoes and meat products, copper in bread and bakery products, cadmium and zinc in meat and meat products, and mercury in fish products (Table 1).

A study of the average per capita consumption of food products by the population of Ufa showed a high level of consumption of milk and dairy products (31% of the total daily intake), bread and bakery products (18%), meat and meat products (12%), and fruit and vegetable products (11%) (Table 2).

The distribution of the studied food groups by the level of contribution to the exposure to metals revealed that the maximum dose load of cadmium, lead, nickel and copper is contributed by milk and dairy products (Table 3). Similar studies have identified areas with elevated levels of exposure to toxic elements. In particular, for certain areas of the Orenburg and Saratov regions, maximum values of the contribution of milk and dairy products to the total dose load of lead and cadmium have also been recorded [4, 8]. In terms of arsenic exposure, priority products are vegetables, and in terms of mercury exposure, meat and meat products. In terms of zinc accumulation, bread and bakery products occupy a leading position.

A quantitative assessment of non-carcinogenic risk, carried out using the method of calculating hazard coefficients (HQ), revealed that for the health of the population of Ufa, exposed to oral exposure to heavy metals with food products, arsenic ($HQ = 1,143$) represents the greatest potential hazard in comparison with other studied elements (Table 4).

An analysis of the health risk of the population for critical organs and systems revealed that the following are at the greatest risk of developing negative effects: the nervous system and human development (the risk index for the development of non-carcinogenic effects $HI = 1,158$), the cardiovascular system, respiratory organs, and skin ($HI = 1,143$). This level of risk is considered acceptable and is associated with the intake of arsenic and mercury with food. Despite the acceptable level of risk, constant monitoring of the content of these elements in food products is required due to the cumulative effect and latency of manifestations (symptoms may appear after 5-15 years). Particular attention should be paid to protecting the health of pregnant women and children, since exposure to toxicants during this critical period can cause persistent, irreversible neurodevelopmental disorders. For the immune system, gastrointestinal tract, kidneys and blood, the

Table 3

Contribution of major foods to total heavy metal exposure, %

Food group Products	Химический элемент						
	Pb	Cd	As	Hg	Ni	Zn	Cu
Meat and meat products	17.26	22.4	7.77	29.38	1.17	30.67	1.17
Bread and bakery products	14.53	8.86	21.63	5.91	9.48	36.86	9.48
Milk and dairy products	27.46	38.37	3.67	1.08	48.78	15.63	48.78
Vegetables	1.79	12.18	23.86	6.44	17.45	6.69	17.45
Potato	17.24	4.78	16.99	4.48	10.46	4.18	10.46
Eggs	1.22	0.38	0.15	1.01	0.21	1.35	0.21
Fish and fish products	0.66	1.33	4.88	9.13	3.21	0.89	3.21
Fruits	10.72	7.85	16.20	22.05	6.05	0.56	6.05
Vegetable oil and other fats	2.95	2.14	0.007	17.78	2.00	0.21	2.00
Sugar and confectionery	6.17	1.71	4.78	2.74	1.19	2.96	1.19

Table 4

Assessment of the hazard coefficient for the development of non-carcinogenic effects on critical organs/systems

Chemical element	Average daily exposure, mg/kg	Safe exposure level of the substance, mg/kg	Hazard factor	Critical organs and systems
Cd	$1.94 \cdot 10^{-5}$	0.0005	0.038	kidneys
As	$4.04 \cdot 10^{-6}$	0.0000035	1.143	development, cardiovascular system, nervous system, respiratory system, skin
Hg	$2.41 \cdot 10^{-6}$	0.00016	0.015	nervous system, development, kidneys
Ni	0.0014	0.02	0.070	systemic
Zn	0.0152	0.3	0.051	immune system, blood
Cu	0.0021	0.04	0.052	Gastrointestinal tract

Table 5

Individual carcinogenic risks from oral intake of heavy metals

Heavy metal	Average daily exposure, mg/(kg·day)	Slope factor (mg/kg·day) ⁻¹	Carcinogenic risk	Level of carcinogenic risk
As	$4.04 \cdot 10^{-6}$	1.5	$6.00 \cdot 10^{-6}$	Acceptable
Pb	$7.79 \cdot 10^{-5}$	0.0085	$6.63 \cdot 10^{-7}$	Minimum
Cd	$1.94 \cdot 10^{-5}$	0.38	$7.22 \cdot 10^{-6}$	Acceptable
Total carcinogenic risk			$1.39 \cdot 10^{-5}$	Acceptable

risk level is minimal ($HI = 0,051 - 0,070$).

A comparative analysis revealed a high consistency of the results with the data of modern studies on the assessment of risks of heavy metals in industrial regions of Russia. The dominant role of arsenic as a priority pollutant in the Orenburg, Arkhangelsk, and Samara regions was revealed [2, 4, 13]. The HQ values for arsenic (our data: 1,143; Orenburg re-

gion: up to 1,8; Arkhangelsk region: 0,9–1,2, Samara region: 1,9) indicate that the threshold is exceeded in industrial zones, with uniform conclusions about critical target systems (nervous, cardiovascular system, skin, respiration).

Individual cancer risk, which refers to the probability of developing a malignant tumor during a person's lifetime, was calculated for the following elements:

arsenic, cadmium, and lead. Cancer risk was estimated based on average daily exposure data and slope factors (Table 5). The slope factor (SF), also known as the carcinogenic potency factor, is a key parameter used to quantify carcinogenic risk. The severity factor value was taken to be 1.

The permissible level of carcinogenic risk is formed due to the content of cadmium and arsenic in food products, which is consistent with the results of tests conducted in the Samara and Saratov regions [2, 8]. The minimum risk was recorded from the intake of lead. The overall risk level from all the metals studied is considered permissible (acceptable) for the population.

Conclusion. Thus, the assessment of potential harm to the health of the population of Ufa revealed the presence of both non-carcinogenic and carcinogenic risks associated with the consumption of food products. A priority non-carcinogenic risk from arsenic ($HQ=1,143$) was identified, chronic exposure to which is associated with damage to the nervous and cardiovascular systems and skin pathology ($HI=1,143-1,158$). An acceptable total carcinogenic risk ($\Sigma CR=1,39 \times 10^{-5}$) was established with the dominance of cadmium (52%) and arsenic (43%).

The obtained data emphasize the need to develop a differentiated approach to quality control of food products, taking into account the specifics of the accumulation of heavy metals in various food products, average per capita consumption, and the characteristics of the toxicological effects of individual elements.

The results of the study create a basis for improving the food safety monitoring system and developing preventive measures aimed at reducing health risks for the population of industrial cities. Of particular importance is taking into account regional characteristics, both in the structure of nutrition and in the nature of food contamination.

In the future, it is also planned to study the health risk of the city's children's population from oral intake of heavy metals with food products, study the seasonal dynamics of food contamination, and conduct biomonitoring of the population

to identify the accumulation of heavy metals in the human body.

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TOPICAL ISSUE

A.A. Tappakhov, N.N. Syromyatnikov, M.V. Yakovleva,
M.V. Yakovleva

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DEMENTIA THROUGH THE EYES OF SOCIETY: KNOWLEDGE, FEAR AND STIGMA PERCEIVED BY RESIDENTS OF YAKUTIA

Objective of the study: The study is devoted to studying the level of awareness of residents of the Republic of Sakha (Yakutia) about dementia.

Materials and methods of the study: As part of the Yakutia DeMind Project, anonymous online survey of 328 residents of Yakutia (81.7% women, 18.3% men) was conducted using Google Forms. The questionnaire included three sections: sociodemographic data, awareness of dementia and its social perception. Statistical analysis was performed in IBM SPSS Statistics 22.0.

Results: The findings revealed that 68% of respondents were able to distinguish between dementia and Alzheimer's disease, while 18.9% considered them synonymous. Additionally, 60% of participants acknowledged that dementia can occur at any age. The most frequently cited risk factors included traumatic brain injury (69.5%), low cognitive activity (68.3%), and heredity (67.7%). Particular attention was drawn to the level of stigmatization: 46% of respondents stated they would conceal their own dementia diagnosis, indicating a high level of self-stigmatization. A comparison between medical professionals (n = 174) and non-medical professionals (n = 154) showed significantly higher awareness among the first (72.4% believed in the possibility of prevention vs. 51.3%). However, even among medical professionals, 13.8% mistakenly regarded dementia as a natural part of aging.

Conclusion: The data highlight the high social relevance of dementia, not only as a clinical condition but also as one that elicits emotional and behavioral responses within society. These findings can serve as a foundation for developing research methodologies aimed at investigating dementia-related stigma, involving both individuals with dementia and their caregivers.

Keywords: dementia, Alzheimer's disease, stigma, awareness

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Introduction. Dementia is one of the most relevant and rapidly growing public health challenges [13, 15]. According to the Global Burden of Disease Study, in 2019 there were 57.4 million people living with dementia worldwide; this number is projected to rise to 152.8 million by 2050 [12]. Over the past five years, the problem of cognitive impairment has become even more pressing due to the COVID-19

pandemic and the ability of the virus to exert a neurotropic effect [7, 16]. In the Republic of Sakha (Yakutia), over 4,000 patients with Alzheimer's disease are expected in the coming decades, against the backdrop of a high rate of underdiagnosis [1].

As reported by the Lancet Commission 2024, nearly half of dementia cases could potentially be prevented by addressing 14 modifiable risk factors, including hearing loss, hypertension, depression, physical inactivity, obesity, social isolation, air pollution, and elevated cholesterol levels etc. Effective prevention requires both individual lifestyle changes and governmental support, particularly aimed at socially vulnerable groups of population [11]. The social significance of cognitive impairment was also demonstrated in the domestic study "Eucalyptus", according to the results of which the risk increases in those living alone, those living in nursing homes, and widows and widowers [8].

At the same time, stigma surrounding dementia remains a major barrier: up to 36% of patients conceal their diagnosis, and two-thirds experience discrimination [10]. One of the key reasons of such attitude is a low level of public awareness, which exacerbates social isolation among affected individuals [3].

Given the aging population and the increasing prevalence of dementia, assessing public awareness is of critical importance. Lack of knowledge about risk factors, common misconception about transmissible character of the disease, and an underestimation of the social impact of dementia may contribute to stigmatization and delays in seeking medical care. Accordingly, the present study aims to assess the level of awareness among residents of the Republic of Sakha (Yakutia) regarding dementia, its causes, associated risks, and public perceptions of the condition.

Materials and Methods. This study was conducted as part of the *Yakutia DeMind Project*, which aims to assess public awareness of dementia. The research employed an anonymous online survey distributed via Google Forms. Data collection took place from March 30 to May 7, 2025. The survey link was disseminated through social media platforms, including messaging apps, regional community networks, and thematic groups, enabling broad participation from residents of the Republic of Sakha (Yakutia) across various age and social demographics. Participation in the survey was entirely voluntary.

The questionnaire consisted of three

TAPPAKHOV Alexey Alekseevich – Candidate of Medical Sciences, Associate Professor of the Department of Neurology and Psychiatry of the Medical Institute of M.K. Ammosov North-Eastern Federal University, senior researcher of the Center of Neurodegenerative Diseases of FSBIS Yakut Science Center of Complex Medical Problems, ORCID: 0000-0002-4159-500X, dralex89@mail.ru; **SYROMYATNIKOV Nikolay Nikolaevich** – M.Sc., neurologist of the Center of neurodegenerative diseases of the Yakut Science Center of Complex Medical Problems, ORCID: 0009-0000-0817-7773, nicholasfrma@yandex.ru; **YAKOVLEVA Marina Vasilyevna** – student of the 6th year of the Medical Institute of M.K. Ammosov North-Eastern Federal University, dydujfff@gmail.com; **YAKOVLEVA Maria Vladimirovna** – senior researcher. Center of Neurodegenerative Diseases FSBIS Yakut Science Center of Complex Medical Problems, head. department of the State Unitary Enterprise of the Republic of Sakha (Yakutia) Yakutsk Republican Psychoneurological Dispensary, ORCID: 0000-0003-0113-6498, jacob83@inbox.ru.

sections: 1) sociodemographic information (age, employment status, income); 2) knowledge of dementia (symptoms, risk factors, prevention); 3) Social perception (attitudes toward people with dementia, stigma, personal experience, and comparisons with other illnesses). The average time required to complete the survey was approximately 10 minutes.

A total of 328 individuals participated in the survey (18.3% male and 81.7% female). Most respondents were between 31 and 60 years old (30.8%) and resided in Yakutsk (76.8%). Higher education was reported by 65.5% of participants, and 5.5% held an academic degree. A detailed breakdown of respondents description is presented in Table 1.

Statistical Analysis. Data were analyzed using IBM SPSS Statistics version 22.0. Descriptive statistics included frequencies and percentages for categorical variables. Group comparisons of categorical data were performed using Pearson's chi-square test (χ^2). When the expected cell frequencies were less than 5 in more than 20% of the contingency table cells, Fisher's exact test was applied. Differences were considered statistically significant at a p-value of less than 0.05.

Results. The majority of participants (68.0%) were able to distinguish dementia from Alzheimer's disease, while 18.9% considered them synonymous, and 13.1% were unsure, which indicates the prevalence of incomplete or distorted perceptions.

A total of 74.5% of respondents identified memory decline as the primary symptom, whereas 12.5% believed it was not necessarily present. Approximately 60% were aware that dementia can develop at any age, while 39.9% perceived it solely as a disease of the elderly.

Most respondents ($n = 205$; 62.5%) believed that dementia can be prevented. Personal experience with the disease was also notable: 22.6% reported having someone with dementia in their immediate environment, and additional 17.7% suspected that someone they knew might be affected.

Responses regarding stigma were mixed. If a close relative were diagnosed with dementia, only 8.2% of participants would choose to conceal it from others, while 46.0% would prefer to keep their own diagnosis secret. This suggests a persistent level of self-stigmatization. 55.5% of respondents did not consider individuals with dementia to be dangerous, and 61.9% would not dismiss them from employment if their work capacity remained intact.

Most participants (64.3%) believed

Table 1

Respondents description

Feature	Male	Abs. (%)
Gender	Female	60 (18.3%)
	18-30 y.o.	268 (81.7%)
Age group	31-45 y.o.	76 (23.2%)
	46-60 y.o.	101 (30.8%)
	Over 60 y.o.	95 (29%)
	Yakutsk	56 (17.1%)
	Central districts	252 (76.8%)
Location	Western districts	55 (16.8%)
	Eastern districts	17 (5.2%)
	Arctic districts	4 (1.2%)
	Academic degree	0
Education	Higher education	18 (5.5%)
	Associate degree	215 (65.5%)
	Secondary education	67 (20.4%)
	Incomplete secondary education	27 (8.2%)
	High	1 (0.3%)
Income level	Average	9 (2.7%)
	Low	198 (60.4%)
	Undecided	97 (29.6%)
	Primarily intellectual work	24 (7.3%)
Occupation	Primarily physical work	170 (51.8%)
	Student	54 (16.5%)
	Pensioner	53 (16.2%)
	Unemployed	46 (14%)
	Безработный	5 (1.5%)

Table 2

Comparison of dementia awareness and perceptions between medical and non-medical respondents (only statistically significant differences shown)

	MPG (n = 174)	NMPG (n = 154)	Statistical values
Dementia is a brain disease or a natural part of aging			
- Brain disease	148 (85.1%)	126 (81.8%)	χ
- Natural aging	24 (13.8%)	16 (10.4%)	
- Undecided	2 (1.1%)	12 (7.8%)	
Dementia and Alzheimer's disease are:			
- Synonymous	26 (14.9%)	36 (23.4%)	χ
- Different conditions	137 (78.7%)	86 (55.8%)	
- Undecided	11 (6.3%)	32 (20.8%)	
Dementia is always accompanied by memory decline			
- Yes	134 (77.0%)	111 (72.1%)	χ
- No	26 (14.9%)	15 (9.7%)	
- Undecided	14 (8.0%)	28 (18.2%)	
Dementia occurs only in old age			
- Yes	56 (32.2%)	75 (48.7%)	χ
- No	118 (67.8%)	79 (51.3%)	
Dementia can be prevented			
- Yes	126 (72.4%)	79 (51.3%)	χ
- No	19 (10.9%)	25 (16.2%)	
- Undecided	29 (16.7%)	50 (32.5%)	
People with dementia should be treated in specialized institutions			
- Yes	44 (25.3%)	21 (13.6%)	χ
- No	104 (59.8%)	107 (69.5%)	
- Undecided	26 (14.9%)	26 (16.9%)	

Abbreviations: MPG – Medical Professionals Group; NMPG – Non-Medical Professionals Group.

that people with dementia should live at home with family members, whereas 19.8% preferred specialized care institutions.

Nearly all respondents (88.4%) agreed that early diagnosis of dementia can slow the disease progression.

When asked about perceptions of serious illnesses, cancer emerged as the most feared condition (41.8%), followed by dementia (28.4%), stroke (25.9%), and myocardial infarction (4.0%). These findings highlight the strong emotional response to neurodegenerative conditions, comparable to that elicited by cancer.

To analyze differences in awareness and perceptions of dementia, respondents were divided into two groups: medical professionals (MPG) and non-medical professionals (NMPG). NMPG participants were more likely to view dementia as a natural part of aging (7.8% vs. 1.1%) and were more often unsure about its distinction from Alzheimer's disease (20.8% vs. 6.3%). However, 13.8% of medical professionals also mistakenly regarded dementia as a normal aspect of aging.

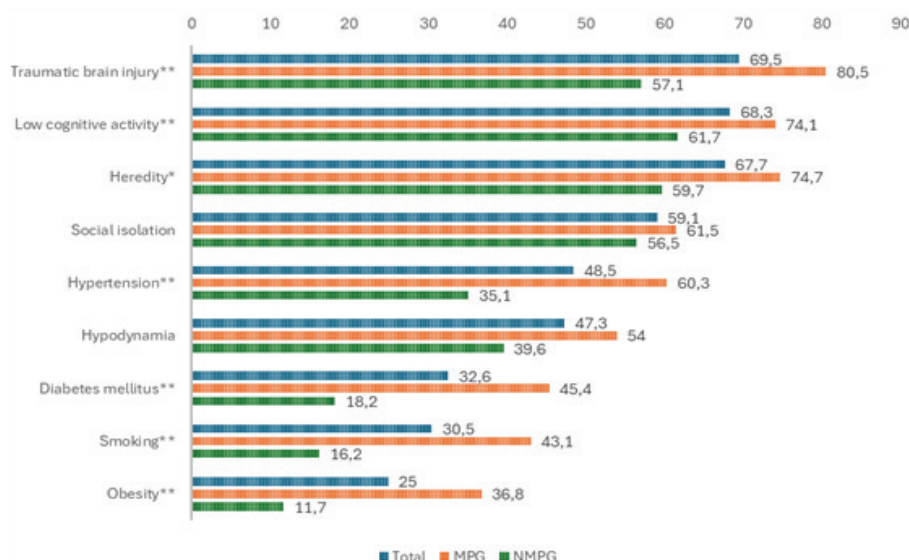
MPG respondents were more optimistic about the possibility of prevention (72.4% vs. 51.3%) and more supportive of institutional care (25.3% vs. 13.6%).

A more detailed comparison is presented in Table 2.

Respondents with medical education placed greater emphasis on modifiable risk factors for dementia, which may be attributed to their professional knowledge (Fig. 1).

Discussion. The findings indicate that the population of Yakutia possesses a basic level of knowledge about dementia; however, significant gaps remain in understanding the nature of the disease, its symptoms, age-related features, and prevention strategies. Comparison between groups revealed that respondents with medical education more frequently provided accurate answers. Nevertheless, misconceptions persisted even among them—13.8% considered dementia to be a natural part of aging. This highlights the need to improve medical education. Importantly, the level of awareness observed in this study was substantially higher than that reported in international studies. According to the World Alzheimer Report 2024, 74% of medical professionals in low- and middle-income countries believe that dementia is part of normal aging [10].

Medical professionals were more likely to acknowledge the potential for dementia prevention (72.4% vs. 51.3%), which aligns with their knowledge of modifiable risk factors. They also more frequently



Dementia risk factors according to respondents MPG – Medical Professionals Group; NMPG – Non-Medical Professionals Group. * – statistically significant difference ($p < 0.01$); ** – statistically significant difference ($p < 0.001$)

avored care in specialized institutions, likely reflecting their understanding of the complexity of behavioral symptoms associated with dementia. This is consistent with the 2021 VCIOM (Russian Public Opinion Research Center) survey, in which most respondents expressed a preference for home care, although actual caregiving strategies may shift in real-life situations [4].

The non-medical group showed a higher level of uncertainty, underscoring the need for expanded public education efforts. Of particular concern is the high level of self-stigmatization: 46% of participants reported they would prefer to conceal a dementia diagnosis if it applied to themselves. This attitude was also observed among medical professionals, suggesting the depth of the issue. Studies from other countries have shown that stigma levels are influenced by gender, age, educational background, and language [14]. In the Russian Federation, several authors have reported that stigma creates barriers to accessing care, and propose revising terminology and focusing on social inclusion [3, 5, 6].

Finally, dementia is perceived as one of the most frightening diseases after cancer. This emotional perception may serve as a potential motivator for preventive behaviors and participation in cognitive screening. Of course, the issues of diagnostics, treatment and prevention of dementia and Alzheimer's disease in the 21st century will be addressed in a comprehensive manner using not only clinical data, but also taking into account genetics, epigenetics, and artificial intelligence

[9]. New application points for anti-dementia therapy are already known today [2, 17]. All this should radically change the social attitude towards dementia in the future.

Conclusion. The level of public awareness about dementia in the Republic of Sakha (Yakutia) remains insufficient, particularly in terms of symptoms, causes, and distinctions from Alzheimer's disease. This calls for the expansion of programs for raising awareness. Stigmatization of dementia is high across all groups, especially regarding one's own diagnosis, which may hinder early help-seeking behavior.

These findings underscore the significant social relevance of dementia—not only as a clinical condition but also as one that carries emotional and behavioral implications in societal perception. The results may serve as a foundation for developing methodologies to study stigma involving people living with dementia and their families.

The authors declare no conflict of interest.

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SCIENTIFIC REVIEWS

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I.Sh. Kurbanaliev, M.V. Jalilov, A.A. Genzheeva,
A.M. Magaramov

PROGNOSTIC BIOMARKERS OF RECOVERY FROM TRAUMATIC BRAIN INJURY: ASSESSMENT OF EFFECTIVENESS AND PROSPECTS OF APPLICATION

Relevance. Traumatic brain injury is one of the leading causes of disability and mortality worldwide. Despite significant progress in treatment strategies, diagnosis and prediction of outcomes remain challenging. Biomarkers such as proteins, metabolites, and other biological molecules found in biological fluids are a valuable tool that can improve understanding of the pathophysiological processes in TBI and contribute to the development of promising therapeutic approaches. Materials and methods. A systematic literature search was conducted in the Web of Science, Scopus, PubMed (MEDLINE), and eLibrary databases.RU and Cochrane Database of Systematic Reviews, focusing on studies containing data on biomarkers associated with recovery from TBI. The entire cycle of search, selection and analysis of publications followed the principles of the PRISMA methodology. As a result, 57 studies meeting the established criteria were included in the analysis out of 4002 initial publications, after duplicates were removed and irrelevant articles were excluded. Results. Studies demonstrate that biomarkers such as GFAP, S-100b, UCH-L1, and others can significantly improve the diagnosis and prediction of outcomes in patients with TBI. They not only reflect the degree of damage to neurons, but also help to distinguish the stages of injury, as well as predict long-term neurological consequences. Conclusions. The results of the systematic review show that biomarkers have significant potential for clinical application, but further standardization of technologies for their detection and analysis is required. The development of new platforms, such as POC systems using electrochemical biosensors, can provide fast and reliable diagnosis at all stages of TBI treatment. For further in-depth study, it is necessary to combine the efforts of the interdisciplinary research community, which will create personalized treatment strategies and improve long-term outcomes for patients.

KURBANALIEV Ismail Shamilevich – student, Dagestan State Medical University, bob_bn@bk.ru, ORCID: 0009-0002-8666-2525; **JALILOV Magamedali Valentinovich** – student, Dagestan State Medical University, magomedbroo@mail.ru, ORCID: 0009-0001-4704-0777 - **GENZHEEVA Amina Alievna** – student, Dagestan State Medical University, Amina.genjeeva@mail.ru, ORCID: 0009-0003-9909-2987; **MAGARAMOV Abdulla Magaramovich** – assistant of the Department of Traumatology, Orthopedics and Agricultural Sciences, head of the educational part, Dagestan State Medical University, abdulla-magaramov@yandex.ru, ORCID: 0009-0005-3150-9664

Keywords: traumatic brain injury, biomarkers of recovery, prognostic biomarkers, diagnosis

of TBI, extracellular vesicles, GFAP, neuroinflammation, S-100b, UCH-L1, recovery from injury, systematic review, proteomic methods, personalized treatment, diagnostic strategies, prognostic models.

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Introduction. Traumatic brain injury (TBI) is a serious public health problem affecting about 69 million people annually worldwide [52]. The success of TBI treatment depends on the effectiveness of trauma care systems and emergency medicine services, which includes rapid diagnosis and surgical interventions [28]. International research supported by the World Health Organization points to TBI as the main cause of neurosurgery, especially in low- and middle-income countries.

Computed tomography (CT) is important for the early diagnosis of primary brain damage, but its limitations in detecting secondary damage and assessing cellular responses create the need for additional examination methods [2]. Advanced neuromonitoring systems are often used to assess secondary changes such as intracranial pressure and cerebral perfusion. Brain tissue damage may also be associated with deficiencies in the organization of medical care, which exacerbates secondary injury [4].

In recent years, biomarkers have been actively researched that can track the progression of damage and predict the degree of brain damage even before they are visualized using traditional methods [5]. Biomarkers are able to detect early cellular, biochemical, and molecular changes, which allows for improved diagnosis and monitoring of TBI treatment. These molecules can detect changes in the microvascular system that are not available for standard imaging techniques [1].

The integration of biomarkers with clinical examinations and imaging techniques helps doctors accurately assess the severity of injury and predict outcomes. The development of reliable biomarkers is important for early diagnosis of TBI, which allows for timely treatment, especially in low-income countries, where up to 25% of patients do not receive adequate medical care in the early stages [6].

The aim of the research is to systematically evaluate current data on prognostic biomarkers associated with TBI recovery in order to improve diagnosis, prognosis, and develop new treatment approaches.

Materials and methods. For a systematic review of prognostic biomarkers of recovery in TBI, a literature search

was conducted in the database: Web of Science, Scopus, PubMed (MEDLINE), eLibrary.RU and Cochrane Database of Systematic Reviews. Keywords relevant to the subject of the study were used, including: "biomarkers of recovery", "traumatic brain injury", "prognosis of the disease" and "recovery after TBI".

As a result of the search, 4002 publications were found. After removing 1,702 duplicates, 2,300 potentially relevant research papers remained. The study of headlines and annotations led to the exclusion of 2,000 articles that did not meet the inclusion criteria. The full texts of the 300 remaining articles were studied in more detail, and the final analysis included 57 studies that meet the criteria of quality and relevance to the research topic. The PRISMA block diagram is shown in the figure (Fig.1).

Inclusion and exclusion criteria: To be included in the analysis, the study had to provide data on biomarkers associated with recovery from TBI, be published in English or Russian, and demonstrate the results of human research. Articles that were reviews without original data, as well as studies that did not fully describe aspects related to TBI, were excluded.

This approach provided a comprehensive overview of current scientific evidence regarding predictive biomarkers that contribute to understanding recovery mechanisms and potential treatment strategies for TBI.

In the table (table.1) All demographic and technical data are listed. Among the 57 selected studies, both randomized controlled trials, meta-analyses, and systematic reviews were reviewed. Special attention was paid to the quality of the methodology and the approaches used in the research.

The obtained results allowed us to draw reasonable conclusions about the influence of the studied factors, as well as to identify areas requiring further research.

Results. The analysis of the conducted studies highlights the importance of biomarkers in clinical practice for the diagnosis and prediction of TBI. Modern biomarkers such as GFAP, S-100b and UCH-L1 demonstrate high efficiency in determining the extent of brain damage and predicting treatment outcomes,

which strengthens their role in medical practice since their identification in the 1950s. Since then, biomarkers have attracted the attention of researchers, and published reviews agree on the need to further explore their capabilities [11, 38].

For the clinical significance of biomarkers, it is important to understand their interpretation.

Each biomarker, whether physical or biological, serves as a surrogate indicator reflecting the patient's well-being, functionality, or survival [12]. An ideal TBI biomarker should accurately reflect the degree of neuronal damage, have a linear relationship with brain function, and predict the outcome of the disease. Prostate-specific antigen (PSA) is an example of successful biomarker use, and similar approaches can improve TBI diagnosis and treatment monitoring [22].

In 1983, Bakay and Ward developed ideal characteristics for TBI biomarkers, but at the moment no biomarker has been found that meets all the criteria. Research shows that it may be more important to use a combination of different biomarkers to improve diagnostic accuracy. For example, lactate dehydrogenase (LDH), first described in 1965, demonstrates changes in TBI levels, but previously expressed doubts about its specificity and sensitivity make interpretation difficult [52, 37, 43].

An analysis of the "methodological shortcomings" of research in the 1970s showed that the use of biomarkers for the diagnosis of TBI requires more rigorous methods and validated scales, such as the Glasgow Coma Scale (GCS). This highlights the need for extensive and high-quality research to improve the clinical diagnosis and management of brain injuries.

Biomarkers of traumatic brain injury: features of manifestations. TBI varies in severity, including mild, moderate, and severe forms [20]. Mild TBI can occur due to bumps or sudden head movements, such as in an accident. While such injuries often do not cause visible brain damage, 15% of those affected may develop long-term cognitive impairments, despite the rapidly passing symptoms in most people [49].

The pathogenesis of TBI includes primary and secondary phases. Prima-

ry trauma is associated with mechanical damage to tissues, causing necrosis and deformation of brain cells [35]. The secondary phase is characterized by processes that exacerbate the effect of primary damage: disruption of the integrity of the blood-brain barrier, triggering inflammatory processes and protein degradation [42]. These changes lead to an imbalance in the blood supply to the brain, hypoxia, decreased mitochondrial functionality and metabolic disorders, and further deterioration of the brain [47].

For effective use of biomarkers in the diagnosis of TBI, they must appear after injury and be easily detectable in biological fluids [40]. The concentration of biomarkers should differ among the victims and correlate with the severity of the injury, consistent with data from methods such as the Glasgow Coma Scale, computed tomography and MRI. Thus, biomarkers can help improve the diagnosis and treatment of TBI.

Glial fibrillar acidic protein. Glial fibrillar acid protein (GFAP) is an important marker of astrocyte damage, the level of which increases dramatically after TBI. GFAP is involved in the support and functioning of astroglia and, along with the fatty acid binding protein, has a significant impact on the diagnosis of TBI, showing sensitivity up to 100% [7, 15]. Interleukin-1 (IL-1), which acts as a mediator of inflammation, is also an important biomarker, especially its IL-1b form, the level of which increases critically during

injury, deepening damage due to the inflammatory cascade [24, 29].

TAU protein (MAPT) and neuron-specific enolase (NSE) also play an important role in the prediction and diagnosis of TBI. MAPT is involved in the maintenance of axonal structures, and its changes in the blood after TBI can serve as a predictor of injury [19]. NSE, released primarily due to cell death, directly indicates neuronal damage, but its level may also increase during hemolysis, which requires careful interpretation [43].

Phosphodiesterases and other markers, such as pro-inflammatory cytokines (for example, IL-1b and TNF- α), play a key role in the development of damage after TBI [15]. Indicators of axonal damage are also important, such as the calpain-cleaved III-spectrin N-terminal fragment, which signals violations in axonal integrity [29]. The development and use of these biomarkers continues to improve the diagnosis and treatment of TBI.

Creatine Kinase. There are three known creatine kinase isotypes, with brain creatine kinase (CK-BB) localized in astrocytes of the central nervous system (CNS). Although lower concentrations of CK-BB may be present in the abdominal organs, they are absent in red blood cells, which causes their physiologically low serum levels [11]. Studies have shown that the concentration of CK-BB in serum and cerebrospinal fluid increases after TBI, reaching a maximum in the acute phase of injury, and then

returning to normal values. There was also a significant increase in the level of CK-BB in the cerebrospinal fluid after hypoxic brain damage, for example, during cardiac arrest. One study revealed the possibility of CK-BB release due to brain hypoperfusion due to systemic trauma. Nevertheless, Ingebrigtsen and Romney concluded that CK-BB has low specificity and sensitivity for the diagnosis of TBI [7].

Biomarkers of inflammation in traumatic brain injury. TBI initiates a complex inflammatory process in the nervous tissue, accompanied by the release of cytokines that enhance the inflammatory response through cascading interactions with target cells [17, 27]. Inflammation plays a dual role: it is necessary for the regeneration and removal of damaged cells, but it can cause chronic damage with excessive activity. Understanding the balance between beneficial and harmful effects of inflammation is key to developing therapies that minimize adverse outcomes in patients with TBI [43].

Biomarkers such as cytokines provide insight into the processes activated after TBI. They regulate the immune response and promote recovery, classified into pro-inflammatory and anti-inflammatory. For example, IL-1, IL-12, and TNF- α stimulate inflammation, while IL-4 and IL-10 reduce it. Despite progress, gaps remain in understanding the relationship between cytokines and the long-term effects of TBI [15, 26].

The constant release of pro-inflammatory cytokines can lead to neurodegeneration, which makes microglia a source of neurotoxic substances such as TNF- α and nitric oxide [16]. Studies show differences in IL-1b levels in patients with acute TBI, emphasizing its role in the early inflammatory response, but the need for further investigation of chronic inflammation remains [26].

Extracellular vesicles and non-coding RNAs in traumatic brain injury. After TBI, secondary processes develop quickly and for a long time, such as excitotoxicity, free radical formation, and neuroinflammation, which cause significant damage to neurons and blood vessels [11]. Primary injury stimulates the release of DAMPs molecules, leading to an active immune response enhanced by microglial activation and the penetration of immune cells [48, 25, 21]. Extracellular vesicles (VNV) produced by CNS cells play a key role in neuroimmune interactions, participating in the regulation of neuroinflammation and intercellular communication [15].

TBI changes the amount and composition of VNV, which may contain specific neurotoxic proteins and microRNAs from

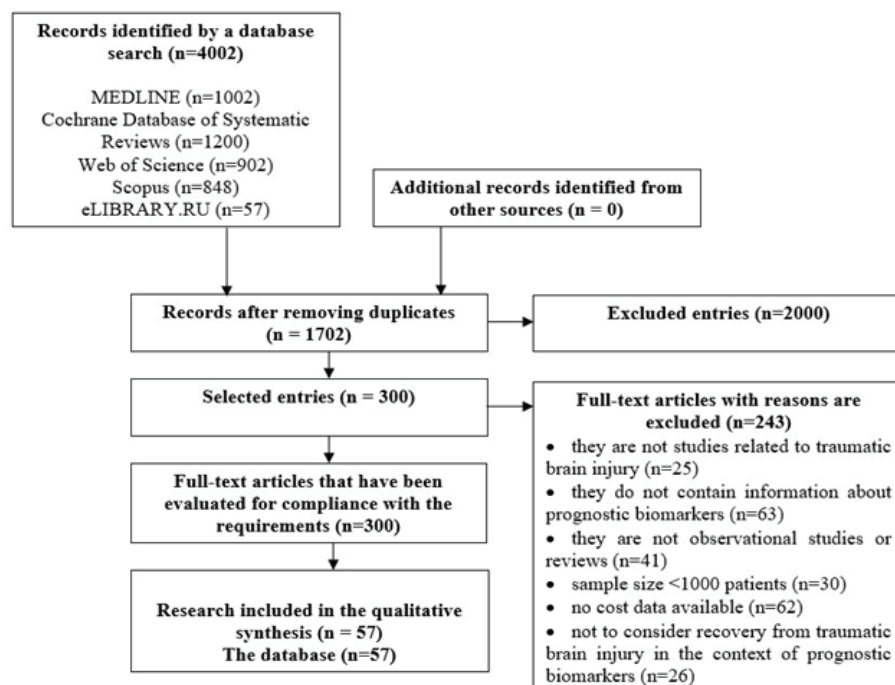


Table 1

**Demographic and technical information on studies on prognostic biomarkers of recovery from traumatic brain injury
(compiled by the authors)**

Reference	Country	Types of injuries	Note
Olczak M, Niderla-Bielinska J, Kwiatkowska M, et al. [48]	Poland	Traumatic brain injury	Postmortem evaluation; investigation of the possibilities of using tau protein as a biomarker
Manivannan S, Makwana M, Ahmed AI, et al. [36]	Great Britain	Traumatic brain injury	Profiling of biomarkers of axonal injury; a mouse-to-human study
Lewis LM, Schloemann DT, Papa L, et al. [56]	USA	Mild TBI	Analysis of serum biomarkers for diagnosis and stratification
Welch REM, Lewis L, Ayaz S, et al. [31]	USA	Traumatic brain injury	Concentrations of various biomarkers in serum are kinetically modeled
Hill-Pryor CWK, Papa L, Lopez M, et al. [50]	USA	Mild TBI	Assessment of the temporal course and diagnostic accuracy of glial and neuronal biomarkers
Mrozek S, Geeraerts T, Dumurgier J, et al. [13]	France	Acute TBI	Investigation of the interest and limitations of biomarkers in the context of acute brain injury
Bazarian J, Zemlan F, Mookerjee S, et al. [44]	USA	Mild TBI	Poor predictors of long-term outcomes for serum biomarkers S-100B and cleaved tau
Lööv C, Nadadthur A, Hillered L, et al. [25]	Sweden	Traumatic brain injury	Extracellular ezrin as a new biomarker for traumatic brain injury
Friedman A, Bar-Klein G, Serlin Y, et al. [46]	Israel	Traumatic brain injury	Investigation of the role of losartan after brain injury
Li J, Yu C, Sun Y, Li Y [45]	China	Traumatic brain injury	Systematic review and meta-analysis of biomarkers
Arun P, Abu-Taleb R, Oguntayo S, et al. [9]	USA	Explosion injury	The potential role of mitochondrial dysfunction after explosive effects
Alluri H, Wiggins-Dohlvik K, Davis ML, et al. [17]	USA	Traumatic brain injury	Dysfunction of the blood-brain barrier after TBI
Ramezani F, Bahrami-Amiri A, Babahajian A, et al. [53]	Iran	Traumatic brain injury	UCHL1 for predicting CT results in brain injury
Dewan MC, Rattani A, Gupta S, et al. [24]	Global assessment	Traumatic brain injury	Assessment of the global incidence of traumatic brain injury
Stenberg M, Koskinen LD, Jonasson P, et al. [21]	Finland	Severe TBI	CT and clinical outcomes in patients with severe traumatic brain injury

astrocytes, which highlights their potential as biomarkers [15]. The involvement of VNV in neuroinflammation is reinforced by their release by brain endothelial cells and microglia, as well as an increase in their concentration in serum and cerebrovascular blood after injury [7, 27, 33, 40, 49, 55]. VNV can carry injury-related molecules such as tau protein and β -amyloid, which is associated with unfavorable neurological outcomes in patients with mild TBI [25, 30].

Changes in the content of VNV in cerebrospinal fluid and peripheral blood open up possibilities for their use in the diagnosis and assessment of the severity of TBI. Protein changes and the expression of specific microRNAs in the VNV can serve as diagnostic tools for assessing the condition after injury [16].

Clinical significance of biomarkers. Neuroimaging is considered the preferred method for diagnosing intracranial injury after traumatic brain injury due to the lack of resources in medical institu-

tions. This stimulated research aimed at reducing the use of imaging in the diagnosis of brain injuries [23].

Several studies have been initiated in the field of neuroproteomics to establish a link between the levels of certain biomarkers in the blood and imaging data. If the indicators are below a certain threshold, this may reduce the use of medical resources. A recent multicenter study (ALERT-TBI) evaluated the usefulness of the GFAP and UCH-L1 proteins for predicting CT TBI in patients with such injuries. The results showed that the use of these proteins with existing criteria achieved 97% sensitivity and 99% specificity in detecting intracranial injuries [15].

Predicting outcomes using biomarkers. Biomarkers are usually used at an early stage of injury and during 6-12 months of disease development. Most studies have identified relationships that help predict patient outcomes. When the S-100b protein level in the blood is more than 0.7 ng/ml, an association with

mortality and functional outcomes is observed six months after injury according to the Glasgow outcome scale [15]. GFAP is also considered as a potential predictor of outcomes and mortality after six months. Evaluation of the UCH-L1 protein together with GFAP helps predict the condition of patients on the second day after injury.

The relationship between biomarkers and the need for surgery. Changes in the levels of various biomarkers in patients with TBI were studied to determine how much the severity of the injury is related to the need for surgery [54]. The study of the levels of GFAP and UCH-L1 biomarkers in combination with computed tomography data made it possible to identify patients who potentially require surgical treatment with 100% accuracy. In addition, the use of the S100b protein to predict the need for surgical intervention in patients turned out to be insufficiently sensitive (Table 2).

Table 2 contains information on the

Table 2

Sensitivity and specificity of key biomarkers in traumatic brain injury, as well as their threshold values in blood tests (compiled by the authors)

Biomarker	Sensitivity (%)	Specificity (%)	Concentration (ng/ml)
S-100b	100	46	0.1376
UCH-L1	100	38	0.05
GFAP	100	55	0.066

Note* GFAP = glial fibrillar acidic protein, S-100b = S-100 beta, TBI = traumatic brain injury, UCH-L1= ubiquitin C-terminal hydrolase-L1.

sensitivity and specificity of biomarkers S100b, UCH-L1 and GFAP in TBI, depending on their concentration in blood samples, as shown in numerous studies. In a study concerning the eS-100b biomarker, 46% specificity and 100% sensitivity were found at a threshold level of 0.1376 ng/ml in patients with mild TBI.

Regarding the prognostic value of UCH-L1, this biomarker showed a significant association with TBI during the first six hours after injury. However, despite this, a number of studies and meta-analysis of biomarker data still show some ambiguity in assessing the severity of damage, and its control values vary according to the results of different studies [39]. The GFAP biomarker, measured in blood at a threshold value of 0.066 ng/ml, demonstrates a specificity of 55% and sensitivity of 100% for detecting pathologies during computed tomography in patients with cranial fractures [10].

Future directions and recommendations. To increase the clinical effectiveness of inflammatory markers in the diagnosis of mild TBI, it is necessary to take into account the variability of research and analysis methods. Multicenter studies such as CENTER-TBI and TRACKING-TBI can improve statistical analysis by taking into account factors such as age and concomitant injuries. It remains important to distinguish neuroinflammation and systemic inflammation from extracranial injuries. [10, 11, 12, 21, 43].

Various strategies can be proposed to solve this problem, including the use of statistical correction, the analysis of inflammatory markers in extractable vesicles, the study of microRNAs, and the use of proteomics to identify unique biomarkers of neuroinflammation [26]. It is also promising to switch to rapid analysis (POC) platforms, which make it possible to quickly determine the concentration of markers at the scene using electrochemical biosensors, which may be useful for early assessment of TBI [18].

Mild TBI can increase the risk of neurodegenerative diseases if recovery is

insufficient, which is especially important for athletes and military personnel. Exosomal biomarkers can function as a "liquid biopsy," providing information about specific changes in the brain after injury and helping to study the long-term effects of TBI, including the risks of diseases such as Alzheimer's disease. [50, 44, 17, 19]. Expanding research in this area and creating an interdisciplinary community is the key to improving diagnosis, prevention, and long term treatment outcomes for patients with mild TBI.

Conclusion. A systematic review of prognostic biomarkers associated with recovery from TBI has shown their significant potential in improving diagnosis and predicting outcomes. Leading biomarkers such as glial fibrillar acid protein (GFAP), S-100b protein, and ubiquitin C-terminal hydrolase-L1 (UCH-L1) have demonstrated high sensitivity and specificity for assessing damage and clinical outcomes. Their use allows not only to diagnose the severity of TBI, but also to predict long-term outcomes and risks of complications. However, for a more accurate application of these biomarkers in clinical practice, standardization of methods for evaluating and interpreting data is necessary, which underscores the need for further research in this area.

The authors declare no conflict of interest.

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E.N. Suprun, S.V. Suprun, G.P. Evseeva, O.A. Lebedko

EXOGENOUS FACTORS INFLUENCING THE COURSE OF BRONCHIAL ASTHMA

This systematic literature review analyzes the environmental factors that affect the course of bronchial asthma. Based on 46 studies, a number of factors have been identified whose impact has been reliably confirmed, including sudden changes in daytime temperatures, vitamin D levels, micronutrient status, persistence of herpes-like viruses, and the specific sensitization spectrum of a particular region.

A comprehensive approach to the diagnosis, prevention, and treatment of bronchial asthma, taking these factors into account, will allow for personalized treatment of individual patients and improve its effectiveness.

Keywords: bronchial asthma, climate, vitamin D, viral infections, sensitization spectrum.

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Khabarovsk branch of the Federal State Budgetary Scientific Institution "Far Eastern Scientific Center for Physiology and Pathology of Respiration" - Research Institute for Maternal and Child Health: **SUPRUN Evgeny Nikolaevich** – Candidate of Medical Sciences, senior researcher, associate professor of the Far Eastern State University, evg-suprun@yandex.ru, orcid.org/0000-0002-1089-8884; **SUPRUN Stefania Viktorovna** – Doctor of Medical Sciences, Chief Science Officer, orcid.org/0000-0001-6724-3654; **EVSEEVA Galina Petrovna** – Doctor of Medical Sciences, Chief Science Officer, orcid.org/0000-0002-752-75; **LEBEDKO Olga Antonovna** – Doctor of Medical Sciences, Director, Head. lab., orcid.org/0000-0002-8855-7422

Introduction. Bronchial asthma (BA) is one of the most common chronic diseases of the respiratory system in both adults and children. In recent decades, there has been an increase in asthma, and by now its incidence has reached 15-18% among the world's child population [21]. Russia as a whole [4] and Khabarovsk Krai [7], in particular, are no exception to this trend. Atopic inflammation, which, as a rule, underlies the pathogenesis of asthma in children, is primarily due to innate factors, however, the probability and duration of their implementation, as well as the course of the disease itself, can be significantly modified by a variety of exogenous influences [10, 17, 29].

The purpose of this review is to analyze environmental factors in asthma, their clinical implementation, and the possibility of selecting a therapy algorithm based on them. Based on a review of the literature data from PubMed, ScienceDirect, Google Scholar, Research Gate, and eLibrary databases.RU for the period 1997-2025. 192 publications were analyzed as a result of a search for the following keywords: "climatic effects in bronchial asthma", "vitamin D in bronchial asthma", "trace elements in bronchial asthma", "viruses in bronchial asthma",

"spectrum of sensitization in bronchial asthma", 46 of them were selected for detailed study and included in this a job.

Climatic factors. The most common factor affecting the human body, including asthma, is climate, with its most obvious manifestation being the temperature difference, seasonal and diurnal. The study of the effect of temperatures in patients with asthma has a long history, including numerous meta-analyses on this problem. For example, one of them studied more than 2,000 articles related to this topic in childhood. Of the 2,633 papers, the authors considered only 23 to meet the criteria for inclusion and exclusion. Fourteen studies reported inverse relationships, which showed that as children's temperature decreased, the number of asthma attacks increased. Nine studies have shown a link between hot weather and asthma attacks. Three studies reported an association between temperature changes and asthma attacks, while two studies found no association. Some studies have shown that an increase in the incidence of asthma in the age group of 5-14 years is associated with the beginning of the school year and, probably, with the spread of viral diseases, rather than with changes in temperature. Based on this, the authors draw a fairly obvious conclusion – extreme temperatures and their fluctuations are likely to cause an exacerbation of asthma in a child [43]. Another meta-analysis presented 19 sources that met the inclusion criteria, 13 papers quantified the effect of absolute temperature on the course of asthma in children, and six papers studied the effect of intraday or inter-day temperature fluctuations. All patients lived in urban areas. There was a discrepancy in the significance of the relationship between absolute temperature and asthma attacks, as well as in the form of this relationship (i.e. linear or nonlinear) and whether there were delayed temperature effects. More and more evidence indicates a non-linear relationship between absolute temperature values and asthma exacerbations in children [41]. Despite this, research in this area continues. Thus, in recent years, Iranian scientists have shown that changes in weather conditions, high relative humidity and cold weather can trigger asthma attacks, especially in young children, while the level of dust and thunderstorms did not significantly affect the frequency of asthma exacerbations in childhood [27]. In Poland, the study and determination of the relationship between the frequency of asthma exacerbation and the state of the environment was carried out in accordance with the UTCI bio-

meteorological index (Universal Thermal Climate Index). At UTCI values in the 5th grade range, describing thermoneutral conditions, asthma exacerbations were observed with an average frequency. A decrease in the UTCI value led to a decrease in the number of asthma exacerbations, while an increase increased their number [33].

The fact that such studies continue, despite the abundance of information obtained as part of previous work, is primarily due to the uniqueness of the climate in each area of residence. The southern part of the Russian Far East is located in a zone with a monsoon climate of temperate latitudes, characterized by harsh cold Siberian winters and hot, humid, tropically sultry summers. Pronounced diurnal changes in air temperature and pressure, characteristic of transitional seasons, lead to changes in the oxygen content in the air, having a negative impact on people with bronchopulmonary diseases, especially children [22]. In recent years, there has been an increase in both seasonal [8] and diurnal temperature differences [3].

In this regard, residents of the Amur region are particularly interested in the relationship between the frequency of asthma, exacerbations and sudden changes in ambient temperature.

Vitamin D. Another regional feature of the environmental impact on the body is the level of sunlight and the ability to perceive it by humans in connection with other climatic features. The Amur region is one of the leaders among the regions of Russia in terms of formal indicators of insolation, the number of sunny days for our region exceeds 300 per year. However, a rather harsh climate with large temperature fluctuations, up to extreme ones, does not allow us to take full advantage of this advantage, so the level of vitamin D in the population is quite low. According to studies conducted in 2020, vitamin D deficiency was detected in almost half of the children's population of our region [2, 6]. Meanwhile, the role of this vitamin in the pathogenesis of asthma is well known. Recent Iranian studies have shown that vitamin D levels in patients with asthma are lower than in the control group and decrease with increasing severity of the disease [38]. Similar results were obtained by Indian researchers in the same year [35]. Several earlier epidemiological and in vivo studies also found an association between low vitamin D levels in blood serum and increased inflammation, decreased lung function, increased exacerbations, and general deterioration in patients with

asthma [12, 23, 37]. Later, a meta-analysis confirmed a significant decrease in objective indicators, such as FEV1, and the appearance of signs of obstruction with low vitamin D levels in children and adults with asthma [30]. A number of scientific papers using meta-analysis methods show the effectiveness of vitamin D in the complex therapy of asthma. Thus, 483 unique studies were studied in one of them, eight of which were randomized and controlled (1,078 people in total) according to a certain methodology, taking into account the adjusted incidence ratio [aIRR]. It was found that vitamin D intake reduced the frequency of asthma, exacerbations in all observed patients requiring treatment with systemic corticosteroids (aIRR – 0.74, 95% CI 0.56-0.97; $p=0.03$; 955 patients in seven studies; high-quality evidence). An analysis of the frequency of exacerbations in participants treated with systemic corticosteroids showed that protective effects of therapy were observed in patients with baseline levels of 25(OH)D is less than 25 nmol/L (aIRR – 0.33, 0.11-0.98; $p=0.046$; 92 participants in three studies; average quality data), but not found in patients with a higher baseline content of 25(OH)D (aIRR – 0.77, 0.58-1.03; $p=0.08$; 764 people in six studies; evidence of average quality; $p=0.25$). A two-stage meta-analysis revealed no signs of heterogeneity of the effect ($I^2=0.0$, $p=0.56$) [47]. One of the Russian studies shows some elements of the therapeutic effects of vitamin D when it is included in the complex therapy of asthma. Vitamin D promotes positive changes in the cytokine network during treatment, which is associated with its ability to regulate Th2 functions and, as a result, reduce the synthesis of IL13 and 17, which are involved in the pathogenesis of allergies [1].

Thus, the detection of vitamin D levels in children of the Amur region suffering from asthma and confirmation of its effect on the course of the disease is of great scientific and practical interest and may have high clinical significance.

Trace elements. The ratio and quantity of trace elements in the human body also has regional characteristics and largely depends on the biogeochemical characteristics of the region. The effect of a number of trace elements on the course of asthma is known [49], but various studies lead to ambiguous results when trying to determine the degree and direction of changes. According to the Iranian authors, the average serum levels of Zn and Se in patients with asthma were lower than in conditionally healthy people in the control group, and the concentration

of Cu in the blood serum of patients was slightly higher than in the control group [46]. In recent work, Turkish scientists have noted a decrease in the level of Zn in the blood of children with asthma compared with healthy ones [48], earlier studies revealed a significant decrease in the level of Cr, Se, Zn in the blood serum of children with asthma, compared with healthy ones, and the level of Cu in their blood serum was significantly higher, than in the control [36], which coincided with the data of the Iranian authors [46]. Studies by Indian scientists have also confirmed significantly lower levels of Zn and higher levels of Cu in patients with asthma, compared with healthy ones [13]. A study by Egyptian authors published in 2022 confirmed a significant ($p < 0.008$) decrease in serum levels of Zn and Mg in patients with asthma, while serum levels of Fe and Cu were significantly ($p < 0.016$) higher than in people without this disease. At the same time, there were no significant differences in the content of these trace elements in the blood serum, depending on the severity of asthma, or its control [45]. On the other hand, according to one of the studies using meta-analysis methods, which included 34 sources, there were no significant differences in the level of Zn and Se between asthma and the control group, but they were found in the level of Cu, and the degree of these differences is not the same for humanity in general and for Mongoloids, in particular, it was revealed. There is a significant difference in Mg levels, which has no ethnic differences [40]. A later meta-analysis involving 66 sources revealed that patients with asthma have significantly lower levels of Zn (SMD = -0.32; 95% CI -0.48, -0.17; I² = 90.9%) and Se (SMD = -0.32; 95% CI -0.48, -0.17; I² = 90.9%) in blood serum compared with healthy individuals [15].

Thus, it is obvious that the nature of the effect of trace elements on the pathogenesis of asthma is closely related to the biogeochemical characteristics of the patient's area of residence, therefore, studies characterizing this problem in a particular region are of particular interest.

Viral infections. The role of viral infection in asthma has long been known, reflected in international conciliation documents, including the latest editions of GINA [21]. New generalizing works on this problem appear periodically [34]. However, the influence of pneumotropic persistent viruses of the herpes group, such as Epstein-Barr virus (EBV) and human herpes virus type 6, on the development and course of asthma is of particular interest. They persist for a long time,

often for life, in the bronchial mucosa and inevitably take part in the pathomorphosis of asthma [5]. There was a significant difference in the interleukin profile in children with asthma infected with and without herpes viruses, in particular, higher levels of TNF α , IL1, 2, 4, 10 and lower levels of IL6 and 8 [9]. Studies have shown a high incidence of EBV in children with asthma, [28], and the frequency of virus DNA isolation in the bronchial epithelium of patients with asthma, has been confirmed in comparison with the population without this disease, which indicates its active reproduction in the target organ, the bronchi. A positive relationship has been established between the activation of EBV and the level of ID in children with asthma, [18]. The role of human herpes virus type 6 in the pathogenesis of asthma is much less reflected in the available literature, there are only isolated articles on this topic, which put forward the thesis of the protective role of the persistence of this virus. In an experiment on mice, it was shown that exposure to type 6 herpes significantly inhibited the production of IL4, 5, and 3 in the lavage fluid and in lung tissue exposed to the virus in asthma [19].

The spectrum of sensitization. Asthma in children is primarily an atopic disease, therefore, sensitization to specific allergens underlies its pathogenesis. The influence of the sensitization spectrum on the course of asthma and its controllability is of great interest. The most common allergen in asthma is the house dust mite, this is a well-known fact, confirmed by the consent documents, including all editions of GINA [21]. In children with asthma, it is registered with a frequency of about 90%, which is why the fact of sensitization to it cannot have a significant effect on the nature of the course of asthma. The house dust mite is an obligate human saprophyte, therefore, the very fact of its presence in the inhaled air cannot act as a relevant predictor for the likelihood of developing asthma. In this regard, more attention is being paid to studying the frequency of occurrence and significance of other respiratory allergens in the development of asthma. For example, fungal spores have been shown to increase the likelihood of developing asthma in both children and adults. [20, 24, 26, 32]. It has long been known that sensitization to fungal spores causes a more severe course of asthma compared to other allergens [42]. More recent studies have shown that not only sensitization to mold, but also to pet hair, cockroaches, and weeds, in particular ragweed, causes a more severe course of asthma

than to other allergens, primarily the house dust mite [25]. A clear association has been found between the concentration of fungal spores in the environment and an increase in clinical asthma-like symptoms in children [14]. Recent studies have confirmed that the concentration of fungal spores in house dust affects not only the severity, but also the controllability of asthma, [31]. Pathogenetic animal models have demonstrated that it is fungal sensitization that causes the most pronounced eosinophilic infiltration of the bronchial mucosa [44].

It is obvious that pollen inhalation leads to asthma exacerbation in patients sensitized by it, including children [16]. This is confirmed by a meta-analysis published in 2020, which shows the effect of pollen concentration on the frequency and severity of asthma, exacerbations [39]. When studying the effect of sensitization to weed pollen, it was found that in people with sensitivity to this allergen, the bronchial wall is somewhat thinner than in patients sensitive to house dust mites, which is probably due to a shorter total exposure time during the year [11].

Thus, we see that differences in the severity and pathogenesis of asthma are caused by sensitization to those allergens that depend on the patient's place of residence and, to some extent, his socio-economic conditions, which is why local studies of these factors in specific regions are of great interest. The area near the Amur River is regularly flooded, resulting in conditions favorable for the uncontrolled spread of fungal allergens outside and inside, in humid and poorly ventilated homes. The catastrophic flood in August-September 2013 was unprecedentedly powerful and protracted, with enormous economic damage. Assessing its consequences in terms of changing the spectrum of sensitization in patients with asthma is important for pediatric allergy and pediatrics in general. In addition, the Amur region is characterized by a wide variety of vegetation, including wind-pollinated, which has been increasing in recent years due to the invasion of species not native to the area, such as ragweed, therefore, an assessment of the impact of the sensitization spectrum on asthma in children of the Amur region is necessary and interesting from a scientific and practical point of view.

Conclusion. From the above, it is obvious that the pathogenesis, course, and, accordingly, severity and susceptibility to therapy are influenced by many multidirectional endogenous and exogenous factors. They form a unique mosaic for each patient. A sufficiently deep study of

them opens up prospects for personalizing the diagnosis, prevention, and therapy of asthma.

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M.M. Davydova, I.D. Ushnitsky, E.Yu. Nikiforova,
T.V. Alekseeva, K.G. Piksaykina -Grigorieva, A.V. Ivanov

ETIO-PATHOGENETIC ASPECTS AND CLINICAL FEATURES OF LOCAL SIGNS OF CONNECTIVE TISSUE DYSPLASIA MANIFESTED WITH DENTOFACIAL ANOMALIES IN SCHOOL-AGED CHILDREN

The literature review presents the problems of congenital connective tissue disorders, characterized by multifactorial origins, associated with aggressive factors from the external and internal environment, manifesting as various general and local phenotypic traits. Recent studies have demonstrated a direct relationship between anomalies of the dental and jaw system and genetically conditioned factors to some extent. As the child grows, the formation and development of the permanent bite ensure the functional activity of the jaws, the dental system's ligamentous apparatus, the functional activity of the muscles in the jaw and facial area, etc. Anatomical-topographic changes in congenital collagenopathy of the organs and tissues of the oral cavity negatively impact the functional activity of the entire dental and jaw system, indicating their biological interconnection which correlates with each other. According to the results of the conducted studies, the most common dental and jaw anomalies in children and adolescents with dentofacial abnormalities are distal occlusion, narrowing and deformation of the dental-alveolar arches of the upper and lower jaws, and deep incisor overlap. The formation of a permanent bite is a multifaceted complex physiological process, where possible reasons for its disruption are identified by quite a few factors from the external and internal environment, including congenital disorders of connective tissue differentiation. In children during the active growth period and ossification of the facial skeleton bones, a correlation of the negative influence of various risk factors on the growth of the middle zone facial bones is determined, which in the future may contribute to the development of dental and jaw anomalies and deformations. As of today, the prevalence of dental and jaw anomalies does not show a tendency to decrease, and their combination with DSD in children and adolescents is insufficiently studied, which requires further research aimed at early detection of local phenotypic signs and improvement of socio-medical rehabilitation with an interdisciplinary approach.

Keywords: osteogenesis, connective tissue dysplasia, phenotypic manifestations, orphan diseases, joint hypermobility, skin hyperextensibility, gothic palate, dentofacial anomalies, temporomandibular joint dysfunction, dentinogenesis imperfecta and amelogenesis.

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DAVYDOVA Maya Maksimovna – Senior Lecturer of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Childhood Dentistry of MK Ammosov North-Eastern Federal University, e-mail: davidova-mayya@mail.ru ORCID .org/0009-0005-4519-8721; **USHNITSKIY Innokentiy Dmitrievich** – MD, Professor, Head of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Childhood Dentistry of MK Ammosov North-Eastern Federal University, e-mail: incadim@mail.ru, ORCID.org/0000-0002-4044-3004; **NIKIFOROVA Ekaterina Yurievna** – PhD, Associate Professor of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Childhood Dentistry of M.K. Ammosov North-Eastern Federal University, e-mail: feay 88@ mail. en, ORCID.org/0009-0000-3825-8806; **ALEKSEEVA Tatyana Vasilyevna** – PhD, head of the Children's Department of the State Academy of Sciences of the Republic of Sakha (Yakutia), e-mail:alekstatvas@mail.ru. ORCID.org / 0000-0001-5860-2029; **PIKSAYKINA-GRIGORYEVA Ksenia Gennadiyevna** – PhD, Associate Professor of the Department of Therapeutic, Surgical, Orthopedic Dentistry and Childhood Dentistry of MK Ammosov North-Eastern Federal University, e-mail: ksupixar@mail.en, ORCID .org/0009-0007-8378-6625; **IVANOV Andrian Vladimirovich** – PhD, Associate Professor of the Department of Surgical Diseases and Dentistry of MK Ammosov North-Eastern Federal University, e-mail: andrian_ivanov@mail.ru ORCID. org/0009-0003-9352-1111

Clinical and epidemiological characteristics of connective tissue dysplasia in children and adolescents. To date, connective tissue dysplasia (CTD) is a common systemic pathology that has a wide range of local and general manifestations, which in some cases can lead to disability in working-age individuals [1, 15]. Meanwhile, the problems of congenital disorders of connective tissue differentiation are not fully understood, which presents certain difficulties in organizing and conducting therapeutic, preventive, and rehabilitation measures [23]. In this regard, further study of genetically determined connective tissue disorders is extremely important for maintaining and strengthening the health of the population, as well as having practical significance for healthcare [1, 3].

The aim of the presented literature review is to analyze data from scientific literature on the etiopathogenetic aspects and clinical features of local signs of connective tissue dysplasia, manifested with

dental and jaw anomalies in school-age children.

In the structure of manifestations of EDS in the musculoskeletal system, joint hypermobility is most commonly observed, including the development of pathological processes in the temporomandibular joint (TMJ). In clinical practice, joint hypermobility is more frequently diagnosed in girls, reaching up to 65% prevalence among all age groups of schoolchildren, and up to 6% among adults. According to literature sources, the prevalence of joint hypermobility in EDS among the Asian ethnic population ranges from 15 to 25%, while in the European population it reaches digital levels of 10% [6, 37]. Currently, there is a lack of unified diagnostic criteria and approaches to treatment and preventive measures for joint hypermobility in children and adolescents with congenital dysgenesis in clinical practice [30, 36]. The benign course of joint hypermobility is characterized by excessive mobility in more than four joints without pain symp-

toms, where its severe form is additionally manifested by arthralgia, which in most cases is associated with the presence of joint dislocations and subluxations. In some clinical cases of joint hypermobility in children, complaints may be absent despite the presence of pathological joint mobility, which may be perceived by doctors of various specialties as age-related and constitutional features. Overall, joint hypermobility in joint hypermobility syndrome (JHS) is formed as a result of metabolic process disorders and endocrine pathologies. In this regard, school-aged children with clinical signs and symptoms of hypermobility of the joints is prone to the development of inflammatory-degenerative anatomical-morphological changes in joint tissues, which may become the main pathogenetic mechanism for the formation of spinal deformities and flat feet [16, 40].

It should be noted that connective tissue participates in the formation of the anatomical shape and morphological structure of cardiac tissue, where the influence of various aggressive risk factors leads to the development of pathological processes affecting the cardiovascular system, including insufficiency of heart valves and septa, as well as arteries and veins [26, 35]. Research has established a high prevalence of "dysplastic heart" in undifferentiated connective tissue dysplasia (uCTD), with a prevalence rate of 80%, where minor developmental anomalies (MDA) of the heart in the form of mitral valve prolapse in children in their first year of life are found in 6%, and by ages 6-14, this figure reaches 21-30%, whereas during adolescence, it decreases to 15% [8]. Congenital connective tissue alteration of the valve leaflets leads to the formation of their functional inadequacy and disruption of the autonomic innervation of heart tissue, where a high probability of arrhythmia development arises. A number of authors characterize the presence of a direct relationship between magnesium deficiency and the appearance of defective collagen, which contributes to the development of infectious endocarditis, associated with thromboembolism of large vessels, leading to a fatal outcome [8, 21].

It should be noted that currently there is insufficient information in the literature regarding the frequency of dental and jaw anomalies depending on the severity of dysplastic syndromes (DTS). On average, among individuals with congenital collagenopathies, the prevalence of dental and jaw anomalies and deformities is 33%, while in children and adolescents without signs of DTS, this indicator is

three times lower. The most commonly observed issue is deep bite, followed by distal, crossbite, and mesial. Meanwhile, a number of authors assert that the most frequently identified anomalies in the structure of dental and jaw anomalies are distal and deep incisal disocclusion [13, 18]. According to studies conducted, the peculiarity of the manifestations of local phenotypic traits related to dental and jaw anomalies is their wide variation from 12% to 93%, which underscores the relevance of their study in order to improve medical care.

It is important to note that the formation of a permanent bite goes through a number of complex stages, and under the influence of many external and internal factors, disturbances in the formation of occlusion may develop. From the first month of embryonic development, the development and formation of the organs and tissues of the oral cavity begins. In this regard, the negative influence of aggressive factors can alter the genetic program of the fetus, which creates the prerequisites for the formation of dental and jaw anomalies and deformations. After the birth of the child, the physiological process of active growth of the bones of the facial skeleton and the formation of the dental-jaw system begins [17, 24]. Thus, the bone tissue of the nasal septum during the period of active growth contributes to the formation of the sutures of the skull until the complete ossification of the vomer and ethmoid bone. Meanwhile, premature mineralization of the sutures of the cranial bones contributes to the appearance of a curvature of the nasal septum, which directly affects the formation of the maxillary complex. In addition, disturbances in the final ossification of the cranial bones negatively impact the formation of the bones in the middle zone of the face, which may be the primary cause of the development of dysocclusions [19].

It should be noted that according to the conducted research, the data on the prevalence of congenital collagenopathy is ambiguous, which is related to the presence of heterogeneous methodological and technological approaches, as well as various classifications [27, 30]. At the same time, the structure of existing DST classifications is organized by general and local phenotypic signs that determine various symptoms and syndromes interpreted by a scoring system [22]. Based on the severity of DST, the total score obtained is determined depending on the identified phenotypic and visceral signs during the research, which define congenital connective tissue differ-

entiation disorders of mild, moderate, and severe severity [27, 34]. Meanwhile, differentiated forms of EDS include Marfan syndrome and Ehlers-Danlos syndrome, familial traits of hereditary mitral valve prolapse, joint hypermobility, osteogenesis imperfecta, imperfect amelogenesis, dentinogenesis, etc. [2, 37]. According to studies, other hereditary syndromes associated with EDS are identified less frequently than the aforementioned orphan diseases [36]. In modern clinical protocols, undifferentiated EDS is characterized as pathological processes with polygenic origins, having a wide range of common and local phenotypic patterns [9]. The severity of EDS manifestations and the nature of their clinical course to some extent depend on the influence of external factors [2, 42].

At the same time, studies conducted by some authors have shown that dental and jaw anomalies have a hereditary nature, while other researchers believe that genetic predisposition phenotypically manifests under 'favorable' conditions influenced by aggressive external and internal environmental factors [14]. Information indicates that disturbances in bite, leading to subsequent formation of dental and jaw anomalies, are significantly influenced by changes in the jaw bones, periodontal ligament tissues, the temporomandibular joint, chewing and facial muscle groups, etc., which negatively affect the functional state of the dental-jaw system, leading to the formation of malocclusions [17]. Meanwhile, a certain feature of dental anomalies and deformities is their predisposition. Congenital anomalies and deformities of teeth are formed in various genetic diseases, including Down syndrome and Ehlers-Danlos syndrome, protruding ears, skin hyperelasticity, and others. In this case, anomalies in the development of teeth are most commonly identified in congenital dysgenesis, which is related to the histological structure of teeth, composed of connective tissue [13, 36].

It should be noted that the clinical features of the manifestations of EDS lead to certain difficulties in their detection and diagnosis verification, which require a wide range of additional research methods and the involvement of related medical specialists for an objective assessment of the extent of organ and tissue involvement. At the same time, initial manifestations of phenotypic signs of EDS can be identified even during the embryonic period of fetal development, where timely implementation of comprehensive preventive measures can minimize the consequences of congenital collagenop-

athy. Other signs, however, progressively manifest clinically as children and adolescents grow and develop, where the severity of EDS can be exacerbated by various aggressive factors in the external and internal environment as they age. Meanwhile, the formation of symptoms and syndromes of congenital collagenopathy minimally manifests during the neonatal period, where some of the earliest manifestations at 20 weeks of gestation are congenital changes in the left ventricle of the heart and the respiratory system. In school age, anomalies of the heart valves and thoraco-diaphragmatic syndromes develop with the appearance of signs of dysplastic changes in the skeletal system and visual organs [2, 8].

Disocclusions occupy one of the leading places in the structure of diseases of the organs and tissues of the oral cavity, with a prevalence that reaches up to 80% [7, 9, 33]. Dentofacial anomalies and deformations manifest as isolated pathological processes, as well as one of the symptoms of genetic diseases. Studies conducted have established a systematic manifestation that reflects the aggressive course of dentofacial anomalies, where deep incisal overlap is found in 52% of cases, crossbite in 15.3%, and normal bite in 8% among examined age groups of schoolchildren. Meanwhile, anomalies in the position of the teeth are identified in 49.3% of those examined, while canine dystopia is found in 32.66% and incisor dystopia in 16.66%. Additionally, among minor genetically predisposed stigmas of dentofacial anomalies, the most frequently diagnosed is a high palate at 20.66%, as well as changes in the sizes and shapes of teeth, including shovel-shaped teeth at 12.66%, micrognathia at 6%, diastemas at 24.66%, and interdental spaces at 6% [18, 23].

Etiological and pathogenetic characteristics of congenital collagenopathies in children and adolescents. It is important to note that congenital collagenopathies contribute to disturbances in the formation of collagen fiber structure, which can lead to morphological changes in the structural components of cartilage tissue, ultimately resulting in pronounced alterations in the maturation of the epiphyseal growth zone. This can lead to the elongation of long bones, manifesting as pathologies of the musculoskeletal system, caused by damage to the formed connective tissue, leading to the development of dolichostenomelia, arachnodactyly, scoliosis, and flatfoot [4].

It should be noted that the metabolism of bone tissue in children and adolescents with DCT is characterized by a

disturbance in the balance of connective tissue synthesis and its resorption [2]. Meanwhile, until the age of 3, a child's musculoskeletal system experiences active growth physiologically, then until puberty, the increase in bone mass slows down [8, 39]. At the same time, a significant portion of the adult population is found to have osteoporosis, where the primary pathogenic mechanism is associated with insufficient accumulation of mineral components during the active growth period in adolescents, which is the main cause of developing osteoporosis with age. In Russia, the total number of people affected is about 14 million, and around 20 million have pronounced signs of osteopenia, which are related to significant disturbances in mineral metabolism that develop during childhood [4, 7]. The frequency of detecting osteopenia among younger and middle school students reaches 32%, while among adolescents it is 57%, with 10% having a history of bone fractures from minor injuries. The presence of the above clinical signs of DCT accounts for a high likelihood of developing osteopenia and osteoporosis in children and adolescents. It has been found that in adolescence, if the level of bone mass decreases from the norm by 5-10%, the likelihood of hip fracture increases by 25-50% in later ages. The above indicates the medical and social significance of the problem of osteoporosis, where further research on bone remodeling processes in adolescents with DCT is a relevant task, including for the prevention of dentofacial anomalies [11].

It should be noted that genetically determined connective tissue disorders are associated with various comorbid conditions of different organs and systems [22]. At the same time, some pathogenetic mechanisms of the development of systemic diseases in schoolchildren with joint hypermobility remain unexplored, which is why in some cases the diagnosis is made by specialists in adulthood [28]. In the development of congenital collagenopathies, genetic predisposition has a direct influence. Thus, in the pathogenesis of joint hypermobility syndrome, specific roles are attributed to the alleles of the *s* gene of collagen COL1A1, which belongs to the 'null' GST M1 genotype, 'slow' NAT2, and 'fast' 4G/4G PAI1 gene. Meanwhile, the high prevalence of the 'null' detoxification system GST T1 genotype indicates a predisposition to the formation of joint hypermobility. Additionally, the Tt genotype of the VDR gene with a Marfan-like phenotype is more frequently identified, where established osteopenia in the lumbar spine of schoolchildren is

associated with the presence of this genotype SS gene COL1A1 [25, 27].

To date, a high prevalence of undifferentiated connective tissue dysplasia (CTD) has been defined in the population of children [20]. In this context, congenital collagenopathy constitutes the morphological basis of multiple organ dysfunctions in children and adolescents, as the majority of organs and systems are genetically composed of connective tissue [11]. Numerous studies have demonstrated the main causal factors in the formation and development of CTD, which include genetically determined changes that lead to disturbances in the synthesis and formation of collagen structures with dysfunctions in protein-carbohydrate metabolism, genetically modified defects in enzymatic activity and their cofactors, resulting in changes in the structure of collagen fibrils, proteoglycans, glycoproteins, and fibroblasts of connective tissue [3, 5].

In the structure of congenital connective tissue differentiation disorders, syndromes and symptoms with symptom complexes associated with genetic mutations in the locus of a specific gene are identified. Thus, the syndrome of dysplasia of the hard tissues of dentin and enamel with osteosclerosis is classified as an autosomal dominant disease. There are numerous gene mutations (currently around 500 are known) that lead to disruptions in the coding of the protein matrix of connective tissue. Furthermore, there is evidence that polygenic forms of genetic changes in connective tissue lead to a high prevalence of dental and jaw anomalies and deformations, with significant increases in indicators with age [3, 6, 12].

It is important to note that disocclusions are not included in the list of life-threatening pathologies, but they can influence the development of severe diseases of the gastrointestinal and respiratory systems, dyslalia, and psycho-emotional disorders. Therefore, early diagnosis and correction of disocclusions, which have pronounced features in congenital collagenopathies requiring an individual approach, are important. In this regard, the study of dental and jaw anomalies and deformations and their connection with congenital genetically determined disorders of connective tissue differentiation is a relevant general medical problem. Some researchers believe that anomalies and deformations of the dental and jaw system are hereditary diseases [3, 24, 32]. From a physiological point of view, all anatomical and morphological structural components of the dental and

jaw system participate in the formation of a permanent bite. Thus, various changes in one of the component parts of the dental and jaw system contribute to the formation of malocclusion [10, 12, 31].

Today, conducted studies have established a high level of prevalence of disocclusion among the population of Russia, which does not show a tendency to decrease, where, on the contrary, a persistent dynamic growth is observed. This confirms the presence of resistant pathogenetic mechanisms for the development of genetically determined disorders of connective tissue differentiation [18, 29, 41]. In this regard, the study of disocclusions has important practical significance in medicine.

Modern aspects of diagnosing local manifestations of connective tissue dysplasia in the maxillofacial area in children. It is important to emphasize that despite extensive research on the problems of congenital collagenopathy, there is currently no unified algorithm of diagnostic criteria and a uniform classification of CTD, which creates difficulties in conducting clinical-epidemiological studies. However, the accepted clinical guidelines for the early diagnosis and treatment of congenital connective tissue differentiation disorders outline the main groups of manifestations of congenital dysgenesis. Based on the results obtained, the severity of CTD is interpreted according to a proposed scale, which allows for the assessment of the practical and diagnostic significance of the scores obtained [30].

During adolescence, the risk of developing decompensated forms of somatic diseases associated with congenital differentiation of connective tissue significantly increases, which is important for their early diagnosis. This pattern is related to the rapid growth of connective tissue during puberty and the growth 'spurt', which leads to the emergence of numerous common and local phenotypic traits of genetically determined connective tissue disorders [15]. The severity of manifestations of congenital collagenopathy largely depends on genetic factors, the deficiency of macro- and micronutrients, vitamins in the body, physical activity, etc., contributing to the manifestation of various dysplastic symptoms and syndromes. In this regard, diagnostic measures for DYST (Dysplastic Syndromes) in children and adolescents should be carried out taking into account the age-related characteristics of the formation of dysplastic phenotypic signs using a wide range of basic and additional research methods [16, 38]. Meanwhile, in individuals aged 35 years and older, the

likelihood of additional signs of DYST is minimized, which, in turn, indicates that adults already have a formed set of phenotypic signs of congenital connective tissue differentiation disorders. Recently conducted studies have established the presence of certain features related to the prevalence rates of congenital collagenopathy in modern children, which are significantly higher compared to adults. This is attributed to the deterioration of the environmental situation as well as familial genetic defects that lead to disruptions in the synthesis and maturation of connective tissue [27, 39].

It is important to note that the prevalence of dentofacial anomalies among residents of various regions of Russia has a correlational relationship with the severity of DSD, which does not show a tendency to decrease, but rather demonstrates a trend of dynamic growth, which to some extent confirms the existence of stable mechanisms for the formation and development of this systemic pathology [21, 26]. In this regard, timely dynamic analysis and assessment of local phenotypic traits in the organs and tissues of the oral cavity are of great importance in dentistry, as they correlate with genetically determined disorders of connective tissue differentiation. This situation necessitates the organization and rational conduct of medical and social rehabilitation of dentofacial anomalies and deformations in schoolchildren with congenital collagenopathy. In this regard, early diagnosis and prompt implementation of rehabilitation measures will contribute to preventing dysfunction of the dental-jaw system. When conducting these measures, special attention must be paid to excluding or neutralizing harmful habits (thumb sucking, pacifier use, biting of the tongue, mucosa of the cheeks and lips, constant pressure of the tongue on the teeth, changing the position of the lower jaw) [18, 23]. Meanwhile, 1/3 of young individuals with congenital collagenopathies exhibit dysocclusions, where retained teeth are often found, which may be associated with manifestations of Down syndrome, Ehlers-Danlos syndrome, and others. According to literature sources, the frequency of manifestations of congenital connective tissue differentiation disorders correlates with anomalies in the shape and number of teeth depending on the severity of congenital collagenopathy. The assessment of the dentofacial manifestations of DSD confirms that in severe cases, there is a significantly increased frequency of anomalies related to the shape or size of teeth, as well as features of tooth erup-

tion. In addition, there is a trend towards an increase in the frequency of caries detection, periodontal diseases, and the prevalence of "non-cariogenic" enamel lesions in the form of various forms of hypoplasia, erosion, wedge defects, and pathological wear at various degrees of severity of DSD [31, 35].

It should be noted that in the case of congenital collagenopathy, a systemic nature of disorders of the organs and tissues of the oral cavity, as well as the jaw-facial area, is determined, which underscores the importance of early diagnosis and prevention. Furthermore, when conducting therapeutic and preventive measures and predicting dental diseases, it is necessary to take into account the morphological and structural features of connective tissue in patients during outpatient-polyclinic and inpatient visits. In this regard, for the prevention of local manifestations of connective tissue dysplasia, an interdisciplinary approach involving other medical specialists is required, which will play a key role in strengthening and preserving the health of the population [11, 17].

It should be noted that there are certain difficulties in diagnosing the symptoms and syndromes of undifferentiated Ehlers-Danlos syndrome (EDS) that are related to the lack of universally accepted diagnostic criteria. Moreover, in clinical practice, the issue of accurately assessing the severity of congenital collagenopathy remains particularly challenging and, in fact, unresolved [1, 2]. One of the important clinical markers of congenital collagenopathy is the involvement of the musculoskeletal system, which includes joint hypermobility, spinal curvature, arachnodactyly, a pectus carinatum, and 'sunken' chest, as well as skin hyper-elasticity. Meanwhile, manifestations of EDS in the gastrointestinal tract include prolapse of internal organs, dysfunction of the hepatobiliary system, etc. [8, 16]. In the diagnosis of manifestations of connective tissue dysplasia (CTD), it is accepted that the presence of three or more external manifestations provides a basis for diagnosing internal organ diseases. Research has established that congenital disorders of connective tissue differentiation are associated with neurovegetative disorders related to vegetative-vascular dystonia, neurotic-like states, and asthenic syndrome with possible panic attacks, which are clinically significant manifestations of genetically determined connective tissue disorders [8, 15, 16].

Thus, the clinical, etiopathogenetic, and diagnostic aspects of the local fea-

tures of dental and skeletal anomalies in school-aged children characterize their prevalence and wide range of manifestations, which require timely diagnostics and the prompt implementation of therapeutic, preventive, and rehabilitation measures that have a positive effect on strengthening and preserving health, as well as improving the quality of life of patients.

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POINT OF VIEW

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V.P. Patrakeeva, E.V. Kontievskaya, V.A. Schtaborov, A.V. Samodova

THE RELATIONSHIP BETWEEN MARKERS OF METABOLIC SYNDROME AND LEVELS OF SPECIFIC IgG TO FOOD PRODUCTS IN HEALTHY PEOPLE AND WITH METABOLIC SYNDROME

Due to the steady increase in the incidence of metabolic syndrome (MetS), studying the ways to reduce the risk of its occurrence is an important task for modern medicine. The aim of the study is to identify the relationship of MetS markers with the levels of specific IgG to various products, as well as to assess the relationship of the content of proinflammatory cytokines and C-reactive protein with MetS. It is shown that for the examined individuals with MetS, more direct correlations are recorded and most often - with the glucose level. Many products can provoke postprandial hyperglycemia, which in a practically healthy person will not cause significant disturbances, but with MetS, a failure of glucose and lipid homeostasis in combination with insulin resistance does not allow effective correction of blood glucose levels. Thus, when introducing elimination diets for MetS, it is necessary to take into account the possibility of postprandial hyperglycemia in this group of people, monitor glucose and insulin levels to prevent the development of insulin resistance.

Keywords: food antigens, metabolic syndrome, specific IgG, correlation relationships.

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N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences, Institute of Environmental physiology: **PATRAKEEVA Veronika Pavlovna** – candidate of biological sciences, leading researcher, head of the Laboratory of Ecological Immunology, ORCID: 0000-0001-6219-5964, patrakeeva.veronika@yandex.ru; **KONTIEVSKAYA Elena Vladimirovna** – junior researcher of Laboratory of Ecological Immunology, ORCID: 0000-0002-4246-8408, kaiyo-kato@yandex.ru; **SCHTABOROV Vyacheslav Anatolievich** – candidate of biological sciences, senior of Laboratory of Ecological Immunology, ORCID: 0000-0002-1142-4410, schtaborov@mail.ru; **SAMODOVA Anna Vasilievna** – candidate of biological sciences, senior researcher, head of the laboratory of regulatory mechanisms of immunity, ORCID: 0000-0001-9835-8083, annapoletaeva2008@yandex.ru.

Introduction. MetS is a set of pathological conditions including visceral obesity, insulin resistance, hyperglycemia and lipid metabolism disorders. This symptom complex increases the risk of developing other diseases, such as cardiovascular, neurodegenerative, oncological diseases and the development of type 2 diabetes mellitus [5, 22, 26]. It is known that inflammatory processes are involved in the pathogenesis of many diseases. The inflammatory response, as a protective mechanism, is based on the permeability of the intestinal epithelium for food antigens and impaired immune regulation. In obesity, the inflammatory process is localized in adipose tissue, liver, muscles and pancreas. These tissues are infiltrated with macrophages and other immune cells that produce proinflammatory cytokines that act in an autocrine and paracrine manner to interfere with insulin signaling in peripheral tissues or cause β -cell dysfunction and subsequent insulin deficiency [16, 19, 25]. Studies show that food antigens can affect the barrier functions of the intestinal wall, facilitating the penetration of harmful substances into the blood, thereby initiating inflammation. Once in the blood, food antigens cause an increase in the concentration of specific IgG [1, 3]. In patients with MetS, 88.5% of cases show an increase in immunoglobulin IgG, which is involved in autoimmune processes [6]. An unbalanced diet with a predominance of fats, circadian rhythm disorders, and stress play a key role in the development of MetS [23]. In turn, MetS increases the risk of anxiety due to an increase in the level of chronic inflammation [9]. Thus, studying the underlying mechanisms of MetS development and associated inflammation may be useful for the treatment, diagnosis and prevention of associated diseases.

The **aim** is to establish the presence of correlations between MetS markers and levels of specific IgG to food antigens, as well as to analyze the relationship between MetS and the content of proinflammatory cytokines and C-reactive protein.

Materials and methods. According to the classification of the International Diabetes Federation (IDF, 2005), the main sign of MetS is the presence of visceral obesity, for women the abdominal circumference should be equal to or more than 80 cm, for men more than 94 cm, as well as any two of the following four factors: elevated triglyceride levels (more than 1.7 mmol / l), decreased high-density lipoprotein levels (less than 1.03 mmol / l in men and less than 1.29 mmol / l in women), elevated blood pres-

sure (systolic more than 130 or diastolic more than 85 mm Hg), elevated fasting plasma glucose (more than 5.6 mmol / l). Laboratory and anthropometric data of 230 people were analyzed. The group with MetS included 110 people, including 71 women and 39 men, the average age was 33.92 ± 1.09 years. The inclusion criterion for patients was the presence of clinical signs of MetS according to the classification of the International Diabetes Federation (IDF, 2005). The diagnosis was confirmed by the results of laboratory tests. The examined individuals with MetS did not have a confirmed diagnosis of diabetes mellitus and, therefore, did not take insulin drugs to regulate blood sugar levels. The control group included 120 practically healthy people, including 100 women and 20 men, the average age was 41.90 ± 1.12 years. According to the questionnaire, none of the examined people had any allergies to any food products. The examination was carried out with the written consent of the volunteers, in compliance with the norms and rules of biomedical ethics approved by the Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research (2013). The study was approved by the Ethics Committee of the Institute of Physiology of Natural Adaptations of the Federal Research

Center for Animal Health, Ural Branch of the Russian Academy of Sciences (Protocol No. 3 dated December 20, 2024). Abdominal circumference was assessed in all patients. The concentration of low-density lipoproteins, high-density lipoproteins, total cholesterol, triglycerides and glucose was determined in blood serum using spectrophotometry kits (Vector-Best, Russia) on a UV-1800 spectrophotometer (Shimadzu, Japan). The enzyme immunoassay method was used to determine the content of C-reactive protein (AccuBind, USA), cytokines IL-6, IL-10, IL-1 β and TNF α (RayBiotech, USA), c-peptide (Monobind Inc., USA), specific IgG antibodies to 90 food allergens (Biomerica, USA) in the blood serum, with the result being assessed on a Multiskan FC enzyme immunoassay analyzer (Thermo Fisher Scientific, USA). Statistical data processing was performed using the Statistica 6 program (StatSoft, USA). Correlation analysis was performed using Pearson's analysis. The normality of distribution of quantitative indicators was checked using the Shapiro-Wilk criterion. The description of the obtained data was carried out using the mean value and standard deviation, median, lower and upper quartiles. Statistically significant differences between groups were identified using the parametric Student t-test

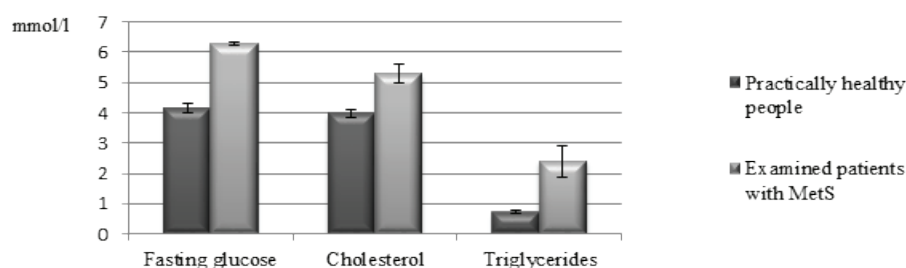


Fig. 1. Concentrations of glucose, total cholesterol and triglycerides ($M \pm m$). *** $p < 0.001$ is the significance of the differences

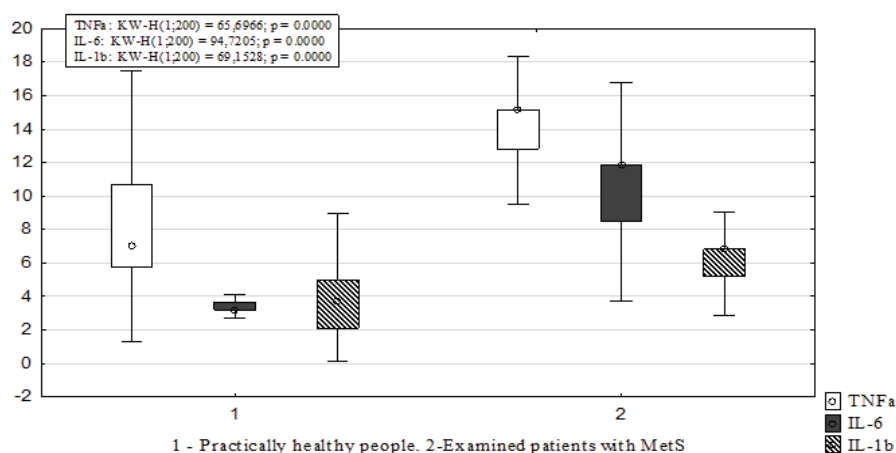


Fig. 2. Concentrations of pro-inflammatory cytokines TNF α , IL-6, IL-1 β

for independent samples and the non-parametric Kruskal-Wallis test. The significance of differences was considered at $p < 0.05$.

Results of the study and their discussion. The results of the examination showed that in the MetS group, the abdominal circumference in women averaged 98.53 ± 2.56 cm, while in men it was 106.71 ± 1.82 cm. In the comparison

group, the abdominal circumference in women was 68.96 ± 1.46 cm ($p < 0.001$), while in men it was 79.50 ± 1.50 cm ($p < 0.001$). The group of volunteers with MetS was characterized by higher levels of glucose, cholesterol, and triglycerides in the blood serum. The comparison data are presented in Figure 1. The groups were assessed for the level of general inflammation. MetS is characterized by the

presence of chronic sluggish inflammation, which is confirmed by higher levels of proinflammatory cytokines IL-1 β , IL-6, and TNF α in the examined individuals with MetS (Figure 2).

The concentration of C-reactive protein, a marker of general inflammation, was determined. It was found that in practically healthy volunteers its content was 1.31 (0.75-2.06) mg/l with elevated

Table 1

Correlations of levels of specific IgG to fish and seafood antigens with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Turbot	Practically healthy	-0.17	0.28	0.37	0.08	-0.13
	MetS	0.14	-0.09	0.08	-0.07	0.43*
Flounder	Practically healthy	-0.09	0.43*	0.41*	0.25	0.34
	MetS	0.13	-0.15	0.08	-0.15	0.44*
Cod	Practically healthy	-0.30	0.34	0.34	0.12	0.28
	MetS	0.42*	-0.14	-0.13	-0.08	0.05
The crab	Practically healthy	-0.10	0.57**	0.49**	0.02	0.37
	MetS	0.34	-0.16	-0.13	-0.17	-0.08
Tuna	Practically healthy	-0.09	0.19	0.40*	-0.07	-0.22
	MetS	0.43*	-0.09	-0.14	-0.05	-0.01
Shrimp	Practically healthy	0.19	0.15	0.54**	0.11	0.28
	MetS	-0.20	0.15	0.25	0.24	0.37*
Trout	Practically healthy	-0.29	0.41*	0.51**	0.32	0.40*
	MetS	0.49**	-0.17	0.08	0.02	-0.16
Hake	Practically healthy	-0.36	0.34	0.38	0.16	0.40*
	MetS	0.26	-0.15	-0.06	-0.04	0.16
Salmon	Practically healthy	-0.17	0.26	0.46*	0.18	0.30
	MetS	0.14	-0.18	0.10	-0.13	0.27

Note. In table 1-6 * - $p < 0.05$. ** - $p < 0.01$. *** - $p < 0.001$.

Table 2

Correlations of levels of specific IgG to fruit antigens with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Avocado	Practically healthy	-0.14	0.02	0.38*	0.28	0.02
	MetS	-0.07	-0.06	0.13	-0.12	0.42*
Orange	Practically healthy	-0.29	-0.11	0.21	0.15	0.31
	MetS	-0.15	-0.04	0.17	-0.08	0.48**
Banana	Practically healthy	-0.20	0.20	0.14	0.07	-0.01
	MetS	-0.01	-0.04	0.10	-0.24	0.50**
The grapes are white	Practically healthy	-0.47**	0.04	0.05	0.04	-0.31
	MetS	-0.02	-0.06	0.17	-0.13	0.44*
Peach	Practically healthy	-0.14	-0.19	0.35	0.43*	0.10
	MetS	-0.16	-0.16	0.28	-0.08	0.41*
Plum	Practically healthy	0.02	0.04	0.30	0.23	0.22
	MetS	-0.14	-0.10	0.29	-0.06	0.47**
Lemon	Practically healthy	-0.11	-0.06	0.27	0.30	0.31
	MetS	-0.11	-0.09	0.19	-0.03	0.41*

Table 3

Correlations of levels of specific IgG in vegetables with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Carrot	Practically healthy	-0.16	-0.013	-0.1	0.07	0.08
	MetS	-0.1	-0.06	0.21	0.0004	0.42*
Eggplant	Practically healthy	-0.22	-0.15	0.28	0.4	0.26
	MetS	-0.28	-0.05	0.32	-0.02	0.39*
Punch	Practically healthy	-0.2	-0.08	0.19	0.26	0.05
	MetS	-0.12	-0.09	0.21	-0.16	0.49**
Green peas	Practically healthy	-0.01	-0.12	0.58**	0.46*	0.1
	MetS	0.12	-0.07	0.32	0.001	0.45**
Green sweet pepper	Practically healthy	-0.12	-0.07	0.24	0.12	0.38*
	MetS	-0.08	-0.1	0.29	-0.12	0.55*
Celery	Practically healthy	-0.22	-0.12	0.32	0.33	0.15
	MetS	0.06	-0.08	0.21	-0.07	0.37*
Cabbage	Practically healthy	-0.23	-0.04	0.01	-0.01	-0.07
	MetS	0.03	-0.06	0.13	-0.08	0.4*
Tomatoes	Practically healthy	0.04	-0.13	0.26	0.35	0.4*
	MetS	-0.13	-0.14	0.07	-0.12	0.44**
Pumpkin	Practically healthy	-0.1	-0.24	0.2	0.19	0.04
	MetS	-0.1	-0.08	0.34	-0.02	0.51*
Corn	Practically healthy	-0.04	0.15	0.09	0.004	-0.07
	MetS	-0.2	0.41*	0.05	0.38*	0.24
Garlic	Practically healthy	-0.05	-0.15	0.5**	0.43*	0.28
	MetS	-0.21	-0.12	0.23	-0.13	0.48**
Onion	Practically healthy	0.04	-0.01	0.2	0.35	0.24
	MetS	-0.22	-0.08	0.12	-0.08	0.37*

Table 4

Correlations of levels of specific IgG to dairy antigens with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Soft cheese	Practically healthy	-0.01	-0.07	0.31	0.19	0.52**
	MetS	0.07	0.02	-0.08	0.07	0.76*
Yogurt	Practically healthy	0.05	0.1	0.41*	0.18	0.5**
	MetS	0.15	-0.03	-0.02	0.09	0.15
Casein	Practically healthy	0.13	-0.12	0.34	0.25	0.41*
	MetS	0.25	-0.04	-0.14	0.13	0.12
Cheddar cheese	Practically healthy	0.01	-0.09	0.54*	0.26	0.29
	MetS	-0.1	0.12	0.14	-0.11	0.66**
Swiss cheese	Practically healthy	0.03	-0.16	0.5**	0.28	0.13
	MetS	-0.09	0.15	-0.08	-0.05	0.72
Butter	Practically healthy	0.1	0.2	0.22	0.05	0.49**
	MetS	0.07	0.002	-0.05	0.19	0.16
Goat's milk	Practically healthy	-0.03	-0.06	0.61***	0.36	0.22
	MetS	0.01	-0.1	-0.06	0.13	0.12

concentrations (over 5 mg/l) recorded in $6.81 \pm 0.15\%$ of those examined. In the group of those examined with MetS, the content of C-reactive protein was 2.86 (2.28 – 3.87) mg/l, elevated levels

were found in $20.34 \pm 1.32\%$ of cases. An increase in the level of inflammation markers increases the risk of vascular endothelial dysfunction, increased insulin resistance, lipid peroxidation and oxida-

tive stress. As a result of chronic sluggish inflammation and impaired immune control, a change in the regulation of food antigen transport occurs through weakening of tight junctions of the epithelium and

Table 5

Correlations of levels of specific IgG to meat antigens with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Sheepmeat	Practically healthy	-0.21	0.03	0.26	0.18	0.09
	MetS	-0.02	-0.09	0.14	-0.15	0.39*
Beef	Practically healthy	-0.44*	-0.36	0.16	0.14	-0.11
	MetS	-0.07	0.13	0.34	-0.16	0.33
Turkey	Practically healthy	-0.09	0.11	0.45*	0.31	0.38*
	MetS	0.44*	-0.16	-0.12	-0.1	0.07
Chicken	Practically healthy	0.02	0.14	0.26	0.28	0.35
	MetS	0.4*	-0.11	-0.11	-0.05	-0.03

Table 6

Correlations of levels of specific IgG to antigens of products with markers of metabolic syndrome, r

		Abdominal circumference	Triglycerides	HDL	LDL	Glucose
Black pepper	Practically healthy	0.05	0.04	0.42*	0.49**	0.23
	MetS	0.25	-0.09	-0.02	-0.16	0.18
Mushrooms	Practically healthy	-0.01	0.11	0.34	0.18	0.39*
	MetS	0.22	-0.06	0.04	-0.08	0.14
Beer yeast	Practically healthy	0.23	0.41	0.21	-0.27	0.39*
	MetS	0.11	-0.09	0.09	-0.09	0.36
Chocolate	Practically healthy	-0.08	0.2	0.46*	0.29	0.33
	MetS	0.4*	-0.08	-0.03	-0.01	0.04
Honey	Practically healthy	-0.28	0.16	0.18	-0.002	-0.1
	MetS	0.09	-0.11	0.14	-0.22	0.41*

dysfunction of M-cells, which increases the permeability of the intestinal epithelium for food antigens. We have previously shown that individuals with MetS have higher levels of IgG to food antigens and their elevated concentrations are more often detected [4].

A correlation analysis of the levels of specific IgG to antigens of products with MetS markers was performed in groups with metabolic syndrome and in practically healthy individuals. Antigens were divided into groups: dairy products, meat, fish and seafood, cereals and nuts, fruits, vegetables.

Regular fish consumption has a positive effect on thyroid homeostasis and improves glucose homeostasis, helping to prevent diabetes and MetS [21, 28]. Analysis of the relationships between IgG to fish and seafood and MetS markers showed that practically healthy volunteers more often show significant positive correlations between IgG to fish and seafood antigens and HDL and triglycerides, and with MetS – with glucose levels (Table 1).

Plant products contain numerous biologically active substances (polyphenols, flavonoids, etc.) and fiber, which have a positive effect on MetS markers, reducing their levels and also regulating the normal functioning of the intestinal microflora [14, 15, 17, 24]. In MetS, statistically significant positive correlations were found between glucose levels and specific IgG to fruits with a high glycemic index - avocado, orange, banana, grapes, peach, plum and lemon (Table 2), which can be explained by metabolic disturbances in glucose absorption.

Analysis of correlations between specific IgG to vegetable antigens and MetS markers showed that in both groups a direct significant relationship between IgG levels to tomatoes and glucose concentration was recorded (Table 3). A relationship was found between IgG to green peas and HDL and LDL in practically healthy subjects. In individuals with MetS, IgG to green peas had a highly significant relationship with glucose levels. Legume fibers, resistant starch, and oligosaccharides can reduce glucose and

lipid levels and have a probiotic effect. In addition, they have a number of other health benefits, such as anti-inflammatory and antitumor effects [10].

Dairy products have different effects on the body when consumed. Cheese does not have a strong effect on blood cholesterol levels, like butter [7]. Casein micelles in the cheese structure can affect the ability of lipases to break down fat. In addition, cheese contains phosphorus, which promotes the formation of insoluble compounds during digestion, which reduces the absorption of fats [12]. The literature describes the beneficial effects of milk proteins on hypertension, dyslipidemia, and hyperglycemia [11]. In both groups of subjects, a highly significant relationship was found between the levels of specific IgG to soft cheese and glucose levels. In individuals with MetS, this relationship was more pronounced ($r = 0.7555$, $p = .034$) than in practically healthy volunteers ($r = 0.5230$, $p = .004$). In individuals with MetS, there are also high significant associations of specific antibodies to Cheddar and Swiss

cheeses with glucose levels ($r=0.6618$, $p=0.014$ and $r=0.7168$, $p=0.010$, respectively). In practically healthy volunteers, there is a significant correlation between Cheddar cheese consumption and HDL levels ($R=0.5386$, $p=0.003$) and cholesterol ($r=0.4176$, $p=0.027$). There is also a high correlation between antibodies to Swiss cheese, yogurt and HDL ($r=0.4992$, $p=0.007$ and $r=0.4090$, $p=0.031$, respectively) in practically healthy people (Table 4).

According to the literature, red meat consumption is associated with a higher risk of MetS, while poultry consumption is associated with a lower risk [8, 20]. A small number of significant relationships are recorded for meat and poultry antigens, so no reliable correlations were found between the levels of IgG to rabbit and pork with MetS markers in either group. For the examined individuals with MetS, a positive significant correlation was found between IgG to turkey and HDL ($r=0.45$, $p=0.02$), glucose ($r=0.38$, $p=0.05$), total cholesterol ($r=0.49$, $p=0.01$); IgG to chicken - with total cholesterol ($r=0.41$, $p=0.03$) and a negative relationship between IgG to beef antigens and abdominal circumference ($r=-0.44$, $p=0.02$). In practically healthy volunteers, abdominal circumference has a direct significant relationship with IgG to turkey ($r=0.44$, $p=0.02$) and chicken ($r=0.40$, $p=0.03$), and IgG to lamb antigens with glucose levels ($r=0.40$, $p=0.03$) (Table 5).

In our study, immunoglobulins G to black pepper have a direct significant correlation with LDL and HDL levels in the group of practically healthy people, and in the group with MetS these indicators have an inverse relationship (Table 6). Black pepper contains a substance - piperine, which has a hypoglycemic effect, and also reduces the level of lipids and cholesterol [2].

Some sources claim that dark chocolate/cocoa products have a beneficial effect on total and LDL cholesterol [27]. According to other sources, cocoa polyphenols contained in chocolate can increase HDL cholesterol concentrations, while chocolate fatty acids can change the fatty acid composition of LDL and make it more resistant to oxidative damage [12]. In our study, a significant association of immunoglobulins G to chocolate with abdominal circumference was observed in individuals with MetS (Table 6).

Conclusion. The examined patients with MetS are characterized by a higher content of proinflammatory cytokines and C-reactive protein, which may be due to the presence of chronic sluggish inflammation associated with the risk of devel-

oping chronic non-infectious diseases, including MetS. It has been shown that with MetS, the range of food antigens to which correlations with markers of MetS and general inflammation are established is wider. Most often, direct significant relationships with glucose levels are recorded. The examined individuals with MetS did not have a confirmed diagnosis of diabetes mellitus and, therefore, did not take insulin drugs to regulate blood sugar levels. Thus, when introducing elimination diets, it is necessary to take into account the possibility of postprandial hyperglycemia in this group of individuals, and monitor insulin levels to prevent the development of insulin resistance.

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T.E. Tatarinova, A.S. Asekritova, O.V. Tatarinova

PROSPECTS FOR THE USE OF REMOTE BLOOD PRESSURE MONITORING AT THE PRIMARY HEALTHCARE LEVEL

To study the effectiveness and prospects of using telemedicine technologies for monitoring blood pressure (BP) in patients with arterial hypertension (AH) at the primary care level, remote BP monitoring was carried out using a digital platform. The study included 146 patients with uncontrolled BP, who measured BP at least twice a day using automatic monitors with Bluetooth data transfer. Measurement data were received by the remote monitoring system, where they were automatically processed and transmitted to the attending physician's personal account.

During the 10-month follow-up of patients with AH, target BP values below 135/85 mmHg were achieved in 83% of cases. During remote monitoring, therapy adjustments were observed: the number of patients on monotherapy decreased from 22.4% to 8% ($p < 0.05$).

Keywords: arterial hypertension, blood pressure, telemedicine, remote blood pressure monitoring.

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Introduction. Modern medicine at the primary care level faces a number of challenges associated with the diagnosis and treatment of chronic noncommunicable diseases, among which arterial hypertension (AH) holds one of the leading places. Its high prevalence, associated complications, and significant share of mortality due to cardiovascular disease make blood pressure (BP) control a priority in healthcare. It is important to note that uncontrolled hypertension is directly associated with the development of cardiovascular catastrophes such as stroke, myocardial infarction, and sudden cardiac death [5].

According to the Ministry of Health of the Republic of Sakha (Yakutia), the main causes of mortality in 2023 were circulatory system diseases (42.4% vs. 38% in 2021), cancer (16.5% vs. 11.8% in 2021),

and external factors (16.6% vs. 10.4% in 2021). Among cardiovascular diseases, coronary heart disease (46.3%, including myocardial infarctions 14.9%) and cerebrovascular diseases (22.2%, including strokes 48.0%) are most common [8]. The increase in mortality from cardiovascular disease is associated with a rise in the number of conditions among the population, particularly those accompanied by elevated blood pressure.

Extensive studies show that lowering blood pressure can significantly reduce the risk of serious cardiovascular diseases, coronary artery disease, heart failure, and death, with the same proportional reduction across different population subgroups [14]. One of the main forms of preventive work with patients with elevated BP is timely enrollment in dispensary observation, with adherence to the required frequency of check-ups [8, 4].

Studies over the past decade confirm that home (ambulatory) blood pressure measurements outperform standard in-clinic measurements for predicting both overall and cardiovascular mortality [6]. However, traditional approaches to BP monitoring, based on keeping self-control diaries and periodic patient visits to the physician, do not always provide timely and sufficient data for effective disease control.

According to the observational study

ESSE RF-2, only 49.7% of patients diagnosed with hypertension and receiving antihypertensive therapy achieved target indicators. Meanwhile, only 24.9% of the general population with hypertension maintained BP control after achieving target results [10].

The use of active remote observation of patients with hypertension receiving antihypertensive therapy (both in Russian and international practice) contributes to achieving target BP values, subsequent monitoring of health indicators, and timely provision of medical assistance [11].

In this regard, remote blood pressure monitoring (RBPM), using modern telemedicine technologies, represents a promising direction that can improve the quality of medical care and reduce the workload on primary healthcare. Integration of RBPM into primary care practice allows not only continuous monitoring of patient status and achievement of targets, but also increases adherence and involvement in the treatment process — especially important for chronic noncommunicable diseases requiring long-term follow-up.

The aim of our study was to evaluate the effectiveness of RBPM in outpatients to improve control of arterial hypertension.

Materials and Methods. The depart-

TATARINOVA Tatyana Evgenevna – clinical pharmacologist of the Republican Clinical Hospital No 3, ORCID: 0000-0002-2616-3655, mixatan@mail.ru; **ASEKRITOVA Alexandra Stepanovna** – Candidate of Medical Sciences, head of the Center of Predictive Medicine and Bioinformatics of the Republican Clinical Hospital No 3, Associate Professor of M.K. Amosov NEFU, ORCID: 0000-0002-5378-2128, my@asekritova-8.ru; **TATARINOVA Olga Viktorovna** – Doctor of Medical Sciences, chief physician of the Republican Clinical Hospital No3, Ph.D., YSC CMP, ORCID: 0000-0001-5499-9524, tov3568@mail.ru.

mental pilot project “Remote blood pressure monitoring in outpatients” was carried out in accordance with the order of the Ministry of Health of the Russian Federation No. 91n of March 1, 2023 [9] and the order of GAU RS(Ya) “Republican Clinical Hospital No. 3” No. 27 of January 30, 2023 “On the implementation of pilot projects ‘Medical Patronage’ and ‘Remote BP Monitoring in Outpatients’ on the basis of GAU RS(Ya) ‘Republican Clinical Hospital No. 3’”. The project lasted 10 months in 2023.

Inclusion criteria:

- age over 18 years;
- established diagnosis of hypertension and/or BP readings above 140/90 mmHg during outpatient measurement;
- basic smartphone user skills and ability to use an automatic BP monitor independently or with assistance;
- valid registration on the Unified State Services portal;
- informed voluntary consent of the patient.

Exclusion criteria: severe somatic and psychiatric diseases; acute infectious diseases; absence of data exchange and contact with the patient.

During participation in the pilot project, patients were conditionally divided into two groups:

- **Group 1 — therapy control group:** BP measurements once every three days, twice a day (morning and evening); 12 people included.
- **Group 2 — therapy selection group:** BP measurements daily, twice a day (morning and evening); 134 people included.

In-person visits of patients to the attending physician were limited to two required appointments: an initial visit (recorded in the medical information system as an outpatient case) and a follow-up. A three-party rental agreement for the device was signed. Patients were instructed on measurement technique, frequency, use of the personal account, and safety rules.

As part of the project, 20 automatic arm blood pressure devices were used, provided under a loan agreement to patients by RT Doctis LLC. The devices had the function of data transmission via Bluetooth to the *GOSTELEMED* mobile application, with subsequent integration into a centralized system.

Within this system, all events occurring during RBPM were classified as medical or non-medical and automatically processed.

A *medical event* was considered any significant deviation of systolic BP (SBP), diastolic BP (DBP), or heart rate (HR) from

the set threshold values by 7.1% or more. A *non-medical event* was considered the absence of data transmission from a patient for a certain period of time.

If data were not received, the system automatically sent the patient a push notification reminding them to perform a measurement and transmit data. If the data still were not received, operators contacted the patient by phone to determine the reason and remind them of the need for a measurement.

Medical events were divided into three categories by urgency:

1. **Critical category:** BP above 180/106 mmHg or below 86/56 mmHg. In such cases, the operator contacted the patient within an hour to provide consultation and recommendations on pressure normalization, or directed the patient to emergency medical services. The attending physician determined further treatment tactics.

2. **Intermediate category:** BP range 151/91 to 179/105 mmHg or 87/57 to 89/59 mmHg. These cases required the physician's attention to assess the patient's condition and decide whether to adjust therapy.

3. **Target category:** BP in the range 90/60 to 150/90 mmHg. Target BP levels were determined individually for each patient.

The results of event interpretation were displayed in the physician's account in the form of a color-coded dashboard. The physician observed each patient's indicators daily throughout RBPM. If values deviated from targets, remote interim consultations were held via the digital platform (chat and audio communication). Patients could also call their physician during working hours on a landline phone.

If necessary, in-person consultations were arranged, with the examination documented in the medical information system and therapy adjusted. The protocol, certified by an electronic signature, was sent to the patient via the *GOSTELEMED* mobile app.

Statistical analysis. Statistical analysis of project data was performed using IBM SPSS Statistics (version 26.0). The distribution of variables was tested with the Shapiro–Wilk and Kolmogorov–Smirnov tests. Interval scale data are presented as mean $\pm$ standard deviation ($M \pm SD$).

To assess differences between two independent samples, the Mann–Whitney U test was applied. To analyze the strength and direction of correlations between quantitative variables, Spearman's rank correlation coefficient was calculated.

Statistical significance of differences in qualitative variables was evaluated using the chi-square test (χ^2), provided that values in each cell of the four-field contingency table exceeded 10.

Differences were considered statistically significant at $p < 0.05$, ensuring at least 95% confidence in the obtained results.

Results. The average duration of RBPM per patient was 22.4 days (range 7 to 57 days). Women made up the majority of the sample — 102 people (69.9%), while men accounted for 30.1% (44 people). The mean age of participants was 56.94 ± 13.15 years. Men (52.93 ± 14.14 years) were not significantly younger than women (58.67 ± 12.37 years), $p > 0.05$.

The clinical and demographic characteristics of RBPM patients are shown in **Table 1**. It should be noted that overweight and obesity were identified in the majority of patients (84%). Women were statistically more likely than men to have lipid profile disorders: 71.6% vs. 54.5%. Harmful habits such as smoking were reported in 43.8% (64 people), significantly more often among men (56.8% vs. 16.7% among women).

The dynamics of BP indicators at the beginning and end of RBPM are presented in **Table 2**. The average SBP/DBP in the first three days of RBPM was 133.97 ± 16.07 / 83.98 ± 11.44 mmHg, gradually decreasing to 126.91 ± 13.13 / 77.85 ± 9.77 mmHg by days 14–22 ($p < 0.05$).

An interesting finding was the distribution of unscheduled measurements and missed BP readings. The frequency of unscheduled measurements decreased by the end of the observation period. The increase in missed measurements by the end of monitoring was likely associated with the stabilization of patients' BP (see **Table 2**).

During RBPM, therapy adjustments were observed: the proportion of patients on monotherapy decreased from 22.6% to 8.2% ($p < 0.05$). Numerous studies confirm that combining drugs from at least two different antihypertensive classes is more effective at lowering BP than increasing the dose of a single agent. In addition, the use of fixed-dose combinations in a single tablet improves patient adherence to treatment [2,6,10].

For 3.4% ($n=5$) of patients, an ambulance was called due to elevated BP during RBPM. There were no emergency hospitalizations for decompensated hypertension during monitoring.

Throughout the monitoring period, no device breakdowns or malfunctions were recorded. Some temporary sys-

Table 1

Clinical and demographic characteristics of RBPM patients

Indicator	Total	Men	Women	p (M=F)
Patients, n (%)	146	44 (30.1)	102 (69.9)	<0.05
Age (M±SD), years	56.94±13.15	52.93±14.14	58.67±12.37	NS
BMI (M±SD), kg/m ²	29.1±4.36	29.49±3.06	29.06±4.83	NS
Overweight & obesity, n (%)	123 (84.2)	41 (93.2)	82 (80.4)	NS
Total cholesterol (M±SD), mmol/L	5.95±1.46	5.39±1.16	6.19±1.52	NS
LDL-C (M±SD), mmol/L	3.68±1.12	3.22±0.95	3.88±1.13	NS
Dyslipidemia, n (%)	97 (66.4)	24 (54.5)	73 (71.6)	<0.05
Smoking, n (%)	64 (43.8)	25 (56.8)	17 (16.7)	<0.05
Impaired glucose tolerance, n (%)	5 (3.4)	1 (2.3)	4 (3.9)	NS
Diabetes mellitus, n (%)	20 (13.7)	6 (13.6)	14 (13.7)	NS
Coronary heart disease, n (%)	19 (13.0)	4 (9.1)	15 (14.7)	NS

Note: BMI – body mass index; NS = no significant differences, p>0.05.

Table 2

Dynamics of indicators at the beginning and end of remote monitoring

Indicator	Start of RBPM (0–3 days)	End of RBPM (14–22 days)	p
SBP (M±SD), mmHg	133.97±16.07	126.91±13.13	<0.05
DBP (M±SD), mmHg	83.98±11.44	77.85±9.77	<0.05
HR	73.88±10.85	73.21±9.30	NS
Proportion of SBP >180 mmHg	5.5%	0.7%	<0.05
Proportion of unscheduled BP measurements	4.8%	1.4%	NS
Proportion of missed BP measurements	0.7%	31.5%	<0.05
Monotherapy	22.6%	8.2%	<0.05

Note: BMI – body mass index; NS = no significant differences, p>0.05. NS = not significant, p > 0,05.

tem failures occurred, such as disabling of individual target BP/HR settings, lack of patient data displayed in graph form, or device detachment from the patient. However, these failures did not significantly affect the overall results of RBPM.

Previous studies in certain regions of Russia demonstrated the high effectiveness of telemedicine technologies in BP control [1, 12, 6]. Remote BP and heart rate monitoring among civil servants in Ufa significantly reduced in-person clinic visits, prevented hospitalizations, and reduced work disability episodes related to hypertension [1].

A study by the TP NMIC conducted in 5 Russian regions, including 3,609 hypertensive patients, showed significant reductions in SBP (–4.7%) and DBP (–4.4%) (p<0.001). During follow-up, 3,364 patients (93.2%) maintained adherence to monitoring, while 245 patients

(6.8%) dropped out [Korsunsky].

Conclusion. The project achieved a significant reduction in SBP, with target values reached in 83% of patients, while decreasing the number of in-person clinic visits. It is also important to note that the decision on the need and urgency of patient contact during RBPM was made by the physician, based on the received data, rather than by the patient as in usual outpatient care. Thus, patient flow regulation for those diagnosed with hypertension was directed by the physician, which can be widely applied in the management of patients under dispensary observation.

Remote BP monitoring in outpatients has proven convenient for both therapy selection and control. It can be successfully used in routine medical practice to improve patient follow-up quality, enhance adherence, and ensure regular BP monitoring, while positively impacting

the workload of primary care physicians. However, it should be taken into account that adherence to BP measurements decreases once indicators stabilize and RBPM duration increases, which requires more active supervision of patients.

It can be assumed that one of the delayed effects of RBPM in hypertensive patients will be a positive impact on overall morbidity and mortality from cardiovascular diseases in the population.

This study has several limitations, including the short observation period and limited statistical power. Further research on larger groups of patients with longer observation periods is promising, as it will allow assessment of the impact of RBPM on clinical outcomes and endpoints.

Given the positive results of the present observation, it can be concluded that the use of telemonitoring methods in physician–patient interaction for BP stabilization should occupy an important place in primary care practice.

The authors declare no conflict of interest.

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CLINICAL CASE

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N.A. Chulakova, A.F. Potapov, K.V. Chulakov, E.E. Matveeva,
I.A. Trimbach, A.A. IvanovaINTENSIVE CARE OF SEVERE
LIFE-THREATENING HYPOKALEMIA
(A CASE REPORT)

A case report describes a severe hypokalemia (0,6 mmol/L) case with severe secondary hypokalemic generalized muscle weakness, bilateral symmetric calcification in the brain in the patients with chronic tubulointerstitial nephritis.

Keyword: Hypokalemia, hypokalemic myoplegia, Gitelman syndrome, tubular disorder

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Introduction. Correction of electrolyte disorder is one of the major challenge in the daily practice of the critical care specialist. The main electrolytes that require surveillance during intensive care are located in the extracellular (Na^+ , Ca^{2+} , Cl^- and HCO_3^-) and intracellular (K^+ , Mg^{2+} , HPO_3^{2-} , H_2PO_4^- , SO_4^{2-}) water sectors and

determine the homeostasis of the human body.

Potassium is the main intracellular cation with concentration about 120-150 mmol/L, which is 98% of all the potassium in the body. Potassium normal range in peripheral blood tests is 3,5-5,5 mmol/L [9]. Potassium content and its transport between the cell and the interstitial space depends on human nutrition, kidney function, drugs and the endocrine system (aldosterone and insulin concentrations) [16]. Potassium homeostasis is maintaining within a narrow range by two mechanisms: the first regulates its excretion through the kidneys and intestines, the second sustains the difference of concentrations in the intra- and extracellular spaces.

The most common electrolyte disturbance in clinical practice is hypokalemia – the decrease in blood potassium below 3.5 mmol/l. Potassium concentration below 3,0 mmol/L is considered as severe hypokalemia, and values below 2.5 mmol/L is an indication for admission and its urgent correction in the hospital. Low potassium levels increase cardiomyocyte membrane excitability, resulting in increased cardiac automaticity and delayed ventricular repolarization leading to fatal arrhythmias [8].

This study describes clinical case of hypokalemia where the minimal blood potassium value was 0,6 mmol/L.

Case report. A male patient 26 years old admitted in the Yakut Republican Clinical Hospital (YRCH) in 2024 with DS: «Severe tubular insufficiency. CKD, stage 2, GFR 85,6 ml/min/1,72m². Solitary kidney? (Bartter's? Gitelman's? Fanconi's?). Acute kidney injury. Renal replacement therapy (haemodialysis) №5 (dated 2022). Complications: Secondary hyperaldosteronism. Severe electrolyte

disorders. Secondary enteropathy. Secondary immunodeficiency. Moderate pneumonia (resolution). Severe dysmetabolic encephalopathy with complete recovery. Mild toxic hepatitis of mild (resolution). Concomitant diagnosis: Erythematous gastropathy. Bilateral maxillary sinusitis on the right side in the exudation stage. Hypoplasia of the thyroid gland. Euthyroidism. Residual encephalopathy. Ischaemic angioretinopathy OU. Late hospitalization».

Complaints on admission were weakness, dry mouth, thirst, loss of appetite, muscle pain, decreased urine and no stools for more than 5-7 days.

Anamnesis morbi. Patient reported that his condition worsened last 2 months, when he stopped taking the previously recommended potassium (300 mg per day per os). Nausea, vomiting and liquid stools, with the higher body temperature 38C were noted, for which he was treated on an outpatient basis. After 2 months of the illness, when 'pulling pains' in the lower extremities, decreased urine and weight loss of more than 5 kg, he sought medical help at the Republican Hospital №2 - Emergency Medical Care Centre (RH №2-EMCC). After examination in the emergency room, the patient was referred to the YRCH (therapeutic unit) and, according to the severity of his condition, was admitted in the intensive care unit (ICU).

Anamnesis vitae. Patient reported that his medical history was a rather healthy, no known hereditary diseases. He graduated lower post-secondary vocational education and works as a chef. He is married.

He has been observed by a nephrologist since 2022 with the diagnosis: N12. Tubulointerstitial nephritis, unspecified as acute or chronic. In the period of 2022-

CHULAKOVA Nadezhda Aleksandrovna – assistant, Department of Anesthesiology, Resuscitation, and Intensive Care with a Course in Emergency Medicine, Faculty of Postgraduate Medical Education, Medical Institute, M.K. Ammosov North-Eastern Federal University; anesthesiologist-resuscitator, Department of Anesthesiology, Resuscitation, and Intensive Care, State Budgetary Institution of the Republic of Sakha (Yakutia), Yakutsk Republican Clinical Hospital, ORCID: 0009-0001-5356-2950, chulakovan@list.ru; **POTAPOV Aleksandr Filippovich** – MD, Professor, Department of Anesthesiology, Resuscitation, and Intensive Care with a Course in Emergency Medical Care, Faculty of Postgraduate Medical Education, Medical Institute, M.K. Ammosov North-Eastern Federal University, anesthesiologist-resuscitator, Department of Anesthesiology, Resuscitation, and Intensive Care, State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Clinical Hospital", ORCID: 0000-0003-2087-543X, potapov-paf@mail.ru; State Budgetary Institution of the Republic of Sakha (Yakutia) "Yakutsk Republican Clinical Hospital", Department of Anesthesiology, Resuscitation, and Intensive Care: **CHULAKOV Kirill Viktorovich** – head of the Department. Department, ORCID: 0009-0001-6781-9550, world@rambler.ru; **MATVEEVA Ekaterina Evgenievna** – anesthesiologist-resuscitator, katya.eryomenko.92@mail.ru; **TRIMBACH Ivan Anatolyevich** – anesthesiologist-resuscitator, trimbach747@gmail.com; **IVANOVA Albina Ammosovna** – MD, PhD, associate professor, head of the Department of Anesthesiology, Resuscitation and Intensive Care with a Course in Emergency Medical Care, Faculty of Postgraduate Training of Physicians, Medical Institute, M.K. Ammosov North-Eastern Federal University, ORCID: 0000-0002-3782-6864, iaa_60@mail.ru

2024 he was repeatedly examined and treated in Yakutsk hospitals, including renal replacement therapy (haemodialysis). In July 2023, he was treated in the ICU in RHN2-CEMP with hypokalaemia – 0.7 mmol/l. To clarify the diagnosis in 2023, a telemedicine consultation with the Federal State Budgetary Institution 'National Medical Research Centre of Endocrinology' of the Ministry of Health of the Russian Federation was conducted and genetic tests to exclude hereditary tubulopathies was recommended. In 2024, he was examined by an endocrinologist and a genetic at the Republican Hospital №1 - National Centre of Medicine named af-

ter M.E. Nikolayev and laboratory results showed hypokalemia (2,36 mmol/L), hypomagnesemia (0,69 mmol/L), hypercalcemia (2,51 mmol/L), urinary calcium excretion (0,78 mmol/L), hyperreninemia (166,2 pg/ml), hyperaldosteronism (761,8 pg/ml) He was recommended a genetic test on the profile 'Tubulopathies'. The patient did not undergo the recommended examinations and tests due to family circumstances.

On admission in ICU patient's condition was severe due to water and electrolyte disorders (severe hypokalemia, hypovolemic hyponatremia), sepsis, hypokalemic weakness of both smooth and

skeletal muscle resultant in myoplegia with intestinal paralysis.

Height – 160 cm, weight – 51 kg, body mass index – 19.9 kg/m². APACHE II – 16 points, SOFA – 2 points. CKD-EPI – 68 ml/min/1.73m².

He was a consciousness (Glasgow coma scale was 15 points), but hypodynamic. Skin and visible mucous membranes were usual and moist. Lung auscultation was carried out in all fields, no adnormal sounds were heard. Haemodynamics were BP 106/63 mmHg, HR 62 per minute. Tongue was dry, with white plaque. The abdomen is retracted, bowel sounds auscultation was barely heard

Table 1

Clinical and laboratory presentation

Variables	On admission	1 day	2 day	3 day	4 day	5 day	6 day	11 day
pH [7,320-7,420]	7.428	7.416	7.311	7.435	7.369	7.476	7.418	7.358
Sodium, mmol/l [135,0-145,0]	120.0	125.0	136.0	140.0	141.0	140.0	146.0	135.0
Potassium, mmol/l [3,7-5,3]	0.9	0.6	1.2	2.9	2.7	4.3	2.4	2.6
Calcium, mmol/l [1,15-1,29]	1.08	1.05	1.19	0.85	1.10	1.19	1.92	1.17
Lactate, mmol/l [0,5-1,6]	1.9	2.1	2.6	2.0	3.1	1.0	1.3	2.7
WBC, 10 ⁹ /л [4,00-9,50]	21.08	17.55	25.75	28.85	19.79	14.68	10.59	7.36
Neutrophils, % [37,0-72,0]	87.0	81.3	96.2	86.9	85.3	83.8	76.5	70.9
Lymphocytes, % [20,0-40,0]	8.3	13.6	1.4	7.7	8.5	10.0	15.5	23.1
Creatinine, мкмоль/л [62,0-106,0]	139.1	169.0	135.0	148.0	151.0	132.0	148.0	92.0
GFR (CKD-EPI) ml/min/1,73m ²	68	53	71	63	61	73	63	115
LDH, U/l [135,0-225,0]	225.2	238.0	210.0	331.0	368.0	661.0	586.9	413.0
CRP, mg/l [0-5,0]	49.66	62.4	29.5	102.1	179.2	232.3	175.53	8.4
PCT ng/ml	0.5	-	2.0	10.0	2.0	0.5	Отр	отр
Diuresis, ml/kg/h (total volume, ml)	3.9 (800 ml)	5.6 (6800 ml)	2.8 (3400 ml)	1.4 (1700 ml)	3.1 (3800 ml)	3.3 (4100 ml)	4.0 (4900 ml)	2.4 (2900 ml)
Intestine	Intestinal paralysis				Stool	-	Stool	-
Infusion volume, ml	1470	7510	5360	3360	2720	2360	2360	1780
KCl 4% intake, ml (mmol/l)	450 ml (241.2)	450 ml (241.2)	450 ml (241.2)	140 ml (75.0)	140 ml (75.0)	80 ml (42.9)	140 ml (75.0)	Per os 300 mg daily
Respiratory support		Invasive mechanical ventilation				Binasal catheter oxygenation 5 l/min		-
Norepinephrine infusion, mcg/kg/min	-	0.2	1.2	0.5	0.5	0.4	0.2/-	-
Haemodialysis, h	-	-	№1 12 ч	№2 12 ч	№3 10 ч	-	№4 10 ч	-

Note – WBC-white blood cells, GFR-glomerular filtration rate, LDH- Lactate dehydrogenase, CRP-C-reactive protein, PCT-procalcitonin.

with sluggish sound. Urination is autonomous, a urinary catheter was installed, through which straw-yellow-coloured urine was excreted. There was no peripheral oedema.

On admission laboratory (complete blood test, biochemical panel and urine analysis) and instrumental investigations (chest and abdominal computed tomography (CT), ultrasound of the abdominal cavity, ECG, echocardiography) revealed low plasma potassium (0.9 mmol/l) and sodium (120 mmol/l), signs of bilateral nephropathy, diffuse changes in both kidneys with signs of the cortical layer hypotrophy, round hypodense formation of the middle third of the right kidney, signs of thickening of the bladder wall and mucous membrane of the large intestine. ECG showed sinus rhythm with heart rate 68 beats/min, incomplete 1st degree atrioventricular block, amplified right ventricular potentials, diffuse myocardial changes, more pronounced in the anterior wall, atrial extrasystoles. Intensive care complex in OARIT included crystalloid infusion with additional microjet infusion of 4% CLI, respiratory, vasopressor, gastroprotective, anticoagulant therapy, enteral nutritional support and symptomatic treatment. Given the pronounced leukocytosis ($21.08 \cdot 10^9/l$), antibiotics were prescribed (Table 1).

The main clinical and laboratory parameters and treatment in the ICU are presented in Table 1 and haemodynamic parameters in Figure 1.

During the patient's treatment in the ICU, it was not possible to perform laboratory assessing of blood magnesium levels. However, considering the clinical and laboratory findings and a history of hypomagnesemia, the patient preventive treatment with magnesium was prescribed (Magnesium sulfate 25%, 10 ml twice daily).

Intensive care included crystalloid infusion with additional prolonged infusion of 4% Kalii chloridum, respiratory and vasopressor support, gastroprotective, anticoagulant therapy, enteral nutritional support and other treatment. Because of leukocytosis ($21.08 \cdot 10^9/l$) antibiotics were prescribed (Table 1).

In a view of the significant hypokalemia duration (according to the anamnesis morbi the last two months), correction was chosen not 'aggressive' and was carried out by prolonged infusion at a dose of 240 mmol.

Despite the initial therapy, muscle weakness and acute respiratory failure (ARF) deteriorated on the 1st day, which was an indication for intubation and initiation of invasive mechanical ventilation

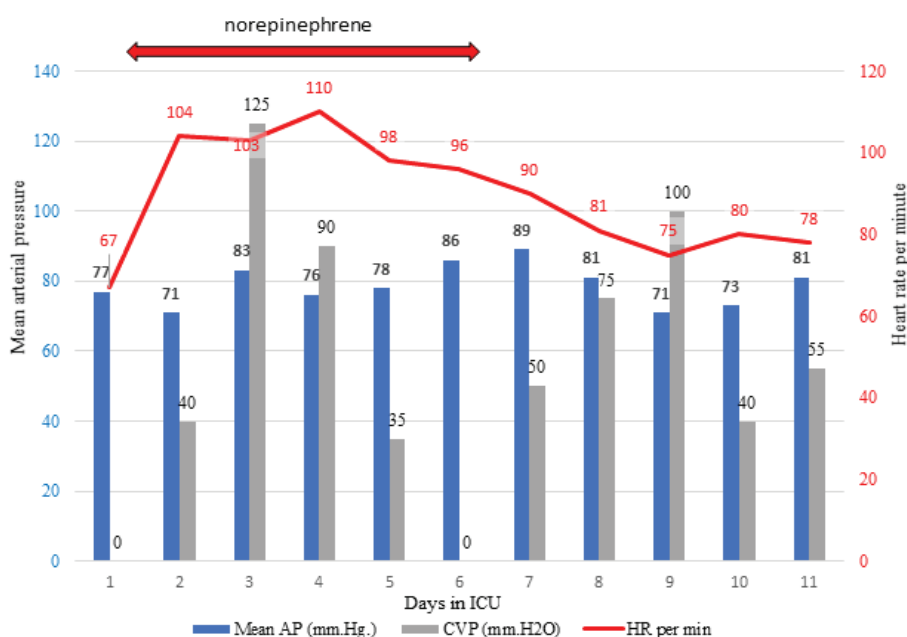


Fig. 1. Main hemodynamic parameters. The red arrow is vasopressor use (norepinephrine)

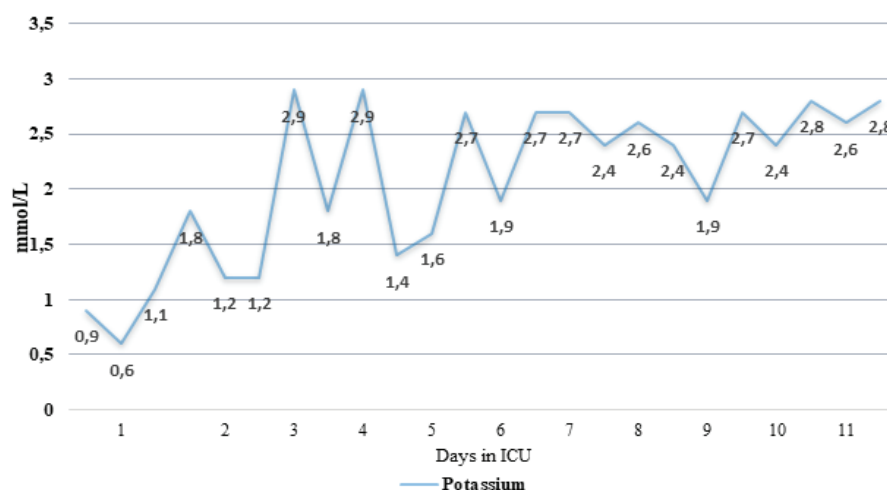


Fig. 2. Dynamics of venous blood potassium level. The blue arrows are haemodiafiltration session

(IMV). Due to arterial hypotension, vasopressor – norepinephrine was administered at a dosage of 0.2-1.2 mcg/kg/min to maintain mean BP at 95 mmHg. Vasopressor therapy was discontinued on the 6th day when haemodynamics stabilised (systolic BP above 100 mmHg).

In addition to the correction of water-electrolyte disorders and due to signs of systemic inflammatory response, a decision was made to perform efferent treatment method – continuous venovenous haemodiafiltration (CDH). The dynamics of potassium level in blood plasma against the background of therapy is presented in Figure 2.

Positive clinical and laboratory dynamics, restoration of muscle tone, adequate spontaneous breathing and intestinal mo-

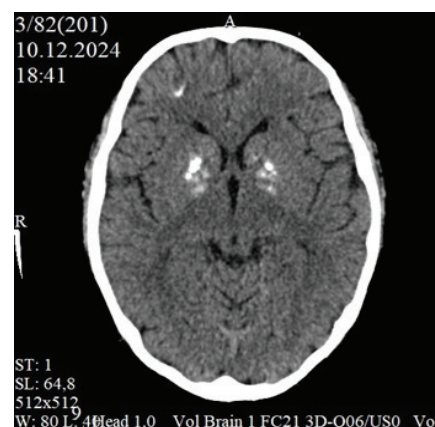


Fig. 3. Bilateral symmetric calcification in subcortical structures and subcortical areas of the middle frontal gyrus

tility were noted against the background of intensive therapy. On day 4, the patient was taken off the ventilator and extubated. After 11 days of intensive care in the ICU the patient with a potassium level of 2.6 mmol/l was transferred to a specialized department for further treatment.

In the ICU, along with intensive therapy, additional studies were conducted to clarify the diagnosis: blood cortisol levels (morning) – 1190.69 nmol/l (N=166-507 umol/L (morning)), thyroid-stimulating hormone – 1.22 mIU/L (N=0.40-4.00 mIU/L), urinary calcium excretion – 0.73 mmol/L (N=2.5-7.5 mmol/L), blood magnesium 0.89 mmol/L (N=0.73-1.06 mmol/L). Secondary hyperaldosteronism was confirmed by the following tests: renin (prone) 166.20 mIU/L (N=4.40-46.10 mIU/L), aldosterone (prone) 761.90 pg/ml (N=30.00-172.00 pg/ml).

The oncological genesis of hypokalemia is excluded – cancer embryonic antigen – 2.5 ng/ml (N less than 5 ng/ml), CA-15-3 – 6,9 U/ml (N=0-25 U/ml), alpha-fetoprotein – 4.4 ng/ml (N=0-8 ng/ml).

A number of autoimmune diseases were excluded (scleroderma, autoimmune systemic vasculitis, IgA nephropathy, autoimmune hepatitis, Crohn's disease, systemic lupus erythematosus, etc.): antineutrophil antibodies (ANCA), antinuclear antibodies (ANA) were negative, antibodies to native DNA – 11 IU / ml (N=0-20), antibodies to cyclic citrullinated peptide (anti-CPP) – 9.4 U/ml (N=0-20), antibodies to myeloperoxidase – 2.2 U/ml (N=0-20), antibodies to nucleosomes – 10 U/ml (N=0-20), autoantibodies of the IgG class to the Sci-70 antigen – 6 U/ml (N=0-15), antinuclear antibodies to the Sm-antigen – 3.2 IU/ml (N=0-15), antibodies to mitochondrial antigens – 7.7 (N=<10 IU/ml). Celiac enteropathy was excluded, antibodies to gliadin IgG were 9.291 U/ml (N=0-25), IgA– 9.426 U/ml (N=0-25).

The brain CT revealed symmetrical calcification in the subcortical structures (caudate nucleus, putamen, globus pallidus, internal capsule), areas of calcification in the subcortical white matter of the middle frontal gyrus of both hemispheres, in the projection of the pineal gland, occipital horns, in both hemispheres of the cerebellum (see Fig. 3).

Thus, differential diagnosis and treatment of hypokalemia remain a complex task. This is due to plenty of diseases and acute conditions that are accompanied by hypokalemia (see Fig. 4) [9, 16].

In the presented clinical case, among the above-mentioned causes of hypokalemia, the most likely is the presence of

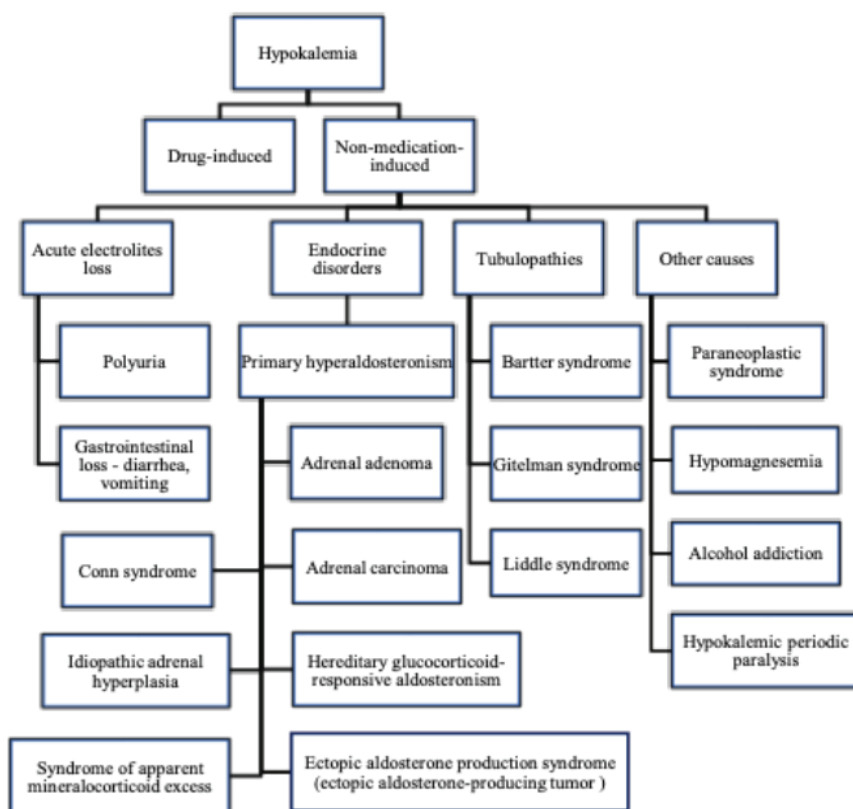


Fig. 4. Flow diagram of hypokalemia etiology

Table 2

Gitelman syndrome symptoms

	Manifestations
Cardiovascular system	ECG – pseudoischemic manifestations, prolongation of QT (with the development of paroxysmal ventricular arrhythmias and sudden death) [1] Tendency to hypotension or normal blood pressure [11]
Nervous system	Fatigue Paresthesia Depression Spasms in the extremities (tetany) Bilateral calcification in the brain [6]
Muscle	Myoplegia [10] Risk of developing myopathy and rhabdomyolysis when prescribed statins
Electrolyte disturbance	Hypokalemia Hypomagnesemia Hypercalcemia
Endocrine system	Aldosteronism Hyperreninemia Body mass deficit
Skin	Dermatitis
Bone	Osteoporosis Chondrocalcinosis (pyrophosphate arthropathy) [2] Arthralgia [4]
Eyes	Sclerochoroidal calcifications [13, 14]
Kidneys	Progressive tubulointerstitial nephritis (before ESRD) AKI (with rhabdomyolysis)
Digestive system	Intestinal paresis (constipation, dynamic acute intestinal obstruction) [4]

Table 3

Differentials between Bartter and Gitelman syndromes with primary hyperaldosteronism

	Bartter syndrome	Gitelman syndrome	Primary hyperaldosteronism
Early manifestation	Early childhood, antenatal period	6-13	At any age, usually 30-40 years old
Polyuria	Severe polyuria/polydipsia	No	Polyuria/polydipsia Nocturia
Laboratory indicators	Hypokalemia Hypocalcemia Normal magnesium levels	Hypokalemia Hypercalcemia Hypomagnesemia Increased renin Increased aldosterone	Hypokalemia Increased aldosterone Low renin
Calcium excretion	High	Low	Normal
Calcification	Nephrocalcinosis	Extrarenal	No
Blood pressure	Nonspecific changes	Low	Persistent increase

Gitelman syndrome (GS), an autosomal recessive disease of the renal tubules caused by a defect in the SLC12A3 gene, which encodes the thiazide-sensitive transporter NCCT in the distal convoluted tubule and leads to a decrease in the reabsorption of sodium, potassium and chlorine. Distinctive hypomagnesemia occurs due to a decrease in TRPM6 activity (transient receptor potential cation channel subfamily M member 6) [5, 13].

Currently, the prevalence of GS is unknown; on average 25 cases per 1 million population are indicated [3, 15]. GS is characterized by hyperaldosteronism, hyperreninemia on the background of normal or low blood pressure [10], increased urinary excretion of potassium and magnesium, as well as decreased calciuria (less than 2.0 mmol/L) [5]. The latter is an important link in the differential diagnosis in favor of GS. The exact mechanism of hypocalciuria is not known, it is assumed that there is an increase in passive calcium reabsorption, a disturbance of sodium intake with subsequent involvement of calcium channels, or a malfunction of the Na/Ca exchanger [3]. Hypercalcemia leads to progressive calcification, cases with progressive bilateral calcification in the brain [6], chondrocalcinosis [2, 13], and sclerochoroidal calcifications [13, 14] have been described. The diagnosis of GS is confirmed by a genetic study of the SLC12A3 gene mutation. According to publications, the symptoms of Gitelman syndrome in adult patients are shown in Table 2.

Additionally, differential diagnosis was performed with Bartter syndrome and primary hyperaldosteronism, the main clinical manifestations of which are shown in Table 3. Bartter syndrome, unlike GS, is characterized by severe polyuria, hypocalcemia, and nonspecific changes in blood pressure. In primary hyperaldoste-

ronism, excessive aldosterone production is autonomous or relatively autonomous from the renin-angiotensin system, and the main clinical sign is hypertension syndrome with changes in fundus vessels and headaches [7, 12]. Primary hyperaldosteronism is also characterized by the presence of macro- and microadenomas of the adrenal glands, thickening of the adrenal pedicles, hyperplasia, changes in the anatomy of veins and other specific changes detected during topical diagnostics (ultrasound, computed and magnetic resonance imaging, scintigraphy of the adrenal glands with ¹³¹I-cholesterol, adrenal phlebography with selective blood sampling).

Conclusion. Thus, differential diagnosis of the cause of severe hypokalemia is a difficult task in clinical practice. There are a lot of diseases and acute conditions, where hypokalemia is one of the leading syndromes, which requires extensive knowledge and experience from a doctor. Of course, in cases of a "difficult diagnosis", the diagnostic potential of a medical organization, the availability of a modern laboratory service and a computer diagnostics department with a wide range of studies play an essential role. No less difficult is the correction of severe hypokalemia itself. In most cases, the usual administration of a potassium solution does not lead to success due to a pronounced water-electrolyte imbalance, as well as the preservation of the causes that support it. The management of a patient with severe hypokalemia requires a multidisciplinary approach and adherence to the principles of continuity at all stages of the patient's treatment. It is impossible to improve the results of severe hypokalemia treatment without clarifying the underlying cause, timely and adequate treatment using modern intensive care management.

The authors declare that there is no conflict of interest

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D.N. Kostromitsky, A.Yu. Dobrodeev, D.P. Koval,
S.G. Afanasyev, A.S. Tarasova, D.I. Azovsky, S.V. Vtorushin

SURGICAL TREATMENT OF MESENCHYMAL HAMARTOMA OF THE LIVER: A CASE REPORT

KOSTROMITSKY Dmitry N. – MD, PhD, Senior Researcher, Abdominal Oncology Department, Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences (RAS), Tomsk, Russia, e-mail: d.n.kostromitsky@tomconco.ru. ORCID: 0000-0001-5691-2349; **DOBRODEEV Aleksey Yu.** – MD, PhD, DSc, Chief Researcher, Abdominal Oncology Department, Cancer Research Institute, Tomsk National Research Medical Center RAS, e-mail: dobrodeev@oncology.tomsk.ru. ORCID: 0000-0002-2748-0644; **KOVAL Daniil P.** – resident of the Department of Oncology, Siberian State Medical University, e-mail: daniil.vova555@gmail.com ORCID: 0000-0001-9056-9986; **AFANASYEV Sergey G.** – MD, PhD, DSc, Professor, Head of Abdominal Oncology Department, Cancer Research Institute, Tomsk National Research Medical Center RAS, e-mail: Afanasievsg@oncology.tomsk.ru. ORCID: 0000-0002-4701-0375; **TARASOVA Anna S.** – MD, PhD, Researcher, Abdominal Oncology Department, Cancer Research Institute, Tomsk National Research Medical Center RAS, e-mail: tarasova.as.tomsk@gmail.com. ORCID: 0000-0001-6247-3434; **AZOVSKY Daniil I.** – MD, Oncologist, Abdominal Oncology Department, Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, e-mail: azovdaniil@yandex.ru. ORCID: 0000-0001-7375-9585; **VTORUSHIN Sergey** – MD, PhD, DSc, Professor, Deputy Director for Research and Translational Medicine, Head of the Department of General and Molecular Pathology, Cancer Research Institute, Tomsk National Research Medical Center RAS, Professor of the Department of Pathological Anatomy, Siberian State Medical University (Tomsk, Russia), e-mail: vtorushin@rambler.ru. ORCID: 0000-0002-1195-4008.

Mesenchymal hamartoma of the liver (MHL) is an uncommon benign tumor that mostly occurs in young children and is extremely rare in adults. Currently, only a few cases of MHL in adults have been reported. Due to the rarity of MHL and insufficient understanding of histogenesis of this tumor, this category of patients is most often followed-up by general surgeons and gastroenterologists. In our report, we present a case of a 45-year-old female patient with MHL. Before surgery, a differentiated diagnosis included cholangiocarcinoma and focal nodular hyperplasia. Attempts of morphological verification, including ultrasound-guided biopsies, were uninformative. The final diagnosis was established after laparoscopic anatomical liver resection with histological and immunohistochemical examination. This case highlights the importance of a comprehensive approach to the diagnosis of liver tumors in adults and the need to include MHL in the differential diagnosis in the case of atypical clinical and radiological presentation.

Keywords: mesenchymal liver hamartoma, benign liver tumor, laparoscopy, liver resection, pathomorphology

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Introduction. Mesenchymal hamartoma of the liver (MHL) is a benign tumor, which was first reported by H.A. Edmondson in the mid-20th century [3]. It generally occurs in young children and has been rarely observed in adults [7]. Currently, about 50 adult cases have been reported [4-6, 9-11]. Macroscopically, the tumor is a clearly defined mass varying in size from a few centimeters to 30 cm or more, and its structure may additionally contain a cystic component [9]. In 30% of cases, these tumors may have a vascular pedicle [10]. The microscopic image of MHL is characterized by lobular

growth of myxomatous connective tissue containing scattered soft stellate mesenchymal cells. Branched bile ducts similar to ductal plate malformation may also often be present in the tumor [7].

Clinical symptoms of the disease are mild and depend on the location and size of the tumor. The most common complaints are general malaise, increased fatigue, and an increase in abdominal size [9]. It should be noted that approximately 75% of MHLs are located in the right lobe of the liver and most often manifest as a violation of the passage of the food bolus through the gastrointestinal tract,

weight loss, anorexia and respiratory failure. Most patients do not experience any symptoms that would prompt them to seek medical attention until the tumor has grown to a large size [10].

The etiology and pathogenesis of MHL is complex and poorly understood. To date, several theories of the origin of liver hamartoma have been described: 1) genetic, 2) vascular, 3) embryonic, and 4) toxic [1, 9, 10].

The main method of treating MHL is radical resection (R0). There is data on the development of angiosarcomas from MHL not only during follow-up for patients, but also over time after performing R1 resection [10]. Cases of liver transplantation have been also reported [1].

Case report. A 45-year-old female patient presented to the local clinic with complaints of general weakness and rapid fatigue. During the examination, moderate anemia of unknown origin was diagnosed. MRI of the abdominal cavity (12/23/2024) revealed 2 lesions in the left lobe of the liver (25×27 mm and 23×26 mm), closely adjacent to each other. Tumor markers, such as CEA, AFP, CA 19-9 were within normal limits. The patient was admitted then to the outpatient department of the Cancer Research Institute (Tomsk). The complexity of the diagnosis was caused by both the lack of convincing morphological findings for the tumor during two ultrasound-guided liver biopsies and the ambiguity of the CT image. The computed tomography scan of the abdomen with intravenous contrast (16.01.2025) demonstrated the presence of two merging hypodense lesions in the II+III segments of the left lobe of the liver, measuring 26×33 mm and 22×27 mm in diameter, located subcapsularly along the visceral surface. The lesions were clearly delineated, without signs of invasion into surrounding structures, with a homogeneous internal structure and no pronounced accumulation of contrast agent. Conclusion: tumor in the left lobe of the liver (cholangiocarcinoma, nodular hyperplasia of the liver) (Fig. 1).

The additional examination of the patient included chest X-ray, pelvic ultrasound, thyroid ultrasound, cervical and axillary lymph node ultrasound, breast ultrasound, video colonoscopy and esophagogastroduodenoscopy. The final clinical diagnosis was a tumor in II + III segments of the left lobe of the liver.

In January, 31, the patient underwent laparoscopic anatomical resection of segments II + III of the left lobe of the liver. The macroscopic examination of 9 × 11 cm specimen, including segments II + III of the left lobe of the liver, revealed a

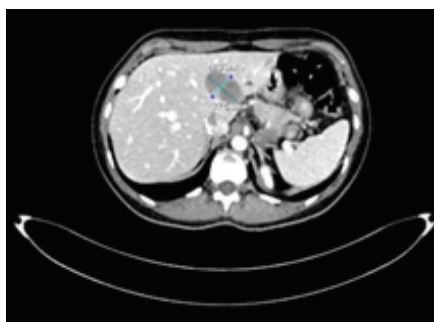


Fig. 1. CT scan of the abdominal cavity with intravenous contrast, axial section. Two merging hypodense lesions in the II+III segments of the left lobe of the liver, with total dimensions of 41×27 mm

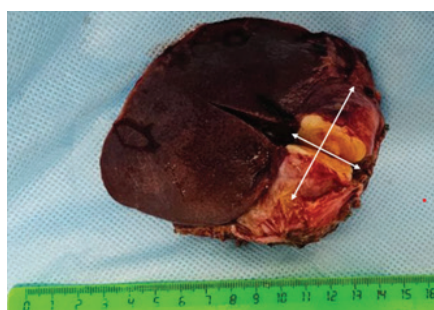


Fig. 2. Specimen macroscopy. A liver specimen measuring 9×11 cm with a subcapsular solid tumor measuring 3×5 cm. The tumor is clearly delimited from the surrounding parenchyma by a thick fibrous capsule, has a yellowish-amber color and a dense consistency

tumor of 3 × 5 cm in size. On the section, the tumor was amber in color, solid in structure with a pronounced capsule (Fig. 2).

The histological examination of the specimen revealed an encapsulated liver lesion with a thick fibrous capsule, heterogeneous in its morphological structure. The majority of cells in the lesion were spindle-shaped, with a normochromic nucleus, eosinophilic cytoplasm, and poorly distinguishable cytolemma. Mitotic figures were not determined. The cells formed bundle, vortex, perivascular structures lying in a moderate loose matrix with uneven diffuse-focal lymphoid infiltration. In places, the mesenchymal component alternated with liver parenchyma (Fig. 3) presented in the form of islets formed by typical hepatocytes. In some fragments, various-sized, cystically dilated, or branching bile ducts were identified. The bile ducts were surrounded by a moderately cellular fibrous stroma, in which numerous various-sized vessels and nerve fibers were seen (Fig. 4).

Considering the predominance of the mesenchymal component with a spindle cell structure in the tumor (Fig. 3), the

differential diagnosis was mainly focused on excluding other tumors with similar morphology. It was necessary to exclude gastrointestinal stromal tumor (GIST), as well as inflammatory myofibroblastic tumor, which can demonstrate similar spindle cell and stromal-inflammatory histoarchitecture. In this regard, an extended immunohistochemical study with a panel of antibodies, including markers of mesenchymal, smooth muscle, neural and epithelial differentiation, was carried out.

The negative expression of S100 (polyclonal, Cell Marque), Cytokeratins (clone AE1/AE3, Leica), DOG-1 (clone SP31, Cell Marque), CD34 (clone QBEnd 10, Leica), Calponin (clone CALP, Leica), SMA (clone asm-1, Leica) (Fig. 6), desmin (clone D33, Leica) and ALK (clone 5A4, Leica Biosystems) (Fig. 4) excluded the diagnosis of GIST and inflammatory

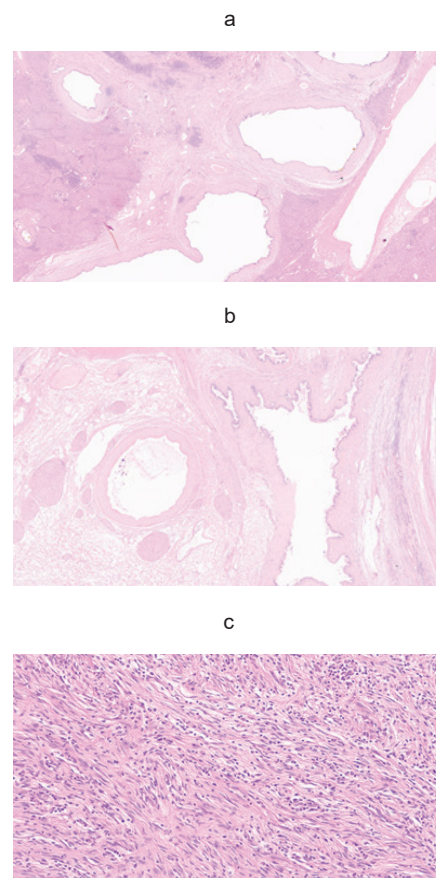


Fig. 3. Histological examination: a - fragment of a tumor with an area of preserved hepatic parenchyma, represented by typical hepatocytes, against the background of loose mesenchymal stroma, hematoxylin-eosin staining, UV, × 40; b - bile ducts surrounded by fibrous stroma, morphology resembles ductal plate malformation, hematoxylin-eosin staining, uv, × 100; c - the tumor component is represented by spindle-shaped cells with a fascicle and vortex arrangement in the connective tissue matrix with scattered lymphocytes, stained with hematoxylin-eosin, UV, × 200

myofibroblastic tumor. In the mesenchymal component, staining was observed only with the antibody to Vimentin (clone V9), and a low rate of proliferative activity was observed in the tumor cells (Ki-67 index less than 5%) (fig. 4). The results of immunohistochemical and histochemical analysis allowed us to verify the benign tumor and morphologically confirm the diagnosis of MHL.

Thus, based on a comprehensive examination and planned morphological study, the final diagnosis was: mesenchymal hamartoma of the left lobe of the liver in segments II + III. In January 2025, the patient underwent laparoscopic anatomical resection (R0) of segments II + III in the left lobe of the liver. The postoperative period was uneventful, and the patient was discharged from the hospital on the 6-th postoperative day. The patient is being followed-up and no recurrence has been noted.

Discussion. Mesenchymal hamartoma of the liver (MHL) is a benign tumor with a reported incidence of less than 1 case per million population per year [8]. Most of them are diagnosed during childhood and they are exceptional in adults [3, 7, 9]. Currently, approximately 50 cases of MHL in adults have been reported [4-6, 9-11]. As mentioned above, the diagnosis of MHL is difficult due to the lack of clinical symptoms specific to this disease, laboratory and radiological data, and the difficulty in differential diagnosis with cystadenoma, cholangiocarcinoma, nodular hyperplasia of the liver and embryonic sarcoma of the liver [2, 7, 8, 11]. The choice of strategy in the management of patients with MHL is of great importance. On the one hand, the possible malignant transformation of mesenchymal hamartoma is reported; on the other hand, there are risks of developing perioperative complications, including profuse bleeding, biliary fistulas and liver failure. All this emphasizes the rarity of this pathology, the relevance of diagnostic and treatment problems, and also clearly demonstrates the clinical significance and uniqueness of the case report we present.

The particular diagnostic difficulty in this case was associated with the absence of pathognomonic clinical and radiological signs. Thus, the patient presented non-specific complaints only of weakness and fatigue, and during the examination, anemia of unknown genesis was detected. This can be considered as a manifestation of paraneoplastic syndrome, especially in tumors with a pronounced inflammatory component. Differentiation of benign from malignant

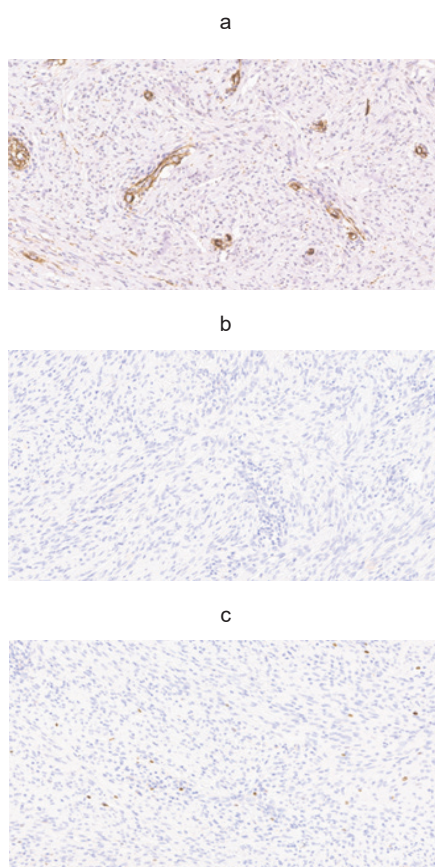


Fig. 4. Immunohistochemical study: a - negative expression of smooth muscle actin (SMA) in tumor cells with positive control in vascular smooth myocytes, reaction to SMA, uv. $\times 200$; b - lack of expression of ALK (clone 5A4) in tumor elements, reaction to ALK, uv. $\times 200$; c - weak proliferative activity of the tumor (Ki-67 index less than 5%), response to Ki-67, uv. $\times 200$

tumors was not possible using CT, and repeated ultrasound-guided biopsies of the liver lesion were uninformative. Thus, the diagnosis was established only after surgery, which indicates the limitations of non-invasive diagnostic methods in cases of atypical course of rare benign liver tumors.

Macroscopically, the tumor was a solid amber-colored node with a dense capsule, which did not exclude the possibility of a malignant neoplasm. Microscopically, there was a spindle cell component located in a loose stroma, with areas of lymphoid infiltration and perivascular structures.

Differential diagnosis included GIST, inflammatory myofibroblastic tumor, and solitary fibrous tumor.

An extensive immunohistochemical study, including both epithelial and mesenchymal markers, was critical for establishing the diagnosis. The negative expression of DOG-1, CD34, SMA,

calponin, desmin and ALK excluded the diagnosis of GIST and inflammatory myofibroblastic tumor. The diagnosis of MHL was supported by the presence of cystically dilated and branching bile ducts, surrounding fibrous structures and neurovascular bundles resembling a ductal plate malformation [7]. Low levels of proliferative activity (Ki-67 less than 5%) and the absence of cytological atypia also confirmed the benign nature of the lesion.

MHL may be a potentially premalignant lesion, with reported cases of malignant transformation to angiosarcoma in adults or to undifferentiated embryonal sarcoma in children [1, 9, 10]. These data justify an aggressive treatment strategy, with preference given to radical resection (R0). In some cases, liver transplantation may be considered for unresectable tumors [1].

Our case demonstrates the key challenges that clinicians and pathologists face when diagnosing rare liver tumors in adults. It highlights the need for a comprehensive multidisciplinary approach that includes imaging methods, clinical and laboratory data, comprehensive morphological and immunohistochemical studies, as well as knowledge of cancer-associated risks in benign neoplasms.

Conclusion. Mesenchymal hamartoma of the liver (MHL) is a benign lesion that is extremely rare in adults. This case report demonstrates the complexity of diagnosing MHL with atypical clinical and radiological manifestations, as well as the limitations of minimally invasive methods for diagnosis verification. A definitive diagnosis of MHL is possible only after comprehensive histopathological analysis of the resected specimen. Our case report confirms the need to include MHL in the differential diagnosis of liver tumors in adults and indicates the importance of a multidisciplinary approach that ensures accurate morphological verification and optimal treatment strategy.

The authors declare no conflict of interest.

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